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EMERGING TRENDS IN PHARMACEUTICAL SCIENCE RESEARCH VOLUME II

Editors:
Dr. Dipti Gohil
Dr. C. Swaminathan
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Emerging Trends in Pharmaceutical Science Research Volume II

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PREFACE

Pharmaceutical science is an ever-evolving field that continuously adapts to new technological advancements, innovative research methodologies, and emerging healthcare challenges. The rapid expansion of knowledge in drug discovery, nanotechnology, pharmacogenomics, and biotechnology has significantly transformed the way we approach disease treatment and patient care. The book "Emerging Trends in Pharmaceutical Science Research" aims to provide a comprehensive overview of the latest developments and breakthroughs shaping the future of pharmaceutical sciences.

This volume brings together contributions from esteemed researchers, scientists, and academicians who delve into various aspects of modern pharmaceutical research. Topics such as targeted drug delivery systems, artificial intelligence in drug development, herbal therapeutics, and regulatory frameworks are explored to give readers a holistic understanding of current trends. Emphasis is placed on interdisciplinary approaches that bridge the gap between fundamental science and clinical applications, ensuring that scientific innovations translate into improved healthcare solutions.

The book is intended to serve as a valuable resource for students, researchers, and professionals in the pharmaceutical sciences. By shedding light on the dynamic advancements in this field, we hope to inspire further research and innovation that will contribute to the development of safer and more effective pharmaceutical interventions.

We extend our heartfelt gratitude to all the contributors, reviewers, and editorial team members who have made this publication possible. Their dedication and expertise have played a crucial role in shaping the content of this book. We also appreciate the unwavering support of our readers and hope this volume enriches their understanding of the ever-evolving landscape of pharmaceutical science research.

- Editors

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AN OVERVIEW OF HERBAL NUTRACEUTICALS: IN THE MANAGEMENT OF LIFE THREATENING AND CANCER DISORDERS

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Abstract:

Nutraceuticals with an herbal component are all-natural medicines produced from plants that have many uses beyond just nourishment. Traditional Indian medical practices like Ayurveda and Siddha use bioactive chemicals found in plants like herbs in these items. Intake of nutraceuticals and nutritious foods is crucial to human health and wellness. Their purported safety and potential nutritional and therapeutic properties have given them a lot of attention. There is mounting evidence that herbal nutraceuticals may help in illness prevention, treatment, and even cure. Interest in their possible use as cancer treatment alternatives has grown in recent years. Understanding the role of nutraceuticals in human health is the focus of this book chapter, which also discusses their impact on obesity, diabetes, Alzheimer's disease, Parkinson's disease, cardiovascular disease, and osteoarthritis. This chapter presents evidence-based information on well-known herbal treatments, including apigenin, curcuminoids, lycopene, berberine, genistein, resveratrol, green tea, and quercetin, with examples and possible benefits provided. This chapter also covered cancer gaps, life-threatening conditions, and the future of nutraceuticals and functional foods made with herbs, as well as their prospects and advancements.

Keywords: Nutraceuticals, Phytochemicals, Diabetes, Cardiovascular Disease, And Cancer Disorder.

Introduction:

Cancer takes a major toll on public health across the globe, including in the United States. According to current research, one in two men and one in three women in the United States will have cancer at some point in their lives. In the upcoming years, it is expected to overtake heart disease as the nation's second-greatest cause of mortality. According to the 2014 World Cancer Report, Africa, Asia, and Central and South America account for 70% of all cancer deaths globally and more than 60% of all new cancer cases. It is estimated that the United States spent $125 billion on cancer care in 2010, and by 2020, that amount could increase to $156 billion. There are numerous treatment options, such as surgery, radiation, and chemotherapy. Death rates for several cancer kinds have decreased as a result of better prevention techniques, earlier detection, and advancements in care. Some cancer rates have still remained the same or even significantly increased [1].

The International Agency for Research on Cancer (IARC) and the American Cancer Society (ACS) collaborated to create the Global Cancer Statistics 2020 study, which verified that about 17 million people received a cancer diagnosis in 2020. The report included 185 nations and 36 forms of cancer [2]. A neoplasm, or tumor, is an abnormal mass of cells in the body. It arises when cells divide more frequently than they should or do not die when they should.

Two types of tumors are distinguished: benign and malignant. Benign tumors stay where they are without spreading to other body areas. They tend to grow slowly, have clearly defined bounds, and do not infiltrate distant locations or close structures. Benign tumors are often regarded as harmless. Malignant tumors include cells that proliferate uncontrolled and spread to distant locations. Because they infect other places, malignant tumors are cancerous. They use the lymphatic or blood systems to travel to far-off places. They call this growth metastasis. In the body, metastasis can occur anywhere, although they are most frequently detected in the liver, lungs, brain, and bone [3].

Herbal nutraceuticals, made from natural plant sources, include bioactive chemicals that target several tumorigenesis-related pathways, providing a potential approach to cancer prevention and control. Using the phrases "nutrition" and "pharmaceutical," Stephen DeFelice coined the term "nutraceutical" in 1989. He claims that foods or dietary ingredients that provide health or medical advantages, such as illness prevention and therapy, are known as nutraceuticals.

The classic quote from the Greek physician Hippocrates, "Let food be your medicine," highlights the importance of prevention as a primary strategy for maintaining good health [4]. Nutraceuticals—isolated products made from food—are mostly offered in medicinal forms to improve health and prevent chronic illnesses. Their favorable physiological effects on the human body and fewer adverse effects have made them increasingly popular than traditional medications. Nutraceuticals are used to treat several illnesses, such as diabetes, Alzheimer's disease, and colon cancer. The natural sources of these include fruits, vegetables, marine life, and medicinal plants [5].

Need for Nutraceuticals

The market for nutraceuticals is expanding as a result of changes in the healthcare sector as well as rising medical and pharmaceutical expenses. People who want to improve their health without breaking the bank on expensive prescription and OTC drugs are driving the rising popularity of nutraceuticals. In this regard, the nutraceutical market has grown significantly in the United States and Canada, with Asia-Pacific and Mexico following closely after [6]. Many of us cannot obtain enough nutrients from the foods we eat on a daily basis. Second, the modern world is highly poisonous and full of pesticides and pollutants, which causes the body to lose its ability to operate correctly. Our bodies can be genuinely strengthened by a high-quality dietary

supplement that is absorbed and used by the body. And contribute crucially, which is why nutraceuticals are necessary [7].

Herbal Nutraceuticals

Due to the high expense and severe adverse effects of current synthetic nutraceuticals, as well as the rise in chronic illness cases, society is searching for safe, side-effect-free alternatives that support human health. The hunt for safe, effective, and nutritionally sound herbal supplements was sparked by the availability and affordability of sources that could be turned into herbal nutraceuticals.

Categories of Nutraceuticals

1. Nutrient: A feed component needs to be accessible and administered at a dosage that will sustain an animal's survival. Proteins, lipids, carbs, minerals, and vitamins are a few of the nutrients included in feed.

2. Dietary Supplement: A product that comprises concentrations, components, extracts, or metabolites of the following substances, as well as one or more of the following nutritional ingredients: vitamin, mineral, herb, or other botanical or amino acid (protein).

3. Nutraceutical: Any non-toxic dietary ingredient with health advantages, such as illness prevention and therapy, that has been scientifically demonstrated.

4. Herbs: Various extracts and concentrations made from herbs or botanical items are used to treat both acute and chronic illnesses [8].

Growth of Nutraceuticals

Nutraceuticals and functional foods have grown to be multibillion-dollar industries in the worldwide marketplace. The need to appropriately label and evaluate the health impacts of functional foods and nutraceuticals is posing serious obstacles to progress in this field on a global scale. The functional food and nutraceutical industry in the United States of America (USA) is now the biggest and fastest growing in the world. Many medicinal plant species, spices, and tree species with sizable domestic markets are found in India. However, the United States and Japan are India's top export destinations [9].

Classification of Nutraceuticals

1. Traditional
   - Chemical constituents Nutrients, Herbals, Phytochemicals.
   - Probiotic organisms.
   - Nutraceutical enzyme.
2. Non-Traditional
   - Fortified nutraceuticals.
   - Recombinant Nutraceutical.
3. Substance with established nutritional functions
   - Vitamins, Minerals, Amino acids, Fatty acids.

4. Herbs (or)Botanical products
5. Reagents derived from other sources
   - Pyruvate, Chondroitin sulphate, Steroid hormone precursors
6. Functional foods
7. Probiotics and prebiotics
8. Polyunsaturated fatty acids
9. Antioxidant vitamin
10. Polyphenols
11. Spices

Present Global Status of Nutraceuticals

The worldwide market comprises 85% vitamins and minerals and 10% antioxidants. The market share of herbal extracts is around 5%. The US is the biggest market for nutraceuticals, with China and India coming in second and third, respectively. Since soy contains antidiarrheal, hypolipidemic, anticancerogenic, and antiosteoporosis properties, it has become a popular food. Prebiotics lower cholesterol and prevent cancer, osteoporosis, allergies, and type 2 diabetes, making them popular as well.

The demand for ingredients used in nutraceuticals has grown by 5.8% per year to $15.5 billion. The markets for nutraceuticals that are expanding the quickest are China and India. Medical practitioners' use of herbal and non-herbal extracts has grown globally, rising from 6.5% per year to $1.85 billion in 2010. The demand for vitamins, minerals, and nutrients increased by 6.3% yearly from 2005 to $9.5 billion in 2010. The market for vitamin components in nutraceuticals grew by up to 4.6% each year to reach $4.2 billion in 2010.

Market Scenario of Nutraceuticals

The demand for pharmaceuticals, food supplements, cosmetics, health goods, and plant-based medications is rising both domestically and globally. Nutraceuticals will continue to be in high demand worldwide. In the coming years, the Indian pharmaceutical industry will have a lot of potential opportunities in the nutraceuticals sector. Many of them have no particular therapeutic benefits and are only nutritional supplements. Its rapid expansion, research and development, lack of standards, marketing zeal, quality control, and regulation will all be crucial factors in determining its success or failure. The basic components of nutraceuticals are nutrients, herbal remedies, and dietary supplements, which enable them to combat various illness conditions, preserve health, and improve quality of life [10].

Nutraceuticals Foods

Numerous phenolic chemicals, terpenoids, sulfur compounds, pigments, and other naturally occurring antioxidants found in vegetables, fruits, whole grains, herbs, nuts, and seeds have been linked to illness prevention and/or therapy, like cancer and cardiovascular disease. Garlic, soybeans, cabbage, ginger, licorice root, and other foods and plants have the strongest

anticancer properties. Dietary phytosterols may protect the majority of prevalent malignancies in Western nations, including colon, breast, and prostate cancer, according to epidemiological and experimental research [11].

Nutraceuticals for Different Diseases

For almost two decades, researchers have been studying the connection between phytochemicals and their health advantages. Eating fruits and vegetables may lower your risk of developing many disorders related to the endometrium, stomach, esophagus, pancreas, throat, and colon [12].

Osteoarthritis (OA)

The degenerative condition known as osteoarthritis (OA) is characterized by inflammation of the synovium and cartilage, which can result in joint stiffness, swelling, discomfort, and decreased mobility. OA is a multifactorial, extremely complicated illness. The high prevalence of OA, which affects a larger proportion of women (18%) than males (9.6%) after menopause, as well as the lengthening of life expectancy, make it one of the leading causes of disability worldwide. Even though OA mostly affects the hands, hips, and knees. Numerous articles in the scientific literature discuss the use of a wide range of nutraceuticals as an alternative treatment for OA; their review emphasizes the significance of non-invasive approaches in the treatment of OA by utilizing the most widely used and accessible nutraceuticals, including botanical extracts, fish oil, and olive oil. Patients with established OA now have more therapeutic choices thanks to the incorporation of nutraceutical substances into their diet, which go beyond non-pharmacologic therapies, drugs, and surgery therapy [13].

Obesity

A chronic condition that poses a threat to public health across the world is obesity. Overeating, a lack of physical activity, environmental factors, the Western diet, and heredity are the causes of the condition. It is acknowledged as a major mediator in the development of several metabolic syndromes, including diabetes mellitus, insulin resistance, hypertension, rheumatoid arthritis, cancer, congestive heart failure, stroke, and hyperlipidemia. Curcumin, bottle gourd, fenugreek, amla, Murraya koenigii, black gram, camellia sinensis, capsaicin, calcium-rich foods, conjugated linolenic acid, polyunsaturated fatty acids, psyllium fiber, Momordica Charantia, flavonoids, ginger components, and other nutraceuticals are currently used to treat obesity [14].

Oral Diseases

A relatively recent idea, "Toronto nutraceuticals," refers to pleiotropic phytotherapeutic substances utilized in dentistry. These substances support oral health by controlling a variety of molecular and biochemical targets. Odonto nutraceuticals, which are high in proanthocyanidins, flavonoids, and polyphenols, include extracts from green tea, grapes, and cocoa seeds. Aloe vera gel assists patients with oral lichen planus disease by reducing discomfort and promoting the

healing of mucosal wounds. Probiotics are also helpful in avoiding dental problems such as periodontitis, gingivitis, dental caries, halitosis, and bad breath.

Diabetes

In people with diabetes mellitus, either inadequate insulin synthesis or impaired insulin action leads to elevated blood glucose levels. The two most prevalent forms of diabetes are Type 2 (95%), which is closely linked to obesity, and Type 1 (5%), which is an autoimmune disease. Furthermore, gestational diabetes may develop throughout pregnancy.

According to estimates, the number of people with diabetes worldwide increased from 171 million in 2000 to 366 million in 2003. Because it supports the demand for essential fatty acids, docosahexaenoic acid (DHA) is crucial for neurovisual development and plays a major role in controlling insulin resistance, especially in pregnant women with gestational diabetes. In Germany, diabetic neuropathy is treated with strong antioxidant lipoic acid. It could provide more defense against complications from diabetes if used as a long-term dietary supplement. The food and pharmaceutical industries extensively use pseudo-synthetic dietary fibers as lipid-lowering treatments for people with hyperlipidemia, glucose control aids for diabetics, and additives in processed foods and weight-management products.

Keeping magnesium levels in check lowers the risk of diabetes and improves insulin sensitivity. Furthermore, chromium extracts from cinnamon and bitter melon can cure and perhaps prevent diabetes. In certain diabetic individuals, picolinate, calcium, and vitamin D have been shown to increase insulin sensitivity and improve glucose control. Nutraceuticals with notable combinations of these substances may be important in preventing diabetes and may even be able to be sold legally, according to certain theories [15].

Cardiovascular Diseases

Most cardiovascular diseases may be managed and prevented. Reports indicate that a high prevalence of cardiovascular disease deaths is associated with a diet low in fruits and vegetables. Multiple studies have shown that a reduced risk of cardiovascular disease is associated with a diet rich in fruits and vegetables. In addition, for the prevention and treatment of CVD, neutraceuticals in the form of vitamins, minerals, dietary fibers, antioxidants, and omega-3 polyunsaturated fatty acids (n-3 PUFAs) are advised in conjunction with physical activity [16].

Alzheimer's Disease

The most prevalent and dreaded type of dementia, Alzheimer's disease (AD), accounts for around 70% of all dementia cases and is experiencing a dramatic epidemic as a result of the massive global increase in the elderly population. Although new epidemiological studies appear to indicate a drop that requires more confirmation, the incidence of dementia has grown in recent years. By 2050, it is anticipated that the annual number of cases in the United States will be close to one million [17]. An alternative term for Alzheimer's disease is senile dementia. It seems that

antioxidants prevent the illness from progressing as quickly. Nutraceuticals with antioxidant properties, such as beta carotene, lycopene, curcumin, lutein, and lavender, are used to prevent brain damage brought on by oxidative stress. These substances can postpone the onset of dementia.

Eye Disorders

As of right now, it is known that one of the goals of the UN Summit on Sustainable Development is to improve eye health, which may be accomplished by including methods for prevention, treatment, rehabilitation, and promotion. Enhancing eye health involves not just having the most remarkable eyesight possible but also lowering impairment and raising well-being. Various antioxidants and nutraceuticals, such as vitamin A and lutein, vitamin C and coenzyme Q10, astaxanthin, trehalose, grape seed extract, and bergamot polyphenolic fraction, are essential for preserving eye health [18].

Parkinson's Disease

Parkinson's disease is a neurological condition that often strikes in mid-to late adulthood and is caused by nerve loss in certain brain areas. It causes stiffness in the muscles, shaking, and trouble walking. According to Canadian experts, eating foods high in vitamin E may help prevent Parkinson's disease. According to a decrease in clinical symptoms, creatine seems to alter the characteristics of Parkinson's disease.

Allergy

An immune system hypersensitivity condition is called an allergy. Because of a kind of antibody known as immunoglobulin E, which causes excessive activation of certain white blood cells known as mast cells and basophils, allergic responses are unique. The inflammatory response that results from this reaction in nursing can range from discomfort to severe. Particularly for blood arteries, quercetin prevents beta lipoprotein (LDL-C) from breaking down. LDL-C is linked to the fundamental cause of cardiopathy in nursing, and quercetin works to scavenge free radicals and act as an antioxidant [19].

Cancer and It's Cause

Cancer was less frequent a century ago, but in the past several decades, its frequency has been rapidly increasing, most likely as a result of our changing habits, lifestyle, and longer life expectancy. In the 21st century, cancer is one of the most dreaded diseases of the 20th century and is continuing to spread and become more common. The fact that one in four people may develop cancer in their lifetime is a concerning issue. Every year, over 11 lakh new cases of cancer are reported in India, compared to over 14 million cases globally. Numerous substances known as carcinogens, which cause cancer, are present in our environment all the time [20].

Cancer is the result of aberrant cell proliferation. Any organ or bodily structure can develop cancer, which is made up of microscopic cells that are unable to stop growing. On rare occasions, a regular radiological exam, laboratory test, or for some other cause, cancer may be

discovered "incidentally." Generally speaking, cancer cannot be identified until it reaches 1 cm in size or has 1 million cells. At this stage, it might be called a "mass," "growth," "tumor," "nodule," "lump," or "lesion." Leukaemia and lymphomas, which are malignancies of the blood and bone marrow that often do not generate a "mass," are exceptions to this general rule. However, they will show up on laboratory testing. It's unlikely that turning a healthy cell into a malignant one is a crucial step in the development of cancer [21].

Until one of four things happens, cancer cells will keep growing: (1) the malignant mass is surgically removed; (2) chemotherapy or another cancer-specific treatment, including hormone therapy, is used; (3) radiation therapy is used; or (4) the cancer cells shrink and go away on their own. Even though it is quite uncommon, certain kidney tumors and melanomas can cause this last catastrophe. Cancer is the top cause of mortality for those under 85 and the second most common cause of death in the US overall. Due to the shutdown of healthcare facilities, loss of jobs and health insurance, and anxiety over COVID-19 exposure, the coronavirus illness 2019 (COVID-19) pandemic delayed the detection and treatment of cancer in 2020 [22].

An estimated 618,120 Americans are expected to lose their lives to cancer in 2025, which equates to almost 1700 fatalities every day. Despite substantial drops in the prevalence of cigarettes, which went from 42% in 1965 to 12% in 2022, smoking remains the greatest avoidable cause of death in the United States, contributing to almost 500 cancer deaths per day in 2025, the majority of which are from lung cancer. In 2025, cigarette smoking will be directly responsible for about 85% (106,150) of lung cancer deaths (124,730), with an additional 3,500 coming from second-hand smoke and 15,100 coming from a combination of other combustible tobacco products (such as cigars or pipe smoking), 29,30 radon, 31 occupational exposures, 32 air pollution, and other environmental exposures. Governments can implement policies that can lower population-level exposure to known cancer risk factors, such as smoking, being overweight or obese, and infections, even if some cancer cases may be inevitable [23].

India's Cancer Standard

Indian people's epidemiological problems have been documented by the "National Cancer Registry Program" since 1991. As predicted, women were somewhat more likely than men to have cancer. Cancers of the esophagus, throat, stomach, lungs, and mouth are among the most complicated illnesses that men may have. Cancers of the mouth, stomach, and esophagus, on the other hand, are the cancers that affect women the most frequently, followed by breast and cervical cancer.

The increasing number of new cases shows the condition of cancer research in India. The present state of research encompasses everything from basic studies required to control carcinogens to techniques to evaluate different biological pathways and new therapeutic drugs [24].

Herbal Nutraceuticals with Anticancer Potential

By lowering cancer cachexia, nutraceuticals may also improve life quality and lessen damage linked to radiation and chemotherapy treatments. At various cellular levels, the phytochemicals have demonstrated distinct mechanisms of action. The majority of them have become a diverse source of antioxidants that impact the signaling pathway associated with redox-mediated transcription factors. Some of the common nutraceuticals used in the treatment of cancer

1. Curcumin (*Curcuma longa* - Turmeric)

Curcuma longa, also referred to as "*Curcuma domestica*," is a perennial herbaceous plant that belongs to the Ginger family (Zingiberaceae) [25]. Two researchers from Harvard College Laboratory, Vogel and Pelletier, isolated it for the first time in 1815. Since then, curcumin has drawn increasing attention from scientists, and more and more health advantages have been identified [26].

In Asia, curcumin has been used for over 2,500 years, particularly in Ayurvedic (traditional Indian medicine). Numerous medical conditions, including wounds, acne, burns, other skin conditions, eye infections, sinusitis, rheumatism, depression, stress, and dyspepsia, have been treated with it.

Curcumin has been proven to have important anticancer effects through several methods. Targeting pathways, including STAT-3, AKT-mTOR, and NF-κB, suppress tumor development by modifying angiogenesis and apoptosis. Research has demonstrated that curcumin can inhibit the growth of cancer cells in the colon, prostate, uterine leiomyosarcoma, and triple-negative breast cancer. Curcumin also improves the effectiveness of chemotherapy and radiation therapy by making colorectal, ovarian, cervical, and head and neck cancer cells more susceptible to treatments like paclitaxel, oxaliplatin, and cisplatin. By downregulating CXCL1 and CXCL2, it also has antimetastatic actions, lowering lung metastases in breast cancer. Additionally, curcumin suppresses oral and colorectal carcinogenesis by blocking tumor-promoting pathways, acting as a chemo-preventive agent. It is an intriguing contender because of its capacity to work in concert with chemotherapeutic medications to increase apoptosis while decreasing resistance [27].

2. Quercetin

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a member of the flavonoid class that the human body is unable to generate and is named after the Latin term "Quercetum," which means Oak Forest. It has a yellow hue, dissolves poorly in hot water, dissolves well in lipids and alcohol, and is insoluble in cold water. Apples, berries, broccoli, and onions are rich sources of quercetin. Flavanones, the second category, are mostly present in citrus fruits. Naringenin is an example of a flavonoid in this category. While anthocyanins are present in strawberries, other

berries, grapes, wines, and tea, flavonoids that belong to the catechins are mostly found in red wine and green and black tea [28].

Quercetin is a flavonoid that is one of the most effective cancer killers. Numerous fruits and vegetables contain quercetin, which has several ways of combating illness, making it a useful substance for both cancer prevention and treatment. According to research, those who consume the most quercetin had far reduced mortality rates from the main cancers, such as breast, stomach, colon, and lung cancer. In the modern world, cancer is the second greatest cause of mortality after cardiovascular disease. On the other hand, individuals receiving traditional cancer treatment are often left debilitated and at risk of developing new cancers as well as recurrent malignant growths. This is due to the fact that these therapies employ lethal radiation and hazardous chemicals, which impair immune function and raise the chance of early death. Chinese researchers studied quercetin's effects on breast cancer cells and discovered that it has anti-tumor qualities. One advantage of quercetin is that it interferes with the process that turns healthy cells into cancerous ones at the cellular level. The anti-inflammatory and antioxidant qualities of quercetin can guard against the harmful alterations in cellular DNA caused by cancer-inducing substances. Additionally, research shows that eating foods high in quercetin on a daily basis reduces the risk of lung cancer. According to research, those who consume the most quercetin had far reduced mortality rates from the main cancers, such as breast, stomach, colon, and lung cancer [29].

3. Lycopene

Recently, lycopene, a carotenoid antioxidant found in food, has garnered a lot of attention as a significant phytochemical that is good for human health. In the West, the leading causes of morbidity and mortality are chronic conditions such as osteoporosis, diabetes, cardiovascular disease, and cancer. In addition to age and genetics, nutrition and lifestyle choices are also thought to be significant risk factors for many illnesses [30].

Ripe tomatoes, grapefruits, and red watermelon contain lycopene, a red carotenoid that has antioxidant, anti-inflammatory, and cancer-preventive qualities. When ingested from heated, lipid-rich food sources rather than raw ones, it is more effectively absorbed by the body. It has been shown to concentrate in the prostate and to have pro-apoptotic and anti-proliferative properties against prostate cancer. Lycopene inhibits singlet oxygen, scavenges free radicals, and shields DNA from oxidative damage. Consequently, it stops normal cells from potentially turning into cancerous ones. Additionally, it affects immunological function, apoptosis, carcinogen-metabolizing enzymes, and gene functions. It enhances pro-differentiation, anti-lipid peroxidation, anti-proliferation, and gap junction communications. Lycopene aids in the body's removal of foreign chemicals and carcinogens by inducing cytochrome P450 and hepatic quinine reductase. It prevents anti-oncogenes like p53 and Rb from becoming phosphorylated. Additionally, it suppresses the cell cycle's S-phase and G0/G1 phases. Lycopene has been shown

to reduce tumor development, invasion, and metastasis by inhibiting the activities of matrix metalloproteinases 2 (MMP-2), platelet-derived growth factor-BB, and MMP-9. Additionally, it controls dysplastic alterations and helps patients with premalignant lesions of the mouth, including leukoplakia and the early stages of oral submucous fibrosis (OSMF). Lycopene promotes mouth opening, reduces mouth burning, and suppresses aberrant fibroblasts and inflammation in OSMF patients. In LEC rats, lycopene has been shown to prevent the fibrogenesis of hepatic tissues. Lycopene is safe and has no negative effects at a dietary dosage of 3 g/kg/day. Because of its antioxidant and multi-targeted anti-carcinogenic qualities, lycopene shows promise in both preventing and treating cancer [31].

4. Berberine

There is evidence that berberine can inhibit the spread of tumors. Tumor cells can penetrate the normal tissue barrier and infiltrate the surrounding normal tissue as well as distant organs because matrix metalloproteinases (MMPs) tear down the tissue matrix. In vitro research has shown that metastasis was considerably decreased by inhibiting FAK, IKK, NF-kB, u-PA, MMP-2, and MMP-9. By blocking the production of MMP-2 from tumor cells, berberine prevents tumor cells from destroying the tissue matrix. The proliferation-related proteins phosphoinositide 3-kinase (PI3K), activator protein-1 (AP-1), NF-kappaB, and Janus Kinase 2 (JAK2) were all activated by berberine. These proteins reduced the TNBC cell line MDA-MB-231's IL-8 expression. Berberine also inhibited the invasion that IL-8 triggered. Additionally, berberine reduced fibronectin, EGF, bFGF, MMP-2, MMP-9, and E-cadherin levels in breast cancer cells. JNK and p38 MAPK inhibitors reduced the impact of berberine, whereas p38 MAPK activators enhanced it. The vasodilator-stimulated phosphoprotein (VASP) is another protein that berberine may bind to. High-mobility breast cancer cells overexpress VASP, which prevents polymerization. Berberine inhibits tumor development and proliferation via binding VASP in MDA-MB-231 cells [32].

5. Sulforaphane

Cruciferous vegetables provide sulforaphane (SF), which has chemoprotective qualities. Additionally, it has the ability to strengthen the antioxidant impact. Dinitrobenzamide mustard contains the prodrug metabolite PR-104A as well as the pre-prodrug PR-104. In order to see this impact, HT29 colon cancer cells are treated with a low dose of SF to produce the Aldo-keto reductase 1C3 (AKR1C3) protein. They treated the majority of HT29 colon cancer cells with 2.5 μM SF in order to identify proteins that were regulated by a low quantity of SF. Stable isotope tagging of amino acids in cell culture has shown changes in protein abundance. Aldo-keto reductase 1C3 (AKR1C3) and bioactivated the DNA cross-linking prodrug PR-104A with the help of 18 proteins that were discovered to be markedly up-regulated. PR-104A's EC50 decreased by 3.6 times when HT29 cells were preconditioned with SF. Reproducing this effect change was possible in the SW620 colon cancer cell line; however, in other colon cancer cell

lines, the abundance and activity of AKR1C3 were either nonexistent or very low, and SF was unable to improve their condition. The increase in PR-104A cytotoxicity was associated with both AKR1C3 abundance and activity, which were both induced via SF in a dose-dependent manner. SF had no similar effect on the cytotoxicity of PR-104A in healthy cells. In conclusion, only cancer cells exhibited the response of PR-104A following preconditioning with SF, and these cells also expressed AKR1C3. Non-cancerous cells did not exhibit this response [33].

6. Genistein

According to several investigations, eating soybeans lowers your chance of developing breast, prostate, and colon cancer because they contain genistein [34]. Numerous epidemiologic studies demonstrated a link between cancer prevention and a diet high in soy. These investigations were prompted by the finding that the incidence of breast and prostate cancers is lower in Asian nations with diets heavy in soy products, such as China and Japan, than in the US and Europe. Indeed, a number of meta-analyses indicate that eating soy products is linked to a lower risk of prostate cancer in males and a negative correlation with the risk of breast cancer in Asian women. This association was not verified for women from the West. Furthermore, eating soy isoflavones can reduce the incidence of breast cancer in Asian women who are premenopausal or have just gone through menopause, according to a recent meta-analysis. Additionally, migration studies revealed that Asians had a higher prevalence of breast and prostate cancer after immigrating to the US, indicating that environmental variables and lifestyle modifications—particularly dietary changes—have an impact on the genesis of this malignancy. These epidemiologic data offer the justification for using suitable cellular and animal models to investigate at the molecular level how genistein, the main isoflavone found in soy, might prevent cancer. Preclinical research on genistein as an anticancer treatment reveals encouraging findings due to its pleiotropic effect, which makes it possible to confirm its clinical usefulness in therapeutic trials. Genistein is crucially present in the biogenesis process in its glycosylated form, mostly with a glucose molecule. The body absorbs the free genistein aglycone following a deglycosylation process in the small intestine, even if genistein is consumed as genistein glycoside. This process has a variety of pharmacologic effects, including anticancer ones. In addition to genistein, synthetic compounds such as genistein glycosides have also been shown to have anticancer properties when tested in vitro. The sugar groups that genistein glycosides have determined how effective they are against cancer. The addition of acetylated sugar hydroxyls to genistein, for instance, increased its selectivity for tumor cells. Depending on its selectivity for the target molecules, genistein and its derivatives have varying anticancer potencies in various cancer types [35].

7. Apigenin

One naturally occurring flavone that is frequently referred to as apigenin is 4′,5,7-trihydroxyflavone. Like many other flavonoids, the term "apigenin" comes from the Apium

genus in the Apiaceae (celery, carrot, or parsley family, commonly known as Umbelliferae). It belongs to a family of flavonoids called flavones and contains hydroxyl groups at locations C-5 and C-7 of the A-ring and C-4′ of the B-ring. Apigenin is a yellow, crystalline powder that is soluble in hot ethanol and dimethyl sulfoxide but insoluble in water. Its molecular weight is MW 270.24, and its formula is $C_{15}H_{10}O_5$. Due to its richness and prevalence in a wide range of natural sources, such as fruits and vegetables, apigenin is considered one of the primary flavonoids. Parsley, chamomile, celery, vine spinach, artichokes, and oregano are important sources of apigenin [36].

Since apigenin comes from a factory, it generally looks to be one of the bioactive compounds that lowers the incidence of cancer. There is evidence linking increased intake of flavonoids from fruits and vegetables to a higher risk of developing cancer. In addition to lung cancer, Knekt *et al.* investigated the connection between flavonoid intake (quercetin, kaempferol, myricetin, luteolin, and apigenin). Flavonoids' protective effect against lung cancer is further supported by their discovery that there is a negative correlation between flavonoid intake and the incidence of cancer in all locations. The scientists concluded that apigenin-rich foods like apples and onions have a protective effect against lung cancer. In the investigation of bone cancer, ovarian cancer, and the risk of neoplasia rush after colon surgery, individuals with cancer looked at how beneficial flavonoids are connected to their defense, among other benefits, the part of cancer danger reduction [37].

8. Resveratrol

The "miracle" nutraceutical resveratrol (3,4',5-trihydroxy-trans-stilbene) has the potential to treat cancer and signal advances in cancer treatment. Resveratrol is a naturally occurring phytoalexin that plants manufacture to defend against pathogenic invasion and environmental stress. In 1940, it was initially separated from the roots of the Veratrum album, also known as the white hellebore. In 1963, it was taken from the roots of Polygonum cuspidatum, also known as Japanese knotweed. Although its cardioprotective properties were originally asserted in 1982, the chemical gained popularity only when resveratrol, which is found in red wine, was proposed to have cardioprotective health advantages in 1992. Topical resveratrol's potential application as a new anticancer medication was brought to light in 1997 when it was shown to inhibit carcinogenesis in a mouse skin cancer model [38].

Numerous fruits and plants, including red wine, grapes, berries, and peanuts, contain phytoalexin resveratrol. Japanese knot weed, or Polygonum cuspidatum, has been used in traditional Chinese and Japanese medicine to treat inflammation, bacterial infections, and dermatitis. Its roots contain the greatest amounts of resveratrol found in nature. Resveratrol is often produced by plants as a defense against viral and fungal diseases, in reaction to mechanical damage, and in response to UV light. According to early research, resveratrol has anticancer properties against a variety of tumor types and influences the genesis and growth of tumors at

different stages. Resveratrol specifically interferes with many signaling pathways that are active in altered cells, causing cancer cells to undergo apoptosis [39].

Conclusion:

It has long been recognized that natural compounds offer therapeutic benefits, such as boosting immunity and possessing antidiabetic, anticancer, antibacterial, and gastroprotective properties. The growing nutraceutical business, which is growing faster than the conventional food and pharmaceutical industries, has made more use of these botanicals in recent years. Nutraceuticals, which are mostly obtained from botanical or herbal sources, are essential for the prevention and treatment of medical problems while concurrently minimizing the bad effects of therapies. In order to guarantee that this product is not only efficient but also risk-free, unadulterated, and of superior quality, it is necessary to implement severe quality control procedures. More study is needed to clarify their methods of action through particular experimental models and human clinical trials, notwithstanding their promise in controlling chronic illnesses such as diabetes, cancer, obesity, osteoarthritis, and neurodegenerative disorders. Comprehensive clinical evidence on these natural compounds' molecular and mechanistic activities is currently lacking. The quality of life for patients may be improved, and therapeutic effectiveness may be increased by using nutraceuticals as adjuvant therapies in addition to traditional treatments like chemotherapy.

References:

1. Prasad S, Gupta SC, Tyagi AK. Reactive oxygen species (ROS) and cancer: Role of antioxidative nutraceuticals. Cancer letters. 2017 Feb 28;387:95-105.
2. Maiuolo J, Gliozzi M, Carresi C, Musolino V, Oppedisano F, Scarano F, Nucera S, Scicchitano M, Bosco F, Macri R, Ruga S. Nutraceuticals and cancer: Potential for natural polyphenols. Nutrients. 2021 Oct 27;13(11):3834.
3. Patel A. Benign vs malignant tumors. JAMA oncology. 2020 Sep 1;6(9):1488-.
4. Kishor K. Dr. Kamal Kishor, Dr. Neha Shukla, Dr. NS Meena, Dr. Prakash Singh and Dr. Amit Singh Vishen. Herbal nutraceuticals, The Pharma Innovation Journal 2021; 10(2): 419-427
5. Nemane ST, Shinde NN, Katu YM, Waghmare RR. A review article on: nutraceuticals. World Journal of Pharmaceutical Research. 2020 Jan 18;9(3):1414-21.
6. Chopra AS, Lordan R, Horbańczuk OK, Atanasov AG, Chopra I, Horbańczuk JO, Jóźwik A, Huang L, Pirgozliev V, Banach M, Battino M. The current use and evolving landscape of nutraceuticals. Pharmacological Research. 2022 Jan 1;175:106001.
7. Manikandaselvi S, Vadivel V, Brindha P. Nutraceuticals–An overview. Int J Pharm Bio Sci. 2016 Jan;7(1):284-96.
8. Srivastava S, Sharma PK, Kumara S. Nutraceuticals: A review. J. Chronother. Drug Deliv. 2015;6:1-0.

9. Rajat S, Manisha S, Robin S, Sunil K. Nutraceuticals: A review. Int. Res. J. Pharm. 2012;3(4):95-9.
10. Srividya AR, Venkatesh N, Vishnuvarthan VJ. Nutraceutical as medicine. Int J Adv Pharma Sci. 2010 Nov;1(2):132-3.
11. Hardy G. Nutraceuticals and functional foods: introduction and meaning. Nutrition. 2000 Jul 1;16(7-8):688-9.
12. Bradbury KE, Appleby PN, Key TJ. Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). The American journal of clinical nutrition. 2014 Jul 1;100:394S-8S.
13. Castrogiovanni P, Trovato FM, Loreto C, Nsir H, Szychlinska MA, Musumeci G. Nutraceutical supplements in the management and prevention of osteoarthritis. International journal of molecular sciences. 2016 Dec 6;17(12):2042.
14. Nijhawan P, Behl T. Nutraceuticals in the management of obesity. Obesity Medicine. 2020 Mar 1;17:100168.
15. Aluko RE. Functional foods and nutraceuticals. New York, NY, USA:: Springer; 2012 Jun 5.
16. Shahidi F. Nutraceuticals and functional foods: whole versus processed foods. Trends in Food Science & Technology. 2009 Sep 1;20(9):376-87.
17. Mecocci P, Tinarelli C, Schulz RJ, Polidori MC. Nutraceuticals in cognitive impairment and Alzheimer's disease. Frontiers in pharmacology. 2014 Jun 23;5:147.
18. Maiuolo J, Bulotta RM, Oppedisano F, Bosco F, Scarano F, Nucera S, Guarnieri L, Ruga S, Macri R, Caminiti R, Musolino V. Potential properties of natural nutraceuticals and antioxidants in age-related eye disorders. Life. 2022 Dec 27;13(1):77.
19. Dighe SA, Nalkar RS, Kakad SB. A review on nutraceuticals and its role in treatment of disease. World J. Pharm. Res. 2020 Aug 20;9(12):1285-97.
20. Roy PS, Saikia B. Cancer and cure: A critical analysis. Indian journal of cancer. 2016 Jul 1;53(3):441-2.
21. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. cell. 2011 Mar 4;144(5):646-74.
22. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. CA: A Cancer Journal for Clinicians. 2025 Jan 16.
23. Wu Z, Xia F, Lin R. Global burden of cancer and associated risk factors in 204 countries and territories, 1980–2021: a systematic analysis for the GBD 2021. Journal of Hematology & Oncology. 2024 Nov 29;17(1):119.
24. Saha S, Roy A, Bahadur S, Chandrakar S, Choudhury A, Das S. Phytochemicals as adjuvant in neoplasia. Asian Journal of Research In Chemistry. 2014;7(8):765-70.

25. Priyadarsini KI. The chemistry of curcumin: from extraction to therapeutic agent. Molecules. 2014 Dec 1;19(12):20091-112.
26. Ojo OA, Adeyemo TR, Rotimi D, Batiha GE, Mostafa-Hedeab G, Iyobhebhe ME, Elebiyo TC, Atunwa B, Ojo AB, Lima CM, Conte-Junior CA. Anticancer properties of curcumin against colorectal cancer: a review. Frontiers in Oncology. 2022 Apr 22;12:881641.
27. Unlu A, Nayir E, Kalenderoglu MD, Kirca O, Ozdogan M. Curcumin (Turmeric) and cancer. J buon. 2016 Sep 1;21(5):1050-60.
28. Lakhanpal P, Rai DK. Quercetin: a versatile flavonoid. Internet Journal of Medical Update. 2007 Jul 1;2(2):22-37.
29. Nimbalkar VV, Hemnani JM, Shelke AB. Quercetin and a review on its importance. Oxidative Medicine and Cellular Longevity. 2019 Apr 16.
30. Rao AV, Ray MR, Rao LG. Lycopene. Advances in food and nutrition research. 2006 Jan 1;51:99-164.
31. Shanbhag VK. Lycopene in cancer therapy. Journal of Pharmacy and Bioallied Sciences. 2016 Apr 1;8(2):170-1.
32. Zhang C, Sheng J, Li G, Zhao L, Wang Y, Yang W, Yao X, Sun L, Zhang Z, Cui R. Effects of berberine and its derivatives on cancer: A systems pharmacology review. Frontiers in pharmacology. 2020 Jan 15;10:1461.
33. Pandey V, Haider T, Gour V, Soni V, Gupta PN. Prodrugs in cancer nanomedicine and therapy. InRecent Advancement in Prodrugs 2020 May 13 (pp. 201-225). CRC Press.
34. Russo M, Russo GL, Daglia M, Kasi PD, Ravi S, Nabavi SF, Nabavi SM. Understanding genistein in cancer: The “good” and the “bad” effects: A review. Food chemistry. 2016 Apr 1;196:589-600.
35. Spagnuolo C, Russo GL, Orhan IE, Habtemariam S, Daglia M, Sureda A, Nabavi SF, Devi KP, Loizzo MR, Tundis R, Nabavi SM. Genistein and cancer: current status, challenges, and future directions. Advances in nutrition. 2015 Jul 1;6(4):408-19.
36. Sung B, Chung HY, Kim ND. Role of apigenin in cancer prevention via the induction of apoptosis and autophagy. Journal of cancer prevention. 2016 Dec;21(4):216.
37. Salehi B, Venditti A, Sharifi-Rad M, Kręgiel D, Sharifi-Rad J, Durazzo A, Lucarini M, Santini A, Souto EB, Novellino E, Antolak H. The therapeutic potential of apigenin. International journal of molecular sciences. 2019 Mar 15;20(6):1305.
38. Ren B, Kwah MX, Liu C, Ma Z, Shanmugam MK, Ding L, Xiang X, Ho PC, Wang L, Ong PS, Goh BC. Resveratrol for cancer therapy: Challenges and future perspectives. Cancer letters. 2021 Sep 1;515:63-72.
39. Rabiya A, Paithankar V, Kochar AC, Bobade N. Review on Chemoprevention of Cancer by Dietry Phytochemicals. World J. Pharm. Res. 2020 Apr 28;9:743-55.

ANTIMICROBIAL BIOMATERIALS: REVOLUTIONIZING MEDICAL APPLICATIONS

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Abstract:

Antimicrobial biomaterials are a new and exciting area of medical technology that promise creative ways to fight infections and improve patient outcomes. Antimicrobial biomaterials are designed to have surface-bound or intrinsic characteristics that actively prevent the growth and colonization of microorganisms. These materials provide antimicrobial capabilities while retaining biocompatibility by a variety of processes, such as surface modification, integration of antimicrobial peptides or nanoparticles, and release of antimicrobial chemicals. Antimicrobial biomaterials have the potential to significantly lower the risk of infections related to medical devices, including those involving implants, prosthesis, and catheters. These nanomaterials can increase patient safety and prolong device functionality by blocking bacteria adhesion and biofilm formation. Antimicrobial biomaterials also present encouraging paths toward tissue regeneration and wound healing. Biomaterials based on scaffolds have the potential to facilitate tissue repair by creating a conductive environment and limiting microbial contamination.

Keywords: Antimicrobial Biomaterials; Medical Technology; Nanomaterials; Medical Application; Inorganic Nanoparticles

1. Introduction

With the development of vascular grafts, stents, implant coatings, wound healing, and drug delivery systems, biomaterials have expanded the biomedical industry Chen X.B. (2019). Biomedical implants, typically composed of metal alloys or polymers, are in high demand and are the main subject of current research. Given that the majority of them are intended to be in contact with the body for extended periods of time, they ought to be biocompatible. The body and implant interact in a number of ways that ultimately determine how well the implant works. Infection-related implant failure and problems have been rising quickly in recent years J.D. Caplin, A.J. Garcia (2019). Post-surgical infections associated with biomaterials present a significant risk to both patients and medical personnel. When an implant is infected, a local tissue reaction is set off, which results in both acute and chronic inflammation as well as a foreign body reaction. These reactions open the door for microbial colonization and infection. Chapman, J., A. Lawlor, E. Weir, B. Quilty, and F. Regan (2010). Biofilm development is the primary cause of infections linked to biomaterials and devices. Since treating these infections

costs more than the initial biomaterial implantation, it also has an impact on the economics. The process of biofilm development begins with the attachment of bacteria to the surface of the biomaterial. In the second stage, as shown in Fig. 1 (M.K. Pal, M. Lavanya, 2022), these microbes begin to accumulate as layers, and this is followed by the maturation and spreading of microbial cells (Samanta Sam, Blessy Joseph and Sabu Thomas, 2023). Bacterial colonization can result in the creation of biofilms, which increase patient mortality by causing a chronic illness that is difficult to treat. By using antimicrobial devices to prevent bacteria from initially attaching to the implanted device, employing agents to kill microorganisms attached to the devices, and removing the infected device even though it will be a time-consuming and complex process one can lessen the risk of implant-associated infection caused by biofilm formation. By preventing bacterial attachment, colonization, and growth, antimicrobial biomaterials have emerged as a viable and efficient means of preventing implant-related illnesses (D. Sun, M. Babar Shahzad, M. Li, G. Wang and D. Xu, 2015).

2. Antimicrobial Biomaterials

Antibiotic biomaterials are employed in the fight against biofilm formation because they can deliver antibiotic substances to the host's body to prevent and treat illnesses caused by these germs. Antimicrobial agents can be introduced to biomedical implants in a variety of methods, including antimicrobial polymers, antimicrobial peptides, antimicrobial nanoparticles, and antimicrobial marine extracts. Antimicrobial materials ought to be non-toxic, stable over time, and have a broad range of applications. Biomaterials that are anti-adhesive and inhibit or treat microbe adhesion can be coated with antimicrobial chemicals, such as superhydrophobic surfaces and zwitterionic polymers. Antibacterial nanoparticles, like zinc (Zn), silver (Ag), and biopolymer having intrinsic antibacterial activity, can be added to biomaterials as a coating or during the polymer production process. It is clear that polymers that are naturally antimicrobial or that become antimicrobially active when antibacterial chemicals are added can be utilized as next-generation antibiotics (Lurie, S. *et al.*, 2003). Depending on the type of application, anti-infectious biomaterials have a very broad range of requirements. To prevent infections, a distinct set of factors must also be taken into account for medically implantable devices. Thus, it is not at all surprising that a range of strategies must be used. The choice of materials for medical purpose is another factor to take into account. A biomaterial or implant should ideally have anatomical geometry and physiological outputs that are comparable to those of living tissue. As a result, the decision on which material to use in a given medical application has a significant influence. The selection of a material is a reflection of how unexpected the substance's overall efficacy is in the medical field.

