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RECENT TRENDS OF INNOVATIONS IN CHEMICAL AND BIOLOGICAL SCIENCES VOLUME II

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PREFACE

Chemical sciences and Biological science play an important role in the evolutionary concept of the living world. This book Recent Trends Innovation Chemical and Biological Science: An Approach towards Qualitative and Quantitative Studies and Applications is a considerable effort taken by different authors in the discipline to provide new methodologies of research, its applications, and practical inducements of chemical sciences and Biological Science. The various themes in the book such as application of biological organisms, ethnomedicinal used in different human disorder, biological activity of Indian medicinal plants, Ethnobotanical study, Ecofriendly energy, Transplastomic plants, Role of Sacred Groves in Biodiversity Conservation, Medicinal property rich plants comphora and different traditional parts in India its application. It covers topic from environment science like effect of toxic chemical on environment. Also covered point from pharmacognosy like as the pharmacological property of Euphorbiaceae. It cover topic like phytochemistry biochemistry and active ingredients Indian medicinal plants. From chemical science subject like organic and inorganic and as well as applied chemistry included such as the Inorganic

Metal Oxide-Polymer Nanocomposites For Near Infra-Red, QSAR: A Useful Tool of Computational Chemistry for Designing New Drug and Predicting Their Biological Activities. It also cover there under medicinal and computational chemistry. This book acts as an intermediary manual between Chemical sciences with other disciplines paving a way for ideas to new research in the respective arena. The experiments described in the boom chapters are such as should be performed by everyone beginning the study of chemistry, and would also serve as an excellent introduction to a course of qualitative and quantitative analysis. All scientists, academicians, researchers, and students working in the fields of chemistry, biology, physics, materials science, and engineering, among other fields, will find this book quite valuable.

This book with valuable book chapters from eminent scientists, academicians, and researchers will surely be a part of almost information for the coming new research taken by the researchers in the field of chemical sciences and other disciplines in the future.

Dr. Bassa Satyannarayana

Mr. Mukul Machhindra Barwant

CONTENT

Chapter

1

A NOVEL LC-MS COMPATIBLE RP-HPLC METHOD FOR THE DETERMINATION OF PAZOPANIB AND IBRUTINIB IN RAW MATERIAL AND PHARMACEUTICAL FORMULATIONS

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ABSTRACT

This research work describes the development, optimization, and validation of a novel LC-MS Compatible RP-HPLC Method for the Simultaneous determination of Pazopanib and Ibrutinib in Raw Material and Pharmaceutical Formulations. An efficient isocratic LC-MS compatible reversed-phase high-performance liquid chromatography method was developed, optimized and validated for the simultaneous estimation of the PZN and IBT in pharmaceutical formulations and raw materials using a D-Optimal design.In this study we have used a mobile phase without the use of buffers making the RP- HPLC method compatible with LC-MS. Chromatographic separations were carried out with the binary mobile phase consisted of a mixture of MeCN and H_2O v/v, adjusted with 0.08% -0.12% Tri fluoro acetic acid and PDA detection at 256nm. Analytes were separated on a Onyx monolithic- C18 column (100×4.6mm). A D-optimal design was used for the simultaneous optimization of three factors; aqueous phase concentration, %TFA and flow rate of the mobile phase. Derringer's desirability function was employed for global optimization of the responses (Capacity factor, resolution, separation factor and retention time) and prediction of separate optimum conditions for the analysis of quality control samples. The predicted optimum conditions were confirmed experimentally. The observed differences between the predicted and experimental responses are found to be in good agreement, within a difference of 4%. The predicted optimum for the quality control samples were: MeCN/H_2O (40.816/59.184, v/v) with 0.120% Trifluro acetic acid as the mobile phase and flow rate of 0.971 ml/min. as flow rate. The method using these optimized conditions showed baseline separation of the PZN and IBT in a shorter analysis time of about 3.43 min.The optimized assay condition was validated according to ICH guidelines and applied for the routine quality control analysis of PZN and IBT in a pharmaceutical product (PZN-200mg, tablet and IBT-140mg capsule). The results achieved when analyzing PAZOPANIB-5 tablets were, 2.48 (0.25) mg of IBRUTINB 2.46 (0.35) mg with the values within parenthesis being the %CV of the six replicates. Good agreement was found between the assay results and the label claim of the product.

KEYWORDS: HPLC, D-optimal design, Ibrutinib and Pazopanib.

INTRODUCTION

Pazopanib-(PZN) is not in any pharmacopoeia, but their monographs are in pending status in USP. The chemical name of Pazopanib is 5[[4[(2, 3-dimethyl-2H-indazol-6-yl) methyl amino]-2-pyrimidinyl] amino]-2-methyl benzene sulphonamide-mono hydrochloride.PZN is a second-generation tyrosine kinase inhibitor (TKI). The physico-chemical properties of PZN are presented in Table 6.1. Pazopanib-PZN is an inhibitor of angiogenesis, multi tyrosine kinase, that block tumor growth which as shown to inhibit the cytokine receptors, vascular endothelial growth factor (VEGF), and platelet derived growth factor. Pazopanib can be used as chemotherapeutic agent for the treatment of advanced soft tissue sarcomas, advanced/metastatic renal cell carcinoma (RCC) and it is official by various regulatory administrations worldwide like FDA, EMA, MHRA and TGA. Pazopanib has been selected as an orphan drug on 24 March 2009 by Australian regulatory administration like Therapeutic Goods Administration (TGA). A detailed survey of the literature for PZN reveals several methods based on different techniques, viz., HPLC-UV, (Escudero-Ortiz *et al*. 2015; Chaitanya *et al. 2015*; Sharada and Ravichandrababu 2015; Rajeshbabu andAppal raju 2017; Khan *et al.* 2013) and estimation of genotoxic impurities in the Pazopanib hydrochloride in manufacturing process by HPLC (Li *et al.,* 2010; Liu *et al.,* 2009) and LC/MS–MS techniques are also used for determination of Pazopanib (Minocha *et al.,* 2012) have been reported for the determination of PZN in pharmaceutical formulations and in biological matrices.

Ibrutinib (IBT) is not official in any pharmacopoeia, but their monographs are in pending status in USP. The chemical name of Ibrutinib is 1-{(3R)-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl] piperdin-1-yl} prop-2-en-1-one. As an inhibitor of Bruton's tyrosine kinase IBT is a small-molecule that targets the ATP binding domain of BTK and leads to inhibition of enzymatic activity of BTK by formation of covalent bond with a cysteine residue (Cys-481) in the binding pocket. Ibrutinib is used in the management of mantle cell lymphoma (MCL), chronic lymphocytic leukemia, Waldenstroms macroglobulinemia. The physical and chemical properties of IBT obtainable in Table 6.2. In the literature, several methods including A detailed survey of the literature for IBT reveals several methods based on different techniques, viz. UPLC (Fouad *et al.,* 2015), stability indicating RP-HPLC (Vykuntam *et al.,* 2016), HPLC (Sureshbabu *et al.,* 2016; Muneer *et al.,* 2017; Wei*et al.,* 2016); UPLC-MS/MS (Iqbal*et al.,* 2016), LC-MS/MS (Veeraraghavan *et al.,* 2015; Rood *et al.,* 2016) have been reported for the estimation of IBT in pharmaceutical formulations and simultaneous estimation of IBT with other ant leukemic drugs in biological matrices.

The Rational behind the selection of these anti leukemic drugs is that in cancer patients, the novel treatment regimen includes either any one of these drugs or in combinations with other TKIs. A typical combination is particular to individuals suffering from cancer this specificity of selecting combination of drugs (TKIs) essentially based on the genomics or gene coding that is specific to individuals. In latest years, there have been several informations on individual determination of selected (TKIs) in pharmaceuticals and biological matrices and additionally many HPLC methods are reported for the simultaneous determination of Imatinib, Ibrutinib, Sorafenib and other tyrosine kinase inhibitors (TKI's) .

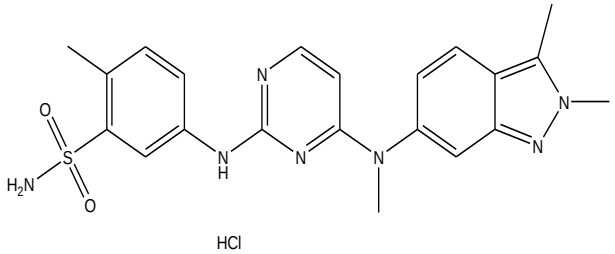


Fig. 1: Chemical Structure of Pazopanib
5-[[4-[(2,3-dimethylindazol-6-yl)-methylamino]pyrimidin-2-yl]amino]-2-methylbenzenesulfonamide;hydrochlorides

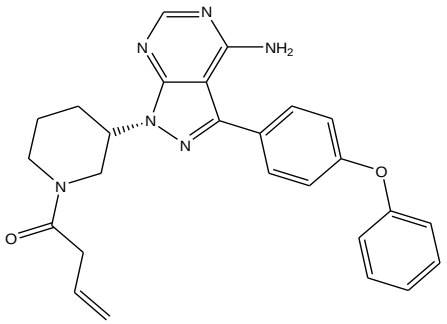


Fig. 2: Chemical Structure of Ibrutinib 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one

Furthermore, most the drawbacks of these methods are complicated procedure, poor retention, expensive use of solvents and instrumentation to achieve better chromatographic separation and low detection capability for estimation in formulations. Till date, there are no methods reported in the literature mentioning the use of design of expert (DoE's) for the development, optimization and validation of HPLC methods or LC-MS methods for the analysis of these TKI's. Hence in our present research work we have employed D-optimal design, as a DoE tool to optimize the chromatographic conditions for the estimation of PZN and IBT in APIs and pharmaceutical dosage forms.

The majority of these reported methods employed mobile phase comprising of buffers which is not compatible with LC-MS. Further these methods employed delicate stationary phases. Further, all of the reported studies employed a univariate optimization by changing one factor at a time, has the disadvantage of being time consuming and of examining only a limited part of the experimental domain. To overcome these troubles, Chemometrics tools such as an D-Optimal experimental design tied with MCDM can be employed. Till date, a Chemometrics approach for development and validation of an LC-MS compatible RP-HPLC method for simultaneous estimation of PZN and IBT has not been reported thus far. This prompted us to develop a new LC-MS compatible RP-HPLC method with shorter run time for the estimation of these drugs employing Chemometrics procedure.

The aim of this research work is to (i) develop and validate a LC/MS compatible RP-HPLC method for estimation of PZN and IBT in bulk and pharmaceutical formulations using Design of Experiments (DoE). (ii) investigate the influence of chromatographic factors and their interaction effects on the separation characteristics of these drugs with the help of D-optimal Design and (iii) to simultaneously optimize the responses: retention factor, resolution, Separation and analysis time and to deduce optimal condition for the analysis of pharmaceutical formulations using multi-criteria decision-making approach.

EXPERIMENTAL DESIGN

CHEMICALS AND REAGENTS

The working standards of Pazopanib [PZN], and Ibrutinib [IBT], Janssen Biotech *Pvt. Ltd*., were donated by the manufacturers. Methanol and Acetonitrile was HPLC grade, Tri Fluoro acetic acid and KH_2PO_4 of analytical grade was purchased from SD fine Chemicals, Mumbai, India. High purity HPLC grade water was prepared by using Milli-Q Academic, Millipore (Bangalore, India).

SOFT WARES

Experimental design, data analysis and desirability function calculations were performed by using Design-Expert® 11.0.0. Trial version (Stat-Ease Inc., Minneapolis). The rest of the calculations were performed using the Microsoft excel 2010 software.

HPLC INSTRUMENTATION AND CONDITIONS

INSTRUMENTATION

The chromatographic method development and validation was performed on Shimadzu HPLC (Shimadzu Corporation, Kyoto, Japan). The system consisted of two LC-20AD solvent delivery modules: an SPD-M 20A PDA detector and a Rheodyne injector (model 7125, USA) valve fitted with a 20µL loop. Chromatographic data were collected and processed using LC solutions® software (Version 1.11SP1). The mobile phase was degassed using Branson sonicator (Branson Ultrasonic, USA).

Chromatographic separations were carried out as described in section 3.3, with the binary mobile phase consisted of a mixture of

CHROMATOGRAPHIC CONDITION

The chromatographic separation was carried out using a mobile phase consisting of a mixture of MeCN and H_2O v/v, adjusted with 0.08% -0.12% Tri fluoro acetic acid and detection at 256nm shown in Fig.3 based on isobestic point. Prior to use, the mobile phase was degassed for 10 min in ultrasonic bath and vacuum filtered through 0.45µm membrane filter (Gelman Science, India). The mobile phase was prepared by mixing appropriate proportions of aqueous content with MeOH and MeCN to the mixture as per design. The HPLC system was used at an ambient temperature (25±2°C)

STOCK AND WORKING STANDARD SOLUTIONS

Stock standard solutions of PZN and IBT, at (1000 µg mL^{-1}) were prepared in mobile phase, as described under section 3.4. The stock solution was freshly prepared, protected from light and stored at 4°C. During the analysis day working standard solutions were freshly obtained by diluting the stock standard solutions with mobile phase. Calibration curves were established in

the range of 0.5-12.5 μg mL^{-1} for PZN and IBT. Standard solution prepared for the optimization procedure constituted PZN (5 μg mL^{-1}), IBT (5 μg mL^{-1}).

FORMULATION SAMPLE PREPARATION

Ten tablets of and Ten capsules of PZN-Votrient tablet 200 mg and commercial capsules of IBT-Imbruvica 140 mg were. weighed and analyzed separately. An amount of powder equivalent to 10mg was weighed and transferred in a 10mL volumetric flask, and 5mL of mobile phase was added. This mixture was subjected to sonication for approximately 15 min to ensure complete solubility of drugs, and the solution was made up to the mark with mobile phase and further dilutions were made to obtain a final concentration of PZN and IBT, are as 2, and 10, μg mL-1, respectively. The resulted solutions were centrifuged at 4000 rpm for 10 min, and clear supernatant was collected and filtered through a 0.2μm membrane filter (Gelman Sciences, India). A 20μl of the final solution was injected in triplicate and chromatographed.

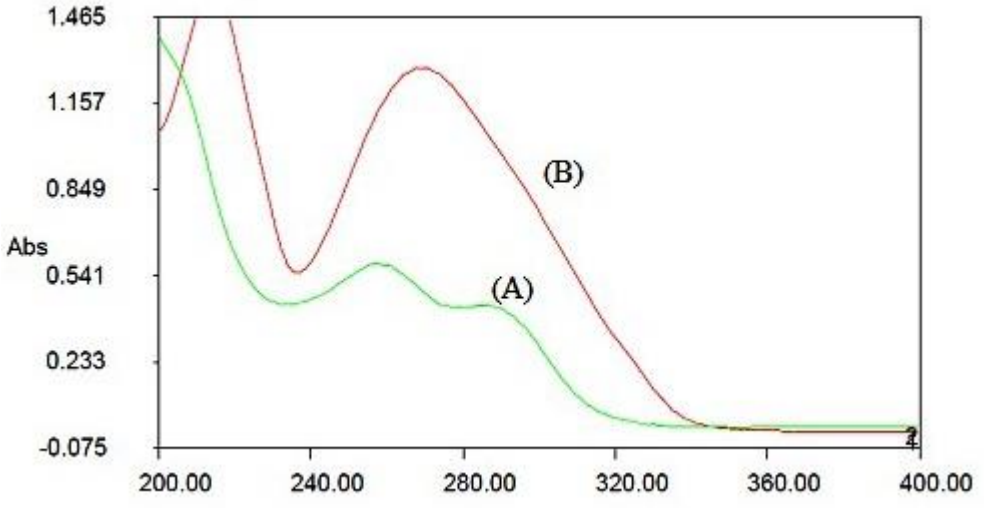


Fig. 3: UV overlain spectra of (A) Pazopanib (PZN), (B) Ibrutinib (IBT)

METHOD VALIDATION PARAMETERS

Validation studies were conducted using the optimized assay conditions based on the principles of validation described in the ICH guidelines "Text on validation of Analytical Procedures "and "Q2B, Validation of Analytical Procedure: Methodology". Key analytical parameters, including, accuracy, precision, linearity, detection limit, quantitation limit was evaluated

RESULTS AND DISCUSSION

INITIAL SCREENING

The current study attempts to develop a novel LC-MS compatible RP-HPLC method for the estimation of Pazopanib and Ibrutinib in raw material and pharmaceutical formulations by using onyx monolithic column C_{18} under reversed phase (RP) mode. The RP mode separation provides successful HPLC analysis by using nontoxic solvents which gives better solubility for polar analytes. Earlier to the development of method, a number of preliminary experiments were done by using different ratios of MeCN, water, and MeOH. Under these conditions PZN and IBT peaks are co-eluted and separation problem.

D-OPTIMAL DESIGN AND DATA ANALYSIS

The major tools for optimization techniques are statistical parameter evaluation and experimental design analysis. While using an appropriate model it is beneficial to use minimum number of runs and identify the most important parameters. The trial-and-error experiment is a time-consuming process, from which the optimal parameter settings may not readily be obtained. We selected a D-optimal design to determine the best experimental conditions in reversed phase chromatography (RP-HPLC). One of the most advantageous properties of this design in the present study was to optimize the response of interest with respect to the proportions of the components, where optimization entails minimizing, maximizing, or targeting a value of the response of interest. This design is built algorithmically to provide the most accurate estimates of the model coefficients. For the construction of best model for the experimental design matrix that fit to the data by D-optimal design the software used to describe the effects of mobile ingredients this design provides an experimental model on the separation efficiency in RP-HPLC. The model used to fit the polynomial model to the data is stepwise regression model. A normal probability plot and Cook's distance were used for the detection of outliers shown in Figure.4. A lack of fit test with the ANOVA model, leverage, a plot of the residuals vs. predicted values, and a graphical demonstration of the experimental vs. predicted values revealed the adequacy of the model shown in Figure 5. Response surfaces and contour plots were constructed to evaluate the optimum conditions for the response variables.

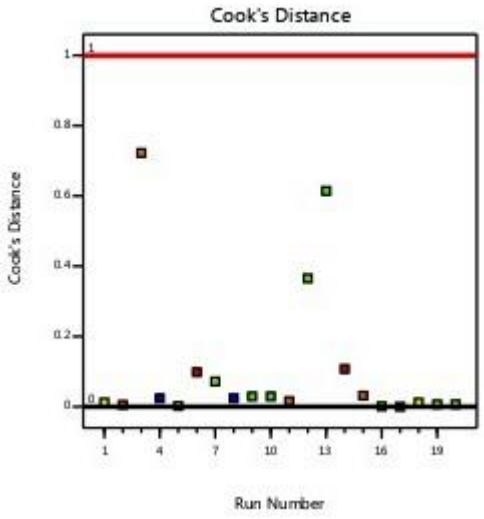


Fig.4: Cook's distance detection

For the final optimization studies three independent variables with four response variables including the Levels of the mixture components % v/v of aqueous phase 55-65 % of organic modifier TFA 0.080-0.120 and Flow rate 0.60-1.0 along with Capacity factor, efficiency, resolution and retention time were selected. The D-optimal mixture design was used to build the experiments. This design is a great tool for the optimization of mixtures when limitations and restrictions regarding the experimental designs are high. It needs fewer optimization trials compared to other optimization techniques. A total twenty experiments were designed and

then experimentally performed for the mobile phase composition and optimization presented in Table 1.

Table 1: Arrangement of D-optimal Design matrix and chromatographic responses measured

Run	Build Type	Factor 1A: Aqueous %v/v	Factor 2 B: TFA %	Factor 3 C: FR mL/min	Response k^1	Response Rs (1,2)	Response tR_2	Response α (1,2)
1	Model	58.5	0.08	1	0.24	6.557	3.34	5.451
2	Model	61	0.12	0.84	0.3	7.506	4.825	5.948
3	Model	65	0.1056	1	0.287	10.031	5.871	9.242
6	Model	60.95	0.096	0.6	0.329	8.647	7.375	6.248
8	Model	65	0.12	0.6	0	1.699	8.456	3.604
9	Model	55	0.12	1	0.189	4.767	2.672	4.284
13	Model	55	0.0962	0.838	0.194	5.496	3.361	4.864
15	Model	65	0.08	0.742	0.296	10.663	8.271	9.512
16	Model	55	0.12	0.6	0.212	5	4.45	4.162
20	Model	55	0.08	0.6	0.212	5.373	4.716	4.602
7	Lack of Fit	56	0.1162	0.8	0.202	4.941	3.334	4.284
11	Lack of Fit	65	0.08	1	0.294	10.924	6.148	8.412
12	Lack of Fit	59	0.104	1	0.195	7.659	4.06	7.971
14	Lack of Fit	60	0.116	0.64	0.329	7.268	6.335	5.598
17	Lack of Fit	62.15	0.098	0.82	0.322	8.57	5.382	6.309
4	Replicate	65	0.12	0.6	0	1.699	8.456	3.604
5	Replicate	55	0.12	0.6	0.21	5	4.45	4.162
10	Replicate	55	0.12	1	0.189	4.767	2.672	4.284
18	Replicate	58.5	0.08	1	0.24	6.557	3.34	5.451
19	Replicate	55	0.08	0.6	0.212	5.373	4.716	4.602

Ten points were chosen for the model, 5 points were chosen for an estimation of lack of fit, 5 points were chosen for replication and four responses were analysed. The stepwise regression was used to describe and fit the obtained data. Hierarchical terms were added after each stepwise regression. Shows the design and results of the experiments carried out by the D-optimal design. For all of the reduced models, p-values <0.05 were obtained, as shown in Table2. Implying that these models were significant.

The factor space of this design was expanded within the following range: aqueous phase (water) concentration was varied from 55-60 % v/v, TFA concentration was varied from 0.08-0.12 % v/v and flow rate 0.6- 1.0 ml/min. The capacity factor for the first eluted peak PZN, (k_1), the resolution of the critical separated peak, PZN and IBT, ($Rs_{1,2}$), separation factor of second eluted peak, IBT, (α) and the retention time of the last peak, IBT,(tR_2) were selected as

responses. In the preliminary study, resolution between peak ($Rs_{1,2}$) were found to be < 1.5, hence these two peaks were considered as critical peaks and included as one of the responses for the global optimization shown in Table 3.

Table 2: Reduced response models and statistical parameters obtained from ANOVA (after backward elimination)

Responses	Regression models [a]	Adjusted R^2	Model P-value	%CV	Adequate precision
k_1	K1 =+0.3291 +0.0224 A -0.0242 B 0.0026 C -0.0620 A +0.0603 AC +0.0402 BC -0.1226 A^2 -0.0046 B^2 -0.0243 C^2	0.770	0.0001	19.62	9.934
$Rs_{(1,2)}$	Rs (1,2)=+8.72+1.71 A -1.04 B +0.3472 C -1.75 AB +1.48 AC +0.9853 BC -1.90 A^2 -0.7654 B^2 -0.2274 C^2	0.9372	0.0001	9.95	20.4494
$\alpha_{(1,2)}$	SEP = +5.95+1.65 A -0.5574 B +0.6002 C -0.7540 AB +0.8475 AC +0.6978 BC	0.7712	0.0001	15.47	10.8928
tR_2	tR2 = +5.07+1.96 A-0.2280 B -1.38 C-0.2851 AB -0.3234 AC +0.1796 BC +0.2038 A^2 -0.2292 B^2+0.4630 C^2	0.9857	0.0001	4.47	36.1945

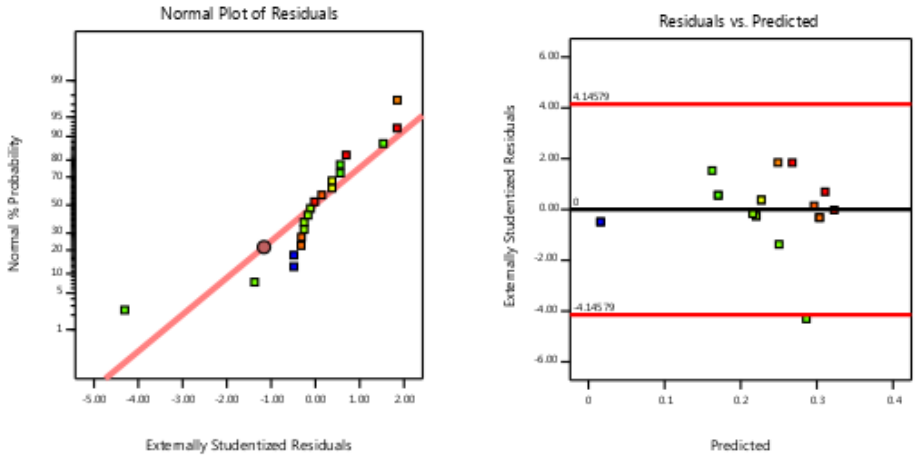
Table 3: Criteria for the optimization of individual responses

Name	Goal	Lower Limit	Upper Limit	Weight	Importance
A: Aqueous	is in range	55	65	1	3
B: TFA	is in range	0.08	0.12	1	3
C:FR	is in range	0.6	1	1	3
K_1	Maximize	0	0.329	1	5
$rs_{(1,2)}$	is in range	1.699	10.924	1	1
tR_2	Minimize	2.672	8.456	1	3
SEP	is in range	3.604	9.512	1	3

The design matrix and the experimental results are presented in Table 1.All the experiments were performed in a randomized order. For an experimental design with three factors, the model including linear, quadratic, and cross terms can be expressed as

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{33} X_3^2$$

Where, Y is the response to be modelled, β is the regression coefficient and X_1, X_2 and X_3 represents factors A, B and C respectively. Statistical Parameters obtained from ANOVA for the reduced models are given in Table 2. The insignificant terms ($P > 0.05$) were eliminated from the model through backward elimination process to obtain a simple and realistic model. The adjusted R^2 were well within the acceptable limits of $R^2 \geq 0.770$, which revealed that the experimental data shows a good fit with the second-order polynomial equations. For all the reduced models, P value of < 0.05 is obtained, implying these models are significant. The adequate precision value is a measure of the signal (response) to noise (deviation) ratio". A ratio greater than 4 is desirable. In this study, the ratio was found to be in the range of 9.934-36.194S, which indicates an adequate signal and therefore the model is significant for the separation process. The coefficient of variation (CV) is a measure of reproducibility of the model and as a general rule a model can be considered reasonably reproducible if it is less than 10%. (Beg *et al.*, 2003). The CV for all the models was found to less than 10% except for *K'*(19.62) and for separation, $\alpha_{(1,2)}$. Hence, the diagnostic plots, (a) normal probability plot of residuals (Choisnard *et al.*, 2003) and (b) plot of residuals versus predicted values were analyzed for response $Rs_{(2,3)}$. The normal probability plot Fig. 5a indicates whether the residuals follow a normal distribution, in which case the points will follow a straight line.



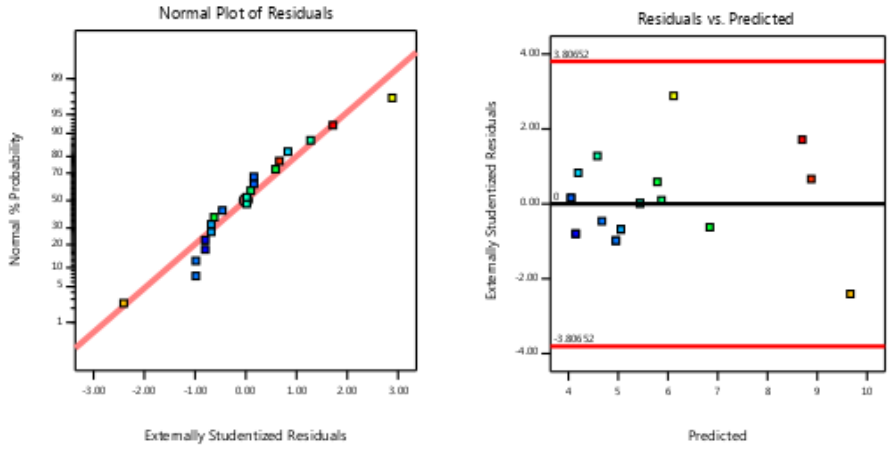
(a) **(b)**

Fig. 5a: Diagnostic plots for K1 response. (a) Normal probability plot of residuals and (b) Plot of residuals verses predicted values

In Fig. 5.b the points on this plot lies fairly close to the straight line, so the model seems appropriate. The plot of residuals vs. predicted values Fig. 5.b is a measure of how many standard deviations the actual value deviates from the value predicted. From this plot, it is possible to conclude that they were randomly distributed around zero and there is no evidence of outliers (no point lies away from the mean more than three times the standard deviation). Since, the assumptions of normality and constant variance of the residuals were found to be satisfied; the fitted model for the $Rs_{(2,3)}$ was accepted.

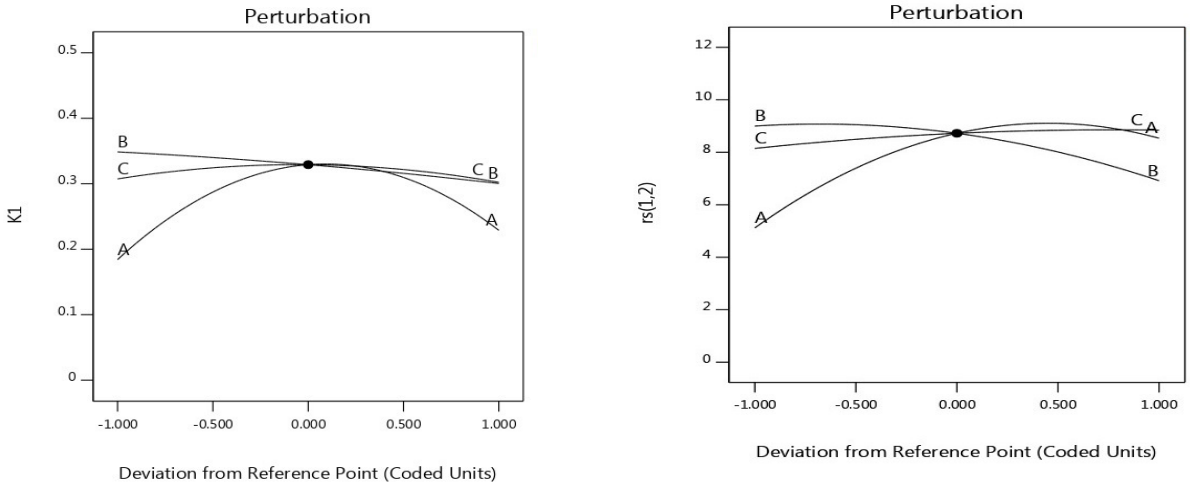
As can be seen in Table 2 the interaction term with the largest absolute coefficients among the fitted models is *AC* (+ 1.49) of $Rs_{(1,2)}$ model. The positive interaction between *A* and Cis

statistically significant (P<0.0001) for $Rs_{(1, 2)}$ model. Non-parallel lines of $Rs_{(1, 2)}$ AC interaction plots as presented in support these observations**.** The study reveals that changing the fraction of aqueous phase from low (−1) to high (+1) results in a rapid decline in $Rs_{(1, 2)}$ both at the low (−1) and high level (+1) of flow rate. The non-parallel lines indicate an interaction between factors A and B. i.e., at low level of factor A, a high level of B will result in a marginal decrease in tR_2.The steep slope in a factor indicates that the response is sensitive to that factor. i.e., the factor A mostly affected tR_2, followed by factor B as shown in Fig 7a, 7b, 7c and 7d as perturbation plots. Analysis of the perturbation plots and response surface plotsFig 8a, 8b, 8c and Fig. 8d of optimization models show that the factor A and C mostly affected the analyte retentions and factor B is of little significance.



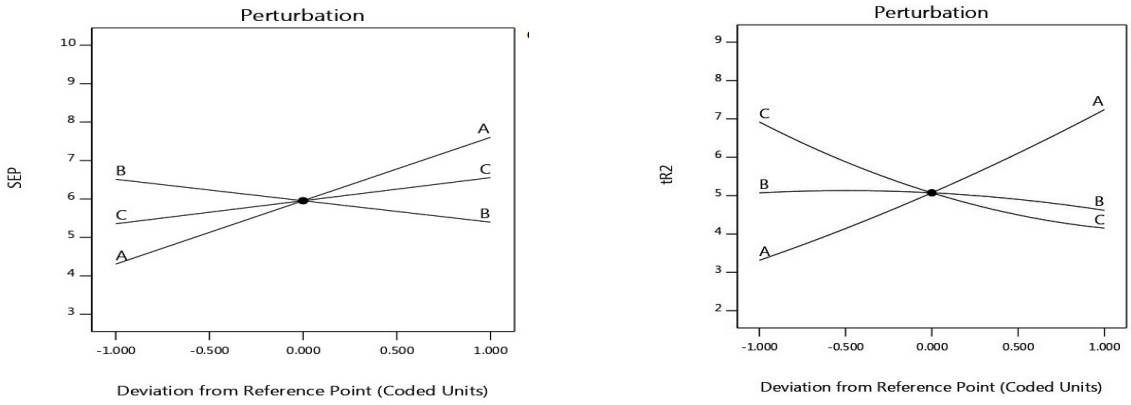
(a) **(b)**

Fig. 6. Diagnostic plots for $\alpha_{(1,2)}$ response. (A) Normal probability plot of residuals and (B) plot of residuals versus predicted values



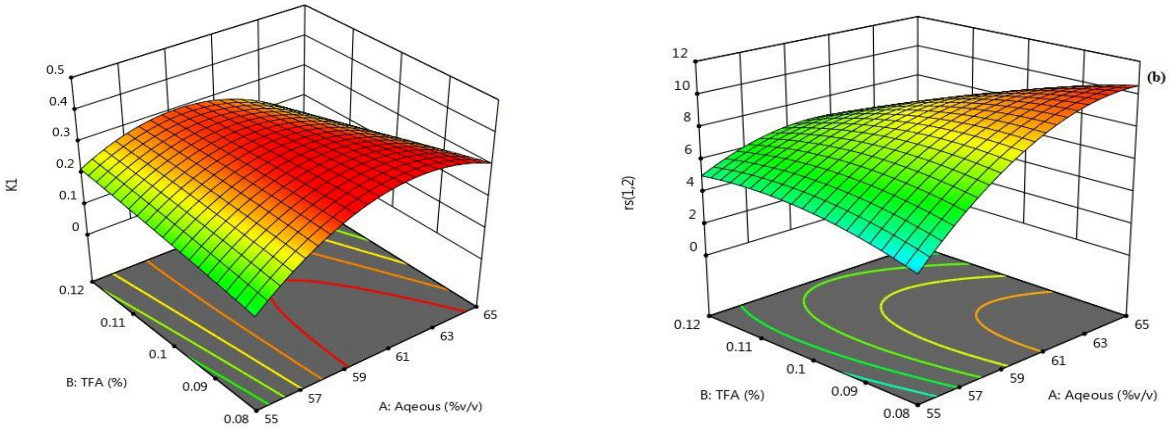
(a) **(b)**

Fig. 7a and 7b: Perturbation plots for k^1 and $Rs_{(1, 2)}$ responses. (a) Shows the effect of each of the independent variables on k^1 and (b) shows the effect each of the independent variables on $Rs_{(1,2)}$ where A is the concentration of aqueous phase, B is % TFA and C is the mobile phase flow rate



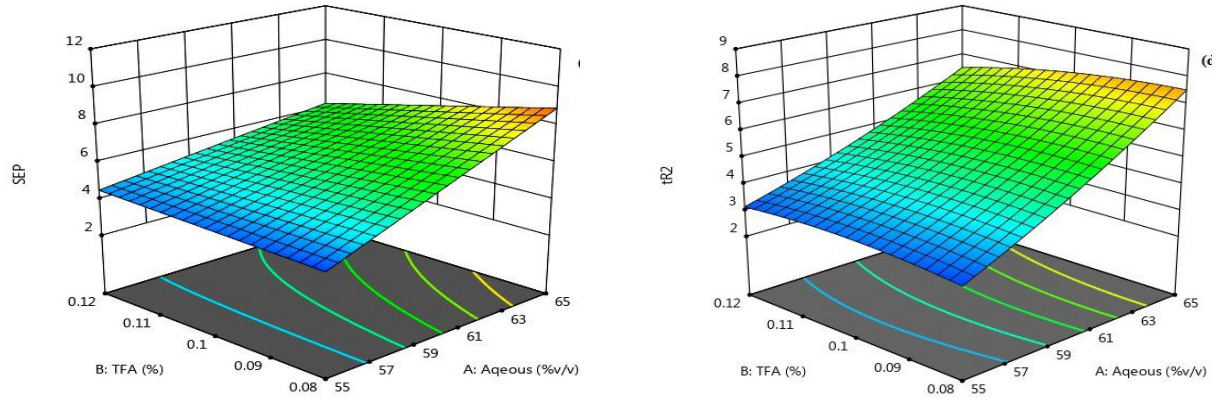
(c) **(d)**

Fig. 7c and 7d: Perturbation plots for $\alpha_{(1,2)}$ and tR2 responses. (c) Shows the effect of each of the independent variables on $\alpha_{(1,2)}$ and (d) shows the effect each of the independent variables on tR_2 where A is the concentration of aqueous phase, B is % TFA and C is the mobile phase flow rate



(a) **(b)**

Fig. 8a and 8b: Response surfaces plots for (a) k^1 and (b) $Rs_{(1,2)}$ Response surface related to percentage of (A) is the concentration of aqueous phase, (B) is % TFA and (C) is the mobile phase flow rate



(c) **(d)**

Fig. 8c and 8d: Response surfaces plots for (c) $\alpha_{(1,2)}$ and (d) tR_2 Response surface related to percentage of (A) is the concentration of aqueous phase, (B) is % TFA and (C) is the mobile phase flow rate held at constant at centre value

MULTI CRITERIA DECISION MAKING

OPTIMAL CONDITION FOR FORMULATION ASSAY

The criteria for the optimization of individual response are shown in Table 3. Criteria have been proposed for selecting an optimum experimental condition for analysing routine quality control samples. The identifiedresponses for the optimization were: capacity factor, resolution between the critical peaks, separation factor and elution time. Derringer's desirability function was used to optimize these responses with different targets. Desirability function (D) can take values from 0 to 1. Weights can range from 0.1 to 10. Weights lower than 1 give less importance to the goal, whereas weights greater than 1 give more Importance to the goal. In the present study, *pi* values were set at 1 for all the four responses. A value of *D* close to 1 indicates that the combination of the different criteria is matched in a global optimum. As can be seen under criteria, the responses tR_2 was minimized, in order to shorten the analysis time. On the other hand, Separation factor (α) was set to be in range. To allow baseline separation of PZN and IBT. In order to separate the first eluting peak (PZN) from the solvent front, k_1 was maximized.

Importance can range from 1 to 5, which gives emphasis to a target value. Following the conditions and restrictions above, the optimization procedure was carried out. The partial desirability functions (d_i) of each of the responses and calculated geometric mean as the maximum global desirability function (D = 0.8943) are presented in Figure.9 where d_i varying from 0 to 1 according to the closeness of the response to its target value. The coordinates of D represents the optimum conditions and the corresponded predicted responses and are shown in Table 4. While using this optimum condition, the drugs were baseline separated with an analysis time of about 3.43 min Fig. 10c. The observed differences between the predicted and experimental responses are found to be in good agreement, within a difference of 2%, the short analysis time of the proposed method makes it viable to be implemented for routine quality control analysis in a pharmaceutical laboratory.