3. Antimicrobial Inorganic Nanoparticles

Because they may cross cell membranes and prevent both Gram positive and Gram negative bacteria from replicating their deoxyribonucleic acid, copper, zinc, and silver nanoparticles in particular are being studied in great detail for their bactericidal qualities. Q., J., *et al.* Feng (2000). The NPs stop the bacteria from breathing by attaching themselves to their

metabolic enzymes. After attaching itself to DNA, it makes the microbes resistant and kills them by stopping their metabolic functions (S. Agnihotri *et al.,* 2017). Strong candidates for usage in implants, tissue scaffolds, wound healing, surgical instrument coating, and many other biomedical applications are Ag, Au, CuO, and ZnO nanoparticles. $AgNO_3$ was added during Kim *et al.* (1998)'s wet chemical process to produce Ag-doped HAs. A dialysis tube experiment demonstrated the bactericidal effect of Ag+, which was linked to the Ag-doped HA's evident antibacterial activity against Escherichia coli. According to Suresh *et al.* (2010), silver nano crystallites were bio fabricated using shewanella oneidensis, and the results showed that both Gram-positive and Gram-negative bacteria may benefit from the antibacterial capabilities of the material. In comparison to Ag nanoparticles, CuO nanoparticles had a lower bactericidal impact. A considerable decrease in the number of bacterial cells was required for the CuO nanoparticle to be as effective as Ag, and this required an increase in concentration. Silver nanoparticle coated plastic catheters have been demonstrated to decrease the formation of biofilm from a variety of organisms, including Staphylococcus aureus and E. coli, despite the fact that applications in the medical area have showed promise (Ren, G., D *et al.,* 2009). It has been discovered that silver is a potent antibacterial. It is utilized in many different medical equipment, such as urinary and vascular catheters, sewing rings, surgical sutures, and many more, due to its antibacterial qualities (D. Sun, M. Babar Shahzad, M. Li, G. Wang and D. Xu 2015). The primary mechanisms of action of nanoparticles are cytoderm injury, cytomembrane destruction, and bacterial cell transformation. On the other hand, certain NPs enhanced with a photocatalytic metal rely on light stimulation to produce free radicals for antibacterial purposes. The fundamental antibacterial activity of AuNPs is shown in Figure 2 (Cui, Y.; Zhao, Y.; Tian, Y.; Zhang, W.; Lü, X and Jiang, X, 2012).

4. Antimicrobial Peptides as Anticancer Agents

Cancer therapy, with its high death rate, continues to be a significant worldwide health concern. Current treatment modalities, which include surgery, radiation, chemotherapy, or a mix of these, are designed to prolong the life of the patient. Because they are bioactive tiny proteins that are protective against bacteria, viruses, and fungi (both gram-positive and gram-negative), antimicrobial peptides (AMP) are now regarded as the next generation of antibiotics (N. Martelli, C. Serrano, H. Van Den Brink, J. Pineau, P. Prognon, I. Borget, S. El Batti 2021). According to J.D. Caplin *et al.* (2019), they have a distinct mode of action that sets them apart from antibiotics and target a broad variety of species. AMPs are divided into four categories based on the sort of secondary structures they have: α helical, β sheet, αβ (both α helical and β sheet), and non-αβ. Their biological origins, including germs, plants, and animals, are another factor used to categorize them. Its main function is to eliminate invasive pathogens. Numerous peptides rich in proline exhibit excellent antibacterial action. However, the development of AMP-coated biomaterials has been hindered by their instability and susceptibility to proteolytic degradation (Mattiuzzo, M. *et al.,* 2014). A new fullerene derivative called C70-(ethylenediamine) was discovered by Zhang *et al.,* 2019). It showed minimal toxicity to mammalian cells and strong

bactericidal effect against super-bacteria that were resistant to many drugs. This new material's distinct molecular structure was credited with its potent antibacterial properties. Because of their intricate membranes, many bacteria and diseases can be very difficult to target and eliminate. Prior to chemical synthesis, a candidate sequence's potential for antibacterial activity can be predicted using computer-aided design of AMPs, which can collect vital data on chemical properties and bioactivities in AMP sequences (Cardoso MH *et al.,* 2020).

5. Biomedical Device Fabrication

3D Printing or Additive Manufacturing

The biomedical industry has greatly benefited from 3D printing thanks to its ability to create customized implants and regenerative scaffolds, among other things. Post-operative infections are decreased by using 3D-printed implants and scaffolds (N. Martelli *et al.,* 2016). This is most frequently applied in the healthcare sector when products tailored to individual patients are created. Three-dimensional (3D) printing is a new method in tissue engineering that can be used to create functional tissue constructions that can be used to replace or heal damaged tissue or organs. It makes it possible to precisely manage, automatically, the materials and other components of the tissue constructs, potentially enabling high throughput production. The process of 3D printing an ink containing one or more biomaterials can result in tissue constructs (Fabio Giudice *et al.,* 2020). While these holds promise for tissue engineering, printed constructs have also been known to cause unanticipated diseases and infections related to biomaterials. Based on the principles of additive manufacturing, a new technique called three-dimensional (3D) printing has emerged. In this method, scaffolds with a three-dimensional structure are created by layer-by-layer printing or depositing a solution of one or more biomaterials, also known as ink. Additive manufacturing can be used in the healthcare industry to produce custom prosthetic body parts for individual patients (L. Hitzler *et al.,* 2018). With this printer, you can also print out a hearing aid shell. AM's capacity to construct intricate models can help with surgical prep. Surgeons can better comprehend a patient's anatomy before surgery by using 3D printed replicas of the patient's anatomy instead of MRI and CT scans. Furthermore, these models can be applied to surgical simulation and training.

Electro Spinning

Nano scaffolds that are porous, provide ventilation, and improve wound healing can be produced via electro spinning. The polymer liquid exits the spinneret during electro spinning, generating a Taylor cone as a result of electrification, which causes fiber to deposit on the grounded drum collector. The resulting nanofibers have several applications, such as bone tissue engineering, medication delivery, and wound dressing. When manufactured in a controlled environment, electrospun fibers exhibit a 3D network with a high surface area to volume ratio, are highly porous, and resemble the extracellular matrix found in biological systems. Due to the release of Ag+ ions from Ag NPs, Qian *et al.* (2019) created novel antimicrobial and osteogenic collagen-coated electrospun scaffolds that exhibited antibacterial activity against S. aureus and Streptococcus mutans (S. mutans). The biocompatible, osteogenic, and antibacterial

characteristics of the produced electrospun nanofibrous scaffold make it suitable for application in craniofacial bone regeneration procedures. Using graphene oxide (GO), polyvinyl alcohol (PVA), and chitosan (CS), Marin *et al.* created an electrospun biocompatible nanocomposite film for use in tissue regeneration and antibacterial devices.

Conculsion:

Next-generation biomaterials must be able to both promote tissue regeneration and inhibit microbial infection in order to be employed in biomedical applications. This is because antimicrobial biomaterials not only kill pathogenic microbes but also help healthy cells adhere and grow. Antimicrobial compounds are included into scaffolds and implants by a variety of techniques to combat infections connected to implants that are brought on by bacteria, viruses, and fungus. Even if all of these methods look beneficial, it's important to consider how cost-effective it will be to upgrade these processes from lab to industrial scale. demonstrated significant bactericidal activity after a second dose, surpassing that of free melting. The incorporation of antimicrobial peptides into AMP-coated biomaterials presents a strong approach to addressing the widespread issue of antibiotic resistance. By leveraging the potential of these naturally occurring compounds, researchers, healthcare professionals, and industry partners can successfully treat infections and improve human health through the development of novel therapeutics and biomedical devices. This can be achieved through further breakthroughs and collaborations.

References:

1. Moretta, C. Scieuzo, A.M. Petrone, R. Salvia, M.D. Manniello, A. Franco, D. Lucchetti, A. Vassallo, H. Vogel, A. Sgambato, P. Falabella (2011). Antimicrobial peptides: a new hope in biomedical and pharmaceutical fields, Front. Cell. Infect. Microbiol, 11, 1–26.
2. Cardoso MH, Orozco R.Q., Rezende S.B., Rodrigues G., Oshiro K.G.N., Candido E.S., Franco O.L (2020). Computer-aided design of antimicrobial peptides: are we generating effective drug candidates? (in English) Front Microbiol, 10.
3. Chapman, J., A. Lawlor, E. Weir, B. Quilty, and F. Regan (2010). Phthalate doped PVC membranes for the inhibition of fouling. Journal of Membrane Science, 365(1), 180–187.
4. Chen X.B. (2019). Extrusion Bioprinting of Scaffolds for Tissue Engineering Applications. Springer International Publishing AG; Cham, Switzerland.
5. Cui, Y.; Zhao, Y.; Tian, Y.; Zhang, W.; Lü, X and Jiang, X (2012). The molecular mechanism of action of bactericidal gold nanoparticles on Escherichia coli. Biomaterials, 33, 2327–2333.
6. D. Sun, M. Babar Shahzad, M. Li, G. Wang and D. Xu (2015). Antimicrobial materials with medical applications, Mater. Technol., 30, B90–B95.
7. Fabio Giudice, Raffaele Barbagall, Giovanna Fargione (2020). A Design for Additive Manufacturing approach based on process energy efficiency: electron beam melted components, Elsevier.

8. Feng, Q., J. Wu, G. Chen, F. Cui, T. Kim, and J. Kim (2000). A mechanistic study of the antibacterial effect of silver ions on Escherichia coli and Staphylococcus aureus. Journal of biomedical materials research, 52(4), 662–668.
9. J.D. Caplin, A.J. García (2019). Implantable antimicrobial biomaterials for local drug delivery in bone infection models, Acta Biomater, 93, 2–11.
10. Junfang Zhang, J, Xu, Haijun Ma, Haotian B, Libing L, Chunying S, Hui L, Shu W, Chunru W (2019). "Designing an amino-fullerene derivative C70-$(Eda)_8$ to fight superbacteria", ACS Appl. Mater. Interfaces, 11, (16), pp. 14597–14607.
11. Kim, T.N., Feng, Q.L., Kim, J.O., .Wu, J., Wang, H., Chen, G.C., Cui F.Z., (1998). 'Antimicrobial effects of metal ions (Ag+, Cu2+, Zn2+) in hydroxyapatite', J. Mater. Sci. Mater. Med., 1998, 9, (3), pp. 129–134.
12. L. Hitzler, F. Alifui-Segbaya, P. Williams, B. Heine, M. Heitzmann, W. Hall, M. Merkel, A. Ochsner, (2018). Additive manufacturing of cobalt based dental alloys: analysis of microstructure and physicomechanical properties, Adv. Mater. Sci. Eng. 2018, 1–12.
13. M.K. Pal, M. Lavanya (2022). Microbial influenced corrosion: understanding bio adhesion and Biofilm Formation, J. Bio- Tribo-Corrosion, 8, 1–13.
14. Mattiuzzo, M.; De Gobba, C.; Runti, G.; Mardirossian, M.; Bandiera, A.; Gennaro, R.; Scocchi, M (2014). Proteolytic activity of Escherichia coli oligopeptidase B against proline-rich antimicrobial peptides. J. Microbiol. Biotechnol, 24, 160–167.
15. N. Martelli, C. Serrano, H. Van Den Brink, J. Pineau, P. Prognon, I. Borget, S. El Batti (2016). Advantages and disadvantages of 3-dimensional printing in surgery: a systematic review, Surgery 159, 1485–1500.
16. Ren, G., D. Hu, E.W. Cheng, M.A. Vargas-Reus, P. Reip, and R.P. Allaker (2009). Characterisation of copper oxide nanoparticles for antimicrobial applications. International journal of antimicrobial agents, 33(6), 587–590.
17. S. Agnihotri, N.K. Dhiman (2017). Development of nano-antimicrobial biomaterials for biomedical applications, Advances in biomaterials for biomedical applications, 66, 479–545.
18. Samanta Sam, Blessy Joseph and Sabu Thomas (2023). Exploring the antimicrobial features of biomaterials for biomedical applications, Results in Engineering, 100979.
19. Suresh, A.K.; Pelletier, D.A.; Wang, W.; Moon, J.-W.; Gu, B.; Mortensen, N.P.; Allison, D.P.; Joy, D.C.; Phelps, T.J.; Doktycz, M.J (2010). Silver Nanocrystallites: Biofabrication using Shewanella oneidensis, and an Evaluation of Their Comparative Toxicity on Gram-negative and Gram-positive Bacteria. Environ. Sci. Technol., 44, 5210–5215.
20. W. Liu, J. Li, M. Cheng, Q. Wang, Y. Qian, K.W.K. Yeung, P.K. Chu, X. Zhang (2019). A surface-engineered polyetheretherketone biomaterial implant with direct and immunoregulatory antibacterial activity against methicillin-resistant Staphylococcus aureus, Biomaterials 208, 8–20.

EXPLORING JAVA PLUM'S ROLE IN DIABETES PREVENTION AND CONTROL

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Abstract:

Java Plum *(Syzygium cumini*), also known as Jamun, has been traditionally used in various medicinal systems for managing diabetes. This chapter explores the potential of Java Plum in diabetes prevention and control by examining its phytochemical composition, mechanisms of action, and clinical relevance. Rich in bioactive compounds such as anthocyanins, ellagic acid, and flavonoids, Java Plum exhibits anti-hyperglycemic, antioxidant, and anti-inflammatory properties. The chapter discusses its role in improving insulin sensitivity, modulating glucose metabolism, and reducing oxidative stress, which are critical factors in diabetes management. Furthermore, the potential applications of Java Plum in functional foods and nutraceuticals are explored, alongside a review of preclinical and clinical studies supporting its efficacy. Challenges related to dosage standardization, bioavailability, and safety considerations are also addressed. By integrating traditional knowledge with modern scientific insights, this chapter highlights the promise of Java Plum as a natural therapeutic agent in diabetes prevention and control.

Keywords: Java Plum, Natural Therapeutic Agent, Diabetes, Modulating Glucose Metabolism

Introduction:

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels due to defects in insulin production, insulin action, or both. It is a global health concern with significant complications affecting multiple organs if left uncontrolled. Understanding the causes and types of diabetes is essential for effective prevention and management.

Causes of Diabetes

The development of diabetes is influenced by a combination of genetic, environmental, and lifestyle factors [1-3]:

1. **Genetic Factors** – A family history of diabetes increases the risk, especially in Type 1 and Type 2 diabetes.
2. **Autoimmune Reactions** – In Type 1 diabetes, the immune system mistakenly attacks insulin-producing beta cells in the pancreas.
3. **Obesity and Physical Inactivity** – Excess body weight, particularly abdominal fat, contributes to insulin resistance, a major factor in Type 2 diabetes.

4. **Unhealthy Diet** – High intake of processed foods, sugary beverages, and refined carbohydrates can contribute to glucose metabolism dysfunction.
5. **Hormonal Changes** – Certain hormonal disorders, such as polycystic ovary syndrome (PCOS) and Cushing's syndrome, can increase the risk of diabetes.
6. **Pancreatic Damage** – Diseases affecting the pancreas, such as pancreatitis or pancreatic cancer, can impair insulin production.

Types of Diabetes

Diabetes is classified into several types, each with distinct causes and management strategies [3]:

1. **Type 1 Diabetes (T1D)** – An autoimmune disorder where the body's immune system destroys insulin-producing beta cells. It is commonly diagnosed in children and young adults and requires lifelong insulin therapy.
2. **Type 2 Diabetes (T2D)** – The most common form, occurring when the body becomes resistant to insulin or fails to produce enough insulin. It is strongly associated with lifestyle factors and is often managed through diet, exercise, and medication.
3. **Gestational Diabetes (GDM)** – A temporary condition that occurs during pregnancy due to hormonal changes affecting insulin action. It increases the risk of developing Type 2 diabetes later in life.
4. **Prediabetes** – A condition where blood glucose levels are higher than normal but not high enough to be classified as diabetes. It serves as a warning sign and can often be reversed with lifestyle changes.
5. **Other Specific Types** – These include rare forms caused by genetic mutations (Maturity Onset Diabetes of the Young - MODY), drug-induced diabetes (from corticosteroids or chemotherapy), and diabetes secondary to other diseases.

Understanding the causes and types of diabetes helps in designing targeted prevention and treatment strategies, emphasizing the need for a healthy lifestyle, early diagnosis, and appropriate medical intervention.

Need for Natural Approaches in Diabetes Management

Diabetes mellitus is a growing global health concern, with increasing prevalence due to lifestyle changes, poor dietary habits, and genetic predisposition. While conventional treatments such as insulin therapy and oral hypoglycemic drugs play a crucial role in managing diabetes, they often come with limitations, including side effects, high costs, and the risk of long-term complications. As a result, there is a growing interest in natural approaches to diabetes management, which focus on holistic, sustainable, and preventive measures [4,5].

Limitations of Conventional Diabetes Treatment

1. **Side Effects** – Common medications, such as metformin and sulfonylureas, can cause gastrointestinal issues, weight gain, and hypoglycemia.

2. **High Costs** – Long-term dependency on pharmaceutical drugs can be financially burdensome, especially in low-income populations.
3. **Limited Effectiveness in Disease Reversal** – Conventional treatments manage blood sugar levels but do not always address the root causes of insulin resistance and beta-cell dysfunction.

Benefits of Natural Approaches

Natural approaches to diabetes management aim to support metabolic health, improve insulin sensitivity, and prevent complications through diet, herbal medicine, lifestyle changes, and alternative therapies. These methods offer several advantages:

1. **Holistic and Preventive** – Natural approaches address the root causes of diabetes, such as poor diet, sedentary behavior, and oxidative stress.
2. **Fewer Side Effects** – Herbal and plant-based remedies are generally well-tolerated when used appropriately.
3. **Cost-Effective** – Lifestyle modifications and dietary interventions are more affordable and accessible in the long run.
4. **Sustainability** – A natural approach promotes long-term well-being rather than short-term glucose control.

Key Natural Approaches in Diabetes Management

1. **Dietary Modifications** – Incorporating fiber-rich, low-glycemic foods, such as whole grains, legumes, and leafy greens, helps regulate blood sugar levels.
2. **Herbal Remedies** – Plants like Java Plum *(Syzygium cumini*), bitter melon, fenugreek, and cinnamon have shown anti-diabetic properties.
3. **Physical Activity** – Regular exercise improves insulin sensitivity and glucose metabolism.
4. **Mind-Body Practices** – Yoga, meditation, and stress management techniques help control blood sugar fluctuations.
5. **Nutritional Supplements** – Vitamins, minerals (magnesium, chromium), and antioxidants play a role in glucose metabolism and insulin function.

With increasing evidence supporting the effectiveness of natural approaches, integrating them with conventional treatments can enhance diabetes management, improve quality of life, and potentially reduce disease progression. A well-balanced, holistic strategy can empower individuals to take control of their health and prevent complications associated with diabetes [6-8].

Java Plum: An Ancient Remedy in Modern Context

Java Plum *(Syzygium cumini*), also known as Jamun, Malabar plum, or black plum, has been a cornerstone of traditional medicine for centuries. Used in Ayurveda, Unani, and traditional Chinese medicine, Java Plum is renowned for its medicinal properties, particularly in

managing diabetes. With the increasing prevalence of diabetes worldwide, there is renewed scientific interest in Java Plum's therapeutic potential [9-11].

Historical Significance and Traditional Uses

Java Plum has been valued for its diverse medicinal applications across various traditional systems:

- **Ayurveda** – Used to regulate blood sugar levels, aid digestion, and improve skin health.
- **Unani Medicine** – Prescribed for liver health, urinary disorders, and digestive ailments.
- **Folk Remedies** – The fruit, seeds, bark, and leaves are used to treat diarrhea, ulcers, and respiratory issues.

Phytochemical Composition and Bioactive Compounds

Modern research has identified key bioactive compounds in Java Plum responsible for its health benefits:

- **Anthocyanins & Flavonoids** – Powerful antioxidants that combat oxidative stress.
- **Ellagic Acid & Gallic Acid** – Contribute to anti-inflammatory and anti-diabetic effects.
- **Alkaloids & Saponins** – Help regulate blood sugar and improve insulin function.
- **Tannins** – Aid in digestion and possess antimicrobial properties.

Java Plum in Diabetes Management

Scientific studies have validated Java Plum's role in diabetes control through multiple mechanisms [12-15]:

1. **Regulating Blood Glucose** – Java Plum seed extracts have shown hypoglycemic effects by enhancing insulin secretion and reducing glucose absorption.
2. **Improving Insulin Sensitivity** – The bioactive compounds help modulate glucose metabolism, reducing insulin resistance.
3. **Reducing Oxidative Stress** – Antioxidants in Java Plum protect pancreatic beta cells from oxidative damage.
4. **Delaying Carbohydrate Digestion** – Inhibits enzymes like alpha-amylase, slowing glucose release into the bloodstream.

Modern Applications and Scientific Research

With growing interest in plant-based medicine, Java Plum is now incorporated into:

- **Functional Foods** – Jamun-based powders, juices, and supplements are gaining popularity for diabetes management.
- **Nutraceuticals & Herbal Medicines** – Standardized extracts are being developed for pharmaceutical use.
- **Clinical Research** – Studies indicate significant reductions in fasting blood glucose and HbA1c levels among diabetic patients consuming Java Plum.

Challenges and Future Perspectives

Despite its potential, Java Plum's integration into mainstream diabetes treatment faces challenges:

- **Dosage Standardization** – Establishing optimal therapeutic doses remains a challenge.
- **Bioavailability Issues** – The absorption and metabolism of active compounds need further study.
- **Safety and Long-Term Use** – More clinical trials are needed to confirm safety in long-term use.

As scientific advancements continue to validate its medicinal properties, Java Plum stands as a promising natural remedy for diabetes management, bridging the gap between traditional wisdom and modern medicine. Its incorporation into functional foods and pharmaceutical products could revolutionize natural approaches to diabetes control, offering a safe and effective alternative for millions worldwide.

Java Plum: Botanical and Nutritional Profile

Java Plum *(Syzygium cumini*), commonly known as Jamun, black plum, or Indian blackberry, is a tropical evergreen tree belonging to the Myrtaceae family. It is widely cultivated in South and Southeast Asia, Africa, and some parts of South America due to its medicinal and nutritional value. Every part of the tree, including the fruit, seeds, leaves, and bark, has been utilized in traditional medicine, making it a valuable plant for both health and environmental benefits [16].

Botanical Description

1. **Scientific Name**: *Syzygium cumini*
2. **Family**: Myrtaceae
3. **Common Names**:
    - Jamun (India)
    - Jambul (Indonesia, Philippines)
    - Black Plum (English)
    - Duhat (Philippines)
    - Malabar Plum (Sri Lanka)
4. **Habitat & Growth**:
    - Java Plum thrives in tropical and subtropical climates.
    - It is a fast-growing tree that can reach heights of 10–30 meters.
    - The tree produces small, fragrant white flowers that develop into deep purple to black fruits with a characteristic astringent taste.

Nutritional Composition (per 100g of fruit)

Java Plum is a nutrient-dense fruit packed with essential vitamins, minerals, and bioactive compounds that contribute to its health benefits.

Nutrient	Amount per 100g	Health Benefits
Calories	60 kcal	Provides energy with low glycemic impact
Carbohydrates	14 g	Slow-releasing natural sugars
Fiber	0.6–1.2 g	Aids digestion and helps regulate blood sugar
Proteins	0.7 g	Supports metabolic functions
Fats	0.2 g	Very low in fat, making it heart-friendly
Vitamin C	18 mg	Boosts immunity and antioxidant defense
Vitamin A	3 IU	Supports vision and skin health
Iron	1–2 mg	Helps in red blood cell formation
Calcium	15–20 mg	Strengthens bones and teeth
Magnesium	15 mg	Aids in muscle and nerve function
Potassium	55 mg	Helps maintain electrolyte balance and blood pressure
Anthocyanins & Flavonoids	High	Antioxidant and anti-inflammatory properties

Bioactive Compounds and Medicinal Properties

Java Plum contains various phytochemicals that contribute to its medicinal benefits:

1. **Anthocyanins** – Strong antioxidants that protect against oxidative stress and improve heart health.
2. **Flavonoids** – Help regulate blood sugar levels and provide anti-inflammatory benefits.
3. **Tannins & Saponins** – Exhibit antimicrobial and digestive health benefits.
4. **Ellagic Acid & Gallic Acid** – Possess anti-diabetic, anti-inflammatory, and anticancer properties.

Health Benefits of Java Plum

- **Diabetes Management** – The fruit and seeds help regulate blood glucose levels and improve insulin sensitivity.
- **Digestive Health** – Rich in fiber and tannins, it aids digestion and prevents gastric issues.
- **Heart Health** – The antioxidants help reduce cholesterol and maintain healthy blood pressure.
- **Immunity Boosting** – High vitamin C content strengthens immune function.
- **Liver Protection** – Acts as a hepatoprotective agent, detoxifying the liver.

Java Plum is a nutritionally rich fruit with a powerful botanical profile that supports multiple health benefits. Its unique combination of essential nutrients and bioactive compounds makes it an important dietary and medicinal resource, particularly in diabetes management. As research continues to uncover its full potential, Java Plum remains a valuable natural remedy in both traditional and modern healthcare.

Java Plum in Diabetes Prevention

Diabetes mellitus is a major global health challenge, driven by lifestyle factors, genetic predisposition, and metabolic imbalances. While pharmaceutical interventions are available, there is growing interest in natural remedies for prevention and management. Java Plum *(Syzygium cumini*), widely used in traditional medicine, has shown promising potential in preventing diabetes due to its rich phytochemical profile and multiple mechanisms of action [17-20].

Role of Java Plum in Diabetes Prevention

1. **Regulation of Blood Glucose Levels**
    - Java Plum seeds, pulp, and leaves contain bioactive compounds that help lower blood sugar levels by enhancing insulin secretion and reducing glucose absorption.
    - Studies suggest that Java Plum seed extract inhibits alpha-amylase and alpha-glucosidase enzymes, slowing down carbohydrate digestion and preventing post-meal blood sugar spikes.
2. **Improvement of Insulin Sensitivity**
    - The presence of flavonoids, ellagic acid, and anthocyanins helps improve insulin receptor function, enhancing glucose uptake by cells.
    - Regular consumption of Java Plum may reduce insulin resistance, a key factor in the development of Type 2 diabetes.
3. **Antioxidant and Anti-Inflammatory Properties**
    - Oxidative stress and chronic inflammation are major contributors to diabetes onset.
    - Java Plum's high content of antioxidants, including anthocyanins, tannins, and vitamin C, helps neutralize free radicals and reduce inflammation, protecting pancreatic beta cells from damage.
4. **Weight Management and Metabolic Regulation**
    - Obesity is a major risk factor for diabetes. Java Plum is low in calories, high in fiber, and has natural appetite-suppressing properties, promoting healthy weight management.
    - The fiber content aids digestion and regulates the release of glucose into the bloodstream, preventing sudden sugar spikes.
5. **Lipid Profile Improvement**
    - Dyslipidemia (abnormal lipid levels) is a common precursor to diabetes.
    - Java Plum has been found to lower bad cholesterol (LDL) and triglycerides while increasing good cholesterol (HDL), reducing the risk of metabolic disorders associated with diabetes.

Scientific Evidence Supporting Java Plum in Diabetes Prevention

Several studies have explored the potential of Java Plum in preventing diabetes:

- **Animal Studies**: Research on diabetic rats has shown that Java Plum seed extract significantly reduces fasting blood glucose levels and enhances pancreatic function.
- **Human Trials**: Preliminary studies indicate that regular consumption of Java Plum seeds or juice improves glucose tolerance and reduces HbA1c levels in prediabetic individuals.
- **Enzyme Inhibition Studies**: Java Plum extracts have demonstrated inhibitory effects on carbohydrate-digesting enzymes, supporting its role in blood sugar regulation.

How to Incorporate Java Plum for Diabetes Prevention

1. **Fresh Fruit** – Consuming raw Java Plum helps regulate blood sugar levels and provides essential nutrients.
2. **Seed Powder** – Dried and powdered seeds can be taken with water or mixed into smoothies and herbal teas.
3. **Juice or Extracts** – Drinking Java Plum juice (without added sugar) can support metabolic health.
4. **Herbal Supplements** – Available in capsule or tablet form, standardized extracts offer a convenient way to incorporate Java Plum into the diet.

Java Plum presents a natural and effective approach to diabetes prevention through its blood sugar-regulating, antioxidant, and anti-inflammatory properties. With growing scientific evidence supporting its role in metabolic health, Java Plum can be a valuable addition to diabetes-prevention strategies, especially for those at risk of developing the disease. By integrating this traditional remedy into modern dietary practices, individuals can take proactive steps toward better health and long-term diabetes prevention.

Clinical Studies on Java Plum and Blood Glucose Control

Java Plum *(Syzygium cumini*), long recognized in traditional medicine for its anti-diabetic properties, has gained scientific interest due to its potential role in blood glucose regulation. Numerous clinical and preclinical studies have investigated its effects on blood sugar levels, insulin function, and overall diabetes management [21,22].

Key Findings from Clinical Studies

1. **Reduction in Fasting and Postprandial Blood Glucose Levels**
    - Several human studies have demonstrated that Java Plum seed and fruit extracts help lower fasting blood glucose (FBG) and postprandial blood glucose (PPBG).
    - A study conducted on Type 2 diabetic patients showed a significant decrease in blood glucose levels after consuming Java Plum seed powder for 30–60 days.
    - The active compounds, including jamboline and ellagic acid, are believed to slow glucose absorption and improve insulin sensitivity.

2. **Improvement in Glycated Hemoglobin (HbA1c) Levels**
    - Long-term studies suggest that Java Plum consumption leads to a reduction in HbA1c levels, indicating better long-term blood sugar control.
    - A randomized controlled trial found that diabetic patients who supplemented with Java Plum seed extract for 12 weeks had an average HbA1c reduction of 0.5%–1.2%.
3. **Insulin Secretion and Beta-Cell Protection**
    - Clinical trials have suggested that Java Plum supports pancreatic beta-cell function, enhancing insulin secretion.
    - Antioxidant-rich anthocyanins and flavonoids present in Java Plum protect beta cells from oxidative damage, potentially delaying diabetes progression.
4. **Inhibition of Digestive Enzymes**
    - Java Plum extracts have been found to inhibit alpha-amylase and alpha-glucosidase enzymes, slowing carbohydrate digestion and reducing rapid glucose spikes post-meal.
    - In a clinical study, patients consuming Java Plum extract before meals experienced reduced glucose surges compared to those on a placebo.
5. **Lipid Profile and Metabolic Health Benefits**
    - Studies indicate that Java Plum not only regulates blood glucose but also improves lipid profiles, reducing LDL cholesterol and triglycerides while increasing HDL cholesterol.
    - A study on diabetic patients found that Java Plum supplementation led to a 10–15% reduction in LDL levels over three months, reducing cardiovascular risk.

How Java Plum affects Glucose Metabolism?

Java Plum *(Syzygium cumini*), a widely used medicinal plant, has been extensively studied for its effects on glucose metabolism. Its bioactive compounds contribute to blood sugar regulation through multiple mechanisms, including enhanced insulin secretion, improved glucose uptake, and inhibition of carbohydrate digestion. These properties make Java Plum a valuable natural aid in diabetes prevention and management.

Mechanisms of Action in Glucose Metabolism

1. **Enhancement of Insulin Secretion**
    - Java Plum has been shown to stimulate pancreatic beta cells, increasing insulin secretion.
    - Alkaloids and flavonoids in Java Plum help regulate insulin production, ensuring better glucose utilization.
    - Studies suggest that regular consumption of Java Plum seed extracts leads to improved insulin response in diabetic individuals.

2. **Improvement of Insulin Sensitivity**
    - Java Plum compounds enhance the sensitivity of insulin receptors, allowing cells to absorb glucose more efficiently.
    - The polyphenols, including ellagic acid and anthocyanins, reduce insulin resistance by modulating cellular signaling pathways.
    - This action helps in lowering blood sugar levels and preventing Type 2 diabetes progression.
3. **Inhibition of Carbohydrate Digestion and Absorption**
    - Java Plum contains tannins and saponins, which inhibit alpha-amylase and alpha-glucosidase enzymes.
    - These enzymes are responsible for breaking down complex carbohydrates into simple sugars; their inhibition results in slower glucose absorption into the bloodstream.
    - This mechanism prevents postprandial glucose spikes, promoting better glycemic control.
4. **Reduction of Hepatic Glucose Production**
    - The liver plays a crucial role in glucose metabolism by releasing glucose into the bloodstream during fasting states.
    - Java Plum extracts have been found to reduce gluconeogenesis (glucose production in the liver), lowering fasting blood sugar levels.
    - This effect is mediated through flavonoids that regulate liver enzyme activity involved in glucose production.
5. **Protection of Pancreatic Beta Cells**
    - Oxidative stress damages pancreatic beta cells, reducing their ability to produce insulin.
    - Java Plum's high antioxidant content (anthocyanins, flavonoids, vitamin C) protects beta cells from oxidative damage.
    - This protective action helps maintain insulin production and delay diabetes progression.
6. **Modulation of Lipid Metabolism**
    - Impaired glucose metabolism is often associated with dyslipidemia (abnormal lipid levels).
    - Java Plum improves lipid profiles by lowering LDL (bad cholesterol) and triglycerides while increasing HDL (good cholesterol).
    - Better lipid control contributes to overall metabolic health and reduces the risk of complications in diabetic patients.

Ways to Consume Java Plum for Diabetes Management

Below are some effective ways to incorporate Java Plum into a diabetes-friendly diet [23,24].

1. Fresh Java Plum Fruit

- Eating fresh Java Plum is one of the easiest ways to benefit from its natural sugars, fiber, and antioxidants.
- Consume in moderation (5–10 fruits per serving) to avoid excessive fructose intake.
- Best consumed on an empty stomach or as a mid-morning snack for steady glucose control.

2. Java Plum Seed Powder

- The seeds contain the highest concentration of anti-diabetic compounds, including jamboline and ellagic acid.
- **How to prepare:**
  - Wash and sun-dry Java Plum seeds.
  - Grind into a fine powder and store in an airtight container.
- **How to consume:**
  - Mix ½ to 1 teaspoon of seed powder with warm water and drink on an empty stomach.
  - Add to smoothies, yogurt, or herbal teas.

3. Java Plum Juice (Without Sugar)

- Fresh Java Plum juice helps regulate postprandial blood sugar levels.
- **How to prepare:**
  - Blend fresh Java Plums with water.
  - Strain and drink without adding sugar.
  - Optionally, add a pinch of black salt and lemon for better taste.
- **Recommended intake:** 50–100 ml per day.

4. Java Plum Leaf Tea

- Java Plum leaves are rich in tannins and flavonoids that enhance insulin sensitivity.
- **How to prepare:**
  - Boil 8–10 fresh or dried leaves in 2 cups of water for 10 minutes.
  - Strain and drink warm.
- **Best time to drink:** Before meals to help control blood sugar spikes.

5. Java Plum Bark Decoction

- The bark has strong anti-diabetic properties due to its alkaloid content.
- **How to prepare:**
  - Boil small pieces of Java Plum bark in water for 15 minutes.
  - Strain and consume in small quantities.

- **Dosage:** 20–30 ml per day, as excessive intake may cause stomach discomfort.

6. Java Plum Supplements (Capsules/Tablets)

- Standardized Java Plum seed extract is available in supplement form.
- **Dosage:** Typically, 250–500 mg per day (consult a healthcare provider before use).
- **Best for:** People who want a convenient way to consume Java Plum without preparation.

Precautions and Recommendations

Monitor Blood Sugar – Java Plum may lower glucose levels significantly, so regular monitoring is essential.

Consult a Doctor – Before adding Java Plum to your routine, especially if taking diabetes medication, to avoid hypoglycaemia.

Avoid Overconsumption – Excessive intake may cause constipation or stomach discomfort due to tannins.

Future Perspectives and Research Scope

The future of Java Plum in diabetes management is promising, with growing scientific interest in its bioactive compounds and therapeutic effects. Expanding clinical trials, developing standardized pharmaceutical products, and integrating Java Plum into functional foods can unlock its full potential. With further research, Java Plum could become a mainstream natural therapy for diabetes prevention and control**,** complementing existing medical treatments.

Conclusion:

Java Plum stands out as a powerful natural aid for diabetes management, offering multiple metabolic benefits without significant side effects. Its effectiveness in lowering blood sugar, improving insulin function, and protecting against diabetes complications makes it a valuable addition to both traditional and modern diabetes care. While further research is needed to refine its clinical applications, its practical use in various forms fresh, powdered, juiced, or as supplements makes it an accessible and promising option for individuals seeking natural diabetes management solutions.

References:

1. Kahn CR. Insulin action, diabetogenes, and the cause of type II diabetes. Diabetes. 1994;43(8):1066-85.
2. Ma RC, Lin X, Jia W. Causes of type 2 diabetes in China. The Lancet Diabetes & Endocrinology. 2014;2(12):980-91.
3. Lin Y, Sun Z. Current views on type 2 diabetes. The Journal of endocrinology. 2009;204(1):1.
4. Kokil GR, Veedu RN, Ramm GA, Prins JB, Parekh HS. Type 2 diabetes mellitus: limitations of conventional therapies and intervention with nucleic acid-based therapeutics. Chemical Reviews. 2015;115(11):4719-43.

5. Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV. Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. Diabetes care. 2001;24(11):1858-62.
6. Tiwari P. Recent trends in therapeutic approaches for diabetes management: a comprehensive update. Journal of diabetes research. 2015;2015(1):340838.
7. Fisher EB, Brownson CA, O'Toole ML, Shetty G, Anwuri VV, Glasgow RE. Ecological approaches to self-management: the case of diabetes. American Journal of Public Health. 2005;95(9):1523-35.
8. Ferguson D, Finck BN. Emerging therapeutic approaches for the treatment of NAFLD and type 2 diabetes mellitus. Nature Reviews Endocrinology. 2021;17(8):484-95.
9. Beers SJ. Jamu: the ancient Indonesian art of herbal healing. Tuttle Publishing; 2012.
10. Das G, Nath R, Das Talukdar A, Ağagündüz D, Yilmaz B, Capasso R, Shin HS, Patra JK. Major bioactive compounds from java plum seeds: An investigation of its extraction procedures and clinical effects. Plants. 2023;12(6):1214.
11. Pal D, Lal P, Mishra A. Black plum seed: morphology, chemistry, and antiproliferative activities. InSeeds: Anti-proliferative Storehouse for Bioactive Secondary Metabolites 2024 Aug 31 (pp. 395-426). Singapore: Springer Nature Singapore.
12. Hussain S, Sajjad A, Butt SZ, Muazzam MA. An Overview of antioxidant and pharmacological potential of common fruits. Scientific Inquiry and Review. 2021;5(1):1-8.
13. Das G, Nath R, Das Talukdar A, Ağagündüz D, Yilmaz B, Capasso R, Shin HS, Patra JK. Major bioactive compounds from java plum seeds: An investigation of its extraction procedures and clinical effects. Plants. 2023;12(6):1214.
14. Fajriyani A, Fitriyani A, Sephia RA, Hidayah H. The Potential of Jamblang Root or Java Plum *(Syzygium cumini*) in Medicinal Uses: A Systematic Review. Eureka Herba Indonesia. 2023;4(2):216-20.
15. Rizvi MK, Rabail R, Munir S, Inam-Ur-Raheem M, Qayyum MM, Kieliszek M, Hassoun A, Aadil RM. Astounding health benefits of jamun *(Syzygium cumini*) toward metabolic syndrome. Molecules. 2022;27(21):7184.
16. Hidayah H, Suherti I, Azzahra SS. Java Plum *(Syzygium cumini* (L.)) Seeds Potentials in Medicinal Uses: A Systematic Literature Review. Eureka Herba Indonesia. 2023;4(2):221-6.
17. Baliga MS, Fernandes S, Thilakchand KR, D'souza P, Rao S. Scientific validation of the antidiabetic effects of Syzygium jambolanum DC (black plum), a traditional medicinal plant of India. The Journal of Alternative and Complementary Medicine. 2013;19(3):191-7.

18. Wulandari S, Dewi RK, Supraptinigsih S. The Effect of Administering Extract of Java Plum Ethanol *(Syzygium cumini*) to the Expression of the Molecular Adhesion 1 (Icam-1) on the Model of Huvecs Preeclampsia. Journal for Quality in Public Health. 2020;4(1):175-80.
19. Fadhilah Z, Elya B, Setiawan H, Nugroho GA, Wediasari F, Masaenah E, Arianti V. Antidiabetic activity and phytochemical constituents of syzygium cumini leave in Kadipaten, Central Java Indonesia, Indonesia. Pharmacognosy Journal. 2021;13(6).
20. Charepalli V, Reddivari L, Vadde R, Walia S, Radhakrishnan S, Vanamala JK. Eugenia jambolana (Java plum) fruit extract exhibits anti-cancer activity against early stage human HCT-116 colon cancer cells and colon cancer stem cells. Cancers. 2016;8(3):29.
21. Revathi G, Elavarasi S, Saravanan K, Bahadur B. Traditional use of herbal plants for the treatment of diabetes in India. Ethnobotany of India, NorthEast India, Andaman and Nicobar Islands. 2017;3.
22. Barceloux DG. Medical toxicology of natural substances: foods, fungi, medicinal herbs, plants, and venomous animals. John Wiley & Sons; 2012.
23. Wulandari S, Dewi RK, Supraptinigsih S. The Effect of Administering Extract of Java Plum Ethanol *(Syzygium cumini*) to the Expression of the Molecular Adhesion 1 (Icam-1) on the Model of Huvecs Preeclampsia. Journal for Quality in Public Health. 2020;4(1):175-80.
24. Swami SB, Thakor NS, Patil MM, Haldankar PM. Jamun *(Syzygium cumini* (L.)): A review of its food and medicinal uses. Food and Nutrition Sciences. 2012;3(8):1100-17.

A CRITICAL ANALYSIS OF MEDICO-LEGAL DIMENSION OF PHARMACEUTICAL INDUSTRY IN INDIA

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Abstract:

The pharmaceutical sector in India plays a crucial role in the worldwide healthcare arena, providing cost-effective medications both locally and abroad. Nonetheless, this field functions at the intricate crossroads of medical ethics, legal structures, and business interests, frequently prompting worries regarding regulatory adherence, ethical practices, and patient entitlements. This paper examines the medico-legal aspects of the Indian pharmaceutical sector, emphasizing the relationship between legal frameworks, medical obligations, and business practices.

The research explores the current legal framework regulating pharmaceuticals in India, which encompasses the Drugs and Cosmetics Act of 1940, the Indian Patents Act of 1970, and the Clinical Trial Rules of 2019. It evaluates their effectiveness in maintaining drug safety, ethical research, and protection of intellectual property while reconciling public health needs with corporate interests. Additionally, the article examines medico-legal issues, such as unethical drug trials, off-label drug marketing, price control, and fake medications, which present major obstacles to patient welfare and regulatory oversight.

Furthermore, the study examines how judicial actions and significant rulings influence the ethical and legal frameworks of pharmaceutical governance in India. It assesses how courts have weighed the rights of patients against the business interests of pharmaceutical firms, especially in situations pertaining to medical malpractice, drug patent disputes, and consumer protections. The document underscores a global viewpoint, contrasting India's regulatory framework with worldwide benchmarks to pinpoint shortcomings and propose improvements.

By meticulously examining statutes, case laws, and policy frameworks, this research highlights the necessity for a stronger regulatory system, improved accountability, and more patient-focused policies. It promotes a unified strategy that combines rigorous regulatory supervision with responsible corporate behavior to guarantee that the pharmaceutical sector places public health above profit.

Keywords: Health, Medico-Legal, Policy, Pharmaceutical, Corporate

Introduction:

The Indian pharmaceutical sector, frequently referred to as the "pharmacy of the world," is vital to international healthcare by providing cost-effective generic drugs to many nations. For

the fiscal year 2023-24, India's pharmaceutical market is estimated to be around USD 50 billion, with domestic consumption making up USD 23.5 billion and exports adding USD 26.5 billion.

The sector is expected to expand by 5.28% from 2025 to 2029, achieving a market size of USD 16.56 billion by 2029.

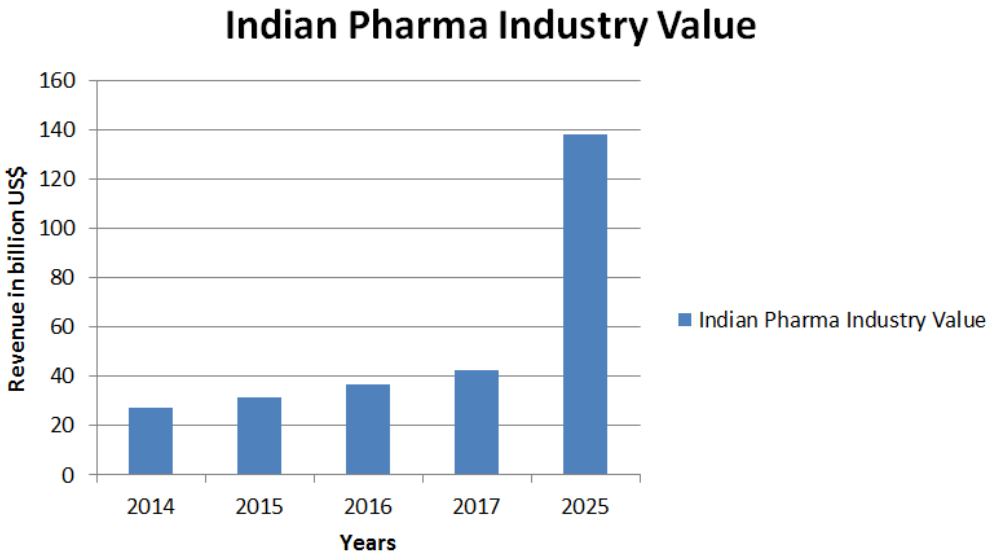

Fig 1: Indian Pharma Industry Value

(Source: Pharmaceutical Industry in India Report Demo Statistics)

Although it has made substantial contributions, the Indian pharmaceutical industry encounters intricate medico-legal issues that affect its functioning and reputation. Recent events have sparked worries regarding the quality of drugs and the effectiveness of regulatory supervision. For example, in September 2024, the Central Drugs Standard Control Organisation found more than 50 medications, such as commonly used antacids and paracetamol, to be substandard or fake. Prominent among these were groups of Alkem Laboratories' antacid Pan-D and Hetero's anti-infective Cepodem.

The regulatory structure overseeing the pharmaceutical sector in India includes several rules designed to guarantee drug safety, effectiveness, and ethical standards. Nonetheless, difficulties continue to exist, encompassing concerns regarding price regulations, intellectual property protections, and adherence to global standards. The Drugs and Cosmetics Act of 1940 is the main law governing the import, production, and distribution of pharmaceuticals in India. Moreover, the Indian Patents Act of 1970 and the Clinical Trial Rules of 2019 significantly influence the legal framework of the industry.

Ethical issues have been significant as well, especially concerning the connection between healthcare providers and pharmaceutical firms. The Indian Psychiatric Society has formulated guidelines to tackle ethical relationships with the pharmaceutical industry, highlighting the necessity for transparency and integrity in these interactions.

The COVID-19 pandemic underscored medico-legal difficulties, as numerous contentious topics arose concerning drug approvals, clinical trials, and the distribution of

vaccines. The need to create and provide treatments quickly resulted in accelerated procedures, occasionally compromising comprehensive regulatory supervision, prompting concerns about the equilibrium between swift access and patient safety.