Table 4: Comparison of experimental and predictive values of different objective functions

Optimum conditions	**Aqueous: MeCN (%)**	**TFA %**	**Flow (ml/min)**	**K_1**	**$Rs_{(1,2)}$**	**$\alpha_{(1,2)}$**	**tR_2**
For Formulation	Desirability Value (D) =0.894						
	59.18:40.81	0.12%	0.9715				
	Experimental value			0.305	7.20	5.99	3.49
	Predicted value			0.309	7.64	6.24	3.69
	Average % error			1.29	5.75	3.780	5.42

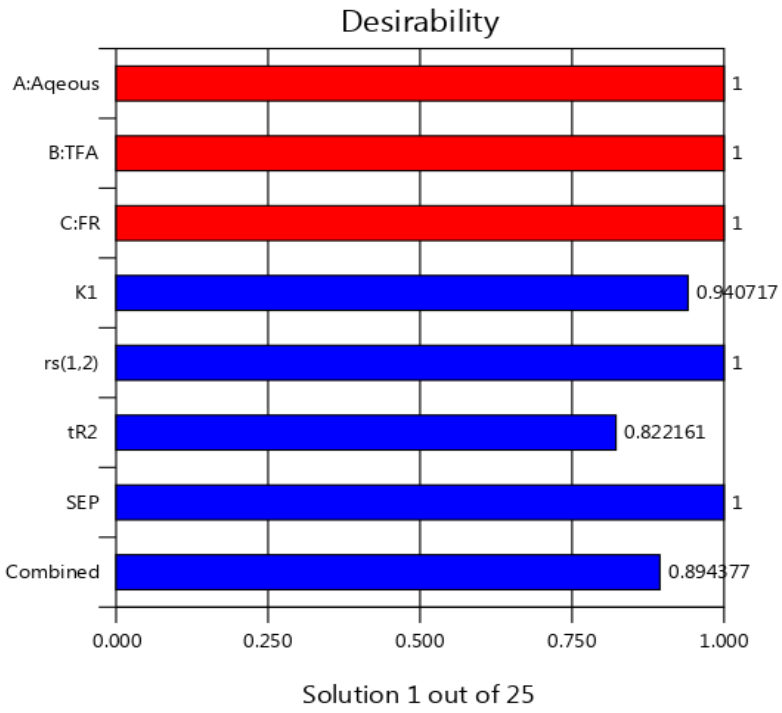


Fig. 9: Bar graph showing individual desirability values (di) of various objective responses and their association as a geometric mean (D) corresponding to formulation samples

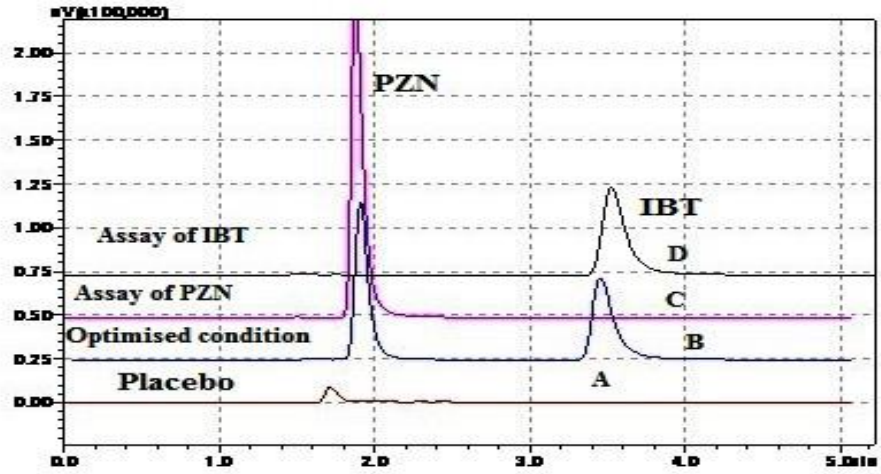


Fig. 10: Separation of PZN and IBT under optimal condition. chromatograms corresponding to (a) a placebo solution; (b) Optimized condition for PZN and IBT (c) Assay condition for PZN (2.0 µg/ml), (d) Assay condition for IBT (10.0 µg/ml)

VALIDATION OF FORMULATION ASSAY METHOD AND ITS APPLICATION

METHOD VALIDATION

The last step of the present study was to check method's validation for specificity, linearity, accuracy, intra/inter-day precision, and robustness. The optimized HPLC method was specific in relation to the placebo used in this study. All placebo chromatograms showed no interference peaks Figure 10 a. An excellent linearity was established at five levels in the range of 0.5 – 12.5 µg/ml. for PZN and IBT, with R^2 of more than 0.983. The slope and intercept of the calibration curve were 97303 and 14528 for PZN, 74155 and 20909 for IBT, respectively. Since the

correlation coefficients are not good indicators of linearity performance of an analytical procedure a one-way ANOVA was performed. For all the analytes, the calculated F- Value (F_{Calc}) was found to be less than the theoretical F-Value (F_{Crit}) at 5% significance level, indicating that there was no significance difference between replicate determinations for each concentration level. The LOD and LOQ were estimated at 2.11 and 26.11 ng/ml for PZN, 13.04 and 39.537ng/mL for IBT. Accuracy, assessed by spike recovery, in which the % recovery of PZN and IBT at each level (n = 3) and mean % recovery (n = 9) was found to be 99.34, 101.3 and 101.4% for PZN and 100.4, 99.1 and 99.85 for IBT. The recoveries of PZN and IBT at each level were found well within the acceptable criteria of bias, ±2%. The mean % recovery (n = 9) for each was also tested for significance by using Student t-test. Since the t_{Calc} is less than the theoretical t value (t_{Crit}=2.306), at 5% significance level, the null hypothesis (the recovery is unity or 100%) was accepted. These results indicate that the method is accurate and therefore the absence of interference from placebo excipients used in this study. The intra and inter-assay precision (n = 6) was confirmed since, the %CV were well within the target criterion of ≤ 2, respectively. Robustness study reveals that small changes did not alter the retention times, retention factor and resolutions more than 2% and therefore it would be concluded that the method conditions are robust.

APPLICATION OF THE METHOD

As a last step, commercial product of PZN-Votrient tablet 200 mg and commercial capsules of IBT-Imbruvica 140 mg were assayed by the proposed HPLC method. Representative chromatograms are presented inFigure 10. The results achieved when analyzing PZN-Votrient tablet was 1.995 (2) μg of PZN and when analyzing IBT-Imbruvica capsules was 9.938 (10) μg of IBT. Good agreement was found between the assay results and the label claim of the product. The %CV for the tablet and capsules were < 2, indicating the precision of the analytical methodology.

CONCLUSION

An efficient isocratic LC-MS compatible reversed-phase high-performance liquid chromatography method was developed, optimized and validated for the simultaneous estimation of the PZN and IBT in pharmaceutical formulations and raw materials using a D-Optimal design.In this study we have used a mobile phase without the use of buffers making the RP- HPLC method compatible with LC-MS. The Chemometrics protocols such as D-Optimal design and Derringer's desirability function and improved method showed higher sensitivity and shorter analysis time (3.4 min) than the existing methods, making it viable to be implemented for routine quality control analysis in a pharmaceutical laboratory.

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Chapter
2

BIOPROSPECTING OF NATURAL RESOURCES

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ABSTRACT

The plant species provide many products that are used worldwide. These products are obtained from wild or cultivated plants. Inspite of richest biodiversity, still today remained poorly understood, under exploited & poorly documented. These plants should be exploited through proper bioprospecting methods. There is growing demand for new bioactive compounds for the pharmaceutical, agriculture and food industries. Plant-associated microbes present an attractive and promising source to this end, but are nearly unexploited. Therefore, bioprospecting of plant microbes is gaining more and more attention. This article highlights the biochemical resources from plants & Scope of Bioprospecting.

KEYWORDS: Bioprospecting, Biodiversity, climate change; conservation; resources

INTRODUCTION

Bioprospecting means the 'Search for the useful biological materials in microorganisms, plants, fungi, animals & humans". (Polski, 2005). Bioprospecting involves characterization of bio resources through different methods, their mapping & conservation of endangered plant species & bio prospective molecules. Bioprospecting of plants is the exploration of wild plants for commercially valuable genetic & biochemical resources". The world microbes are almost remained unidentified, under exploited & unexplored. The Bioprospecting of such microbes in pharmaceutical industry, antibiotic industry, enzymes, toxins, hormones, alkaloids & vaccines is very promising & challenging task for life science researchers.

Bioprospecting means systematic search for and development of new sources of chemical compounds, genes, micro-organisms, macro-organisms, and other valuable products from nature. It entails the search for economically valuable genetic and biochemical resources from nature. So, in brief, bioprospecting means looking for ways to commercialize biodiversity. Lately, exploration and research on indigenous knowledge related to the utilization and management of biological resources has also been included into the concept of bioprospecting. Thus, bioprospecting touches upon the conservation and sustainable use of biological resources and the rights of local and indigenous communities.

The bioprospecting of microbes in agriculture is a vast scope because microbes have been used for bio mining, biogas production, bioremediation, bio sorption, biogas production etc.

The Bioprospecting for plants contribute greatly to environmentally sound development & returns benefit to indigenous people or local people, who are the custodians of these resources.

India with 65 crores acres of land, surrounded by water & Himalayas with plenty of flora & fauna, provide us great opportunity for Bioprospecting.

SCOPE

There is vast scope for Bioprospecting in India because we have rich biodiversity. *Saccharum* plant is useful for sugar production; sugar is used for various purposes. On this single genus variety of industries have been setup such as alcohol industries, distilleries etc. similarly in case of medicinal plants used by tribals, villagers. In India Neem was used as ecofriendly pesticide, since long time by the farmers through indigenous knowledge of bioprospecting.

The anticancer drug Taxol from Gymnospermic plant *Taxus* had also made million-dollar history in the world. Bio resources obtained from plants are high valued. The increased interest in bioprospecting is mainly because the uniqueness & innovativeness in such plants, which is not seen in synthetic chemicals. Due to advance research in biotechnology, genetics, proteomics the progress in bioprospecting is possible.

BIOPIRACY

Bio piracy means any activity by biodiversity prospectors to steal the plants or their products & traditional knowledge about biodiversity & use that to earn money without reimbursement to the owner. Various organizations such as NGOs (Non-Government Organizations) will help largely to protect Bio resources from Bio piracy. The laws & regulations help to protect property knowledge etc.

Fig 1: Various Organizations & NGO's

BIOCHEMICAL RESOURCES FROM PLANTS

The plants of earth full of bio chemical's including amino acids, carbohydrates, starch, polysaccharides like cellulose, gum, resins, lignin's, cutins, waxes, suberins etc. The plant

consists of various secondary metabolites like alkaloids, tannins, phenols, flavonoids, glycosides, anthocyanin's etc.

Some plants are the sources of oils, fats, fatty acids, lipids, membrane lipids, structural lipids, essential oils, perfumes & aromatic compounds. The plants like tea, coffe had served us as beverages through their tannins & coffins. The pigments & dyes are also obtained from plants. Dyes are ecofriendly in nature which are used to dye our cloths, foods, drinks, ice-creams etc. the rubber & other plants are the base of our expanding rubber industry through the chemicals present in their latex i.e. hydrocarbons.

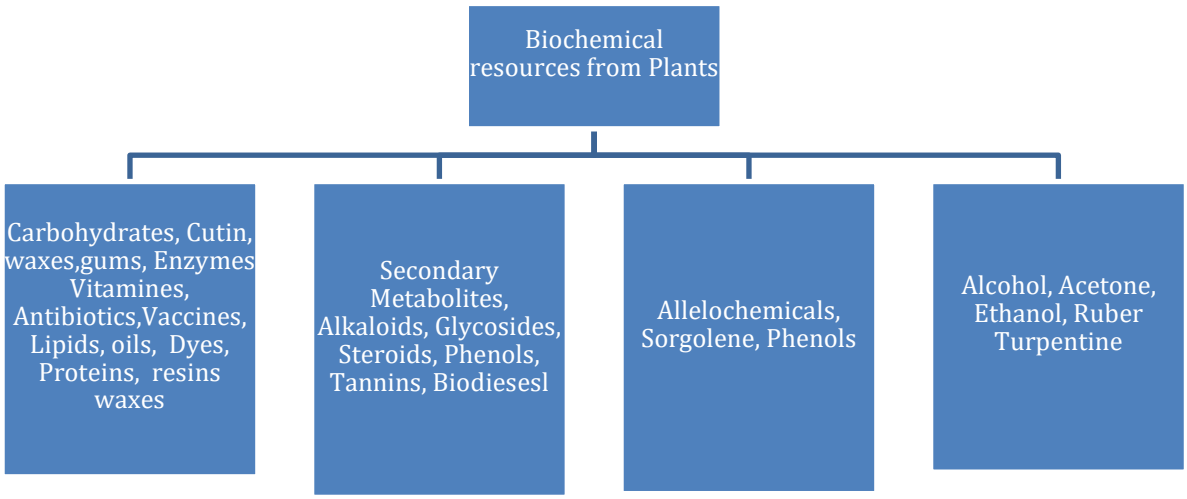

Fig. 2: Biochemical Resources from Plants

ALLELOCHEMICALS

Plants released specific type of stimulatory or inhibitory chemicals into environment known as allelochemicals. These chemicals inhibit the growth of surrounding plant species. Many grasses are rich in such allelochemicals. Some crops like *Sorghum,* Wheat, and Sunflower also release some chemicals in environment through root exudates. The residue of weeds & crops after decomposition release variety of allelochemicals like alkaloids, terpanoids, phenols, flavanoids etc.

BIOCHEMICAL RESOURCES FROM FUNGI

The fungal species are useful as they produce many chemicals, medicines, antibiotics, organic acids, amino acids. They also produce some enzymes; secrete many chemicals attacking the host plants. Some fungi produce phenols, other defense compounds, vitamins phytoharmones like gibberellins etc.

Some fungi like yeast produce vitamins, *Claviceps* produces ergot alkaloids *and Penicillium* produces antibiotics like penicillin. Edible mushrooms like *Agaricus, Pleurotus* are the best source of soluble proteins.

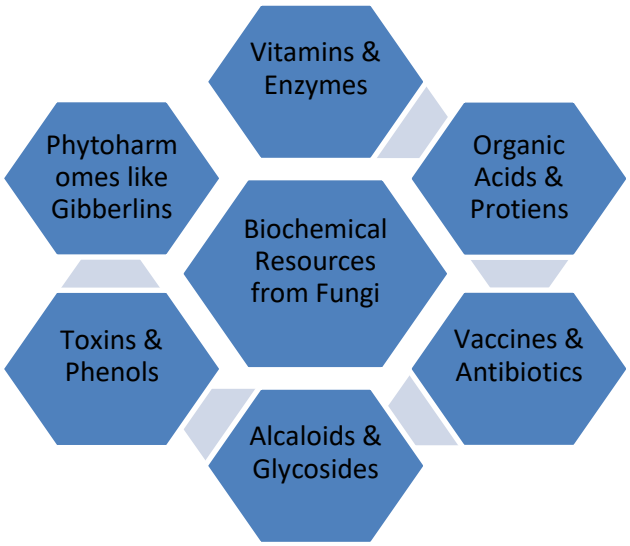

Fig 3: Biochemical Resources from Fungi

MEDICINAL PLANTS

WHO (world Health Organization) has listed over 21,000 plant species worldwide, which are having medicinal value. More than 2500 species of plants are used in Ayurveda, Sidha, Unani & other traditional health care systems. Earth has rich biodiversity, but most of the plants remained untapped. So lot of scope is there to find the untapped medicinal plants, especially for cancer, obesity, diabetes, HIV & other dreadful diseases. Researchers have to work on this line because thousands of medicinal plants remained untapped.

The knowledge of tribal's, indigenous & traditional knowledge of villagers must be explored to bring new medicinal plants under use. Taxol obtained from *Taxus* had made miracle in cancer cure. Aloe it is effective for treat minor burns and some skin problems. Also used in various cosmetics.

WILD ORNAMENTAL PLANTS

Many wild plants have very attractive & beautiful flowers, with better vase life. The flora of western ghat can be exploited as untapped resources of wild ornamentals e.g. species of *Ixora, Iris*, Orchids like *Vanda*, *Jasminum* are ornamental plants. The wild *Curcuma* species having very attractive & colorful flowers may be exploited as new ornamentals. The wild fern species will serve the purpose of ornamental foliage.

FOREST RESOURCES

Trees are the most important plants in forests. Most of the other organisms in the forest depend on the tree's ability to turn the sun's energy into sugars using photosynthesis. There are big trees and small trees e.g. *Eucalyptus, Ficus, Bamboo* etc. Many timber yielding plant species are fast growing forest plants, producing huge biomass has remained untapped. There are many plant species which can substitute Teak e.g *Gmelina arborea*, it should be exploited for timber.

CONCLUSION

We have the highest & massive genetic resources. India should take lead to form bio-partnership & being senior partner in man power & genetic resources amongst all the third

world countries. Indeed, this is the need of time. The bioprospecting depends on successful exploration & utilization of our plant & biochemical resources. Biodiversity-rich countries often face serious problems with regard to the prevention of unauthorized bioprospecting, due to weak law enforcement, a first step in order to avoid bio piracy would be to develop an integrated and comprehensive national policy on access or -rather- on access and benefit sharing.

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Chapter 3

THE SCIENCE OF NEUROREGENERATIVE MACROFUNGI

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ABSTRACT

The macrofungi family is a rich source of macromolecules that have piqued the interest of researchers due to their medicinal potential. Many edible and therapeutic mushrooms, which belong to the basidiomycetes and ascomycetes, are used as nutraceuticals on a regular basis. Proteins such as PSK or krestin, lentinan, pleuran, and grifolan, to name a few species-specific therapeutically important chemicals recovered from mushrooms. The anti-inflammatory, immunomodulatory, antioxidant, anticytotoxic, and neuroregenerative qualities of mushrooms have enabled them to cure illnesses and disorders ranging from diabetes, hypertension, cognition, Alzheimer's disease, Parkinson's disease, impaired immunity, and so on. Several researches have been conducted in recent decades to investigate the neuroprotective and neuroregenerative capabilities of mushroom extracts derived from their fruiting bodies and mycelia. It has been determined that they can enhance memory and cognitive abilities by halting the onset of dementia and neurodegeneration at a prodromal stage. The fungi-biomolecules develop defence mechanisms at the molecular level, such as acetylcholinesterase inhibition, oxidative stress reduction, and encouraging appropriate mitochondrial and endoplasmic reticulum function. Numerous species are being thoroughly researched for use as food or dietary supplements to prevent neuronal degeneration, including *Antrodia camphorata, Ganoderma lucidum, Hericium erinaceus, Grifola frondosa, Mycoleptodonoides aitchisonii, Sarcodon scabrosus, Pleurotus giganteus, Lignosus rhinocerotis, Paxillus panuoides,* and *Dictyophora indusiate.*

KEYWORDS: Macrofungi, Neuroregeneration, Mushrooms, anti-oxidant, Neuroprotective, anti-inflammatory

INTRODUCTION

Mushrooms are continually valued for their great medical, gastronomic, and nutraceutical value, and a variety of bioactive compounds are being extracted from them. The Basidiomycota and Ascomycota macrofungi are coveted gene pool sources that are used in the field of biotechnology to create innovative medicines and foods. The nutritional properties of culinary and medicinal mushrooms are their main and most important purpose. The mushrooms can thus be categorised as either (a) protein-rich, (b) carbohydrate-rich, or (c) carbohydrate-and-protein-rich. The majority of the sugars found in mushrooms are low molecular weight saccharides, such as trehalose, mannitol, and arabinitol. Typically, people associate mushrooms with having minimal calories in relation to their weight. When the mushrooms are sun-dried, the component ergosterol transforms into vitamin

D. There are also plenty of other vitamins including thiamine (B1), riboflavin (B2), and niacin. The concentration of minerals is as follows: K > Na > P > Ca > Fe (Mizuno & Kawai, 1992). The supporting character is said to possess the appetite-stimulating qualities of mushrooms. The existence of Monosodium Glutamate (MSG), which has the nucleotides GMP and AMP as subsidiary, is what gives macrofungi its delicious feature. Tricolomic acid and ibotenic acid, respectively, are present in *Tricoloma muscarium* and *Amanita pantherina*, which further recall the flavour (Mizuno, 1995). Numerous edible mushrooms, from medicinal species like Ganoderma, Cordyceps, and Trametes to edible varieties including Russula sp., Agaricus sp., Lentinus sp., Pleurotus sp., and Tremella sp., are powerful makers of biomolecules that may be employed as pharma-polysaccharides. The anti-tumor, immunomodulatory, anti-inflammatory, anti-thrombotic, and antiviral modes of action of these mushrooms have now been discovered. Additionally, they have a hypotensive effect and are known to lower blood sugar levels, regulate blood pressure, promote nerve growth factors, and be hypotensive (Lakhanpal & Rana, 2005). The label "neurodegenerative diseases" (NDD) comes from the selective and gradual loss of neurons that occurs in these conditions (Dugger & Dickson, 2017). These illnesses provide the public significant clinical symptoms that interfere with their daily lives. Age raises the likelihood of developing several illnesses, including ALS, Parkinson's disease, and amyotrophic lateral sclerosis (AD) (Checkoway *et al.,* 2011). It is thought that a mix of genetic and environmental factors contributes to the epidemiology. They all work together to modify and influence the behaviour of those who are at risk for NDD. The outward symptoms that the patients display are the result of a variety of dysregulated molecular processes. These illnesses, which display a variety of signs and symptoms, really have certain common molecular process flaws. Genetic research has linked Aβ, α-synuclein, and SOD to the development of ALS, Parkinson's disease, and AD, respectively (Pihlstrøm *et al.,* 2018). One of the main processes that either prevents neuronal cells from functioning or pushes the cells to increase the activity of harmful cascades is oxidative stress (Barnham *et al.,* 2004). The production of amyloid-plaques brought on by mutations in the APP (Amyloid precursor protein) gene distinguishes the autosomal dominant condition AD. The APP codes for the Aβ from which fragments are cut off by enzymes such as α-secretase, alternatively β-secretase and γ-secretase. The function of γ-secretase is to cleave off the Aβ at two positions, producing two chains of 40 and 42 amino acids respectively (Aβ40 and Aβ42). The Aβ42 thus formed is more prone to aggregation. Furthermore, mutations in the genes PSEN1 (Sherrington *et al.,* 1995) and PSEN2 were also identified to be the causative factors (Levy-Lahad, 1995). Parkinson's disease (PD) is characterised by Lewy body accumulation in neurons and the lack of dopaminergic neurons in the substantia nigra. The synthesis and accumulation of α-synuclein contribute to neuronal degeneration (Davie, 2008). Since 1977, many SNCA gene mutations have been linked to autosomal dominant PD. Mutations in PARK2, PARK7, and PINK-1 are associated with recessive PD ((Pihlstrøm, L., 2018). Table 1 summarises the facts because it is beyond the scope of this paper to describe the genetics of all NDD. Friedreich ataxia, Huntington's disease, Lewy body disease, and spinal muscular atrophy are further illnesses. Because of its anti-oxidant and anti-inflammatory capabilities, the kingdom of fungus has already produced a wide range of potential medications that are now emerging as neuroprotective.

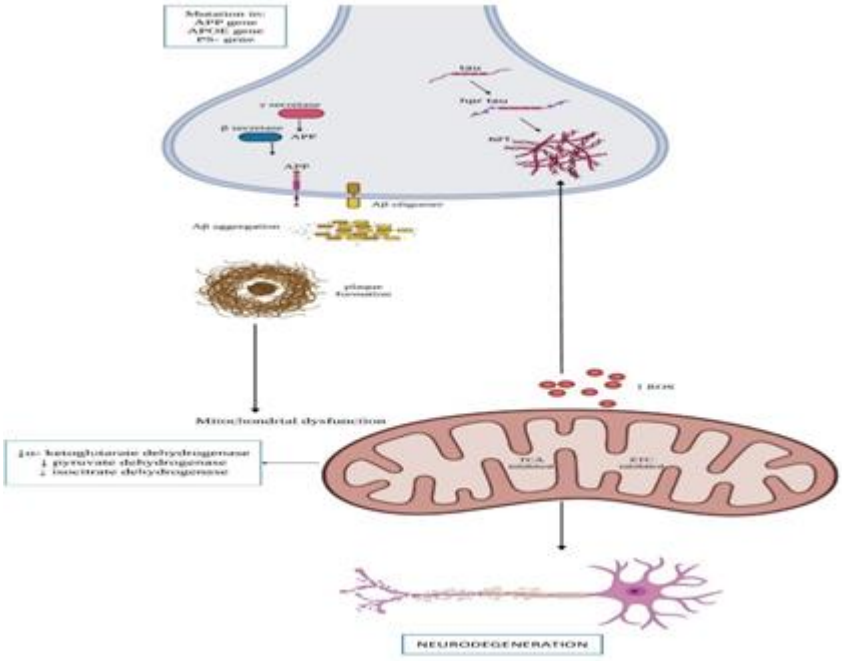

Fig. 1: Mechanisms of neurodegeneration in AD

Table 1: Genetics of neurodegenerative diseases (Pihlstrøm, 2018)

Toxic protein	Protein deposit	Gene mutated	Familial disease
β-amyloid and Tau	Senile plaques and Neuronal and glial inclusions	*APP, PS1, PS2, MAPT*	Familial AD
α- synuclein	Lewy bodies, Lewy neurites	*SNCA*	Familial PD
Polyglutamine repeat expansion	Nuclear and cytoplasmic inclusions	*HD, ATXN*	Huntington's disease, SCA
PrP	PrP resistant to protease	*PRNP*	Familial prion protein disease
SOD	Hyaline inclusion	*SOD1*	Autosomal dominant familial ALS
ABri/ADan	Amyloid plaques	*BRI*	Familial British/Danish dementia
Neuroserpin	Collins bodies	*SERPINI1*	Familial encephalopathy with neuroserpin inclusion bodies.

MUSHROOMS AND NEUROREGENERATION

ANTRODIA CAMPHORATA

Antrodia camphorata, sometimes called "Niu-chang-chih" or "Chang-ku," is parasitic on ball camphor, which is native to Taiwan. Hepatocarcinoma, hives, diarrhoea, drug overdoses, hypertension, and strange aches are among the conditions it is frequently used to treat. For their antioxidant and anti-

inflammatory properties, polysaccharides and triterpenoids are being isolated extensively (Geethangili&Tzeng, 2011). In recent years, neuroinflammation has been cited as one of the primary pathologies in neurodegenerative diseases. In PD, neuroinflammation in the substantia nigra with NLRP3 inflammasome participation was revealed by activated microglia. The *A. camphorata* polysaccharides (ACP) were given to a mouse PD model. Analysis revealed that the substantia nigra had much higher levels of dopamine and NLRP3 activity was reduced, indicating the survival and regeneration of the otherwise damaged dopaminergic neurons (Han *et al.,* 2019). By scavenging reactive oxygen species (ROS) and boosting the immune system, *A. camphorata* also demonstrates antioxidant characteristics. *A. camphorata* mycelium extracts inhibit JNK and p38 activity and block the PKA-dependent pathway that leads to apoptosis in serum-depleted PC-12 cells (Huang *et al.,* 2005). Another study explained how *A. camphorate's* potent antioxidant and anti-inflammatory properties prevented neurotoxicity in a mouse model of AD. Additionally, it has been demonstrated to reduce tau protein hyperphosphorylation (Wang *et al.,* 2012).

HERICIUM ERINACEUS

Hericium erinaceus, sometimes referred to as the lion's mane mushroom in Western nations, is highly sought after for its medicinal biocompounds. Broadleaf trees that are old or dead typically house them. Numerous investigations on neuroinflammation, anti-neurotoxicity, neuroregeneration, etc. have shown its positive effects on neuronal health in general. It is continually investigated for its potential to stimulate neuronal development and for its potential to have neuroprotective effects (TrovatoSalinaro *et al.,* 2018). By raising neurotrophic factors like nerve growth factor (NGF) in human astrocytoma cells, bioactive substances derived from their fruiting bodies and mycelium, respectively, have been shown to contribute to the induction of nerve cell differentiation.

The reduction in these variables in neurodegenerative patients is currently countered by using the tiny compounds found in this mushroom extract. These tiny compounds increase the endogenous synthesis of neurotrophic factors because they can pass across the blood-brain barrier (Mori *et al.,* 2008). Additionally, it is clear from in vitro studies that HE inhibits the production of reactive oxygen species and halts the hyperconcentration of Ca^{2+}. Acetylcholine and choline acetyltransferase were more readily available in the hypothalamus and serum thanks to the polysaccharide-enriched aqueous extract of HE. *Hericium erinaceus* extracts addressed the ER stress brought on by prolonged calcium ion depletion, which was shown by a decrease in stress-related neuronal cell death (Ueda *et al.,* 2008).

GANODERMA LUCIDUM

This mushroom has a reputation for improving health and long life, as well as for treating and managing a number of illnesses such liver damage, chronic fatigue syndrome, etc. The molecular underpinnings of this species' neuroprotective actions are currently the subject of in-depth research. It has been demonstrated to raise toll-like receptor activity, boost mitochondrial function, lessen stress, inhibit acetylcholinesterase, and lessen neuroinflammation (Lee *et al.,* 2019).According to Zhang *et al.,* the proinflammatory and cytotoxic substances generated by microglial cells, including as nitric oxide (NO), interleukin- 1β (IL-1β), and tumor necrosis factor- α (TNF- α), were all reduced by *G. lucidum* extracts.TNF- α and IL-1β expressionwas discovered to be downregulated at the mRNA level. Avoided stress-induced cell death, which is a defining feature of neurodegenerative disorders in the broad area (Zhang, 2011 & Ding, 2010).

Fig. 2: Some mushrooms with neuroregenerative properties-*Agaricus bisporus* (Sonnenberg *et al.*, 2020), *Coprinus comatus* (Jang *et al.*, 2009), *Auricularia auricular*- judae (Wu *et al.*, 2015), *Ganoderma lucidum* (Zhou *et al.*, 2015), *Flammulina velutipes* (Rezaeian *et al.*, 2017), *Dictyophora indusiata* (WA *et al.*, 2020), *Hericium erinaceus* (Khan *et al.*, 2013), *Boletus edulis* (Catcheside *et al.*, 2012)

Erinacine A **Hericenone A**

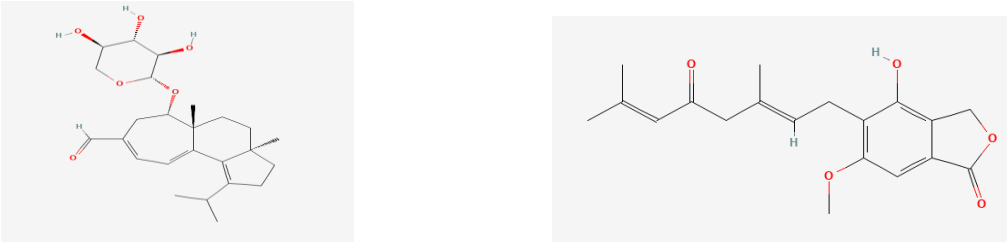

Fig. 3: Erinacines and hericenones

In certain investigations, the usefulness of *G. lucidum* (EGL) ethanolic extracts against neurodegeneration was investigated (Lakshmi *et al.*, 2003). After administering ethanol extracts of this mushroom, it was shown that the activity of enzymes like succinate dehydrogenase (SDH), pyruvate dehydrogenase (PDH), and beta-ketoglutarate dehydrogenase (α-KGDH) increased (Ajith *et al.*, 2009). The same outcomes of reduced of NO, TNF- α, IL-1β and prostaglandin E2 activity with EGL were seen in a second investigation.The NF-B and TLR pathways were shown to be reduced in the same research, and this resulted in an attenuation of lipopolysaccharide-stimulated inflammatory responses (Yoon *et al.*, 2013).*G. lucidum* extracts have been shown by Zhou et al to reduce oxidative stress and mitochondrial dysfunction (Zhou *et al.*, 2012). Additionally, methyl ganoderate A and n-butyl ganoderate H, two putative biomolecules, have been isolated from the fruiting bodies of this fungus (Fig 1). These are thought to possess anti-acetylcholinesterase

capabilities. Due to the therapeutic value of acetylcholinesterase inhibition in AD, this is a preferred option for pharmacological supplementation (Lee *et al.*, 2011).

Methyl ganoderate A acetonide **N-butyl ganoderate**

Fig. 4: Methyl ganoderate A and N-butyl ganoderate

SARCODON SCABROSUS

The bitter, inedible *Sarcodon scabrosus* mushroom is a common occurrence non Japan's coniferous woodlands. Scabronines, cyathanditerpenoids derived from the fruiting bodies of *S. scabrosus*, have been studied extensively for their antibacterial, antimicrobial, anti-inflammatory, and antiproliferative activities despite the fact that the fungus is unpleasant to eat. There are certain analogues of the various scabronines that have been shown to stimulate neurite growth, much like the erinacines found in the fruiting bodies of *H. erinaceus*. *H. erinaceus* and scabronines have a comparable chemical mechanism (Wender *et al.*, 2001). Because NGF cannot cross the BBB, smaller substances that can, such erinacines and scabronines, increase the generation of NGF. Among the several scabronine analogues, scabronines A and G have been found to be the most potent inducers of NGF synthesis (Cao *et al.*, 2018). Another class of analogues of interest is sarcodonins, and it has been shown that sarcodonins A and G likewise significantly enhance neurite outgrowth. As evidence mounts, it may be possible to treat Alzheimer's disease-related microglia-mediated neuroinflammation by regulating the ratio of M1 to M2 microglial phenotypes (AD). A *Sarcodon scabrosus*-isolated antigen reduced LPS-induced M1 polarisation in microglia via the MAPK/NF-B pathway (Cao *et al.*, 2022).

Scabronine A **Sarcodonin A**

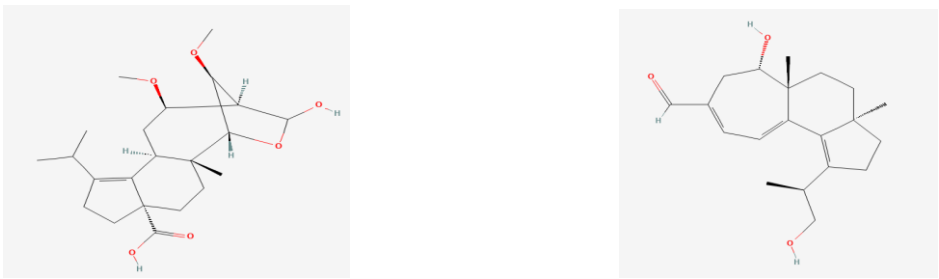

Figure 5: Scabronine A and Sarcodonin A

MYCOLEPTODONOIDES AITCHISONII

Mycoleptodonoides aitchisonii, also known as "Bunaharitake" in Japan, is a fungus that is cultivated on dead broadleaf trees in Asia from summer to fall. It is recognised for lowering blood pressure among other health benefits (Choi *et al.*, 2011). Additionally, fruiting body extracts have been shown to have strong antioxidant properties, as shown by their high total oxyradical scavenging activity.

The ability of *M. aitchisonii* extracts to reduce blood glucose levels in mice with hyperglycemia has been demonstrated in both in vitro and in vivo investigations, underlining the plant's potential as a treatment for diabetes mellitus. As shown in the same study by Choi *et al.*, that proved the mushroom's ability to decrease total cholesterol, triglyceride, and LDL cholesterol, fruiting body extracts may be utilised to treat hyperlipidemia (Choi *et al.*, 2014). TG, an inhibitor of the Ca^{2+} ATPases in the endoplasmic reticulum, produces ER stress by disrupting the Ca^{2+} homeostatic balance in the ER. *M. aitchisonii* has components that support ER Ca^{2+} homeostasis, protecting the neuron against cell death brought on by ER stress (Choi *et al.*, 2014 & Choi *et al.*, 2009). Another effect of this mushroom on the health of neuronal cells is an increase in NGF production. The aqueous extract of *M. aitchisonii* dramatically boosted NGF synthesis in the cerebral cortex and hippocampus when administered to new-born rats, according to Okuyama *et al.*, They also found that the mushroom extracts stimulated the synthesis of catecholamine metabolites and NGF (Okuyama *et al.*, 2004).

PLEUROTUS GIGANTEUS

This mushroom has organoleptic qualities and is used in cooking. It is frequently used to treat neurological illnesses, hypercholesteremia, hypertension, and inflammatory conditions. It successfully lowers cholesterol, blood glucose, and blood pressure in hyperglycemic individuals. It is considered a possible treatment option for neurological diseases due to its high carbohydrate, phenolic, triterpenoid, and potassium content. By mimicking the actions of NGF, it can cause the development of neurites and the differentiation of neurons. This is accomplished by means of the MEK/ERK and PI3K signalling pathways (Phan *et al.*, 2015). The STAT-3 and COX-2 pathways were suppressed in in vitro tests, demonstrating the anti-inflammatory effects of this fungus. Additionally, it cleans out the cells' ROS (Baskaran *et al.*, 2017).

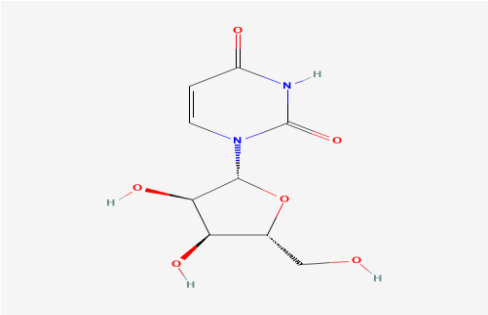

Fig. 6: Uridine

LIGNOSUS RHINOCEROTIS

The polypore *Lignosus rhinocerotis*, popularly known as "tiger's milk mushroom," is abundant only in a restricted geographic area and is regarded as a national treasure in Malaysia. This mushroom's extracts can help humans become more resilient and alert. Additionally, it is used to treat hepatitis, stomach ulcers, food poisoning, asthma, and colds, coughs, and fevers (Tan *et al.*, 2012). The sclerotium of this mushroom has a higher concentration of therapeutic compounds than its basidiocarp. Sliced, cooked, and ingested as a tonic for general health is sclerotium (Lee *et al.*, 2009).Neuritogenesis is associated with ongoing neuronal differentiation and neurite growth, which promotes the development of functional networks. It has been demonstrated that nerve growth factor injection can treat neurodegenerative diseases. However, because it is a big polypeptide, it

finds it challenging to pass the blood–brain barrier. Therefore, smaller polypeptides having the same biological function must be used in place of such molecules. The bioactive *L. rhinocerotis* compounds were discovered to replicate the neurotogenic effects of nerve growth factor in PC-12 cells by activating the MEK/ERK1/2 signalling pathway. The findings showed that the heated aqueous and ethanolic extracts promoted neuronal survival and proliferation (Seow *et al.,* 2015).The sclerotium also has a potent anti-inflammatory effect, which lowers nitric oxide (NO) levels, activates STAT3, and upregulates the production of interleukin 10 (IL-10) (Baskaran *et al.,* 2015 &Lin *et al.,* 2003). The sclerotium of *L. rhinocerotis* crude polysaccharides, hot aqueous, and ethanol extracts were shown to be non-cytotoxic to BV2 microglial cells (Nallathamby *et al.,* 2013).

PAXILLUS PANUOIDES

Free radicals may be scavenged by *Paxillus panuoides*, an inedible mushroom that grows on dead pine trees in North America and East Asia. Leucomentins, the p-terphenyl compounds found in *P. panuoides*methanolic extract, have been shown in studies to be effective regulators of lipid peroxidation in rat liver microsomes (Quang *et al.,* 2006). Free radical-induced oxidative stress has been related to the aetiology of neurological diseases. Antioxidants are now regarded to be a potential therapeutic target for treating neurodegenerative diseases since they would protect against stress-induced cell death. Therefore, leucomentins' effect on the health of neurons has been studied.One study found leucomentins to have neuroprotective effects, and its molecular mechanism has also been studied. In the investigation by Lee *et al.,* leucomentins were shown to be strong inhibitors of lipid peroxidation and H_2O_2 neurotoxicity but did not participate in the scavenging of reactive oxygen species (ROS) (Lee *et al.,* 2003).

Leucomentin 4 **Leucomentin 6**

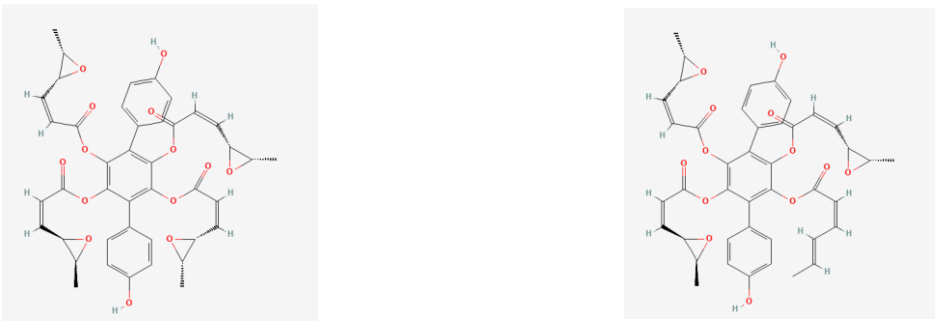

Fig. 7: Leucomentin 4 and Leucomentin 6

GRIFOLA FRONDOSE

Grifola frondosa, sometimes referred to as maitake, is a saprophytic plant belonging to the Meripilaceae family (Poryporales). Naturally, it occurs in Asia, Europe, and North America. The growth of *G. frondosa* tends to be supported by the rhizosphere of a variety of hardwoods, particularly fagaceous species like *Castanopsis cuspidate, Faguscarenata, Quercuscrispula*, or *Q. serrata*, as well as other species like *Prunus ume, P. salicina, P. armeniaca, P. persica*, and *Diospyros kaki* (Pinya, 1995). It tends to prefer situations where there are both open fields and forested areas. This plant is often classified as a saprophyte even though it occasionally grows on dead trees (Stamets, 2005). Growing evidence suggests that neuroinflammation is essential for the development of neurodegenerative disorders. To put it more simply, aberrant microglial or astrocyte activation or functional impairment in the brain are the causes of neurodegenerative disorders. The distinctive

characteristic of this inflammatory process has been identified as microglial activation. The results show that astrocytes and microglia are significantly less inflammatory when exposed to the naturally occurring chemical o-orsellinaldehyde that is isolated from the *G. frondosa* mushroom. However, the BBB's impenetrability or lack thereof is a frequent criticism of natural substances' possible effects on the CNS. It's noteworthy to note that the computational prediction indicates that o-orsellinaldehyde may be able to cross the BBB due to its physicochemical characteristics (Tomas-Hernandez *et al.*, 2021).

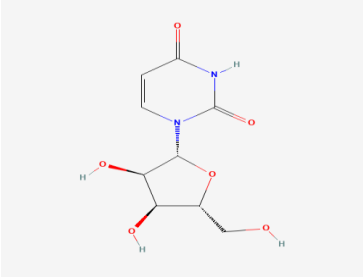

Fig. 8: o-orsellinaldehyde

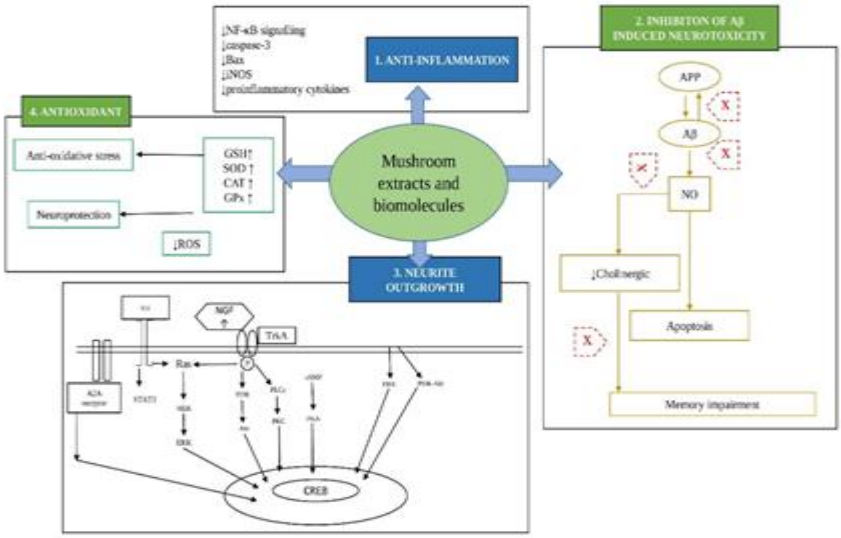

Fig. 9: Biochemistry of mechanism of mushroom extracts (Phan *et al.*, 2015)

Table 2: Some common mushroom and their mechanism of action contributing to neurogenesis

Scientific names	Common names	Active biomolecule	Mechanism of action	References
Agaricus bisporus	Button mushroom	Ergosterol	Decreases the risk of neurodegeneration	Phan *et al.* (2015)
Auricularia auricular- judae	Jelly ear	Glutathione, ergothioneine, vitamin D2, selenium	Supresses oxidative stress and damages	Zhang *et al.* (2011)
Auricularia polytricha	Wood ear mushroom	AAPS-1, AAPS-2 and AAPS-3	Suppresses activity of β-secretase	Sillapachaiyaporn *et al.* (2022) Liu *et al.* (2019)

Boletus edulis	The king mushroom	Ergothioneine	Inhibits hyperactivation of microglia	Kosanić et.al., (2012)
Cantharellus cibarius	Chanterelle	CC2a, CC3	Inhibits the neurodegeneration caused by hyperactivated glutamatergic system	Lemieszek *et al.* (2018)
Cordyceps cicadae	Caterpillar fungi	CPA-1, CPB-2	Decreases accumulation of ROS, Ca^{2+}	Olatunji *et al.* (2016)
Cordyceps militaris	Caterpillar fungi	Ergosterol, cordycepin	Suppressed acetylcholinesterase , β-secretase activity	He et.al., (2021)
Coprinus comatus	Shaggy mane	Catechin, p-hydroxybenzoic acid	Suppressed acetylcholinesterase activity	Pejin et. al., (2019)
Dictyophora indusiata	Bamboo mushroom	Dictyoquinazols A, B, C and β-(1-3)-D- glucan	Inhibits Aβ- mediated and polyglutamine-neurotoxicity	Habtemariam (2019)
Flammulina velutipes	Velvet foot	Phenolics	Antioxidative, anti-apoptotic	Zhang *et al.* (2018)
Fomitopsis officinalis	Agarikon	Triterpenes, Dehydrosulfurenic acid	Neuroprotective	Muszyńska *et al.* (2020)
Ganoderma lingzhi	Red Reishi	Oligosaccharide	Reduces degeneration pattern	Aguirre-Moreno *et al.* (2013)
Ganoderma lucidum	Reishi	Psilocybin, sterols, triterpenoids	Increase NGF and BDNF production	Phan *et al.* (2015)
Grifola frondosa	Maitake	β-glucans	Reduces degeneration and has neuritogenic activity	Pinya (2019)
Hericium erinaceus	Lion's mane mushroom	Hericenones and erinacines	Stimulates NGF	Li *et al.* (2018)
Lentinula edodes	Shiitake	Xylane, heteroxylane	Neuroprotective; improves microcirculation in brain	Rai *et al.* (2021)
Pleurotus citrinopileatus	Golden oyster		Suppress chronic hyperactivation of microglia	Rai *et al.* (2021)
Pleurotus eryngii	King trumpet mushroom	Adenosine	Increased the neurite-bearing cells, reduced the NO level	Kushairi *et al.* (2020)
Pleurotus ostreatus	Oyster mushroom	Ergothioneine	acetylcholinesterase and tyrosinase inhibition	Ćilerdžić *et al.* (2019)

CONCLUSION

The kingdom of fungus has repeatedly shown itself to be a pioneer source of several nutraceuticals and pharmaceutical lead products, and it has also been utilised in its natural state since antiquity. They attribute their biological constituents' antioxidant, anti-inflammatory, antitumorigenic, anti-diabetic, antiviral, antithrombotic, and hypotensive properties. Surprisingly, when taken early on, they have been proven to have neuroregenerative capabilities and to prevent neurodegeneration and ageing in the brain. The senior population across the world is affected by a number of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), as well as Friedreich ataxia, Huntington's disease, Lewy body disease, and spinal muscular atrophy. By scavenging reactive oxygen species, maintaining the health of mitochondria and endoplasmic reticulum, and suppressing the enzymes that cause neuronal malfunction, the compounds—either singly or in combination help prevent the death of brain neurons. These fungi compounds would become known as novel nutraceuticals after further study, which would offer up new treatment avenues for neurological illnesses.

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Chapter
4

APPLICATION OF N-HETEROCYCLIC CARBENE (NHC) COMPLEXES IN CATALYSIS

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ABSTRACT

NHCs have drawn a major attraction in organometallic chemistry. This field has been elevated to a center of curiosity because of its enormous practical significance. Outstanding features like stereoelectronic diversity, easy to prepare and ability to stabilize metals/main group elements in variable oxidation state make it suitable ligand. Steric influence of N-substituent are evaluated by 'buried volume' parameter ($\%V_{bur}$) and electronic properties comprehensively measured by "Tolman electronic parameter" (TEP). NHC-complexes are found to be robust and these are very much active in catalytic transformations. Tremendous successes of NHC-complex in difficult catalysis have been witnessed during past few decades. In this chapter physical properties of NHC, preparation of their precursor and complexation strategies are briefly discussed. Although NHC-Complexes have vast applications, few of the important catalytic activities such as Olefin metathesis, C-C cross coupling, acceptorless dehydrogenation, C-H functionalization and CO_2 activation are explained here.

KEYWORDS: Carbene, Synergistic effect, Catalysis, Cross coupling, Activation.

INTRODUCTION

AN OVERVIEW OF NHC-COMPLEX

NHCs are broadly defined as heterocyclic species containing carbon and at least one nitrogen atom within the ring structure. Their ability to behave as strong donor ligand has been immensely explored in organometallic chemistry and catalysis (Huynh, 2018). Their enormous popularity can be attributed to different factors (Figure 1).

(i) NHC ligands have large structural and stereoelectronic diversity.

(ii) It can coordinate with both transition metals and p-block elements, leading to substantially strong bonds.

CLASSIFICATION

NHCs derived from heteroaromatic species have greater structural variation. Alterations in their structural motif can be done by several ways including changes in heteroatom and at ring-substituent. NHC ligands are broadly classified into seven major categories and their structural change highly affects on donor/ acceptor properties (Figure 2, Glorius *et al.,* 2014). The most

common types of NHCs are used in organometallic chemistry derived from imidazole type (a) heterocyclic compound. Many carbenes in this category like IMes, IAd, SIMes etc. are found to be very stable in free state and these are applied in complexation with various metals and non-metals (Wanzlick *et al.*, 1968; Öfele, 1968). Replacement by another heteroatom like oxygen (**b**), sulphur (**c**) and introduction of one more nitrogen (**d**) leads to another class of NHCs which exhibit different electronic properties. Bertrand group introduced a series of CAACs (**e**) with one nitrogen atom in heteroaromatic ring, have achieved considerable attention in modern era of research (Bertrand *et al.*, 2005). These are widely used to stabilize low valent main group elements like Si, Ge, Sn etc. Mesoionic carbene (MIC, **f**), which can coordinates through C4 site instead of C2 that gives rise to stronger σ-donation. Hence, it is commonly described as abnormal carbene (Aldeco-Perez, E. *et al.*, 2009). DAC (**g**) is another special class of NHC bearing larger N^1-C^2-N^3 bond angle with amido linkage, has greater π-accepting ability than other NHCs. These are relatively less explored in organometallic chemistry.

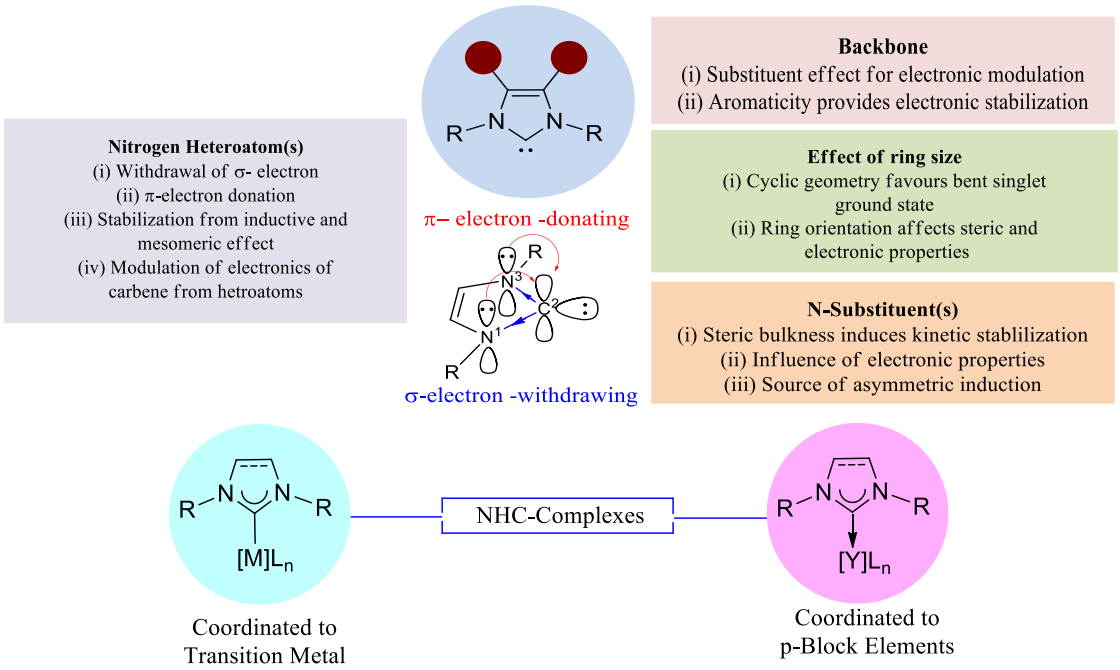
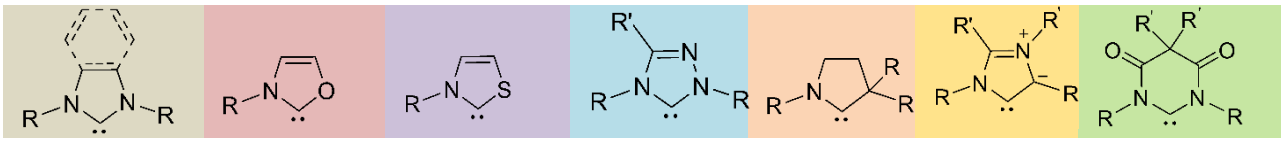


Fig. 1: General features of NHCs

NHC Ligand



Imidazolylidene type (**a**)	Oxazolylidene (**b**)	Thiazolylidene (**c**)	Triazolylidiene (**d**)	Cyclic alkyl amino carbenes (CAAC, **e**)	Abnormal/ Mesoionic Carbene (MIC, **f**)	N,N′-Diamidocarbene (DAC, **g**)

Fig. 2: Different types of NHC ligand

STRUCTURE AND BONDING OF NHC-COMPLEX

NHC adopts bent structure due to its cyclic nature. Heteroatom present in NHC ring possesses σ-electron withdrawing property and thus it inductively stabilizes the σ-nonbonding orbital as a result of increasing s character. P_π-orbital is perturbed by interaction with substituent lone pair and it increases its energy. The overall effect results the effective increase in σ-p_π gap (Figure 3a, Bertrand *et al.*, 2000). This favors singlet state of NHC. It donates nonbonding electron in σ-orbital (HOMO) to metal and accepts π-electron in vacant p_π-orbital (LUMO) which is known as synergistic effect (Figure 3b,).

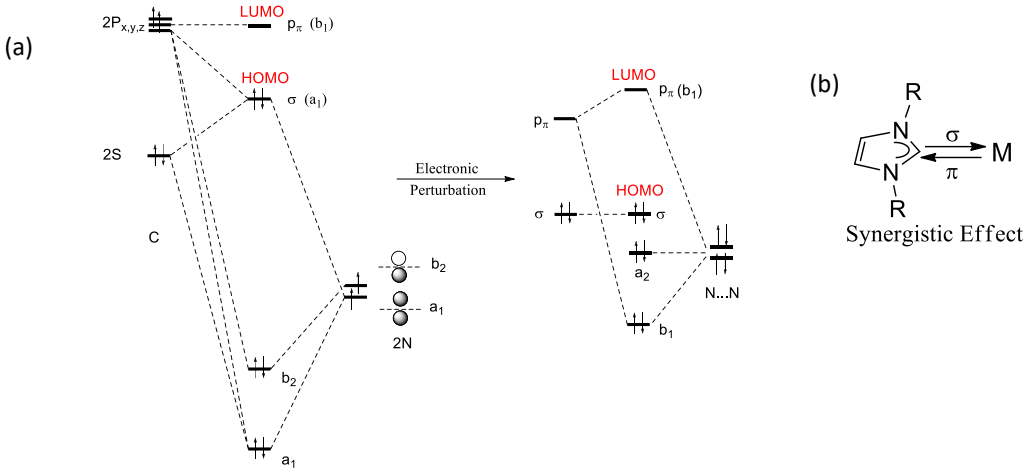


Fig. 3: (a) Molecular orbital diagram of NHC, (b) bonding in NHC-Complexes

MEASUREMENT OF STERIC AND ELECTRONIC PARAMETER

Conventionally, steric properties of NHCs are measured by 'buried volume' ($\%V_{bur}$) parameter, developed by Nolan, Cavallo and co-workers. It is defined as the percentage of a sphere occupied or 'buried' by the ligand upon coordination to a metal at the centre of the sphere (Figure 4a). $\%V_{bur}$ is increased with increase in steric bulkiness. Typical values of d 2.0Å and for r 3.0 Å or 3.5 Å are considered to be grater steric influence from ligand on metal centre. $\%V_{bur}$ is determined from X-ray crystallographic date or from DFT calculation.

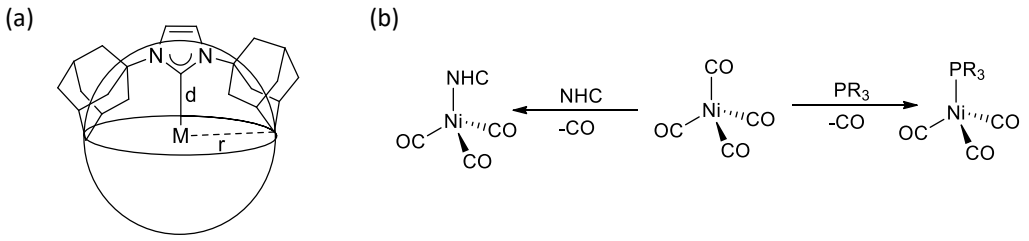


Fig. 4: (a) Measurement of buried volume, (b) Evaluation of Tolman electronic parameter of NHC vs phosphine

Electronic properties of NHCs are evaluated by Tolman electronic parameter (TEP) (Tolman, 1977). It uses the stretching frequency of CO in T_d complex like $[Ni(CO)_3(NHC)]$ to determine the donor/acceptor ability of NHCs (Figure 4b). A stronger donor ligand can make Ni-complex more electron rich which enhances the back donation to CO. Overall effect is observed in weakening the CO bond, and a smaller stretching frequency is obtained. For this evaluation

$[Ni(CO)_3(NHC)]$ are synthesized by reaction of free NHCs or their precursor. However, the complex of the type $[Ni(CO)_3PR_3]$ can also be prepared to compare the electronic influence between NHCs and phosphines. Tolman found ν_{CO} of 2056 cm^{-1} in DCM for $P(^tBu)_3$, which is considered as the strongest donor in his original series. TEPs of different NHCs are summarized below (Chart 1, Huynh, 2018), which indicates that NHCs have better σ-donating ability than that of phosphines. In the context of TEP, solvent/media has very sensitive role that affects on CO stretching frequencies.

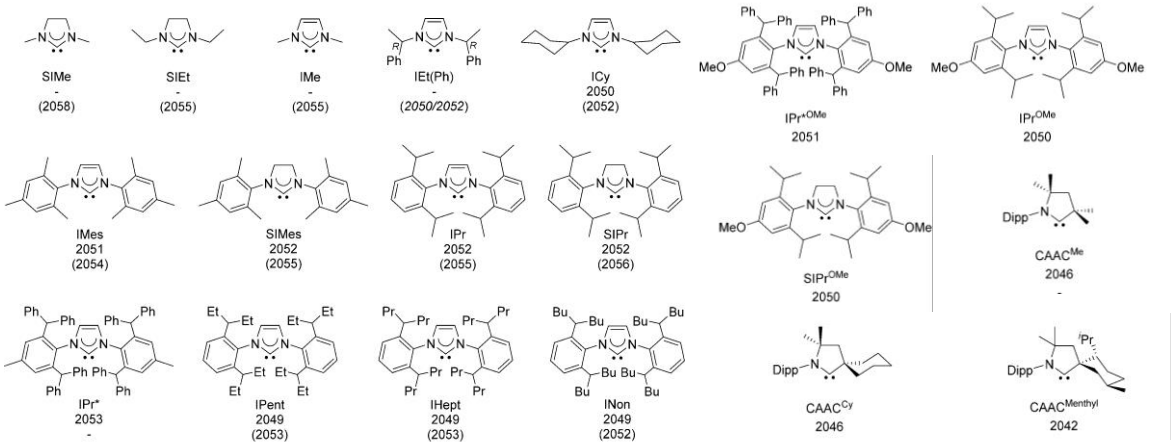


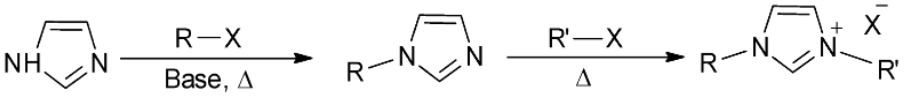
Chart 1: CO stretching frequencies of $[Ni(CO)_3(NHC)]$ complexes in DCM (Hexane)

SYNTHESIS

Generally, NHCs are prepared via the deprotonation of their corresponding azolium salts which are collectively known as NHC precursor. pK_a values of azolium salts such as imidazolium, triazolium, pyrazolium, benzimidazolium, oxazolium, thiazolium varies from 21-24. Strong bases like KO^tBu, NaH, *n*-BuLi, LHMDS etc. are commonly used in this deprotonation. Bulky substituents are inserted in N-side arm to avoid dimerization. Sometimes, NHCs are generated *in situ* via deprotonation at the time of metallation.

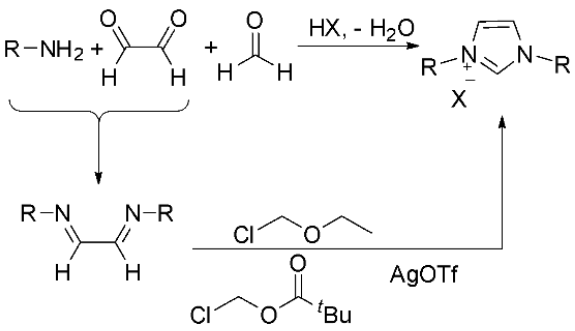
Synthesis of NHC Precursors

(I) Substitution Method

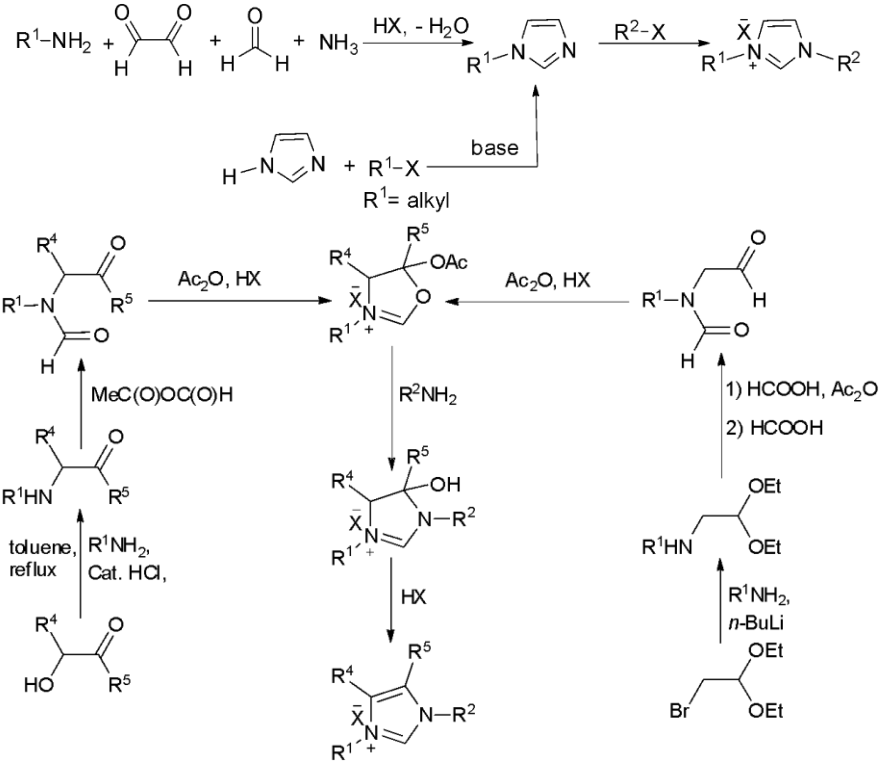


(II) Synthesis of Imidazolium ring

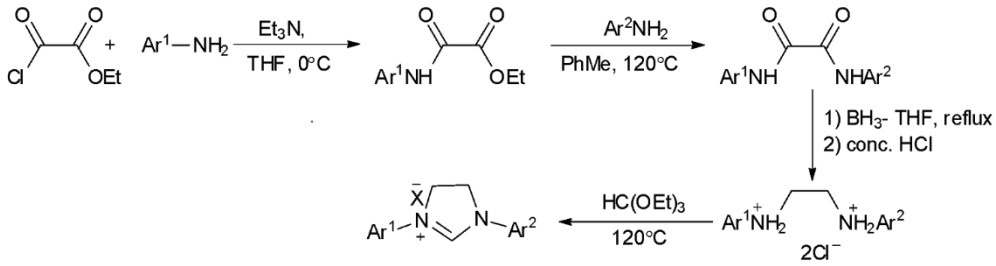
(a) Symmetric Synthesis



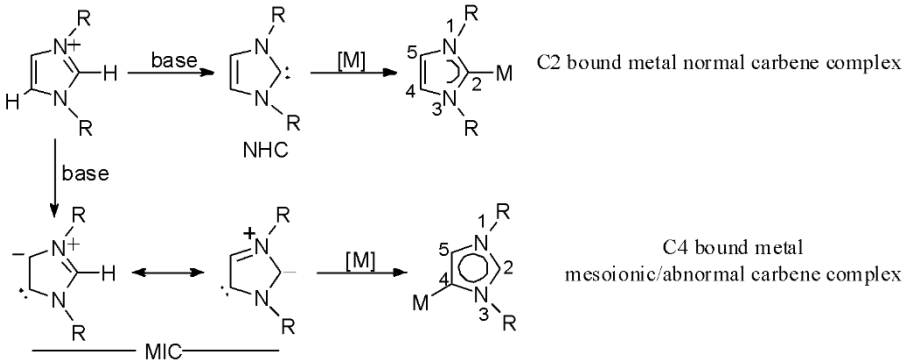
(b) Unsymmetric Synthesis



(III) Synthesis of Imidazolidinium ring



Metallation Strategy in Normal vs Abnormal Carbene

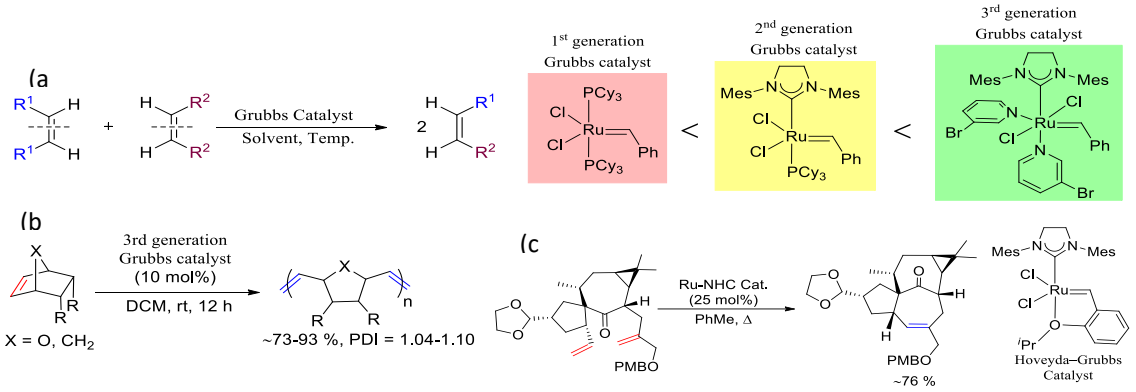


NHC-COMPLEXES IN CATALYSIS

OLEFIN METATHESIS

Olefin metathesis is a catalytic transformation, in which alkenes undergoes rearrangements via the cleavage of C=C bond. Grubs catalyst is very well known for this transformation. Installation of NHC moiety in such catalyst increases its activity which is attributed to increased stability in M-C bond and thereby lowers the rate of catalyst decomposition. Catalytically more

convenient binding of the π-accepting alkene substrates was found to be more favorable for the more electron-rich NHC stabilized Ru(II) centre over PCy_3 coordinated Ru(II) centre. Hence, better efficiency is observed on going from Grubbs 1st generation to 3rd generation catalyst (Scheme 1a, Grubbs *et al.*, 2010; Grela *et al.*, 2010). Metathesis reaction happens for both ring closing (RCM) and ring opening (ROM) reaction (Nicolaou *et al.*, 2005). ROM has a greater application in polymerization reaction (Scheme 1b, Grubbs *et al.*, 2001). Widely utilized Hoveyda–Grubbs catalyst also developed for application in RCM reaction (Scheme 1c).

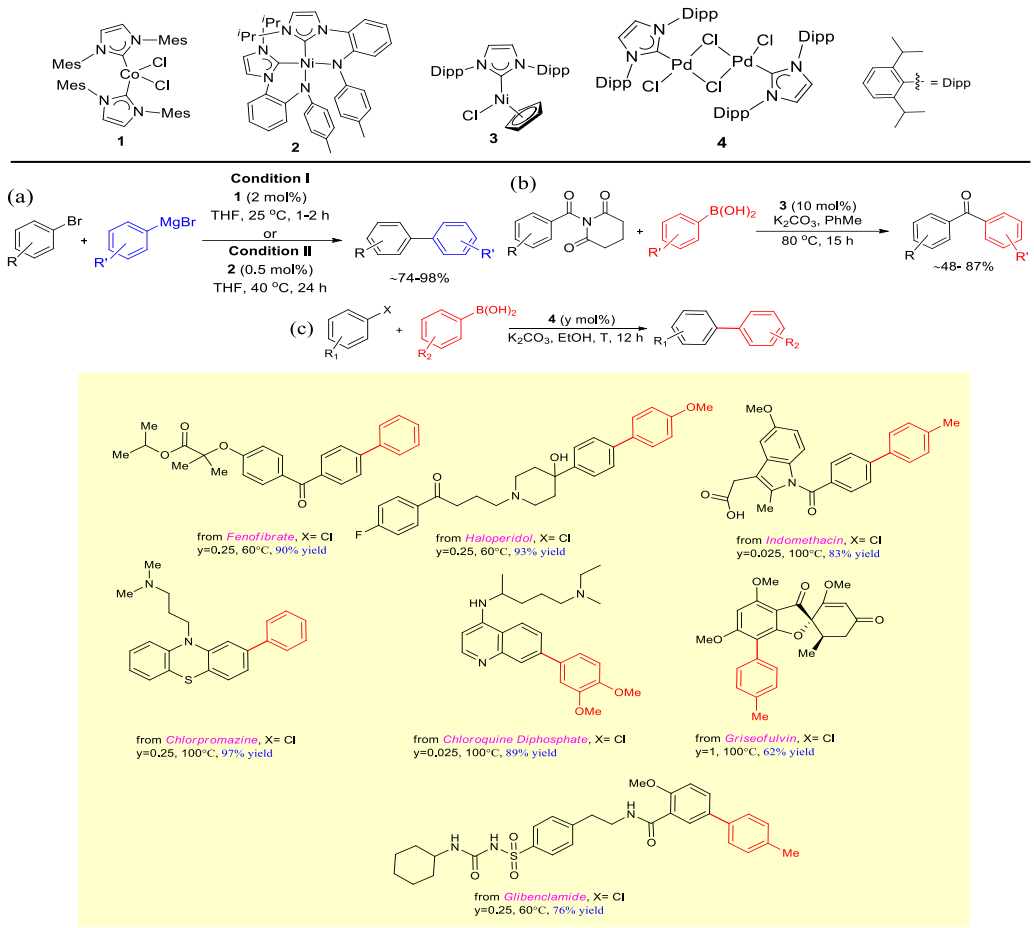


Scheme 1: **(a) Olefin metathesis using Grubbs catalysts and comparison of their reactivity, (b) ring opening metathesis using 3rd generation Grubbs catalyst, (c) ring closing metathesis using Hoveyda-Grubbs catalyst**

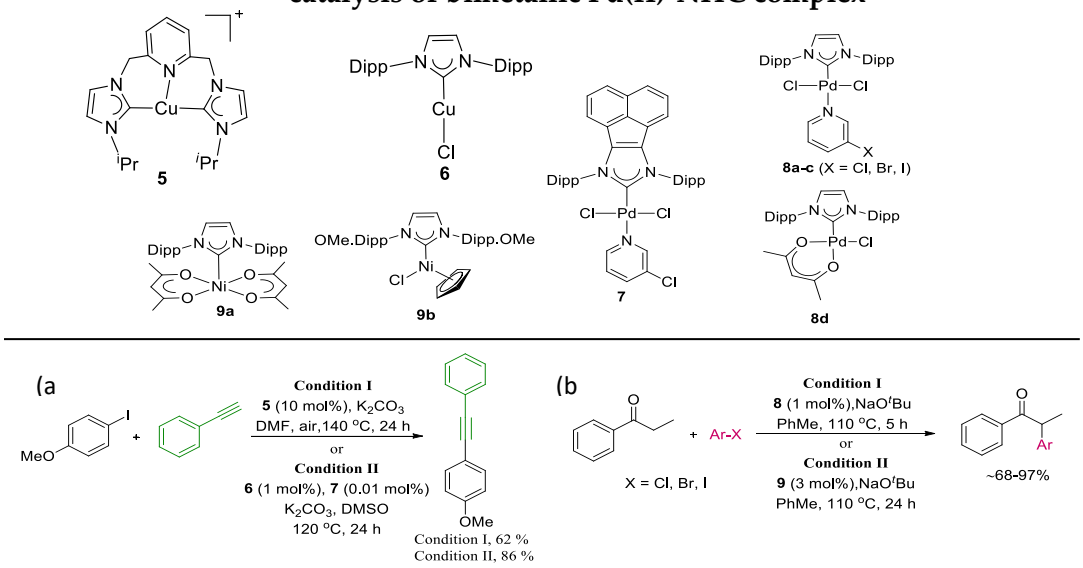
C-C CROSS COUPLING REACTION

Cross coupling is an important tool for synthetic chemist for the combination of unequal fragments. Huge success of NHC as a ligand in C-C cross coupling reaction has been observed during past few decades. NHC provides robustness in the complex; it can stabilize metal in variable oxidation state. These features make the catalyst susceptible for such transformation. NHC functionalized Co(II) complex (**1**)can acts as a good catalyst for Kumada coupling reaction of aryl halides and aryl Grignard reagents to create new C-C bond between two aryl derivatives (Scheme 2a, Tonzetich *et al.*, 2012). Similar reaction is also performed by Ni(II)-NHC catalyst (**2**) under slightly different condition (Fenske *et al.*, 2016).

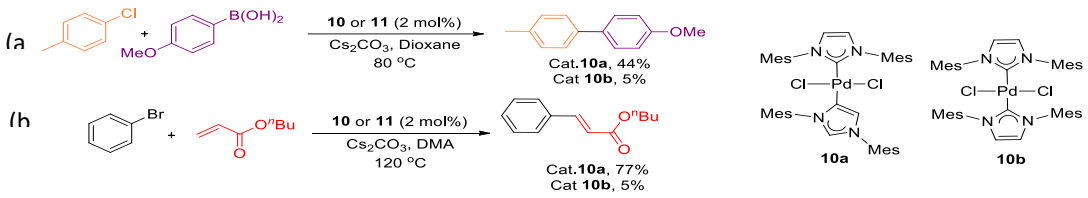
Well-defined Ni-catalyst **3** shows dominant action in activating amide bond for Suzuki–Miyaura cross-coupling between amides and aryl boronic acid derivatives (Scheme 2b, Szostak *et al.*, 2020). In a similar type of coupling reaction, a bimetallic Pd(II)-NHC complex (**4**) efficiently catalyzes to generate bio-inspired molecules (Scheme 2c, Szostak *et al.*, 2020). Sonogashira coupling is an useful method for the functionalization of terminal alkyne. A chelate Cu(I)-NHC complex (**5**) is found to catalyze such coupling (Tahsini *et al.*, 2018). The use of Cu(I)-NHC (**6**) in combination Pd-PEPPSI-NHC complex (**7**) enhances the catalytic efficacy and better conversion is achieved with lower catalyst loading (Scheme 3a, Tu *et al.*, 2018). In current trend, NHC complexes also successfully employed in various arylation of activated mythelenes. In this regard, activity of Pd(II)-NHC (**8**) and Ni(II)-NHC (**9**) for the α-arylation of ketones using aryl halides also have been evaluated (Scheme 3b, Ananikov *et al.*, 2021).