Although the Indian pharmaceutical sector remains an important contributor to global healthcare, it must manage a complicated array of medico-legal obstacles. Tackling these problems is crucial to sustain public confidence, guarantee patient safety, and preserve the sector's standing globally.

The Intersection of Medicine and Law

The convergence of healthcare and legal regulations in India's pharmaceutical sector creates a complex framework where medical needs align with regulatory standards. This convergence is essential for ensuring that healthcare practices comply with legal requirements, thus protecting patient welfare and maintaining public health.

India's pharmaceutical industry, famous for its major role in worldwide medicine provision, especially in generic medications, functions under a rigorous legal system aimed at overseeing drug quality, effectiveness, and safety. The Drugs and Cosmetics Act of 1940, along with its later amendments, acts as the foundation of this regulatory framework, governing the importation, production, distribution, and sale of drugs and cosmetics within the nation. This law seeks to guarantee that all pharmaceutical products adhere to established standards, thus safeguarding consumers from inferior or dangerous medications.

Even with these regulatory actions, difficulties continue to exist. Recent reports have pointed out cases where commonly used drugs, such as antacids and paracetamol, were found to be either substandard or counterfeit by the Central Drugs Standard Control Organisation. Such events highlight the persistent problems concerning drug quality and the efficacy of regulatory oversight in India.

The legal framework also includes the regulation of clinical trials, vital for the advancement of new medications. In 2005, India updated its pharmaceutical regulations to promote a rise in international clinical trials conducted within the nation. Nevertheless, this transition raised worries about ethical norms and the safeguarding of trial participants, leading to demands for tougher oversight and the creation of thorough ethical guidelines.

Medical records are essential at the crossroads of healthcare and legal matters. In legal cases, medical records can be accepted as evidence according to Section 3 of the Indian Evidence Act of 1872, as revised. This clause highlights the significance of precise and comprehensive documentation by healthcare professionals, as such records can be crucial in medico-legal matters.

The ethical marketing of pharmaceuticals is a vital domain where medicine and law converge. Research has revealed attitudes and obstacles regarding ethical promotion among

medical representatives and physicians, emphasizing the necessity for explicit guidelines and strong enforcement systems to deter unethical behaviors in drug marketing.

The connection between healthcare providers and pharmaceutical firms adds more complexity to this intersection. Interactions frequently encompass the delivery of information and incentives, potentially impacting prescribing practices. This situation brings up ethical and legal concerns regarding possible conflicts of interest and their effect on patient care.

Informed consent is an essential ethical and legal obligation in healthcare, especially regarding vaccinations and clinical procedures. It is crucial to ensure that patients are thoroughly informed about the advantages and risks of a procedure or medication to uphold patient autonomy and prevent legal issues linked to negligence or malpractice.

The release of "The Truth Pill: The Myth of Drug Regulation in India" in 2022 revealed fundamental problems in India's drug regulatory system. The writers, Dinesh Thakur and Prashant Reddy, promote increased transparency and reforms, highlighting the necessity for strong enforcement of rules to guarantee the safety and effectiveness of drugs.

The convergence of healthcare and legal systems in India's pharmaceutical sector is marked by a complicated interaction of regulatory guidelines, ethical issues, and practical obstacles. Tackling these challenges necessitates ongoing assessment and modification of current legislation, efficient enforcement strategies, and a dedication to principled medical practice to safeguard patient welfare and the integrity of the healthcare system.

Application of Law in Pharamaceutical Industry

The pharmaceutical sector in India functions under a complicated regulatory system aimed at guaranteeing the safety, effectiveness, and quality of medications. This framework is consistently developing to meet new challenges and to conform to international standards. Recent research offers important insights into different facets of this regulatory landscape.

One research investigates the regulatory, safety, and financial aspects of over-the-counter (OTC) medications in India. The authors emphasize the government's acknowledgment of the necessity for a strong policy framework to efficiently make use of OTC medications, underlining the significance of balancing accessibility and safety.

Another article explores progress in regulatory flexibility, regional cooperation, and dependency models in India's pharmaceutical industry. It highlights that the Central Drugs Standard Control Organisation (CDSCO) is systematically enhancing and restructuring India's pharmaceutical regulatory frameworks, concentrating on the function of state licensing authorities.

A separate study examines the effects of Indian patent law on the pharmaceutical sector. The study explores the transition durations permitted for India to modify its patent laws, examining the effects on pharmaceutical innovation and medicine accessibility.

An in-depth analysis of pharmaceutical regulations in India reveals gaps in the regulatory structure. The research examines existing literature on the regulations related to manufacturing standards, pharmacy education, and drug pricing, proposing improvements to increase the efficacy of the regulatory framework.

Finally, a review of the difficulties, prospects, and effectiveness of the Indian pharmaceutical sector after adhering to TRIPS reveals how the industry has adjusted to the updated patent regulations. The chapter assesses the industry's performance and recognizes areas where additional policy measures could be advantageous.

These sources together provide a detailed insight into the present situation of pharmaceutical regulations in India, emphasizing both advancements and aspects requiring more focus.

a) Regulatory Bodies

In India, the Central Drugs Standard Control Organization (CDSCO) primarily oversees the pharmaceutical industry, operating under the Directorate General of Health Services within the Ministry of Health and Family Welfare. The CDSCO oversees the authorization of new medications, clinical studies, and the setting of standards for drugs, guaranteeing their safety, effectiveness, and quality. The CDSCO is led by the Drug Controller General of India (DCGI), who supervises the enforcement of the Drugs and Cosmetics Act of 1940 and its later amendments.

Another key organization is the National Pharmaceutical Pricing Authority (NPPA), created to oversee the pricing of pharmaceutical drugs in India. Functioning within the Department of Pharmaceuticals under the Ministry of Chemicals and Fertilizers, the NPPA implements the Drug Price Control Orders (DPCO) and guarantees the accessibility of vital medications at reasonable costs.

Furthermore, the Department of Pharmaceuticals develops and executes policies and strategies for the pharmaceutical industry, addressing matters related to intellectual property rights, research and development, and encouraging investment in the sector.

b) Policies Existing in the Scenario

The pharmaceutical sector in India is regulated by numerous policies designed to guarantee drug quality, affordability, and availability. The Drugs and Cosmetics Act of 1940, together with the Drugs and Cosmetics Rules of 1945, establishes the legal structure for the importation, production, distribution, and sale of drugs and cosmetics. These regulations require strict quality control procedures and establish benchmarks for medications to guarantee patient safety.

The DPCO, established under the Essential Commodities Act of 1955, authorizes the NPPA to oversee the pricing of essential medications. The most recent version, DPCO

2013, includes the National List of Essential Medicines (NLEM) and seeks to ensure that these medicines are affordable for the public.

Additionally, the New Drugs and Clinical Trials Rules, 2019, were established to enhance clinical research in India while protecting the rights, safety, and welfare of participants in trials. These regulations simplify the approval procedure for new medications and specify the criteria for carrying out clinical trials, thus promoting a climate favorable to innovation.

c) Gap Analysis

In spite of the extensive regulatory framework, some gaps remain in the pharmaceutical sector's regulatory environment. A major problem is the uneven application of regulations among various states, resulting in differences in the quality and availability of drugs. A research study emphasized that although the CDSCO establishes consistent standards, the execution at the state level differs, leading to inconsistent regulatory monitoring.

Another disparity relates to the regulatory frameworks for clinical trials. While the New Drugs and Clinical Trials Rules, 2019, have simplified procedures, there are still challenges in maintaining ethical standards and ensuring the safety of participants. Reports of unethical practices and insufficient informed consent have surfaced, highlighting the necessity for stronger monitoring systems.

Moreover, the existing policies frequently fail to sufficiently tackle the swift progress in biotechnology and personalized medicine. The current regulatory system is mainly tailored for traditional pharmaceuticals and might not adequately address the challenges linked to new therapies, resulting in delays in approval and market access.

d) Implementation Aspect

Successful execution of pharmaceutical laws and policies requires a comprehensive strategy that includes regulatory bodies, the pharmaceutical sector, and healthcare practitioners. Enhancing the abilities of regulatory agencies such as the CDSCO and state drug control organizations is essential. This involves improving infrastructure, offering specialized training to staff, and implementing digital technologies for improved oversight and enforcement.

Aligning regulations among states can reduce variations in enforcement. Creating a centralized database for drug approvals, quality criteria, and compliance status can promote consistent implementation and decrease the occurrence of substandard or fake drugs in the market.

Involving stakeholders such as pharmaceutical firms, healthcare professionals, and patient advocacy organizations is crucial for successful policy execution. Frequent

consultations can offer understanding into real-world issues and assist in creating guidelines that are both rigorous and attainable.

In addition, it is essential to revise the regulatory framework to align with scientific progress. This entails updating current regulations to include measures for new therapies, creating specialized groups to assess intricate products, and promoting international cooperation to align with worldwide best standards.

Suggestive Reforms

The Indian pharmaceutical sector, although competitive on a global scale, faces complex medico-legal issues that require immediate reform. A comprehensive approach combining legal reforms, tighter regulations, and ethical adjustments is essential to strengthen the sector's legal and ethical foundations.

The Drug and Cosmetics Act of 1940 needs a significant revision to be in tune with modern medical progress. Creating a centralized, AI-powered pharmacovigilance platform would facilitate real-time tracking of drug effectiveness and side effects, thus reducing post-market irregularities.

A self-governing regulatory organization, free from government interference, should be established to manage drug approvals. Compulsory double-blind, peer-reviewed clinical studies, along with rigorous ethical oversight, must be fundamental to drug approval procedures to remove commercial bias and guarantee patient safety.

Pharmaceutical lobbying and unethical incentives for medical professionals have compromised the integrity of prescriptions. A legal code of conduct, supported by punitive measures, ought to govern interactions between pharma and physicians. It is essential to make the disclosure of financial connections between pharmaceutical companies and healthcare providers mandatory.

Although patents encourage innovation, a fair structure that balances patent rights with access to vital medications is crucial. India needs to improve its compulsory licensing regulations to avoid monopolistic pricing while protecting investments in research and development.

Creating a decentralized pharmacovigilance network integrated with AI can improve the real-time identification of adverse drug reactions, enabling quick market withdrawals of inferior drugs.

To prevent malpractice, corporate executives should face criminal liabilities for intentional regulatory violations. A dedicated fast-tracked court for pharmaceutical conflicts should be created to speed up medico-legal resolution.

If consistently implemented, these reforms would strengthen the medico-legal integrity of India's pharmaceutical sector while safeguarding public health.

Conclusion:

The pharmaceutical sector in India functions at the crossroads of medical science and legal regulations, making its oversight vital for public health and the protection of consumers. Although India excels as a global leader in producing generic medications, issues regarding drug quality, ethical marketing practices, transparency in clinical trials, and patient safety remain problematic. The medico-legal environment of this field is influenced by several regulations, such as the Drugs and Cosmetics Act of 1940, the Consumer Protection Act of 2019, and the ethical guidelines set by the Medical Council of India. Nevertheless, enforcement weaknesses, regulatory shortcomings, and the influence of the industry on healthcare professionals frequently undermine their efficacy.

An in-depth examination indicates the necessity for enhanced regulatory supervision, tougher consequences for non-compliance, and increased responsibility in drug production, pricing, and promotion. The emergence of online pharmacies and telemedicine makes it essential to update legal regulations. Ethical issues, including deceptive advertising and inappropriate pressure on healthcare professionals, need immediate attention. Enhancing consumer awareness, guaranteeing transparency in clinical trials, and promoting cooperation between medical and legal experts are crucial for achieving a balance between industry development and public health needs. A strong medico-legal framework will not only improve patient safety but also strengthen India's reputation as a global pharmaceutical center.

References:

1. Central Drugs Standard Control Organisation. (2024, September 26). India flags quality issues with some widely used antacids and paracetamol. Reuters. Retrieved from https://www.reuters.com/world/india/india-flags-quality-issues-with-some-widely-used-antacids-paracetamol-2024-09-26/
2. Statista. (n.d.). Pharmaceuticals - India | Statista Market Forecast. Retrieved from https://www.statista.com/outlook/hmo/pharmaceuticals/india
3. Press Information Bureau. (2024, December). India's pharmaceutical market for FY 2023-24 is valued at USD 50 billion. Retrieved from https://pib.gov.in/PressReleaseIframePage.aspx?PRID=2085345
4. Indian Psychiatric Society. (2022, March). Ethics in Dealing with Pharma Industry. Indian Journal of Psychiatry, 64(Suppl 1), S11–S20. Retrieved from https://journals.lww.com/indianjpsychiatry/fulltext/2022/03001/ethics_in_dealing_with_pharma_industry.11.aspx
5. The Financial Express. (2021, May 31). Indian pharma market: Emerging medico-legal issues in COVID era. Retrieved from https://www.financialexpress.com/life/indian-pharma-market-emerging-medico-legal-issues-in-covid-era-2276151/

6. Food and Drug Law Institute. (2017, October). India: Pharmaceutical Legal & Regulatory Environment. Retrieved from https://www.fdli.org/2017/10/india-pharmaceutical-legal-regulatory-environment/
7. Srinivasan, S., & Johari, V. (2018). How Civil Society Organisations Changed the Regulation of Clinical Trials in India. Science as Culture, 27(4), 466–488.
8. Kumar, R. (2021). Medical Records. In Legal Medicine (pp. 545–556). Springer, Singapore.
9. Siddiqui, S., & Malik, M. (2020). Perceptions of and barriers to ethical promotion of pharmaceuticals in Pakistan: perspectives of medical representatives and doctors. BMC Medical Ethics, 21(1), 1–9.
10. Alssageer, M. A., & Kowalski, S. R. (2012). Doctors' opinions of information provided by Libyan pharmaceutical company representatives. Libyan Journal of Medicine, 7(1), 19708.
11. Chatterjee, P. (2011). Informed consent in vaccination in India: Medicolegal aspects. Human Vaccines, 7(7), 723–727.
12. Thakur, D. S., & Reddy, P. (2022). The Truth Pill: The Myth of Drug Regulation in India. Simon & Schuster India.
13. Regulatory, safety and economic considerations of over-the-counter drugs in India. (2023). Journal of Pharmaceutical Policy and Practice, 16(1), 32.
14. Advancements in regulatory agility, regional collaboration, and reliance models in India's pharmaceutical sector. (2024). Journal of Pharmaceutical Policy and Practice, 17(1), 102.
15. Indian Patent Law and Its Impact on the Pharmaceutical Industry. In Intellectual Property Rights: Unleashing the Knowledge Economy (pp. 213-230). Springer, Singapore.
16. Pharmaceutical regulations in India: the missing links. (2012). BMC Proceedings, 6(Suppl 5), P9.
17. The Challenges, Opportunities and Performance of the Indian Pharmaceutical Industry after TRIPS Compliance. In The Rise of Indian Multinationals: Perspectives on Indian Outward Foreign Direct Investment (pp. 221-237). Springer, Singapore.
18. Department of Pharmaceuticals. (n.d.). *About Us*. Retrieved from https://pharmaceuticals.gov.in/about-us
19. National Pharmaceutical Pricing Authority. (n.d.). *About Us*. Retrieved from https://www.nppaindia.nic.in/en/about-us/

NANO TRANSFEROSOMES

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Transferosomes: Versatile and Flexible Nano-Vesicular Carriers

The word transferosome is a registered trademark by the German company IDEA AG and the name derives from the Latin word “transferre” meaning “to carry across” and the Greek word “soma” meaning “body”. The technology was first described in 1991 by Çevc and Blume and has been the subject of several patents and research over the last 30 years.[28]

Transferosomes are lipid-based vesicular carriers that compared to the rigid lipid bilayers (liposomes) or non-ionic surfactant single layer vesicles (niosomes) are elastic, ultra deformable and stress-responsive. When drug delivery systems, such as liposomes, nanoparticles and niosomes are deposited on the skin, usually they are only able to permeate through the upper layers of the SC, resulting in accumulation in the epidermal layer but failing to reach deeper areas of the skin such as the dermis or effective systemic levels.[29]T he structure of transferosomes are depicted in figure 1. When compared with subcutaneous administration, transferosomes improved in-vitro skin permeation of various drugs, penetrate the intact skin from in-vivo studies and 12 effectively transfer the therapeutic amount of drugs.

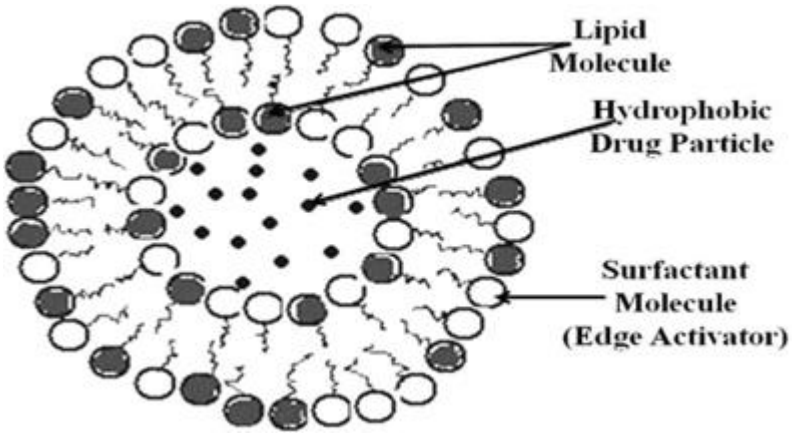

Fig. 1: Transferosomes

Transferosomes are composed by four key elements:

i) Phospholipids (such as phosphatidylcholine, dipalmitylphosphatidylcholine, distearylphosphatidylcholine),
ii) An edge activator such as a surfactant or bile salt ranging from 10-25% (e.g. Sodium cholate, sodium deoxycholate, tween® 80, span® 80, dipotassium glycyrrhizinate),
iii) Ethanol in a lower percentage usually below 10 % (as higher concentrations are described as ethosomes)
iv) Water as a vehicle

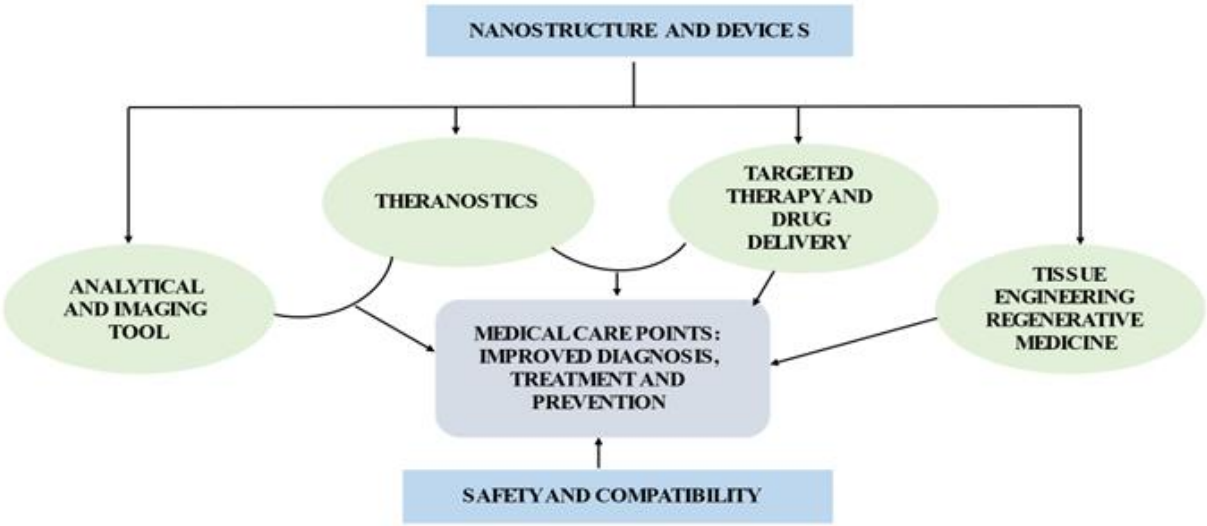

Fig. 2: Nanostructures and devices

Historical Background of Transferosomes

The name "transfersomes," which is a trademark of IDEA AG, Munich, Germany, and was initially used by Cevc, refers to the first generation of ultradeformable vesicles. It has been the topic of numerous patents and literature reports since the 1990s. These elastic vesicles' capacity to penetrate and permeate the skin is the result of a synergistic interaction between their

carrier qualities and access enrichment capability. Transfersomes are supramolecular, ultradeformable lipid bundles of aggregates made up of at least one inner aqueous segment and a lipid bilayer with specific properties that are acceptable when there are surfactants present in the vesicular membrane (edge activator (EA)). Even if it is generally accepted that the permeation of, usually, liposomes is limited to the outer layer of the stratum corneum, thus providing a drug or cosmetic localizing effect within the skin, transferosomes are claimed to infuse as intact vesicles through the skin layers to the complete circulation. [30]

Mechanism of Action of Transferosomes

The present investigation indicates that the transfersomes are drug mover systems that can penetrate across intact skin. It is believed that the unimpeded passage of such carriers is based on two key factors: the high elasticity (deformability) of the vesicle bilayers and the reality of an osmotic gradient across the skin.[31]

Because of their high deformability, transferosomes with the help of EAs generate a transepidermal osmotic gradient; and further squeeze among the stratum corneum cells and carry drug across the whole skin. The transpore hydrostatic force difference is liable for the penetration or passage of transferosomes intact throughout the stratum corneum, i.e. the penetration of transferosome is an outcome of hydrotaxis and the permeation is governed by principles of elastomechanics. When a transfersome reaches a pore, it is capable of changing its membrane work reversibly as an effect of its self-optimizing deformability. To go throughout the pore, the mechanism of the transferosome liable for its deformability starts accumulating at the site of tension, whereas the less elastic mechanism experiences dilution, which significantly reduces the active rate of membrane deformation and allows the highly elastic particles to go throughout the pores.[32]

The passage of transferosomes through the skin and the epithelial obstacle is greatly prejudiced by the flexibility of their membrane, which can be achieved via a suitable ratio of surfactants. The flexibility of the transferosomal membrane decreases the risk of complete vesicle rupture in the skin and permits the ultradeformable transferosomes to change their membrane composition locally and reversibly when they are pressed against or attracted into a narrow pore. This dramatically lowers the energetic cost of membrane deformation and permits the resulting highly flexible particles first to enter and then to pass through the pores rapidly and efficiently.

The first mechanism proposes that vesicles can act as drug carrier systems, whereby intact vesicles enter the stratum corneum carrying vesicle-bound drug molecules into the skin under the influence of the naturally occurring in vivo transcutaneous hydration gradient.

Regulatory Aspects of Transferosomes[33]

Recently, advances in pharmaceutical science and skill have made available a range of new excipients, such as lipids, surfactants, and solvents; though, of late, there have been

reservations within the scientific community regarding the dullness of excipients and that they in some capacity have unfavourable effects. Selection of an excipient throughout the research of a transferosome based formulation is limited by safety and toxicity concerns associated with these excipients. Hence, a small range of excipients are obtainable for planning any highly porous drug deliverance system. Thus, inert excipients are usually measured when developing a transferosome-based formulation and these are used as vesicle forming agents, surfactants, EAs, and solvents. Mitigating the safety concerns, a narrow range of excipients are obtainable for crafting any highly porous drug delivery system, such as a transferosome. Different national regulatory agencies (WHO, International Pharmaceutical Excipients Council, US Food and Drug Administration (FDA), Japanese Ministry of Health and Welfare, and International Conference on Harmonisation of Technical necessities for muster of Pharmaceuticals for Human Use) have maintained a confidential list of excipients as 'Generally Regarded as Safe' (GRAS), which have been clinically categorized not to be toxic. The FDA keeps a record entitled 'Inactive Ingredient Guide', which includes a catalogue of permitted excipients. This documentation provides information about the excipients with a value of their utmost dosage stage by a fastidious route of direction or dosage form.

Phospholipid is a crucial element for the formation of a transferosome based drug delivery system. It is also roughly always true that the fluid-chain vesicles with a rather elastic bilayer promote drug transport across skin obstruction better than the more rigid liposomes. Therefore, nearly all the common phosphatidylcholine (PC) used to organize stretchy liposomes is unsaturated PC (i.e. soybean phosphatidylcholine (SPC) or egg phosphatidylcholine (EPC)). SPC is a GRAS-listed phospholipid and also complies with specifications of the Food Chemicals Codex.

Edge activator plays an important role in determining the skin permeation behavior of elastic liposomes. An overview of the differences among EAs is helpful for the selection of an ideal EA for optimal formulation. Sodium deoxycholate is a water-soluble ionic surfactant. Valsartan-loaded elastic liposomes containing sodium deoxycholate as the EA were then investigated. Similarly, sodium cholate, which is used as an EA, is reported to be non-toxic but has been kept in the hazardous category as it causes skin and eye irritations as well as respiratory sensitization. Surfactants can cause severe gastrointestinal discomfort when used above certain concentrations; the maximum safe limit of surfactant concentration is 10–25%. Ethanol is known to act as an efficient skin-penetration enhancer. It can interact with the polar head group region of the lipid molecules, resulting in a reduction of the melting point of the stratum corneum lipids, thereby increasing their fluidity and cell membrane permeability.

Transferosomes Versus Other Carrier Systems [34]

Transferosomes can prolong the release and improve the pharmacological activity of drugs in-vivo.

Recently, advances in pharmaceutical science and skill have made available a range of new excipients, such as lipids, surfactants, and solvents; though, of late, there have been reservations within the scientific community regarding the dullness of excipients and that they in some capacity have unfavourable effects. Selection of an excipient throughout the research of a transferosome based formulation is limited by safety and toxicity concerns associated with these excipients. Hence, a small range of excipients are obtainable for planning any highly porous drug deliverance system. Thus, inert excipients are usually measured when developing a transferosome-based formulation and these are used as vesicle forming agents, surfactants, EAs, and solvents. Mitigating the safety concerns, a narrow range of excipients are obtainable for crafting any highly porous drug delivery system, such as a transferosome.

Factors affecting Properties of Transfersomes

In the process of obtaining an optimized formulation of transferosomes, there are number of process variables that could affect the properties of the transferosomes. These variables basically involve the manufacturing of transferosomal formulations.

1. Effect of Phospholipids: Edge Activator Ratio

The phospholipid: Edge activator (lecithin:surfactant) should be an optimized ratio due to the fact that this greatly affects the entrapment efficiency, vesicle size and permeation ability. In general, it has been reported that the EE could be reduced due to the presence of a higher surfactant concentration. This may be due to the result of increased vesicles' membrane permeability because of the arrangement of surfactant molecules within the vesicular lipid bilayer structure, which could generate pores within the vesicular membrane and lead to an increased fluidity and prompt the leakage of the entrapped drug. A further increase in the edge activator content may lead to pore formation in the bilayer and a reduced permeation ability of the vesicles, whereas the incorporation of low concentrations of surfactants may result in growth of the vesicle size. In addition, the decrease in vesicles size at high phospholipid concentrations has been reported in various studies. [35]

2. Effect of Various Solvents

Various solvents such as ethanol or methanol are used. Selection of the appropriate solvent depends on the solubility of all the formulation ingredients in the solvent and their compatibility with the solvent. Preferably, all the excipients, including the drug, should completely dissolve in the solvent and should obtain a clear transparent solution to produce a better film-forming ability and good stability after hydration. Solvents used in the formulation can also exert their function as penetration enhancers that improve drug flux through the membrane. Ethanol was used in various studies to enhance the flux of hydrocortisone, 5-fluorouracil, estradiol and levonorgestrel through rat skin. For an example, ethanol increases the permeation through different mechanisms, such as increasing the drug solubility in vesicles by acting as a solvent, moreover permeating into the stratum corneum and altering the solubility

properties of the respective tissue and, consequently, improving the drug partitioning into the membrane. Increasing the ethanol concentration in the formulation may result in a decrease in the %EE, which could be attributed to the increased permeability of the vesicular phospholipid bilayer. This may promote the consequent leakage of the encapsulated drug.[36]

3. Effect of Various Edge Activators (Surfactants)

Deformability, as well as the entrapment efficiency of transferosome vesicles, are affected by the type of edge activators used in their formulations. This could be due to the difference in the chemical structure of the EA. Generally, the vesicle size decreases by increasing the surfactant concentration, the hydrophilicity of the surfactant head group, carbon chain length and the hydrophilic lipophilic balance (HLB). The three surfactants, including tween 80, span 80 and sodium deoxycholate, were used to prepare the transferosomes, and a reduction of the vesicle size was found when the higher surfactant concentration used. This might be due to the fact that the high surfactant concentrations (more than 15%) induce micelle formation rather than vesicle formation. A small polydispersity index (PDI) was reported with the higher surfactant concentration. A small PDI is responsible for consistent size distribution, which is thought to be an important factor for the reduction of interfacial tension and provides a homogeneous formulation. Additionally, an increased surfactant concentration may lead to an increase in charge of the vesicles, which results in a reduction of vesicle aggregation and enhances the stability of the system. In addition, surfactant properties are one of the properties that are responsible for the entrapment efficiency of the vesicles, as, for an example, the entrapment of a lipophilic drug would be enhanced with the use of a surfactant with a low HLB value. [37]

4. Effect of the Hydration Medium

The hydrating medium may consist of either water or saline phosphate buffer (pH 6.5–7). The pH level of the formulation should be suitable to achieve a balance between both the formulation properties and biological applications, as well as the route of administration. The lipid bilayer of transferosomes mimics the phospholipid layer of the cell membrane, and only unionized drugs remain membrane-bound to the phospholipid bilayer and penetrate through the intracellular route. It is important to use the suitable pH of the hydration medium, which keeps the drug unionized to increase the entrapment and permeation of the drug.[38]

Composition of Trasnsferosomes[39]

Materials which are widely used in the formulation of transferosomes are various phospholipids, surfactants, alcohol, dye, buffering agents etc. Different additives used in the formulation of transferosomes are summarized in Table 1.

Table 1: Different additives used in the formulation of transferosomes

S. No	Class	Example	Use
1	Phospholipids	Soya phosphatidylcholine, egg phosphatidylcholine, dipalitoylphosphatidyl choline	Vesicle forming component
2	Surfactants	Sodium cholate, sodium deoxycholate, Tween 80, Span 80, Tween 20	Vesicle forming component
3	Solvents	Ethanol, Methanol, Isopropyl alcohol, Chloroform	As a solvent
4	Buffering agent	Saline phosphate buffere (pH 6.4), Phosphate buffer (pH 7.4)	As a hydrating medium
5	Dye	Rhodamine-123, Rhodamine-DHPE, Flurescein-DHPE, Nile Red	For CSLM study

Methods to Fabricate Transferosomes [40]

1. Thin-Film Hydration

This process is also known as the rotary evaporation technique. Desired quantity of phospholipid and edge activator is weighed and added into a suitable solvent such as solvent and chloroform. The prepared solution is then transferred into the rotary flask, which is rotated at constant temperature and reduced pressure. When all the organic solvent is evaporated as a result of it, a thin film formed on the bottom of the flask. The film is then hydrated with an aqueous medium containing a drug for the complete swelling of lipid vesicles. Particles of the desired size are obtained by sonication or extrusion process. The method is illustrated pictorially in Figure 3.

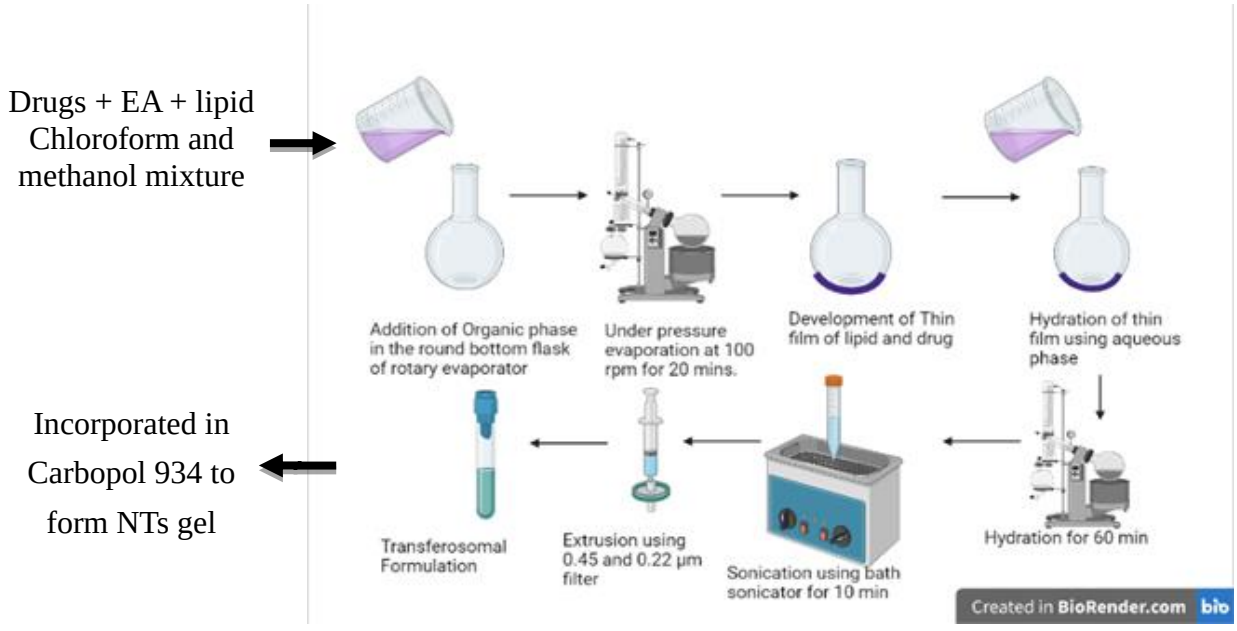

Fig. 3: Preparation of Nanotransferosomal gel by thin film hydration technique

2. Reverse Phase Evaporation Method

Phospholipid and edge activator were dissolved in an organic solvent in a round bottom flask. Based on the solubility profile, the drug can be added either into the lipid or the aqueous solution. Following the addition of drug, the aqueous media is incorporated in the organic phase. The resulted suspension was then sonicated for 35 min at 4 ℃ until the desired size vesicles were obtained. The organic phase was removed under vacuum.

3. Vortex Sonication Method

Phospholipid, drug, and edge activator in different ratios were dissolved in ethanol in a beaker. Then phosphate buffer solution of pH 7 was transferred into the above solution with continuous vortex shaking to achieve cloudy suspension of vesicles. The resultant vesicles formed were sonicated for 15 min to obtain smaller size vesicles.[41]

4. Ethanol Injection Method

In this process, an ethanolic solution comprised of a phospholipid, edge activator, and drug was injected into an aqueous solution dropwise under homogenizer mixing. As the ethanolic solution comes into direct contact with the aqueous solution, lipid molecules arranged themselves and formed bilayer vesicles.

5. Freeze- thawed Method

This method includes the exposure of multilamellar vesicles to alternate cycles of very low temperature for freezing followed by exposure to very high temperature. The geared-up suspension is transferred to a tube and dipped in a nitrogen bath (−30°C) for 30 s. After freezing, it is exposed to a high temperature in a water bath. This course is repeated eight–nine times.

Characterization of the Transfersomes[42]

There are several published methods used to determine the characterization parameters of the transferosomes, such as the vesicle shape and size, size distribution, polydispersity index, zeta potential, number of vesicles for cubic mm, entrapment efficiency, degree of deformability and skin permeability measurements, which are beneficial for the optimization of the transferosomal formulation.

1. Size, Zeta Potential and Morphology

The vesicle size is one of the important parameters during transferosome preparation, batch-to-batch comparison and scale-up processes. During storage, the changing of the vesicle size is an important variable in terms of the physical stability of the formulation. Vesicles smaller than 40 nm are prone to fusion processes because of the high curvature state of their bilayer membranes, whereas much larger and electroneutral transferosomes are aggregated through van der Waals interactions due to relatively greater membrane contact areas.

2. Number of Vesicles Per Cubic mm

This parameter is important for the optimization of the composition of the transferosomes and other process variables. The transferosomes with a vesicle size of more than 100 nm can be

observed by optical microscope. The number of transferosomes in small squares are counted and calculated using the following formula

3. Entrapment Efficiency (%EE)

The entrapment efficiency (%EE) is the amount of drug entrapped in the formulation. The EE is determined by separating the unentrapped drug from the vesicles using various techniques, such as mini-column centrifugation. In this process, direct or indirect methods can be used to determine the %EE.

4. Degree of Deformability

This parameter is important, as it affects the permeation of the transferosomal formulation. This study is done using pure water as the standard.

5. *In Vitro* Drug Release[43]

The *in vitro* drug release profile can provide fundamental information on the formulation design and details on the release mechanism and kinetics, enabling a scientific approach to optimize the transferosomal formulation. The *in vitro* drug release of transferosomes is typically evaluated in comparison to the free drug or the reference product. In brief, Franz diffusion cells are employed in the *in vitro* drug release study.

6. *In Vitro* Skin Permeation Studies

This study is performed to determine the transport efficiencies of the transdermal delivery systems and identify the factors that increase the transdermal flux of the drugs, which is typically expressed in units of µg/cm2 /h.

7. Stability of Transferosomes

The stability of transferosome vesicles can be determined by assessing the structure and the size of vesicles with respect to time. The optimized transferosomal formulations can be stored in tightly sealed amber vials at different temperature conditions.

The parameters and the testing methods are summarized in the following (Table 2)

Table 2: Parameters and the testing methods of transfersomes.

Parameter	Method/Equipment
Vesicle size, size distribution	Dynamic light scattering (DLS) method by Malvern Zetasizer
Zeta potential	Electrophoretic mobility technique by Malvern Zetasizer
Vesicle morphology	DLS method, Photon correlation spectroscopy, Transmission electron microscopy
Number of vesicles for cubic mm	Hemocytometer and optical microscope Directly or indirectly using high-performance liquid chromatography (HPLC) or spectrophotometric method
Entrapment efficiency	$\%\text{Entrapment efficiency} = \frac{\text{Amount of the drug entrapped}}{\text{Total amount of the drug added}} \times 100$

	$\%\text{Entrapment efficiency} = \frac{\text{Total amount of the drug added} - \text{Amount of the free drug}}{\text{Total amount of the drug added}} \times 100$
Drug content	Modified HPLC method using an ultraviolet detector, auto sample, column oven, pump and computerized analysis program depending upon the analytical method of the active pharmaceutical agent
Degree of deformability	Microporous filter with DLS, Transmission electron microscopy
Surface charge and charge density	DLS method by Malvern Zetasizer, Thin-layer chromatography
In-vitro drug release	Franz diffusion cell with cellulose membrane, Extrusion method
In-vitro skin permeation studies	Franz diffusion cell
In-vivo skin permeation ability	Confocal scanning laser microscopy (CSLM), Fluorescence microscopy, histological study used to determine the bioadhesive potential and retention of transferosomes in the skin
Stability studies	DLS method, Transmission electron microscopy

Comparison of Transferosomes with Different Vesicles [44]

Table 3: Comparison of transferosomes with different vesicles

S.No	Method	Advantage	Disadvantage
1	Liposomes	Phospholipid vesicle, Biocompatible, Biodegradable	Less skin penetration, Less stable
2	Proliposomes	Phospholipid vesicle, more stable than liposomes	Less penetration, cause aggregation & fusion of vesicles
3	Physical methods E.g. Iontophoresis	Increase penetration of intermediate size charged molecule	Only for charged drug, transfer efficiency is low (less than 10%)
4	Niosomes	Non-ionic surfactants vesicles	Less skin penetration, easy handling, but will reach upto deeper skin layer
5	Proniosomes	Greaterstability, will convert into noisome in-situ, stable	-

6	Transferosomes and Protransferosomes	More stable, high penetration due to high deformability, biocompatible & biodegradable, suitable for both low and high molecular weight & also for lipophilic as well as hydrophilic drugs & reach upto deeper layers.	-

Over the past decades, the applications of the transferosomes in the field of transdermal drug administration have been extensively studied. Some of these applications are described in the section below

1. Delivery of Antioxidants

In 2017, Avadhani *et al.* developed nano transferosomes containing epigallocatechin-3-gallate (EGCG) and hyaluronic acid by using a modified thin-film hydration method followed by the high-pressure homogenization technique in order to enhance their efficacies as UV radiation protectors, antioxidants and antiaging substances. In 2019, Wu *et al.* prepared transferosomes combined with resveratrol using the high-pressure homogenization technique. It was found that the obtained transferosomes could improve the stability, bioavailability, solubility and safety of resveratrol.

2. Delivery of Anticancer Drugs

The prevalence of skin carcinoma is reportedly more than all types of cancer. Every year, over and above millions of cases are reported worldwide. Transferosomes have opened new horizons for the treatment of skin cancer. Researchers found that sulforaphane-loaded ultra-deformable vesicles showed anti-proliferative action against skin carcinoma. Anti-proliferative activity of sulforaphane was tested on human SKMEL 28 malignant cells. Research conducted by Jiang *et al.* in 2018 was associated with the topical chemotherapy of melanoma by transferosome-embedded oligopeptide hydrogels containing paclitaxel prepared by the thin-film dispersion method. Transferosomes composed of phosphatidylcholine, tween 80 and sodium deoxycholate were shown to effectively penetrate intotumor tissues. A research group in China reported that paclitaxel-modified transferosomes effectively retard the growth of melanoma when used with systemic chemotherapeutic agents. Hyaluronic acid-based ultra-deformable transferosomes loaded with doxorubicin was fabricated by a research lab in China to treat a tumor in the lymph nodes. Docetaxel-entrapped Transferosomes were prepared to treat the glioblastoma multiforme. The result of in vitro cellular uptake assay suggested that Transferosomes showed high selectivity to tumor cells and high permeability to 2D U-87 MG cell lines.

3. Delivery of Corticosteroids

The biological activity and characteristics of halogenated corticosteroid triamcinolone-acetonide loaded transferosomes prepared by the conventional thin-film hydration technique were studied by Cevc and Blume in 2003 and 2004. The results showed that transferosomes had increased the biological potency and prolonged effect, as well as the reduced therapeutic dosage.

4. Delivery of Anti-Inflammatory Drugs

Diclofenac sodium, celecoxib, mefenamic acid and curcumin-loaded transferosomes were developed and studied for the purpose of topical administration by several research groups. Research findings suggested that transferosomes could improve the stability and efficacy of the anti-inflammatory drugs.

5. For Transdermal Delivery of NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most generally used drugs in the world. Due to their analgesic, antipyretic, and anti-inflammatory effects, they are prescribed for both chronic and acute types of conditions, which include rheumatoid arthritis, migraine, mild to moderate pain, gout, and menstrual pain. NSAIDs produce gastrointestinal undesirable effects that can be recovered by the use of specially designed ultra-deformable liposomes. Rheumatoid arthritis (RA) is an autoimmune disorder correlated with chronic inflammation of joints and synovial membrane that may ultimately lead to joint dysfunction and bone erosions. For the treatment of RA celecoxib-loaded transferosomes, anti-inflammatory activity was tested in Wistar rats. Results showed a significant reduction in inflammation due to deeper penetration of the gel into skin layers. In similar research, meloxicam-loaded transferosome were tested for their anti-inflammatory activity for the treatment of rheumatoid arthritis. As compared to meloxicam-loaded liposome, the transferosomal gel of meloxicam penetrated the deeper layer of the skin and showed maximum anti-inflammatory action. Naproxen sodium is associated with a lot of side effects when taken systemically such as GIT-related problems, arrhythmias, and bronchospasm. Meanwhile, it is reported in the literature that when naproxen-loaded transferosomes were prepared, they not only avoided side effects but also provide prolonged drug release. Oral delivery of lornoxicam is associated with severe gastrointestinal problems; to overcome this problem, lornoxicam-loaded transferosomes were formulated. The prepared formulation showed high entrapment efficiency of 99.34% and zeta potential of−33.35 mV. Pharmacodynamic findings indicated that lornoxicam-loaded transferosomes have the potential to treat acute or chronic pains. Piroxicam transferosomal gel was fabricated by a research group to treat rheumatoid arthritis. Carrageenan-induced arthritis model was developed to check the efficacy of transferosomal gel; results of in vivo experiments indicated that transferosomes gel formulation has significant potential to treat rheumatoid arthritis.

References:

1. Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. *Int J Mol Sci*. 2019;20(6):1475. Published 2019 Mar 23. Doi:10.3390/ijms20061475
2. Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. *Can Fam Physician*. 2017;63(4):278-285.
3. Winterfield LS, Menter A, Gordon K, *et al* Psoriasis treatment: current and emerging directed therapies *Annals of the Rheumatic Diseases* 2005;**64:**ii87-ii90.
4. Oji V, Luger TA. The skin in psoriasis: Assessment and challenges. Clin Exp Rheumatol. 2015;33:S14-9
5. Langley RGB, Krueger GG, Griffiths CEM Psoriasis: epidemiology, clinical features, and quality of life *Annals of the Rheumatic Diseases* 2005;**64:**ii18-ii23.
6. Lebwohl M. Topical application of calcipotriene and corticosteroids: combination regimens. J Am Acad Dermatol. 1997;37(3 pt 2): S55–S58.
7. Reich K, Bewley A. What is new in topical therapy for psoriasis? J EurAcad Dermatol Venereol. 2011;25(Suppl 4):15–20.
8. Mason AR, Mason J, Cork M, Dooley G, Hancock H. Topical treatments for chronic plaque psoriasis. Cochrane Database Syst Rev. 2013;3:CD005028.
9. Fleming C, Ganslandt C, Guenther L, *et al.* Calcipotriol plus betamethasone dipropionate gel compared with its active components in the same vehicle and the vehicle alone in the treatment of psoriasis vulgaris: a randomised, parallel group, double-blind, exploratory study. Eur J Dermatol. 2010;20(4):465–471.
10. White S, Vender R, Thaçi D, *et al.* Use of calcipotriene cream (Dovonex cream) following acute treatment of psoriasis vulgaris with the calcipotriene/betamethasone dipropionate two-compound product (Taclonex): a randomized, parallel-group clinical trial. Am J Clin Dermatol. 2006;7(3):177–184.
11. Langley R, Gupta A, Papp K, Wexler D, Østerdal M, Curčić D. Calcipotriol plus Betamethasone Dipropionate Gel Compared with TacalcitolOintment and the Gel Vehicle Alone in Patients with Psoriasis Vulgaris: A Randomized, Controlled Clinical Trial. Dermatology. 2011;222(2):148–156.
12. National Center for Biotechnology Information (2022). Pubchem Compound Summary for CID 5288783, Calcipotriol. Retrieved June 9, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Calcipotriol.
13. National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 21800, Betamethasone dipropionate. Retrieved January 18, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Betamethasone-dipropionate.
14. Fernández-García, R., Lalatsa, A., Statts, L., Bolás-Fernández, F., Paloma Ballesteros, M., & Serrano, D. R. (2019). *Transferosomes as nanocarriers for drugs across the skin:*

quality by design from lab to industrial scale. International Journal of Pharmaceutics, 118817.

15. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur. J. Pharm. Sci. 14(2), 101–114 (2001)
16. Singh S, Verma D, Mirza MA, Das AK, Dudeja M, Anwer MK, Talegaonkar S, Iqbal Z. Development and optimization of ketoconazole loaded nano-transfersomal gel for vaginal delivery using Box-Behnken design: In vitro, ex vivo characterization and antimicrobial evaluation. J Drug DelivSci Technol. 2017;39:95-103.
17. Cevc G, Gebauer D, Stieber J, Schatzlein A, Blume G. Ultraflexible vesicles, transfersomes, have an extremely low pore penetration ¨ resistance and transport therapeutic amounts of insulin across the intact mammalian skin. Biochim. Biophys. Acta 1368(2), 201–215 (1998).
18. Ali MF, Salem HF, Abdelmohsen HF, Attia SK. Preparation and clinical evaluation of nano-transferosomes for treatment of erectile dysfunction. Drug Des DevelTher. 2015;9:2431-47.
19. Alvi IA, Madan J, Kaushik D, Sardana S, Pandey RS, Ali A. Comparative study of transfersomes, liposomes, and niosomes for topical delivery of 5-fluorouracil to skin cancer cells: preparation, characterization, in-vitro release, and cytotoxicity analysis. Anticancer Drugs 22(8), 774–782 (2011).
20. Lei W, Yu C, Lin H, Zhou X. Development of tacrolimus-loaded transfersomes for deeper skin penetration enhancement and therapeutic effect improvement in vivo. Asian J. Pharm. Sci. 8(6), 336–345 (2013).
21. Garg V, Singh H, Bhatia A *et al.* Systematic development of transethosomal gel system of piroxicam: formulation optimization, in vitro evaluation, and ex vivo assessment. AAPS PharmSciTech 18(1), 58–71 (2017).
22. Garg V, Singh H, Bhatia A *et al.* Systematic development of transethosomal gel system of piroxicam: formulation optimization, in vitro evaluation, and ex vivo assessment. AAPS PharmSciTech 18(1), 58–71 (2017).
23. Duangjit S, Opanasopit P, Rojanarata T, Ngawhirunpat T. Evaluation of meloxicam-loaded cationic transfersomes as transdermal drug delivery carriers. AAPS PharmSciTech2013;14:133-40
24. Gatne, M & Tambe, K & Chaudhary, Adarsh & Ravikanth, K. (2015). Acute dermal irritation study of polyherbal gel mastilep in rabbits. International Journal of Pharmaceutical Sciences and Research. 6. 3473-3476. 10.13040/IJPSR.0975-8232.6(8).3473-76.

25. Jain S, Jain P, Maheshwari UR, Jain N. Transfersomes – A novel vesicular carrier for enhanced transdermal delivery: Development, characterization, and performance evaluation. Drug Dev Ind Pharm 2003; 29:1013-26
26. Modi CD and Bharadia PD, "Transfersomes: New Dominants for Transdermal Drug Delivery", American Journal of Pharmtech Research, 2012; 2(3):71-91
27. Bnyan, R.; Khan, I.; Ehtezazi, T.; Saleem, I.; Gordon, S.; Neill, F.O.; Roberts, M. Surfactant effects on lipid-based vesicles properties. J. Pharm. Sci. 2018, 107, 1237–1246.
28. Iskandarsyah; Rahmi, A.D.; Pangesti, D.M. Comparison of the characteristics of transfersomes and protransfersomes containing azelaic acid. J. Young-Pharm. 2018, 10, S11–S15.
29. Van Hoogevest, P.; Wendel, A. The use of natural and synthetic phospholipids as pharmaceutical excipients. Eur. J. Lipid Sci. Technol. 2014, 116, 1088–1107. [CrossRef]
30. Jadupati, M.; Kumar, N.A. Transferosome: An opportunistic carrier for transdermal drug delivery system. Int. Res. J. Pharm. 2012, 3, 35–38.
31. Cevc, G.; Blume, G.; Schätzlein, A.; Gebauer, D.; Paul, A. The skin: A pathway for systemic treatment with patches and lipid-based agent carriers. Adv. Drug Deliv. Rev. 1996, 18, 349–378.
32. Mandal, U.K.; Mahmood, S.; Taher, M. Experimental design and optimization of raloxifene hydrochloride loaded nanotransfersomes for transdermal application. Int. J. Nanomed. 2014, 9, 4331–4346.
33. Cipolla, D.; Wu, H.; Gonda, I.; Eastman, S.; Redelmeier, T.; Chan, H.-K. Modifying the release properties of liposomes toward personalized medicine. J. Pharm. Sci. 2014, 103, 1851–1862.
34. Dudhipala, N.; Mohammed, R.P.; Youssef, A.A.A.; Banala, N. Effect of lipid and edge activator concentration on development of Aceclofenac loaded transfersomes gel for transdermal application: In vitro and ex vivo skin permeation. Drug Dev. Ind. Pharm. 2020, 46, 1–28.
35. Wu, P.-S.; Li, Y.-S.; Kuo, Y.-C.; Tsai, S.-J.J.; Lin, C.-C. Preparation and evaluation of novel transfersomes combined with the natural antioxidant resveratrol. Molecules 2019, 24, 600.
36. Yang, Y.; Ou, R.; Guan, S.; Ye, X.; Hu, B.; Zhang, Y.; Lu, S.; Zhou, Y.; Yuan, Z.; Zhang, J.; *et al.* A novel drug delivery gel of terbinafine hydrochloride with high penetration for external use. Drug Deliv. 2014, 22, 1–8.
37. Balata, G.F.; Faisal, M.M.; Elghamry, H.A.; Sabry, S.A. Preparation and characterization of ivabradine HCl transfersomes for enhanced transdermal delivery. J. Drug Deliv. Sci. Technol. 2020, 60, 101921.

38. Vasanth, S.; Dubey, A.; Ravi, G.S.; Lewis, S.A.; Ghate, V.M.; El-Zahaby, S.A.; Hebbar, S. Development and investigation of vitamin c-enriched adapalene-loaded transfersome gel: A collegial approach for the treatment of acne vulgaris. AAPS Pharm. Sci. Tech. 2020, 21, 61.
39. Qushawy, M.; Nasr, A.; Abd-Alhaseeb, M.; Swidan, S. Design, optimization and characterization of a transfersomal gel using miconazole nitrate for the treatment of candida skin infections. Pharmaceutics 2018, 10, 26.
40. Williams, A.C.; Barry, B.W. Penetration enhancers. Adv. Drug Deliv. Rev. 2004, 56, 603–618.
41. Shamma, R.N.; Elsayed, I. Transfersomal lyophilized gel of buspirone HCl: Formulation, evaluation and statistical optimization. J. Liposome Res. 2013, 23, 244–254. [CrossRef] [PubMed]
42. Jain, S.K.; Jain, P.; Umamaheshwari, R.B.; Jain, N.K. Transfersomes—A novel vesicular carrier for enhanced transdermal delivery: Development, characterization, and performance evaluation. Drug Dev. Ind. Pharm. 2003, 29, 1013–1026.
43. N'Da, D.D. Prodrug strategies for enhancing the percutaneous absorption of drugs. Molecules 2014, 19, 20780–20807.
44. Singh, S.; Vardhan, H.; Kotla, N.G.; Maddiboyina, B.; Sharma, D.; Webster, T.J. The role of surfactants in the formulation of elastic liposomal gels containing a synthetic opioid analgesic. Int. J. Nanomed. 2016, 11, 1475–1482.
45. Baboota S, Alam MS, Sharma S, Sahni JK, Kumar A, Ali J. Nanocarrier-based hydrogel of betamethasone dipropionate and salicylic acid for treatment of psoriasis. Int J Pharm Investig2011;1:139-47.
46. Lin YK, Huang ZR, Zhuo RZ, Fang JY. The combination of calcipotriol and methotrexate in nanostructured lipid carriers for topical delivery. Int J Nanomed2010;5:117-28.
47. Pal R, Pandey M. Transferosomes: a novel carrier for enhanced dermal delivery of drug. World J Pharma Pharm Sci 2015;4:1816-32

NANOSPONGES - A MODERN DRUG DELIVERY

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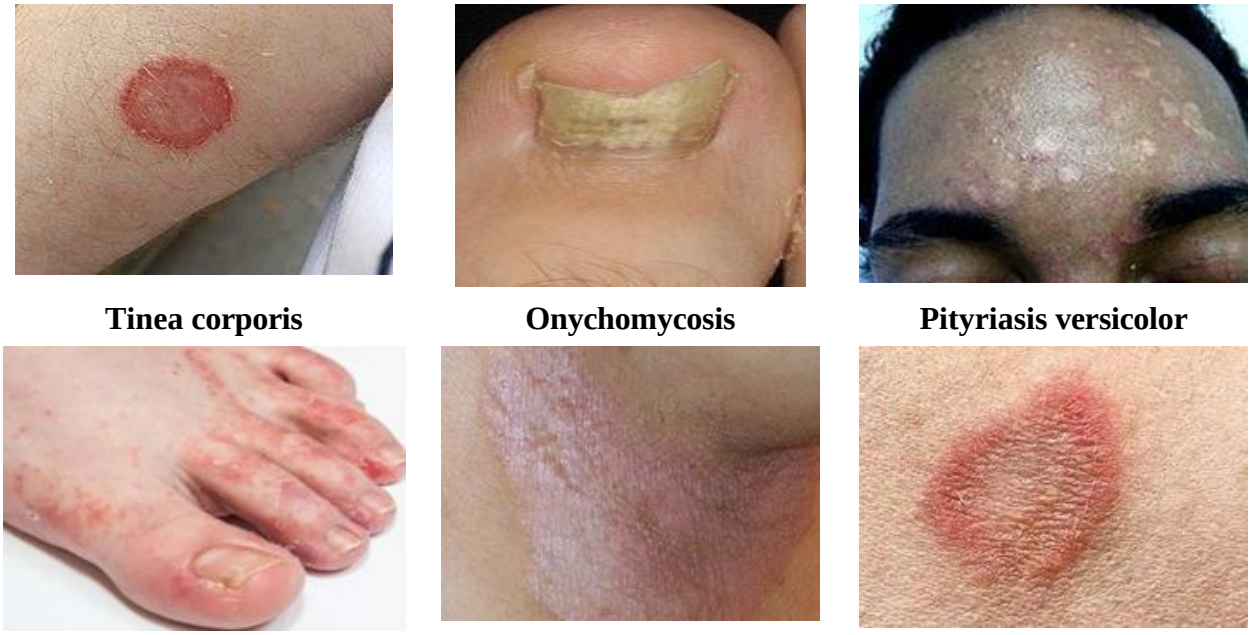
Introduction:

Fungal infections have a worldwide distribution and are common, affecting more than one billion people every year. [1]A fungal infection also called mycosis is a disease caused by a fungus. There are millions of species of fungi. They live in the dirt on plants, on household surfaces, and on your skin. Fungi are microorganisms characterized by a substance in their cell walls called chitin. Some fungi, like many types of mushrooms, are edible. Other types of fungi, like *Aspergillus*, can be extremely dangerous and lead to life-threatening diseases. Different types of fungi can cause fungal infections.

In some cases, fungi that are not typically found on or inside your body can colonize it and cause an infection. In other cases, fungi that are normally present on or inside your body can multiply out of control and cause an infection. Fungal infections can be contagious. They can spread from one person to another. Sometimes, they can lead to skin problems like rashes or bumps. A fungal skin infection might cause irritation, scaly skin, redness, itching, swelling, and blisters. Fungal skin infections can happen anywhere in your body. Some of the most common are athlete's foot, Joc itch, ringworm, and yeast infections.[2-3]

Fungal infection of the skin is nowadays one of the common dermatological problems. It involves the epidermis, dermis as well as deeper layers of skin that require customizing the drug delivery in such a way that localizes high drug concentrations at the epidermis and dermis layers.[4] Antifungal drugs are classified according to their chemical structure as azoles, polyenes, allylamines, and echinocandins.

Fungal infections have been divided into superficial and systemic infections.[5] Superficial fungal infections include common tinea of the skin, such as tinea of the body, groin, hands, feet, and beard, and yeast infections such as pityriasis versicolor.[6] Systemic fungal infections are more serious and include cryptococcosis, histoplasmosis, pneumocystis pneumonia, aspergillosis, and mucormycosis.[7] There is usually a rash with a superficial infection.[8] Fungal infection within the skin or under the skin may present with a lump and skin changes. Treatment is generally performed using antifungal medicines, usually in the form of a cream or by mouth or injection, depending on the specific infection and its extent. [9]



Tinea corporis **Onychomycosis** **Pityriasis versicolor**

Athlete's Foot **Jock itch** **Ringworm**

Fig. 1: Types of Fungal infections

To treat fungal infections various drugs of different classes are available. These classes include azoles, echinocandins, allylamines, antibiotics, and antimetabolites. Azole class is further divided into imidazole and triazoles [10-12]. Imidazole (clotrimazoles, miconazole, ketoconazole, meconazole) has high side effects, toxicity, and interactions. Azole has a better safety profile with a border spectrum than imidazole. 1st generation azole drugs (itraconazole, fluconazole) are fungistatic resulting in resistance. 2nd generation azole drugs (voriconazole, Posaconazole) are fungicidal with broader spectrum [13-16]. Echinocandins (caspofungin, micafungin, anidulafungin) are newer fungicidal agents with better safety profile [17,18]. Allylamines (terbinafine, naftifine, amorolfine, butenafine) is a newer class and better than azoles. Antibiotics class is divided

further into two subclasses polyenes and heterocyclic benzofuran. Polyene antibiotics (amphotericin B, natamycin, nystatin, hamycin) are fungicidal with border activity and nephrotoxicity limiting on lytopicaluse[19-21]. Antimetabolite includes single-agent flucytosine used only in adjunctive therapy [22].

Drug resistance, poor bioavailability, drug interactions and toxicity issues are the challenges making antifungal therapy one of the complicated therapies despite the availability of various drugs. Widespread use of antifungal agents in human and animal health care, agriculture, and timber preservation results in the emergence of drug resistance making antifungal therapy challenging [23,24]. Azoles, echinocandins and polyene classes are facing drug resistance against *Candida species* (*Candida glabrata, Candida tropicalis, Candida parapsilosis*) and *Aspergillus species* (*Aspergillus fumigatus, Aspergillus flavus*). *Candida auris* has raised with alarming multidrug resistance challenges globally [25-27]. The majority of antifungal agents are lipophilic resulting in low water solubility, poor bioavailability, and formulation challenges. A variety of available dosage forms tablets, capsules, creams, and injectables are ineffective in overcoming these challenges [28].

Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. The main advantage of the topical delivery system is to bypass first-pass metabolism. Avoidance of the risks and inconveniences of intra-venous therapy and of the varied conditions of absorption, like pH changes, the presence of enzymes, and gastric emptying time are other advantages of topical preparations [29].

Conventional topical systems such as ointments and creams are less effective for skin permeation due to their poor efficiency and are associated with side effects such as burning, contact dermatitis and stinging sensation leading to uncontrolled release of drugs[30,31].

Therefore, the focus is shifting towards the development of particulate carrier systems such as microspheres and liposomes for controlled delivery of drugs to specific skin regions[32]. These systems will presumably control drug input rate and minimize the absorption of drugs into the systemic circulation and consequently adverse reactions. Various studies have shown nanoparticulate carriers to be viable substitutes for liposomal carriers to achieve enhanced cutaneous delivery [33]. Therefore, nano-technology approaches have been major areas of interest in the past few decades. One such novel nano-carrier system which offers topical delivery especially when formulated as hydrogel is a nanosponge (NS) based delivery system [34,35].

Nanosponges have emerged as one of the most promising fields of science because of their perceived application in controlled drug delivery. Nanosponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. This system is employed for the improvement of the performance of topically applied drugs. These nanosponges can be effectively incorporated into the topical hydrogel drug delivery system for prolonged drug

release and retention of dosage form on sin, thus reducing drug toxicity and improving patient compliance by prolonging dosage intervals. [36,37]

Hydrogel is the most promising alternative drug delivery system for improving the bioavailability and therapeutic availability of drugs. Hydrogels are polymeric material that exhibits the ability to swell and retain a significant fraction of water within their structure but will not dissolve in water. Hydrogels have received considerable attention in the past 50 years, due to their exceptional promise in a wide range of applications. The ability of hydrogels to absorb water arises from hydrophilic functional groups attached to the polymeric backbone, while their resistance to dissolution arises from cross-links between network chains [38].

Clotrimazole is a topical, azole group of synthetic fungistatic agents with a broad spectrum of activity based on the imidazole or triazole nucleus. The primary mechanism of action of Clotrimazole is against the division and growth of fungi. It is used in the topical treatment of tinea infections like ringworm; 60-100% cure rates are reported with 2-4 weeks of application and, a twice-daily schedule. It is also effective in skin infections caused by Corynebacteria**.** To improve solubility, dissolution and sustain the release of Clotrimazole, it was proposed to prepare nanosponges of Clotrimazole and incorporate them in a suitable gel base. Clotrimazole interacts with yeast 14-α demethylase, a cytochrome p-450 enzyme that converts lanosterol to ergosterol, an essential component of the membrane.

In this way, clotrimazole inhibits ergosterol synthesis, resulting in increased cellular permeability. [39,40]

Beclomethasone dipropionate is 9a-chloro-11b–hydroxy-16b– methyl-3, 20- dioxopregna 1, 4-diene-17, 21- diyldipropionate. It is a synthetic halogenated glucocorticoid with anti-inflammatory and vasoconstrictive effects, is used for treating steroid-dependent asthma, and allergic or nonallergic rhinitis. The anti-inflammatory actions of corticosteroids are thought to involve phospholipase A2 inhibitory proteins, and lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes. [41,42]

Nanosponge:

NS are porous, spongy, spherical, small-sized polymeric structures that release the drug in a controlled and predictable manner [43]. They are free-flowing, self-sterilizing, cost effective and stable over range of pH of 1–11 and temperatures upto130°C. Many advantages of NS like improved safety, better product stability, enhanced aesthetic characteristics and non- irritancy make them a suitable approach for the development of topical preparations [44]. Several topical agents can safely be incorporated into nanosponges for controlled release [45]. Local anesthetics, antifungals and anti-acne are the potential categories of drugs that may be easily delivered as topical nanosponge preparations.

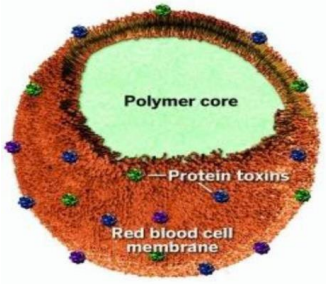


Fig. 2: Nanosponges

Nanosponges can be prepared by the solvent method, crosslinking of β-cyclodextrins, ultrasound assisted method and emulsion solvent diffusion method which is one of the effective and economical methods for the preparation of NS[46]. It can be formulated by various techniques such as complexation, encapsulation and conjugation to entrap the drug molecules within its core. Complexing nanosponges are the complexing nanoparticles, which attract the drug molecules by electrostatic charges. Conjugating nanosponges are prepared using natural derivatives, where they form covalent bonds between host molecule and guest molecule. They are water soluble however, does not breakup with chemicals in water.

Sustained release NS can also be developed, various factors that are to be considered during development to such formulations include physical and chemical properties of entrapped actives, physical properties of NS and properties of vehicle in which the NS are finally dispersed. Our selection of the vehicle was hydrogel, that when applied to the skin forms a thin transparent film suitable for incorporation of a topical agent intended for sustained release.[47]

Composition of Nanosponge Preparation

Multiple compounds have provided positive results that can be used in the preparation of NSs and their use depends on the type of NS required and the level of crosslinking needed. The level of crosslinking is an important aspect in NSs, and depends on the concentration of crosslinkers used since the drug release pattern and drug encapsulation depend on it. These are the various materials like polymer, co-polymer and cross-linker used for the fabrication of nanosponges and represented in table 1.

Table 1: Materials used in the preparation of nanosponges

Polymers	Hyper cross linkage polystyrenes, Cyclodextrins (alkyl β-cyclodextrins, alkoxy carbonyl cyclodextrins, hydroxy propyl betadex), and some deblock polymers like ethylcellulose, polyvinylchloride, Chitosan,etc.
Crosslinkers	Diarylcarbonates, Dichloromethane, Diphenyl carbonate, carbonyldiimidazole, pyromellitic-anhydride, glutaraldehyde, carboxylic acid dianhydrides, di-isocyanates and dichloramine [48].
Copolymers, Stabilizing agent, Surfactant	Polyvinylalcohol[49], Poly(ValerolactoneallylValerolactone) and Poly (Valerolactone allyl Valerolactone oxypanedione)

Method of Preparations of Nanosponges

Generally, in practical aspects, various methods are used for the preparation of nanosponges.

Solvent Method

Mix the polymer with a suitable solvent, in particular in a polar aprotic solvent such as dimethylformamide, dimethyl sulfoxide. Then add this mixture to excess quantity of the

crosslinker, preferably in crosslinker/polymer molar ratio of 4 to 16. Carry out the reaction at temperature ranging from10°C to the flux temperature of the solvent, for time ranging from 1 to 48h. Preferred crosslinkers are carbonyl compounds (Dimethyl carbonate & Carbonyl di imidazole). After completion of their action, allow the solution to cool at room temperature, then add the product to large excess of bi-distilled water and recover the product by filtration under vacuum and subsequently purify by prolonged Soxhlet extraction with ethanol. Dry the product under vacuum and grind in a mechanical mill to obtain homogeneous powder [50].

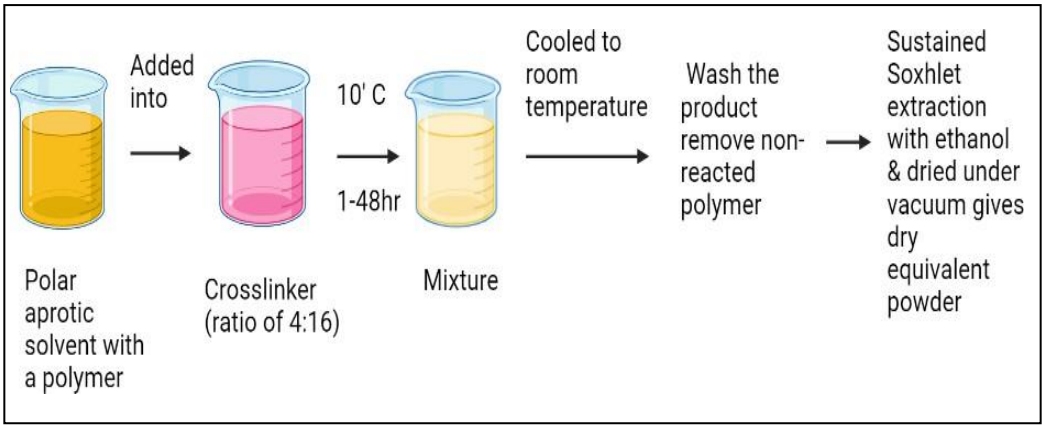


Fig. 3: Graphical image of solvent method

Melt Based Synthesis

The second method is fusion melt-based synthesis in which cross-linking agent and cyclodextrins are merged at high temperatures. This method is green because of no use of organic solvents [51].

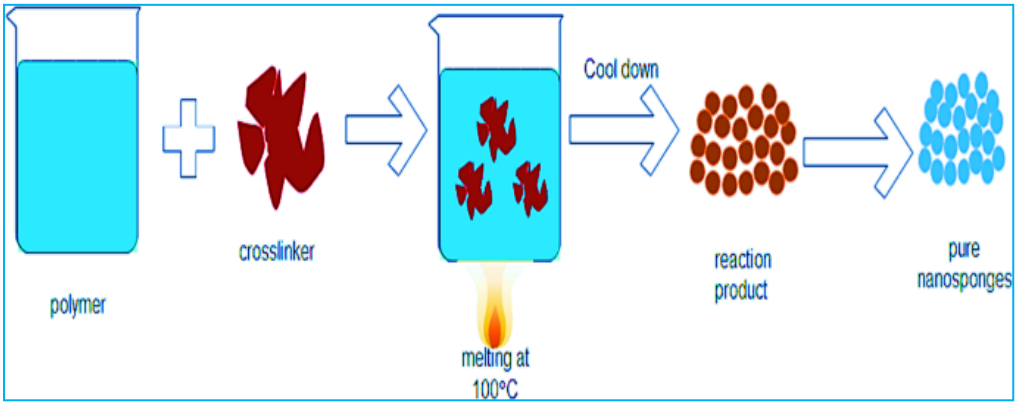


Fig. 4: Graphical image of Melt method technique

Ultrasound-Assisted Synthesis

In this method, nanosponges can be obtained by reacting polymers with cross-linkers in the absence of solvent and under sonication. The nanosponges obtained by this method will be spherical and uniform in size. Mix the polymer and the cross-linker in a particular molar ratio in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90°C.

Sonicate the mixture for 5 hours. Then allow the mixture to cool and break the product roughly.

Wash the product with water to remove the on reacted polymer and subsequently purify by prolonged Soxhlet extraction with ethanol. Dry the obtained product under vacuum and store at 25°C until further use [52].

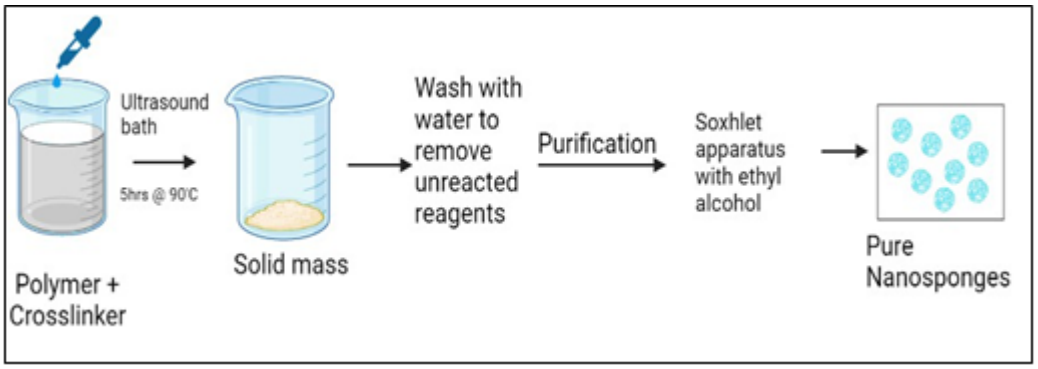


Fig. 5: Graphical image of Ultrasound assisted synthesis

Emulsion Solvent Diffusion Method

In this method, two phases are used. One is the dispersed phase and the other is the continuous phase. The disperse phase contains ethylcellulose and a drug which is then added in 20 ml dichloromethane. Along with an equal amount of polyvinyl alcohol this mixture is then added to 150 ml of the continuous aqueous phase. This mixture is then magnetically stirred. Then the product is dried [53].

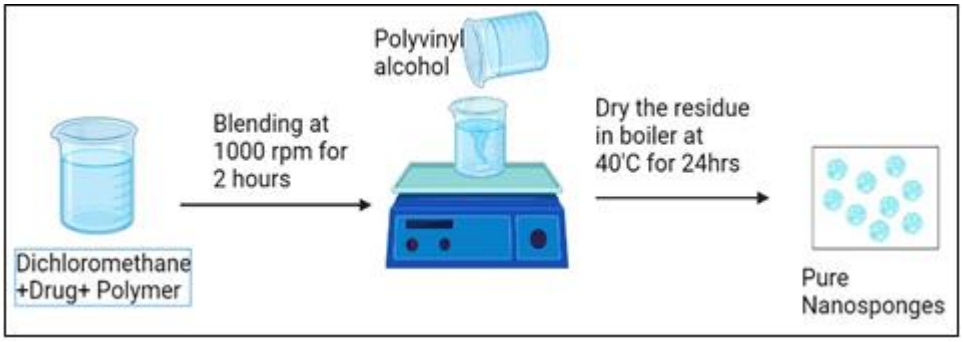


Fig. 6: Graphical image of Emulsion solvent diffusion method

Microwave-assisted synthesis

The microwave-assisted synthesis produces crystalline NS. In this method, microwaves are used for the preparation of nanosponges [54] .

From hypercrosslinked β-cyclodextrins

Mostly cyclodextrins(CDs) are used for the formation of nanosponges as a polymer. They are non-reducing cyclic oligosaccharides having almost 6 or 8 glucose units bounded with *a* 1,4-glycosidic linkage having a bridged conestructure[55]. Its outer part is hydrophilic and its inner part is lipophilic. Cyclodextrins are prepared by enzymatic action on starch and alpha, beta, and gamma CDs are formed comprised of six, seven, and eight glucopyranose subunits[56]. In nanosponges beta cyclodextrins condensing polymerization reaction takes place. There is a regiospecific addition of reactants, balanced reaction conditions, and well removal of excess product in nanosponges preparation. In a solution with small molecules of crosslinking agents

that work as small joining hook-ups that connect polymers together, cyclodextrins are heated. Nanosponges are prepared by different methods according to the nature of polymer and crosslinker. Cyclodextrins-based urethane/carbamates Nanosponges were made by reacting β-CD and hexamethylene diisocyanate and toluene diisocyanate in dimethylformamide for 20- 24 hours at 70℃ in N_2 environment.

Characterization of Nanosponges

Loading Efficiency

The loading efficiency of nanosponge complexes is estimated by dissolved in suitable solvent, sonicated to break the complex, diluted suitably and then analyzed by HPLC methods and UV spectrophotometer.

Microscopic Study

Microscopic studies of nanosponges or drugs can be conducted by using a transmission electron microscope and scanning electron microscope. 0.5%W/V suspension of nanosponges is sprayed on Edon copper grids and this must be air dried before observation. This method indicates the difference in the crystallization rate of the starting material and product. NIH image software is used [56].

Determination of size, zeta potential, and polydispersity

Zeta potential is the measure of surface charge or electrical potential at the slipping plane. This can be used by using specific electrodes in particle size measurement equipment. Polydispersity is the variation within particle size distribution. NS sizes and polydispersity parameters are determined by dynamic light scattering. This method uses 90 90-plus particle sizer with MASOPTION particle sizing software. 95℃ and 25℃ scattering angles are mostly used. All samples are diluted with deionized water before any measurement [56].

Fourier Transform Infrared (FTIR) Analysis

Fourier transform infrared analysis was used to verify the possibility of interaction of chemical bonds between drug and polymer. Samples were scanned in the range from 400-4000cm^{-1}.

In-vitro Drug Release of Nano sponges

The multi-compartment rotating cell is used. It has two compartments one of which is a donor that is filled with an aqueous suspension of nanosponges with drugs and the other is a receiver compartment filled with suitable PH phosphate buffer. These two compartments are separated by a hydrophilic dialysis membrane. The receptor buffer is completely withdrawn at specific time intervals and fresh buffer is added. The sample is then analyzed by HPLC or other tool specified in individual monographs of the drug [57].

Thermal Analysis

Differential scanning calorimetry (DSC), differential thermal analysis (DTA) and thermogravimetric analysis (TGA) are most important. These studies are used to determine melting point, degree of crystallinity (Xc), crystallization temperature (Tc) and thermostability of

nanosponges. In TGA, the sample is heated in N2 environment and loss of mass is noted. Weight loss is another indicator of formation on inclusion complex formation. Then sample is heated in the presence of oxygen and loss of mass and oxidized products are identified. DTA and DSC patterns of nanosponges can be observed for any enlargement, shifting and appearance of new peaks shows the molecular dispersion of drug in polymer [58].

Moisture analysis

Nanosponges are non-hygroscopic. The retention of crystal structure during moisture absorption and desorption can be confirmed by dynamic vapor sorption studies [57].

X-ray diffractometry and single crystal X-ray structure analysis

The diffraction pattern is noted in the solid state. In liquid form, the mixture not show any diffraction pattern. The diffraction is completely different of un complexed NS from complexed NS. This difference indicates the complex formation. The diffraction peaks are important to determine the chemical decomposition and complex formation [59]. The single crystal X-ray structure analysis reveals the complete structure and interaction of nanosponges. The precise geometric relationship can be identified [60].

Photodegradation Study

In this study, UV lamp is used. The sample is taken at10cm from UV lamp. The sample is stirring under dark. The sample is analyzed at different time intervals using HPLC [60].

Advantages of nanosponges[57,58]

- It provide extended release condition
- Protected from degradation of drug
- It is non-mutagenic, non-irritating, non-toxic and no side effects
- The superior properties of nanosponges have been attributed to tunability, that is the ability to control the structure of particles and control the nature and size of aperture.
- Nanosponges can produce predictable/ controlled drug release.
- Nanosponges can be tagged with specific linkers to target diseased cells hence achieving greater efficacy while reducing side effects, decreasing dose and dosing frequency and in turn increasing patient compliance.
- Nanosponges can significantly reduce the irritation of drugs without reducing their efficacy.
- Biodegradable in nature and easy to scale up for commercial production.
- They mix with water and are used as a transport fluid. They can be used to mask unpleasant flavors.
- The formulations are cost-effective.
- Dosing frequency can be reduced
- Better patient compliance.
- Act as an absorbent and remove toxic and venom substances from the body.

Disadvantages of nanosponges[59,60]

- ❖ Large molecules cannot encapsulated into nanosponges
- ❖ Dose dumping
- ❖ May retard the release
- ❖ Depend only upon loading capacity

Application of Nanosponges

Nanosponges for drug delivery

Nanosponges can transport water-insoluble medicines due to their nanoporous properties. Nanosponge can speed up the dissolution of medications, improve their solubility and stability, hide undesirable flavors, and convert liquids to solids. Nanosponges made of cyclodextrin are said to transport drugs to the target place more effectively than direct injection. Nanosponge can be formed into oral, parenteral, topical, or inhalation dosage forms due to its solid structure. They could be mixed with excipients, diluents, lubricants and anticaking agents to make capsules or tablets for oral delivery. They can be transported in sterile water, saline, or other aqueous solutions for parenteral delivery. They can be mixed into a topical hydrogel for topical delivery.[61]

Nanosponges for cancer therapy

Because of their low solubility, anticancer medication distribution is one of the most difficult jobs in the pharmaceutical industry today. According to one study, the nanosponge combination is three times more effective than direct injection in suppressing tumour growth. A specific peptide is firmly linked to a top layer of radiation-induced cells on the tumour receptor after a complex loading of the nanosponge with a medication. When the nanosponges come into contact with a cancer cell, they adhere to its surface and beg into release medication molecules. Targeting medicine administration has the advantage of achieving a more effective therapeutic impact at the same dose with fewer side effects.[62]

The role of nanosponges in fungal infection treatment

One of the most serious diseases in the world is fungal skin infections. Topical therapy is a promising therapeutic option for skin infections because it has a number of advantages, including the ability to target medications directly to the infection site and lowering systemic side effects. Itraconazole is an antifungal medicine classified as a class II biopharmaceutical, with a slow dissolution rate and low bioavailability. Itraconazole nanosponges is found to boost its solubility and alleviated the bioavailability problem. The solubility of itraconazole can be increased in these nano sponges if cyclodextrins utilized as a carbon cross linked and loaded with itraconazole.[63]

To improve the poor solubility of drugs

One of the most important issues to address throughout the design and development of materials is poor solubility. The efficacy of a formulation can be harmed by medication solubility issues. Nanosponge serves as a carrier for molecules, encapsulating the mint score and

attempting to improve the formulation's solubility. The current way for increasing solubility is using a -cyclodextrin nanosponge.[64]

In the treatment of blood poisoning as an absorbent

By absorbing the toxin, nanosponges can remove the hazardous poisonous chemical from our blood. Instead of utilizing antidotes, we can use nanosponges to absorb toxins by injecting them into the bloodstream. The nanosponge imitates a red blood cell in the bloodstream, leading toxins to assault and absorb it.[65]

Antiviral application

Nanosponges can be useful in the ocular, nasal, pulmonary administration routes. The selective delivery of antiviral drugs or small interfering RNA (siRNA) to then as a epithelia & lungs can be accomplished by nanocarriers in order to target viruses that infect the RTI such as respiratory sincytial virus, influenza virus & rhinovirus. They can also be used for HIV, HBV and HSV. The drugs which are currently in use as nano delivery system are zidovudine, saquinavir, interferon- α, acyclovir.

Hydrogel technical features

The functional features of an ideal hydrogel material can be listed as follows [61]:

- The highest absorption capacity (maximum equilibrium swelling) in saline.
- Desired rate of absorption (preferred particle size and porosity) depending on the application requirement.
- The highest absorbency under load (AUL).
- The lowest soluble content and residual monomer.
- The lowest price.
- The highest durability and stability in the swelling environment and during the storage.
- The highest biodegradability without formation of toxic species following the degradation.
- pH-neutrality after swelling in water.
- Colorlessness, odorlessness and absolute non-toxic.
- Photo stability.

Re-wetting capability (if required) the hydrogel has to be able to give back the imbibed solution or to maintain it depending on the application requirement (e.g., in agricultural or hygienic applications

References:

1. Nakazato G, Alesandra A, Lonni SG, Panagio LA, de Camargo LC, Goncalves MC,etal.Applicationsofnanometalsincutaneousinfections".InRaiM(ed.).Nanotechnology in Skin, Soft Tissue, and Bone Infections. Switzerland: Springer. 2020. ISBN 978-3-030-35146-5.
2. https://www.webmd.com/skin-problems-and-treatments/guide/fungal-infections-skin
3. https://www.healthline.com/health/fungal-infection

4. Kumaretal.Preparationofluliconazolenanocrystalsloadedhydrogelforimprovement of dissolution and antifungal activity. Heliyon. 2018; 5 2019: 1-10.
5. Kumaretal.Formulationandevaluationoftopicalhydrogelcontainingantifungaldrug. Pharmacy & Pharmacology International Journal. 2020: 8(4):249–254.
6. Kutzner H, Kempf W, Feit J, Sangueza O. “Fungal infections". Atlas of Clinical Dermatopathology: Infectious and Parasitic Dermatoses. Hoboken: Wiley Blackwell. 2021; 77–108. ISBN 978-1-119-64706-5.
7. Barlow G, Irving WL, Moss PJ. "Infectious diseases". In Feather A, Randall D, Waterhouse M (eds.).Kumar and Clark's Clinical Medicine(10thed.). Elsevier 2020. 559–563. ISBN 978-0-7020-7870-5.
8. "FungalDiseasesHomepage|CDC".www.cdc.gov.29March2021.
9. Graininger W, Diab-Elschahawi M, Presterl E 2019. Antifungal agents". In Presterl E (ed.).ClinicallyRelevantMycoses:APracticalApproach.Springer.31–44.ISBN978- 3-319-92299-7.
10. MahajanM2019Pathogenesis and Practice, Antifungal Agents : Classification.
11. DixonDMetal.,Walsh,Antifungalagents.1996.
12. Nett JE, Andes. Antifungal agents: spectrum of activity, pharmacology, and clinical indications. Infect Dis Clin North Am 2016; 30(1): 51-83.
13. Moriyama B, Henning SA, Leung J, Falade-Nwulia O, Jarosinski P, *et al.* Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. Mycoses. 2012; 55(4): 290-297.
14. AndesDR, DismukesWE. Essentials of Clinical Mycology. Springer (2011). 61-93.
15. Saravolatz LD, Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. Clinical Infectious Diseases 2003; 36(5): 630-637.
16. ChenSC, SorrellTC. Antifungal agents. Med J Aust 2007;187(7): 404-9.
17. Grover ND 2010 Echinocandins: A ray of hope in antifungal drug therapy. Indian J Pharmacol 42(1): 911.
18. Stan CD, Tuchilus C, Stan CI 2014 Echinocandins-new antifungal agents. Rev Med Chir Soc Med Nat Iasi 118(2): 528-536.
19. Shukla PK, Singh P, Yadav RK, Pandey S, Bhunia SS. Past, present, and future of antifungal drug development. Communicable Diseases of the Developing World.2016; 125-167.
20. Rotta, Otuki, Sanches, Correr CJ. Efficacy of topical antifungal drugs in different dermato mycoses : asystematic review with meta-analysis. Rev Assoc Med Bras(1992) 2012; 58(3): 308-318.
21. Kathiravan MK, Salake AM, Chothe AS, Dudhe PB, Watode RP, *et al.* The biology and chemistry of antifungal agents: a review. Bioorg Med Chem. 2012; 20(19): 5678- 5698.

22. CampoyS, AdrioJL2017 Antifungals.BiochemPharmacol133: 86-96.
23. Kontoyiannis DP Antifungal resistance: emerging reality and a global challenge. J Infect Dis. 2017; 216(3): S431-S435.
24. Fisher MC, Hawkins NJ, Sanglard D, Gurr SJ. Worldwide emergence of resistance to antifungal drugs challenges human health and food security. Science 2018;360(6390): 739-742.
25. Alcazar-FuoliL,MelladoE. Current status of antifungal resistance and its impact on clinical practice. Br J Haematol 166(4): 471-484.
26. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo. The global problem of antifungal resistance: prevalence, mechanisms, and management. Lancet Infect Dis. 2017; 17(12): e383-e392.
27. HendricksonJA, HuC, AitkenSL ,BeydaN. Antifungal resistance : a concerning trend for the present and future. Curr Infect Dis Rep. 2019; 21(12): 47.
28. SolimanGM. Nanoparticles as safe and effective delivery systems of antifungal agents: achievements and challenges. Int J Pharm 2017; 523(1): 15-32.
29. Ashni Verma *et al.* Topical gels as drug delivery systems: A review. International Journal of Pharmaceutical Sciences Review and Research. 2013; 23(2):374-382.
30. Nor SB, Woi PM, Ng SH. Characterisation of ionic liquids nanoemulsion loaded with piroxicam for drug delivery system. J Mol Liq. 2017; 234: 30-39.
31. Butani D, Yewale C, Misra A. Amphotericin B topical microemulsion: formulation, characterization and evaluation. Colloids Surf B Biointerfaces.2014;116: 351-358.
32. Ghanbarzadeh S, Arami S. Enhanced transdermal delivery of diclofenac sodium via conventional liposomes, ethosomes, and transfersomes. BioMed Res Int. 2013; 2013: 1-7.
33. Jain AK, Jain A, Garg NK, Agarwal A, Jain A, Jain SA, Tyagi RK, Jain RK, Agrawal H, Agrawal GP. Adapalene loaded solid lipid nanoparticles gel: an effective approach for acne treatment. Colloids Surf B Biointerfaces 2014; 121: 222-229.
34. Batheja P, Sheihet L, Kohn J, Singer AJ, Michniak-Kohn B. Topical drug delivery by a polymeric nanosphere gel: Formulation optimization and in-vitro and in-vivo skin distribution studies. J Control Rel 2011; 149(2): 159-167.
35. Sharma *et al.* Evaluation of the Kinetics and Mechanism of Drug Release from Econazole nitrate Nanosponge Loaded Carbapol Hydrogel. Indian Journal of Pharmaceutical Education. 2011; 45(1): 25-31.
36. Cromellin D, Schreier K. Liposomes, in: Colloidal Drug Delivery Systems. Kreuter J editor. New York: Marcel Dekker; 1994. 73–123.
37. Nacht S, Kantz M. The Microsponge: A Novel Topical Programmable Delivery System, In: Topical Drug Delivery Systems. David WO, Anfon HA editors. NewYork: Marcel Dekker; 1992. 42: 299-325.

38. Selva muthukumar S, Anandam S, Krishnamoorthy K, Rajappan M. Nanosponges: A novelclassofdrugdeliverysystem-review.J.PharmPharmSci2012;15(1):103-111.
39. EnasMA. Hydrogel: Preparation, characterization, and applications: A review. Journal of Advanced Research, 1, 2013, 106-121.
40. Rang HP, Dale MM, Pitter JM. and Moore PK.: Pharmacology; Elesvier, New Delhi, 15th Edn; 2005:666-671.
41. Joel GH. and Lee EL.: Goodman and Gilman's The Pharmacological basis of Therapeutics; McGraw Hill Publishers, New York, 9th Edn; 1996:356- 362.
42. Delattre L, Delneuville I. Biopharmaceutical aspects of the formulation of dermatological vehicles. J Eur Acad Derm Vener. 1995; 5: S70- 76.
43. JenningV, Schafer-Korting M, GohlaS. Vitamin A loaded solid lipid nanoparticles for topical use: drug release properties. J Control Release. 1999; 66: 115-126.
44. Bolmal UB, Manvi FV, Rajkumar K, Palla SS, Paladugu A, Reddy KR. Recent advances in nanosponges as drug delivery system. Int J Pharm Sci Nanotechnol 2013; 6: 1934-1944.
45. AldawsariHM, Badr-EldinSM, LabibGS, El-KamelAH. Design and formulation of a topical hydrogel integrating lemongrass-loaded nanosponges with an enhanced antifungal effect: in vitro/in vivo evaluation. Int J Nanomedicine 2015; 10: 893-902.
46. Sharma R, Pathak K. Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through topical hydrogel formulation. Pharm Dev Technol 2011; 16(4): 367-376.
47. Tripathi KD. Essentials of Medical Pharmacology; Jaypee Brothers Medical Publishers, New Delhi, 6th Edn, 2008:245-249,275.
48. Yates *et al.* Beclomethasone dipropionate: absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral, intranasal and inhaled administration in man. British journal of Clinical pharmacology. 2001 May; 51(5): 400–409.
49. Selvamuthukumar S, Anandam S, Krishnamoorthy K, Rajappan M. Nanosponges: A novel class of drug delivery system-review. Journal of Pharmacy & Pharmaceutical Sciences 2012. 15(1): 103-111.
50. KrabicováI, AppletonSL, TannousM, HotiG, CalderaF, etal. History of Cyclodextrin Nanosponges. Polymers. 2020. 12(5): 1122.
51. Shivani S, Poladi KK. Nanosponges-Novel Emerging Drug Delivery System: A Review. International Journal of Pharmaceutical Sciences and Research. 2015. 6(2): 529-540.
52. Shringirishi M, Prajapati SK, Mahor A, Alok S, Yadav P, *et al.* Nanosponges: a potential nanocarrier for novel drug delivery are view. Asian Pacific journal of Tropical Disease. 2014. 4(2): S519-S526.
53. SilpaGS, Deepa MR, Mathan S, Shaiju SD. Nanosponges: A Potential Nanocarrier: A Review. Journal of Pharmaceutical Sciences and Research. 2020. 12(10): 1341- 1344.

54. Shende PK, Trotta F, Gaud RS, Deshmukh K, Cavalli R, *et al.* Influence of different techniques on formulation and comparative characterization of inclusion complexes of ASAwithβ-cyclodextrinandinclusioncomplexesofASAwithPMDAcross-linkedβ-cyclodextrin nanosponges. Journal of inclusion phenomena and macrocyclic chemistry. 2012. 74(1-4): 447- 454.
55. Trotta F. Cyclodextrin nanosponges and their applications. John Wiley & Sons, Inc.: Hoboken, NJ, 2011; pp: 323-342.
56. Sherje AP, Dravyakar BR, Kadam D, Jadhav M. Cyclodextrin-based nanosponges: a critical review. Carbohydrate Polymers. 2017; 173: 37-49.
57. TejashriG, AmritaB, DarshanaJ. Cyclodextrin based nanosponges for pharmaceutical use: A review. Acta pharmaceutica. 2013; 63(3): 335-358.
58. Selvamuthukumar S, Anandam S, Krishnamoorthy K, Rajappan M. Nanosponges: A novel class of drug delivery system-review. Journal of Pharmacy & Pharmaceutical Sciences. 2012; 15(1): 103-111.
59. SilpaGS, DeepaMR, MathanS, ShaijuSD. Nanosponges: A Potential Nanocarrier: A Review. Journal of Pharmaceutical Sciences and Research. 2020; 12(10): 1341-1344.
60. MandanS, ChavanM, BhadaneY, KalalC. Nanosponges: a new drug delivery system. Journal of Drug Delivery and Therapeutics. 2018;8(6- A):141-3.
61. Praveen Kumar, Chinna Eswaraiah. Formulation and evaluation of topical hydrogel containing antifungal drug. Pharm Pharmacol Int J. 2020;8(4):249–254.