Scheme 2. (a) Kumada coupling catalyzed by Co(II), Ni(II)-NHC complexes, (b) Ni(II)-NHC-catalyzed Suzuki–Miyaura cross-coupling between amides and aryl boronic acids, (c) syntheses of biologically important molecules through Suzuki–Miyaura coupling under the catalysis of bimetallic Pd(II)-NHC complex



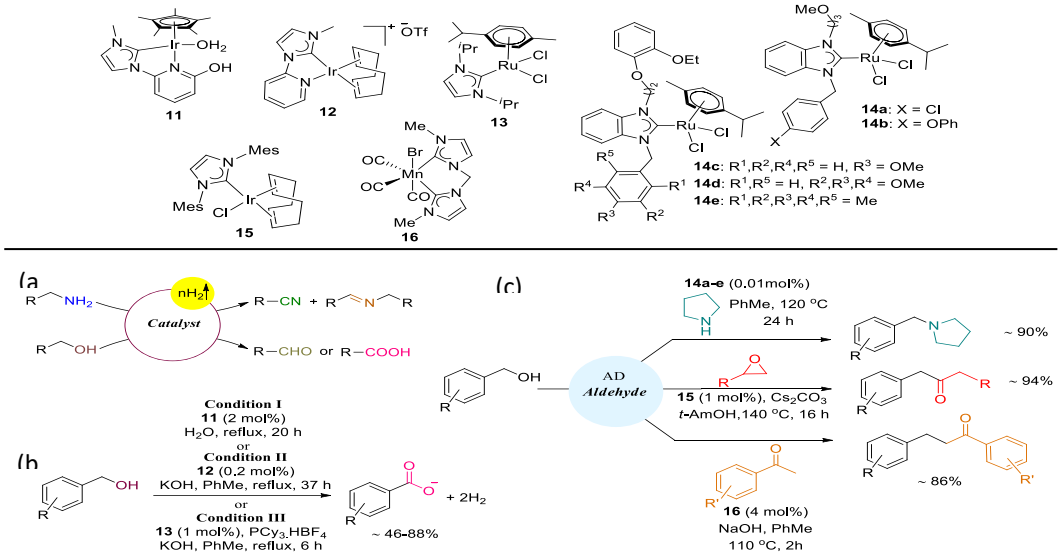
Scheme 3: (a) Sonogashira coupling by Cu(I), Pd(II)-NHC catalysts, (b) *α*-arylation of ketones using Ni(II), Pd(II)-NHC catalysts



Scheme 4: Competitive catalytic experiment between normal and abnormal Pd(II)-NHCs

A competitive catalytic experiment demonstrates the superior activity of the Pd(II)-MIC complex (**10a**) over the normal NHC analogue (**10b**). In the Suzuki–Miyaura and Mizoroki–Heck cross-coupling reactions, **10a** results much better yields of products when it is applied under same reaction condition as provided for **10b** (Scheme 4a and 4b, Nolan *et al.*, 2004). MIC being a good σ-donor makes the metal centre electron rich and thus it facilitates faster catalytic transformation (Bertrand *et al.*, 2019).

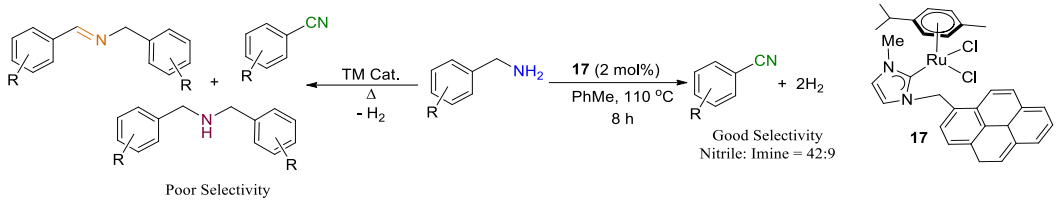
Acceptorless Dehydrogenation (AD)



Scheme 5:(a) Possible products for AD of alcohols and amines, (b) AD of alcohols to acid salts by Ir(I), Ru(II)-NHC catalysts, (c) metal-NHC-catalyzed various alkylation reactions via the AD of alcohols

AD has important aspect in the context of green chemistry. In contrast to traditional method, that requires stoichiometric oxidants like $KMnO_4$, $K_2Cr_2O_7$, $HClO_4$ etc. produces copious waste that are hazardous to our environment. AD offers a benign protocol in which H_2 is obtained as only byproduct with a good E factor (Scheme 5a, Grützmacher *et al.*, 2021). This methodology is used in now a days for the synthesis of value added chemicals. Studies show that Ir-NHC complexes like **11**, **12** are found to be active for the AD of alcohols to give acid salt in alkaline medium (Scheme 5b, Yamaguchi *et al.*, 2017; Williams *et al.*, 2018). Sole byproduct H_2 liberated in this reaction can act as energy resource and also helps to enhance atom economy. Similar behavior is also found in Ru(II)-NHC complex (**13**) (Madsen *et al.*, 2016). AD of alcohol is also

useful as a key step in functional group transformation (Scheme 5c). A series of NHC-stabilized half-sandwich Ru(II) complexes (**14a-e**) have been developed and utilized for the *N*-alkylation of amines using alcohol as an alkylating agent (Kaloglu, 2019). Among them 14d performs most efficient activity which may be attributed to proper modulation stereoelectronic modulation by the substituent. Besides, C-alkylation of ketones and epoxides are also found to be catalyzed by Ir(I)-NHC (**15**) and Mn(I)-NHC (**16**) respectively (Gülcemal *et al.,* 2021; Ke *et al.,* 2019). Catalyst **15** is effective in selective ring opening of terminal epoxides and gives its corresponding ketones. Above alkylation reactions use alcohol as H_2 source for hydrogenation in further step which is also known as "Borrowing Hydrogenation" strategy (Morrill *et al.,* 2021).



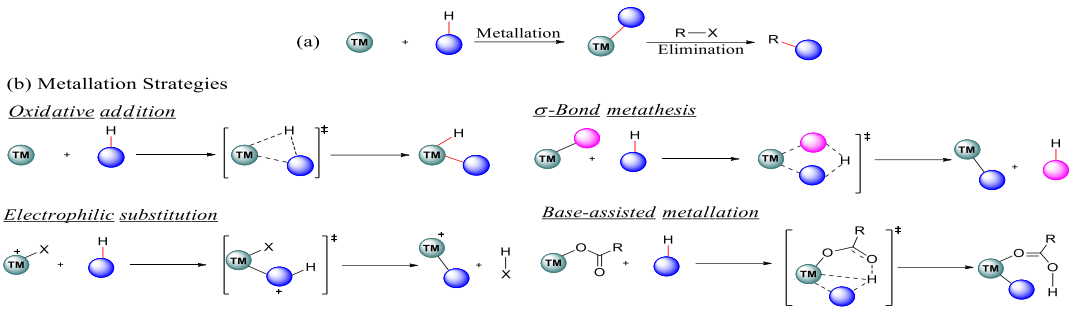
Scheme 6: **AD of amines and its selectivity**

Notably, AD of primary amine suffers from selectivity issue, as it produces different products like nitrile, imine and even alkylated amines. NHC has significant implication in order to accrue better selectivity. For example, Ru(II)-NHC (**17**) is capable of H_2 production from primary amines which finally gives rise to nitriles with improved selectively (Scheme 6, Mata *et al.,* 2016).

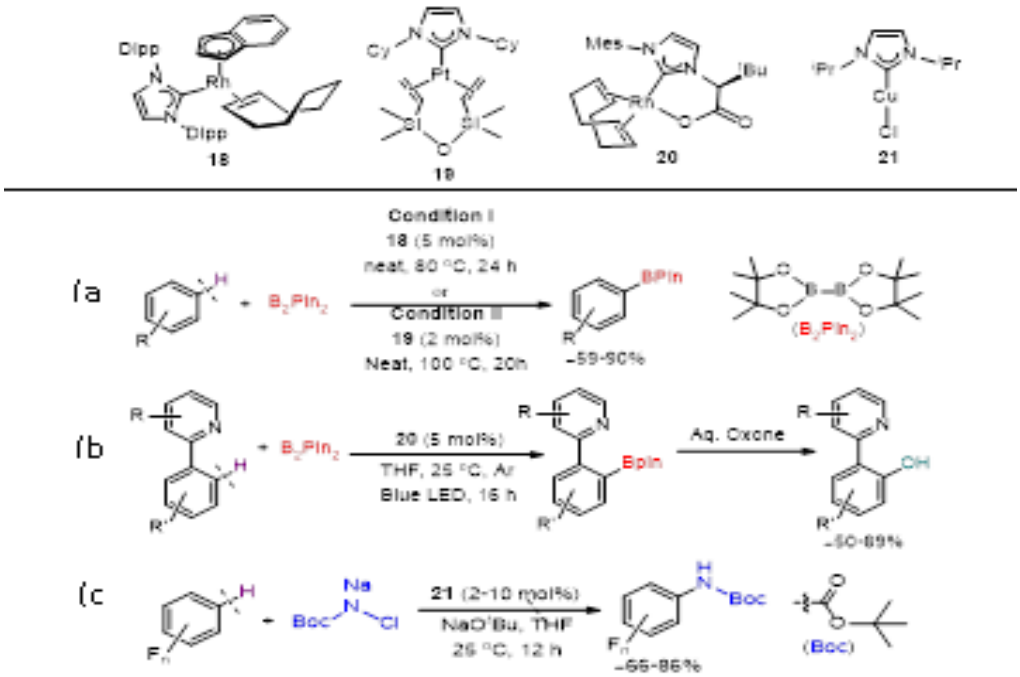
C-H FUNCTIONALIZATION

C-H functionalization has greater utility in catalysis as it offers a single step reaction to synthesize useful chemicals. This reaction proceeds via metallation and nucleophilic addition followed by subsequent elimination of products from metal's coordination sphere (Scheme 7a). Metals in low valent state stabilized by NHC ligand are very much active for such transformation. The initial metallation can be done through different pathways such as oxidative addition, σ-bond metathesis, electrophilic substitution and sometimes assisted by base present in reaction (Scheme 7b, Ackermann *et al*., 2021).

C-H borylation is one of the important C-H functionalization as it generates potential synthons for various coupling reactions. Rh(I)-NHC (**18**) and Pt(0)-NHC (**19**) gives borylated products via the cleavage of B-B bond in B_2Pin_2 (Scheme 8a, Mansell *et al.,* 2021; Chatani *et al.,* 2015). Directing group assisted borlation is also performed by (cod)Rh(I)-NHC catalyst (**20**) under the influence of visible light (Scheme 8b, Baslé *et al.,* 2019). Photoexcitation helps in the cleavage of C-H bond in substrate and thus it indulges oxidative addition in metallation step. C–H amidation of fluoroarenes is also known by Cu(I)-NHC (**21**) catalyst (Scheme 8c). Here base assisted addition of fluoroarenes takes place to the metal centre (Chang *et al.,* 2016).

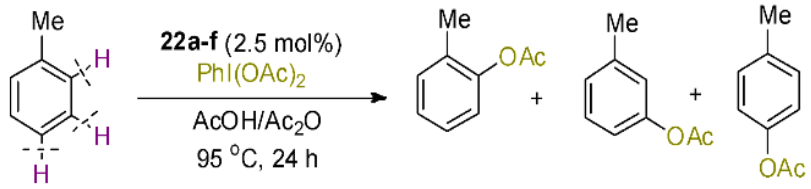


Scheme 7:(a) Progress of reaction for C-H activation, (b) different pathways of metallation



Scheme 8: (a) C-H borylation by Rh(I), Pt(0)-NHC catalysts, (b) photocatalytic C-H borylation by Rh(I)-NHC catalyst (c) C-H amidation of fluoroarenes catalyzed by Cu(I)-NHC complex

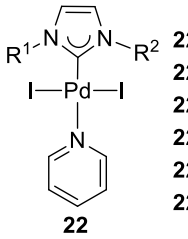
Following C–H acetoxylation reaction catalyzed by Pd(II)-NHC (**22**) explains the steric influence in selectivity (Scheme 9). A series of Pd catalysts (**22a-f**) with different N-substituents in NHC architecture are employed in this reaction in presence of acetylating agent $PhI(OAc)_2$ (Choudhury *et al.*, 2021). Catalyst **22d** having bulkiest NHC ligand with % V_{burr} value 33.4 shows lowest selectivity for *ortho*-H (16%) and highest selectivity for *para*-H (47%). Hindered ligand disfavors *ortho*-C-H activation relative to *meta*/*para*-C-H bond. Hence, *ortho* selectivity can be improved by the lowering of steric bulkiness in one of the side arm (**22a**, **e** and **f**) and thus distal versus proximal selectivity can be monitored (Table 1).



Scheme 9: C–H acetoxylation reaction catalyzed by Pd(II)-NHC complexes

Table 1: **Steric effect of NHC in the selectivity of C-H acetoxylation reaction**

Catalyst	% V_{burr}	Selectivity (%)		
		ortho	*meta*	*para*
22a	27.2	23	34	43
22b	28.6	19	37	44
22c	28.7	18	36	46
22d	33.4	16	37	47
22e	32.3	23	33	44
22f	30.8	25	35	40



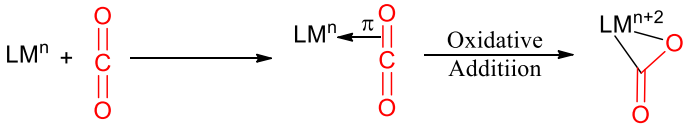
22

22a: R^1, R^2 = Me
22b: R^1, R^2 = ^{n}Bu
22c: R^1, R^2 = Cy
22d: R^1, R^2 = Mes
22e: R^1 = Me, R^2 = ^{t}Bu
22f: R^1 = Me, R^2 = Ph

CO_2 ACTIVATION

Continuous emission of CO_2 in atmosphere is a worldwide problem because of its detrimental impact on environment. Current research focus on capture and utilization of atmospheric CO_2 for the production of value added chemicals. CO_2 has very stable ground state; its reactivity can be enhanced upon activation. Activation of CO_2 can takes place by altercations of several of geometric and electronic properties (Zhong *et al.*, 2021).

1. Bending of the O–C–O bond angle from 180°,
2. Elongation of at least one of the two C–O bonds,
3. Polarization of the charges on C and O, leading to the transfer of charge/electron to CO_2,
4. Hydride transfer,
5. Redistribution of charges.

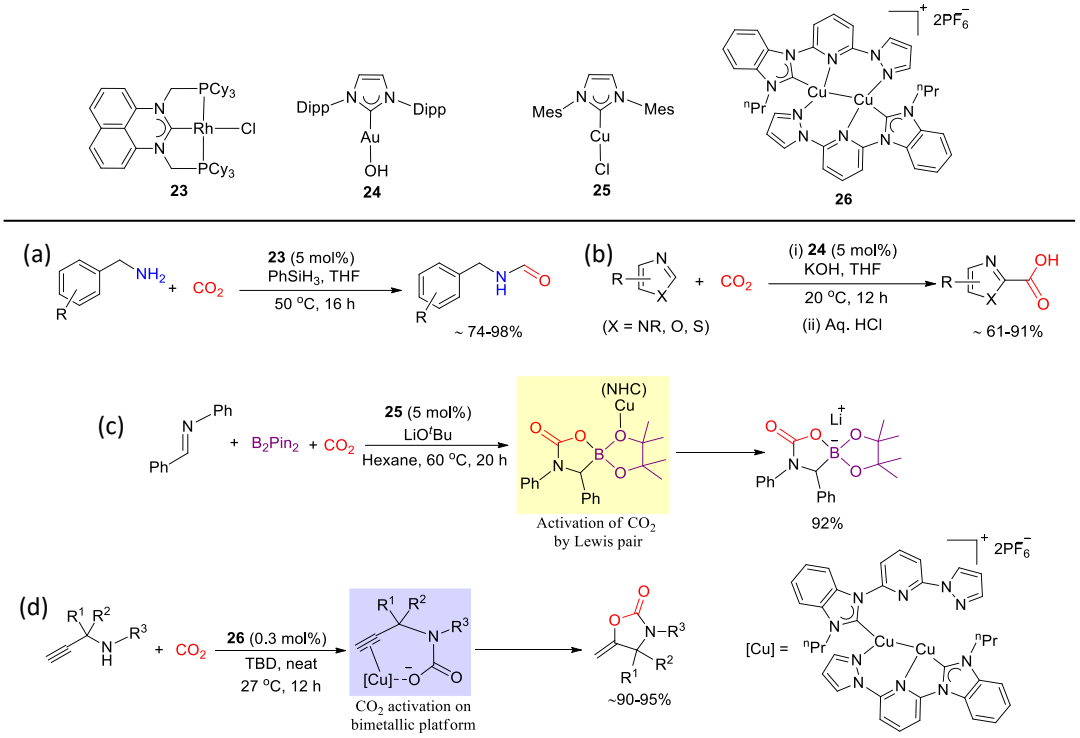


Scheme 10: Mode of CO_2 activation by transition metals

In solution phase, transition metal can directly coordinates to form M-CO_2 complex. Transfer of π-electron to the vacant d orbital of transition metal causes oxidative addition of CO_2 (Scheme 10). Sometimes in multi-metal complex, CO_2 is captured and activated by bridging between metals. IR is an excellent tool for the evaluation of such M-CO_2 interaction. In many catalytic processes, bases like TBD, DBU, DABCO, and TEA are utilized as CO_2 capturing agent and it increases the reactivity of CO_2.

In this regard, *N*-formylation using CO_2 is one of the useful transformations. Rh(I)-NHC complex (**23**) exhibits its catalytic efficacy in formylation of amines in presence of $PhSiH_3$ (Scheme 11a, Messerle *et al.*, 2019). Carboxylation of arenes is already known to be catalyzed by Au(I)-NHC complex (**24**) under basic medium (Scheme 11b, Nolan *et al.*, 2010). In difunctionalization of imines CO_2 is activated by Lewis pair generated by Cu(I)-NHC catalyst (**25**) and B_2Pin_2 (Scheme 11c, Hou *et al.*, 2020). Bimetallic [Cu(I)-Cu(I)] platform in complex **26** also offers an unique approach where CO_2 is activated and utilized into oxazolidinones from propargylic amines by the cooperative assistance from hemilabile ligand (Scheme 11d, Dai *et al.*,

2020). Hemilabile behavior of pyridine-pyrazole ring originates due to strong trans effect of NHC which allows the empty space for the combination of C≡C, -NH and CO_2 on [Cu(I)-Cu(I)] platform to give oxazolidinones.



Scheme 11: **(a) Rh(I)-NHC-catalyzed *N*-fromylation of amine using CO_2, (b) Carboxylation of arenes by Au(I)-NHC catalyst, (c) activation of CO_2 by Lewis pair, (d) Bimetallic Cu(I)-NHC-catalyzed syntheses of oxazolidinones via the activation of CO_2**

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Chapter 5

EFFECTS OF HEAVY METAL TOXICITY: FROM FISH TO HUMANS

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ABSTRACT

Heavy metals such as lead (Pb), arsenic (As), mercury (Hg) and cadmium (Cd) are known to has little functional role in any life forms with myriads of toxic effects. Excessive release of heavy metals in water reducing the quality life of aquatic animals such as fish. Accumulation of heavy metals in various tissues suppresses the immunity of fish and other aquatic organisms. Fish, as an essential source of the human diet, bioaccumulation of metals in fish is a concern for human health. Much heavy metal can cause serious health threat to humans when it goes beyond its permissible limit. Functional similarities have been found between fish and mammalian (human) immune system. Through understanding molecular mechanism of the activation of NF-κB pathway, in fish, a key regulator of inflammation and apoptosis due to heavy metal stress, human health could be monitored in a better way.

KEYWORDS: Heavy metals, Fish, human health, immunity, NF-κB.

INTRODUCTION

Water, the most indispensable constituent of life, plays a vital role in the maintenance of health in all lifeforms. As an essential natural resource, it is used for various activities especially for domestic needs, irrigation, aquaculture, industry, etc. However, natural activities as well as the advancement of technology, modernization and urbanization, mining, enhanced agricultural activities have led to exposure of the aquatic environment to various types of pollutants such as suspended solids, organic and inorganic compounds, heavy metals, pesticides, herbicides, etc. The contamination of aquatic environment has been a cause of concern since decades and has witnessed significant attention as it not only deteriorates the life-sustaining quality of water but also cause damage to different aquatic species.

Among different types of pollutants, heavy metals such as mercury (Hg), cadmium (Cd), arsenic (As) lead (Pb), aluminium (Al), tin (Sn), etc. are of greatest concern because of their persistent and bio accumulative nature, responsible for deleterious effects both on the aquatic flora and fauna and also to their consumers including human. Heavy metals are generally high atomic elements with density 5 times greater than that of the water (Banday and Usmani, 2017).

FACTORS INVOLVED IN METAL UPTAKE

Bioaccumulation of metals in fish takes place mainly through the food, water and sediment (Afshan*et al.,* 2014). Accumulation of metals in tissues triggers various toxic effects which may pose a serious threat and eventually cause death of the fish. The entry of heavy metals to the fish bodies can be through three possible ways i.e., by gills, body surface and digestive tract. The gills are considered to be the direct passage for the uptake of metals. Environmental factors such as alkalinity and temperature play an important role in uptake of metals in different functionally important organs. The studies reported higher rate of Cd uptake in fish exposed to low alkaline water. In water, presence of high calcium and magnesium ions reduced the uptake of other metals and impart protection against heavy metals. So it is evident that high alkalinity may protect fish from metal toxicity. Rise in water temperature promotes high rate of metal uptake and accumulation in various tissue of fish (Abram *et al.,* 2017). High rate of cadmium accumulation in fish was reported in summer especially in the most metabolically active organs: liver and kidney. This may be due to increase in metabolic rate under high temperature. Though bioaccumulation of Pb was not affected by temperature variance.

FISH IMMUNE SYSTEM

The immune system is critical for survival and fitness of organisms and it enables to distinguish between self, non-self (e.g., pathogens) and altered self. Fish are the first group of vertebrates with both innate and adaptive immune responses and are essential for proper understanding of the system and its evolution.

The immune system of fishes can be subdivided into broadly three categories, having different speed and specificity of response. The first line of defence is presented by the external barriers separating the fish from its environment, i.e., the epithelia of skin, gills and alimentary canal. Epithelia work as mechanical barriers to invading pathogens, but they also contain chemical (antibodies, lysozyme, etc.) and cellular (immune cells) defence system.

The second immune category is the innate immune system which enables a rapid response to invading pathogens and probably the earliest system of defence formed in the phylogenetic scale. This system provides non-specific responses by recognizing pathogen associated molecular patterns (PAMP), a highly preserved portion of any microorganism such as lipopolysaccharide, viral or bacterial nucleic acids. Main effector elements of the innate immune system in fishes include humoral factors such as lysozyme or complement factors, as well as phagocytic cells such as granulocytes, monocytes/ macrophages and natural killer cells.

Phagocytosis is one of the most important processes in fish as it is least influenced by temperature. The main cells involved in phagocytosis in fish are neutrophils and macrophages. These cells remove bacteria mainly by the production of reactive oxygen species (ROS) during a respiratory burst. And neutrophils possess myeloperoxidase in their cytoplasmic granules, which in the presence of halide and hydrogen peroxide kills bacteria by halogenation of the bacterial cell wall.

The third line of immune defence is the adaptive or acquired immune system. Cells involved in this system are T- and B-lymphocytes which mediate the cellular and humoral response respectively. Fish lymphocytes show morphological, developmental and functional similarities

with that of mammalian counterparts i.e., mammalian unconventional or innate-like lymphocytes (mILL).

Cytokines also has an important role in fish immune response. It involves induction of the innate response to the generation of cytotoxic T cells and the production of antibodies. Cytokines are secreted proteins with growth, differentiation, and activation functions that regulate the nature of immune responses. It modulates immune responses through an autocrine or paracrine manner upon binding to their corresponding receptors. Cytokines are produced by macrophages, lymphocytes, granulocytes, dendritic cells, mast cells, and epithelial cells, and can be categorised into interferons (IFNs), interleukins (ILs), tumor necrosis factors (TNFs), colony stimulating factors, and chemokines. TNFα (tumor necrosis factor alpha) is a pro-inflammatory cytokine that plays an important role in various host responses, including cell proliferation, differentiation, necrosis, apoptosis, and the induction of other cytokines.

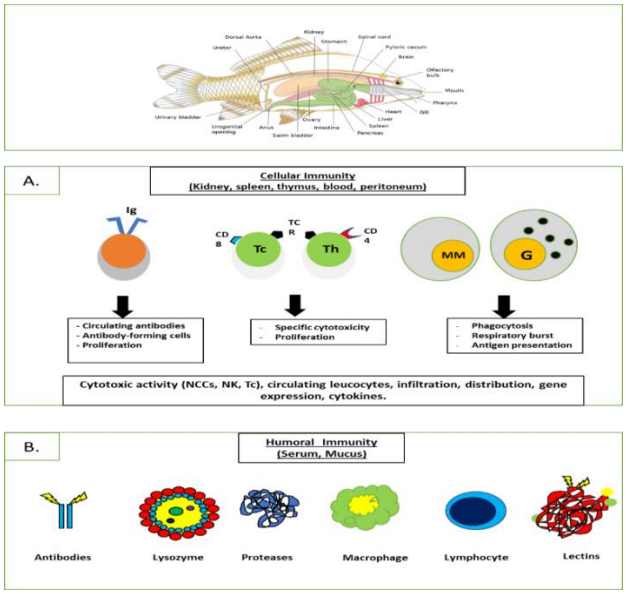

Fig. 1: Immune cells represent cellular and humoral immunity in fish

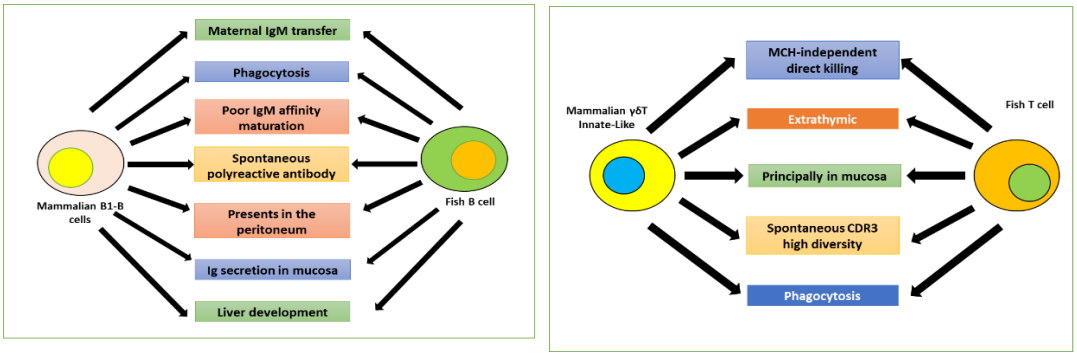

Fig. 2: Homology between fish and mammalian lymphocytes support that mammalian γδTcells and B_1-B cells are evolutionarily related to fish lymphocytes

EFFECTS OF HEAVY METALS (PB, AS, HG, CD) ON FISH AND HUMAN IMMUNE SYSTEM

LEAD (Pb)

According to the studies conducted in two commercial fish species (*Orechromis niloticus* sp. and *Hoplosternum littorale* sp.) it was noted that upon exposure to high concentrations of Pb exposure leads to decreased level of C3; a complement protein indicates inflammation, IgM production and lysosome activity. It is reported that Pb at its high dose (1.25 mg/L) causes suppression of immunological functions.

ARSENIC (As)

Arsenic is a naturally occurring metal found in air, water and soil. Inorganic arsenic predominantly existing in trivalent form (As3+) and is more toxic than the pentavalent ones (As5+). Arsenic has been found to upregulate the activation of glutathione transferases in zebra fish lead to generation of reactive oxygen species (ROS) induce stress. Some of the effects induced by arsenic on innate immunity of fish includesability to mount adequate respiratory burst response, express essential antiviral genes and produce sufficient levels of TNF-α in zebrafish within the concentration range of contaminated water.

Table 1: Source of heavy metal (Pb, As, Hg and Cd) contamination in aquatic system and its effect on fish

Heavy metals	Primary sources	Effects in fish	Permissible level (ppm)	References
Lead (Pb)	Paint, pesticide, smoking, automobile mission, burning of coal.	Genotoxic; in some fish cytotoxic effects in gill and epithelial cells whereas effects in delay in embryonic development, growth inhibition, kidney dysfunction, and hypertrophy of gills in some fish can be observed in some fish.	0.1	Alluri *et al.*, 2007
Arsenic (As)	Pesticides, fungicides and metal smelters	Suffocation leading to death; suppression in antibody levels; change in proper functioning of T-cells and B-cells and making them inclined to infection.	0.02	Alluri *et al.*, 2007
Mercury (Hg)	Pesticides, batteries and paper industry.	Blood parameters, gill arches, Liver, kidney, nervous system and olfactory epithelium damage.	0.01	Alluri *et al.*, 2007
Cadmium (Cd)	Welding, electroplating, pesticide, nuclear fission plant	Myocardial disease, kidney disease has been observed.	0.06	Alluri *et al.*, 2007

MERCURY (Hg)

Mercury is considered as one of the most toxic pollutants and it enters into the aquatic system from both natural as well as man-made activities. Exposure to Hg through dietary uptake leads to alterations in the immune response. When freshwater snakehead (*Channa punctatus*) was exposed to 0.3 mg/L of HgCl2 for 7 days, it showed an up-regulation in pro- inflammatory cytokines such as TNF- α and interleukin 6 (IL-6) (Begam and Sengupta, 2015). Study has also been made widely on soluble humoral factors of fish. Exposure to different concentrations of $HgCl_2$, activity of lysosome increased in goldfish (*Carrasius auratus*) or in rainbow trout but decreased in *Pleuronectes platessa*. In addition, *in-vitro* treatment of European sea bass leukocytes with $HgCl_2$, apoptosis as well as ROS production were induced with reduced macrophage activating factors (MAF).

CADMIUM (Cd)

Cadmium is one of the trace elements that is absolutely toxic to all forms of life including fish, birds, mammals including humans. One of the study reported cadmium as most toxic metal among 63 tested heavy metals. In its elemental form cadmium is nondegradable and found to exist in the environment in form of different compounds (e.g., cadmium sulfoselenide, cadmium sulphide and cadmium lithopone). In fresh water fish, cadmium is mostly found to be accumulated in gills, kidney and liver.

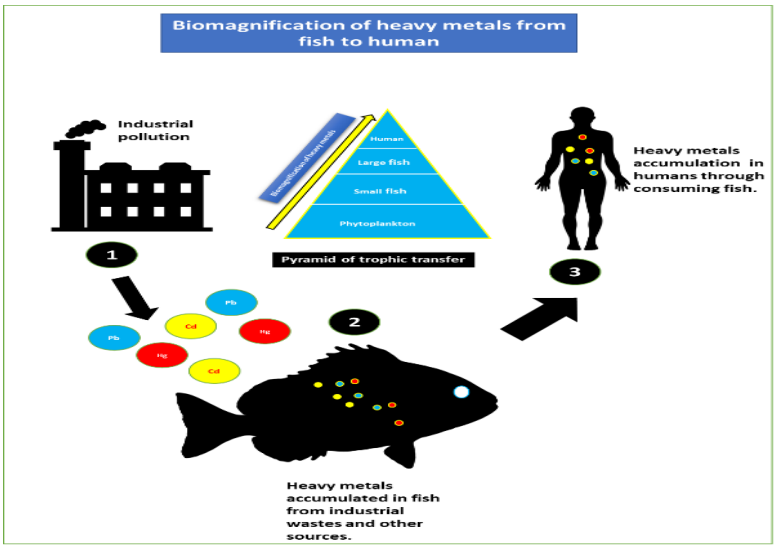

Fig 3: Release of industrial wastes increase the concentration of heavy metals (Pb, As, Hg, Cd) in aquatic system. Uptake of these metals occurs in fish through gills, skin or digestive system. Organisms situated in higher level of trophic transfer are prone to accumulate high amounts of metals inside their body through biomagnification

MOLECULAR MECHANISM OF HEAVY METALS (PB, AR, HG, CD)

NF-KB PATHWAY: A CENTRAL MEDIATOR OF IMMUNE AND INFLAMMATORY RESPONSES

Nuclear factor-κB (NF-κB) represents a family of inducible transcription factors, which regulates a large array of genes involved in immune and inflammatory responses. This family is

composed of five structurally related members, including NF-κB1 (named p50), NF-κB2 (named p52), RelA (named p65), Rel B and c-Rel, which mediate transcription of targeted genes by binding to a specific DNA element, as various hetero- or homo- dimers. NF-κB proteins are normally sequestered in the cytoplasm by a family of inhibitory proteins, including IκB family and its related proteins characterized by the presence of ankyrin repeats. To date, the best studied and most important IκB family member is IκBα. In addition, the precursor proteins of NF-κB1 and NF-κB2 i.e., p105 and p100, serve as IκB-like proteins, because their C-terminal portion resembles the structure of IκB and has NF-κB inhibitory functions.

STRUCTURAL COMPONENTS OF NK-KB PATHWAY

The most common form of NF-κB is a heterodimer p50 and p65(Rel A), which is located in the cytoplasm in its inactive form. The association of this heterodimer with various inhibitory molecules including IκBα, IκBβ, IκBε, p105 and p100 helps it to maintain the state of inactiveness. Toxic and heavy metals as stimuli induce the degradation of IκB or partial degradation of the C-termini of p105 and p100 precursor which tends to translocate the NF-κB into the nucleus (Chen and Shi, 2002). Many of the genes targeted by NF-κB are important in mediating intracellular communication, cell to cell signalling amplification or spreading of primary pathogenic signals, cell recruitment or transmigration and initiation or acceleration of carcinogenesis.

TNF- A AND IL-1B INDUCE REGULATION OF NF-KB PATHWAY

Studies have suggested that a wide range of metals are capable to induce transcription of NF-kB (Chen and Shi, 2002). It has been reported that lower concentration of AS(III) inhibit IKK by phosphorylation, resulting in decrease expression of NF-κB. Different arsenic concentrations display different effects of arsenic on NF-κB signalling in the same cell. As2O3 of 105 μmol/L dose for 48 h in HEK cells has shown significantly increased NF-κB activity. In *Chana punctatus* Bloch, Cd exposure resulting in upregulation of NF-κB through TNF-α and IL-1β cascades (Choudhury *et al.,* 2021). In fish among various NF-κB pathways, those emanating from TNF-α and IL-1β has been most extensively studied (Zhang *et al.,* 2012).

CONCLUSION

It has become a well understood fact that the metals have a very diverse toxic effect in fish and human. Oxidative stresses due to heavy metals increase the level of various pro-inflammatory cytokines which promotes cell death. Fish as a model organism helps to evaluate the quality of aquatic biological system and decipher novel signalling pathways linked to stress inflammation and cell death.

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Chapter
6

TRADITIONAL KNOWLEDGE OF MEDICINAL PLANTS AMONG RURAL WOMEN OF THE KARANPRAYAG TEHSIL, DISTRICT CHAMOLI, UTTARAKHAND

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ABSTRACT

The present paper deals with traditional knowledge of medicinal plants among rural women of Karanprayag tehsil, district Chamoli of Uttarakhand. 90 women from 26 villages were interviewed based on their traditional knowledge of the various uses of medicinal plants found in the adjoining forest and agricultural areas. A total of 113 medicinal plant species were recorded during the intensive surveys and discussions held with the rural women.

KEYWORDS: Traditional Knowledge, Medicinal Plants, Karanprayag, Ethnomedicine

INTRODUCTION

Traditional medicine, which is used to maintain health as well as to prevent, diagnose, improve, or treat physical and mental illness, has been defined as the culmination of knowledge, skills, and procedures based on theories, beliefs, and experiences inherent to various cultures, whether or not they can be rationalized[1].

A sizable portion of the populace, particularly in rural parts of many developing nations, relies mostly on traditional medicine for their primary health care. In ancient Hindu literature, the local knowledge of therapeutic plants is thoroughly documented. Many significant modern-day drugs have been discovered thanks to traditional medical knowledge that dates back to the time of the Great Sage Charak[2]. Currently, traditional medicine is still used by roughly 65 percent of Indians[3].

In the past, plants have been man's most effective tool against pathogens. All segments of society use medicinal plants extensively, whether directly as home cures, medicines for various indigenous systems, or in contemporary medicine [4,5]. The Himalayan woodlands are home to a wide variety of flowers, the majority of which have significant therapeutic value. The Himalayan population has a very high level of expertise in the use of therapeutic herbs. A portion of the community that is economically weaker gathers medicinal plants from the forests for commercial usage as a means of subsistence. Women in the Himalayan region have a close, historical relationship with the forests that surround them to meet their daily requirements for food, fuel, and other forest products.

The only people in the Himalayas who are knowledgeable about the characteristics of plants and how to use them to their best advantage are rural women. Therefore, all efforts to protect and grow in rural regions must consider their knowledge as a crucial component. This

indigenous ethnobotanical knowledge would be lost to humanity forever if it wasn't documented. Given the grave threat to the diversity of medicinal plants in this area, it is encouraging to learn that several research organizations and individuals have recommended cultivation methods and documentation of traditional knowledge of medicinal plants commonly found in the Himalayan region for their long-term conservation[2,6]. The major goals of the current study were to chronicle indigenous rural women's expertise in ethnobotany and to recommend effective conservation methods.

FIELD OF STUDY

For its abundance of biodiversity and complex cultural mosaic, Uttarakhand is highly renowned. There are 13 districts in the state, which are located between 28° 43′ and 31° 8′ N and 77° 35′ and 81° 2′ E. The current study was limited to 26 distinct villages in the Chamoli district's Karanprayag tehsil (Fig. 1) (Table 1). Every community is bordered by subtropical to temperate woodland and agricultural lands and is located between 700 and 1500 meters above sea level. The entire Chamoli district is covered with several kinds of forest. The locals live an agrarian lifestyle and rely on conventional farming methods in part. The majority of the study area's women have some native knowledge of therapeutic herbs.

METHODOLOGY

The study's approach was based on interviews with women who were knowledgeable about the therapeutic plants in their region. Documentation was completed based on an interview, unstructured conversation, and observation. To gather the information, group discussions among women in various age groups were also considered. The data so gathered and recorded includes the local name of the plant, portions utilized to treat diseases, habitat, and local status. The villages were visited on field excursions from December 2021 to June 2022. To acquire as much information as possible about the plants used in traditional medicine, two to three interviews and discussions were conducted in each hamlet.

RESULTS AND ANALYSIS

Based on their innate knowledge of the local medicinal plants, 90 women were surveyed in 26 different communities (Table 1). After performing the survey and speaking with women of various ages, 113 therapeutic plant species in total were noted. The majority of the women in the research region use medicinal plants for a variety of therapeutic purposes in their daily lives for basic healthcare, according to the poll. The responses ranged in age from 20 to 65. The majority of respondents (65%) were educated, and the remaining 35% were illiterate. They were eager to share information and pass on the traditional knowledge of medicinal plants from one generation to the next. It was discovered that although the young women knew less about indigenous knowledge, they were the most concerned about preserving it and the biodiversity of the region.

The study shows that the local population still relies on a variety of plants, particularly medicines, for their everyday requirements. The majority of the 113 medicinal plants that have been identified are typically located close to villages, wasteland, and forest areas. In the vicinity of the village, some tree species are planted by the locals. These trees are primarily used to treat stomach pain, fever, colds, coughs, bleeding and wounds, fungal infections, burns, rheumatic

pain, and insect bites. The plants that respondents utilized are listed alphabetically by plant name, local name, and usage (Table 2).

Table 1: Study villages and respondents

Villages	Number of respondents	Villages	Number of respondents
Bagoli	**4**	Tefna	**4**
Ghandiyal	**3**	Kanda	**3**
Jakh	**3**	Maikhura	**3**
Koti	**2**	Khairsain	**2**
Nauti	**6**	Ratura	**4**
Bainoli	**3**	Kanda	**7**
Kankhul Talla	**5**	Simli	**2**
Kankhul Malla	**4**	Sunali	**5**
Sonla	**6**	Thirpak	**3**
Top	**6**	Majyari	**2**
Chhatauli	**3**	Umrakot	**3**
Pudiyani	**3**	Uttarain	**2**
Deyarkot	**5**	Gauchar	**2**
Sainu	**5**	Total	**100**

Table 2: List of medicinal plant species used against various human ailments

Botanical Name	Local Name	Uses
Abrus precatorius	*Rattidana*	Roots are used for treatment of ulcers and rheumatic pains.
Acacia catechu	Kher	Root paste is used for the treatment of ulcers.
Aconitum heterophyllum	Aatis	The root is used for the treatment of high fever and other stomach problems.
Acorus calamus .	*Baj*	A rhizome is useful in curing stomachache, fever, asthma, epilepsy, and dysentery. Nervine tonic is prepared from the rhizome.
Adhatoda vasica	*Basingu*	Flowers are used for the treatment of bronchitis, asthma, cough and cold.
Aegle marmelos	*Bel*	The fruit pulp is used for curing stomachache and dysentery.
Aloe vera	*Patvaar*	Leaf paste is used for treating burns.
Amaranthus spinosus	*Kadyasagoti*	Root paste and seeds are used in curing ulcers.
Angelica glauca	*Chora*	The root is useful for toothache, stomachache and gastric problems.
Argemone mexicana	*Kandaru*	Root paste is used for insect bites and fever.
Arisaema intermedium	*Bagmungari*	Roasted fruit paste is used for treatment of burns.
Arisaema tortuosum	*Nagdaman*	Tuber paste is used in rheumatism. A dry tuber is useful in breathing problems.
Artemisia wallichiana	*Kundju*	Leaf paste is used for curing skin infections, ringworm and wound. Leaf juice is useful for earache.

Asparagus adscendens	*Ghirunu*	Root extract is useful in dysentery and general debility. Plant paste is used for relieving body temperature.
Barleria cristata	*Kularkattya*	Leaf paste is applied on cuts as Antiseptic.
Bauhinia vahlii	*Malu*	The root is used as a toothbrush in pyorrhoea.
Bauhinia variegata	*Kachnar, Kurail*	Leaf paste is used in skin diseases. Bark powder is useful in blood pressure.
Berberis lycium	*Kingod*	Rootstock is used as an antiseptic and blood purifier, in conjunctivitis and urine urinogenital disorders.
Bergenia ciliata	*Silphodi*	Root extract is used for the treatment of kidney stones, diabetes and heart problems. Root paste is used for swelling and body pain.
Bistorta affinis	*Kukdi*	Root paste is applied to the forehead to control fever. The root stock is used in stomachache.
Boerhavia diffusa	*Pundari*	The root is applied to wounds and swelling.
Butea monosperma	*Dhak/Plash*	Seeds, Flowers and gum are used in the treatment of dysentery, roundworm and ringworm. Gum mixed with water is useful for body swelling and wounds.
Callicarpa macrophylla	*Daiya*	Leaves are used for rheumatic pain.
Cannabis sativa	*Bhang*	Leaf paste is used for cuts, skin ulcers and insect bites.
Cassia tora	*Chakunda*	Seed powder decoction is given as tea for stomachache, cough and cold.
Celastrus paniculatus	*Malkangi*	Oil is applied in arthritis.
Centella asiatica	*Brahmi*	Plant paste and juice are used for mental weakness and skin diseases.
Centipeda minima	*Nakh-chhiki*	Seed is put in the nose to sneeze to clear a blocked nose. Plant paste taken with butter is useful for gastric problems.
Cinnamomum tamala	*Kikhudu/Dalcheenee/ Tejpatra*	A leaf is useful in blood pressure and digestion.
Cleome viscosa	*Jakhiya*	Seeds are used as carminative and are useful in high blood pressure.
Cocculus hirsutus	*Pahari*	Root, stem and leaf juice are given in fever.
Colebrookia oppositifolia	*Bindu*	Leaf juice is useful for eye injury.
Coriandrum sativum	*Dhaniya*	Leaf and fruits are used as a condiment. Leaf paste is applied to skin diseases.
Cucumis sativus	*Kakdi*	Seed paste mixed with water is useful for urinary problems.
Cuscuta europaea	*Akashbail*	Plant juice is used for skin diseases.
Cynodon dactylon	*Dhoob*	Plant juice is used for fever and burning sensation.
Cynoglossum lanceolaturn	*Lichkuru*	The root is useful in ulcers.

Cynoglossum zeylanicum	*Rajpatti*	Leaf paste is applied to wounds and ulcers. Juice is useful for the treatment of earache.
Cyperus rotundus	*Morya*	The root powder is useful to control fever.
Datura stramonium	*Dhatura*	Leaves, flowers and seeds are used for the treatment of bronchitis, asthma and cough. Seed paste with hot leaves is applied to control body swelling.
Dioscorea bulbifera	*Genthe*	A tuber is used as a tonic for diabetes, skin diseases and burns.
Diplocyclo spalmatus	*Shivlingi*	Fruit is used for cooling body temperature.
Emblica officinalis	*Amla*	Fruit is useful for the digestive system, cough, high blood pressure and asthma.
Equiseitum debile	*Sarsyot*	Plant paste is used in gums to control pyorrhoea.
Eupatorium adenophorum	*Basya*	Leaf paste is applied on cuts and wounds. Paste mixed with mustard oil is useful for ulcers.
Euphorbia royleana	*Surae*	Latex is used for earache.
Evolvulus nummularis	*Harajhaad*	Leaf paste mixed with oil is applied for skin infection.
Ficus bengalensis	*Bad/Bargad*	Bud paste mixed with curd is applied on burns.
Ficus glomerata	*Umaru/Gular*	Latex mixed with milk iss prescribed for rickets.
Ficus palmata	*Bedu*	Latex is used to control bleeding wounds.
Ficus religiosa	*Pepal*	Ash of the bark is applied on swelling. Fruits are beneficial in leucorrhoea.
Ficus cuneata	*Khaino*	Ripe Fruits are useful for fever.
Fumaria indica	*Pitphapara*	Leaf paste is useful for headache and fever.
Galium aparina	*Kurighass*	Plant juice is applied to cuts and wounds.
Galium pauciflorum	*Kumaya*	Leaf paste is useful in cuts.
Gentiana kurroo	*Neilkanthi*	Leaf powder mixed with oil is applied to ulcer and fungal infections.
Geranium wallichianum	*Mundailo*	Leaf and root parts are applied as antidandruff.
Girardinia diversifolia	*Dhondkandali*	Root and Leaf paste is applied to ulcers.
Gloriosa superba	*Langali/Kukadmakri*	Rhizomes and seeds are used for the treatment of chronic ulcers and parasitic skin diseases.
Glycine max	*Kala bhatt*	Seed paste is useful for eyesores.
Gnaphalium polycaulon	*Bukhlu*	Plant ash mixed with coconut oil is applied to burns.
Hedychium spicatum	*Jangalihaldi*	A rhizome is used in blood purification and rheumatic pain.
Impatiens balsamina	*Balsam/Majethi*	Leaf paste is externally applied in burns.
Jatropha curcas	*Pahari arand/ Lankabel*	Seeds are used to check to vomit but taken in large quantities is harmful.
Juglans regia	*Akhrot*	Root bark and branches are used for cleaning teeth. Fruit peel is used for the treatment of ringworm.
Leucas mollissima	*Upanya*	Leaves are used as an insect repellent.

Lyonia valifolia	*Aiyaar*	Leaf paste is applied for allergy and fungal infections.
Mallotu sphilippensis	*Ruenau*	The red outer layer of fruits is used for the treatment of intestinal worms and parasitic skin diseases.
Melia azadirachta	*Dainkan*	Leaf, seeds, bark and root boiled in oil are applied for treating skin disease.
Mentha longifolia	*Ban Pudina*	Leaves are used in indigestion, vomiting, cough and cold.
Micromeria biflora	*Gorkapaan*	Leaf powder mixed with oil is useful in ulcer and fungal infections.
Mucuna pruriens	*Kaunch*	The root is used in nervous disorders and paste is used in skin diseases.
Murraya koenigii	*Currypatta/Gandalu*	Leaves are used as a condiment, for high blood pressure and diabetes.
Musa paradisica	*Kaila*	The soft part of the stem is useful to control abortion.
Myrica esculenta	*Kafal*	Stem bark powder is used for cough.
Origanum vulgare	*Jungalitulsi*	Leaf paste is applied for skin diseases, insect bites and earache. Leaf with hot water is useful for cough and cold.
Oxalis corniculata	*Khatibuti/ Tipati*	Leaf paste is applied to skin ulcers and wounds.
Paeonia emodi	*Dhandura*	Leaf as the vegetable is used for high fever.
Perilla frutescens	*Bhangzeera*	Leaf juice is used in earache.
Pinus roxburghii	*Kulai/ Cheer*	Resin is used as crack cream. Pollen dust and resin with water are useful for cancer and tuberculosis.
Plantago major	*Esabgol*	Used for digestion.
Pongamia pinnata	*Karanjua*	Root and stem paste is used for curing ulcers.
Potentilla fulgens	*Bjardanti*	Leaf paste is used in mouth ulcers.
Prunus armeniaca	*Choole*	Seed paste mixed with water is given to children with a stomachache.
Prunus cerasoides	*Painya*	Boiled bark in water is useful for swelling.
Pyracantha crenulata	*Ghangara*	Leaf paste is applied on burns.
Pyrus pashia	*Molu*	Fruit juice is used for eye injury.
Quercus leucotrichophora	*Baanj/Bandalis*	Dry resin with water is taken for stomach pain.
Rheum australe	*Dolu/Archu*	Root paste is applied to swelling and wounds.
Rhododendron arboreum	*Burans*	Flower juice is useful for blood pressure.
Ricinus communis	*Arand*	Root and bark are used for asthma, Bronchitis and skin diseases. Fruits are used to cure jaundice. Leaf with hot steam is applied for knee pain.
Rubus ellipticus	*Hisool*	Root paste is applied to ulcers and skin infections.
Rumex hastatus	*Almoda*	Leaf paste is applied for fungal infection.
Sapium insigne	*Khennu*	Leaf paste is used on burns.
Sidar hombifolia	*Bhuanlya*	Root juice is useful for children with a stomachache.

Solanum nigrum	*Geahwai*	Leaf paste and branches are used in jaundice and high fever.
Solanum surattense	*Biskandaru/Kantkari*	Root paste is applied to the ulcer. Fruits are useful in jaundice.
Stephania glabra	*Gindaru*	The root powder is used for cooling body temperature.
Syzygium cumini	*Jamun*	Seed powder is used for diabetes; bark with milk is used for curing excessive menstruation. Ripe fruits are useful for stones.
Tagetes minuta	*Gainda*	Boiled leaf juice is useful for earache.
Taraxacum officinalis	*Kadvae*	Root stock is used for a high fever.
Terminalia arjuna	*Arjuna/Aseen*	Stem bark mixed with honey is useful for high blood pressure and heart disease.
Terminalia bellirica	*Bahera*	Fruits are used for cough, fever, dropsy and stomach disorders.
Terminalia chebula	*Harad*	Fruits are used in urinary diseases, asthma, cough, enlargement of the liver, worms, dysentery and fever.
Tinospora cordifolia	*Giloya*	The root powder is eaten for high blood pressure, fever and weakness. Root powder mixed with honey is prescribed for cough.
Urtica dioica	*Kandali*	A leaf is used for menstrual disorders, paralysis, diabetes and arthritis.
Valeriana jatamansi	*Sumaya*	Root extract is given for nervous disorders and fits. Leaf juice is useful for stomachache.
Verbascum thapsus	*Hamaku*	Leaf paste is applied to the ulcer.
Viola pilosa	*Banafsha*	Flowers are used in the treatment of cough, liver disorders, kidney disease and sore throat.
Vitex negundo	*Siwali/ Nirgundi*	The boiled leaf is applied on wounds. Leaf as vegetable is useful in paralysis. Stem paste is used to control fever and juice for gallbladder problems. Leaf with hot water is useful for rheumatic pain.
Woodfordia fruticosa	*Dhaula*	Dried flowers are used in dysentery.
Zanthoxylum armatum	*Timru*	Bark, fruits and branches are used for toothache. Branches are used as toothbrush and in gum troubles.

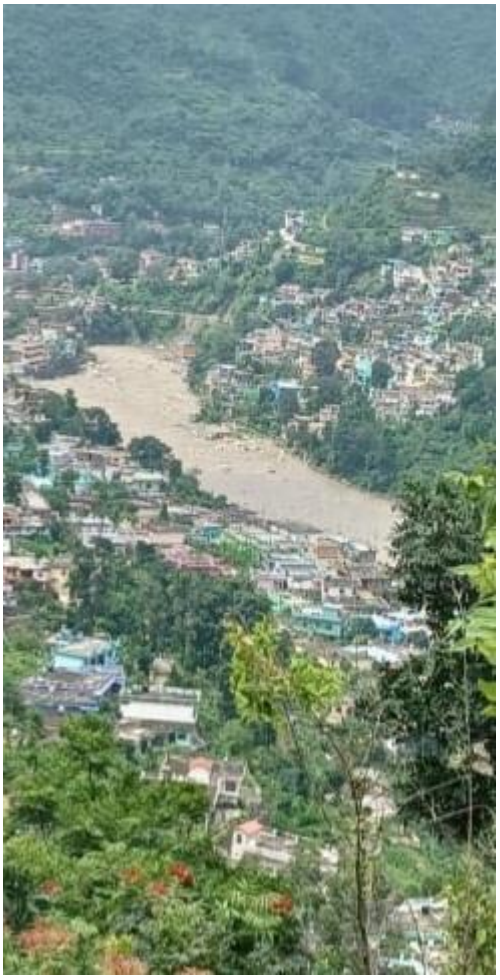

Fig. 1: A view of the Karanprayag valley

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Chapter
7

BIOCHEMICAL INVESTIGATION OF MUSHROOM

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ABSTRACT

Mushroom cultivation is getting more popular worldwide because many farmed mushrooms have valuable bio-chemical qualities that are essential for human health. Mushrooms provide exceptional health advantages and are a reliable source of nutrients, including vitamins, minerals, dietary fibres, vital fatty acids, polysaccharide, enzymes, trace elements, and antioxidants. Therefore, edible mushrooms are well-known for their antibacterial, anti-diabetic, anticoagulation, anti-ageing, immunologic, anticarcinogenic, and antihyperlipidemic properties, making them more suitable for use in healthy meals, biomedicines, cosmetics, and widely acknowledged as an excellent source of immune-modulatory substances that have immune-stimulation attributes. Furthermore, mushroom farming helps to prevent environmental pollution caused by the burning of agricultural leftovers such as sugarcane trashes, crop stubbles, and paddy straw because it requires these raw materials, which operate as an alternative source of energy, it acts as a natural feasible alternative to regulating such by-products and converting agricultural waste into food with great and healthy nutritional value. Several mushroom species are popular delicacies in Central and Eastern Europe. It hasestablished that fungi, especially mushrooms, are a significant biosourceof metabolites with a wide range of chemical components and different bioactivities. Mushroom metabolites are hugely important for pharmaceuticals and agrochemicals industries.

KEYWORDS: Chemical composition, anti-bacterial, anti-microbial, chemical constituents.

INTRODUCTION

A mushroom is a type of macrofungus that has a characteristic fruiting body, is large sufficient to seen with the bare eye, and manually harvested [Chang *et al.,* 2018]. Agaricaceae is the family to which mushrooms belong. Different varieties of mushrooms have distinct colours, forms, surfaces, and behaviours [Assemie *et al.,* 2022]. They grow on soil or on their sources of food, like as decomposing wood, in a wet, chilly climate [Assemie *et al.,* 2022]. There are an estimated 1.5 million species of fungi, 14,000 of which have been named, and at least 2,000 of which are edible and produce fruiting bodies huge enough being termed mushrooms (Zhang *et al.,* 2014).

In contrast to preliminary and morels, which take time to grow, some oyster- and elm-like mushrooms grow quickly [Kumla *et al.,* 2020]. The usage of mushrooms as food has been widespread [Falconer, 1990; Degreef *et al.,* 1997] and they are frequently considered to be pleasant and wholesome meals [Vinceti *et al.,* 2013; Rahi & Malik., 2016]. Mushrooms are mostly

composed of water (85–95%), followed by carbohydrates (35–70%), protein (15–34.7%), fat (10%), minerals (6–10.9%), and nucleic acids (3–8%). Additionally, it includes a lot of vitamins, including thiamine (1.4–2.2 mg), riboflavin (6.7–9.0 mg), niacin (60–67.3 mg), biotin, ascorbic acid (92–144 mg), pantothenic acid (21–33.3), and folic acid (1.2–1.4 mg)/100 g on a dry weight basis [Hossain *et al.,* 2007]. According to Alam *et al.* (2007), the minerals present in mushrooms include calcium, iron, manganese, magnesium, zinc, and selenium. Mushrooms regarded as a nutritious food with nutritional benefits since they include a variety of nutrients that are rich in their fruit bodies, including potassium, iron, copper, zinc, and manganese. They also contain fibre, necessary amino acids, essential fatty acids, vitamins, unsaturated fatty acids, and unsaturated fatty acids. Because of their biological effects, mushroom extracts and their secondary metabolites have developed antioxidant, antibacterial, anticancer, anti-inflammatory, antiobesity, and immunomodulatory capabilities. Because of this, the phytochemical components of mushrooms have attracted the attention of phytochemists, nutritionists, and consumers. These components have positive impacts on humans in terms of health promotion and lowering the chances of developing diseases [Thu *et al.,* 2020]. Bioactive substances obtained from mushrooms that are advantageous to human health and have antiviral action against DNA and RNA viruses include polysaccharides, carbohydrate-binding proteins, peptides, proteins, enzymes, polyphenols, triterpenes, and triterpenoids [Seo & Choi, 2021].

According to current estimates, there are around 1.5 million distinct species of fungi on earth, however only 7% of those species have been described [Hawksworth, 2004; Hawksworth, 2001]. China overtakes all other countries as the world's top mushroom producer, producing more than 30% of all mushrooms [Miles and Chang 2004; Fletcher and Gaze 2007; Aida *et al.,* 2009; Mohammadreza *et al.,* 2011; Patel and Goyal 2012; Mishra and Mishra 2013].

In mushroom 2000 of the 14000 known species of mushrooms that are known to exist are thought to be safe for eating by people, and 650 of those species have medicinal characteristics [Rai *et al.,* 2005]. Because it involves less space, effort, and capital than other agricultural pursuits but has the potential to generate more lucrative returns than horticulture and field crops, mushroom cultivation has become popular in various nations. As a result, new types of mushrooms are being produced more frequently by growers in various nations. Mushroom farming helps to manage and turn agricultural and agro-industrial waste into food with high nutritional value, preventing air pollution from residual burning of harvested crops and being seen as a naturally practical alternative [Pontes *et al.,* 2018].

In places in central and Eastern Europe, eating wild mushrooms has become more popular than eating cultivated fungi. A statistical mean of 5.6 kg of fresh mushrooms are picked annually per family in the Czech Republic, making mushroom picking a "national hobby" [Šišák, 2007]. However, some people eat more than 10 kg each year.

According to a widely accepted adage, "Plants serve as producers, animals serve as consumers, and fungus serve as restorers and decomposers." In other words, by photosynthesis, plants produce organic substances that are consumed by animals. Bring the plants and animals back to the earth, fungi, such as mushrooms, are crucial. You can find fungi in variousvariety of habitats.

Survival of fungi have developed a variety of defence and communication techniques using various kinds of secondary metabolites. Mushroom-forming fungus produce metabolic products that differ from those produced by plants and mammals in terms of their structural makeup. Several metabolites with a wide range of chemical structures and different bioactivities have been found in fungi, including mushrooms, according to research by König *et al.,* (2006) and Strobel (2003), investigating several bioactive substances generated by mushrooms. The extraction of active substances and characterization of structure came about because of bioactivity-guided fractionation of mushroom extract.

NUTRITIONAL COMPOSITION OF MUSHROOMS

Mushrooms are extremely nutrient-dense, significantly in relation of their protein and carbohydrate contents. These are not the only components that edible mushrooms provide; they] are also a reliable source of vitamins and minerals [Kayode *et al.,* 2015; Han *et al.,* 2016). Table 1 lists the average nutritional values of mushrooms.

Table 1: Mean nutrients content in raw mushrooms per 100 g edible portion
(Source: USDA 2019; nd: no data)

S.No	Nutrients	White mushroom	Oyster mushroom	Shiitake mushroom	Chanterelle mushrooms	Enoki mushrooms
1.	Moisture (g/100 g)	92.45	89.18	89.74	89.85	88.34
2.	Energy (kcal/100g)	22	33	34	32	37
3.	Protein (g/100 g)	3.09	3.31	2.24	1.49	2.66
4.	Fat (g/100 g)	0.34	0.41	0.49	0.53	0.29
5.	Mono-unsaturated	0.00	0.031	nd	nd	0.00
6.	fatty acids (g/100 g)	0.16	0.123	nd	nd	0.124
7.	Dextrose (g/100 g)	1.48	1.11	2.38	1.16	0.22
8.	Carbohydrate (g/100 g)	3.26	6.09	6.79	6.86	7.81
9.	Ash (g/100 g)	0.85	1.01	0.73	1.26	0.91
10.	Total dietary fiber (g/100 g)	1.0	2.3	2.5	3.80	2.7
11.	Niacin (mg/100 g)	3.607	4.956	3.877	4.085	7.032
12.	Thiamin (mg/100 g)	0.081	0.125	0.015	0.015	0.225

13.	Riboflavin (mg/100 g)	0.402	0.349	0.217	0.215	0.2
14.	Pantothenic acid (mg/100 g)	1.497	1.294	1.5	1.075	1.35
15.	Ergosterol (mg/100 g)	56	64	85	61	36
16.	Pyridoxine (B-6) (mg/100 g)	0.104	0.11	0.293	0.044	0.10

BIOCHEMICAL COMPOSITION OF MUSHROOMS

Phytochemicals with antioxidant activity and high nutritional status, such as ascorbic acid, carotenoids, phenolics, ergosterol, and tocopherols, found in mushrooms, according to an analysis of their biochemical composition listed in **Table-2**. They are also a good source of non-starchy carbs, proteins, vitamins (B1, B2, B12, C, D, and E), minerals, dietary fibres, polysaccharides, folates, and important elements [Barros *et al.,* 2008; Yamanaka, 1997; Mattila *et al.,* 2000; Adejumo *et al.,* 2015; Kozarski *et al.,* 2015; Vetter, 2019]. On a dry weight basis, mushrooms have a protein content of 20–40% and no cholesterol [Nour *et al.,* 2011].

Table 2: Usual content (mg kg^{-1} of dry matter) of major mineral and trace elements in mushroom fruting body (adapted from (adapted from Kalacˇ and Svoboda, 2000; Kalač., 2009).

S.No.	Element	Usual content
1.	Sodium	100-400
2.	Potassium	20,000-40,000
3.	Calcium	100-500
4.	Magnesium	800-1800
5.	Phosphorus	5000-10,000
6.	Sulphur	1000-3000
7.	Antimony	0.05-0.15
8.	Arsenic	<1
9.	Beryllium	<0.5-5
10.	Cadmium	0.5-5
11.	Caesium	3-12
12.	Chromium	0.1-2
13.	Cobalt	<0.1-3
14.	Copper	10-70
15.	Gold	<0.02
16.	Iron	30-150
17.	Lead	1-5

18.	Manganese	5-60
19.	Mercury	<0.5-5
20.	Nickel	0.4-2
21.	Selenium	1-5
22.	Silver	0.2-3
23.	Strontium	5-10
24.	Thallium	<0.25
25.	Zinc	30-150

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Chapter 8

ROLE OF METALS IN BIOLOGICAL SYSTEMS

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ABSTRACT

The ions of metals are fundamental elements for the existence of the lifespan of plantsand humans. Their perfect role in biological systems was discovered a long time ago. So they are most essential for the maintenance of life and their absenteeism cause disorders such as growth disorders, severe malfunction, carcinogenesis or even death. They are divided into macro or microelements in different structural and functional roles and participates in many biochemical reactionswhich are present invarious forms. They help to provide a route in inter and intracellular communications, in maintaining electrical charges and osmotic pressure, in photosynthesis and electron transfer processes, in the maintenance of pairing, stacking, and the stability of nucleotides bases, and also in the regulation of DNA transcription. In humans, they mainly contribute to the best functioning of nerve cells, muscle cells, the brain, and the heart along with the transport of oxygen and in many other biological processes up to the point that we cannot even imagine a life without metals.

KEYWORDS: Metals, Elements, Molecules, Ions, Biological System, Human System.

INTRODUCTION

The perfect role of metals and their ions in biological systems has been discoveredfor a long time. Out of all metals, some metals are known to be essential while other are non-essentials.While some are considered to be toxic.The study of metals and their roles in biological system can be considered in a branch of chemistry known as Bio-Inorganic Chemistry. Its main role are depicted in Figure 1. When we talk about transition metals, the thought is considered different compared to that of the main group metals. The Scandium has been known with the least biological effects, and it is present in +2 and +3 oxidation states in its various isotopic forms. Some metals are hypoallergenic for example Titanium (Ti). Iron and Zinc are known to be essential for all forms of life. It has been reported that the metal Zinc (Zn) is playing an essential role in around 300 enzymes in different biological systems. The aim of this chapter is to highlight the role of metals and their application in the biological system. The researchers are paying extreme attention to the role of essential and nonessential elements role of the main from the first transition metal series of the periodic table. Likewise, the metal iron in their two oxidation forms such as Fe^{2+} and $Fe^{3+}$is the most important metal ion not only within the first transition series but also in the whole odic table. It can be called that without iron, there will be no life.

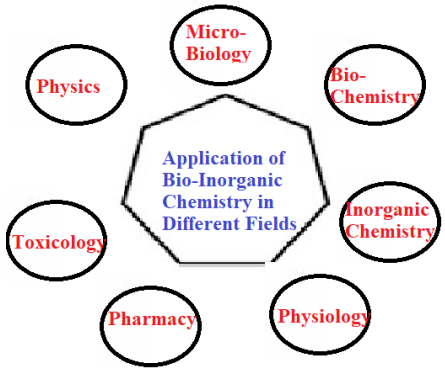

Fig. 1: Application of Bio-Inorganic Chemistry in various fields

While other metals which areChromium (III) or (Cr 3+) in theirthird form may have a great role in glucose metabolism. While the toxic effect of Chromium (VI) or (Cr $^{6+}$) is very much accepted withresearchers to search for specific Cr^{6+}chelators. The sixth valency of chromium (Cr^{6+}) is also considered to be carcinogenic. Other metals from the first transition metal series are Vanadium (V), Manganese (Mn), Cobalt (Co), Nickel (Ni), and Copper (Cu). The researchers concluded that the role of Vanadium (V) is very limited in all systems. In addition, the role of Manganese (Mn) in the process of photosynthesis and the application of Co in Vitamin B_{12}. Copper is existing in nature such as (Cu^{2+}) and it is the most reliable oxidation state. Copper is the essential trace metal ion involved in different metalloproteins such as ceruloplasmin, cytochrome oxidase, superoxide dismutase, dopamine-β-hydroxylase, ascorbate oxidase, lysyl oxidase, and tyrosinase [1, 2].

ELEMENTS IN ATOMIC FORM IN HUMAN BODY

The human body is almost made up of around six (06) elements as Oxygen (O), Carbon (C), Hydrogen (H), Nitrogen (N), Calcium (Ca), and Phosphorus (P) and about 0.85% is made from other elements such as Potassium (K), Sulfur (S), Sodium (Na), Chlorine (Cl), and Magnesium (Mg). These total eleven (11) elements are very important for life. The percentage of these elements are given in table 1. Rest elements from the periodic table are known as Trace Elements. These are also in requirement for the sustenance in life [3].

Table 1: Percent mass of elements present in the Human Body.

S.No	Elements	Percent Mass
1	Oxygen (O)	65.00
2	Carbon (C)	18.50
3	Hydrogen (H)	10.00
4	Nitrogen (N)	3.20
5	Calcium (Ca)	1.50
6	Phosphorus (P)	1.00
7	Potassium (K)	0.40
8	Sulfur (S)	0.30
9	Sodium (Na)	0.20
10	Chlorine (Cl)	0.20
11	Magnesium (Mg)	0.10
12	Others	< 0.10

Pictorial distribution of elements in human body is given in Figure 2.

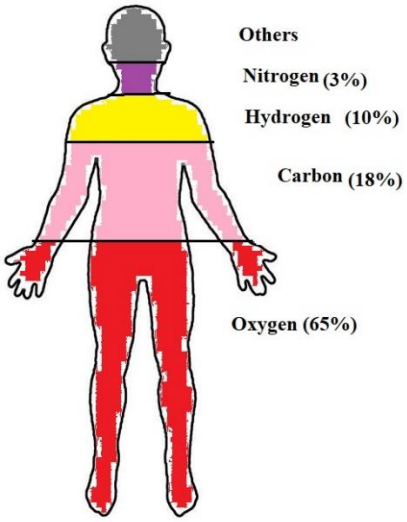

Fig. 2: Pictorial distribution of elements in human body

It is also to note from the literature that all elements which are present in very minute or trace quantity are useful for human life as they can reach to human body as contaminants and remains functionless for example Titanium and Caesium. The concentration of this intake of elements must also be monitored as they can take toxic form and harm the body for example Mercury, Lead, Arsenic and Cadmium. So their intake in dietary product must be monitored well regularly. Bromine plays a great role in the synthesis of collagen IV in human body [4, 5]. The best function of fluorine present in body is the strethning of tooth enamels [6].

ELEMENTS IN MOLECULAR FORM IN HUMAN BODY

The atoms present in and out of the human body make molecules whose present are also essential requirement for the growth and development in human body. Some of these molecules are given here with there molecular structures in Table 2.

Table 2: The molecules and their molecular formula in the human body.

S.No	Molecules	Molecular Formula
1.	Water	H_2O
2.	Protein	$RCH(NH_2)COOH$
3.	Fats	$C_{15}H_{31}COOH$
4.	Glycogen	$C_{24}H_{42}O_{21}$
5.	Glucose	$C_6H_{12}O_6$
6.	Bicarbonate	HCO_3-
7.	Phosphate	PO_4^{3-}
8.	DNA	$C_{15}H_{31}N_3O_{13}P_2$
9.	RNA	$C_{27}H_{34}N_6O_{22}P_2$
10.	Carbon-di-oxide	CO_2
11.	Carbon monoxide	CO
12.	Superoxide	O_2^-
13.	Hydroxyl	OH^-

ELEMENTS AND THEIR IONS

Titanium (Ti), which is known as the greatest element in the atmosphere and the earth's crust with different examples of bioactive properties, which are widely used in the cosmetic industry.The nanoparticle of Titanium like Titanium dioxide (TiO_2) ismainly included in sunscreens as superficial sun blockers which absorbultraviolet (UV) radiation. Sharma et. al reviewed the activity of TiO_2 NPs in the seepage bodies of water which was causing can threat to the environment and aquatic life, and examined TiO_2NP's effects on human skin and health in general, and especially on the human body and the bloodstream. [7].

Zinc (Zn) ions especially cations have antioxidant and antimicrobial activities [4]. To prove this Kalinowska *et al.*, recognized the antimicrobial activity of the Zn(II) complex of 5-CQA and 5-CQA against the activities of Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, Salmonella enteritidis and Candida albicans [8].

ELEMENTS IN THE FORM OF INORGANIC IONS IN THE HUMAN BODY

Elements in the form of Inorganic ion present in living beings or human body mainly plays vital roles in cellular activities [9]. They are also well known as Electrolytes if present in body tissues, which mainly helps in neuron activation and muscle contractions. It can be also very much seen from the literature that the deficiency of these ions in human body may leads to diseases. The table 3 given is depicting the presence of ions and their deficiencies if present in lower amount.

Table 3: Ions and deficiency diseases in human body.

S.No	Ions	Deficiency
1	Ca^{2+}	Hypocalcaemia
2	Zn^{2+}	Zinc fingers
3	K^{+}	Hypokalemia.
4	Na^{+}	Hyponetremia
5	Mn^{2+}	Parkinson's disease
6	Mg^{2+}	Electrolyte disturbance
7	Cl^{-}	Cystic Fibrosis
8	Co^{2+}	Disfunctioning of neurotransmitters
9	PO_4^{3-}	Bone disfunctinong
10	Fe^{2+}/Fe^{3+}	Anaemia

Out of these ions some are very important for running biological ion channels in body such as:

a. SODIUM (Na^{+}) CHANNEL

These channels gives an integral service throughout the body, as they are capable enough to transmitthe depolarizing impulses in the range of cellular and intracellular. This all allowsthese ions to coordinate much more intensive processes like movement and cognition. Again these ion channels contains different subunits and have four internally homologous domains, which contains six transmembrane segments and resemble a single subunit of a voltage-dependent potassium ion channel.These four domains fold together, making a central pore.That central pore of the sodium ions dictates the selectivity of the channel: both ionic radius and ionic charge are key in channel selectivity [10].

b. CHLORIDE (Cl^-) CHANNEL

These channels may vary fromother differention channels as they are being controlled by the anionic chloride ions. These can be considered as pore-forming membrane a protein that helps to transportchloride ions across biological membranes. The channels involvesboth voltage-gated and ligand-gated mechanisms to transport the ions along thecellular membranes. They always play a crucial role in the development of human diseases, such as, mutations in the genes encoding chloride ion channels lead to a variety of deleterious diseases in muscle, kidney, bone, and brain, including cystic fibrosis, osteoporosis, epilepsy, and similarly their activation is supposed to be responsible for the progression of glioma in the brain and the growth of malaria-parasite in the red blood cell [11].

c. POTASSIUM (K^+)

These channels playa a vital role in maintaining the membrane's electric potential. These ion channels are present in many various biological systems. They frequently play a role in regulation of cellular level processes, many of these processes including muscle relaxation, hypertension, insulin secretion etc. Some examples of potassium ion channels within biological systems include KATP channels, Big potassium channels, and Ether-à-go-go potassium channels [12].

ELEMENTS IN PLANT SYSTEM

Like other living organisms such as Human beings, plants are also prone to both deficiency and excess of elements (micronutrients including trace elements). So heavy metals are also essential in nature since they are in need for normal growth of plant. Some of the essential heavy metals such as Copper (Cu), Zinc (Zn), Iron(Fe), Maganese (Mn), Molybdenum (Mo), and Nickel (Ni) playssignificant roles in biochemical and physiological functions in plants [13]. Some of these metals may provide a role in reactions such as electron transfer, redox reactions, and many metabolisms. The existence of essential metals in specific medium at different concentration level, while there excess concentrations leads to toxicity effects [14].

As there level of concentration is very low in the environment so they can be best called as Trace Elements.

In addition with these essential trace elements, another class of heavy metals called as class B metals, which are known as non-essential trace elements like Mercury (Hg), Silver(Ag), Lead (Pb) and Nickel (Ni), etc. are very toxic in nature [15]. The excess or deficiency of metals in the plant system depicts in Table 4.

Table 4: depicts elements in need for the plant system and their deficiencies.

S.No	Elements	Deficiency/Excess
1	Copper	Leaf chlorosis
2	Cadmium	cytotoxic effects
3	Zinc	Leaf chlorosis
4	Arsenic	Growth affected
5	Nickel	Membrane disfunction
6	Chromium	Impaired metabolic processes

CONCLUSION

The presence and concentration of metals/elements are important topic for the inorganic contaminants which when goes into the soil and water through different natural and anthropogenic sources. The metals such as iron (Fe), copper (Cu), zinc (Zn) and nickel (Ni), etc. must be present in required levels that are essential for the normal growth and metabolism human body and that plants, but, their long-term exposures at elevated concentration may highlight negative impacts. Different metals such as arsenic (As), lead (Pb), chromium (Cr), Cadmium (Cd), etc. are known as non-essentials, and theirpresence in food chain contamination in the growing medium may effect the health. For the plant system, the environment having metals may effect adversely.

To survive in extreme conditions, plants have evolved different processes to cope up with metallic toxicity.

Therefore, a piece extensive knowledge from various research domains will greatlyenhance our understanding about the fundamental mechanism involved in the digestion of metals in human body or in plants.

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Chapter 9

NEUROPROTECTIVE EFFICACY OF MUSHROOM NUTRACEUTICALS

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ABSTRACT

A Neurodegenerative disease is affecting a large population worldwide and is on increase every year. Neurodegeneration is more related to oxidative stress in neuronal cells which is facilitated through the action of reactive oxygen species that is generated spontaneously in the brain regions leading to the various forms of neurodegenerative diseases. Understanding the mechanism and treatment for the disease is not accomplished in an ease manner till date and has several shortcomings. It is believed that nutritional supplements for combatting the neuronal health are on the way. In this context, Mushrooms are regarded as one of the potential species on the earth for the source of nutraceuticals. Various mushrooms have been reported for their medicinal and therapeutic values.Several data suggest the promising role of mushroom compounds in alleviating the neurodegeneration to a considerable extent through different mechanism of action. This article attempt to pile up the available information for neuroprotective ability of mushrooms.

KEYWORDS: Oxidative stress, neurodegeneration, mushrooms, antioxidants, therapy.

INTRODUCTION

Neurodegenerative Diseases (NDs) are defined as a fatal and debilitative condition resulting in the intensifying death of nerve cells (Chaturvedi *et al.,* 2018). According to the World Health Organization, more than 300 million people or 4.4% of the world's population suffer from depression, representing a substantial global health problem. Depression can greatly impact one's daily life and can lead to suicidal thoughts (WHO, 2017).

There are many recognised mental health disorders or mental illnesses including anxiety disorders, mood disorders (depression, bipolar disorder, and cyclothymic disorder) psychotic disorders (schizophrenia), eating disorders (anorexia nervosa, bulimia nervosa), impulse control and addiction disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) and personality disorders. Each mental illness manifests with a variable array of symptoms that differ depending on the illness present; it is accepted, however, that a person's mood, thinking, perceptions, anhedonia (pleasure sensation) and behaviours are affected.

Oxidative stress has been linked to several neurological diseases (i.e., Parkinson's disease, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis, depression, and memory loss) (Halliwell, 2001; Singh *et al.,* 2004; Christen, 2004; Butterfield, 2002).

ROS are particularly active in the brain and neuronal tissue as the excitatory amino acids and neurotransmitters, whose metabolism is factory of ROS, which are unique to the brain and serve as sources of oxidative stress. ROS attack glial cells and neurons, which are post-mitotic cells and therefore, they are particularly sensitive to free radicals, leading to neuronal damage (Gilgun-Sherki*et al.,* 2001). Oxidative stress and free radical generation catalysed by redox metals have been shown to play pivotal role in regulating redox reactions *in vivo* contributing RNS and ROS, main culprits in neurodegeneration (Emerit and Edeas, 2004). ROS comprises hydrogen peroxide (H_2O_2), nitric oxide (NO), superoxide anions and the highly reactive hydroxyl and monoxide radicals (OH·, NO·) (Klaus and Heribert, 2004).

Antioxidants are exogenous or endogenous moleculesthose act against any form of oxidative stress and its associated ill effects on cellular system. They neutralize ROS and other kinds of free radicals produced and have attracted the attention of clinicians due to therapeutic potential (Lepoivre *et al.,* 1994).

Mushrooms have been considered as ingredient of gourmetcuisine across the globe; especially for their unique flavor andhave been valued by humankind as a culinary wonder. Morethan 2,000 species of mushrooms exist in nature, but around25 are widely accepted as food and few are commerciallycultivated.Mushrooms are considered as a delicacywith highnutritional and functional value, and they are also acceptedas nutraceutical foods; they are of considerable interestbecause of their organoleptic merit, medicinal properties, and economic significance (Chang and Miles, 2008; Ergonul *et al.,* 2013).