ENHANCING BEAUTY NATURALLY: BLUSH COSMETICS WITH PLANT-BASED COLORANTS

PART 1: BLUSH COSMETICS, SKIN, AND NATURAL COLORANTS

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Abstract:

The cosmetics industry is moving towards natural and sustainable alternatives due to concerns over synthetic ingredients. Blush products, traditionally made with artificial dyes, are now replaced by plant-based options to address skin sensitivity and environmental impact. This chapter explores natural blush cosmetics, their types, characteristics, and suitability for various skin types. It highlights the benefits of plant-based formulations, such as antioxidant protection and skin nourishment. Key botanical coloring agents, including beetroot, hibiscus, roselle, dragon fruit, rose, and strawberry, are examined for their properties, phytochemical composition, and extraction methods. By promoting plant-derived pigments, this review encourages research and innovation in eco-friendly blush cosmetics.

Keywords: Natural Cosmetics, Blush Types, Plant-Based Pigments, Botanical Extracts, Structure of Skin, Skin-Friendly Cosmetics, Anthocyanins, Betalains, Natural Colouring Agents.

Introduction:

Cosmetics have been used for beauty and skincare since ancient civilizations. Over time, cultural and social influences have shaped their acceptance and usage. While synthetic cosmetics dominate the market, concerns over chemical ingredients have led to a shift toward natural alternatives. Herbal cosmetics, enriched with plant-based compounds, offer skin-nourishing and protective benefits. Their anti-inflammatory and antimicrobial properties make them a safer choice for sensitive skin. As consumer awareness grows, natural beauty products are gaining popularity for their sustainability and effectiveness [1].

Fig. 1: Blush

Blush:

Blush enhances the cheeks with a youthful, sculpted look and comes in various shades to suit different skin tones [2]. Herbal blushes, made from plant-based ingredients, offer a skin-friendly alternative by nourishing and protecting the skin while adding colour [3].

The following qualities are essential for an excellent blush:

- Blendability
- Prevention of local irritation
- Uniformity
- Strong absorption capacity [4]

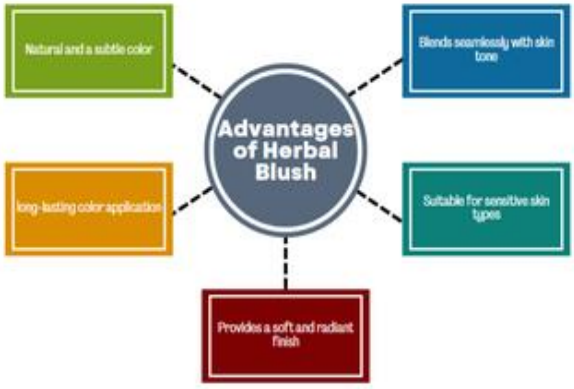


Fig. 2: Advantages of herbal blush [5]

Types of Blushes:

1. Compact Blush: Compact blush is a portable cosmetic for easy touch-ups, offering long-lasting color, a smooth finish, and skincare benefits. It is made with plant-based ingredients and provides a skin-friendly and eco-friendly alternative to chemical-based products [6].

2. Loose Powder Blush: Loose blush powders are gentle on sensitive skin and less likely to clog pores. Blending complementary colours or adding a highlighter creates a radiant, youthful, and luminous flush [7].

Fig.3: Compact blush

Fig. 4: Loose powder blush

Fig. 5: Cream blush

3. Cream Blush: Cream blush provides a natural, dewy glow with skincare benefits, blending seamlessly for a fresh-faced look. Ideal for dry or mature skin, it hydrates and smooths, while oily skin may prefer powder blush for a matte finish [8].

4. Cheek Tint: This water-based blush offers a matte or satin finish and doubles as a lip color for a coordinated look. Its lightweight, long-lasting formula provides a natural, lifted effect, making it easy for quick, portable touch-ups throughout the day [9].

5. Stick Blush: This cream-based stick is portable for quick touch-ups, blending smoothly with fingers or a brush for a customizable finish. It's ideal for those seeking convenience and a natural or defined look [10].

Fig.6: Cheek tint

Fig. 7: Stick blush

Ideal Characteristics of a Blush Stick [11]:

Fig. 8: Ideal characteristics of a blush stick

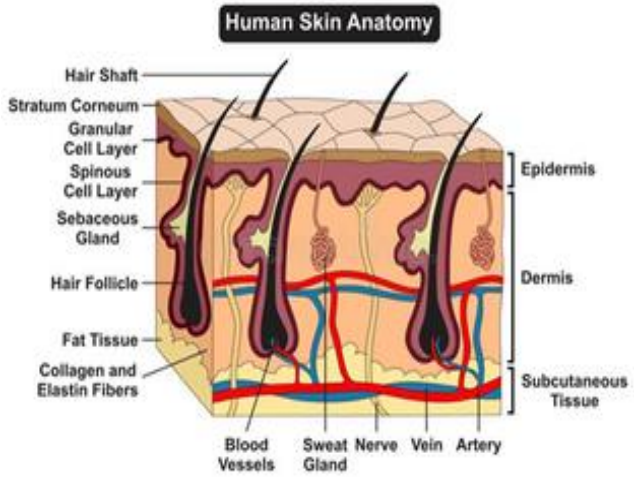


Fig. 9: Structure of skin

Structure of skin:

The skin consists of three layers: the epidermis, which acts as a protective barrier and contains melanin-producing cells; the dermis, which provides structure, and elasticity, and houses blood vessels, hair follicles, and nerve endings; and the subcutaneous layer, composed of fat and connective tissue, which insulates, stores energy, and anchors the skin to muscles and bones [12].

1. Epidermis: The *epidermis* is the outermost layer of the skin, made up of several distinct cell types and sublayers:

Key Components:

- *Keratinocytes* are the main cells in the epidermis, producing keratin, a protein that helps protect the skin from damage.

- *Melanocytes* are found here too, and they produce melanin, which gives the skin its colour and offers some protection from UV radiation
- The epidermis is avascular, lacking blood vessels, so it relies on the dermis underneath for nutrients and oxygen [13].

Epidermal Layers (from deepest to most superficial):

- *Stratum basale (basal layer)*: The deepest layer, where new skin cells are generated through mitosis.
- *Stratum spinosum*: A layer of keratinocytes connected by desmosomes that provide structural support.
- *Stratum granulosum*: Cells here start to die and form the skin's protective barrier
- *Stratum lucidum*: A thin, clear layer found only in thick skin, such as the palms of the hands and soles of the feet.
- *Stratum corneum*: The outermost layer, made of dead keratinized cells that form a tough, protective barrier [14].

2. Dermis: The *dermis* is the layer beneath the epidermis, containing connective tissue and offering structural support:

Papillary Layer:

- Made of loose connective tissue
- Houses blood vessels, lymphatics, and nerve endings, which supply the epidermis with nutrients and provide sensory functions [15].

Reticular Layer:

- Composed of dense irregular connective tissue.
- Contains a mix of collagen and elastin fibres, which give the skin strength and flexibility.
- This layer also plays a role in the skin's ability to resist tension and stretching [16].

3. Subcutaneous Layer: The *subcutaneous layer*, or hypodermis, is the deepest skin layer:

- Made up primarily of fat and connective tissue
- Acts as an insulator, helping to regulate body temperature
- Stores energy and also serves to anchor the skin to underlying muscles and bones [17].

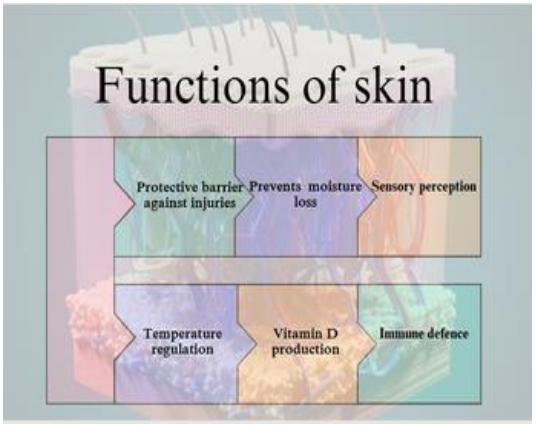


Fig. 10: Functions of skin [18]

Types of Skin:

1. Normal Skin: Normal skin, being well-balanced and free of extreme oiliness or dryness, is versatile enough to use a variety of blush formulations [19].

Blush Recommendation:

1. Loose Powder Blush: Loose powder blush is ideal for normal skin, offering a natural, buildable finish without emphasizing texture or oiliness. Its lightweight formula blends smoothly, creating a fresh, polished glow with a matte or satin effect [20].

2. Oily Skin: Oily skin produces excess oil, which can make makeup slide off or become shiny during the day. Therefore, it is essential to use blushes that can absorb excess oil and offer a long-lasting finish [21].

Blush Recommendation:

- **Loose Powder Blush**: Ideal for oily skin, loose powder blush provides a matte finish, absorbs excess oil, and reduces shine. Its lightweight formula prevents a cakey look and ensures long-lasting wear by controlling oil throughout the day.
- **Powder Blush (pressed)**: A powder blush is also a good choice for oily skin, as it sets the makeup and keeps oil at bay, preventing the blush from fading. Look for long-wearing, oil-controlling formulas that help maintain a matte appearance [22].

3. Dry Skin: Dry skin tends to look more textured and can feel tight or rough, especially during colder weather. For this skin type, choosing products that add moisture and do not emphasize dry patches is key [23].

Blush Recommendation:

- **Cream or Liquid Blush**: Cream or liquid blushes hydrate dry skin, providing a dewy finish for a plump, moisturized look. They blend smoothly without clinging to dry patches, ensuring a fresh, hydrated appearance.
- **Compact Blush (cream-based)**: Compact cream blushes offer more moisture than powders, providing a smooth, hydrating finish. They blend easily into dry skin without emphasizing flakes, ensuring an even, natural look [24].

4. Combination Skin (Dry + Oily): Combination skin requires a more tailored approach, as it has both oily and dry areas. This means that a balance of products that work well on both zones is needed [25].

Blush Recommendation:

- **Loose Powder Blush**: For oily areas, such as the T-zone, loose powder blush works well to absorb excess oil and prevent the makeup from looking shiny. It offers a matte finish and helps keep makeup intact throughout the day.

Compact Blush (Powder or Cream): For dry areas like the cheeks, both powder and cream blush work well. Powder stays in place without highlighting dryness, while cream adds a dewy flush. Layering powder over cream controls shine while maintaining hydration [26].

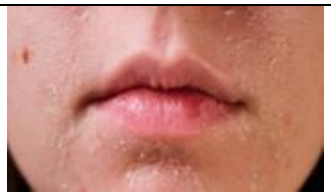
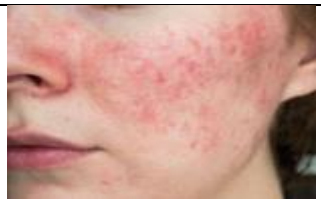
5. Sensitive Skin: Sensitive skin is prone to irritation, redness, and discomfort, so the key is to choose blushes that are gentle, soothing, and free of harsh chemicals or fragrances [27].

Blush Recommendation:

Mineral-Based Loose Powder Blush: Mineral blushes, being hypoallergenic and fragrance-free, are perfect for sensitive skin. Their lightweight, natural formula provides a smooth finish without irritation.

Cream Blush (Hypoallergenic): For sensitive skin, a cream blush with soothing ingredients like aloe vera or chamomile is ideal, providing hydration and comfort without irritation [28].

Table 1: Types of skin [29]

	**Oily Skin:** Visible, enlarged pores, glossy, oily skin, and recurrent acne attacks, including blackheads and pimples.
	**Dry skin:** Skin seems stretched, flaky, dry, and lifeless, with no apparent pores.
	**Combination skin:** T-zone oily, cheeks, and other dry or normal; occasional blackheads around the nose; slight skin sensitivity.
	**Normal skin:** Clear, smooth skin with typical pores and no imperfections or too dry or greasy areas.
	**Sensitive skin:** Genetically or externally predisposed to skin allergies that result in redness, irritation, and rashes.

List of natural ingredients used in blushes as colouring agents

1. Beetroot

Beetroot (*Beta vulgaris* L.) is gaining popularity as a natural colouring agent in cosmetics, especially for blush, due to its vibrant red hue from betalains, providing a natural alternative to synthetic dyes [30].

Synonyms: Beet, chard, spinach beet, sea beet, garden beet, white beet, and Chukander (in Hindi).

Biological source: Beets, used for both human food and cattle, were first cultivated in the Middle East. The 12th century recorded sugar beets with enlarged roots, and in the 18th century, German scientists began breeding beets for higher sugar content, with the white Silesian beet being the ancestor of the sugar beet.

Family: *Amaranthaceae* (previously *Chenopodiaceae*) [31].

Geographical source: Beet (Beta) likely originated near the Tigris and Euphrates Rivers, spreading across the Atlantic coast and Mediterranean. Geographic isolation in the Canary Islands led to unique species, while beets in Turkey, Iran, and Russia evolved into more perennial varieties. The cultivated sugar beet likely originated from the wild maritime beet (B. vulgaris subsp. maritima) through selective breeding [32].

Macroscopic features:

Table 2: Macroscopic features of beetroot [33]

Colour	Deep red
Odour	Characteristic, earthy
Shape	Round or slightly oval
Taste	Slightly sweet and earthy
Size	Weight: ~180g, length: ~16 cm, diameter: ~ 5cm

Microscopic features

Table 3: Microscopic features of beetroot [34]

Features	**Description**
Cell structure	Parenchymat ous cells with large vacuoles containing betalain pigment.
Vascular bundles	Collateral vascular bundles with xylem and phloem tissues.
Pigment localization	Betalin pigments located in vacuoles of epidermal and cortical cells
Calcium oxalate crystals	Presence of irregular prismatic-shaped calcium oxalate crystals.
Starch granules	Detection of starch granules within the root tissue.

Phyto-Constituents: The plant contains 9.96g of carbohydrates, 1.68g of protein, and 0.18g of fat per 100g. It provides 0.067mg of Vitamin B6, 80mg of Vitamin B9, 3.6mg of Vitamin C, and key minerals like 16mg of calcium, 0.79mg of iron, and 23mg of magnesium, along with 291mg of betalains contributing to its red pigmentation.

Extraction process:

Figure 11: Extraction process of beetroot extract [35]

Identification Tests:

1. **Spectrophotometric Analysis**: Measures betalain absorbance at 538 nm (betacyanins) and 480 nm (betaxanthins) for quick quantification.
2. **pH Sensitivity Test**: Betacyanins turn red in acidic and yellow in alkaline conditions, aiding identification and stability assessment.
3. **Paper Chromatography**: Separates betalains on paper; betacyanins form red bands, betaxanthins yellow, for easy identification.
4. **Thin-Layer Chromatography (TLC)**: Uses silica gel to separate betalains, showing distinct spots for composition and purity analysis.

Uses:

a. **Natural Colorant:** Betalains, responsible for the red and yellow hues of beetroot, are used as natural dyes in cosmetics like lipsticks and blushes.
b. **Antioxidant Properties:** Betalains act as antioxidants, helping protect the skin from environmental damage and oxidative stress.
c. **Antimicrobial Activity:** Betalains have antimicrobial properties, which can improve the safety and preservation of cosmetic products [36].

6.2 Roselle (*Hibiscus sabdariffa L.)* Flower Extract

Roselle (*Hibiscus sabdariffa*) is valued for its deep red pigmentation and anthocyanin content, offering a natural alternative to synthetic dyes in blush products. It also provides antioxidant properties, benefiting the skin in cosmetics.

Synonyms: Sorrel, Jamaica sorrel, Red sorrel, Rozelle, Florida cranberry, Hibiscus sabdariffa.

Biological source: The biological source of roselle is the dried calyces (sepals) of the plant *Hibiscus sabdariffa*. The plant is commonly used for its potential health benefits, including in teas and as a natural food colorant.

Family: *Malvaceae*

Geographical source: Roselle (*Hibiscus sabdariffa* L.), originally from West Africa, is now widely cultivated in regions across Africa, Asia, the Americas, Oceania, and the United States, showcasing its adaptability to various climates and soils [37].

Macroscopic features:

Table 4: Macroscopic features of roselle

Characteristics	Description
Colour	Calyces: deep crimson red
Size	Calyces ~ 3-3.5 cm
Shape	Stout, bulging
Taste	Cranberry-like, slightly acidic

Microscopic features:

Table 5: Microscopic features of roselle [38]

Features	Description
Calcium oxalate crystals	Raphides, druses, prisms
Vascular bundles	Xylem and phloem
Pigment localization	Anthocyanins found in vacuoles
Starch granules	Spherical structures composed of amylose and amylopectin

Phyto-constituents:

The nutritional content of roselle varies by part: calyces provide 2g protein, 10.2g carbohydrates, 17mg Vitamin C, and 150mg calcium per 100g; seeds offer 28.9g protein, 25.5g carbohydrates, 21.4g fat, and 350mg calcium; leaves contain 3.5g protein, 8.7g carbohydrates, 1000 IU Vitamin A, and 240mg calcium. Each part offers unique health benefits.

Extraction process:

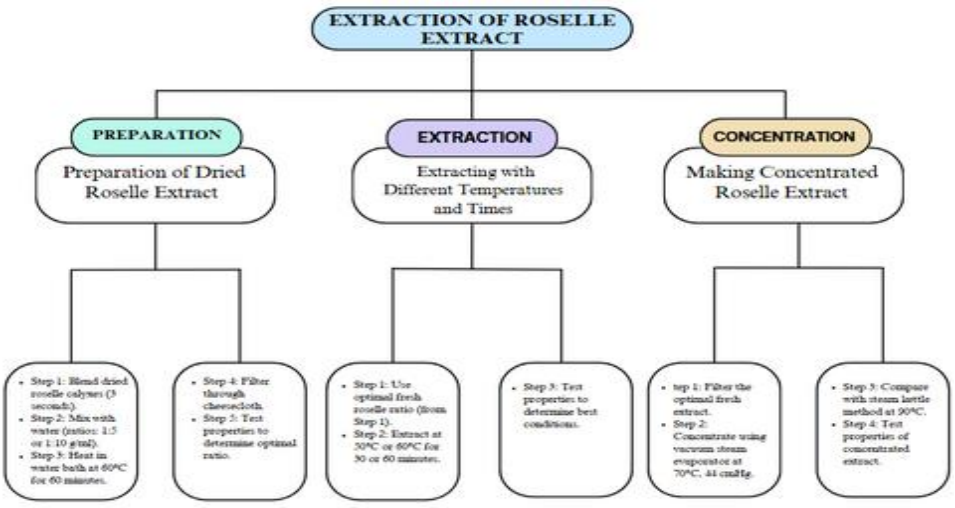


Fig. 12: Extraction of roselle extract [39]

Identification tests:

1. Protein Content: The Kjeldahl method is used to determine protein content by measuring nitrogen levels in the sample. A conversion factor of 5.7 is applied to estimate total protein.
2. Total and Reducing Sugars: The Luff-Schoorl method quantifies sugars based on their ability to reduce cupric ions in an alkaline solution, followed by titration for accurate measurement.
3. Anthocyanin Content: The pH differential method measures anthocyanins by recording absorbance at pH 1.0 and 4.5, with results expressed as delphinidin 3-O-xylosylglucoside equivalents.
4. Ascorbic Acid: High-Performance Liquid Chromatography (HPLC) with an RP18e column and UV detection at 254 nm is used for ascorbic acid analysis, employing an external standard for calibration. All tests are performed in triplicate for accuracy and reliability.

Natural Skin Care: Rich in antioxidants, roselle extracts are used in skincare for anti-aging, pigmentation in blush, and skin protection.

Hair Care: Found in hair products to enhance health and shine [40]

References:

1. Schneider, G., Gohla, S., Schreiber, J., Kaden, W., Schönrock, U., Schmidt-Lewerkühne, H., ... & Diembeck, W. (2000). Skin cosmetics. *Ullmann's Encyclopedia of Industrial Chemistry*. https://doi.org/10.1002/14356007.a24_219
2. Fitriana, R. (2023). Penetapan Kadar Antosianin Dan Formulasi Sediaan Blush On Compact Powder Ekstrak Beras Merah (Oryza Rufipogon Griff.). *Jurnal Medika Nusantara*, *1*(4), 296-314.https://doi.org/10.59680/medika.v1i4.630
3. Bushra S.Sayyed, Rajeshwari B.Tungar, & Laxmi S.Sarode. (2024). Formulation and evaluation of blush preparation by using natural coloring from red beetroot powder. International Journal of Advance Research And Innovative Ideas In Education, 10(3), 2949-2958.
4. S.S, S., M.P, S. C., & G.R, P. (2022). An over view on blushing Powder. In Sree Krishna College of Pharmacy and Research Centre, Sree Krishna College of Pharmacy and Research Centre, & Sree Krishna College of Pharmacy and Research Centre, *International Journal of Pharmaceutical Research and Applications* (Vol. 7, Issue 2, pp. 1176–1182). https://doi.org/10.35629/7781-070211761182
5. Formulation and evaluation of powder blush prepared using hibiscus petal extract. (2023). In *International Journal of Innovative Research in Technology* (Vols. 9–9, Issue 12, pp. 1381–1383). https://ijirt.org/publishedpaper/IJIRT160190_PAPER.pdf
6. Hitesh V. Shahare, Nayana S. Baste, Gayatri Y. Dane, Aditi N. Vyavahare, Mitul M. Mehta, & Nikhil B. Jagtap. (2023). Formulation and Development of Compact Powdered Blush by Using Natural Colour from Flowers of Butea Monosperma. *Journal for ReAttach Therapy and Developmental Diversities*, *6*(6s), 1059–1062. https://doi.org/10.53555/jrtdd.v6i6s.3264

7. J.B, A., Chandran, S., & G.R, P. (2022). An overview on loose blush powder. In Sree Krishna College of Pharmacy and Research Centre, Sree Krishna College of Pharmacy and Research Centre, & Sree Krishna College of Pharmacy and Research Centre, *International Journal of Pharmaceutical Research and Applications* (Vol. 7, Issue 2, pp. 1036–1042). https://doi.org/10.35629/7781-070210361042
8. Butler H, Purchers perfumes, cosmetics and soaps 2000 10th edition springer, Netherlands.
9. Yaliana A, Nurdianti L, Fitriani F and Amins; Formulasi dan evaluation cosmetics dekaratifperana dengan menggunation lesitin sehagai pelembab kulit Fitoformoka journal llmian farmais 2020; 10(1): 1-11.
10. De Los Ángeles Mosquera Tayupanta, T., Espadero, M., Mancheno, M., Peña, S., Uguña, A., Álvarez, S., & Vega, M. A. (2018). Sensory analysis of cosmetic formulations made with essential oils of Aristeguietia glutinosa (matico) and Ocotea quixos (ishpingo). *International Journal of Phytocosmetics and Natural Ingredients*, *5*(1), 5. https://doi.org/10.15171/ijpni.2018.05
11. De Los Ángeles Mosquera Tayupanta, T., Espadero, M., Mancheno, M., Peña, S., Uguña, A., Álvarez, S., & Vega, M. A. (2018). Sensory analysis of cosmetic formulations made with essential oils of Aristeguietia glutinosa (matico) and Ocotea quixos (ishpingo). *International Journal of Phytocosmetics and Natural Ingredients*, *5*(1), 5. https://doi.org/10.15171/ijpni.2018.05
12. Brito, S., Baek, M., & Bin, B. (2024). Skin structure, physiology, and pathology in topical and transdermal drug delivery. *Pharmaceutics*, *16*(11), 1403. https://doi.org/10.3390/pharmaceutics16111403
13. McGrath, J. A., & Uitto, J. (2024). Structure and Function of the Skin. *Wiley*, 1–50. https://doi.org/10.1002/9781119709268.rook002
14. Lopez-Ojeda, W., Pandey, A., Alhajj, M., & Oakley, A. M. (2022, October 17). *Anatomy, skin (Integument)*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK441980/
15. Monteiro-Riviere, N. (2005). Structure and function of skin. In *CRC Press eBooks* (pp. 1–19). https://doi.org/10.1201/9780203020821.ch1
16. Lotfollahi, Z. (2024). The anatomy, physiology and function of all skin layers and the impact of ageing on the skin. *Wound Practice and Research*, *32*(1). https://doi.org/10.33235/wpr.32.1.6-10
17. Yousef, H., Alhajj, M., Fakoya, A. O., & Sharma, S. (2024, June 8). *Anatomy, skin (Integument), epidermis*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK470464/
18. Montagna, W. (2012). *The structure and function of the skin*. Elsevier.

19. Lodén, M. (1995). Biophysical properties of dry atopic and normal skin with special reference to effects of skin care products. *Acta Dermato Venereologica*, *75*, 1–48. https://doi.org/10.2340/00015555192148
20. Mohiuddin, A. K. & Dr. M. Nasirullah Memorial Trust. (2019). An extensive review of face powders: Functional uses and formulations. In *International Journal of Pharmacy and Pharmaceutical Science* (Vol. 1, Issue 1, pp. 01–12)
21. Baumann, L. (2008). Understanding and treating various skin types: The Baumann Skin Type Indicator. *Dermatologic Clinics*, *26*(3), 359–373. https://doi.org/10.1016/j.det.2008.03.007
22. Segot-Chicq, E., Compan-Zaouati, D., Wolkenstein, P., Consoli, S., Rodary, C., Delvigne, V., Guillou, V., & Poli, F. (2007). Development and validation of a questionnaire to evaluate how a cosmetic product for oily skin is able to improve well-being in women. *Journal of the European Academy of Dermatology and Venereology*, *21*(9), 1181–1186. https://doi.org/10.1111/j.1468-3083.2007.02193.x
23. Proksch, E., Berardesca, E., Misery, L., Engblom, J., & Bouwstra, J. (2019). Dry skin management: practical approach in light of latest research on skin structure and function. *Journal of Dermatological Treatment*, *31*(7), 716–722. https://doi.org/10.1080/09546634.2019.1607024
24. Hahnel, E., Blume-Peytavi, U., & Kottner, J. (2019). Associations of dry skin, skin care habits, well-being, sleep quality and itch in nursing home residents: Results of a multicentre, observational, cross-sectional study. *Nursing Open*, *6*(4), 1501–1509. https://doi.org/10.1002/nop2.351
25. Youn, S. W., Na, J. I., Choi, S. Y., Huh, C. H., & Park, K. C. (2005). Regional and seasonal variations in facial sebum secretions: a proposal for the definition of combination skin type. *Skin Research and Technology*, *11*(3), 189–195. https://doi.org/10.1111/j.1600-0846.2005.00119.x
26. Parraga, S. P., Duong, J. Q., Shanmugam, S., Moran, S. K., Taylor, S. L., & Feldman, S. R. (2024). Skin type classifications: does the perfect assessment exist? *Journal of Dermatological Treatment*, *35*(1). https://doi.org/10.1080/09546634.2024.2427325
27. Berardesca, E., Farage, M., & Maibach, H. (2012). Sensitive skin: an overview. *International Journal of Cosmetic Science*, *35*(1), 2–8. https://doi.org/10.1111/j.1468-2494.2012.00754.x
28. Manav, V., & Karaali, M. G. (2023). Skin Care and Colour Cosmetics in Patients with Sensitive Skin. *Clinical and Experimental Health Sciences*, *13*(3), 485–490. https://doi.org/10.33808/clinexphealthsci.1011049
29. Baumann, L. (2008b). Understanding and treating various skin types: The Baumann Skin Type Indicator. *Dermatologic Clinics*, *26*(3), 359–373. https://doi.org/10.1016/j.det.2008.03.007

30. Sari, S. W., Djamil, R., & Faizatun, F. (2021c). Formulation of Blush Preparations by Using Natural Coloring from Red Beetroot Extract (Beta vulgaris L.). *Indonesian Journal of Chemistry*, *21*(4), 860. https://doi.org/10.22146/ijc.60414
31. McGrath, J. M., & Panella, L. (2018). Sugar beet breeding. *Plant Breeding Reviews*, 167–218. https://doi.org/10.1002/9781119521358.ch5
32. Lange, W., Brandenburg, W. A., & De Bock, T. S. M. (1999). Taxonomy and cultonomy of beet (Beta vulgaris L.). *Botanical Journal of the Linnean Society*, *130*(1), 81–96. https://doi.org/10.1111/j.1095-8339.1999.tb00785.x
33. Statistics Canada, table 32-10-0359-01. Estimated areas, yield, production, average farm price, and total farm value of principal field crops in metric and imperial units, Statistics Canada. [2022.]
34. Qamer, F., & Noor, K. (2024). Phytochemical evaluation and antibacterial assessment of beetroots (Beta vulgaris): Efficacy of ethanol extracts against gram-positive and gram-negative bacteria. *Journal of Pharmacognosy and Phytochemistry*, *13*(6), 403–408. https://doi.org/10.22271/phyto.2024.v13.i6e.15209
35. Shevante, T. B., Khathuriya, R., & Jadhav, S. L. (2024). Qualitative analysis of root of Beta vulgaris L. International Journal of Creative Research Thoughts (IJCRT), 12(2). ISSN: 2320-2882.
36. Sahani, V., Lalhminghlui, & Patil, S. (2023). A brief study on beetroot: A review. I International Journal of Novel Research and Development (IJNRD).
37. Wong, P., Yusof, S., Ghazali, H., & Man, Y. C. (2002). Physico-chemical characteristics of roselle (Hibiscus sabdariffa L.). *Nutrition & Food Science*, *32*(2), 68–73. https://doi.org/10.1108/00346650210416994
38. Khoswanto, N. C., Rahman, N. F. J., & Setiabudi, N. H. (2023). The effect of roselle (Hibiscus sabdariffa l.) flower petal extract on smear layer removal of crown dentin. *World Journal of Advanced Research and Reviews*, *20*(1), 1106–1113. https://doi.org/10.30574/wjarr.2023.20.1.2184
39. Kane, A., Achir, N., Cisse, M., Pallet, D., Sakho, M., & Dornier, M. (2018). Identification of roselle varieties through simple discriminating physicochemical characteristics using multivariate analysis. *Food Science and Technology*, *39*(2), 321–327. https://doi.org/10.1590/1678-457x.29417
40. Shruthi, V. H., & Ramachandra, C. T. (2019). Roselle (Hibiscus sabdariffa L.) calyces: A potential source of natural color and its health benefits. In *Food Bioactives* (1st ed.)

ENHANCING BEAUTY NATURALLY: BLUSH COSMETICS WITH NATURAL INGREDIENTS
PART 2: NATURAL PIGMENTS IN BLUSH COSMETICS

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Abstract:

Blush formulations are evolving with natural ingredients as consumers seek safer, eco-friendly alternatives to synthetic colorants. This chapter explores botanical sources like *Hibiscus rosa-sinensis*, which provides a deep red hue and antioxidant benefits, and dragon fruit peel (*Hylocereus spp.*), rich in betacyanins for vibrant pigmentation and free radical protection. Rose petals (*Rosa spp.*) contribute anthocyanins and carotenoids for soft pink tones, hydration, and antibacterial effects, while strawberries (*Fragaria* × *ananassa*) offer anthocyanins and vitamin C for pigmentation, anti-aging, and brightening. Other botanicals like beetroot and roselle enhance color and skincare benefits, promoting sustainable, multifunctional cosmetics. This study highlights their potential, emphasizing the need for further research on stability and formulation.

Keywords: *Hibiscus rosa-sinensis*, Anthocyanins, Natural Pigments, Antioxidants, Skincare, Sustainable Cosmetics

1. List of natural ingredients used in blushes as colouring agents

1.1. Hibiscus rosa-sinesis

Hibiscus (*Hibiscus rosa-sinensis*) is valued in cosmetics for its red pigmentation from anthocyanins, providing a rich hue in blushes and other products. It also offers skin-nourishing benefits, making it a multifunctional ingredient [1].

Fig. 1: Hibiscus

Synonyms: *Hibiscus liliflorus, Hibiscus fragilis, Hibiscus boryanus, Hibiscus arnottianus, Hibiscus kokio, Hibiscus storckii, Hibiscus denisonii* [2].

Biological source: Hibiscus is a perennial shrub with a tap root system and ovate or lanceolate leaves. It contains bioactive constituents such as glycosides, terpenoids, saponins, and flavonoids.

Family: *Malvaceae* [3]

Geographical source:

The plant is native to Tropical Asia, with specific origins disputed. It is believed to have originated from India, though some sources suggest alternative origins. The plant is widely distributed across: India (southwestern regions) Sri Lanka (tropical regions) Thailand South Africa Philippines Myanmar China, and Pakistan [4].

Macroscopic features:

Table 1: Macroscopic features of hibiscus [5]

Characteristic	Description
Colour	Bright red in wild type and variations including white, yellow, orange, and pink
Size	Approx. 20cm wide, with 5 whorled oval petals
Odour	Characteristic to odourless
Taste	Slightly sweet and mucilaginous

Microscopic features

Table 2: Microscopic features of hibiscus [6]

Features	Description
Calcium oxalate crystals	Rosette crystals
Stomata	Few anamocytic stomata
Pollen grains	Spherical, spinus yellow in color
Starch granules	Numerous, simple and compound

Phyto-constituents:

The quantitative phytochemical evaluation of *Hibiscus rosa-sinensis* flowers revealed several important constituents. Flavonoids were present at 0.171 mg/g, while total phenolics accounted for 0.092 mg/g, and tannins were measured at 0.073 mg/g. The flowers also contained carbohydrates (0.356 mg/g) and protein (0.247 mg/g), alongside essential vitamins such as thiamine (0.072 mg/g), niacin (0.075 mg/g), ascorbic acid (0.0339 mg/g), and riboflavin (0.087 mg/g). These findings highlight the diverse chemical composition of hibiscus, contributing to its potential health benefits [7].

Extraction process:

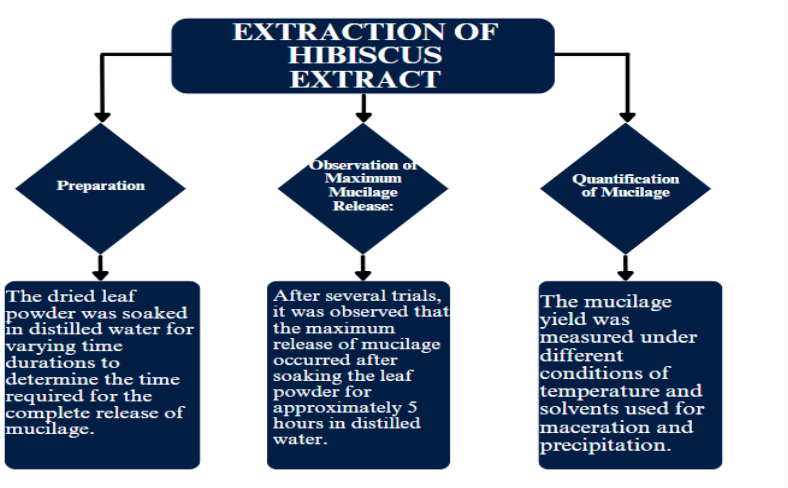


Fig. 2: Extraction process of hibiscus [8]

Identification tests:

1. Spectrophotometric Method: The pH differential method measures anthocyanins using buffer solutions (pH 1.0 and 4.5) and absorbance readings at 520 nm and 700 nm.

2. Chromatographic Techniques - TLC – Determines pigment Rf values. - HPLC – Provides precise separation and quantification.

3. Chemical Identification- Acid-Base Tests – Identify pigments through colour changes.- Phytochemical Screening – Detects bioactive compounds. These methods ensure accurate pigment and phytochemical analysis.[9].

Uses: Hibiscus rosa-sinensis extracts, especially from leaves and flowers, have shown strong UV-protective properties, with leaf extracts demonstrating the highest SPF (22.10), making them promising for natural sunscreen formulations. Their incorporation into cosmetics can help shield the skin from sun damage, reducing premature aging. Additionally, the vibrant flower pigments serve as a natural alternative to synthetic colorants in blushes and other cosmetics. With both medicinal and cosmetic benefits, Hibiscus rosa-sinensis also holds the potential for treating skin conditions, offering nourishment and protection [10].

1.2 Dragon fruit peel

Fig. 2: Dragon fruit

Dragon fruit (*Hylocereus spp.*), particularly the red-fleshed variety, is a natural source of betacyanins, which contribute to its intense pink-red coloration. These pigments make dragon

fruit an attractive option for natural blush formulations, offering a vibrant and skin-friendly alternative to artificial dyes. Its high antioxidant content also adds skincare benefits to cosmetic applications [11].

Synonyms: Pitaya Peel, Pitahaya Peel, Strawberry Pear Peel [12].

Biological source: It includes three main species: *Hylocereus undatus*, known as white-fleshed pitaya with red skin; *Hylocereus costaricensis*, which has red flesh and red skin; and *Hylocereus megalanthus*, referred to as yellow pitaya, featuring white flesh and yellow skin.

Family: *Cactaceae* [13]

Geographical source:

Dragon fruit, or pitaya, is native to Central America, particularly Mexico and Guatemala. It is now widely cultivated in various regions across the globe, including Southeast Asia, South America, and Australia. The key species within the *Hylocereus* genus that produce dragon fruit are:

- *Hylocereus undatus*: Mainly grown in Vietnam and other tropical areas.
- *Hylocereus costaricensis*: Primarily cultivated in Costa Rica and throughout Central America.
- *Hylocereus megalanthus*: Predominantly found in South American countries such as Peru, Colombia, and Ecuador [14].

Macroscopic features:

Table 3: Macroscopic features of dragon fruit [15]

Feature	**Description**
Colour	Thick, leathery skin with scales, red, deep red with white and yellow.
Odour	Floral, tropical
Size	~4-6 inches long
Taste	A combination of pear, kiwi, and citrucy

Microscopic features:

Table 4: Microscopic features of dragon fruit [16]

Feature	**Description**
Calcium oxalate crystals	Present as druse crystals
Vascular bundles	Granular forms are scattered throughout the peel.
Starch	Xylem and phloem
Stomata	Elliptical and scattered

Chemical constituents:

Betalains: It include betacyanins and betaxanthins, which give dragon fruit its distinct red and yellow colours. They are powerful antioxidants that enhance the fruit's health-promoting properties.

Flavonoids: Dragon fruit contains flavonoids such as quercetin, myricetin, and kaempferol, recognized for their antioxidant, anti-inflammatory, and anticancer effects.

Phenolic Compounds: The fruit is rich in phenolic acids like gallic acid, ferulic acid, and p-coumaric acid, which are known for their strong antioxidant activity.

Vitamin C: Dragon fruit is an excellent source of vitamin C, a nutrient that boosts immune function and acts as a potent antioxidant. Tannins: These natural compounds possess astringent qualities and contribute to the overall antioxidant effects of the fruit.

Tannins: These natural compounds have astringent properties and contribute to the fruit's antioxidant activity [17].

Extraction process:

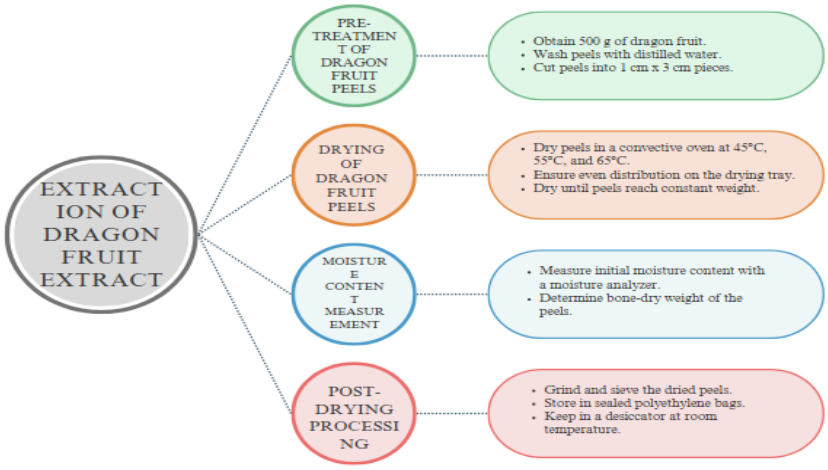


Fig. 4: Extraction of dragon fruit extract [18]

Identification tests:

1. Phytochemical Screening - A preliminary test to identify bioactive compounds in dragon fruit peel. - Detects alkaloids, flavonoids, saponins, tannins, steroids, and phenolic compounds.
2. Dragendorff's Test - Used to identify the presence of alkaloids in dragon fruit peel.
3. Ferric Chloride Test - Used to detect phenolic compounds in dragon fruit peel.
4. Foam Test - Used to identify saponins in dragon fruit peel.
5. Thin Layer Chromatography (TLC) - A technique to separate and identify chemical constituents of dragon fruit peel [19].

Uses: Dragon fruit peel extract has been successfully incorporated into blush-on compact powders, providing natural pigmentation, as shown in a study by Suena *et al.* (2023). While challenges in color stability and texture were noted, panelists favored the formulation for its shape, color, and fragrance. Rich in antioxidants, dragon fruit peel helps protect the skin from

free radicals, enhancing the skincare benefits of blush products. Its vibrant red pigment makes it a promising natural dye for decorative cosmetics, offering a non-toxic, sustainable, and eco-friendly alternative. [20].

1.3 Rose petals

Rose (*Rosa spp.*) is a well-known natural ingredient used in cosmetics for both its color and skincare properties. The petals contain natural pigments, primarily anthocyanins and carotenoids, that impart a soft pink hue, making them ideal for blush formulations. Additionally, rose extract is valued for its soothing and hydrating effects on the skin [21].

Fig. 5: Rose

Synonyms: *Rosa damascene, Rosa gallica, Rosa rugosa* [22]

Biological source: *Rosa damascena*, or the Damask rose, is renowned for its strong fragrance and is widely used in blushes, perfumes, and essential oils. *Rosa centifolia*, known as the cabbage or Provence rose, is highly fragrant and a key source of rose oil. *Rosa gallica*, often called the French rose, holds historical significance and has been used medicinally. *Rosa rugosa*, or the Japanese rose, is prized for its resilience and ability to thrive in diverse climates.

Family: *Rosaceae* [23]

Geographical source: The Damask rose, or Rosa damascena, is thought to have originated in the Middle East, more precisely in the area surrounding Syria. However, genetic research indicates that it originated in Iran or the foothills of central Asia [24].

Macroscopic features:

Table 5: Macroscopic features of rose [25]

Characteristic	**Description**
Colour	Red, pink, yellow, white.
Odour	Sweet, rich aroma.
Size	2.5-3 inches in diameter.
Taste	Sweet and slightly perfumed.

Microscopic features:

Table 6: Microscopic features of rose [26]

Feature	Description
Calcium oxalate crystals	Raphides
Vascular bundles	Xylem and phloem tissues
Starch	Starch is stored in rose petals and can be detected using iodine staining.
Stomata	Elliptical-shaped pores are scattered on the petal surface.

Phyto-constituents:

Anthocyanins and carotenoids are the main pigments responsible for the vivid colours of rose petals. The vast array of colours seen in roses is caused by these chemical components.

The colour intensity and hue of roses are also influenced by co-pigmentation interactions. This phenomenon involves colourless compounds, often flavonoids, that bind to anthocyanins, stabilizing them and enhancing their colour expression.

Geraniol: A monoterpenoid alcohol, that contributes to the sweet and floral aroma.

Nerol: Like geraniol, it provides a fresh, rose-like scent.

Citronellol: Adds a sweet, citrusy note to the fragrance profile [27].

Extraction process:

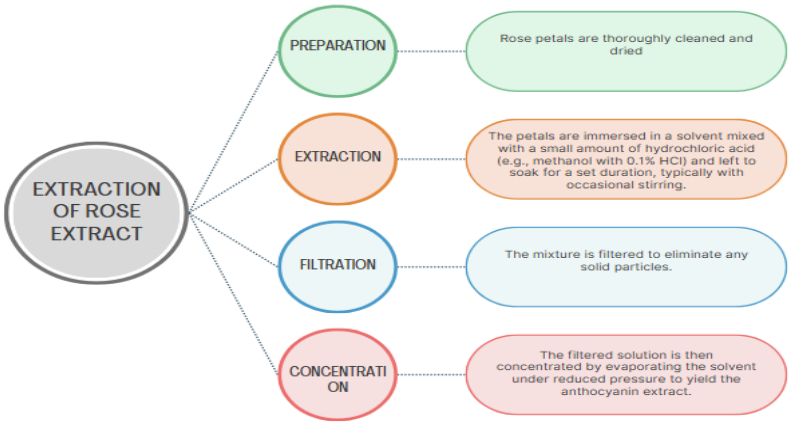


Fig. 6: Extraction of rose extract [28]

Identification tests: Mayer's test detects alkaloids by forming a creamy precipitate, while Wagner's test produces a brownish precipitate upon reaction. Hager's test confirms alkaloids through yellow precipitate formation with picric acid, and Marme's test yields white or yellow precipitates when alkaloids react with Marme's reagent [29].

Uses: Rose extract naturally enhances blush formulas with a soft pink tint, eliminating the need for artificial coloring. Rich in antioxidants, it protects the skin from free radicals, promoting a youthful glow. Additionally, its antibacterial properties, attributed to flavonoids and phenolics,

help combat harmful bacteria like *Vibrio cholerae*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus* [30].

1.4 Strawberry

Strawberry (*Fragaria* × *ananassa*) is a rich source of natural red pigments, particularly anthocyanins, contributing to its vibrant colour. These pigments make strawberries a desirable natural alternative for blush formulations. Moreover, strawberries provide antioxidant and vitamin C benefits, enhancing the skin's overall health while adding a natural rosy tint to cosmetic products [31].

Fig. 7: Strawberry

Synonyms: Earthberry, Garden strawberry, Red berry, Fragaria [32].

Biological source: *Fragaria* × *ananassa*, the garden strawberry, is the most widely cultivated species, originating in Europe in the 18th century. *Fragaria chiloensis* is native to Chile and parts of western South America, while *Fragaria vesca*, known as the woodland or wild strawberry, grows across Europe, Asia, and North America.

Family: *Rosaceae* [33]

Geographical source: *Fragaria* × *ananassa*, or the garden strawberry, was first bred in Brittany, France, in the 1750s and is now cultivated worldwide, especially in temperate regions. *Fragaria chiloensis*, the Chilean strawberry, is native to the western coast of South America, particularly Chile. *Fragaria vesca*, the wild strawberry, thrives in the temperate regions of Europe, Asia, and North America.[34].

Macroscopic features:

Table 7: Macroscopic features of strawberry [35]

Characteristic	**Description**
Colour	Bright red when ripe due to anthocyanins.
Odour	Sweet, green, fruity, and buttery.
Size	Approx. 2-5 cm in length.
Taste	Sweet and slightly acidic.