According to a large number of chemical and myco-pharmacological studies, mushrooms areproducer of different bioactive compounds (BAC) with neuroprotective effect (NPE) (Friedman,2015; Chen *et al.,* 2018a,b; Gupta *et al.,* 2018; Badalyan *et al.,* 2019; Lee *et al.,* 2019; Yadav *et al*., 2020; Badalyan and Rapior, 2021). Although the mechanism of neuroprotective action of mushroomderivedBAC has not been thoroughly investigated, recent literature and research reviews revealtheir potential to prevent the development and mitigate the symptoms of NDD (Sabaratnam and Phan, 2018; Yadav *et al.,* 2020; Badalyan and Rapior, 2021).The pathological hallmarks of AD and other forms of dementiaare characterized by impairment of neurite outgrowthbecause of amyloidogenic processing and subsequent bamyloidcascade, neuroinflammation, and free radical generation in the brain (Nevzglyadova *et al.,* 2015; Klein *et al.,* 2013; Li *et al.,* 2014).

Available evidence suggests that mushrooms exhibit antioxidant, antitumor, antivirus, anticancer, anti-inflammatory, immunomodulating, antimicrobial, and antidiabetic activities (Roupas *et al.,* 2012; Patel and Goyal, 2012; Ren *et al.,* 2012). Mushrooms with anti-inflammatory properties can beused as functional foods to suppress inflammation, which contributes to many age-related chronic diseases includingneurodegenerative diseases (Gunawardena *et al.,* 2014).

Like Alzheimer's disease (AD) and Parkinson's disease (PD), the other NDs like Huntington's disease (HD), Multiple sclerosis (MS), and Motor neuron disease (MND) disease occurrence

have controlled by mushrooms bioactive compounds. Some edible mushrooms such as *Pleurotus ostreatus*, *Lentinula edodes*, *Agaricus bisporus*, *Flammulina velutipes*, and *Auricularia auricular-judae* with their metabolites has been employed by several researchers to treat NDs (Valverde*et al.,* 2015; Rahi and Malik, 2016). The edible mushroom compounds and their secondary metabolites include polyphenols, acids, terpenoids, alkaloid sesquiterpenes, lactones, sterols, and metal chelating agents employed as a medicine to treat NDs (Phan *et al.,* 2017, 2018; Venditti *et al.,* 2017; Phan *et al.,* 2015).

Table 1: Mushroom species and their compounds having neuroprotective effects

Mushroom species	**Bioactive compound**	**Function**	**Reference**
Hericium erinaceus	Dilinoleoyl-phosphatidylethanolamine	ER stress attenuation	Nagai *et al.,* 2006
Ganoderma lucidum	Ganoderic acid S1, methyl ganoderic- A, and methyl ganoderic-B, as well as ganolucidic acid A	NGF- and BDNF-like neuronal survival-promoting effects	Li *et al.,* 2005; Zhang *et al.,* 2011; Phan*et al.,* 2014
Mycoleptodonoides aitchisonii	Phenylpentane	Improved dopamine liberation	Okuyama*et al.,* 2004a
Dictyophora indusiata	Eudesmane-type sesquiterpenes, dictyophorines A and B	Promote NGF synthesis by astroglial cells	Kawagishi *et al.,* 1997
Grifola frondosa	Lysophosphatidylethanolamine (LPE)	Induce neurite outgrowth and it upregulated the neurofilament M expression in cultured PC12 cells	Nishina *et al.,* 2006
Pleurotus ostreatus	Ergothioneine	Anti-depressant and reduce stress effects	Famii and Seleke-Ere, 2019
Auricularia polytricha	Polysaccharides AAPS-1, AAPS-2, and AAPS-3	Suppressed activity of beta secretase	Zhao *et al.,* 2019
Inonotus obliquus	Acid protein-bound polysaccharide	Antioxidative effects in neuronal cells	Chen *et al.,* 2010
Termitomyces albuminosus	TermitomycesphinsA–D, E–Fand G–H	Potentiate neuritogenesis in PC12 cells	Qi *et al.,* 2000, 2001, 2012
Pleurotus eryngii	Adenosine	Ameliorate memory and learning deficit	Liang *et al.,* 2020

Bioactive compounds which promote neuro plasticity and induce long term changesin mood, emotion and cognition may offer therapeutic options to chronically mentally illpatients (Olson, 2021).Bioactives found in higher fungi such as mushrooms have chemical structures similarto neurotransmitters and can act as agonists of receptor pathways involved in psychiatricconditions. Harnessing this activity as therapy for chronic mental health and pain diseasesmay offer benefits where therapeutic needs are currently unmet (Meade *et al.*, 2022).

CONCLUSION

The incidence of neurodegenerative diseases is increasing gradually due to enhanced understanding and improved diagnosis. The available treatment methods and approaches are not promising in practice as it poses many disadvantages. There is a search for safer and promising source of therapeutics which includes mushrooms as a better option. The mushroom compounds have been found to be effective in alleviating neurodegeneration as displayed by recent researches. The evaluation and further exploitation of the mushroom compounds will through a light on the better adoption for treatment of neurodegenerative diseases in the near future.

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Chapter 10

ANTIMICROBIAL PROPERTIES OF INDIAN TRADITIONAL MEDICINAL PLANTS

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ABSTRACT

Nature has given us medicinal plants as a gift so that we can live healthy, disease-free lives. It is essential for keeping our health intact. In the past, plants were a primary source of remedies. Since the beginning of civilization, plants have been employed as a source of medicine in almost all societies. They are typically used to treat moderate or long-term illnesses and typically comprise a number of biologically active components. Despite the fact that over 2000 plant species are used therapeutically, only 400 to 600 plant species have been documented (examined) and researched for use as medicines. Because they are a cheap and abundant source of antibacterial action, traditional medicinal plants are frequently employed to treat microbial infections. The various plant parts, including the seed, fruit, root, bark, stem, leaf, and even the entire plant, were used.

KEYWORDS: Medicinal Plant, Antibacterial, Antifungal.

INTRODUCTION

In India, medicinal plants are widely used by all demographic groups, both directly as folk medicines in numerous indigenous medical systems like Ayurveda, Siddha, and Unani, and indirectly as ingredients in pharmaceutical formulations. The annual output of raw materials from medicinal and aromatic plants is estimated to be worth Rs. 200 crore. This is anticipated to reach 1150 USD by the year 2000 and 5 trillion USD by 2050 (Thomas *et al.,* 1988). Plant medications are expected to account for up to 25% of total drugs in developed countries such as the UnitedStates, while they account for up to 80% in rapidly emerging countries such as China and India. As a result, the economic relevance of medicinal plants is significantly greater in countries like India than in the rest of the world. A huge number of researchers from all around the world have researched the impact of plant extracts on bacteria (Reddy *et al.,* 2001).

There are over 4.5 million plant species in India, and thousands of them are said to have medicinal properties that can treat a variety of human illnesses. Infectious disease prevention and treatment are made possible by the widespread use of plant medicines (Soulsby, 2005). The abundance of secondary metabolites found in plants, including tannins, terpenoids, alkaloids, flavonoids, glycosides, etc., has been linked to their in vitro antimicrobial properties (Dhanukar,*et al.,* 2000). They may be used as an alternative, efficient, affordable, and safe antimicrobial for the treatment of microbial infections.There are an increasing number of

reports about the antimicrobial properties of medicinal plants. According to the World Health Organization, plant extracts or their active components are used as folk medicine by about 80% of people worldwide (Cown, 1999).

PLANTS USED AS MEDICINE IN TRADITIONAL SYSTEMS

Ayurveda, Siddha, and Unani are three of the traditional medical systems of India. Even in the ancient Vedas and other books, we find references to medical systems. India saw the emergence and development of the Ayurvedic idea between 2500 and 500 BC. A wide variety of medicinal plants used in traditional medical procedures can be found throughout the Indian subcontinent. Herbal pharmaceuticals are produced exclusively from medicinal plants, whereas alternative medicines are produced in traditional systems using herbs, minerals, and organic elements. India's healthcare system mainly relies on this practice of using plants as a source of medicine.About 70% of India's rural population relies on the traditional Ayurvedic medical system. A little over 40% of people in Western nations use herbal remedies to cure a variety of illnesses. The majority of medicinal plant production occurs in India. Ayurvedic medicine now has roughly 250,000 certified medical practitioners, compared to about 700,000 in contemporary medicine. There are thought to be 20,000 medicinal plants in India. Ayurveda uses 2000, Siddha 1300, Unani 1000, Homeopathy 800, Tibetan 500, Modern 200, and folk 4500 in the many Indian medical systems. Indian traditional and folk medicine uses about 25,000 potent plant-based medicines. In India, the traditional medical system is used by more than 1.5 million practitioners. More than 1500 herbal supplements and ethnic traditional treatments are available. Some commonly used medicinal plants with nutraceutical potential and primary applications in traditional medicine (Pandey *et al.,* 2008; Patwardhan *et al.,* 2005; Samy *et al.,* 1998).

POTENTIAL VALUE OF TRADITIONAL MEDICINE

The World Health Organization (WHO) has been using traditional medicine for the last twelve years or so, and the rest of the world has been using it for at least a few thousand years. WHO's approach to traditional medicine aims to take advantage of its components that offer secure and efficient treatments for use in primary healthcare (WHO, 2005).Human civilization has used higher plants as a source of drugs for many thousands of years. In reality, ancient man relied entirely on green plants for his daily medicine. The significance of plants as a source of pharmaceutical raw materials has significantly decreased with the development of modern medicine, synthetic drugs, and antibiotics.

ANTIMICROBIAL PROPERTIES

Antibacterial activities are produced by medicinal plants' immunomodulatory and antioxidant properties. They are known to stimulate both non-specific and specific immunity, exhibiting versatile immunomodulatory activity. Utilizing phytochemicals and plant extracts, both of which have known antimicrobial properties, can be extremely important in therapeutic procedures. Many plants have been used due to their antimicrobial properties, which are brought about by substances created in the plant's secondary metabolism. (Pandey,*et al.,* 2006; Nascimento,*et al.,* 2000). Medicinal herbs are useful to have on hand to treat common ailments. Plant-based antimicrobial compounds have high therapeutic potential because they have fewer

side effects than synthetic drugs and have a lower risk of resistance development. Antibacterial and antifungal chemotherapeutic chemicals can be derived in large quantities from medicinal herbs.

As a result, the antimicrobial properties of eight medicinally important plants are presented in Table I.

Table 1: antimicrobial properties of eight medicinally important plants

Plant Name	Common name	Properties
Azadirachta L.	Neem	It has strong health alleviating activity, used as a tonic and astringent that promotes healing. The extract has antispasmodic action. Its usage in Ayurvedic medicine for thousands of years has proved its detoxifying properties. It has shown most beneficial effects for the circulatory, digestive, respiratory, and urinary systems.
Asparagus racemosus	Shatavari	A potent Ayurvedic rejuvenative. It supplies many female hormones and mostly recommended for those women who have hysterectomies. It also helps to maintain urinary tract and strengthens the immune system and also purifies the blood.
Tinospora cordifolia Miers	Guduchi	Guduchi is a rich source of natural vitamin C and effective in inhibiting the growth of bacteria and in building up the immune resistance and has immune-boosting ability. Use of this plant increases white blood cells the killing ability of macrophages, the immune cells responsible for fighting invaders.
Withania somnifera	Ashwagandha	In Ayurvedic medicines Ashwagandha holds a place similar to Ginseng in traditional Chinese medicinal therapies. It is also called the "Indian Ginseng." It has been used for thousands of years as a popular remedy in Ayurvedic systems for many conditions. It is one of the best health tonics and restorative agents that have been used to treat general debility
Ocimum tenuiflorum	Tulsi	Tulsi has been found to protect organs and tissues against chemical stress from industrial pollutants and heavy metals, and physical stress from prolonged physical exertion, ischemia, physical restraint and exposure to cold and excessive noise.
Bacopa monnieri	Brahmi	Brahmi is used for Alzheimer's disease, improving memory, anxiety, attention deficit-hyperactivity disorder (ADHD), allergic conditions, irritable bowel syndrome, and as a general tonic to fight stress.

Curcuma longa	Turmeric	Turmeric is most active compound, it has many scientifically proven health benefits, such as the potential to improve heart health and prevent against Alzheimer's and cancer. It's a potent anti-inflammatory and antioxidant. It may also help improve symptoms of depression and arthritis.
Aloe barbadensis miller	Aloevera	People have used it for thousands of years for healing and softening the skin. Aloe has also long been a folk treatment for many maladies, including constipation and skin disorders. Modern-day research into aloe vera's benefits is mixed, with some evidence showing it can cause cancer in lab animals.

AZADIRACHTA INDICA

Azadirachta indica also known as nimtree, neem, or Indian lilac, is one of the two species of the genus Azadirachta and is indigenous to the Indian subcontinent and the majority of the African nations. It is a tree in the mahogany family, Meliaceae. It is typically grown in tropical and semi-tropical regions. Its fruits and seeds are the source of neem oil. (Barstow *et al.*, 2018; Roy *et al.*, 2000).

ANTIMICROBIAL PROPERTIES

It has been established that neem leaf and its constituent parts have anti-inflammatory, anti-ulcer, anti-fungal, antibacterial, anti-hyperglycemic, anti-carcinogenic, anti-oxidant, anti-mutagenic, and properties. By using the tube dilution technique, leaf and seed extracts of *A. indica* were found to have anti-dermatophytic activity against some dermatophytes, including *Trichophyton rubrum, T. violaceaum, Microsporum nanum,* and *Epifermophyton floccosum.* The antibacterial activity of *A. indica* was observed against *Bacillus cereus, Staphylococcus aureus, Listeria monocytogenes, Escherichia coli,* and *Salmonella infuntis*

CLASSIFICATION OF *AZADIRACHTA INDICA*

Kingdom: Plantae
Order: Sapindales
Family: Meliaceae
Genus: Azadirachta
Species: *A. indica*

Fig. 1 Leaves and fruits of Neem

ASPARAGUS RACEMOSUS

The Indian Himalayas are home to *Asparagus racemosus*, also known as Satavar, Shatavari, or Shatamull. Many diseases are successfully treated using it in Ayurveda. Shatavari is regarded as a female tonic and is frequently used to treat a variety of illnesses, such as dysentery, inflammations, tumours, bronchitis, nervous disorders, hyperacidity, some infectious diseases, neuropathy, conjunctivitis, spasms, chronic fevers, and rheumatism.

ANTIMICROBIAL ACTIVITY

Asparagus Racemosus roots have potent antimicrobial activity against gram-positive and gram-negative bacteria. *Asparagus racemosus* methanolic extract can be used to effectively treat bacterial and fungal diseases.Because of the presence of the constituent 9, 10 dihydrophenanthrene, Shatavarihas significant antidepressant and antibacterial efficacy against *Escherichia coli, Shigella sonnei, Shigella dysenteriae, Shigella flexneri, Vibrio cholerae,* and *Salmonella typhi* (Patel,*et al*., 2013).

CLASSIFICATION OF *ASPARAGUS RACEMOSUS*

Kingdom: Plantae
Order: Asparagales
Family: Asparagaceae
Subfamily: Asparagoideae
Genus: Asparagus
Species: *A. racemosus*

Fig. 2: Leaves, flowers and roots of Shatavari

TINOSPORA CORDIFOLIA

Tinospora cordifolia, also known as guduchi, is a crucial treatment in the Indian medical system. It is a member of the Menispermaceae family and has been used medicinally for centuries.Guduchi is mentioned as a medication to treat a variety of ailments in the traditional Ayurvedic textbooks like Charaka, Sushruta, and other texts.

ANTIMICROBIAL ACTIVITY

Guduchi has strong antibacterial properties and has great potential for use against microorganisms such as *S. typhi, E. coli, P. aeruginosa*, and *S. aureus*. Therapeutic treatments may benefit from its active ingredients like stems, leaves, and roots. Its antifungal activity is shown in *Aspergillus niger* and *Candida sp. T. cordifolia* is also useful in reducing respiratory issues like

recurrent colds and coughs, asthma, and tonsillitis due to its anti-inflammatory properties. Its stem and leaves actively contribute to the treatment of arthritis, diabetes, and ageing by acting as antioxidants (Sinha *et al.*, 2004).

CLASSIFICATION OF *TINOSPORA CORDIFOLIA*

Kingdom: Plantae
Order: Ranunculales
Family: Menispermacea
Genus: Tinospora
Species: *T. cordifolia*

Fig. 3: Leaves, stem and fruits of Guduchi

WITHANIA SOMNIFERA

Withania somnifera belongs to Solanaceae family commonly known as Ashwagandha/Indian ginseng/winter cherry. Withania somnifera's primary active ingredients are alkaloids, flavonoids, steroidal lactones, tannin, and others. These plants' withanolides, their main chemical components, are primarily found in their leaves.

ANTIMICROBIAL PROPERTIES

The aphrodisiac properties of Ashvagandha might be more important than all of its other exceptional qualities. For all adverse aging-related conditions, it ought to be regarded as the top herb; this includes its application to Alzheimer's disease and arthritis a sedative, antitussive, anti-inflammatory, antiseptic, and as a rejuvenator. When Jaffer *et al.,* (1988) investigated the antimicrobial activity of *Withania somnifera* extract against various gram-positive, gram-negative, and candida species, they found that gram-negative bacteria did not exhibit any antimicrobial activity. However, the most significant antibacterial activity against gram-positive bacteria was seen in leaf chloroformic, leaf methanolic, and stems chloroformic extracts. (Kuppuurajan, 1980, Kulkarni R. 1991)

CLASSIFICATION OF *WITHANIASOMNIFERA*

Kingdom: Plantae
Order: Solanales
Family: Solanaceae
Genus: Winthania
Species: *W. somnifera*

Fig. 4: Leaves, stem and fruits of Ashwagandha

OCIMUM TENUIFLORUM

Ocimum tenuiflorum, also called Ocimum sanctum, Tulsi, or Holy Basil, belongs to the Lamiaceae family and has been referred to as the "Queen of Plants" and the "mother medicine of Nature" because of its alleged therapeutic properties.Tulsi is used in various ways in traditional medicine; aqueous extracts from the leaves (fresh or dried as powder) are added to herbal teas or blended with other herbs or honey to increase their medicative potency.

ANTIMICROBIAL PROPERTIES

Measure the volatile substances found in flower spikes, leaves, and essential oil from Tulsi and look into the compounds responsible for any activity. Blackheads, acne, and premature ageing are all conditions that are treated with tulsi leaves. Tulsi is also used to treat insect bites. Additionally, fevers, illnesses, and respiratory issues can also be treated with tulsi.Pathogens like *Staphylococcus aureus, Pseudomonas aeruginosa, E. coli, Klebsiella pneumonia, Proteus mirabilis, Salmonella typhimurium*, and *Salmonella* are inhibited by tulsi extract (Prakash,*et al.,* 2005)

CLASSIFICATION OF OCIMUMTENUIFLORUM

Kingdom: Plantae
Order: Lamiales
Family: Lamiaceae
Genus: Ocimum
Species: *O. tenuiflorum*

Fig 5: Leaves and flowers of *Ocimum tenuiflorum*

BACOPA MONNIERI

Bacopa (*Bacopa monnieri*) has long been used in Ayurvedic medicine for therapeutic purposes. It is also referred to as Brahmi. Some brain chemicals related to memory, learning, and thinking may be increased by bacopa. It may also shield brain cells from substances linked to Alzheimer's disease.

ANTIMICROBIAL ACTIVITY

B. monnieri shows antibacterial activity against Gram-positive (*Staphylococcus aureus*), Gram-negative (*Escherichia coli*) bacterial strains and antifungal activity against strains of *Aspergillus flavus*, and *Candida albicans*. Brahmi may reduce inflammation, ADHD symptoms, prevent anxiety and stress, helps lower blood pressure and have antioxidant properties (Calabres,*et al.,* 2008).

CLASSIFICATION OF BACOPA MONNIERI

Kingdom: Planteae
Order: Lamiales
Family: Plantaginaceae
Genus: Bacopa
Species: *B. monnieri*

Fig. 6: Leaves and flowers of *Bacopa monnieri*

CURCUMA LONGA

Curcuma longa has been used as a remedy for a variety of illnesses, including inflammation, infectious diseases, and problems with the stomach, gastritis, liver, and blood for thousands of years in traditional Indian and folk medicine.

ANTIMICROBIAL ACTIVITY

Turmeric is a superior antioxidant and has excellent anti-inflammatory properties. The main curcuminoid compound in turmeric, curcumin, has demonstrated extensive antimicrobial activity, inhibiting the growth of numerous fungi, bacteria, and viruses.Turmeric's ability to fight cancer may be closely linked to its capacity to reduce inflammation. Additionally, the active components in turmeric have excellent anti-inflammatory, anti-tumor, and neuroprotective properties (Adamczak *et al.,* 2020).

CLASSIFICATION OF CURCUMA LONGA

Kingdom: Planteae
Order: Zinziberales
Family: Zinziberaceae
Genus: Curcuma
Species: *C. longa*

Fig. 7: Leaves, flowers and root of *Curcuma longa*

ALOE BARBADENSIS MILLER

In the field of cosmetology, aloe vera is a natural product that is now widely used. Many cultures, including Greece, Egypt, India, Mexico, Japan, and China, have used aloe vera for medicinal purposes for thousands of years.It can be found in a wide range of consumer products, including drinks, lotions for the skin, cosmetics, ointments, and a gel for minor burns and sunburns.

ANTIMICROBIAL PROPERTIES

Aloe vera has potent antibacterial, antifungal, and antiviral properties. Natural anthraquinones found in Aloe vera have been linked to the plant's antimicrobial properties. These compounds have been shown to inhibit *Bacillus subtilis* and Mycobacterium tuberculosis in vitro. Aloe juice showed antibacterial activity against the gramme negative bacteria E.Coli, pseudomonas aeruginosa, and salmonella typhimurium. Aloe juice was investigated by agar disc diffusion against bacteria. It was found that preserved aloe gel extract was more effective in controlling bacterial growth (Kamble *et al.*, 2013)

CLASSIFICATION OF ALOE BARBADENSIS

Kingdom: Plantae
Order: Asparagales
Family: Asphodelaceae
Subfamily: Asphodeloideae
Genus: *Aloe*
Species: *vera*

Fig. 8: Leaves of Aloevera

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Chapter 11

BIO-FUNCTIONAL COMPOUNDS OF EDIBLE MUSHROOMS AS IMMUNITY BOOSTERS

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ABSTRACT

The nutritional benefits of the bio-functional substances in the mushrooms can be utilized to their extensive potential in the diet. These have a well-known nutritional value because to factors including their high protein, low fat, and low energy contents. These are abundant in vitamins like riboflavin, thiamine, ergosterol, niacin, and ascorbic acid as well as minerals like iron and phosphorus. In addition, they contain bio-functional components such as lectins, fungal immunomodulatory proteins (FIPs), and polysaccharides, primarily -glucans, as well as secondary metabolites (terpenes, terpenoids, amino acids, alkaloids, sesquiterpenes, polyphenolic compounds, lactones, steroids, nucleotide analogues and vitamins). Numerous medical benefits from sugar-binding proteins have been documented, including anticancer, antiviral, antibacterial, immunomodulatory, and antidiabetic effects. Due to their low fat and high fibre content, as well as the fact that they are the main sources of natural antioxidants beneficial in lowering oxidative damages, they have a tremendous potential to prevent cardiovascular illnesses.

KEYWORDS: Bio-functional, Lectins, FIP, Terpenoids.

INTRODUCTION

Mushrooms are a delicacy with outstanding nutritional value and a naturopathic food; they are of great importance due to their general acceptability worth, therapeutic qualities, and economic usefulness. Humans have long viewed mushrooms as a delicacy item, particularly for their distinctive flavor, and as a culinary miracle. Mushroom that can be eaten and has physiological effects on both people and animals. Proteins, carbohydrates, vitamins, unsaturated fatty acids, and organic substances are all in great abundance in mushrooms. As a source of biologically active compounds with potential medical applications, such as anticancer, antiviral, immune-boosting, hypocholesterolemic, and hepatoprotective agents, mushrooms have recently acquired prominence.Shiitake, Enokitake, Yiner, Hericium, Oyster, Maitake, and Auriculariaare some common helpful edible mushrooms. Mushrooms are macrofungi, enormous organisms that release spores. Numerous civilizations have used mushrooms as food and medicine since antiquity. The business has now made a clear distinction between culinary mushrooms that are grown commercially and wild ones that are used directly or indirectly as food or ingredients. (HuiHu *et al.,* 2006; Phull *et al.,* 2022; Riaz *et al.,* 2022).

BIO-FUNCTIONAL COMPONENTS PRESENT IN MUSHROOMS AS IMMUNITY BOOSTERS

Terpenes and terpenoids, lectins, fungal immunomodulatory proteins (FIPs), and polysaccharides (especially β-d-glucans, but also including polysaccharopeptides and polysaccharide proteins) are the principal types of chemicals from medicinal mushrooms having immunomodulatory characteristics. Terpenes and terpenoids from *Ganoderma lucidum* have the potential to alter immune system processes by inducing the expression of genes encoding for proteins in the nuclear factor (NF)-kB pathway. By raising the expression of tumour necrosis factor (TNF), interleukin (IL)-1, and IL-12 and promoting nitric oxide generation, the heteroglycan and heteroglycan-peptide from the *Hericium erinaceus* mushroom can alter the immuno-effects. (Gao *et al.,* 2002; Lee *et al.,* 2009; Enshasy and Hatti 2013; Zhao *et al.,* 2020).

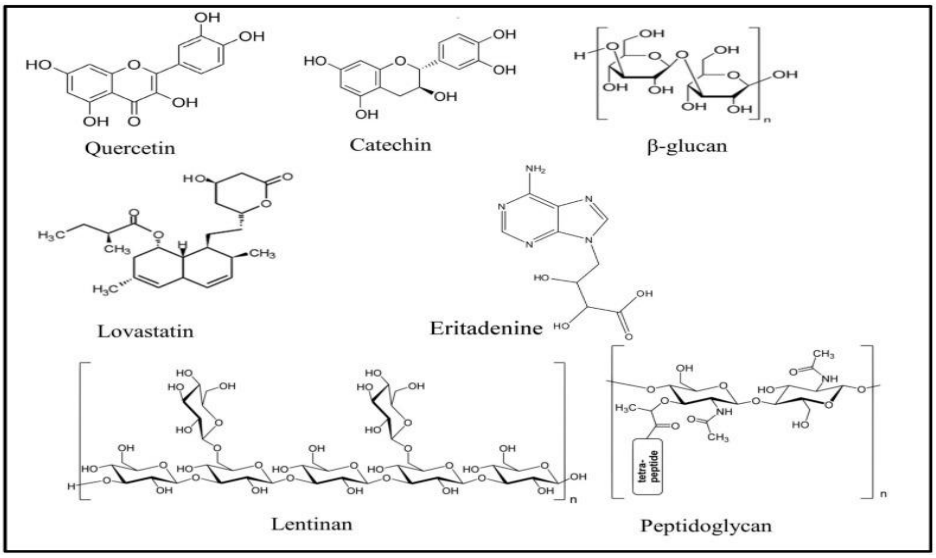

Fig. 1: Biofunctional Compounds in Edible Mushrooms

POLYSACCHARIDES

The most often reported bio-functional molecules with immunomodulatory properties obtained from mushrooms are those based on polysaccharides, with or without side chain modifications (including polysaccharopeptides and polysaccharide proteins). The most well-known of the reported polysaccharides having immunomodulatory and anticancer properties is lentinan, which was extracted from shiitake mushrooms, along with schizophyllan, which was isolated from Schizophyllum commune. Schizophyllan and lectinan both have β-1,3-d-glucans with β-1,6 branches. Particularly, schizophyllan proved efficacious against head and neck cancer whereas lentinan shown immunomodulatory characteristics against gastric cancer. In tumour-bearing mice, a polysaccharide-protein complexisolated from *T. giganteum* demonstrated that it could aid in restoring and improving the phagocytic function of macrophages (Ooi 2001; Moradali *et al.,* 2007; Biedron *et al.,* 2012; Ina *et al.,* 2013; Ngwuluka *et al.,* 2016; Chakraborty and Sen, 2019; Zhao *et al.,* 2020).

MUSHROOMPROTEINS AND PROTEIN–CONJUGATE COMPLEXES

As immunomodulatory substances, mushroom proteins and protein-conjugate complexes are also widely known. These protein-based immunomodulatory chemicals in medicinal mushrooms can also be divided into many categories, just like the polysaccharide-based compounds. These substances are divided into two main categories here: lectins and FIPs. FIPs lack a conjugate, whereas lectins each have a particular carbohydrate attached to a polypeptide. It has been demonstrated that these lectins can increase the expression of interleukins and tumour necrosis factor (TNF)-α activate lymphocytes, and stimulate the synthesis of macrophage-activating factors, among other things. There are several different therapeutic mushroom species that contain these lectins, including *Floccularia luteovirens, Ganoderma capense, Grifola frondosa, Pseudospermaum brinellum, Pholiota adipose, Pleurotus citrinopileatus, Russuladelic* Other powerful antiviral, mitogenic, antibacterial, and antioxidant actions have been demonstrated for a number of mushroom lectins. Many FIPs have also demonstrated anticancer activity in pharmacological testing in addition to immunomodulation, including the suppression of cell growth and proliferation, the induction of apoptosis and autophagy, and the reduction of tumour cell invasion and migration. (Ngai and Ng 2004; Li *et al.,* 2008; Zhao *et al.,* 2009, 2010; Enshasy and Hatti, 2013; Zhao *et al.,* 2020).

TERPENES AND TERPENOIDS

The vast and varied class of hydrocarbon molecules known as terpenes is produced biochemically from isopentenyl pyrophosphate units from mushrooms. Terpenoids are created when functional groups, typically oxygen-containing ones, are added to terpenes. Many medicinal mushrooms produce terpenes and terpenoids that have demonstrated immunoregulatory actions with clinical relevance. As an illustration, *Ganoderma sp.* is well-known for its high triterpene content, and these triterpenoids have demonstrated strong immunomodulating and anti-infective activities. According to a study, mitogen-activated protein kinases and the genes encoding proteins in the nuclear factor (NF)-kB pathway are two examples of the immune system processes that terpenes and terpenoids influence. (Gao *et al.,* 2002; Wang *et al.,* 2013; Chen *et al.,* 2014; Ma *et al.,* 2014; Zhao *et al.,* 2020).

BIO-FUNCTIONAL COMPOUNDS OF MUSHROOMS WITH HEALTH BENEFITS

Mushrooms are priced for flavor, texture, and potential medicinal benefits. Additionally, according to numerous research, mushrooms have antiviral, anticancer, antithrombotic and immuno-modulating properties since they contain bio-functional components. The antioxidant, antidiabetic, anticarcinogenic, and immune-modulating properties of the polysaccharides derived from edible mushrooms, particularly β-glucans, are attracting the interest of scientists and other food sectors. Research on various varieties of mushrooms has advanced as a result of the growing popularity of edible mushrooms as health enhancers. Due to their capacity to increase protein content as well as their valuable health advantages, they can be used widely as supplements to many basic food products. (Perera and Li, 2011; Kumar *et al.,* 2021).

Mushroom	Common Name	Bioactive Compounds	Health Benefits
Agaricus bisporus	Button Mushroom	Pyrogallol, hydroxybenzoic acid derivatives, flavonoids, lectins	Anti-inflammatory, enhanced insulin secretion, anti-ageing property
Auricularia auricular	Jew's ear mushroom	Glucan, acidic polysaccharides	Immunomodulatory, anti-tumour, anti-inflammatory, lowers cholesterol and triglycerides, hypoglycaemic activity, immune tonic, and beneficial in coronary heart disease
Ganoderma lucidum	Reishi, Lingzhi	Ganoderic acids, ganodermanontriol, ganoderiol, polysaccharides, germanium, triterpenoids, nucleotides and nucleosides, β-glucan	Anti-metastatic, anti-tumour, anti-viral, anti-HIV, immunomodulatory, antibiotic properties, liver protection, prevents cholesterol synthesis
Lentinu laedodes	Shiitake Mushroom	Lentinan, glucan, mannoglucan, fucomannogalactan, lentin, catechinflavonoids, eritadenine	Immunomodulatory, anti-tumour, anti-inflammatory, anti-fungal, antioxidant, anti-bacterial, antifungal, antioxidant, hypolipidemic activity
Pleurotus florida	White oyster	β-glucans	Antioxidant, anti-microbial
Grifola frondosa	Ram's head	Lectins, polysaccharides	Decrease blood glucose improves insulin secretion and ovulation
Volvariella volvacea	Paddy straw mushroom	Fip-vvo	Immunomodulatory
Hericium erinaceus	Monkey head mushroom	Hericenones and erinacines	Neuritogenic effects

Pleurotus ostreatus	Oyster mushroom	Functional proteins (ubiquinone-9, ubiquitin-like peptide, nebrodeolysin, and glycoprotein), proteoglycans pleuran (β-1, 3-glucan with galactose, and mannose), glucans, proteoglycan, laccase, pleurostrin	Immunomodulatory, hyperglycemia, anti-tumour, antioxidant, anti-viral, anti-fungal
Pleurotus pulmonarius	Lung oyster mushroom	Polysaccharides such as β (1,3)-glucopyranosyl, and Polysaccharides (1,3), (1,6)-linked β-glucan	Anti-inflammatory

Due to the substantial number of bio-functional and nutraceutical components present, edible mushrooms offer a wide range of medicinal effects. These are regarded as having a high level of effectiveness against a variety of lifestyle disorders, including cancer, diabetes, cardiovascular disease, and liver ailments. In addition to acting as an antibacterial, immune system stimulant, and cholesterol-lowering agent, mushrooms may minimise the risk of diseases like Parkinson's, Alzheimer's, hypertension, stroke, and cancer (Kumar *et al.,* 2014; Valverde *et al.,* 2015; Kumar *et al.,* 2021; Riaz *et al.,* 2022). The following subheadings cover several health advantages of edible mushrooms:

ANTI- CARCINOGENIC PROPERTIES

Numerous bio-functional compounds with potential anticancer effects can be found in mushrooms. Different cancer cell lines were used by Daba and Ezeronye (2003) to investigate the anti-tumour effects of fruit bodies and mushroom mycelial extracts. Mushroom polysaccharides shown possible anti-tumour efficacy against leukaemia L-1210, mammary adenocarcinoma 755, and sarcoma 180. According to Patel and Goyal (2012), the genera *Pleurotus, Phellinus, Agaricus, Clitocybe, Ganoderma, Trametes, Antrodia, Xerocomus, Cordyceps, Schizophyllum, Calvatia, Flammulina, Inonotus, Suillus, Albatrellus, Inocybe, Funlia, Russula, Lactarius*, and *Fomes*mushrooms contain substances with anti-cancer properties that are significant as reactive oxygen species inducers, anti-mitotic, mitotic kinase inhibitors, topoisomerase inhibitors, and suppression of angiogenesis inducing apoptosis of cancer cells, eventually inhibiting cancer proliferation.

Phellinuslinteus was found to have anti-tumour, immune-modulating, and anti-metastasis effects, according to Baker *et al.* (2008). On colon cancer HT-29 cells, polysaccharide from *Pleurotus ostreatus* has pro-apoptotic and anti-proliferative properties. The anti-carcinogenic efficacy of polysaccharides isolated from edible mushrooms was further demonstrated by the polysaccharide from *Agaricus blazei*, which reduced angiogenesis in vivo. *Pleurotus pulmonaris*, *Phellinus rimosus*, *Pleurotus florida*, and *Ganoderma lucidum*, four medicinal mushrooms from south India, were discovered to have strong antioxidant and anti-tumour properties. These are

said to be excellent sources of antioxidant and anticancer compounds, as well as having possible anti-mutagenic and anti-carcinogenic properties. Due to their ability to decrease aromatase activity and oestrogen production. According to research, button mushrooms have a significant potential to reduce the risk of breast cancer because of their ability to reduce oestrogen production and aromatase activity. (Chen *et al.,* 2006; Lavi *et al.,* 2006; Ajith and Janardhanan, 2007; Niu *et al.,* 2009; Kumar *et al.,* 2021).

ANTI-OXIDATIVE PROPERTIES

Mushrooms have also been referred to as a rich source of antioxidant components because of their phenolic components and other polysaccharides. By boosting antioxidant defences, dietary supplements of edible mushrooms can minimise oxidative stress. Both cultivated and wild mushrooms exhibit strong antioxidant properties, which are primarily brought on by bio-functional substances such polyphenolic compounds, carotenoids, polysaccharides, and vitamins. Edible mushrooms are frequently utilised as a gourmet meal due to the presence of antioxidants and other health-promoting ingredients. As a result, including mushrooms in our diet regularly as a source of natural antioxidants may help prevent or lessen oxidative damage and associated lifestyle diseases. (Kozarski *et al.,* 2015; Kumar *et al.,* 2021).

HYPO-CHOLESTEROLEMIC AGENTS

The best diet for preventing heart diseases is edible mushrooms because of their high fibre and low-fat content. In oriental medicine, eating more edible mushrooms is frequently advised as a natural hypocholesteromic and anti-sclerotic diet. It has been found that eating *Termitomyces microcarpus* mushrooms significantly reduces the risk of developing blood lipid-related illnesses. It has also been hypothesised that the mushrooms' high fibre content can lower triglycerides, LDL cholesterol, and total serum cholesterol. Exo-polymers produced in the submerged culture of *Grifola frondosa*, *Flammulina velutipes, Hericium erinaceus, Phellinus pini,* and *Auricularia auricula-judae* show a hypolipidemic effect on the test animals. Eritadenine [2(R), 3(R)-dihydroxy-4-(9-adenyl)-butyric acid], an active hypo-cholesterolemic component, was extracted and discovered by Rathee *et al.* (2010) in the shiitake mushroom. Eritadenine can lower blood cholesterol levels in mice by accelerating the metabolic breakdown and excretion of ingested cholesterol. (Ishikawa *et al.,* 1984; Yang *et al.,* 2002; Nabubuya *et al.,* 2010; Kumar *et al.,* 2021).

HEPATOPROTECTIVE EFFECTS

According to studies done on mice poisoned with carbon tetrachloride, the ethanolic extract from *Calocybe indica* has a protective effect against liver damage brought on by CCl4-induced hepatotoxicity. Ganoderic acids R and S, as well as gannosporeric acid A, demonstrated in vitro anti-hepatotoxic effects on primary cultured rat hepatocytes when examined using the galactosamine-induced cytotoxic test. While *Tricholomalo bayense* mycelial aqueous extracts showed hepatoprotective effects at higher doses, extracts from the basidiomass of *Ganoderma frondosa* and *Lentinus edodes* were found to be highly effective in reducing the paracetamol-induced proliferation of alanine transaminase and aspartate transaminase levels. *Pleurotus florida* hepatoprotective properties were investigated by Sumy *et al.* (2014) in albino rat studies on the damage induced by paracetamol use. The ethanolic extract of the *Morchellaesculenta*

mycelium's strong antioxidant and hepatoprotective activities were revealed by the testing results. (Hirotani *et al.,* 1986; Ooi 1996; Chatterjee *et al.,* 2011; Kumar *et al.,* 2021). As a supplement, *Hericium erinaceus* polysaccharides can be used to prevent a number of liver illnesses. *Pleurotus eryngii's* polysaccharide-rich extract has been shown to have hepatoprotective and hypolipidemic properties and can be used as a crucial functional food additive. *Agaricus blazei* extracts have demonstrated comparable effectiveness against paracetamol-induced liver damage (Refaie *et al.,* 2010; Zhang *et al.,* 2012; Chen *et al.,* 2012; Soares *et al.,* 2013).