Microscopic features:

Table 8: Microscopic features of strawberry [36]

Feature	Description
Vascular bundles	Xylem & Phloem.
Epidermal cells	Stomata on the abaxial side.
Pigment localization	Anthocyanins in vacuoles.
Genetic composition	Octoploid

Phyto-constituents: *Fragaria* × *ananassa* (strawberry) contains bioactive compounds such as carotenoids, vitamin C, phenolics, and flavonoids. Key phenolics include anthocyanins (cyanidin glucoside, pelargonidin glucoside, pelargonidin rutinoside), ellagic acid derivatives (ellagitannins, agrimoniin, lambertianin), and flavonols (quercetin hexuronide, kaempferol glucoside, kaempferol malonyl hexoside). Pelargonidin-3-glucoside is the dominant anthocyanin, varying across varieties. Ellagitannins, formed from ellagic acid and hexahydroxydiphenic acid, play a crucial medicinal role. Other compounds, including methyl-EA-pentose conjugates and flavonols like kaempferol and quercetin, contribute to strawberries' antioxidant and health benefits [37].

Extraction process:

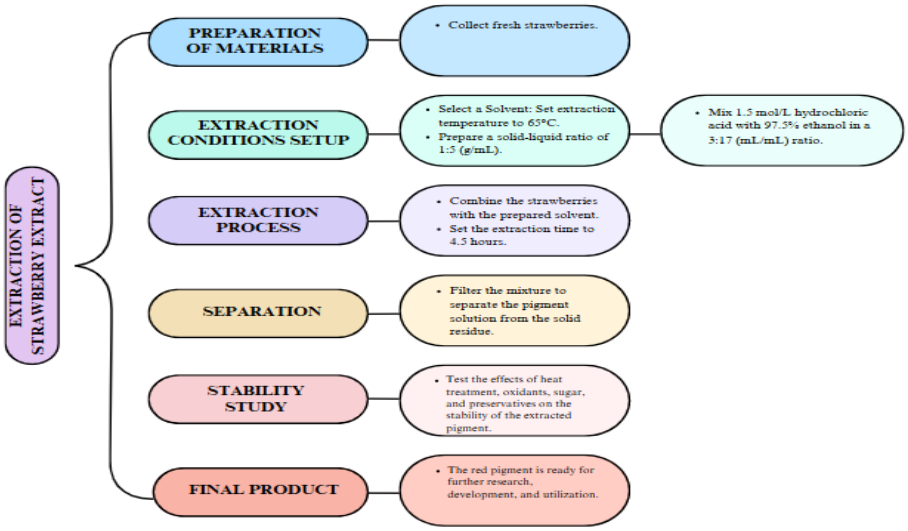


Fig. 8: Extraction process of strawberry extract [38]

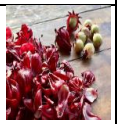
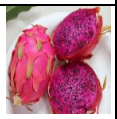
Identification tests:

HPLC is commonly used to identify and quantify phenolic compounds, flavonoids, and other bioactives in strawberries with high resolution and sensitivity. GC-MS analyzes volatile compounds like esters, aldehydes, ketones, and terpenes, helping determine aroma and flavor profiles. LC-MS provides detailed insights into sugars, organic acids, and metabolites, offering a comprehensive chemical composition analysis of strawberries [39].

Uses:

Strawberries offer anti-aging benefits by combating free radicals with vitamin C, promoting a youthful glow. Their high vitamin C content also provides natural photoprotection against UV damage. With a high-water content, they help keep the skin hydrated and prevent dryness. Additionally, their enzymes and antioxidants brighten the skin, reducing dark spots, hyperpigmentation, and uneven tone [40].

Table 9: Table for the list of natural ingredients used in blushes as colouring agents

Sr.no	Botanical name	Image	Common name	Family	Part used	Chemical constituents	Uses
1.	*Beta vulgaris L.*		Beetroot	Amaranthaceae	Root	Betalains, Vitamin C, Calcium, Iron, Magnesium.	Natural colorant in blushes, antioxidant, antimicrobial
2.	*Hibiscus sabdariffa*		Roselle	Malvaceae	Sepals	Vitamin A, Thiamine, Riboflavin, Niacin, Vitamin C	Natural blush in cosmetics, anti-aging, haircare
3.	*Hibiscus rosa-sinesis*		Hibiscus	Malvaceae	Flower	Flavonoids, Thiamine, Ascorbic Acid, Riboflavin	Sunscreen, blushes, skincare
4.	*Hylocereus spp.*		Dragon fruit	Cactaceae	Fruit	Betalains, Flavonoids, Vitamin C, Tannins	Antioxidant, dye, blushes
5.	*Rosa spp.*		Rose	Rosaceae	Flower	Anthocyanins, Carotenoids**,** Citronellol, Geraniol	Pigment, antioxidant, antibacterial
6.	*Fragaria × ananassa*		Strawberry	Rosaceae	Fruit	Carotenoids, Vitamin C, Phenolic compounds, and Flavonoids	Anti-aging, photoprotection, hydration, anti-pigmentation

Conclusion:

The growing demand for natural and eco-friendly cosmetics has paved the way for plant-derived blush formulations that offer both aesthetic and skincare benefits. The use of natural colouring agents such as beetroot, hibiscus, roselle, dragon fruit, rose, and strawberry provides an effective alternative to synthetic dyes, ensuring safer and more skin-compatible products. Understanding the structure and function of the skin, along with its different types, is crucial in formulating blush cosmetics that cater to diverse consumer needs. The analysis of these natural ingredients, their extraction methods, and identification tests further underscore their significance in cosmetic science. This review reinforces the potential of natural blush cosmetics in achieving sustainable beauty solutions, encouraging further research and innovation in the field. By integrating nature with modern cosmetic technology, the industry can move towards a future that prioritizes both beauty and wellness.

References:

1. Govindarajan, N., Sundharamoorthy, S., Kannan, N., & Raju, I. (2019). Macro-Microscopic Identification of Dried Flowers of Hibiscus rosa-sinensis L. and its Differentiation from Adulterant Rhododendron arboreum Sm. *Pharmacognosy Journal*, *11*(3), 613–616. https://doi.org/10.5530/pj.2019.11.98
2. Khan, I. M., Rahman, R., Mushtaq, A., & Rezgui, M. (2017) *Hibiscus rosa-sinensis L. (Malvaceae): Distribution, chemistry and uses*. *International Journal of Chemical and Biochemical Sciences*. ISSN 2226-9614
3. Carvajal-Zarrabal, O., Barradas-Dermitz, D. M., Orta-Flores, Z., Hayward-Jones, P. M., Nolasco-Hipólito, C., Aguilar-Uscanga, M. G., Miranda-Medina, A., & Bujang, K. B. (2012). Hibiscus sabdariffa L., roselle calyx, from ethnobotany to pharmacology. *Journal of Experimental Pharmacology*, 25. https://doi.org/10.2147/jep.s27974
4. Vasudeva, N., & Sharma, S. K. (2008). Biologically Active Compounds from the GenusHibiscus. *Pharmaceutical Biology*, *46*(3), 145–153. https://doi.org/10.1080/13880200701575320
5. Esmail Al-Snafi, A. (2018). Chemical constituents, pharmacological effects and therapeutic importance of Hibiscus rosa-sinensis- A review. *IOSR Journal of Pharmacy*, *8*(7), 101–119.
6. Vignesh, R. M., & Nair, B. R. (2018). Extraction and characterization of mucilage from the leaves of *Hibiscus rosa-sinensis* Linn. (Malvaceae). *International Journal of Pharmaceutical Sciences and Research*, *9*(7), 2883-2890.
7. R, S. R., M, V., S, K., G, A. S., Sp, T., & K, G. (2022). Standardisation of anthocyanin extraction techniques from hibiscus (Hibiscus rosa-sinensis) petals for biocolour utilisation. *The Pharma Innovation*, *11*(8), 303–309. https://doi.org/10.22271/tpi.2022.v11.i8d.14647

8. Radhakrishnan, B. N., Narayanan, R., Dharmar, B., R, P. D., & C, V. (2022). Optimization of extraction conditions for anthocyanin from Hibiscus rosasinensis and its characterisation by Chromatography techniques. *The Journal of Phytopharmacology*, *11*(2), 128–132. https://doi.org/10.31254/phyto.2022.11214
9. Sağlam, A., Özüsağlam, M. A., & ÇeliK, İ. (2023). Determination of Sun Protection Potential of Hibiscus rosa-sinensis as Natural Additive for Cosmetic Industry. *Bulletin of Biotechnology*, *4*(1), 13–16. https://doi.org/10.51539/biotech.1215927
10. Zulkurnain, E. I., Ramli, S., Ali, A. A., James, R. J., Kamarazaman, I. S., & Halim, H. (2023). The Phytochemical and Pharmacological Effects of Hibiscus rosa-sinensis: A Review. *International Journal of Pharmaceutical Investigation*, *13*(3), 422–431. https://doi.org/10.5530/ijpi.13.3.053
11. Gupta, A., Singh, R., & Mishra, P. (2023). An eye-catching and comprehensive review on dragon fruit (an exotic super fruit). *Phytopharmaceuticals*, *12*(6), 243-251. https://doi.org/10.22271/phyto.2023.v12.i6c.14790
12. Akhil, N. K., Prahadeeswaran, M., Shivakumar, K. M., Sivakumar, V., & Selvi, R. G. (2024). Exploring the dynamics of dragon fruit production and its constraints in southern states of India4. *Plant Science Today*, *11*(sp4), 01-06 https://doi.org/10.14719/pst.5592
13. Karunakaran, G., Arivalagan, M., & Sriram, S. (2022). Dragon fruit country report from India1. *Indian Council of Agricultural Research*
14. Ahmed, Y., Jamil, S., Hashimi, A., Siraj, M. B., & Jahangir, U. (2019). Rosa Damascene Mill. (Rose): A versatile herb in cosmetology. *TANG [HUMANITAS MEDICINE]*, *9*(4), 2. https://doi.org/10.5667/tang.2019.0017
15. Chandana, J., Kumar, G. A., & Vaishnavi, B. (2024). A review on antioxidant activity of Rosa Damascena. *International Journal of Research and Review*, *11*(3), 156–162. https://doi.org/10.52403/ijrr.20240321
16. Younis, A., Khan, M. A., Khan, A., Riaz, A., & Pervez, M. A. (2007). *Effect of Different Extraction Methods on Yield and Quality of Essential Oil from Four Rosa Species*.
17. Demir, N., Yildiz, O., Alpaslan, M., & Hayaloglu, A. (2014). Evaluation of volatiles, phenolic compounds and antioxidant activities of rose hip (Rosa L.) fruits in Turkey. *LWT*, *57*(1), 126–133. https://doi.org/10.1016/j.lwt.2013.12.038
18. Verma, R. S., Padalia, R. C., Chauhan, A., Singh, A., & Yadav, A. K. (2011). Volatile constituents of essential oil and rose water of damask rose (Rosa damascenaMill.) cultivars from North Indian hills. *Natural Product Research*, *25*(17), 1577–1584. https://doi.org/10.1080/14786419.2010.520162
19. Dubois, C., Plainfossé, H., Delcroix, M., Trinel, M., Verger-Dubois, G., Azoulay, S., Burger, P., & Fernandez, X. (2022). Anti-Aging Potential of a Rosa centifolia Stem Extract

with Focus on Phytochemical Composition by Bioguided Fractionation. *Chemistry & Biodiversity*, *19*(7). https://doi.org/10.1002/cbdv.202200158

20. Gudin, S. (1999). Rose: Genetics and Breeding. *Plant Breeding Reviews*, 159–189. https://doi.org/10.1002/9780470650134.ch3
21. Zang, F., Ma, Y., Wu, Q., Tu, X., Xie, X., Huang, P., Tong, B., Zheng, Y., & Zang, D. (2023). Resequencing of Rosa rugosa accessions revealed the history of population dynamics, breed origin, and domestication pathways. *BMC Plant Biology*, *23*(1). https://doi.org/10.1186/s12870-023-04244-5
22. Shin, H., Lieth, J., & Kim, S. (2001). EFFECTS OF TEMPERATURE ON LEAF AREA AND FLOWER SIZE IN ROSE. *Acta Horticulturae*, *547*, 185–191. https://doi.org/10.17660/actahortic.2001.547.22
23. Saati, E. A., Ramadhan, A. H., Lutfi, M., Wahyudi, V. A., & Manshur, H. A. (2020). Utilization of rose flower extract as an antioxidant-rich drink. *IOP Conference Series Earth and Environmental Science*, *458*(1), 012035. https://doi.org/10.1088/1755-1315/458/1/012035
24. Matsushima, U., Hilger, A., Graf, W., Zabler, S., Manke, I., Dawson, M., Choinka, G., & Herppich, W. B. (2012). Calcium oxalate crystal distribution in rose peduncles: Non-invasive analysis by synchrotron X-ray micro-tomography. *Postharvest Biology and Technology*, *72*, 27–34. https://doi.org/10.1016/j.postharvbio.2012.04.013
25. Cavallini-Speisser, Q., Morel, P., & Monniaux, M. (2021). Petal cellular identities. *Frontiers in Plant Science*, *12*. https://doi.org/10.3389/fpls.2021.745507
26. Gonzáles, C. B. a. M. N. (1989). A simple test for starch in rose petals. *Advances in Horticultural Science*, *3*(1), 24–28. https://www.jstor.org/stable/42883028
27. Younis, A., Riaz, A., Khan, M., Khan, A., & Pervez, M. (2008). EXTRACTION AND IDENTIFICATION OF CHEMICAL CONSTITUENTS OF THE ESSENTIAL OIL OF ROSA SPECIES. *Acta Horticulturae*, *766*, 485–492. https://doi.org/10.17660/actahortic.2008.766.65
28. Saati, Pusparini, Wachid, Winarsih, E., AD, M, S. (2018). The anthocyanin pigment extract from the red rose is an antibacterial agent. *Malaysian Journal of Fundamental and Applied Sciences*, 184–187.
29. Baydar, N. G., & Baydar, H. (2012). Phenolic compounds, antiradical activity and antioxidant capacity of oil-bearing rose (Rosa damascena Mill.) extracts. *Industrial Crops and Products*, *41*, 375–380. https://doi.org/10.1016/j.indcrop.2012.04.045
30. Shohayeb, Abdel-Hameed, Bazaid, Maghrabi, M., ES, SA, I. (2014). Antibacterial and antifungal activity of Rosa Damascena MILL. Essential oil, different extracts of rose petals. *Global Journal of Pharmacology*, *Volume 8*.

31. Warner, R., Wu, B., MacPherson, S., & Lefsrud, M. (2021). A review of strawberry photobiology and fruit flavonoids in controlled environments. *Frontiers in Plant Science*, *12*. https://doi.org/10.3389/fpls.2021.611893
32. Zurn, J. D., Hummer, K. E., & Bassil, N. V. (2022). Exploring the diversity and genetic structure of the U.S. National Cultivated Strawberry Collection. *Horticulture Research*, *9*. https://doi.org/10.1093/hr/uhac125
33. Prasad, R., Lisiecka, J., & Raj, K. (2022). Strawberry– More than a Popular Summer Fruit: A Mini-Review. *Advances in Nutrition and Food Science*, *2022*(02). https://doi.org/10.37722/anafs.2022201
34. Bhangotra, B., Sadawati, R. K., & Sourav. (2020). A review on characterisation and evaluation of strawberry germplasm for growth, yield, and quality traits under controlled environmental and open field conditions. *International Journal of Chemical Studies*, *8*(6), 2746–2749. https://doi.org/10.22271/chemi.2020.v8.i6am.11199
35. Kumari, Kumar Sharma, Kumar, S., S, A. (2019). Molecular characterization of different strawberry (Fragaria x ananassa duch.) cultivars growing under mid hill conditions of Himachal Pradesh. *International Journal of Agriculture, Environment and Biotechnology*, *4*(12).
36. Milosavljević, D., Maksimović, V., Milivojević, J., Djekić, I., Wolf, B., Zuber, J., Vogt, C., & Maksimović, J. D. (2023). Sugars and organic acids in 25 strawberry cultivars: Qualitative and Quantitative evaluation. *Plants*, *12*(12), 2238. https://doi.org/10.3390/plants12122238
37. Rapuru, R., Bathula, S., & Kaliappan, I. (2022). Phytochemical constituents and pharmacological activities of strawberry. In *IntechOpen eBooks*. https://doi.org/10.5772/intechopen.103973
38. Taghavi, T., Patel, H., & Rafie, R. (2023). Extraction solvents affect anthocyanin yield, color, and profile of strawberries. *Plants*, *12*(9), 1833. https://doi.org/10.3390/plants12091833
39. Gasparrini, M., Forbes-Hernandez, T. Y., Afrin, S., Alvarez-Suarez, J. M., Gonzàlez-Paramàs, A. M., Santos-Buelga, C., Bompadre, S., Quiles, J. L., Mezzetti, B., & Giampieri, F. (2015). A pilot study of the photoprotective effects of Strawberry-Based cosmetic formulations on human dermal fibroblasts. *International Journal of Molecular Sciences*, *16*(8), 17870–17884. https://doi.org/10.3390/ijms160817870
40. Gasparrini, M., Forbes-Hernandez, T., Afrin, S., Reboredo-Rodriguez, P., Cianciosi, D., Mezzetti, B., Quiles, J., Bompadre, S., Battino, M., & Giampieri, F. (2017). Strawberry-Based Cosmetic Formulations Protect Human Dermal Fibroblasts against UVA-Induced Damage. *Nutrients*, *9*(6), 605. https://doi.org/10.3390/nu9060605

ANCIENT REMEDIES, MODERN HOPE: THE ROLE OF TRADITIONAL MEDICINE IN CANCER TREATMENT

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Abstract:

Non-Communicable Diseases (NCDs), especially cancer, have become leading contributors to global mortality, outpacing infectious diseases in many areas. Cancer is defined by the uncontrolled growth of cells, resulting in the formation of tumors, invasion of surrounding tissues, and metastasis. Major risk factors include DNA mutations from environmental exposures such as tobacco, asbestos, ionizing radiation, and hormonal imbalances, as well as lifestyle factors like poor diet, lack of physical activity, and obesity. Despite advancements in treatment, cancer continues to be a significant health threat worldwide, with rising incidence and death rates. Consequently, there is increasing interest in complementary and alternative therapies to supplement traditional cancer treatments. Plant-based remedies, such as paclitaxel from the Western yew tree, Vinca alkaloids from Periwinkle, and herbs like green tea, ginger, and astragalus, have shown promising anti-cancer effects with fewer adverse reactions. Research suggests these compounds can slow cancer cell growth, trigger apoptosis, and limit metastasis. Among them, green tea is especially recognized for its antioxidant effects and ability to reduce cancer recurrence, while ginger's active compound, 6-gingerol, has anti-proliferative and anti-invasive properties. Furthermore, astragalus has been found to boost immune response and enhance chemotherapy efficacy. Hypericin, derived from *Hypericum perforatum*, has also attracted attention for its tumor-fighting potential via photodynamic therapy (PDT). These natural treatments present viable alternatives to synthetic chemotherapy, potentially offering reduced toxicity and improved outcomes in cancer care. Ongoing research into these herbal remedies may lead to transformative cancer treatments that are both more effective and less harmful.

Keywords: Cancer, Green Tea, Ginger, And Astragalus

Introduction:

Non-Communicable Diseases (NCDs) emerged as the primary causes of death worldwide, surpassing infectious diseases in many regions, particularly in high-income countries. Among the NCDs, cancer is one of the most significant contributors to this alarming rise in mortality, leading to a marked decline in global life expectancy. Cancer is not a single disease but a broad category of diseases that share a common characteristic: uncontrolled cell

growth. This unchecked proliferation of abnormal cells forms tumors, invades surrounding tissues, and can spread to distant parts of the body via a process called metastasis. As cancer cells travel through the bloodstream or lymphatic system, they can form secondary tumors in other organs, further complicating the disease and making treatment more difficult. The increasing incidence of cancer can be credited to a range of risk factors, many of which are associated to modern lifestyle and environmental exposures. One of the primary causes of cancer is mutations in the DNA of cells, which can be triggered by exposure to chemical carcinogens. Substances like tobacco smoke, asbestos, and certain chemicals used in industrial processes have been identified as major contributors to genetic mutations that lead to cancer. Ionizing radiation, including radiation from the sun and medical imaging procedures like X-rays, is another significant risk factor for cancer.[1]

In addition to environmental exposures, hormonal imbalances have been found to play a crucial role in certain types of cancer, particularly those related to reproductive organs. For example, women with prolonged exposure to estrogen are at higher risk for breast and ovarian cancers. The failure of the immune system to identify and abolish abnormal cells is another factor contributing to cancer development. A weakened immune system, which can result from conditions like HIV/AIDS or from the use of immunosuppressive drugs, makes it more difficult for the body to combat cancerous cells. Furthermore, genetic predisposition is a key factor in cancer risk, as certain inherited genetic mutations can significantly increase the likelihood of developing specific types of cancer. Aside from genetic and environmental factors, modern lifestyle choices have also played a pivotal role in the rising prevalence of cancer. Poor alimentary habits, comprising high consumption of processed foods, red meat, and alcohol, have been connected to cancers of the digestive system, liver, and breast. Lack of physical activity and obesity are also known to increase the risk of several types of cancer, including endometrial, breast, and colon cancers. Environmental pollution, including exposure to air and water pollutants, has further contributed to the growing cancer burden. Cancer is classified into several types based on the tissue or cell type from which it originates. The most common category is carcinomas, which arise from epithelial cells that line the surfaces of organs and structures in the body. Prostate, breast, lung, and colon cancers are all examples of carcinomas. Sarcomas, another category of cancer, develop from connective tissues such as bones, muscles, and fat. Blood cancers, such as lymphoma and leukemia, affect the lymphatic system and blood cells, respectively. Germ cell tumors are cancers that arise from totipotent cells, which can develop into various tissue types, and these are often found in the ovaries or testes. Lastly, blastomas, or blastic tumors, are cancers typically found in children and consist of immature or embryonic tissue.[1]

The global cancer burden is staggering. According to a 2015 study by WHO, cancer was the leading or second leading cause of death for individuals under the age of 70 in 91 out of 172

countries. In an additional 22 countries, it categorised as the third or fourth leading cause of death. This growing global trend highlights the urgent need for effective prevention strategies, initial detection programs, and improved treatment options. As the world faces the rising challenge of cancer, addressing the risk factors and improving access to healthcare resources will be crucial in combating this deadly disease.

Present Situation

Recent studies have highlighted the growing trend of cancer patients using one or more complementary or alternative therapies, particularly herbal or natural remedies, alongside conventional treatments. This growing interest in alternative treatments reflects a desire for more holistic approaches to managing cancer. Among the most widely used natural treatments is Paclitaxel, a drug derived from the bark of the Western yew tree. Paclitaxel has become an integral part of chemotherapy regimens due to its ability to target cancer cells. It works by binding to the beta subunit of tubulin, a protein that is essential for the formation of microtubules, structures that are critical for cell division. By forming stable, non-functional microtubule bundles, Paclitaxel disrupts cell division, preventing the cancerous cells from multiplying and spreading.[2] Another critical group of chemotherapy drugs that are based on natural sources are the Vinca alkaloids. These drugs, which include vinblastine, vincristine, and vindesine, are derived from the Periwinkle plant (Vinca rosea). Vinca alkaloids have been extensively used in the treatment of cancers such as breast and ovarian cancer. They possess unique properties, including anti-angiogenic and apoptotic effects, which make them effective in targeting cancerous cells. The drugs work by binding to tubulin, which impedes the formation of the mitotic spindle, a structure required for proper cell division. By disrupting this process, the Vinca alkaloids induce cell cycle arrest, halting the growth of cancer cells. A semi-synthetic derivative of the Vinca alkaloids, vinorelbine, also shares these properties and is used to treat certain types of cancer.[2]

Vinca alkaloids and Paclitaxel are usually administered through intravenous infusion, as they are poorly absorbed when taken orally. This method of administration is necessary due to the drugs' inability to be absorbed efficiently through the digestive system. Furthermore, Vinca alkaloids can be highly irritating when taken orally, making intravenous infusion the preferred method for delivering these medications. Despite their effectiveness in treating cancer, these drugs come with significant toxicities and side effects. Vinca alkaloids, for instance, can cause intestinal obstruction due to severe constipation, peripheral neuropathy (nerve damage), ataxia (loss of coordination), and tremors. Paclitaxel, on the other hand, has been associated with bone marrow suppression, which can result in a decrease in blood cell counts, raising the risk of infection, anaemia, and bleeding. Other side effects of Paclitaxel include bradycardia (slow heart rate), silent ventricular tachycardia (a heart rhythm disorder), hair loss, and hypersensitivity reactions. The adverse effects of synthetic chemotherapeutic drugs, including Vinca alkaloids

and Paclitaxel, have spurred the search for safer and more effective replacements. While synthetic drugs have been the mainstay of cancer treatment, their incapability to cure cancer without causing significant toxic side effects underscores the urgent need for new treatment options. Many chemotherapeutic agents, including those mentioned, result in common side effects such as nausea, vomiting, and hair loss. In addition, the severe toxicities associated with Vinca alkaloids and Paclitaxel raise concerns about their long-term use and the potential harm to patients' overall health. This situation has led to increased interest in plant-based drugs, which have been shown to have fewer or no serious side effects while still offering effective treatment for cancer.[2]

Plant-derived drug molecules have gained attention due to their safer profiles and promising efficacy against a range of cancers. Unlike synthetic drugs, which often cause significant toxic effects, many plant-based compounds have demonstrated the ability to treat cancer with minimal harm to healthy cells. The natural compounds found in plants often possess unique mechanisms of action that can complement or enhance the effects of conventional chemotherapy. As a result, researchers and pharmaceutical companies are increasingly turning their attention to herbal medicines and their extracts as potential game-changers in cancer treatment. The development of new plant-based therapies could help reduce the reliance on toxic synthetic drugs and offer patients more effective, less harmful options.

Given the success of plant-derived drugs in treating various types of cancer, including breast cancer, researchers are motivated to conduct further studies on the therapeutic potential of these natural remedies. Plant-based treatments have the potential to modernise cancer care by providing more targeted, less toxic treatment alternatives. This review highlights some of the promising plant-derived drugs that are paving the way for innovative cancer therapies, with the hope that they will contribute to the development of safer and more effective cancer treatments in the future. With continued research and investment in plant-based drugs, there is a real possibility of discovering breakthrough therapies that will change the landscape of cancer treatment.

Herbal Remedies

Herbal treatments have been considered for their potential in cancer therapy, serving as a complementary option alongside traditional methods. These treatments often rely on naturally occurring compounds that may more effectively target cancer cells with fewer side effects. Some natural remedies help hinder the growth of cancer cells, induce cell death, or prevent tumors from spreading. Many of these remedies come from plants or other natural sources, offering a milder alternative to conventional chemotherapy. Ongoing research shows promising results, suggesting that these alternatives could improve cancer care by boosting the effectiveness of standard treatments and minimizing toxicity.

Thea sinensis

Green tea, extracted from the leaf buds of *Thea sinensis* (family Theaceae), is a widely used herbal remedy known for its numerous health benefits. Studies show that its extracts possess antioxidant properties that help safeguard the body against oxidative stress. Green tea has been found to inhibit cancer development in various organs, including the mouth, esophagus, stomach, skin, lungs, liver, prostate, and kidneys. These benefits have been demonstrated in both clinical trials and laboratory studies using cancer cell lines and animal models. The leaves of the plant are also a rich source of caffeine, theobromine, and theophylline, which have stimulating effects. Consequently, green tea is viewed as a promising natural approach for cancer prevention and overall wellness, with continued research aimed at uncovering its full therapeutic potential.[3]

Several animal and clinical studies have demonstrated that green tea leaf extracts have anti-cancer properties. In a Japanese study involving 1,160 women with invasive breast cancer, averaging 51.5 years old, it was found that drinking three cups of green tea daily significantly reduced the chances of cancer reappearance, predominantly in early-stage cases. A Chinese study, using a questionnaire, showed that increased occurrence and duration of green tea consumption lowered the risk of ovarian cancer when compared to non-drinkers. This study included 254 ovarian cancer patients and 652 controls. Another study in China revealed that consuming 1.5 kg of green tea leaves annually lowered the risk of prostate cancer, involving 130 prostate cancer patients and 274 controls. Furthermore, a prospective study in Japan with 8,552 participants found that drinking 3-10 cups of green tea daily was allied with an abridged risk of stomach and colorectal cancers. Remarkably, individuals who consumed more than 10 cups per day experienced an even greater reduction in risk. These studies collectively support the potential of green tea in cancer prevention, suggesting its significant role in reducing the likelihood of various cancer types.[3-6]

The information provided highlights the considerable potential of green tea's phytochemical compounds in combating a variety of cancers. Studies suggest that the bioactive molecules, such as catechins and polyphenols, play a vital role in preventing the growth of cancer cells, stopping metastasis, and reducing recurrence rates. With an increasing body of research supporting green tea's anti-cancer effects, it is crucial for future studies to delve deeper into these natural compounds, harnessing their properties for both prevention and treatment. Moreover, incorporating green tea's herbal elements into conventional medical treatments could serve as a valuable complementary strategy, helping to alleviate side effects from traditional therapies while improving their overall effectiveness. Moving forward, it is essential for healthcare professionals, researchers, and policymakers to prioritize these findings, advocating for green tea as part of a broader cancer care approach and ensuring its accessibility as a preventive measure. By further exploring green tea's therapeutic potential, we can help develop

safer, more effective cancer treatments that align with the growing demand for natural and alternative healthcare solutions.

Zingiber officinale

Ginger (*Z. officinale*) is rich in a variety of plant-derived compounds, including volatile oils, anthocyanins, tannins, and pungent phenolic substances such as gingerols, shogaols, and sesquiterpenes. These bioactive compounds have been widely studied for their potential beneficial effects. In particular, ginger has added attention for its promising anti-cancer properties. Numerous preclinical studies have highlighted ginger's capability to inhibit cancer cell growth, induce apoptosis (programmed cell death), and prevent the spread of cancerous cells. These studies suggest that the compounds found in ginger may show a noteworthy role in both the treatment and management of several types of cancer. The following paragraphs will provide an overview of some of the key research and findings supporting ginger's potential as an adjunctive therapy in cancer care.[7]

A study has shown that ginger extract (EG) and its active compound, 6-gingerol, demonstrate anti-proliferative, anti-cancer, and anti-invasive properties by modulating several biological pathways, such as NFB, STAT3, Rb, MAPK, PI3K, AKT, ERK, cIAP1, cyclin A, cyclin-dependent kinase (Cdk), cathepsin D, and caspase 3/7. In another experiment, rats with hepatic carcinoma induced by a choline-deficient diet combined with ethionine experienced a notable decrease in tumor size after treatment with ginger extract. A separate study on human mammary carcinoma (MDA-MB-231) cells showed that 6-gingerol had no effect on cell adhesion at concentrations up to 5 units, but it led to a 16% decrease in adhesion at 10 units. Additionally, higher doses of 6-gingerol resulted in a dose-dependent reduction in cell migration and motility, both critical for cancer metastasis. Treatment of MDA-MB-231 cells with 6-gingerol also reduced the activities of matrix metalloproteinases (MMP) 2 and MMP9—key enzymes involved in cancer invasion and metastasis—in a dose-dependent manner. Studies involving human colorectal cancer cells demonstrated that 6-gingerol decreased cell survival in a dose-dependent manner. Furthermore, 6-gingerol induced cell cycle arrest in the G2/M phase without affecting the sub-G1 phase and reduced levels of proteins like CDK1, cyclin A, and cyclin B1, which are essential for cell division. In cervical cancer patients, it was observed that 6-gingerol enhanced the cytotoxic effects of cisplatin, a standard chemotherapy drug. These findings propose that 6-gingerol could be a valuable treatment option either on its own or in combination with conventional cancer therapies to improve treatment effectiveness and minimize side effects.[8-12]

Astragalus membranaceus

Astragalus root, which belongs to the Fabaceae family, is a widely recognized adaptogenic herb with a long history in traditional Chinese medicine. Known for its numerous health benefits, the root's therapeutic effects are primarily attributed to key active compounds

such as D-β asparagine, calycosin, cycloastragenol, and astragalosides I-VII. Additionally, it contains other beneficial substances, including pigments like formononetin and astraisoflavan. These compounds are highly regarded for their potent antioxidant properties, enabling them to neutralize harmful free radicals and protect the body from oxidative stress. For centuries, astragalus has been a cornerstone in Traditional Chinese Medicine, particularly for treating "spleen deficiency" — a condition that affects the body's energy and immune function. Beyond this, astragalus has also been extensively used to support cardiovascular health, with its compounds believed to promote circulation, strengthen the heart, and maintain overall cardiovascular well-being. The herb's diverse therapeutic potential continues to make it a popular choice for promoting overall health and vitality.[13-15]

Studies involving both humans and animals have shown that astragalus, when combined with other herbs in the Juzentaihoto formula, enhances immune function by increasing NK cell activity and interleukin levels. This combination also improves chemotherapy effectiveness, reduces cancer recurrence, and decreases chemotherapy-induced toxicity. In a trial with small cell lung cancer (SCLC) patients, those treated with astragalus and Chinese herbs alongside existing therapy had significantly better survival rates, with 10 out of 12 patients surviving 3-17 years. Another randomized trial with 120 participants receiving chemotherapy and intravenous astragalus showed slower disease progression, reduced damage to white blood cells and platelets, and improved immune function compared to the placebo group. Additionally, a study on gastrointestinal cancer patients found that combining astragalus with ginseng effectively minimized white blood cell suppression caused by chemotherapy.[16-18]

Hypericum perforatum

Hypericin, often known as St. John's Wort, is a flowering plant in the Hypericaceae family, falling under the genus Hypericum. It is a hybrid species, resulting from the cross between *H. maculatum* and *H. attenuatum*. Hypericin is classified as a naphthodianthrone, which is an anthraquinone derivative, and is considered one of the primary active compounds in Hypericum, along with hyperforin. This plant has attracted interest because of its possible medicinal benefits, particularly in the realm of cancer treatment. Despite significant progress in medical and surgical interventions, the prognosis for many cancer patients remains poor, with limited treatment options in some cases. As a result, numerous pilot studies have been conducted to explore the effectiveness of hypericin as a possible therapeutic agent in cancer care, exploring its mechanisms of action and potential to complement existing treatments.

Recent research in animals has shown that hypericin, a photochemical dye, can be activated by green light to produce harmful radical species within tumors. In a study involving mice, hypericin meaningfully inhibited the growth of pancreatic cancer cells both in vitro and in vivo, while laser or dye alone had no effect. The combination of hypericin and laser therapy showed potential as a treatment for patients with inoperable pancreatic cancer. Photodynamic

therapy (PDT) has proven effective for treating superficial tumors, and one pilot study found that laser-based PDT with hypericin caused more tumor necrosis than laser alone, suggesting it could be a less invasive treatment for recurrent or inoperable squamous cell cancers of the head and neck. Additional studies on hypericin's effects on osteoclasts showed that it could suppress the NFATc1 signaling pathway and reduce calcium oscillations, which may help prevent osteoclastogenesis in breast cancer. Moreover, hypericin demonstrated potential in reducing tumor burden, osteolysis, and bone metastasis in breast cancer models, and improved survival rates in experimental metastasis models. These findings suggest that hypericin could be a promising treatment for preventing bone damage in breast cancer patients with bone metastases.[19-21]

Conclusion:

In conclusion, the increasing prevalence of Non-Communicable Diseases, particularly cancer, underscores the urgent need for effective prevention, early detection, and treatment strategies. Cancer, driven by a combination of environmental exposures, genetic factors, and modern lifestyle choices, presents a complex challenge to global health. While conventional therapies have made progress, their side effects highlight the potential of complementary and alternative treatments. Plant-based remedies such as green tea, ginger, astragalus, and hypericin show promise in enhancing cancer treatment, reducing side effects, and offering more targeted therapies. Continued research into these natural alternatives could revolutionize cancer care, providing safer and more effective options for patients worldwide.

References:

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. Satoskar RS. Antimitotic Natural Products. 24th edition, Section 12, Elsevier publishing. pp 836.
3. Luo J, Inoue M, Iwasaki M, Sasazuki S, Otani T, Ye W, *et al.* Green tea and coffee intake and risk of pancreatic cancer in a large-scale, population-based cohort study in Japan (JPHC study). Eur J Cancer Prev. 2007; 16(6):542-8.
4. Liang Y, Lu J, Zhang L. Comparative study of cream in infusions of black tea and green tea [Camellia sinensis (L.) O. Kuntze]. Int J Food Sci Tech. 2002; 37(6):627-34.
5. Jian L, Xie LP, Lee AH, Binns CW. Protective effect of green tea against prostate cancer: A case-control study in southeast China. Int J Cancer. 2004; 108(1):130-5.
6. Fujiki H, Suganuma M, Imai K, Nakachi K. Green tea: Cancer preventive beverage and/or drug. Cancer lett. 2002; 188(1- 2):9-13.
7. Semwal RB, Semwal DK, Combrinck S, Viljoen AM. Gingerols and shogaols: Important nutraceutical principles from ginger. Phytochem. 2015; 117:554-68.

8. Prasad S, Tyagi AK. Ginger and its constituents: role in prevention and treatment of gastrointestinal cancer. Gastroenterol Res Pract. 2015. Article ID 142979.
9. Yusof Y, Ahmad N, Das S, Sulaiman S, Murad N. Chemopreventive efficacy of ginger (Zingiber officinale) in ethionine induced rat hepatocarcinogenesis. African J Tradit Complement Altern Med. 2009; 6(1):87-93.
10. Park M, Bae J, Lee DS. Antibacterial activity of [10]-gingerol and [12]-gingerol isolated from ginger rhizome against periodontal bacteria. Phytotherapy Res. 2008; 22(11):1446-9.
11. Yeh HY, Chuang CH, Chen HC, Wan CJ, Chen TL, Lin LY. Bioactive components analysis of two various gingers (Zingiber officinale Roscoe) and antioxidant effect of ginger extracts. LWTFood Sci Tech. 2014; 55(1):329-34.
12. de Lima RM, Dos Reis AC, de Menezes AA, Santos JV, Filho JW, Ferreira JR, *et al.* Protective and therapeutic potential of ginger (Zingiber officinale) extract and [6]-gingerol in cancer: A comprehensive review. Phytotherapy Res. 2018; 32(10):1885-907.
13. Beinfeield H, Korngold E. The cauldron of Chinese herbs. Heaven Earth. 1991. 265-321.
14. Wang D, Shen W, Tian Y, Sun Z, Jiang C, Yuan S. Protective effect of active components extracted from radix Astragali on human erythrocyte membrane damages caused by reactiveoxygen species. China J Chin Mat Med. 1996; 21(12):746-8.
15. Sun Y, Hong WJ, Deng J. 10-year follow-up study of cancer patients with fu-zheng therapy. Chin J Modern Dev Tradit Med. 1987; 7(12):712-7.
16. Gupta S, Agarwal SS, Epstein LB, Fernandez G, Good RA. Panax ginseng: A new mitogen and interferon inducer. Clin Res. 1980; 504A:28-32.
17. Duan P, Wang ZM. Clinical study on effect of Astragalus in efficacy enhancing and toxicity reducing of chemotherapy in patients of malignant tumor. Chin J Integr Med. 2002; 22(7):515-7.
18. Li NQ. Clinical and experimental study on shen-qi injection with chemotherapy in the treatment of malignant tumor of digestive tract. Chin J Integr Med. 1992; 12(10):588-92.
19. Liu CD, Kwan D, Saxton RE, McFadden DW. Hypericin and photodynamic therapy decreases human pancreatic cancer in vitro and in vivo. J Surg Res. 2000; 93(1):137-43.\
20. Chung PS, Rhee CK, Kim KH, Paek W, Chung J, Paiva MB, *et al.* Intra tumoral hypericin and KTP laser therapy for transplanted squamous cell carcinoma. Laryngoscope. 2000; 110(8):1312-6.
21. Ouyang Z, Guo X, Chen X, Liu B, Zhang Q, Yin Z, *et al.* Hypericin targets osteoclast and prevents breast cancerinduced bone metastasis via NFATc1 signaling pathway. Oncotarget. 2018; 9(2):1868.

THE GREEN MEDICINE CABINET: NATURE'S SOLUTIONS TO SKIN ISSUES

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Abstract:

Herbal remedies have been a cornerstone of holistic health practices, especially in the treatment of skin conditions. Combining ancient traditions with modern scientific knowledge, plants have long been valued for their ability to promote skin healing. This review explores the historical importance and current uses of herbal treatments for skin health, highlighting their effectiveness in addressing a range of skin issues. Across cultures, plant-based remedies have been used to treat skin problems, with recent research confirming their therapeutic benefits. Herbs like Aloe vera, calendula, garlic, and witch hazel are known for their anti-inflammatory, antimicrobial, and healing properties. Aloe vera, for example, has shown anti-inflammatory and wound-healing effects, with clinical trials supporting its potential for treating conditions such as psoriasis. Calendula has been found to speed up wound healing and relieve skin irritations, while garlic, due to its antifungal compound ajoene, is effective in treating fungal infections. Witch hazel's anti-inflammatory properties also make it useful in managing acne and other skin inflammations. These herbal treatments not only address the visible symptoms of skin conditions but also aim to restore internal balance, providing a holistic approach to skin health. In contrast, conventional treatments, while effective, often come with side effects and may not tackle the underlying causes of skin issues. As a result, many people are turning to natural remedies as alternatives, seeking long-term, personalized solutions for skin care. With growing scientific evidence supporting their benefits, herbal remedies present promising, sustainable options for managing various skin conditions.

Keywords: Skin Conditions, Aloe Vera, Calendula, Garlic, Witch Hazel

Introduction:

Herbal remedies have long been an essential part of holistic health practices, offering a natural and effective approach to treating various skin conditions. Throughout history, plants and herbs have been highly regarded for their ability to heal and refresh the skin, combining ancient wisdom with modern scientific insights. This introduction explores the deep-rooted history and present-day uses of herbal treatments for skin health, emphasizing the blend of traditional knowledge with modern innovations. For thousands of years, cultures worldwide have turned to herbs to treat skin issues. Remarkably, our closest relatives in the animal kingdom, the great apes, instinctively use plants to self-medicate, underscoring the therapeutic value of herbs.

Humans, too, have long understood the healing potential of plants for skin care. From one culture to another, the practice of using plant-based remedies has been passed down, reflecting their enduring effectiveness and cultural significance. Traditional healing systems such as Ayurveda from India, Traditional Chinese Medicine, and various Indigenous traditions have long utilized herbal treatments to address skin concerns, offering a broad range of solutions tailored to the specific needs of individuals. These well-established approaches highlight the profound connection between plants, the environment, and skin health. They aim to treat not only the visible symptoms but also the deeper balance of mind, body, and spirit. The health and appearance of our skin are influenced by a variety of factors, including genetics, overall health, lifestyle choices, and environmental impacts. Daily habits, work-related stress, diet, and personal skincare routines all play a role in determining the condition of our skin and hair. As our understanding of these interconnected factors grows, so does the potential for herbal remedies to address both the symptoms and root causes of skin issues. By embracing nature's healing power, individuals can promote and restore their skin health with natural, holistic solutions.[1-4]

Prolonged exposure to heat during the summer can lead to skin dehydration, which may cause a variety of problems, such as wrinkles, blemishes, pigmentation, and sunburn. Similarly, the harsh winter conditions can have damaging effects on both the skin and hair, contributing to issues like dandruff, infections, hair loss, and cracks. Skin concerns are common and affect people across all age groups, with causes ranging from exposure to chemicals, microorganisms, and biological toxins to nutritional deficiencies. For centuries, herbal remedies have been explored for treating skin ailments, and modern research continues to uncover the medicinal properties of various plants. Recent scientific studies have expanded our understanding of the bioactive compounds present in herbs and their role in promoting skin health. Aloe vera, for example, has been found to have anti-inflammatory and wound-healing effects that aid in collagen production and tissue repair. Its calming properties make it especially effective for treating sunburn and other skin irritations caused by external factors. Another widely used herb, calendula, is known for its antiseptic and anti-inflammatory qualities. Research indicates that calendula can accelerate wound healing and soothe skin irritations. Its anti-inflammatory effects also make it useful for treating conditions such as eczema and dermatitis. Skin diseases encompass a wide variety of disorders that affect the integumentary system, with various causes and symptoms. Common conditions such as acne vulgaris, eczema, psoriasis, skin cancer, rosacea, vitiligo, and dermatophytosis present significant global health challenges. The impact of these skin diseases on individuals' daily lives has driven the search for effective treatments, particularly those based on natural remedies. This section explores the use of herbal remedies in skin care, focusing on their historical significance, modern-day relevance, and the scientific studies that support their therapeutic effects. By examining the knowledge accumulated over centuries, we gain a deeper understanding of how specific herbs can address skin conditions and offer a holistic approach to skin health. With increasing scientific evidence, herbal remedies continue to show promise as effective, natural alternatives to conventional skincare products.[5-8]

Shortcomings of Conventional Treatments

While conventional treatments for skin diseases have proven effective for addressing various conditions, they often come with limitations that can impact both their long-term effectiveness and safety. A significant concern is the potential for side effects, especially with the prolonged use of synthetic drugs, corticosteroids, and antibiotics. These treatments, though beneficial in the short term, can cause a range of undesirable effects, such as thinning of the skin, irritation, allergic reactions, and in some cases, even the development of antibiotic resistance. This resistance can make it harder to treat future infections and complicates the overall management of skin conditions. Moreover, conventional treatments are primarily designed to target and alleviate the symptoms of skin conditions, rather than addressing their underlying causes. As a result, patients often experience recurring flare-ups once they stop using the medication, as the root cause of the condition has not been resolved. In many cases, individuals may find themselves relying on prescription medications for ongoing relief, creating a cycle of dependence that does not provide a permanent solution to the problem. This reliance on continuous treatment may also increase the risk of developing further side effects over time.

Another challenge with conventional treatments is their cost. Many skin medications, particularly those that require long-term use, can be financially burdensome. This can make it difficult for some individuals to maintain consistent treatment, particularly if they do not have adequate insurance coverage or if the medication is not covered by health plans. For people with chronic skin conditions, the financial strain of ongoing treatment can be overwhelming, limiting their access to the care they need. Additionally, conventional treatments often follow a one-size-fits-all approach, which may not be effective for everyone. These treatments typically fail to consider the unique characteristics of each individual, such as their specific skin type, lifestyle habits, environmental factors, and overall health. As a result, some individuals may not experience the desired results, or their conditions may worsen due to the treatment's inability to address their specific needs. These limitations of conventional treatments have led to a growing interest in alternative and natural remedies. Many individuals are turning to herbal and holistic therapies, which offer a more personalized, gentle, and long-term approach to managing skin conditions. Natural remedies tend to focus not only on treating symptoms but also on restoring balance within the body, promoting overall skin health in a more sustainable manner. As awareness of these alternatives increases, there is a shift toward embracing these natural options, which aim to offer effective and lasting solutions without the potential downsides associated with traditional treatments. [9-12]

Plant-based Remedies for Skin Conditions

Herbal approaches for treating skin diseases involve using natural, plant-based substances to promote healing and improve skin health. These treatments often emphasize the use of compounds that possess anti-inflammatory, antimicrobial, and antioxidant properties, which can help alleviate symptoms such as redness, irritation, and infection. Unlike conventional treatments, which may rely on chemicals and synthetic medications, herbal remedies are often

considered gentler on the skin and have fewer side effects. Additionally, these natural methods may support the skin's barrier function, promoting long-term health by nurturing the skin's ability to regenerate and defend against environmental stressors. The holistic nature of herbal treatments also focuses on improving overall wellness, with many approaches seeking to balance internal health, which can reflect positively on the skin's appearance and condition.