ANTI-DIABETIC EFFECTS

Mushrooms can be useful foods for managing diabetes. These are great sources of bio-functional substances with anti-diabetic effects. Various types of mushrooms are very good at regulating blood sugar levels and managing diabetic issues. Numerous research has suggested that certain types of mushrooms, including *Agaricus subrufescens, Agaricus bisporus, Coprinus comatus, Cordyceps sinensis, Inonotus obliquus, Ganoderma lucidum, Pleurotus spp., Phellinus linteus, Sparassis crispa,* and *Poria cocos*, have hypoglycemic properties. The edible mushrooms are regarded as low-calorie foods for diabetic people since they have very low levels of fat, cholesterol, and carbs and are high in protein, vitamins, and minerals. Exopolysaccharides produced in the submerged culture of *Tremella fuciformis* in mice were found to have anti-diabetic properties by Cho *et al.* in 2007.

The effects of *Pleurotus citrino pileatus* methanolic extract against streptozotocin-induced type-2 diabetes mellitus in rats were investigated by Rushita*et al.,* in 2013. The fasting blood glucose level and serum catalase activity both significantly decreased, but the serum insulin level significantly increased in the groups treated with a high dose of mushroom extract compared to the control group. Mushroom polysaccharide β-glucan has been reported to improve insulin secretion by β -cells, which lowers blood glucose levels while repairing the functions of pancreatic tissues. Rat pancreatic tissues containing islets of Langerhans were stimulated to release more insulin by lectins derived from *Agaricus campestris* and *Agaricus bisporus* (Cui *et al.,* 2009; De *et al.,* 2012; Kaur *et al.,* 2015).

ANTI-MICROBIAL EFFECTS

Some edible mushrooms have the ability to fight against numerous human diseases and have antimicrobial properties. These were discovered to have anti-bacterial and anti-fungal properties against hardy pathogens. Numerous mushrooms, including *Inonotushispidus*, and ergosterol peroxide have been discovered to have antiviral properties in vitro against influenza viruses. Compared to other mushroom kinds, Shiitakerwas shown to have the strongest antibacterial activity. Comparing Saccharomyces cerevisiae to other microbial isolates, *Pleurotus aeruginosa* was more sensitive and somewhat resistant. (Ali *et al.,* 2003; Sharma *et al.,* 2014; Kumar *et al.,* 2021). According to Menaga *et al.* (2012), *Pleurotus florida* biofunctional components can be used in place of conventional therapies like antibiotics. The study came to the conclusion that mushrooms can also be utilised pharmaceutically to treat a variety of illnesses. In response to the rising demands for food quality and safety, Shen *et al.* (2017) found that mushroom

extracts can be used as food additives with antioxidant and antibacterial activity, avoiding the deterioration of food products.

MUSHROOMS AS NATURAL RESOURCES OF IMMUNOTHERAPY

It is generally recognised that mushrooms are a substantial source of natural immunotherapeutic ingredients. These can be used to treat some immunodeficiency illnesses such cancer, tumours, HIV, and tuberculosis by acting as immune-stimulating and immune-modulating drugs. Bio-functional substances that were derived from *Pleurotus* mushrooms have the power to boost or stabilise the immune system in people. Polysaccharide-proteins, polysaccharopeptides, functional proteins (ubiquitin-like peptide, ubiquinone-9, glycoprotein, and nebrodeolysin), proteoglycans, and glucans are some examples of these bio-functionalsubstances. In vitro the maturation of immune cells in the human immune system, proteins derived from *Ganoderma lucidum* and lectins, the sugar-binding proteins from edible mushrooms, can influence human immune function (Wang *et al.,* 1996; Cui *et al.,* 2009; Oloke and Adebayo, 2015). According to Guggenheim *et al.* (2014), mushrooms have an immunomodulating impact that causes tumorsdestruction. Natural killer cell activity has been shown to increase in mice when white button mushrooms are consumed. An important component of the immune system, NK cells are in charge of fighting viruses and tumors. Better IFN-g and TNF-a production can be used to counteract the enhanced NK activity. The T-helper 1 response shifted after consuming white button mushrooms, and there is a propensity for greater IL-2 and lymphocyte production (Wu *et al.,* 2007; Kumar *et al.,* 2021).

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Chapter 12

CARBON FIBER: A BENCHMARK FOR THE DEVELOPMENT OF THE REQUISITE FUTURE MATERIALS

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ABSTRACT

The products having high tensile strength, light in weight and increased durability attract everyone. The carbon fiber composites consisting of carbon fiber have fulfilled all these requirements well in commercial market. The carbon fiber shows good electrical and thermal conductivity.This article outlines the available developmental methodologies, importance and utility of carbon fiber with special emphasis to encourage the manufacturing units, researchers and scientific communities to develop novel products of carbon fiber associated with better properties.

KEYWORDS: Tensile strength, Carbon fiber, Electrical conductivity, Thermal conductivity.

INTRODUCTION

Carbon fiber is a long thin strand consisting of carbon atoms bonded together in the form of hexagonal rings along the axis of fiber. It has a diameter 5 to 10 micro meter i.e. it is thinner than human hair. Its strands can be twisted like yarn and woven together like a cloth. In carbon fiber carbon atoms are bonded together in microcrystals aligned along the axis of fiber. The micro crystals are made up of hexagonal rings similar to graphite. Therefore, carbon fiber is also called graphite fiber. The graphite fiber contains about 99% of carbon by weight. In present scenario the carbon fiber industry is growing rapidly to meet the demands of different sectors. In graphite hexagonal array of carbon atoms is in sheet form but in carbon fiber it is in the form of ribbon. The carbon fiber has very high tensile strength and it is commonly available in the form of continuous tow wound on to a reel. Thousands of carbon fiber may be woven together into a yarn to cater to numerous end uses

MANUFACTURING

There are two types of methods involved in the manufacturing process of carbon fiber.

(a) Polyacrylonitrile method (PAN): In PAN method the raw material is polyacrylonitrile which is obtained from polymerization of acrylonitrile. Polyacrylonitrile is called a precursor in this method. In general, 90% of carbon fiber is obtained from polyacrylonitrile method. In polyacrylonitrile method raw fiber is kept in stretched state throughout their fabrication

(b) Pitch method: In this method petroleum pitch is known as precursor.About 10% carbon fiber is obtained from pitch method. In pitch method the raw material is pitch which is obtained by distillation of crude oil and coal. In case of pitch method raw fiber is not held in tension in all steps. Usually, the steps of manufacturing are common in both the methods and involve following processes.

SPINNING

In this process the raw material is transformed into a fiber strand. Viscous solution of polyacrylonitrile or pitch in organic solvent like dimethyl sulfoxide, $ZnCl_2$ or NaSCN (Morgon, 2005) is formed. It is called precursor dope. Dope is allowed to pass through the holes of spinneret and on oozing out of the holes of spinneret the solvent gets evaporated leaving behind the gelatinous and fragile threads. The threads are now washed, dried and stretched to the desired length.

STABILIZATION

During stabilization the threads are spread out on a sheet called wrap. Thereafter the threads are loaded on roller bars, fitted into an oven.The threads are heated to 450-500K for 30 to 120 minutes in presence of air causing crosslinking and oxidation of threads. This increases the density of fiber and it's utility. The stabilization is basically a cyclization and oxidation reaction which is exothermic in nature so heat must be dissipated to prevent charring of the fiber. The cyclisation is generally initiated by free radicals (Fitzer & Muller, 1975) and (Fitzer *et al.,* 1986). At the end of this step the carbon content in fiber is 50-60% while the rest amount is hydrogen, nitrogen and oxygen.

CARBONIZATION

In this step the fiber is heated in absence of oxygen preferably in an inert atmosphere of argon gas with a series of furnaces where each furnace is showing a little increased temperature than that of the previous one. Initially the temperature is kept at about 1000K and lastly at 2000K. In this process the fiber does not char due to the absence of oxygen. The hydrogen, Nitrogen and Oxygen are expelled out as gases. The strength of carbon fiber increases with the increase of carbonization temperature at around 1500K but further increase decreases its tensile strength (J *et al.,* 1990). Thus, the carbon content of fiber increases to 95% and the carbon skeleton is aligned parallel to the axis of the fiber.Rapid carbonization produces defects in carbon fiber while slow rate promotes loss of too much nitrogen at the early stages of carbonization.

GRAPHITIZATION

It is done to increase the elasticity of the fiber. This is carried out at about 2500 K to 3000 K. This enhances the preferred orientation of graphite like crystals within each fiber. Graphitization changes the molecular bond structure of the fiber. During Graphitization narrow sheets of graphene are formed which eventuallymerge to form a single filament. The process of Graphitization further enhances the carbon content and tensile strength of the fiber.

SURFACE TREATMENT

The carbon fiber is coated with organic material before its commercial utility. This increases the durability of the fiber and stops its clumping. For better adhesion of the coating material, the fiber is made ready for surface treatment. It is done by partial oxidation of fiber strand either by

oxygen, ozone, nitric acid or sodium hypochlorite. The process of oxidation roughens the surface of filament and paves the way for better mechanical adhesion of the coat. Oxidation also converts some of the carbon atoms into carboxylic acid functional group. The functional groups of the coating material react with the functional group of carbon skeleton of fiber and thus provide better chemical adhesion with the fiber strand.

SIZING

The application of coating material after oxidation is called sizing. The fiber without coating becomes curly and gets entangled easily. Coating provides strength to the fiber and the coated threads remain in segregated form. The common coating materials are epoxide, polyester, nylon and urethane. After sizing, the fiber is wound to cylinders called bobbins. The bobbins are loaded into spinning machine that weaves fiber into yarn. The fiber may be embedded with other chemicals to yield composites e.g. carbon fiber combines with graphite to produce fiber reinforced graphite composite.

FLOW DIAGRAM OF PAN MANUFACTURING PROCESSES OF CARBON FIBER

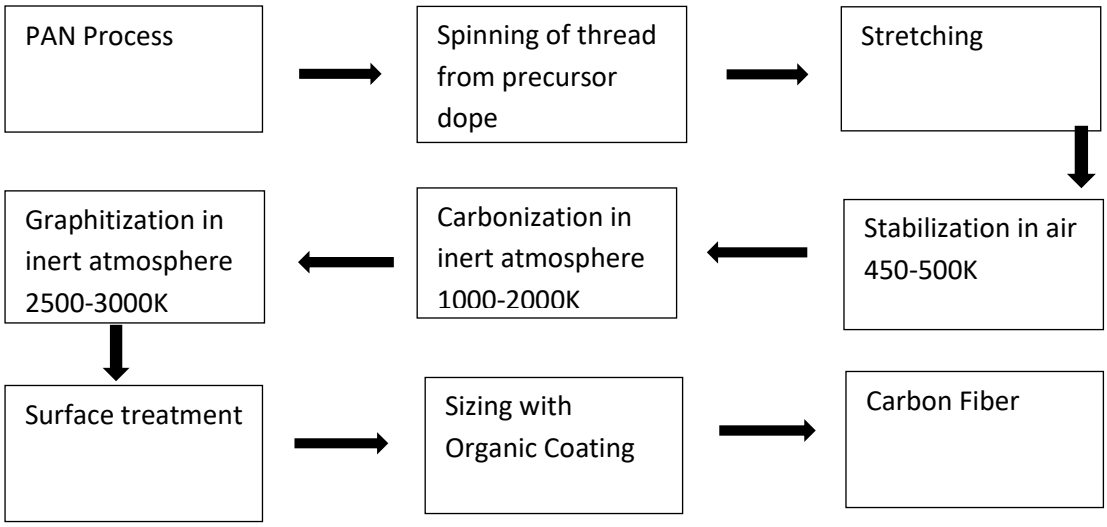

Fig. 1: PAN manufacturing process

FLOW DIAGRAM OF PITCH MANUFACTURING PROCESSES OF CARBON FIBER

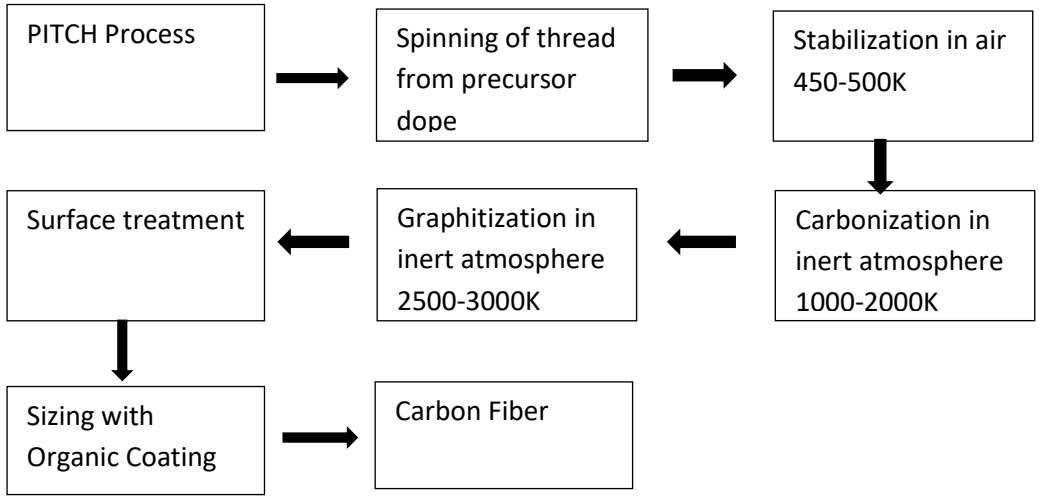

Fig. 2: PITCH manufacturing process

STRCTURE AND PROPERTIES

The structure of carbon fiber depends upon the kind of precursor used and prevailing processing conditions. Various models have been proposed regarding the microstructure of carbon fiber. According to Wick's model (Wicks, 1975; Morley, 1987) the graphite layers are stacked randomly in transverse direction but aligned parallel to the direction of fiber. Watt and Johnson (Watt *et al.*, 1969.) worked of PAN carbon fiber and reported a branched microfibrillar structure in which the fibrils aligned in axial direction. Kobets and Deev (Kobets and Deev, 1997] also worked on PAN and hydrated cellulose carbon fibers and their findings supported a microcomposite structure.

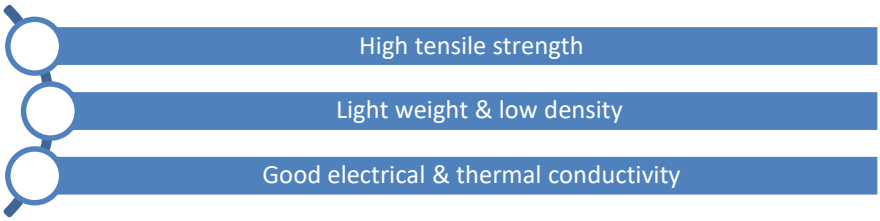

Fig. 3: Properties of Carbon fiber

The carbon fiber has high strength to weight ratio. It is having a high tensile strength. It is very light in weight and density is also low. The carbon fiber shows good electrical and thermal conductivity. It has a lower coefficient of thermal expansion. The carbon fiber shows good corrosion resistance. Besides this, the carbon fiber has high abrasion, wear and fatigue resistance.

USES

Carbon fiber has numerous applications in various fields as mentioned in Fig. 4. Some of them are discussed below

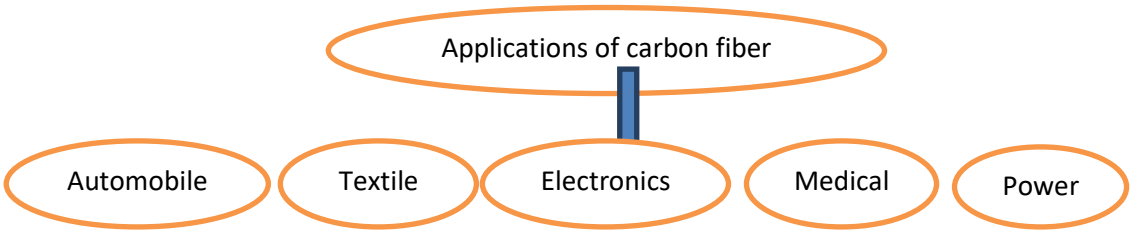

Fig. 4: Flow chart of applications of Carbon Fiber

TEXTILE INDUSTRY

It can be knitted into a textile material. The Carbon fiber is used in fabrication of IR-heated clothing and blankets due to its good thermal conductivity.

AERONAUTICAL INDUSTRY

The fan containment cases of aircrafts and blades of fans are made up of carbon fiber. The use of carbon fiber has increased the efficiency of aircrafts due to its light weight.

AUTOMOBILE INDUSTRY

Several internal components of automobiles like engine covers, bonnet, bumper, seat frames and musical instrument casings are made up of carbon fiber.

ELECTRONIC INDUSTRY

Carbon fiber is agood conductor of electricity therefore it is used to prepare microelectrodes of voltammetry and amperometry devices. It is also used to fabricate rechargeable batteries, mobile covers and fuel cell electrodes.

SPORTS INDUSTRY

Various sport items like tennis racquets, golf clubs, racing gloves, hulls for racing boats, helmets of rock climbers and horse riders are made up of carbon fibers. The carbon fiber of racing gloves due to its high tear resistance protects fingers of motor cycle racers at the time of accident.

MILITARY EQUIPMENT

Carbon fiber due to its high tensile strength and low weight is widely used to prepare protective helmets of military personnel and flapping wings for surveillance drones.

MEDICAL FIELD

The carbon fiber is used in x-ray machines and radiation therapy equipments due to its radiolucent property i.e. transparent to high energy rays. Formation of artificial limbs and Robots for internal operations is also done with the help of carbon fiber.

POWER GENERATION

The blades of modern windmills are made up of carbon fiber.

CIVIL ENGINEERING

The carbon fiber has wide applications in civil engineering.

ADVANTAGES OF CARBON FIBER

The wide application of carbon fiber is due to its unique properties such as

a) It has long working life.
b) Its compressive strength is greater than all other reinforcing materials.
c) It is insensitive to temperature changes.
d) It is light in weight.
e) Its density is lower than steel.
f) It has potential to replace other metals in terms of utility and services.

DISADVANTAGES OF CARBON FIBER

In spite of various advantages of using carbon fiber to increase the efficiency of the system, there are certain disadvantages also mentioned in the diagram below.

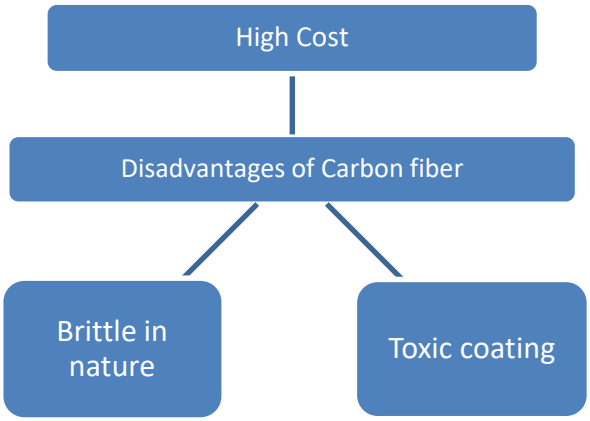

Fig. 5: Disadvantages of Carbon Fiber

The products made up of carbon fiber composite are generally costly. The products made up of carbon fiber composite some time develops cracks due to the brittle nature of Carbon fiber. Besides it, the organic coating used during sizing process in manufacturing is toxic in nature.

CONCLUSION

The carbon fiber is about 75% lighter than steel. It is having greater tensile strength than steel. It shows two times higher stiffness than steel. It has greater temperature tolerance. In recent processes of carbon fiber development the tiny carbon tubes are generated having a diameter of about 0.001mm. These nanotubes have great mechanical and electrical properties that can be used in the fabrication of high strength carbon fibers and a good quality semiconductor material for integrated circuits. The future work on carbon fiber is mainly focused on cost reduction and improvement in its tensile and compressive strength properties. The mechanical properties of carbon fiber depend upon its microstructure and the alterations can be made in microstructure by varying spinning temperature, spinning rate and the type of copolymer used. Many polymers have been examined to be used as precursor for the production of a low cost carbon fiber e.g.Lignin. However, more research is still to be carried out to chalk out the most appropriate processing conditions to improve the properties of the carbon fiber.

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Chapter
13

WASTE MANAGEMENT- AN OVERVIEW

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ABSTRACT

We all have a right to clean air, water and food. This right can be achieved through keeping a clean and healthy environment. Waste generation happens in every home, no matter how big or small. Since the beginning of civilization, humanity has gradually turned away from nature, and today, the way of life in human society has undergone a dramatic change. The nature and quantity of waste generated by a community are direct reflections of this transformation. By managing the waste properly, we can recycle or dispose of the waste while making money. Indian cities, which are quickly catching up to the world's economies in their pursuit of rapid economic growth, have so far been unable to efficiently manage the enormous amount of waste produced. In India, there are around 5,000 towns and 593 districts. According to the Census of 2001, 27.8% of India's more than 1 billion people reside in urban areas. By 2026, a 33.4 percent urban population share is anticipated. Increased development of solid wastes in both urban and rural areas of the nation is a result of the country's growing population and bettering lifestyles. Due to ever progressive urbanization, rapid development of 'use & throw principle '& equally fast connection between urban & rural areas the gap between the two is decrease.

KEYWORDS: Environment, Waste Management, Waste problem.

INTRODUCTION

What exactly is a waste is a key question in today's waste management? Waste is the ineffective by product of human activity that physically contains the same material as the valuable product (White *et al.*, 1995). The term "waste management" refers to the various plans for handling and getting rid of waste. Wastes can be disposed of, destroyed, and processed, recycled, reused, or controlled. Reducing the amount of waste and avoiding potential health and environmental risks are the main goals of waste management. Waste is produced by most human activities. However, as it has always been since before recorded history, waste production is still a significant cause for concern. Both the rate and the amount of waste generation have accelerated recently (Demirbas, 2011; Dixon & Jones, 2005; White *et al.*, 1995). The variety of wastes also increases as the volume of wastes does. Compared to the developing nations in the region, the developed nations produce significantly more waste per person. The management of even small amounts of waste, though, can be extremely difficult in some situations. Most industrialized nations went through a phase of environmental development. However, most of these nations have now successfully addressed most of the problems with health and environmental damage

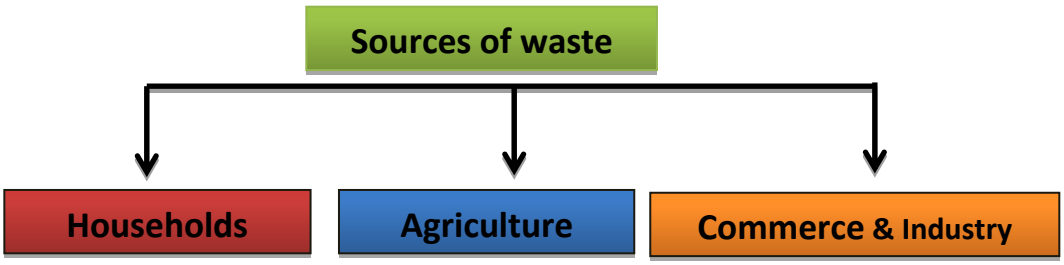
brought on by the generation of waste. Instead, the rapid urbanization and growth of developing nations is now causing a recurrence of the same historical issues that developed countries have had to deal with in the past (Wilson, 2007; Dijkema *et al.*, 2000; Cheremisinoff, 2003).

THE ISSUE OF "WASTAGE": PAST AND PRESENT

Man has always assembled waste materials that are either byproducts of his actions that he could not find a purpose for, or items that have reached the end of their useful life. Although this has been going on for centuries, it was not a concern until recently because nature's own waste treatment processes, such as dispersion, dilution, and degradation, took care of these issues. Today's condition is more complicated. The difficulty stems from the quantitative and qualitative nature of the garbage we generate. Natural degradation processes are slow and can only handle a certain amount and a particular type of waste. The toxic vapor's produced by today's so-called civilized society are too numerous for the atmosphere to disperse, particularly in urban areas. The rivers are unable to dilute and degrade the huge quantity of industrial wastewater discharged into them every day. And it would take a long time for heaps of trash metallic material discharged to mix back into the earth's crust as ores. This will not occur because we are dumping waste at a rate faster than nature can degrade and absorb it. Furthermore, many modern waste items, such as plastics and detergents, are not biodegradable. All of this will pose a danger to our planet.

SOURCES AND ORIGIN OF WASTE (Source: National Audit Office of Estonia)

Fig. 1: waste classification by origin different activities generate different types of waste

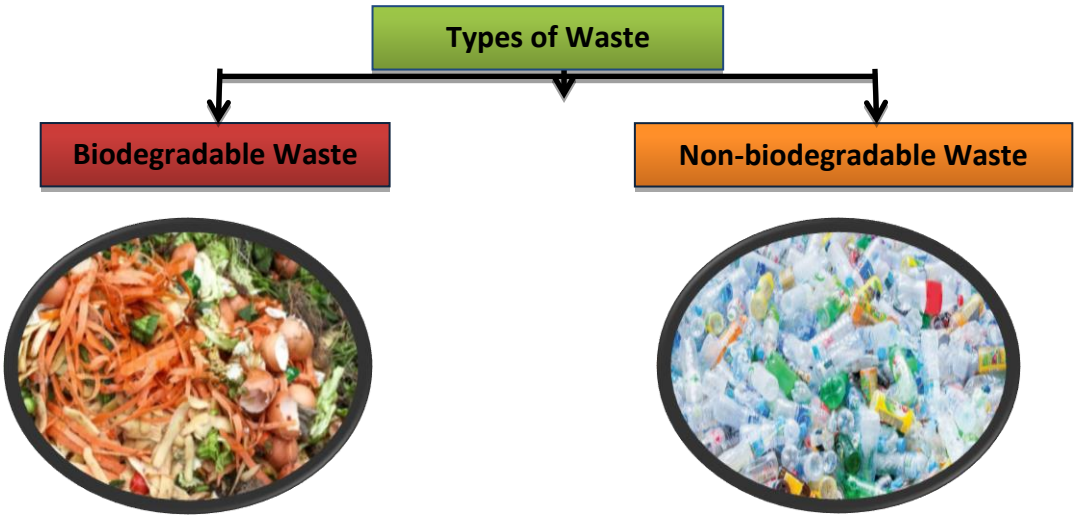


CLASSIFICATION OF WASTE

Waste can come in a variety of forms, including household waste, industrial waste, oil refineries waste, e-waste, construction waste, agricultural waste, food processing waste, bio-medical waste, nuclear waste, and waste from slaughterhouses, among others. We can be categorized waste as follows:

a. Solid waste includes food scraps, kitchen waste, and other types of garbage.
b. E-waste includes old/discarded electronics including computers, TVs, music players, etc.
c. Liquid waste includes water from distilleries, tanneries, and thermal power plants.
d. Plastic waste includes plastic bags, bottles, bucket, etc.
e. Metal waste- metal scraps, unused metal sheet etc.
f. Nuclear waste- unused materials from nuclear power plants.

Further we can group all these types of waste into Biodegradable (wet waste) and Non-Biodegradable (dry waste)-



BIODEGRADABLE (WET WASTE) INCLUDES THE FOLLOWING-

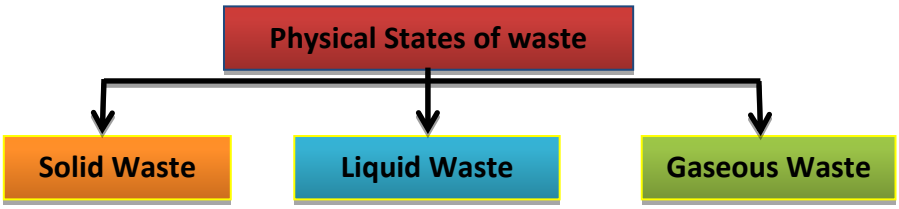
a. Kitchen waste consists of all types of cooked and uncooked food waste, as well as eggshells and bones.
b. Flower and fruit waste, including peels from juice, and wastes from indoor plants.
c. Waste from indoor plants and flowers, including juice peels.
d. Waste from tea and food businesses, stalls, etc.
e. Sanitary wastes.
f. Green waste from fruit and vegetable vendors or businesses.

NON- BIODEGRADABLE (DRY WASTE) INCLUDES THE FOLLOWING

a. All kinds of Paper and plastic.
b. Cardboard and cartons.
c. All containers, excluding those that contain dangerous materials.
d. Packaging of all kinds
e. Glass of all kinds
f. Metals of all kinds

g. Rags, rubber
h. Cleaning the home (dust etc.)
i. Discarded electronic objects from offices and colonies, such as cassettes, computer diskettes, printer cartridges, and electrical parts.
j. Wasted apparel, furniture, and equipment.

A different kind of waste known as "Domestic Hazardous Waste" may also be produced at the household level in addition to the above-mentioned wastes. These include used aerosol cans, household cleaners for the kitchen and drains, batteries, car batteries and car care products, cosmetics, pesticides insecticides and with a chemical base, light bulbs, tube lights, paint, oil, compact fluorescent lamps (CFL), and lubricants, as well as their empty containers. Waste that is toxic or could be damaging to human health or the environment is generally considered hazardous waste. Liquid, solid, gaseous, or sludge-based hazardous wastes are all possible. They could be abandoned commercial goods like insecticides or cleaning agents, or they could be leftovers from manufacturing processes. Liquid, solid, gaseous, or sludge-based hazardous wastes are all possible. They could be abandoned commercial goods like insecticides or cleaning agents, or they could be leftovers from manufacturing processes (Cruz *et al.*, 2010; McDougall *et al.*, 2001). And also waste can be classified on the basis of their Physical states-



WASTE MANAGEMENT

Waste from regular individuals can be disposed of using standard techniques. But waste disposal is turning into a major issue for all human habitations worldwide. The complexity of waste management increases with the level of human habitation. There is an ongoing quest for effective answers to this issue, but it is becoming clearer and clearer that these solutions cannot be sustained for very long without human participation, which only serves to complicate the situation further (Marchettini, *et al.*, 2007; Ghiani, *et al.*, 2014).

An organization's approach for disposing of, reducing, recycling, and preventing waste is called a waste management system. Recyclables, compost, waste to energy, landfills, incineration, bioremediation, and waste minimization are all potential waste disposal techniques. Solid and Liquid Waste Management (SLWM) is a fundamental component of the Swachh Bharat Mission (SBM) (G), which was started with the goal of improving cleanliness, hygiene, and overall quality of life. Each year, 62 million tonnes of waste are produced in India. A total of 43 million tonnes are collected (about 70%), of which 12 million are processed and 31 million are disposed in landfills. In 2030, it is predicted that metropolitan municipal solid trash generation will increase to 165 million tonnes due to changing consumption patterns and strong economic expansion. (Gollakota *et al.*, 2020; Liquid waste, 2020).

SOLID WASTE MANAGEMENT

Solid waste management is a distinct field concerned with the control of solid waste generation, storage, collection, transfer and transport, processing, and disposal in accordance with the principles of public health and environmental consideration. The best method to manage solid waste is to properly separate it into its component parts and then scientifically recycle each one of those parts (Robinson, 1998). Solid waste disposal out of sight does not alleviate the issue; rather, it only serves to amplify it more and, eventually, render it impossible for anybody to regulate. The negative effects of this practice, including health risks, pollution of the soil, water, air, and food supply, unfavorable environmental conditions, and the depletion of valuable resources that could have been recovered from solid waste, are well documented. Because of this, it is crucial to concentrate on proper waste management on a global scale. Concerns about waste management have grown both domestically and internationally (Tchobanoglous *et al.*, 1997).

Fig. 2: Door to door collection of solid waste and transporting to dump yard

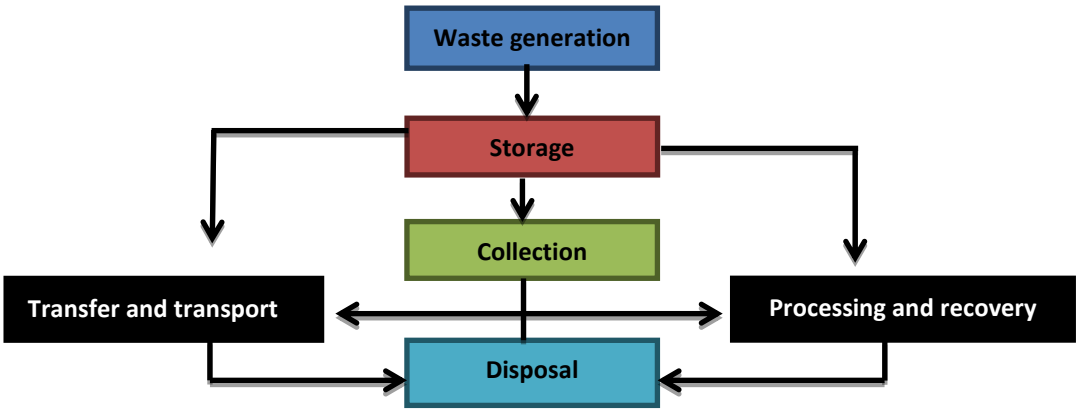


Fig. 3: Interrelationships of the functional aspects in a solid waste management system

FUNDAMENTALS OF SOLID WASTE MANAGEMENT

4-R: REFUSE, REDUCE, REUSE & RECYCLE

- Separation at the source: Separate containers should be used for organic or biodegradable and inorganic or non-biodegradable solid waste recycles all the parts with the least amount of work and expense.
- Different treatments for various solid waste types: One must use the methods that are appropriate for the specific type of waste. For instance, a technique that works for waste from general markets might not work for waste from slaughterhouses.

- Treatment at the closest location: The treatment of solid waste should be as decentralized as possible. The best place to treat the rubbish produced is at the source, which is each individual home.

LIQUID WASTE MANAGEMENT

Liquid waste is a significant area in waste management because it is so challenging to manage, Liquid wastes are more difficult to collect and remove from an environment than solid wastes are. Wastes in liquid form spread out and can quickly contaminate other liquid sources when they come into touch.

WASTEWATER TREATMENT

Fig. 4: Liquid Waste

It involves following process:

- Techniques for removing pollutants including metals, dissolved solids, and oils via physical and chemical treatment.
- Liquid Direct Injection technology that assists in the destruction of many different waste streams.
- Organizations with anaerobic digester facilities help convert organic waste streams into renewable energy.
- Products made from clean oil are gathered, sold, or reused.

Waste can be classified into three types: origin, destination, and content. The latter is further categorized as follows:

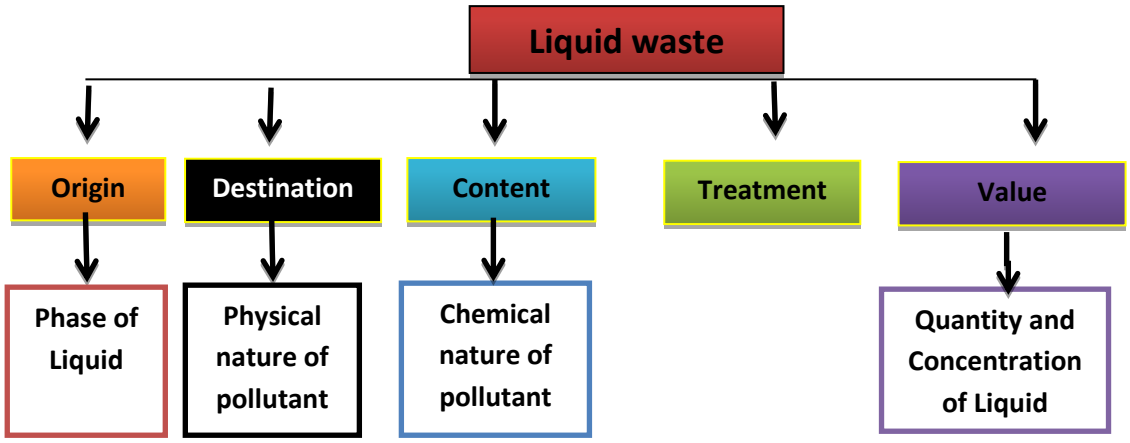


Fig. 5: Classification of Liquid Waste

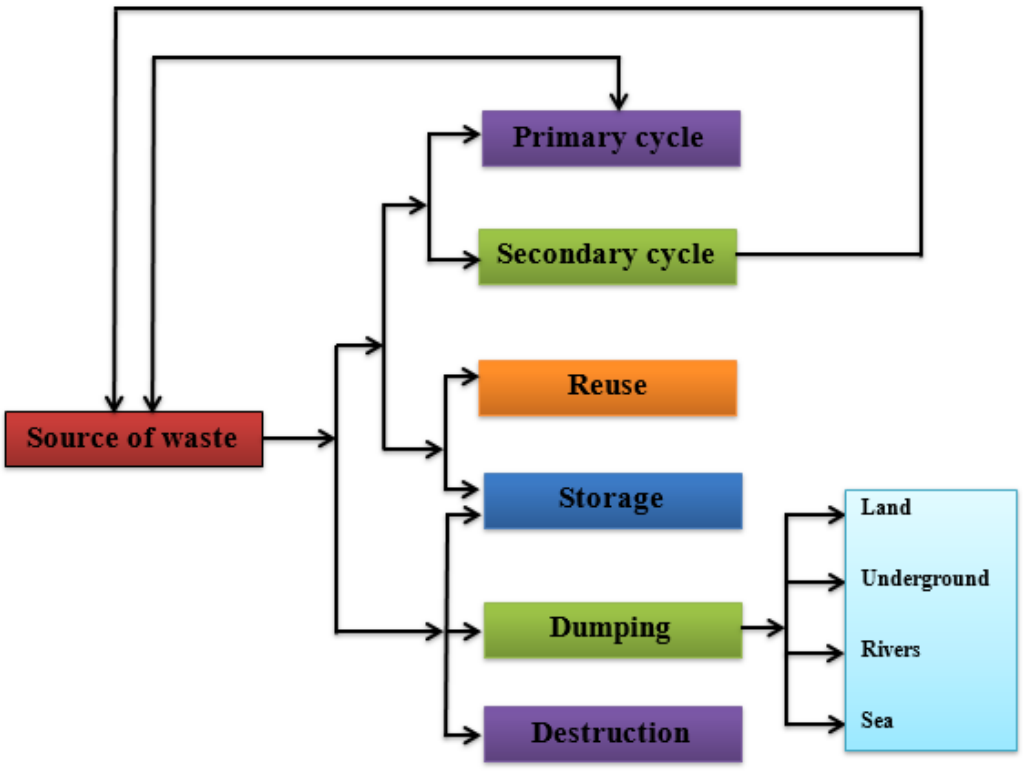


Fig. 6: Liquid waste classification according to destination

ORIGIN

It would seem unnecessary to categories wastes based on their origin as both the producer and the disposal contractor should be aware of where their waste is being collected. But it's possible that neither the producer nor the contractor is aware of the several options for treatment or disposal or of the potential worth of the trash if it's recycled or used again. Source or origin-based categorization by itself is not particularly useful unless it is connected to other classification strategies. As a result, it might serve as a helpful beginning point for a characterization scheme and a discussion of features, impacts, or treatment options (Stockholm, 1975; Degremont, 1973; Lund, 1971; Southgate, 1948; Linder, G. and Nyberg, K, 1973; Ciaccio L.L. 1971; Tomlinson, T.G. 1973). A thorough list of the most important sources organized by industrial type is provided below: Sewage metal manufacturing (including mining) treatment of metal, processing of meat, poultry, eggs, vegetables, food and a natural product Agricultural water and inorganic chemicals etc. When it comes to method of treatment, it is simple to separate this list into wastes typically treated by a biological system (starred) and others. As a result, the categorization becomes easier: This leads to a simpler classification:

- "Synthetic" organic wastes, which are generally not water-based,
- "Natural" organic wastes which are generally water-based, and
- "Inorganic" wastes water-based

DESTINATION-

The destination or treatment of wastes is much easier to evaluate and classify than its origin.