Garlic

Ajoene, an effective antifungal compound found in garlic (*Allium sativum*), has shown considerable promise in the treatment of skin infections. In a study involving 34 participants with tinea pedis, applying a 0.4% ajoene cream daily led to significant improvements. Within a week, 79% of the participants experienced complete symptom relief, while the others saw improvement within 14 days. Notably, a three-month follow-up indicated no signs of recurrence, showcasing ajoene's long-lasting efficacy in treating fungal infections like tinea pedis. Beyond its antifungal capabilities, garlic is recognized for its broad health benefits, particularly in strengthening immune function and promoting skin health. Studies have found that consuming garlic can enhance the immune system, improve skin circulation, protect against UVB radiation, and even aid in cancer treatment, further solidifying its status as a potent natural remedy. Garlic extract, when applied topically, has also proven to be beneficial for a range of skin conditions. It has been shown to assist in the treatment of leishmaniasis, psoriasis, alopecia areata, cutaneous corn, and signs of aging, as well as both viral and fungal infections. Additionally, it supports wound healing and can improve the appearance of keloid scars. When compared to conventional treatments like Vaseline, a 30% garlic ointment resulted in more aesthetically pleasing scars during surgical wound healing, highlighting its potential to promote healthier skin regeneration. These findings emphasize garlic's versatile applications, demonstrating that it is not only effective in treating fungal infections but also serves as a powerful agent for overall skin health and healing.[13-15]

Milk thistle

The German Commission E has authorized the use of silymarin, a flavonoid found in milk thistle (*Silybum marianum*), as a remedy for liver diseases due to its powerful antioxidant effects. Milk thistle, traditionally recognized for supporting liver health, has been used in herbal medicine for centuries. The active compound, silymarin, is believed to help protect liver cells from toxins, promote liver regeneration, and reduce inflammation. However, recent studies have broadened the scope of silymarin's potential, suggesting it may offer additional benefits in preventing cancer. A study was conducted to assess whether the antioxidant properties of silymarin could also offer protection against the promotion of tumors. The results, based on experiments with mice, were promising. Topical application of silymarin showed significant protective effects against skin tumors caused by chemical carcinogens. The underlying mechanism is thought to involve a reduction in oxidative stress, a major contributor to cancer initiation. Additionally, silymarin may help prevent the increased growth of skin cells, as well as reduce hyperplasia (the abnormal increase in cell number) and edema (swelling), both of which

are often associated with tumor development. These findings are promising as they suggest that silymarin could be an effective tool in preventing or slowing the development of certain types of skin cancer. However, while the results are encouraging, they are based on animal models, and further research involving human trials is necessary to establish the safety and effectiveness of silymarin for this purpose. Additional studies will help determine if the antioxidant properties of milk thistle can be translated into a viable treatment for preventing skin cancer in humans.[16]

Witch-hazel

Witch hazel, scientifically referred to as *Hamamelis virginiana L.*, is a plant that has long been used in traditional medicine for its ability to treat various inflammatory skin issues. Known for its calming effects, witch hazel has been a remedy for skin irritations and minor wounds for centuries. Although research on its effectiveness for acne treatment is still limited, early studies show that it has significant anti-inflammatory properties for the skin. For instance, a study found that a glycolic extract from the bark of *Hamamelis virginiana* could reduce the release of IL-6, a pro-inflammatory cytokine triggered by *Cutibacterium acnes*, a bacteria associated with acne. This reduction was partly due to the inhibition of NF-κB activation, a critical pathway in inflammation. Furthermore, when TNF-α, another pro-inflammatory factor, was introduced, witch hazel extract showed even greater anti-inflammatory effects, significantly lowering IL-8 release. This activity is believed to be partly attributed to the antioxidant properties of witch hazel, particularly in its ability to inhibit VEGF (vascular endothelial growth factor), a molecule involved in inflammation and tissue regeneration.[17] Witch hazel is also highly regarded for its astringent properties, mainly due to its high tannin content. This makes it effective for treating various skin issues, especially those involving irritation, inflammation, or swelling. Topically, witch hazel has been commonly used for conditions like hemorrhoids, varicose veins, and minor cuts or abrasions. It helps alleviate discomfort by promoting vasoconstriction, which reduces swelling by constricting blood vessels. Additionally, animal studies suggest that witch hazel extract may offer localized vasoconstrictive and styptic (bleeding-stopping) effects, further enhancing its role in managing skin conditions that affect both the skin and mucous membranes.[18]

Aloe vera

Aloe vera has been highly regarded in traditional medicine for its powerful healing properties. As one of the most prominent plants used for medicinal purposes, Aloe vera has been utilized for centuries, particularly for its role in wound healing. It is classified as Class 1 for internal use and Class 2d for external use, demonstrating its broad range of therapeutic applications. While its effectiveness for addressing skin-related issues is well-established, recent studies have revealed its potential in treating conditions such as psoriasis, further cementing its place in modern medical practice. Recent clinical trials investigating Aloe vera's effects on psoriasis have yielded encouraging results. In one such study, patients with mild to moderate plaque psoriasis were treated with either an Aloe vera-based cream or a placebo. Those in the Aloe vera treatment group showed significant improvement, especially in reducing psoriasis

symptoms, while the placebo group had only minimal changes. Notably, the Aloe vera group reported no adverse side effects, highlighting its safe and effective use in treating skin conditions. This research underscores Aloe vera's potential as an alternative treatment for psoriasis, offering relief for those affected by this chronic skin condition. Aloe vera's benefits extend beyond psoriasis, with extensive research examining its role in wound healing. Studies have shown that Aloe vera has a positive impact on collagen production and structure during the healing process. Collagen is a key protein involved in tissue repair, and Aloe vera has been found to enhance its quality in granulation tissue by increasing collagen content and improving crosslinking. These changes lead to stronger, more stable tissue at the wound site. Additionally, Aloe vera treatment resulted in higher aldehyde levels and lower acid solubility, both of which indicate enhanced collagen integrity. The plant also increased the levels of type III collagen, an important component of wound healing, while reducing the type I/type III collagen ratio, which is typically higher in untreated wounds. Aloe vera's healing properties are not confined to topical use. Research on animal models, particularly rats, has demonstrated that both topical and oral administration of Aloe vera produce similarly positive results in wound healing. This suggests that Aloe vera's beneficial effects extend beyond just external application, providing a more holistic approach to tissue repair. In addition to its wound-healing properties, Aloe vera offers a variety of other therapeutic benefits. It is known for its antibacterial and anti-inflammatory effects, which make it effective in treating various skin conditions, including burns, insect bites, and allergic reactions. Aloenin, the primary active compound in Aloe vera, plays a key role in skin repair by helping to alleviate irritation and damage. Aloe vera has also been shown to reduce symptoms such as itchiness and swelling, making it a valuable remedy for improving skin comfort and appearance. Aloe vera's healing potential also extends to cellular repair. In studies involving corneal epithelial cells, Aloe vera was found to enhance the activity of collagen-degrading enzymes, which can promote the healing of corneal wounds. This suggests that Aloe vera could be beneficial in treating eye injuries or conditions affecting the cornea. Furthermore, Aloe vera's active ingredient, aloin, has protective effects on the skin, reducing inflammation, preventing DNA damage, and guarding against oxidative stress. Aloe vera also boosts antioxidant defenses by increasing the activity of key enzymes like superoxide dismutase (SOD) and raising levels of glutathione, a vital antioxidant in the body.

In summary, Aloe vera's longstanding use in traditional medicine is supported by modern scientific research, which continues to reveal its wide-ranging therapeutic benefits. Its ability to aid in wound healing, treat conditions like psoriasis, and provide antibacterial and anti-inflammatory effects makes Aloe vera a valuable plant in both traditional and contemporary medicine.[19-23]

Jewelweed

Jewelweed, or *Impatiens biflora*, is commonly believed to be effective in treating poison ivy contact dermatitis when applied to the skin, though research results are mixed. In one study, jewelweed was found to be as effective as conventional treatments for poison ivy dermatitis,

with 108 out of 115 participants reporting symptom relief within two to three days. However, a different study concluded that jewelweed extract did not improve symptoms of poison ivy dermatitis.[24-25]

Conclusion:

In conclusion, herbal remedies have a long-standing history in skin care, offering effective and natural alternatives to conventional treatments. From ancient traditions to modern scientific advancements, plants such as Aloe vera, garlic, calendula, and witch hazel have been shown to provide significant benefits for treating a variety of skin conditions. Their healing, anti-inflammatory, and antimicrobial properties make them valuable tools in promoting overall skin health. While conventional treatments can be effective, they often come with side effects and may not address the root causes of skin problems. As more people turn to natural solutions, herbal remedies continue to offer sustainable, holistic options for achieving and maintaining healthy skin.

References:

1. Huffman MA. Self-medicative behaviour in the African great apes: An evolutionary perspective into the origins of human traditional medicine. Bioscience. 2001;51(8):651–61.
2. Kapoor LD. CRC handbook of Ayurvedic medicinal plants. CRC press; 2018.
3. Xu Y. Dermatology in traditional Chinese medicine. Donica publications; 2004.
4. Kole PL, Jadhav HR, Thakurdesai P, Nagappa AN. Cosmetic potential of herbal extracts. 2005.
5. Cosmetics [online], Available from:http://en.wikipedia.org/wiki/Cosmetics.
6. Harry RG, Mumford PB. Modern cosmeticology. 1962.
7. Surjushe A, Vasani R, Saple DG. *Aloe vera*: a short review. Indian Journal of Dermatology. 2008;53(4):163.
8. Preethi KC, Kuttan R. Wound healing activity of flower extract of *Calendula offlcinalis*. Journal of Basic and Clinical Physiology and Pharmacology. 2009;20(1):73-80.
9. Wang AS, Armstrong EJ, Armstrong AW. Corticosteroids and wound healing: clinical considerations in the perioperative period. The American Journal of Surgery. 2013;206(3):410-7.
10. Karadag AS, Aslan Kayıran M, Wu CY, Chen W, Parish LC. Antibiotic resistance in acne: changes, consequences and concerns. Journal of the European Academy of Dermatology and Venereology. 2021;35(1):73-8.
11. Rahman M, Alam K, Zaki Ahmad M, Gupta G, Afzal M, Akhter S *et al.* Classical to current approach for treatment of psoriasis: a review. Endocrine, Metabolic & Immune Disorders-Drug Targets. 2012;12(3):287-302.
12. Karadag AS, Aslan Kayıran M, Lotti T, Wollina U. Immunosuppressive and immunomodulator therapy for rare or uncommon skin disorders in pandemic days. Dermatologic Therapy. 2020;33(5):e13686.

13. Ledezma E, Sousa LD, Jorquera A, Sanchez J, Lander A, Rodriguez E *et al.* Efficacy of ajoene, an organosulphur derived from garlic, in the short-term therapy of tinea pedis. Mycoses. 1996;39(9-10):393-5.
14. Pazyar N, Feily A. Garlic in dermatology. Dermatology reports. 2011;3(1):e4.
15. Alhashim M, Lombardo J. Effect of topical garlic on wound healing and scarring: A clinical trial. Dermatologic Surgery. 2020;46(5):618-27.
16. Lahiri-Chatterjee M, Katiyar SK, Mohan RR, Agarwal R. A flavonoid antioxidant, silymarin, affords exceptionally high protection against tumor promotion in the SENCAR mouse skin tumorigenesis model. Cancer Research. 1999;59(3):622-32.
17. Piazza S, Martinelli G, Vrhovsek U, Masuero D, Fumagalli M, Magnavacca A *et al.* Anti-Inflammatory and Anti-Acne Effects of *Hamamelis virginiana* Bark in Human Keratinocytes. Antioxidants. 2022;11(6):1119.
18. McGuffin M, Hobbs C, Upton R, Goldberg A, editors. Botanical Safety Handbook. Boca Raton, FL: CRC Press; 1997.
19. Syed TA, Ahmad SA, Holt AH, Ahmad SA, Ahmad SH, Afzal M. Management of psoriasis with *Aloe vera* extract in a hydrophilic cream: a placebo-controlled, double-blind study. Tropical Medicine & International Health. 19961(4):505-9.
20. Chithra P, Sajithlal GB, Chandrakasan G. Influence of *Aloe vera* on collagen characteristics in healing dermal wounds in rats. Molecular and Cellular Biochemistry. 1998;181:71-6.
21. Badole SL, Bagul PP, Menaa F. *Aloe vera*: Use for Skin Disease. In Bioactive Dietary Factors and Plant Extracts in Dermatology 2012:475-479. Totowa, NJ: Humana Press.
22. Curto EM, Labelle A, Chandler HL. *Aloe vera*: an in vitro study of effects on corneal wound closure and collagenase activity. Veterinary Ophthalmology. 2014;17(6):403-10.
23. Liu FW, Liu FC, Wang YR, Tsai HI, Yu HP. Aloin protects skin fibroblasts from heat stress-induced oxidative stress damage by regulating the oxidative defense system. PLoS One. 2015;10(12):e0143528.
24. Lipton RA. Comparison of jewelweed and steroid in the treatment of poison ivy contact dermatitis. Annals of Allergy. 1958;16:526–67.
25. Guin JD, Reynolds R. Jewelweed treatment of poison ivy dermatitis. Contact Dermatitis. 1980;6:287–8.

PSYCHOBIOTICS: A BRIDGE BETWEEN GUT MICROBIOTA AND MENTAL HEALTH

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Abstract:

Psychobiotics refer to a category of probiotics that positively influence mental health by interacting with the gut-brain axis, that have emerged as promising therapeutic agents for mental health disorders. The bilateral link between the gut bacteria and the central nervous system plays a significant role in neurodevelopment, emotional regulation, and cognitive function. Modifications in the gut microbiota's makeup have been associated to mental illness such as depression, anxiety, schizophrenia, and autism spectrum disorders. Psychobiotics exert their effects through modulation of neurotransmitters, immune responses, and the hypothalamic-pituitary-adrenal (HPA) axis. This chapter explores the mechanisms of psychobiotics, their clinical applications, and emerging evidence supporting their role in mental health management. While preclinical and clinical studies indicate beneficial outcomes, challenges remain in standardizing psychobiotic formulations, optimizing dosages, and understanding individual microbiome variations. Future research should focus on large-scale clinical trials to establish psychobiotics as an adjunct or alternative to conventional psychiatric treatments**.**

Keywords: Psychobiotics, Gut-Brain Axis, Mental Health, Microbiota, Neurotransmitters

Introduction:

Multiple neuro-immune and metabolic circuits connect with the brain and nervous system using the vagal pathway or through endocrine peptides, gut hormones, and metabolites that the gut microbiome(GM) produces.[1] Thus, it is currently being investigated that keeping a healthy GM is crucial to sustaining mental health. Probiotics, synbiotics, and prebiotics have been studied in preclinical models of psychiatric diseases as well as in people with known diagnoses or susceptibility to psychiatric disorders.[1] When given in sufficient quantities, live microorganisms (such as bacteria and yeast) known as psychobiotics can improve mental health. Dr. Ted Dinan and associates first used the term “psychobiotics” in 2013, highlighting the link between the gut microbiota and the central nervous system.

The gut-brain axis, a network of bidirectional communication between the enteric nervous system, the central nervous system, and the gut microbiome, is where the idea of psychobiotics originated. Over the past 20 years, research on the gut-brain axis has changed dramatically, and we now know more about how the gut microbiota affects mood, behaviours,

and cognitive function. There is a difference between individuals (such as those suffering from substance use disorders, psychotic disorders, depressive disorders, etc.) and other people in general, according to research on the variety of GM and changes in taxonomic abundance in clinical settings.[2-4] Since the majority of the findings pertaining to gut microbiota composition are generated following the initiation of a particular pathology, it is challenging to explain the relationship between gut microbiota and the development or maintenance of psychological disorders. Complicating matters further, a number of psychotropics have been linked to alterations in gut microbiota diversity; for example, antipsychotics may have a dose dependence detrimental impact on phylogenic diversity and the Shannon index.[5] Additionally, antidepressants alter the representation of different GM species in vitro; the majority of these effects are antimicrobial.[6]

Relevance to Research on Mental Health

Research on mental health has increasingly highlighted the relevance of psychobiotics due to their potential to influence many facets of mental health. Psychobiotics can alter the gut-brain axis, impacting the synthesis of hormones, neurotransmitters, and other molecular signalling that regulate mood and cognitive function. Studies have shown that they can reduce the symptoms of mental health disorders such as depression and anxiety. Additionally, psychobiotics may enhance stress tolerance and resilience, helping individuals better cope with adversity. As a novel and innovative therapeutic approach, psychobiotics could potentially reduce the reliance on traditional pharmaceutical treatments for mental health conditions.

Numerous psychiatric problems have been linked to high rates of recurrence, different forms of impairment, increased non-adherence, and resistance to treatment.[7-8] For individuals with psychiatric diseases and even for the prevention of such disorders, these poor prognostic indicators point to the necessity of developing novel therapeutic approaches. A review of the literature was done to confirm the existing understanding of the effectiveness and adverse event characteristics of psychobiotics in the management and/or prevention of mental illnesses. Probiotics, prebiotics and synbiotics are all included in the category of "psychobiotics" in this evaluation.[9]" An organism that is alive and can help people with mental illnesses when consumed in sufficient quantities" is how Dinan *et al.* define psychobiotics.[10] "Psychobiotics are defined as probiotics that interact with colonized gut bacteria to improve mental health in the host when consumed in a specific amount," according to Del Toro-Barbosa *et al.* who add the dimension of GM regulation. [11]Additionally, a group with documented adverse reactions to their existing therapy (e.g., weight gain, diabetes, dyslipidaemia, extrapyramidal symptoms, etc.) may benefit more from psychobiotics due to their superior tolerability.[11,12] Because psychobiotics have a minimal chance of dependency, allergy, or adverse effects, it is anticipated that they will be a good adjunct for patients with psychiatric illnesses.[11] "Adequate viable bacteria that enter the intestine in an active form to have a beneficial impact on health" is how

probiotics are also defined. Numerous species, including lactobacilli, bifidobacteria, enterococci, streptococci, strains of Escherichia coli, and others, are employed in probiotic foods, especially milk products that have undergone fermentation. Prebiotics are defined as "substances that have undergone fermentation to permit particular changes in the gastrointestinal microflora's composition and/or activity that confer benefits upon host wellbeing and health". The most studied compounds from this class of psychobiotics are bifidogenic, indigestible oligosaccharides. Synbiotics are probiotic and prebiotic combinations that work well together.[9] Although the precise processes by which psychobiotics work are not fully understood, research has looked into the immunomodulatory pathways' induction and physiological stress-reduction benefits, pathogen growth inhibition, modification of the microbiota, and enhancement of the colonic epithelium's barrier function .[13]

Researchers looking into the impact of psychobiotics in clinical practice have presented a number of difficulties The necessity of more precise target subpopulation definitions, a lack of well-designed clinical trials, especially those with extended durations, and the considerable diversity of the microorganisms and products used in various clinical and preclinical studies are some of the difficulties facing psychobiotic research.[13,14]

The Gut-Brain Connection

The gut-brain axis (GBA) is a two directional network linking the enteric nervous system (ENS) and the central nervous system (CNS) to regulate gastrointestinal and brain functions. Advances in technology and research have significantly contributed to the development and solidification of this concept, emphasizing the intricate relationship between gut microbiota and, neurotransmitter activity, and brain function. [15] Large-scale research such as Metagenomics of the Human Intestinal Tract (MetaHIT), sequencing of the next generation, and "omics" platforms have all contributed to the last ten years by offering crucial information on microbiota composition and biomarkers.[16] Understanding the gut-brain crosstalk and the adage "you are what you eat" has improved due to the advent of advanced computing platforms and integrated systems data analyses.[17,18]

The gut microbiota, consisting of trillions of bacteria, plays a vital role in mental health by producing metabolites, hormones, and neurotransmitters that can influence behaviour, mood, and cognitive function. Anxiety, sadness, and bipolar disorder are among the mental health illness that have been connected to dysbiosis which refers to an imbalance in the gut microbiota. In addition to providing essential support, our microbiome's proper composition is linked to several health issues, such as problems of the reproductive system, gastrointestinal tract, and mental health.

Ancient societies understood the significance of gut health and nutrition for an individual's general well-being. Some of the ancient beliefs and practices are starting to have their mechanisms and foundations dissected by Western science and contemporary scientific

approaches. The gut microbiota, along with its metabolites, hormones, and biological sex, plays a role in influencing various health conditions, including mental health disorders, obesity, gastrointestinal diseases, and cardiovascular disorders.

According to a cross-sectional study, over 700,000 individuals die by suicide each year , and over 37% (n = 473) of teenager's experience depression.[20,21] Poor sleep, excessive consumption of ultra-processed foods, substance abuse, inadequate nutrition, and social isolation exacerbate the impact of mental health disorders on overall well-being.Because of this, it is critical to treat the increasing prevalence of depression. Restoring the microbiome is still a non-invasive approach of treatment for treating mental health conditions including anxiety and depression.

Psychobiotics

Probiotic bacteria such as *Lactobacillus* species (*L. rhamnosus*, *L. plantarum*, *L. helveticus*, *L. casei*, *L. reuteri*) and *Bifidobacterium* species (*B. longum*, *B. breve*, *B. bifidum*, *B. infantis*) have been extensively studied for their role in reducing stress, anxiety, and depression. Other beneficial strains include *Streptococcus thermophilus*, *Enterococcus faecium*, and yeast such as *Saccharomyces boulardii*. These psychobiotics contribute to mental well-being by influencing neurotransmitter production, reducing inflammation, and regulating gut microbiota composition.[22]

Classification Standards for Psychobiotics

For a microbe to qualify as a psychobiotic, it needs to:

1. Demonstrate a significant impact on mental health conditions, including stress, anxiety, and depression.
2. Engage in gut-brain axis interaction.
3. Generate neurotransmitters or metabolites that affect mood and cognitive abilities.
4. Show effectiveness and safety in clinical trials involving humans.

Psychobiotics can be categorized into the following types based on their mechanism of action and effects on mental health:

- Probiotic Psychobiotics – Beneficial live bacteria, including Lactobacillus and Bifidobacterium species, enhance mood, reduce anxiety, and improve cognition by regulating gut microbiota and neurotransmitter production.
- Prebiotic Psychobiotics – Non-digestible fibers, like fructooligosaccharides (FOS) and galactooligosaccharides (GOS) support the growth of beneficial gut bacteria, indirectly supporting mental well-being.
- Postbiotic Psychobiotics – Metabolic byproducts of probiotics, including short-chain fatty acids (SCFAs) and neurotransmitters (e.g., serotonin and GABA), that exert neuroprotective and anti-inflammatory effects.

- Synbiotic Psychobiotics – A synergistic blend of probiotics and prebiotics that supports gut microbiota balance and promotes better mental health.
- Paraprobiotic Psychobiotics – Inactivated or heat-killed probiotic bacteria that still provide health benefits by modulating immune responses and gut-brain interactions.

Mechanism of Action

Psychobiotics contribute to neurotransmitter production, regulate inflammatory cytokines, influence the stress response through the hypothalamic-pituitary-adrenal (HPA) axis, and promote the synthesis of brain-derived neurotrophic factor (BDNF).Certain psychobiotics, such as *Bifidobacterium* and *Lactobacillus*, contribute to serotonin production, a key neurotransmitter engaged in regulation of mood, appetite, and sleep.[23] Additionally, *Lactobacillus brevis* has been found to produce gamma-aminobutyric acid (GABA), that helps manage stress and anxiety responses.[24]

Psychobiotics also exhibit anti-inflammatory effects by regulating the synthesis of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which may reduce systemic inflammation. [25] Furthermore, they interact with immune cells to regulate the immunological response, thereby lowering inflammation and promoting immune homeostasis.[26]

Psychobiotics also play a vital role in regulating the HPA axis, which controls the body's stress response. By influencing cortisol levels, psychobiotics can help modulate stress reactions and promote relaxation.[27] A diverse and complete native microbiota, comprising both aerobic and anaerobic bacteria—especially anaerobic strains like *Bifidobacterium*—may mitigate the adverse effects of elevated plasma glucocorticoid levels, thereby reducing stress-induced physiological disturbances.[28]

Moreover, psychobiotics have a positive impact on the production of BDNF, a protein essential for neuronal growth, differentiation, and survival. Increased BDNF levels support neuroplasticity and neuroprotection, contributing to overall brain health and cognitive resilience.[29] By enhancing BDNF synthesis, psychobiotics may aid in the treatment of neurodegenerative and mood illness.[30]

Psychobiotics In Mental Health Disorder

- **Depression**

Psychobiotics, play a role in modulating the gut-brain axis and have gained recognition as adjunctive therapies for depression. They work by restoring gut microbiota balance, reducing neuroinflammation, enhancing neurotransmitter production, regulating the HPA axis, and increasing BDNF expression. Specific probiotic strains promote production of neurotransmitters like as serotonin, GABA, and dopamine, reduce cortisol levels, and lower pro-inflammatory cytokines, thereby mitigating stress and anxiety. Microbial metabolites like SCFAs improve brain function by modulating neuroinflammation and energy metabolism.[31]

Preclinical studies support the role of psychobiotics in depression. For instance, *Lactobacillus rhamnosus* in mouse models has shown reduced anxiety and depressive-like behavior by modulating GABA receptors, lowering corticosterone levels, and improving stress response. Similarly, *Bifidobacterium longum* has demonstrated the ability to restore gut microbiota balance, reduce neuroinflammatory markers, and increase BDNF expression in stress-induced depression models. Clinical trials further reinforce these findings. A double-blind trial involving a control group involving *Lactobacillus helveticus* and *Bifidobacterium longum* showed notable decreases in stress and anxiety, along with improvements in mood and cognitive function. [32] A meta-analysis published in *Gut Pathogens* in 2023 examined the effects of probiotics on depression and anxiety. The analysis found that probiotics containing *Lactobacillus* (*L. acidophilus, L. paracasei, L. casei, L. plantarum, L. salivarius*) and *Bifidobacterium* (*B. bifidum, B. lactis, B. breve, B. longum*) strains are commonly linked to a noteworthy reducation in depressive symptoms, as measured by the Beck Depression Inventory (BDI). However, decreases in the Hamilton Depression Rating Scale (HAM-D), which measures depressed symptoms were not statistically significant.[33] Emerging evidence also suggests that fecal microbiota transplant (FMT) from healthy individuals may improve depressive symptoms by modifying gut microbiota composition. [34]

- **Schizophrenia**

Psychobiotics, have been recognized as an innovative therapeutic strategy for influencing the gut-brain axis in schizophrenia by working on restoring gut microbiota balance, reducing neuroinflammation and oxidative stress, enhancing neurotransmitter regulation (dopamine, glutamate, GABA), modulating immune responses and the HPA axis, and improving metabolic and cognitive impairments. Preclinical trial have demonstrated that specific probiotic strains can enhance dopamine and glutamate activity, reduce pro-inflammatory cytokines, decrease cortisol levels, and provide antioxidant effects, thereby protecting against neuronal damage. [35]

Clinical research on psychobiotics in schizophrenia includes a randomized, double-blind, placebo-controlled trial demonstrating that probiotic supplementation reduced symptom severity in patients receiving antipsychotic treatment.The study also found improvements in gastrointestinal dysfunction, a common issue in individuals with schizophrenia. [36]

- **Stress and Resilience**

Psychobiotics have been recognized as key modulators of stress and resilience by influencing the gut-brain axis, restoring gut microbiota composition, regulating the HPA axis, and reducing neuroinflammation. By increasing the synthesis of neurotransmitters like as serotonin, GABA, and dopamine, psychobiotics help mitigate the adverse effects of stress. Additionally, the gut microbiota produces short-chain fatty acids (SCFAs), which are involved in neuroprotection and anti-inflammatory effects, promoting resilience against stress.[37]

Preclinical studies have demonstrated that *Lactobacillus rhamnosus* reduces stress-induced corticosterone levels, anxiety-like behaviour, and modulates GABA receptor expression, thereby improving stress resilience. Similarly, *Bifidobacterium breve* has been found to enhance neuroplasticity and reduce neuroinflammation in stress-exposed mice. [38]

Clinical trials further support these findings. According to a double-blind, placebo-controlled investigation, Bifidobacterium longum and Lactobacillus helveticus supplementation significantly reduced perceived stress and cortisol levels in healthy individuals while improving mood and cognitive function. Another study on medical students experiencing exam-related stress revealed that probiotic intake enhanced emotional resilience and reduced anxiety, correlating with gut microbiota alterations. Moreover, emerging evidence suggests that faecal microbiota transplant (FMT) from resilient individuals may enhance stress tolerance and emotional regulation. [39]

- **Cognitive disorder**

Probiotics and prebiotics that target the gut-brain axis are known as psychobiotics, and they have shown promise as treatment for cognitive disorders. They modulate neuroinflammation, oxidative stress, and neurotransmitter synthesis while improving gut microbiota balance. Psychobiotics enhance the production of beneficial metabolites, such as short-chain fatty acids, which support neuroprotection. Certain probiotic strains also influence acetylcholine, dopamine, and serotonin levels, supporting cognitive function and memory retention.[39]

Preclinical research has shown that certain strains of Lactobacillus and Bifidobacterium have the ability to reduce amyloid-beta accumulation, decrease neuroinflammation, and improve learning and memory performance in rodent models of Alzheimer's disease. In clinical settings, according to a comprehensive analysis of randomized clinical studies, taking supplements of psychobiotics, particularly with strains of Lactobacillus and Bifidobacterium, was effective in improving symptoms of psychiatric and cognitive disorders.

Commercially available Psychobiotics

The Align® Probiotic, containing Bifidobacterium longum subsp. infantis 35624™, is a strain developed help promote intestinal health and reduce irritable bowel syndrome (IBS) symptoms. It has been shown to improve gastrointestinal symptoms.[40] The Cultureelle® Daily Probiotic, containing Lactobacillus rhamnosus GG, is renowned for its capacity to restore gut microbiota balance and support digestive health.[41] The Florastor® Probiotic, containing Saccharomyces boulardii lyo CNCM I-745, helps balance gut flora and may contribute to improved mental health and cognitive function. The Visbiome® High Potency Probiotic supports gut health and may influence stress levels, cognition, and overall mental wellness.

Procs and Cros of Psychobiotics

Psychobiotics, a specialized category of probiotics and prebiotics, have attracted considerable interest for their potential role in improving mental health by influencing the gut-brain axis, as they have been associated with the alleviation of anxiety, depression, and stress symptoms, likely due to their role in neurotransmitter production, such as serotonin and gamma-aminobutyric acid (GABA).[42] Additionally, psychobiotics contribute to cognitive enhancement, improved memory, and reduced neuroinflammation, which may be beneficial for neurological disorders such as Alzheimer's and Parkinson's disease.[43] They have also been linked to better sleep quality and overall gut microbiota regulation, which further supports mental well-being.[44] Furthermore, psychobiotics generally have fewer adverse effects compared to traditional psychotropic medications, making them a promising adjunctive treatment in psychiatry.[45]

Despite these potential benefits, several challenges remain. A key limitation is the absence of robust clinical evidence, as more high-quality, large-scale human trials are required to validate their efficacy.[46] The effects of psychobiotics are strain-specific, meaning that not all probiotic formulations exert mental health benefits, and individual responses may vary based on gut microbiota composition.[47] Furthermore, psychobiotics may take weeks to months to exhibit noticeable effects, which could limit their immediate clinical applicability.[48] Regulatory challenges also pose a concern, as there are no standardized guidelines for their use in psychiatric conditions, and high-quality supplements may be costly.[49] Some people may encounter minor side effects, including bloating, gas, or digestive discomfort which could impact adherence to treatment.[50] Despite these challenges, the growing body of research suggests that psychobiotics hold promise as a novel therapeutic approach in mental health and neurological disorders, necessitating further studies to establish their efficacy and safety. Future research should focus on large-scale clinical trials to establish standardized guidelines for psychobiotic use in mental health care. Additionally, exploring personalized approaches based on microbiome analysis may enhance therapeutic outcomes.

Conclusion:

Psychobiotics represent a novel and expanding field in the management of mental health disorders, bridging the gap between microbiome research and neuropsychiatry. Current evidence supports their potential in modulating neuroinflammation, neurotransmitter synthesis, and stress responses, offering new avenues for intervention in conditions like depression, anxiety, and schizophrenia. However, despite promising findings, challenges such as inter-individual variability, dosage standardization, and long-term safety require further investigation. The future of psychobiotic therapy lies in personalized medicine, leveraging microbiome profiling to tailor interventions. Continued research and clinical trials will be essential to establish psychobiotics as a validated, evidence-based approach in mental healthcare.

References:

1. Sonali S, Ray B, Tousif H, Rathipriya A, Sunanda T, Mahalakshmi A, *et al.* Mechanistic insights into the link between gut dysbiosis and major depression: an extensive review. Cells. (2022) 11:1362. Doi: 10.3390/cells11081362
2. Engen P, Green S, Voigt R, Forsyth C, Keshavarzian A. The gastrointestinal microbiome: alcohol effects on the composition of intestinal microbiota. Alcohol Res. (2015) 37:223–36.
3. Munawar N, Ahsan K, Muhammad K, Ahmad A, Anwar M, Shah I, *et al.* Hidden role of gut microbiome dysbiosis in schizophrenia: antipsychotics or psychobiotics as therapeutics? Int J Mol Sci. (2021) 22:7671. Doi: 10.3390/ijms22147671
4. Vasiliu, O. Is fecal microbiota transplantation a useful therapeutic intervention for psychiatric disorders? A narrative review of clinical and preclinical evidence. Curr Med Res Opin. (2022) 39:161–77. Doi: 10.1080/03007995.2022.2124071
5. Tomizawa Y, Kurokawa S, Ishii D, Miyaho K, Ishii C, Sanada K, *et al.* Effects of psychotropics on the microbiome in patients with depression and anxiety: considerations in a naturalistic clinical setting. Int J Neuropsychopharmacol. (2021) 24:97–107. Doi: 10.1093/ijnp/pyaa070
6. Cussotto S, Clarke G, Dinan T, Cryan J. Psychotropics and the microbiome: a chamber of secrets. Psychopharmacology (Berl). (2019) 236:1411–32. Doi: 10.1007/s00213-019-5185-8
7. Agenagnew L, Kassaw C. The lifetime prevalence and factors associated with relapse among mentally ill patients at JIMMA university medical center, ethiopia: cross sectional study. J Psychosoc Rehabil Ment Health. (2020) 7:211–20. Doi: 10.1007/s40737-020-00176-7
8. Howes O, Thase M, Pillinger T. Treatment resistance in psychiatry: state of the art and new directions. Mol Psychiatry. (2022) 27:58–72. Doi: 10.1038/s41380-021-01200-3
9. De Vrese M, Schrezenmeir J. Probiotics, prebiotics, and synbiotics. Adv Biochem Eng Biotechnol. (2008) 111:1–66. Doi: 10.1007/10_2008_097
10. Dinan T, Stanton C, Cryan J. Psychobiotics: a novel class of psychotropics. Biol Psychiatry. (2013) 74:720–6. Doi: 10.1016/j.biopsych.2013.05.001
11. Del Toro-Barbosa M, Hurtado-Romero A, Garcia-Amezquita L, García-Cayuela T. Psychobiotics: mechanisms of action, evaluation methods and effectiveness in applications with food products. Nutrients. (2020) 12:3896. Doi: 10.3390/nu12123896
12. Muench J, Hamer A. Adverse effects of antipsychotic medications. Am Fam Physician. (2010) 81:617–22.
13. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nat Med. (2019) 25:716–29. Doi: 10.1038/s41591-019-0439-x

14. Tremblay A, Lingrand L, Maillard M, Feuz B, Tompkins T. The effects of psychobiotics on the microbiota-gut-brain axis in early-life stress and neuropsychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry. (2021) 105:110142. Doi: 10.1016/j.pnpbp.2020.110142
15. Lewandowska-Pietruszka, Z.; Figlerowicz, M.; Mazur-Melewska, K. The History of the Intestinal Microbiota and the Gut-Brain Axis. Pathogens 2022, 11, 1540.
16. Zhu, S.; Jiang, Y.; Xu, K.; Cui, M.; Ye, W.; Zhao, G.; Jin, L.; Chen, X. The Progress of Gut Microbiome Research Related to Brain Disorders. J. Neuroinflamm. 2020, 17, 25.
17. Bhargava, A.; Knapp, J.D.; Fiehn, O.; Neylan, T.C.; Inslicht, S.S. The Lipidome of Posttraumatic Stress Disorder. BioRxiv 2024.
18. Cullen, C.M.; Aneja, K.K.; Beyhan, S.; Cho, C.E.; Woloszynek, S.; Convertino, M.; McCoy, S.J.; Zhang, Y.; Anderson, M.Z.; Alvarez-Ponce, D.; *et al.* Emerging Priorities for Microbiome Research. Front. Microbiol. 2020, 11, 491374.
19. Monroe, S.M.; Harkness, K.L. Major Depression and Its Recurrences: Life Course Matters. Annu. Rev. Clin. Psychol. 2022, 18, 329–357.
20. Nirudya, V.; Mohan Reddy, M.; Chandrasekhar, R.S.; Purushotham, A.; Mano Ranjitha, V. Prevalence of Depression in School- Going Adolescents and Its Impact on Scholastic Performance: A Cross-Sectional Study. Cureus 2023, 15, e38340.
21. Suicide. Available online: https://www.who.int/news-room/fact-sheets/detail/suicide (accessed on 30 May 2024).
22. Sarkar A, Harty S, Lehto SM, Moeller AH, Dinan TG, Cryan JF, *et al.* The microbiome in psychology and cognitive neuroscience. Trends Cogn Sci. 2018;22(7):611-36
23. Dinan TG, Stanton C, Cryan JF. Psychobiotics: a novel class of psychotropic. Biol Psychiatry. 2013;74(10):720-6.
24. Mazzoli R, Pessione E. The neuro-endocrinological role of microbial glutamate and GABA signaling. Front Microbiol. 2016;7:1934.
25. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, *et al.* Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A. 2012;109(38):16089-94.
26. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. Ther Adv Gastroenterol. 2013;6(1):39-51.
27. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behavior. Nat Rev Neurosci. 2012;13(10):701-12.
28. Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: regulation by the microbiome. Neurobiol Stress. 2017;7:124-36.

29. Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci. 2013;14(1):7-23.
30. Allen AP, Hutch W, Borre YE, Kennedy PJ, Temko A, Boylan G, *et al.* Bifidobacterium longum 1714 as a translational psychobiotic: Modulation of stress, electrophysiology and neurocognition in healthy volunteers. Transl Psychiatry. 2018;8(1):1-12.
31. Junzhe Cheng, Hongkun Hu, Yumeng Ju, Jin Liu, Mi Wang, Bangshan Liu, Yan Zhang - Gut microbiota-derived short-chain fatty acids and depression: deep insight into biological mechanisms and potential applications: General Psychiatry 2024;37:e101374.
32. Griffiths A, Rucklidge JJ, Kuijer RG, Frampton C. A double-blind, randomized, placebo-controlled trial of Lactobacillus helveticus and Bifidobacterium longum for the symptoms of depression. Aust N Z J Psychiatry. 2017;51(8):810-821. doi:10.1177/0004867416686694.
33. Rahmannia, M., Poudineh, M., Mirzaei, R. *et al.* Strain-specific effects of probiotics on depression and anxiety: a meta-analysis. Gut Pathog 16, 46 (2024). https://doi.org/10.1186/s13099-024-00634-8
34. Meyer N, Steinmann J, Kiderlen AF, *et al.* Dietary nitrate intake and its potential role in human health: A review. Nutrients. 2024;16(9):1352. doi: 10.3390/nu16091352.
35. Duan J, Yin H, Zhang Y, Zhang J, Fu W, Jin F. Psychobiotics: The next-generation probiotics for the brain. *Appl Microbiol Biotechnol.* 2021;78:449–63. doi:10.1007/s00253-020-11050-1.
36. McNiel D, Fenton M, McFarland BH, *et al.* Effect of probiotic supplementation on schizophrenia symptoms and association with gastrointestinal functioning: A randomized, placebo-controlled trial. Prim Care Companion CNS Disord. 2014;16(1):e1-6. doi: 10.4088/PCC.13m01579.
37. Binda S, Tremblay A, Iqbal UH, *et al.* Psychobiotics and the microbiota–gut–brain axis: Where do we go from here? Microorganisms. 2024;12(4):634. doi: 10.3390/microorganisms12040634.
38. Reddy A, Mankal N, Sagar YN, *et al.* Comprehensive review on psychobiotics: The next-generation microbial biomedicine and biotherapeutics. Acta Sci Microbiol. 2025;8(1): [page numbers].
39. Ķimse L, Reinis A, Miķelsone-Jansone L, *et al.* A narrative review of psychobiotics: Probiotics that influence the gut–brain axis. Medicina. 2024;60(4):601. doi: 10.3390/medicina60040601.
40. PG Science Behind. Align® clinical data. Available from: https://www.pgsciencebehind.com/en-ca/align/clinical-data/.
41. Culturelle Probiotic. Digestive Daily Probiotic. Available from: https://culturelleprobiotic.ca/products/digestive-daily-probiotic/.

42. Dinan TG, Cryan JF. The microbiota-gut-brain axis in health and disease. Gastroenterol Clin North Am. 2017;46(1):77–89.
43. Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PW. Psychobiotics and the manipulation of bacteria–gut–brain signals. Trends Neurosci. 2016;39(11):763–81.
44. Liu RT, Walsh RFL, Sheehan AE. Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials. Neurosci Biobehav Rev. 2019;102:13–23.
45. Wallace CJK, Milev R. The effects of probiotics on depressive symptoms in humans: A systematic review. Ann Gen Psychiatry. 2017;16:14.
46. Westfall S, Lomis N, Kahouli I, Dia SY, Singh SP, Prakash S. Microbiome, probiotics, and neurodegenerative diseases: Deciphering the gut-brain axis. Cell Mol Life Sci. 2017;74(20):3769–87.
47. Clapp M, Aurora N, Herrera L, Bhatia M, Wilen E, Wakefield S. Gut microbiota's effect on mental health: The gut-brain axis. Clin Pract. 2017;7(1):987.
48. O'Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF. Serotonin, tryptophan metabolism and the brain–gut–microbiome axis. Behav Brain Res. 2015;277:32–48.
49. Huang TT, Lai JB, Du YL, Xu Y, Ruan LM, Hu SH. Current understanding of gut microbiota in mood disorders: An update of human studies. Front Genet. 2019;10:98.
50. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: Mechanisms of intestinal immunomodulation and neuromodulation. Therap Adv Gastroenterol. 2013;6(1):39–51.

GREEN SYNTHESIS AND NANOPARTICLES

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Introduction:

Because of its cheap cost, benign precursors, and ease of maintenance, the green approach—which uses a variety of plants and bacteria to synthesize nanoparticles (NPs)—may be superior to chemical and physical approaches. (Zhu *et al*., 2019). The experimental setup of high-performing but reasonably priced technology that is safe for both humans and the environment is the focus of green synthesis. It seeks to reduce the amount of chemical waste produced and guarantees sustainable operations to support economic growth. It focuses on nanoparticles (NPs) made using environmentally friendly methods as functional materials with exceptional qualities that have a broad range of uses in industries like electronics, food, medicine, agriculture, textiles, energy, and the environment. Numerous natural resources, including plant extracts (Sithara *et al*., 2017), cyclodextrin (Abou-Okeil *et al*., 2012), chitosan (Mokhena and Luyt, 2017), and several others, have been studied for the production of nanoparticles. Green methods for creating nanoparticles (NPs) include using biological components and natural extracts from plant parts (leaves, roots, flowers, and fruit) as well as biometabolites from organisms like bacteria, algae, fungus, etc. Improved rate performance was shown by using convenient plant extracts for the manufacture of transition metal-based oxide (TMO) nanoparticles. For instance, in the environmentally friendly manufacturing of metal or metal oxide nanoparticles, plant products such as phytochemicals made up of ketones, aldehydes, flavones, amides, terpenoids, carboxylic acids, phenols, or ascorbic acids from leaves are utilized. These substances can transform metal salts into metal nanoparticles. (Doble *et al*., 2010).

However, the high-dose usage of broad-spectrum antibiotics in the medical or agricultural sectors resulted in acquired resistance or increased systemic toxicities in the host. Some of the available antimicrobials include decreased specificity at the site of infection, decreased permeability against the host body, or partial or total destruction of the pathogens' chemical structure by endogenous restriction enzymes. Enhancement is especially necessary for adequate

dissemination from the administration site and effective local control in the infected areas. (Khezerlou *et al.,* 2018). Given the aforementioned instances, the development of novel and effective antimicrobial medications that either eradicate germs or at the very least stop their growth at relatively low doses without endangering the host species is imperative. Advanced nanotechnology research has led to the discovery of novel antimicrobial compounds with considerable antibacterial efficacy against multidrug-resistant infections, suggesting a new strategy to prevent microbial pathogenesis. (Jiang *et al.,* 2009, Sen *et al.,* 2014).

Some unique properties of green synthesized nanoparticles (GrNPs) about their antimicrobial properties are summarized as follows:

Biological substances serve as both capping and reducing agents in the production of GrNPs. There are several benefits to this bio-encapsulation, including.

i. Preventing the NPs from clumping together

ii. Lowering the toxicity and

iii. Enhancing NPs' antibacterial activity.

GrNPs can maintain size, shape, and colloidal stability by being encapsulated within relatively non-toxic capping agents.

- The reducing and capping materials of the GrNPs contain various naturally occurring compounds such as alkaloids, terpenoids, phenolics, vitamins, co-enzymes carbohydrates, enzymes, and proteins that increase the probability of attachment and action of GrNPs on the microbial cells.
- The coating agents of GrNPs sometimes show antimicrobial action, a synergistic effect of NPs and the capped bio-molecules hence fortifying the antimicrobial action.
- Fast growth and prompt participation of bio-materials in the GrNPssynthesis eliminate the technical hurdles of downstream processing.
- The process is simple and cost-effective. There is no requirement for high pressure, energy, temperature, or chemicals.
- The risk of contamination is also lower and has great potential as a prospective nano-medicine.

To date, NPs of different sizes and shapes have been produced using plant extracts. It is particularly advantageous over the microbiological technique or the physical and chemical route because the rate of synthesis reaction is much faster and the range of NPs' sizes and forms is unconstrained. (Devatha and Thalla, 2018). One of the main challenges in producing NPs for environmental remediation is controlling particle size and form. In green synthesis techniques, it was shown that factors including pH, temperature, and reaction duration affected these characteristics. The green synthesis process using plant extracts has garnered significant attention due to its main advantages, which include its cost, convenience of application, nontoxicity, efficacy, viability, and potential to generate stable nanoparticles on a large scale (Figure 1), which doesn't lose quality nor display any physical change even after a long period.

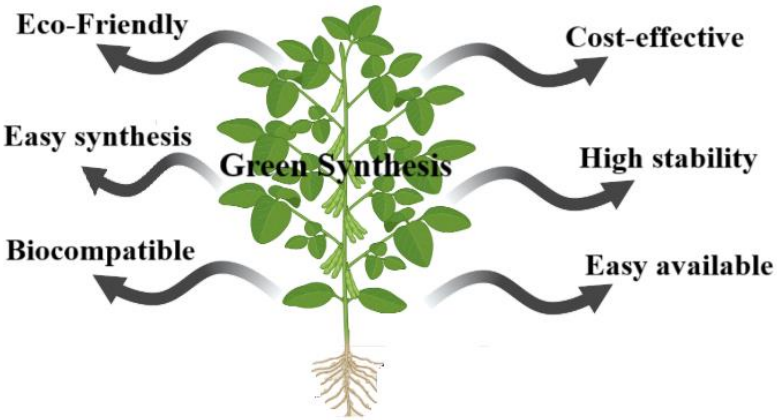

Fig. 1: The main advantages of green synthesis.

History of Nanoparticles

Although they have existed for a long time, nanoparticles are considered a contemporary scientific discovery. Ancient people have been using nanotechnology for thousands of years. It's unclear, though, when the advantages of nanoparticles in several sectors were first realized. Nanoparticles have been used in painting since before the fourth century AD due to their optical qualities. The most well-known example is the Lycurgus cup in Figure 2. The optical nature of nanoparticles is one of its primary and fundamental properties.

Fig. 2. Lycurgus cup that displays different colors (Tiwari *et al.*, 2012)

This cup is at the British Museum in London. This amazing cup is an ideal example of history. It is made of a special type of glass known as dichroic glass. It can change color when exposed to light. When light hits the cup at a 900 angle, its opaque green hue transforms into a beautiful transparent color.

The British Museum in London is home to this cup. This beautiful cup is the perfect illustration of history. It is composed of dichroic glass, a unique kind of glass. When it is exposed to light, it can change color. The cup's opaque green tint changes to a stunning translucent tone when light strikes it at a 900 angle.

In the seventeenth century, a colorant known as the "Purple of Cassius," which was created from tin dioxide and gold particles, was used in glasses. In 1718, Helcher wrote a thorough treatise on colloidal gold. (Horikoshi and Serpone, 2013).

In a well-known paper from 1857, Michael Faraday (Brust *et al.*, 1994) outlined how colloidal gold creates bright red solutions when phosphorus lowers an aqueous solution of chloroaurate (AuCl4) in the presence of CS2. Furthermore, he looked at thin coatings' optical properties. He added that films can change from bluish-purple to green in a reversible manner. The synthesis, assembly, properties, and alteration of metal nanoparticles were later the subject of several academic publications. After that, metal nanoparticles were used as extra substrates and other solvents. James Clerk Maxwell presented a new concept for nanotechnology and a tiny creature known as the "Maxwell Demon" in 1867. It was he who invented color photography.

Maxwell states that the creation of light-sensitive nanoparticles is essential to color photography.

"Old nanotechnology" is the term used to describe chemical catalysis. In the first decade of the twentieth century, Richard Adolf Zsigmondy used the darkfield technique with an ultramicroscope to measure and analyze the size of gold and other nanoparticles. The first word he used was "nanometer." He won the 1925 Nobel Prize in Chemistry for his groundbreaking research. In 1974, Nario Taniguchi came up with the phrase "nanotechnology." He explained the material, which is less than a millimeter. (Komanduri *et al.*, 1997).

In the subject of nanotechnology (Ulman, 2013), Eric Drexler popularized (Drexler,1992) and is a well-known scientist (Drexler, 1994). In 1986, He wrote a book called "Engine of Creation." In this study, he first used a universe of tiny mechanics and assemblers. Gred Bining and Heinrich Rohrer earned the Nobel Prize in 1986 for their creation of a scanning tunneling microscope (STM), and these small mechanics and assemblers created a unique structure in 1981 with atomic-level accuracy. It is possible to locate specific surface atoms using STM. In 1980, Richard E. Smalley discovered a Buckminsterfullerene with a collaborator. It is a carbon molecule shaped like a soccer ball. Buckminsterfullerene is an artificially produced carbon allotrope. Richard E. Smalley won the Nobel Prize in 1996 because he discovered Buckminster. SumioIijima discovered carbon nanotubes (Iijima, 1991).

Classification of Green Synthesis

A rapidly growing technical sector and a burgeoning area of research in several application domains are nanoparticles (NPs) and nanomaterials (NMs). because of their modifiable physicochemical characteristics, which include melting point, catalytic activity, thermal and electrical conductivity, light absorption, wettability, and scattering. The importance of NPs and NMs in technological advancements has grown. An SI (System International of Units, SI) unit of length equivalent to 10^{-9} meters is called a nanometer. Although NMs are commonly regarded as having a diameter of 1-100 nm, they are technically defined as materials with at least one dimension length of 1-1000 nm.

Research in nanotechnology has gained popularity during the past century. The term nanotechnology was coined by Richard P. Feynman in his famous 1959 speech, "There is a Plenty of Room at the Bottom" (Feynman, 1960). At the nanoscale Nanotechnology has

generated a wide range of materials. Nanoparticles can be synthesized using a variety of techniques (Figure 3).

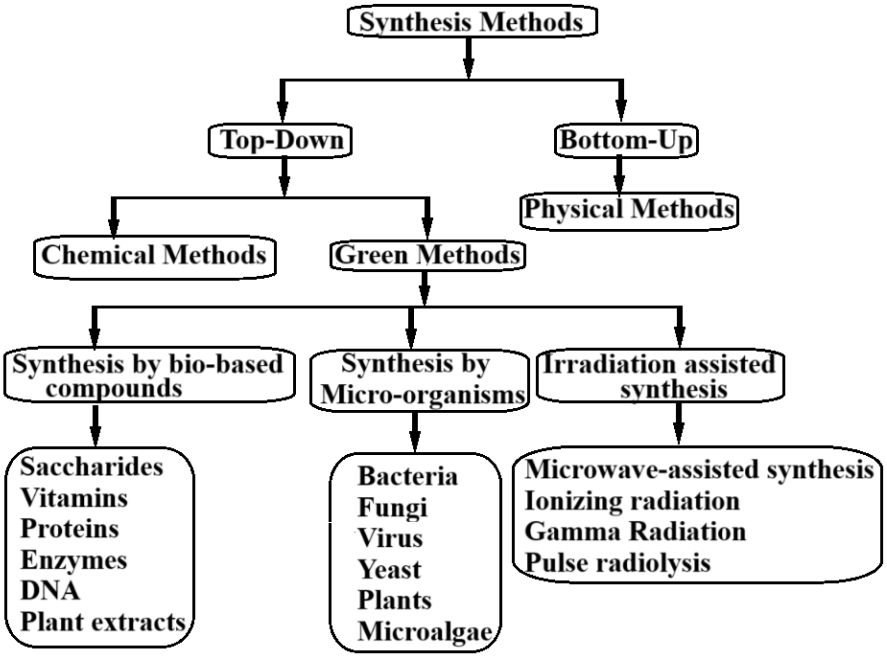

Fig. 3: Synthetic method of Nanoparticles

A simple, effective, cost-effective, and environmentally friendly biological synthesis method can be used to produce green-synthesized NPs (Maurya *et al.,* 2016). As illustrated in Figure 4, metallic nanoparticles can be produced from cell or cell-free extracts of a range of biological resources. Green chemistry principles, such as the choice of a solvent medium, environmentally friendly reducing agent, and non-toxic material for nanoparticle stabilization, should be the primary consideration during the nanoparticle creation process (Baruwati and Varma, 2009).

Additionally, it was shown that substances from coffee and tea extracts, such as peptides, polyphenolics, sugars, vitamins, and water, were suitable for the creation of nanoparticles [Baruwati *et al.,* 2009, Polshettiwar *et al.,* 2009]. Plant extract reduces metal ions faster than microbial NPs and plant-based NPs are more stable and monodispersed. Among the methods for creating nanomaterials is microbial synthesis.

At the nanoscale Nanotechnology has generated a wide range of materials. Nanoparticles are classified into different classes. Particles with sizes ranging from 1 to 100 nm are known as nanoparticles (Laurent *et al.,* 2008). Depending on their shape, the nanoparticles can be 0D, 1D, 2D, or 3D (Tiwari JN *et al.,* 2012). When scientists discovered that size might impact a substance's physio-chemical characteristics, including its optical qualities, they recognized the importance of these nanoparticles. Figure 5 illustrates the three layers that make up nanoparticles, which are not simple molecules.

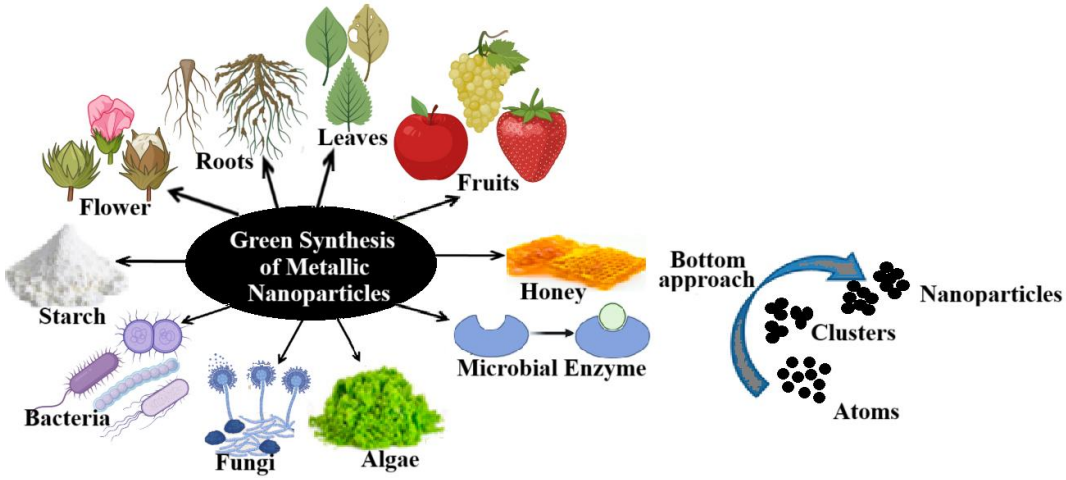

Fig. 4: Different types of green synthesis are used for the preparation of metal nanoparticles

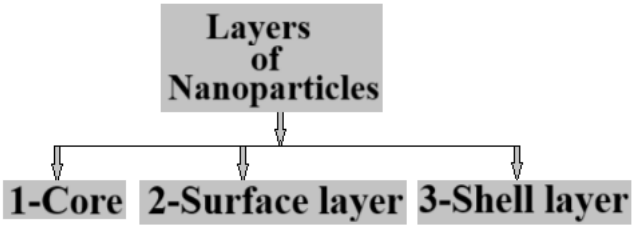

Fig. 5: Different layer of nanoparticles (Shin *et al.*, 2016)

Classification of Nanoparticles

Based on the origin nanomaterials are classified into Natural and artificial nanoparticles (Tiwari *et al.*, 2022, Khan and Hossain, 2022).

1. Natural nanomaterials

Viruses, protein molecules, minerals like clay, natural colloids like milk and blood (liquid colloids), fog (aerosol type), gelatin (gel type), mineralized natural materials like shells, corals, and bones, insect wings and opals, spider silk, lotus leaves, gecko feet, volcanic ash, and ocean spray are just a few examples of the diversity of natural nanomaterials that can be found in nature (Tiwari *et al.*, 2022, Khan and Hossain,2022).

2. Artificial nanomaterials

Examples of artificial nanomaterials that are purposefully created utilizing exacting mechanical and manufacturing processes are carbon nanotubes and semiconductor nanoparticles like quantum dots (QDs). Depending on their structural composition, nanomaterials are classified as metal-based materials, dendrimers, or composites (Tiwari *et al.*, 2022, Khan and Hossain, 2022). Further, the nanoparticles are also classified into different types based on morphology, size, and shape. Some of the important classes of nanoparticles are mentioned as follows:

3. Organic nanoparticles

These properties make organic nanoparticles the perfect option for medication delivery. Then, target drug delivery is another common application for nanoparticles. Ferritin, liposomes,

dendrimers, and micelles are examples of organic nanoparticles. Certain organic nanoparticles, such as liposomes and micelles, have a hollow sphere and are biodegradable and non-toxic. Additionally, it is familiar under the name of heat- and light-sensitive nanocapsules (Cho *et al.,* 2019). Micelles, dendrimers, liposomes, nanogels, polymeric nanoparticles, and layered biopolymers are a few of the several forms of organic nanoparticles shown in Figure 6.

Micelles and liposomes are examples of organic nanoparticles with hollow spheres that are both biodegradable and non-toxic. Additionally, organic nanoparticles can decompose spontaneously. Nanocapsules, which are highly sensitive to heat and light, are also referred to by this name (Rao and Geckeler, 2011). Organic nanoparticles are a great choice for pharmaceutical transportation because of these characteristics. Transporting target drugs to their designated places is another common application for nanoparticles. Polymeric nanoparticles is another term occasionally used to describe organic nanoparticles. The most well-known type of organic or polymeric nanoparticle is the nanosphere or nanocapsule (Pantic, 2010).

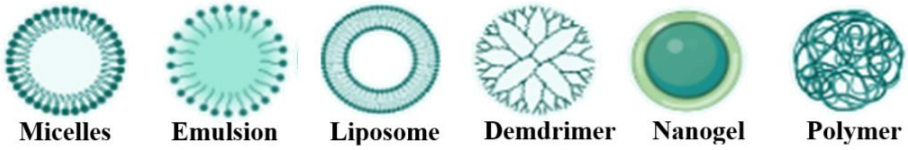

Fig. 6: Organic nanoparticles

4. Inorganic nanoparticles

Inorganic nanoparticles do not contain carbon. There is no toxicity from the inorganic nanoparticles. The inorganic nanoparticles exhibit hydrophilia and biocompatibility. Compared to organic nanoparticles, inorganic ones are much more stable. Large material chunks can be divided (the top-down method) to create inorganic nanoparticles, or individual atoms and molecules can be integrated into larger nanostructures (the bottom-up method). Regarding the range of sizes of achievable objects, both approaches converge (Figure 7). The bottom-up technique mostly applies to chemical processes used to create nanoparticles. The top-down strategy, on the other hand, is typically founded on mechanical and physical techniques. But top-down production also frequently uses chemical methods, particularly in nanolithography.

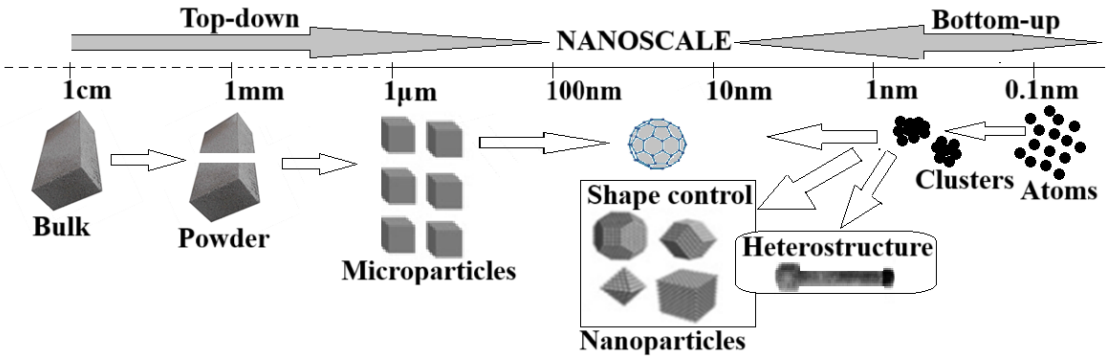

Fig. 7: Method for synthesis of inorganic nanoparticles

Since they don't include carbon atoms, they are referred to as inorganic nanoparticles. Metal-based or metal oxide-based nanomaterials are the usual categories for inorganic nanoparticles.

4.1. Metal-based nanoparticles

Destructive or constructive methods can be used to create metal-based nanoparticles. Metals that are commonly utilized in the synthesis of nanoparticles include aluminum (Al), cadmium (Cd), cobalt (Co), copper (Cu), gold (Au), iron (Fe), lead (Pb), silver (Ag), and zinc (Zn). In addition to their electrical, catalytic, thermal, and antibacterial qualities, metal nanoparticles have exceptional UV-visible sensitivity due to their quantum effects and large surface-to-volume ratio. Due to their exceptional optical characteristics, metal nanoparticles are employed in many different research domains.

4.2. Metal oxide nanoparticles

Positive metallic ions and negative oxygen ions makeup metal oxide nanoparticles, also referred to as metal oxide nanomaterials. Silicon dioxide (SiO_2), titanium oxide (TiO_2), zinc oxide (ZnO), and aluminum oxide (Al_2O_3) are examples of commonly manufactured metal oxide nanoparticles. When compared to their metal counterparts, these nanoparticles show exceptional properties (Khan*et al.*, 2022)

5. Ceramic Nanoparticles

Nonmetallic solids are another name for ceramic nanoparticles. Heating or subsequent cooling is used to create the ceramic nanoparticles. Polycrystalline, amorphous, porous, dense, or hollow ceramic nanoparticles are all possible (Sigmund *et al.*, 2006). Because of their many uses, including dye photodegradation, photocatalysis, catalysis, and imaging applications, the researcher concentrates on these nanoparticles (Thomas *et al.*, 2015).

6. Biological nanoparticles or Bionanoparticles

Numerous bio-mechanisms have been documented for the use of microbes in the synthesis of GrNPs (Figure 8). For example, microbial cells' surface or interior can trap metallic ions, which are then arrested and reduced into nanoparticles (NPs) by the enzymatic processes. Green biologically based techniques that use microbes and plants to create nanoparticles are safe, affordable, and environmentally beneficial, according to recent studies (Gowramma *et al.*, 2015, Makarov *et al.*, 2014). It has long been known that both plants and microbes can take up and retain inorganic metallic ions from their surroundings. Because of these appealing characteristics, a large number of biological entities are effective biological factories that can recover metals from industrial waste and drastically reduce environmental pollution. Crucially, a relatively new and mainly unexplored field of study has emerged as a result of a biological entity's capacity to convert inorganic metallic ions into metal nanoparticles using its natural biochemical processes (Baker *et al.*, 2013). Thus far, several biotechnology applications, including bioremediation and bioleaching, have taken use of microorganisms' capacity to

interact, remove, and collect metallic elements from their environment (Stephen and Macnaughton, 1999, Bollag *et al.,* 1994). Because of the makeup of their lipid-based amphipathic membranes, which allow a range of oxidation-reduction processes to occur and encourage metabolic transformations, microbes can actively interact with their surroundings (Mann, 1996, Bhattacharya and Gupta, 2005, Sastry *et al.,* 2004). According to studies, both unicellular and multicellular organisms can synthesize inorganic micron and nano-sized materials both extracellularly and intracellularly, as shown in Table 1. In the case of nanoparticle synthesis, culturing microorganisms in specific environments can also help them promote the coupled oxidation and reduction phenomenon (Mann, 1996, Bhattacharya and Gupta, 2005, Sastry *et al.,* 2004, Mandal *et al.,* 2006).

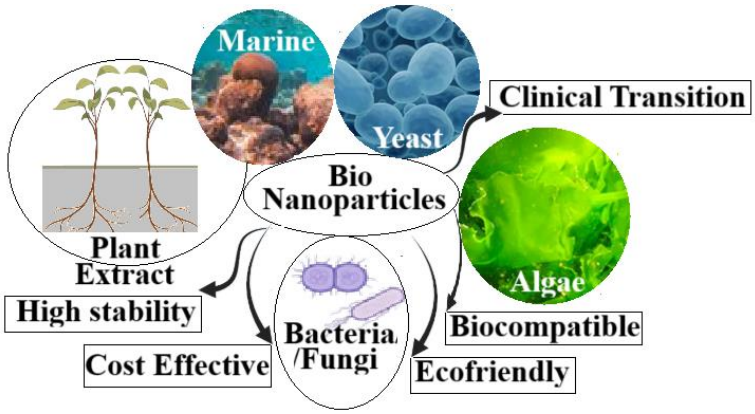

Fig. 8: The synthesis sources include but are not limited to bacteria, fungi, algae, yeasts, marine and plant sources

Table 1: Some examples of microorganisms used to synthesize nanoparticles

Microorganism	NPs	Size(nm)	Ext/Int	Application	Ref.
Bacteria					
Bacillus subtilis	Fe_3O_4	3-20	-----	Antimicrobial agent	Sundaram*et al.,* 2012
Cupriavidus sp.	Ag	10-50	Ext.	Antibacterial agent	Markus*et al.,* 2016
Desulfovibrio vulgaris	Pt	10-30	Ext.	Catalysts	Martins*et al.,* 2017
Escherichia coli	dS, Ag	2-5	Ext.	Antimicrobial agent	Sweeney*et al.,* 2004, Saeed*et al.,* 2020
Lactobacillus acidophillus	Ag	-----	Ext.	Gene Toxicity	Namasivayam*et al.* 2010
Lactobacillus kimchicus	Au	5-140	Int.	Antioxodent	Markus*et al.,* 2016
Pseudomonas aeruginosa	Au	15-30	Ext.		Husseiny*et al.,* 2007
Pseudomonas stutzeri	Ag	15-20	Int.	Antimicrobial agent	Klaus*et al.,* 1999

Paracoccushaeundaensis	Au	20	Ext.	Antioxidant	Pati*ent al*., 2019
Staphylococcus aureus	ZnO	100	Int.	Antibacterial agent	Rauf*et al.,* 2017
Fungi					
Aspergillus flavus	Ag	8-10	Int.		Vigneshwaran*et al.,* 2007
Aspergillus niger	Ag	3-20	Ext.	Antifungal agent	Gursoy, 2020
Aspergillus niger	Cu	-----		Antidiabetic	Zhang*et al.,* 2020
Colletotrichum sp.	Au	20-40	Ext.		Shankar *et al.,* 2003
Cladosporium cladosporioides	Ag	80-100		Antioxidant	Zhang*et al.,* 2020
Cladosporium cladosporioides	Ag	-----	Ext.	Antimicrobial	Zhang*et al.,* 2020
Cladosporium cladosporioides	Au	-----	Ext.	Antioxidant	Bhargava*et al.,* 2016
Fusarium oxysporum	Au	20-40	Ext.		Mukherjee*et al.,* 2002
Fusarium oxysporum	Cu	20-50	Ext.	Antibacterial	Ghosh*et al.,* 2021
Penicillium chrysogenum	Pt	5-40		Cytotoxicity	Gursoy, 2020
Volvariella volvacea	Au,Ag	20-150	Ext.		Philip, 2009
Actinomycetes					
Rhodococcus sp.	Au	5-15	Int.		Mishra *et al.,* 2012
Thermomonospora sp.	Au	8	Ext.		Sastry *et al.,* 2011
Algae					
Chlorella vulgaris	Au	40-60	Int.		Luangpipat*et al.,* 2011
Chlorella vulgaris	Pd	5-20	Ext.	Adsorbent	Arsiya*et al.,* 2017
Chaetomorpha linum	Ag	30	----	Anticancer	Acharya*et al.,* 2021
Sargassum wightii	Au, Ag	5-40	Int.		Singaravelu*et al.,* 2007
Spirulina platensis	Ag	25-50	Ext.	Antiviral	Muthusamy*et al.,* 2017
Spirulina platensis	Ag	----	Int.	Antiviral	Muthusamy*et al.,* 2017
Tetraselmiskochinensis	Au	5-35	----	Antiviral	Senapati *et al.,* 2012
Yeasts					
Baker's yeast	Fe_2O_3	----	Ext.	Detection of Glucose	Mishra *et al.,* 2011

Candida glabrata	CDs	2	Int.		Dameron*et al.*, 1989
Candida guilliermondii	Au	50-70	Ext.	Antimicrobial agent	Mishra*et al.*, 2011
Candida guilliermondii	Au	----	Int.	Antibacterial	Agnihotri*et al.*, 2009
Candida albicans	CdS	1.4	Int.	Bactericidal	Patil*et al.*, 2019
Saccharomycetes cerevisiae	Sb_2O_3	3-10	Int.		Jha*et al.*, 2009
Saccharomycetes cerevisiae	ZnS	10-20	Int.	Antibacterial	Mala*et al.*, 2014
Schizosaccharomyces pombe	CdS	1-2	Int.		Kowshik*et al.*, 2002, Gericke and Pinches, 2006
Torulopsis sp.	PBS	2-5	Int.		Kowshik*et al.*, 2002
Yeast strain MKY3	Ag	2-5	Ext.		Kowshik*et al.*, 2002

NPs: Nano Particle; Ext:Extracellular; Int:Intracellular

Application of Nanoparticles

Figure 9 illustrates the wide range of applications for nanomaterials, including chemical and cosmetic industries like nanoscale chemicals and compounds, paints, and coatings, and nanomedicine sectors like tissue engineering, medical devices, and nanodrugs.

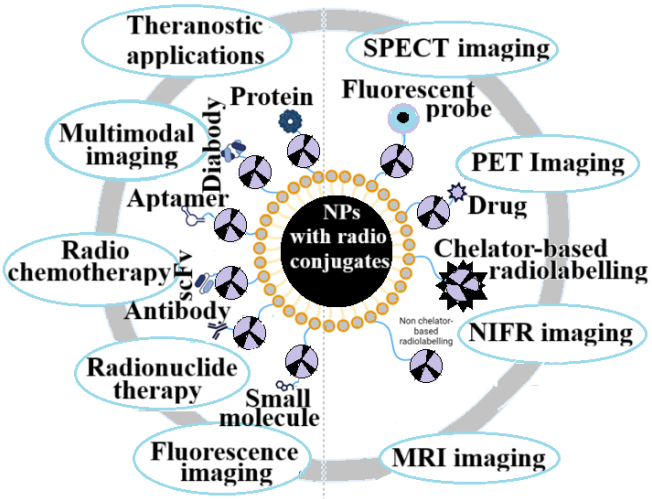

Fig. 9: Application of Nanoparticles

The fields of nanoparticles, carbon nanotubes, biopolymers, paints, and coatings; food sciences, including processing, nutraceutical foods, and nanocapsules; environment and energy, including fuel cells, photovoltaics, and water and air purification filters; military and energy, including biosensors, weapons, and sensory enhancement; electronics semiconductors, including chips, memory storage, photonic, and optoelectronics; and scientific tools, including atomic

force, microscopic and scanning tunneling microscopes (Huynh*et al.,* 2020, Naghdi*et al.*, 2018).

Conclusion:

To do this, there is increasing interest in using environmentally friendly methods, such as the use of biopolymers, plant extracts, and biomolecules. Because they meet the requirements for accessibility and biocompatibility and have multiple functions, including capping, reducing, and shape-modulating agents, they are perfect reagents. Figure 10 illustrates the number of benefits of biogenic synthesis as well as its significance.

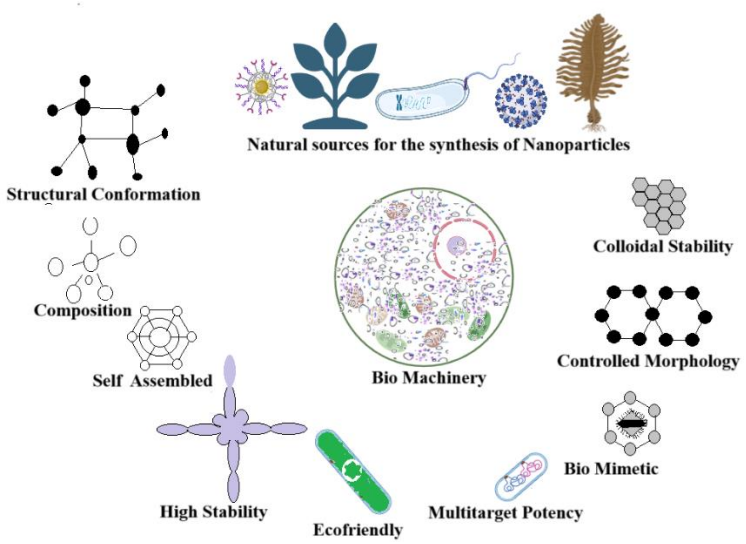

Fig. 10: Various advantages of biogenic synthesis

In specific domains, such as clean analytical methods, environmentally friendly analytical chemistry, and green analytical chemistry, the use of chemicals to assist prevent contamination is known as 'green chemistry.' Green synthesis can be used to create nanoparticles since it is environmentally safe, inert, and biocompatible.

References:

1. Zhu, X., Pathakoti, K., & Hwang, H. M. (2019). Green synthesis of titanium dioxide and zinc oxide nanoparticles and their usage for antimicrobial applications and environmental remediation. In *Green synthesis, characterization and applications of nanoparticles* (pp. 223-263). Elsevier.
2. Sithara, R., Selvakumar, P., Arun, C., Anandan, S., &Sivashanmugam, P. (2017). Economical synthesis of silver nanoparticles using leaf extract of Acalypha hispida and its application in the detection of Mn (II) ions. *Journal of advanced research*, *8*(6), 561-568.
3. Abou-Okeil, A., Amr, A., & Abdel-Mohdy, F. A. (2012). Investigation of silver nanoparticles synthesis using aminated β-cyclodextrin. *Carbohydrate polymers*, *89*(1), 1-6.
4. Mokhena, T. C., & Luyt, A. S. (2017). Electrospun alginate nanofibres impregnated with silver nanoparticles: Preparation, morphology and antibacterial properties. *Carbohydrate Polymers*, *165*, 304-312.

5. Doble, M., Rollins, K., & Kumar, A. (2010). *Green chemistry and engineering*. Academic Press.
6. Khezerlou, A., Alizadeh-Sani, M., Azizi-Lalabadi, M., & Ehsani, A. (2018). Nanoparticles and their antimicrobial properties against pathogens including bacteria, fungi, parasites and viruses. *Microbial pathogenesis*, *123*, 505-526.
7. Jiang, W., Mashayekhi, H., & Xing, B. (2009). Bacterial toxicity comparison between nano-and micro-scaled oxide particles. *Environmental pollution*, *157*(5), 1619-1625.
8. Sen, I. K., Mandal, A. K., Chakraborty, R., Behera, B., Yadav, K. K., Maiti, T. K., & Islam, S. S. (2014). Structural and immunological studies of an exopolysaccharide from Acinetobacter junii BB1A. *Carbohydrate polymers*, *101*, 188-195.
9. Devatha, C. P., &Thalla, A. K. (2018). Green synthesis of nanomaterials. In *Synthesis of inorganic nanomaterials* (pp. 169-184). Woodhead Publishing.
10. Tiwari, J. N., Tiwari, R. N., & Kim, K. S. (2012). Zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanostructured materials for advanced electrochemical energy devices. *Progress in Materials Science*, *57*(4), 724-803.
11. Horikoshi, S., &Serpone, N. (Eds.). (2013). *Microwaves in nanoparticle synthesis: fundamentals and applications*. John Wiley & Sons.
12. Brust, M., Walker, M., Bethell, D., Schiffrin, D. J., & Whyman, R. (1994). Synthesis of thiol-derivatised gold nanoparticles in a two-phase liquid–liquid system. *Journal of the Chemical Society, Chemical Communications*, (7), 801-802.
13. Komanduri, R., Lucca, D. A., & Tani, Y. (1997). Technological advances in fine abrasive processes. *CIRP annals*, *46*(2), 545-596.
14. Drexler, K. E. (1992). *Nanosystems: molecular machinery, manufacturing, and computation*. John Wiley & Sons, Inc..
15. Drexler, K. E. (1994). Molecular nanomachines: physical principles and implementation strategies. *Annual Review of Biophysics and Biomolecular Structure*, *23*(1), 377-405.
16. Ulman, A. (2013). *An Introduction to Ultrathin Organic Films: From Langmuir--Blodgett to Self--Assembly*. Academic press.
17. Iijima, S. (1991). Helical microtubules of graphitic carbon. *nature*, *354*(6348), 56-58.
18. Feynman, R. (2018). There's plenty of room at the bottom. In *Feynman and computation* (pp. 63-76). CRC Press.
19. Maurya, S., Bhardwaj, A. K., Gupta, K. K., Agarwal, S., Kushwaha, A., Vk, C., ... & Singh, M. P. (2016). Green synthesis of silver nanoparticles using Pleurotus and its bactericidal activity. *Cell. Mol. Biol*, *62*, 131.
20. Baruwati, B., & Varma, R. S. (2009). High value products from waste: grape pomace extract—a three-in-one package for the synthesis of metal nanoparticles. *ChemSusChem: Chemistry & Sustainability Energy & Materials*, *2*(11), 1041-1044.

21. Baruwati, B., Polshettiwar, V., & Varma, R. S. (2009). Glutathione promoted expeditious green synthesis of silver nanoparticles in water using microwaves. *Green chemistry*, *11*(7), 926-930.
22. Polshettiwar, V., Baruwati, B., & Varma, R. S. (2009). Self-assembly of metal oxides into three-dimensional nanostructures: synthesis and application in catalysis. *ACS nano*, *3*(3), 728-736.
23. Laurent, S., Forge, D., Port, M., Roch, A., Robic, C., Vander Elst, L., & Muller, R. N. (2008). Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. *Chemical reviews*, *108*(6), 2064-2110.
24. Shin, W. K., Cho, J., Kannan, A. G., Lee, Y. S., & Kim, D. W. (2016). Cross-linked composite gel polymer electrolyte using mesoporous methacrylate-functionalized SiO2 nanoparticles for lithium-ion polymer batteries. *Scientific reports*, *6*(1), 26332.
25. Tiwari, D. K., Behari, J., & Prasenjit Sen, P. S. (2008). Application of nanoparticles in waste water treatment, 3(3), 417-433
26. Khan, S., & Hossain, M. K. (2022). Classification and properties of nanoparticles. In *Nanoparticle-based polymer composites* (pp. 15-54). Woodhead Publishing.
27. Cho, G., Park, Y., Hong, Y. K., & Ha, D. H. (2019). Ion exchange: an advanced synthetic method for complex nanoparticles. *Nano Convergence*, *6*, 1-17.
28. Rao, J. P., &Geckeler, K. E. (2011). Polymer nanoparticles: Preparation techniques and size-control parameters. *Progress in polymer science*, *36*(7), 887-913.
29. Pantic, I. (2010). Magnetic nanoparticles in cancer diagnosis and treatment: novel approaches. *Rev. Adv. Mater. Sci*, *26*, 67-73.
30. Khan, Y., Sadia, H., Ali Shah, S. Z., Khan, M. N., Shah, A. A., Ullah, N., & Khan, M. I. (2022). Classification, synthetic, and characterization approaches to nanoparticles, and their applications in various fields of nanotechnology: A review. *Catalysts*, *12*(11), 1386.
31. Sigmund, W., Yuh, J., Park, H., Maneeratana, V., Pyrgiotakis, G., Daga, A., & Nino, J. C. (2006). Processing and structure relationships in electrospinning of ceramic fiber systems. *Journal of the American Ceramic Society*, *89*(2), 395-407.
32. C Thomas, S., Kumar Mishra, P., & Talegaonkar, S. (2015). Ceramic nanoparticles: fabrication methods and applications in drug delivery. *Current pharmaceutical design*, *21*(42), 6165-6188.
33. Gowramma, B., Keerthi, U., Rafi, M., & Muralidhara Rao, D. (2015). Biogenic silver nanoparticles production and characterization from native stain of Corynebacterium species and its antimicrobial activity. *3 Biotech*, *5*, 195-201.

34. Makarov, V. V., Love, A. J., Sinitsyna, O. V., Makarova, S. S., Yaminsky, I. V., Taliansky, M. E., & Kalinina, N. O. (2014). "Green" nanotechnologies: synthesis of metal nanoparticles using plants. *Acta Naturae*, *6*(1 (20)), 35-44.
35. Baker, S., Harini, B. P., Rakshith, D., & Satish, S. (2013). Marine microbes: invisible nanofactories. *Journal of Pharmacy Research*, *6*(3), 383-388.
36. Stephen, J. R., &Macnaughtont, S. J. (1999). Developments in terrestrial bacterial remediation of metals. *Current opinion in biotechnology*, *10*(3), 230-233.
37. Bollag, J. M., Mertz, T., & Otjen, L. (1994). Role of microorganisms in soil bioremediation, 563, 2–10.
38. Mann, S. (Ed.). (1996). *Biomimetic materials chemistry*. John Wiley & Sons.
39. Bhattacharya, D., & Gupta, R. K. (2005). Nanotechnology and potential of microorganisms. *Critical reviews in biotechnology*, *25*(4), 199-204.
40. Sastry, M., Ahmad, A., Khan, M. I., & Kumar, R. (2004). Microbial nanoparticle production. *Nanobiotechnology: concepts, applications and perspectives*, 126-135.
41. Mandal, D., Bolander, M. E., Mukhopadhyay, D., Sarkar, G., & Mukherjee, P. (2006). The use of microorganisms for the formation of metal nanoparticles and their application. *Applied microbiology and biotechnology*, *69*, 485-492.
42. Sundaram, P. A., Augustine, R., & Kannan, M. (2012). Extracellular biosynthesis of iron oxide nanoparticles by Bacillus subtilis strains isolated from rhizosphere soil. *Biotechnology and bioprocess engineering*, *17*, 835-840.
43. Markus, J., Mathiyalagan, R., Kim, Y. J., Abbai, R., Singh, P., Ahn, S.,& Yang, D. C. (2016). Intracellular synthesis of gold nanoparticles with antioxidant activity by probiotic Lactobacillus kimchicus DCY51T isolated from Korean kimchi. *Enzyme and microbial Technology*, *95*, 85-93.
44. Martins, M., Mourato, C., Sanches, S., Noronha, J. P., Crespo, M. B., & Pereira, I. A. (2017). Biogenic platinum and palladium nanoparticles as new catalysts for the removal of pharmaceutical compounds. *Water research*, *108*, 160-168.
45. Sweeney, R. Y., Mao, C., Gao, X., Burt, J. L., Belcher, A. M., Georgiou, G., & Iverson, B. L. (2004). Bacterial biosynthesis of cadmium sulfide nanocrystals. *Chemistry & biology*, *11*(11), 1553-1559.
46. Saeed, S., Iqbal, A., & Ashraf, M. A. (2020). Bacterial-mediated synthesis of silver nanoparticles and their significant effect against pathogens. *Environmental Science and Pollution Research*, *27*(30), 37347-37356.
47. Namasivayam, S. K. R., Gnanendra, E. K., &Reepika, R. (2010). Synthesis of silver nanoparticles by Lactobaciluus acidophilus 01 strain and evaluation of its in vitro genomic DNA toxicity. *Nano-Micro Letters*, *2*, 160-163.

48. Husseiny, M. I., Abd El-Aziz, M., Badr, Y., & Mahmoud, M. A. (2007). Biosynthesis of gold nanoparticles using Pseudomonas aeruginosa. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *67*(3-4), 1003-1006.
49. Klaus, T., Joerger, R., Olsson, E., & Granqvist, C. G. (1999). Silver-based crystalline nanoparticles, microbially fabricated. *Proceedings of the National Academy of Sciences*, *96*(24), 13611-13614.
50. Patil, M. P., Kang, M. J., Niyonizigiye, I., Singh, A., Kim, J. O., Seo, Y. B., & Kim, G. D. (2019). Extracellular synthesis of gold nanoparticles using the marine bacterium Paracoccushaeundaensis BC74171T and evaluation of their antioxidant activity and antiproliferative effect on normal and cancer cell lines. *Colloids and Surfaces B: Biointerfaces*, *183*, 110455.
51. Rauf, M. A., Owais, M., Rajpoot, R., Ahmad, F., Khan, N., & Zubair, S. (2017). Biomimetically synthesized ZnO nanoparticles attain potent antibacterial activity against less susceptible S. aureus skin infection in experimental animals. *RSC advances*, *7*(58), 36361-36373.
52. Vigneshwaran, N., Ashtaputre, N. M., Varadarajan, P. V., Nachane, R. P., Paralikar, K. M., &Balasubramanya, R. H. (2007). Biological synthesis of silver nanoparticles using the fungus Aspergillus flavus. *Materials letters*, *61*(6), 1413-1418.
53. Gursoy, N. (2020). Fungus-mediated synthesis of silver nanoparticles (agnp) and inhibitory effect on Aspergillus spp. in combination with antifungal agent. *Cumhuriyet Science Journal*, *41*(1), 311-318.
54. Zhang, C. L., Liu, J. T., Li, H., Qin, L., Cao, F. H., & Zhang, W. (2020). The controlled synthesis of Fe3C/Co/N-doped hierarchically structured carbon nanotubes for enhanced electrocatalysis. *Applied Catalysis B: Environmental*, *261*, 118224.
55. Shankar, S. S., Ahmad, A., Pasricha, R., & Sastry, M. (2003). Bioreduction of chloroaurate ions by geranium leaves and its endophytic fungus yields gold nanoparticles of different shapes. *Journal of Materials Chemistry*, *13*(7), 1822-1826.
56. Bhargava, A., Jain, N., Khan, M. A., Pareek, V., Dilip, R. V., & Panwar, J. (2016). Utilizing metal tolerance potential of soil fungus for efficient synthesis of gold nanoparticles with superior catalytic activity for degradation of rhodamine B. *Journal of Environmental Management*, *183*, 22-32.
57. Mukherjee, P., Senapati, S., Mandal, D., Ahmad, A., Khan, M. I., Kumar, R., & Sastry, M. (2002). Extracellular synthesis of gold nanoparticles by the fungus Fusarium oxysporum. *ChemBioChem*, *3*(5), 461-463.
58. Ghosh, S., Ahmad, R., Zeyaullah, M., & Khare, S. K. (2021). Microbial nano-factories: synthesis and biomedical applications. *Frontiers in Chemistry*, *9*, 626834.

59. Philip, D. (2009). Biosynthesis of Au, Ag and Au–Ag nanoparticles using edible mushroom extract. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *73*(2), 374-381.
60. Mishra, A., Tripathy, S. K., & Yun, S. I. (2012). Fungus mediated synthesis of gold nanoparticles and their conjugation with genomic DNA isolated from Escherichia coli and Staphylococcus aureus. *Process Biochemistry*, *47*(5), 701-711.
61. Sastry, M., Ahmad, A., Khan, M. I., & Kumar, R. (2003). Biosynthesis of metal nanoparticles using fungi and actinomycete. *Current science*, 162-170.
62. Luangpipat, T., Beattie, I. R., Chisti, Y., & Haverkamp, R. G. (2011). Gold nanoparticles produced in a microalga. *Journal of Nanoparticle Research*, *13*, 6439-6445.
63. Arsiya, F., Sayadi, M. H., & Sobhani, S. (2017). Green synthesis of palladium nanoparticles using Chlorella vulgaris. *Materials Letters*, *186*, 113-115.
64. Acharya, D., Satapathy, S., Somu, P., Parida, U. K., & Mishra, G. (2021). Apoptotic effect and anticancer activity of biosynthesized silver nanoparticles from marine algae Chaetomorpha linum extract against human colon cancer cell HCT-116. *Biological Trace Element Research*, *199*(5), 1812-1822.
65. Singaravelu, G., Arockiamary, J. S., Kumar, V. G., & Govindaraju, K. (2007). A novel extracellular synthesis of monodisperse gold nanoparticles using marine alga, Sargassum wightii Greville. *Colloids and surfaces B: Biointerfaces*, *57*(1), 97-101.
66. Muthusamy, G., Thangasamy, S., Raja, M., Chinnappan, S., & Kandasamy, S. (2017). Biosynthesis of silver nanoparticles from Spirulina microalgae and its antibacterial activity. *Environmental Science and Pollution Research*, *24*(23), 19459-19464.
67. Senapati, S., Syed, A., Moeez, S., Kumar, A., & Ahmad, A. (2012). Intracellular synthesis of gold nanoparticles using alga Tetraselmiskochinensis. *Materials Letters*, *79*, 116-118.
68. Mishra, A., Tripathy, S. K., & Yun, S. I. (2011). Bio-synthesis of gold and silver nanoparticles from Candida guilliermondii and their antimicrobial effect against pathogenic bacteria. *Journal of nanoscience and nanotechnology*, *11*(1), 243-248.
69. Dameron, C. T., Reese, R. N., Mehra, R. K., Kortan, A. R., Carroll, P. J., Steigerwald, M. L., & Winge, D. R. (1989). Biosynthesis of cadmium sulphide quantum semiconductor crystallites. *Nature*, *338*(6216), 596-597.
70. Agnihotri, M., Joshi, S., Kumar, A. R., Zinjarde, S., & Kulkarni, S. (2009). Biosynthesis of gold nanoparticles by the tropical marine yeast Yarrowialipolytica NCIM 3589. *Materials Letters*, *63*(15), 1231-1234.
71. Jha, A. K., Prasad, K., Prasad, K., & Kulkarni, A. R. (2009). Plant system: nature's nanofactory. *Colloids and Surfaces B: Biointerfaces*, *73*(2), 219-223.
72. Mala, J. G. S., & Rose, C. (2014). Facile production of ZnS quantum dot nanoparticles by Saccharomyces cerevisiae MTCC 2918. *Journal of biotechnology*, *170*, 73-78.

73. Kowshik, M., Deshmukh, N., Vogel, W., Urban, J., Kulkarni, S. K., &Paknikar, K. M. (2002). Microbial synthesis of semiconductor CdS nanoparticles, their characterization, and their use in the fabrication of an ideal diode. *Biotechnology and bioengineering*, *78*(5), 583-588.
74. Gericke, M., & Pinches, A. (2006). Biological synthesis of metal nanoparticles. *Hydrometallurgy*, *83*(1-4), 132-140.
75. Kowshik, M., Vogel, W., Urban, J., Kulkarni, S. K., &Paknikar, K. M. (2002). Microbial synthesis of semiconductor PbSnanocrystallites. *Advanced Materials*, *14*(11), 815-818.
76. Kowshik, M., Ashtaputre, S., Kharrazi, S., Vogel, W., Urban, J., Kulkarni, S. K., & Paknikar, K. M. (2002). Extracellular synthesis of silver nanoparticles by a silver-tolerant yeast strain MKY3. *Nanotechnology*, *14*(1), 95.
77. Huynh, K. H., Pham, X. H., Kim, J., Lee, S. H., Chang, H., Rho, W. Y., & Jun, B. H. (2020). Synthesis, properties, and biological applications of metallic alloy nanoparticles. *International Journal of Molecular Sciences*, *21*(14), 5174.
78. Naghdi, S., Rhee, K. Y., Hui, D., & Park, S. J. (2018). A review of conductive metal nanomaterials as conductive, transparent, and flexible coatings, thin films, and conductive fillers: Different deposition methods and applications. *Coatings*, *8*(8), 278.

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