RECYCLING OF LIQUID WASTE

Recycling can provide the primary material for the waste producer to reuse, like electroplating salts from plating wastes, or a secondary substance that is linked, like metal or metal oxides for smelting back into metal from plating wastes. When used for a different purpose, a waste may be reused rather than recycled. For instance, waste solvents or lubricating lubricants may be burned for their heat content. However, it necessitates a thorough examination of sequential material flows across connected industries and understanding of marketing considerations. Additional sub-classification of primary and secondary recycle and reuse by industrial source could be made. Only very particular materials, like non-ferrous metals, can benefit from such an exercise.

DISPOSAL OF LIQUID WASTE

Liquid waste can be disposed of in a variety of ways, such as by dumping it on land, in rivers, or in the sea. However, in order to comply with regulations, some waste treatment may be required before disposal. Destruction, such as burning, is also included. Liquid wastes, such as solvents, are piled up until the process of recovery is feasible and practicable, at which point they are dumped for short-term future recovery. With the exception of radioactive liquid wastes, which are a special case, long-term storage has only been seriously suggested for solid wastes. (Bridgwalen and Gaskartn, 1974).

CONTENT

PHASE OF LIQUID:

Waste is often defined by its composition, and the dense literature on liquid waste is invariably related to the treatment of a particular waste, frequently by a particular method. Phase of liquid is the simplest and most evident way to classify something. Essentially, aqueous and non-aqueous liquid phases may be differentiated. These may occur together and hence forming a third, for instance, greasy waste water from the processing of petroleum and emulsions. This is a particularly useful initial screening test because it distinguishes between wastes that can safely have their main constituent, water, discharged (for example, to rivers), usually after the pollutant has been separated, and wastes that must be completely recycled or disposed of in another manner (Deposit of Poisonous Waste Act, 1972; Control of Pollution Act, 1974; Deposit of Poisonous Waste Act, 1972).

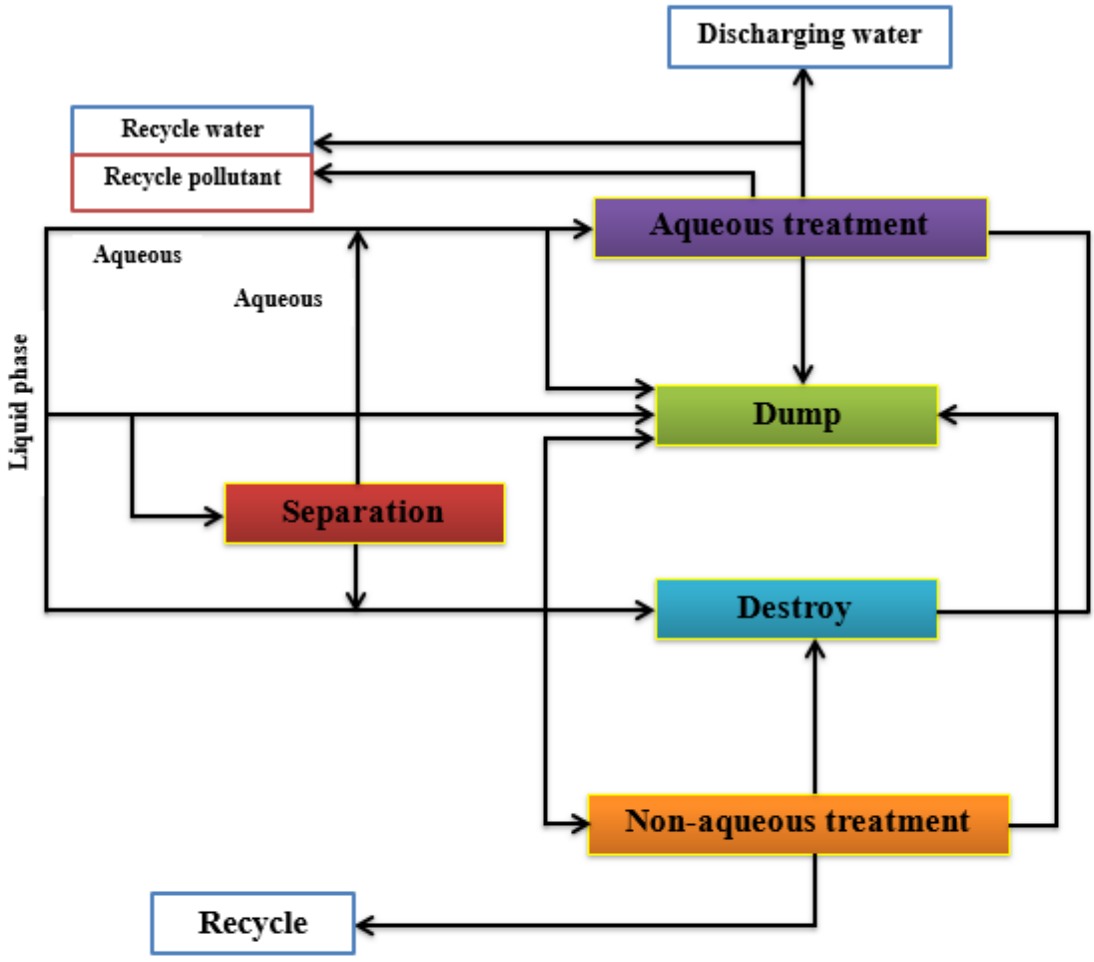


Fig. 7: Liquid Waste Classification according to Phase

PHYSICAL NATURE OF POLLUTANT

Phase-based classification distinguishes between effluents that are completely toxic (non-aqueous or "synthetic" organic wastes) and effluents that require pollutant removal or modification to become an aqueous liquid that is suitable for release. Other than what is necessary for safe handling and disposal, non-aqueous and mixed wastes don't require much identification before disposal.

TREATMENT-

This is the most typical system for categorizing waste. A series of procedures may be applied to the treatment of garbage for recycling or before disposal.

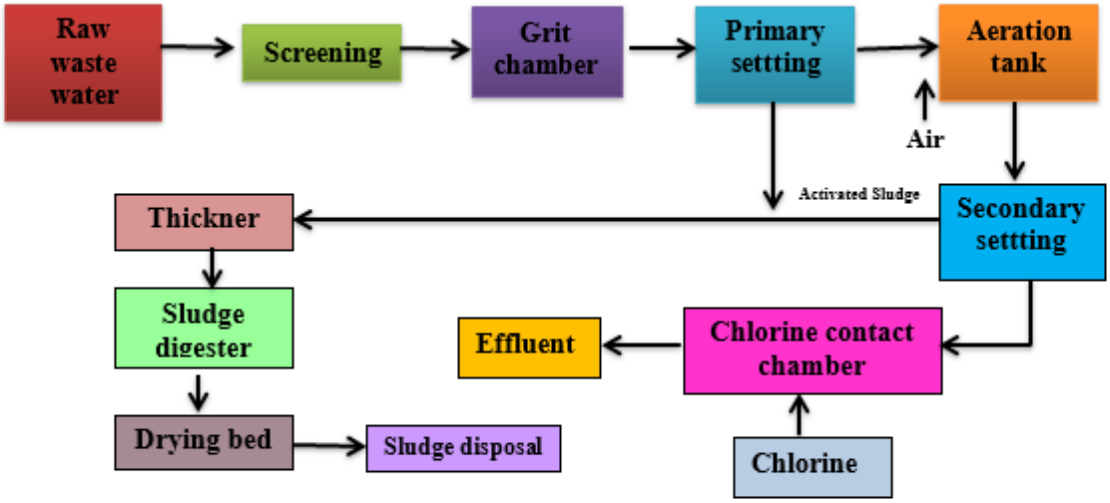


Fig. 8: Treatment of waste waster

VALUE:

A waste material's value can be calculated by multiplying its quantity by its concentration and then by the value of each recoverable component.

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Chapter
14

ADULTERATION IN DAIRY PRODUCTS, THEIR DETECTION TECHNIQUES AND ITS HARMFUL EFFECTS- AN OVERVIEW

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ABSTRACT

Dairy products are one of the essential food commodities and play a crucial role in the diet of human nutrition. The quality of milk has been one of the challenges in this country due to high ambient temperature and also due to man-made menace of adulteration as well as presence of contaminants. In the recent times, media has highlighted many instances of adulteration of milk and milk products with various kinds of adulterants. In general, every milk industry in India is facing problem of adulterated milk at reception dock. Therefore, milk collection centers needs simple tests for detection of adulteration. In this article, we have discussed the different adulterants present in the dairy products and their detection techniques.

KEYWORDS: Dairy, Milk, adulteration, detection.

INTRODUCTION

Milk is a nutrient – rich liquid food produced by the mammary glands of mammals. It is consumed by young mammals as well as every human being in the form of milk and also as dairy products. The practice of adulteration of milk reduces its quality and may affect the consumers health. Some substances such as water, foreign proteins, whey proteins, melamine, urea, sucrose, starch, glucose, hydrogen peroxide, maltodextrin, salt, neutralizers and vegetable fat or animal fat are added to milk and milk products as adulterants. Many methods have been developed for detection of milk adulteration in recent technology. Let us discuss about some of them in upcoming headings.

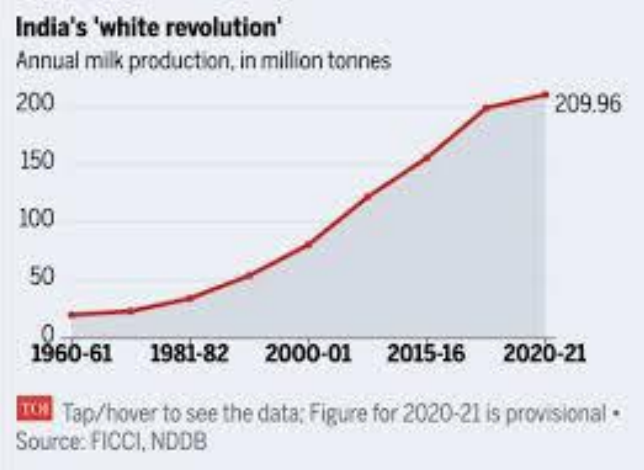

Fig. 1: Annual milk production in million tonnes at India

ADULTERATION IN MILK

There are many ways to adulterate the milk which affects the human health. The adulterants like detergents in milk, synthetic components, urea, caustic soda, formalin are added to milk for various reasons. Mainly adulteration is done to increase the carbohydrate content, density of milk and solid contents. Some of them are discussed below.

a. Table sugar is added as an adulterant to increase the carbohydrate content and density of milk.
b. Starch is added to increase the solid contents in milk.
c. Water is the common adulterant which is added to the milk. It increases the volume of milk in which the water added cannot be detected with a lactometer test.
d. Benzoic acid and Salicylic acid are added to the milk which increases the shelf life.
e. Formalin is added to preserve it for a long time.
f. Ammonium Sulphate is used to increase the density of milk which increases the lactometer reading.
g. Urea is added to the milk to increase the SNF (solid-not-fat) content and also whitens the milk.
h. Hydrogen Peroxide is added to the milk to increase the quality of milk and to prolongs the freshness of milk.
i. Maltodextrin is a common additive used in milk which increase the volume of milk and milk products.
j. Salt is added to milk to make up the density to prevent the detection of added water.

EFFECTS OF ADULTERATION

Sometimes, to make the milk thick, soap is added which leads to severe health issues related to stomach and kidney. Also formalin which is added for preservation is highly toxic and leaves a damaging effect on the liver and kidney. Mostly the adulterants added affect the kidney, sometimes causes gastrointestinal complications which leads to gastritis and inflammation. The adulterants like detergents, synthetic components, caustic soda, urea and formalin leads to

catastrophic effects on health if taken for a long time as it can cause severe health problems like food poisoning, impairments, heart problems, kidney problems, cancer and leads to death.

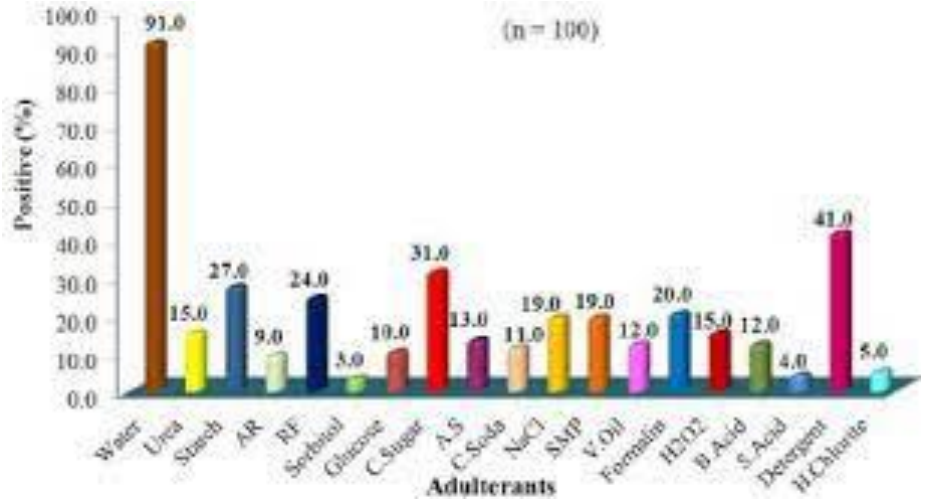

Fig. 2: Graph depicting the percentage of adulterants

DETECTION OF MILK ADULTERATION

There are various new techniques which involves in detecting the adulteration of milk. The detection techniques involve qualitative and quantitative methods in which qualitative detection of adulterants is easy to detect while quantitative detection of adulterants is a tedious process. NDRI is working proactively for developing various analytical techniques and simpler methodology for the detection of adulteration in milk and milk products. The practice of adulteration of milk is one of the vital problems that stands against the progress of dairying in India and may have detrimental effect on our export of dairy products. The image of milk has been considerably deteriorated due to its adulteration with harmful chemicals. With the analytical methods developed for most of the adulterants, unscrupulous traders are finding more innovative ways to adulterate the milk with cheaper ingredients. In the recent past, the menace of adulteration has taken serious proportion as highlighted by many media reports as well as by the report of FSSAI. Over the years, efforts have been made to develop simpler methods to detect adulteration of milk and milk products.

QUALITATIVE DETETCTION

Qualitative techniques are easy to detect the adulterants in milk which are simple color based chemical reactions. It can be performed in laboratory with the availability of chemical reagents and necessary precautions. This technique is very advantageous than quantitative techniques as it is simple, rapid and very easy to perform. The procedure for detecting the adulterants is given below.

Adulterant	**Procedure**	**Observation**
Sugar	Take 5 mL milk sample in a test tube. Add 1 mL conc. HCl and 0.1 g resorcinol solution. Place the test tube in water bath for 5 min.	Appearance of red color indicates he presence of added sugar.
Starch	Take 3 mL sample in a test tube. After boiling it thoroughly, cool it to room temperature. Add 1 drop of 1% iodine solution.	Appearance of blue color indicates he presence of starch.
Glucose	Take 1 ml of milk sample in a test tube. Add 1 ml of modified Barfoed's reagent. Heat the mixture for exact 3 min in a boiling water bath. Rapidly cool under tap water.	Immediate appearance of deep blue color indicates the presence of glucose.
	Add one ml of phosphomolybdic acid reagent to the turbid solution.	
Common salt	Take 5 ml of milk sample into a test tube. Add 1 ml of 0.1 N silver nitrate solution. Mix the content thoroughly and add 0.5 ml of 10% potassium chromate solution.	Appearance of yellow color indicates the presence of added salts, whereas, brick red color indicates the milk free from added salt.
Formalin	Take 10 mL milk sample in attest tube. Add 5 mL conc. sulfuric acid with a little amount of ferric chloride without shaking.	Appearance of violet or blue color at the junction of two liquid layers indicates the presence of formalin.
	Take about 5 ml of milk in a test tube. Take 1 ml of 10% ferric chloride solution in a 500 ml volumetric flask and make up the volume using concentrated hydrochloric acid. Add 5 mL from this solution to the sample in test tube. Keep the tube in boiling water bath for about 3-4 min.	Appearance of brownish pink color indicates the presence of formalin.

Urea	Take 5 mL milk sample in a test tube. Add equal volume of 24% TCA to precipitate fat and proteins of milk. Take 1 mL filtrate and add 0.5 mL 2% sodium hypochlorite, 0.5 mL 2% sodium hydroxide and add 0.5 mL 5% phenol solution, then mix.	A characteristic blue or bluish green colour develops in presence of added urea whereas pure milk remains colourless.
Benzoic and salicylic acid	Take 5 mL milk sample in a test tube. Upon acidification with sulfuric acid, 0.5% ferric chloride solution is added to it drop by drop. Mix it. Five ml of milk is taken in a test tube and acidified with concentrated sulphuric acid. 0.5% ferric chloride solution is added drop by drop and mixed well. Development of buff colour indicates presence of benzoic acid and violet colour indicates salicylic acid.	Appearance of buff color indicates the presence of benzoic acid whereas that of violet color indicates salicylic acid.
Detergent	Take 5 mL of milk sample into a 15 mL test tube. Add 1 ml of Methylene blue dye solution and 2 ml chloroform. Vortex the contents for about 15 sec and centrifuge at about 1100 rpm for 3 min.	Relatively, more intense blue color in lower layer indicates presence of detergent in milk. Relatively more intense blue color in upper layer indicates absence of detergent in milk

QUANTITATIVE DETECTION

Quantitative detection techniques are rapid, sensitive and accurate which is mostly used in developed countries as adulteration should not be done more than the permissible limit given by FSSAI. The type of detection techniques depends on the nature of adulterants added to milk. Some of the detection techniques are listed below.

a) Soy proteins, rice and almond proteins are intentionally added to the milk products and supplied for consumers with lactose tolerance. Soy, wheat and almond proteins are labeled as allergens by Food Allergen Labeling and Consumer Protection (FALCPA) of 2004 whereas pea, rice, lupin and maize proteins are recognized as allergens. Soy protein is cheaper than milk protein so the manufacturers adulterate the milk with soy proteins.
b) The soy milk detection in milk is detected by polarimetric method, isometric precipitation, Sodium Doecyl Sulphate Polycrylamide Gel electrophoresis (SDS-PAGE), High Performance Liquid Chromatography (HPLC) and immunodiffusion method. The soy milk is 70% cheaper than normal milk so it is used as an adulterant.
c) Milk powder adulterated with vegetable protein is detected by Near Infra Red (NIR) spectroscopy.

d) Pasteurized milk powders adulterated with soy and wheat proteins is detected by using ELISA with polyconal antibodies.

e) Skimmed milk powder adulterated with soy, brown rice and hydrolyzed wheat protein has been detected by using Ultra High Performance Liquid Chromatography (UHPLC).

ADULTERATION IN MILK AND MILK PRODUCTS

Products	Adulterants	Procedure
Ghee	Vegetable oil	Take a sample of ghee and add trichloro-methyl in it. Mix it well followed by addition of the acetic anhydride and then-after heat the mixture. The melting point of the unadulterated ghee is 114-115^{0}F while that of adulterated ghee is 117^{0}F.
	Sesame oil	For this Baudouin test has been carried out. Take a ghee sample and add 2ml of furfural solution in alcohol and HCl(5ml) in it. The crimson red color (after 5 minutes) indicates the presence of the hydrogenated oil (sesame oil) in the ghee. It is helpful in differentiating between desi ghee and vanaspati ghee. The vanaspati ghee contains 5% sesame oil. Pure ghee not contains sesame oil.
	Animal fat	Take the sample of ghee and add a mixture of alcohol and acetate as reagent and heat the mixture. The slight deposition of the crystals at the bottom of the test tube indicates the presence of the mutton or beef fat in the ghee.
Butter		Take some water/oil in a transparent glass bowl.Add ½ teaspoon of butter to it. Add 2-3 drops of iodine solution to the bowl.If the butter is unadulterated, no colour change will be observed in the solution.The solution with adulterated butter will change its colour to blue.

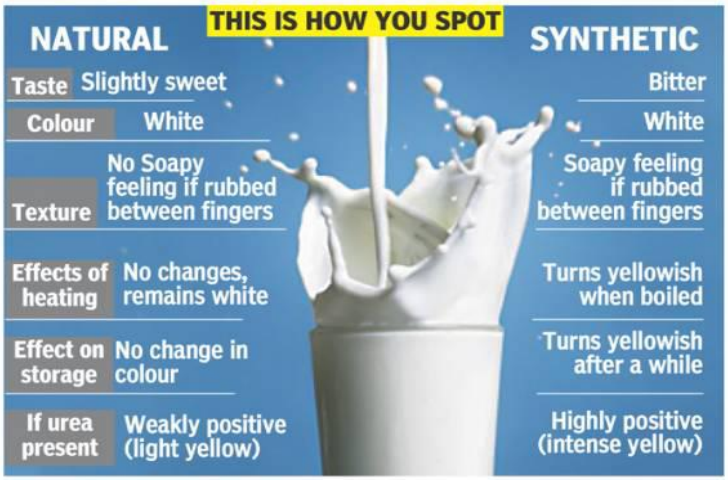

Fig. 3: Picture depicting the adulteration spot in milk

ADULTRATION AND ITS HARMFULNESS

Adulterant	Purpose	Damages
Water	Increase the volume of milk	Decreases the nutritive value of milk; poses health risk especially to infants and children.
Starch	Increase the quantity and to maintain SNF values in synthetic milk.	Can cause diarrhea due to the effects of undigested starch in colon. Its accumulation in the body may prove fatal for diabetic patients.
Detergents	Increase the foaming of milk to give it whiteness & thickness.	Causes Gastro- intestinal & Kidney complications.
Urea	Provide whiteness; increase the consistency of milk and for improving the solid-not-fat(SNF)% to imitate natural milk.	Overburdens the kidneys and can even cause kidney failure
Ammonium Sulphate	Increase the lactometer reading of milk by maintaining its density	Can cause irritation in the gastro-intestinal tract like nausea, vomiting & diarrhea. Although it isn't toxic unless consumed in large quantities. It is also a neurotoxin, i.e. it can cause confusion and behavioral changes.
Carbonates and bicarbonates	Mask the pH and acidity values of badly preserved milk to pass it off as fresh milk	Can cause disruption in hormone signaling that regulate development and reproduction.
Benzoic acid and Salicylic acid	Increase its shelf life for long distance transport etc.,	Linked to Asthma problems and increased levels of Hyperactivity in children.
Formalin	Increase its shelf life for long distance transport etc.	Causes liver and kidney damage, as it is highly toxic.

CONCLUSION

Money is considered as one of the reasons for adulteration and also inadequate supply of milk to the humans has lead to adulteration. Major adulterants and their detection methods are discussed as qualitative techniques which can be done in laboratory level whereas rapid and sensitive detection methods like ELISA, HPLC, etc., are discussed as quantitative techniques which are mainly done in developed and developing countries. Awareness about adulteration should be taught among the consumers in which this issue can be solved.

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Chapter
15

TYPES AND IMPORTANCE OF NATURAL PRODUCTS

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ABSTRACT

Plants are responsible for the production of a vast array of natural goods that can take on a variety of forms. In contrast to "primary metabolites," which are necessary for the growth and development of plants, these by products are referred to as "secondary metabolites," which is a frequent phrase. In the past, secondary metabolites were considered to be "waste products" because there was no accepted physiological role for them in the plant. However, with the advent of the discipline of chemical ecology approximately 30 years ago, it became clear that these naturally occurring compounds serve crucial functions in the interaction that takes place between plants and the biotic and abiotic environment in which they are located. They may, for instance, function as hormones or signal molecules; as defence compounds against herbivores and pathogens; as flower pigments that attract pollinators; or as floral pigments that attract pollinators. Natural products, in addition to serving a physiological purpose in plants, have a significant impact on human culture and have been utilised as seasonings, colours, and medicines for the entirety of human history.

This chapter provides a general introduction to the primary and secondary metabolites that are abundant in plants, as well as the natural compounds produced by bacteria. Natural products derived from fungi and animals each have a wide variety of biological functions and a complex cultural history. Because more than 200,000 different structures of natural products derived from plants are already known, we will only give a selection of categories and compounds.

KEYWORDS: Metabolites, Natural Products, Biological functions, Biotic and Abiotic.

INTRODUCTION

What exactly does the phrase "natural product chemistry" refer to, and why should we be interested in obtaining a deeper understanding of this topic in general? Anything that is manufactured by life can be considered a natural product, and this includes biological materials (such as wood and silk), bio-based materials (such as bioplastics and cornstarch), bodily fluids (such as milk and plant exudates), and other natural materials that were once found in living organisms. Other natural materials that were once found in living organisms include things like cornstarch and bioplastics. The most all-encompassing definition of a natural product is anything that can be attributed to the activity of living things (e.g. soil, coal). A natural product can be thought of as any organic compound that is produced by a living organism. This is one definition of the term. The phrase "natural product" is subject to more strict standards after the adoption of this definition.

Because of natural selection and evolutionary processes that have formed their value over hundreds of thousands of years, natural goods have a high structural diversity and distinctive pharmacological or biological activity. In reality, the structural diversity of natural compounds much exceeds the capability of laboratory-based synthetic organic chemists. As a result, natural products have been used to treat ailments in both traditional and modern medicine. Natural products are frequently utilised as beginning points for medication discovery, with synthetic modifications added to assist reduce adverse effects and boost bioavailability. In fact, natural goods are the inspiration for over half of all FDA-approved medications in the United States. Natural goods and their derivatives are often employed as food additives in the form of spices and herbs, antibacterial agents, and antioxidants to safeguard food freshness and longevity, in addition to medicine. In fact, natural organic items can be found in practically every aspect of our life, from the clothes we wear to plastics and rubber products, health and beauty products, and even the energy we use to power our cars. Natural products can be classed based on their biological function, metabolic process, or origin.

When it comes to the treatment of infectious diseases, bioactive natural products (NPs) and the semisynthetic derivatives of those NPs have traditionally been an unrivalled source of potential therapeutic agents. In point of fact, nearly 80 percent of the antibiotics currently available for use in clinical settings are derived directly (or indirectly) from NPs [1]. This success was achieved by capitalising on the enhanced properties of small molecules that are produced by microorganisms, specifically their extensive chemical diversity, intrinsic cell permeability, and target specificity as compared to those typically reflected in combinatorial or synthetic libraries. NPs are a reflection of a reservoir of privileged chemical scaffolds that have been naturally selected by microbes to specifically interact with a diversity of biological targets in the environment. This provides an advantage to the fitness of the organism that is producing the NPs by increasing the organism's ability to reproduce. Because of the selectivity with which they interact with their targets and the inherent pharmacological qualities they possess, naturally generated small molecules are also useful as beginning points in the development of new drugs. While the discovery of antibacterial agents has led to the development of more than a dozen unique and clinically relevant chemical scaffolds [2], all of which are derived from natural sources with the exception of oxazolidinones, quinolones, and sulfonamides, the diversity of antifungal agents is noticeably more limited and is only represented by three structural classes. Two of these structural classes, polyenes and echinocandins, are naturally [3].

NATURAL PRODUCT FUNCTION

Natural products are frequently classified into two categories: primary and secondary metabolites. Primary metabolites are organic compounds with an inherent function critical to the survival of the organism that creates them (i.e., the organism would die without these metabolites). The essential building block molecules (nucleic acids, amino acids, sugars, and fatty acids) required to produce the key macromolecules (DNA, RNA, proteins, carbs, and lipids) responsible for life are examples of primary metabolites. Secondary metabolites, on the other hand, are organic substances with an extrinsic function that primarily affects species other

than the producer. Secondary metabolites are not required for survival, but they do improve the organism's competitiveness in its environment.

Natural products, particularly in organic chemistry, are frequently characterised as primary and secondary metabolites. Within the domains of medicinal chemistry and pharmacognosy, the study and application of natural products in medicine, a narrower definition limiting natural products to secondary metabolites is widely utilised.

PRIMARY METABOLITES

Primary metabolites are components of basic metabolic pathways that are required for life. They are associated with essential cellular functions such as nutrient assimilation, energy production, and growth/development. They have a wide species distribution that span many phyla and frequently more than one kingdom. Primary metabolites include the building blocks required to make the four major macromolecules within the body: carbohydrates, lipids, proteins, and nucleic acids (DNA and RNA).

These are large polymers of the body that are built up from repeating smaller monomer units (Fig.-1). The monomer units for building the nucleic acids, DNA and RNA, are the nucleotide bases, whereas the monomers for proteins are amino acids, for carbohydrates are sugar residues, and for lipids are fatty acids or acetyl groups.

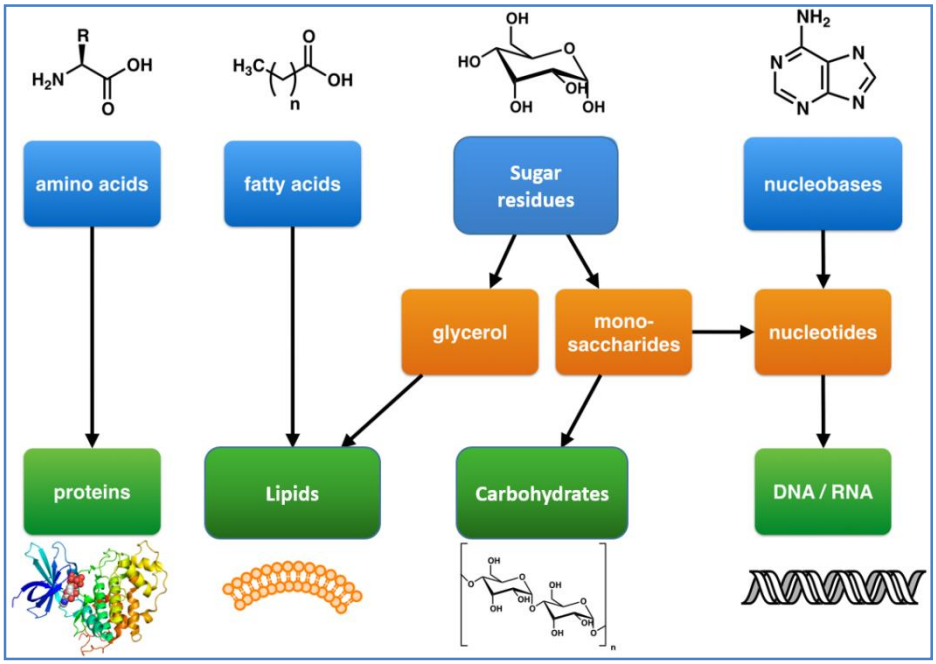

Fig. 1: The Molecular building blocks of life are made from organic compounds

Numerous enzymes are among the primary metabolites that are engaged in the process of producing energy. These enzymes are responsible for breaking down food molecules, such as carbohydrates and lipids, and capturing the energy that is produced in the form of molecules of adenosine triphosphate (ATP). The pace at which chemical reactions occur can be sped up with the help of biological catalysts known as enzymes. Typically, these are proteins, which are made up of the fundamental components known as amino acids. Primary metabolites are also responsible for the construction of the fundamental framework of cells and organisms. These

components include phospholipids, which are found in cell membranes, peptidoglycan, which is found in cell walls, and chitin, which is found in cytoskeletons (proteins). Nucleic acid primary metabolites are the building blocks of DNA and RNA, the two molecules responsible for storing and transmitting genetic information. The term "primary metabolites" refers to molecules that are also engaged in the transport, communication, and signalling processes of cells.

SECONDARY METABOLITES

In contrast to primary metabolites, secondary metabolites are not necessary for an organism's continued existence and can be eliminated if necessary. In addition to this, the species distribution of secondary metabolites is often somewhat limited. The deadly nightshade, also known as Atropa belladonna, is an example of a plant species that is capable of producing lethal hallucinogenic compounds, such as scopolamine, while other plant species are unable to do so. To this day, there have been hundreds of thousands, if not millions, of secondary metabolites found.

The tasks that are performed by secondary metabolites are extremely diverse. These include pheromones, which are molecules that act as social signalling agents with other individuals of the same species; other communication molecules, which attract and activate symbiotic organisms; siderophores, which are agents that solubilize and transport nutrients; and competitive weapons, which include things like repellants, venoms, and toxins, which are used against competitors, prey, and predators. There are a lot of different secondary metabolites whose functions are a mystery. One possible explanation is that they provide the organism that makes them with a strategic advantage in the marketplace. A different point of view contends that, in comparison to the immune system, these secondary metabolites do not serve a particular purpose; however, it is essential to have the machinery in place to be able to synthesise a variety of chemical structures. Because of this, only a few secondary metabolites are created, and these are the ones that are prioritised for selection based on what the organism is subjected to throughout its lifetime.

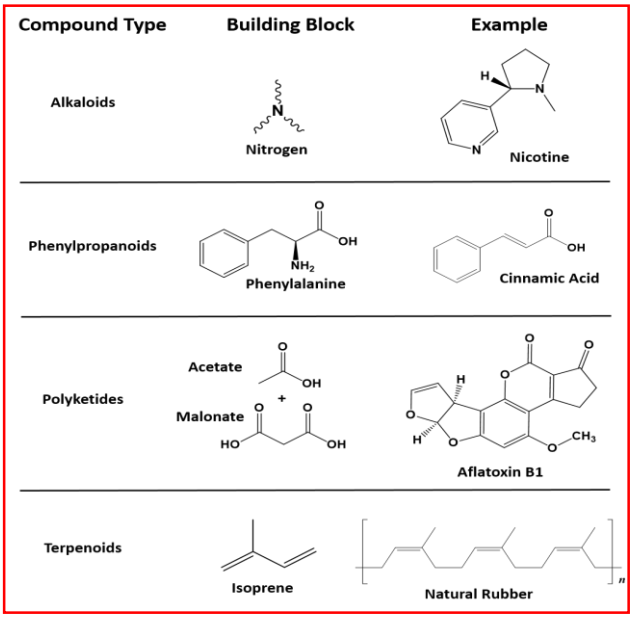

Fig.2: Representative examples of each of the major classes of secondary metabolites

WHERE DO WE FIND NATURAL PRODUCTS?

Cells, tissues, and even the secretions of microorganisms, plants, and animals can all be mined for their potential to provide natural products. A crude extract, also known as an unfractionated extract, can come from any of these many sources, and it will contain a wide variety of structurally distinct and frequently unique chemical components. Researchers have to go to great lengths to collect samples from all over the world so that they can study and evaluate them using drug discovery screens or bioassays. Chemical variety in nature is dependent on biological diversity. Bioprospecting is the term used to describe the process of looking for natural products.

The study of natural products having biological activity is known as pharmacognosy, and this field of research gives the tools necessary to recognise, choose, and process natural products that are destined for use in therapeutic applications. Typically, a natural extract possesses some form of biological activity that can be identified and ascribed to either a single chemical or a series of related compounds that were created by the organism. This type of activity can be discovered and assigned. These active chemicals may be utilised in medication discovery and development either in their natural state or after undergoing synthetic modifications to improve their biological capabilities or lessen the severity of their adverse effects. The following provides some examples of biological sources that are utilised in the discovery of new natural products.

PROKARYOTIC ORGANISMS

A prokaryote is a unicellular organism that does not have a membrane-bound nucleus (karyon), mitochondria, or any other membrane-bound organelle. Prokaryotes are classified as prokaryotes. The term "prokaryote" originates from the Greek words "pro" (meaning "before") and "karyon," which means "nut" or "kernel." Archaea and Bacteria are the two different domains that can be used to classify prokaryotes. In contrast, organisms that have nuclei and organelles, such as animals, plants, fungi, and protists, are classified as members of the domain Eukaryota.

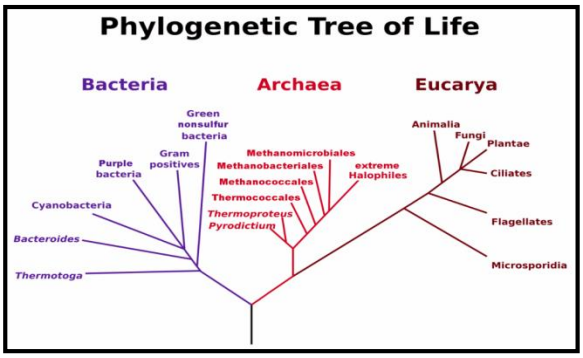

Fig. 3: Phylogenetic Tree of Life Based on Genetic Sequencing of Ribosomal RNA

In the prokaryotes, all the internal water-soluble components proteins, DNA and metabolites) are contained together in the cytoplasm enclosed by the cell membrane, rather than in discrete cellular compartments. Eukaryotic cells are significantly larger in size compared to their prokaryotic counterparts.

BACTERIA

Bacteria are typically quite small, measuring just a few micrometres in length, and can take on a variety of shapes, including spheres, rods, and spirals. Bacteria were among the earliest forms of life

to emerge on Earth and may be found in virtually every environment on the planet. Bacteria can be found in a variety of environments, including radioactive waste, acidic hot springs, radioactive waste, soil, and water. In addition, bacteria can coexist alongside plants and animals in mutually beneficial or mutually destructive ways. The vast majority of bacterial species have not been characterised, and only about half of the phyla that make up bacteria have species that can be cultured in the lab. Bacteriology is a subfield of microbiology that focuses specifically on the investigation of bacteria. In general, one millilitre of fresh water has one million bacterial cells, while one milligrams of dirt contain approximately 40 million bacterial cells. Bacteria are a significant contributor to the production of natural products. The diagram labelled "Figure 6.4" provides a few examples of bacterial natural products that have had an effect on our society, including various antibiotics.

The accidental discovery of penicillin and its subsequent success in clinical trials sparked a widespread hunt for other environmental bacteria that might create anti-infective natural compounds. This hunt is still ongoing. It was determined that bacteria, and not simply fungi, are a significant source of antibacterial natural products after collecting soil and water samples from all over the world. This led to the discovery of streptomycin, which was obtained from the bacterium known as Streptomyces griseus. This, in turn, led to the development of an astonishing arsenal of antibacterial and antifungal medicines, such as amphotericin B, chloramphenicol, erythromycin, neomycin B, daptomycin, and tetracycline (all from Streptomyces spp.), the polymyxins (from Paenibacillus polymyxa), and the Rifamycins (from Amycolatopsis rifamycinica).

In spite of the fact that the vast majority of antibiotics are generated from bacteria, several of these medications have found applications in other areas of medical practise. Examples include botulinum toxin, which is produced by Clostridium botulinum, and bleomycin, which is produced by Streptomyces verticillus. Botulism, often known as botulism food poisoning, is caused by a neurotoxin called botulinum toxin (Fig- 4). The bacterium Clostridium botulinum, which can grow in canned meats and other preserved foods if they are not adequately sterilised, is the culprit behind this condition. The severity of the poisoning is directly proportional to the amount of the toxic substance that was consumed. It can lead to paralysis and weakening in the muscles. This toxin is now employed in the cosmetics industry to help decrease the appearance of wrinkles on the face. It is injected in very low doses into specific locations, like as the forehead, to cause paralysis in the muscles that are responsible for wrinkle formation. Additionally, the glycopeptide bleomycin is employed in the treatment of a variety of cancers, including but not limited to Hodgkin's lymphoma, cancer of the head and neck, and testicular cancer. The metabolic profiling and isolation of natural products from novel bacterial species that are found in underexplored habitats are two of the more recent advancements in this sector of the industry. Examples of this include the identification of secondary metabolites produced by endophytes or symbionts. Symbionts are creatures that live in intimate relationship with another organism, known as a host, that is often much larger than themselves. At least a portion of a plant's life cycle is spent in association with endophytes, which are beneficial symbionts that live inside of plants. In addition, the finding of species that live in tropical conditions, subterranean bacteria that were located deep underground by mining or drilling, and marine bacteria continue to add to the complexity of secondary metabolites that have been uncovered.

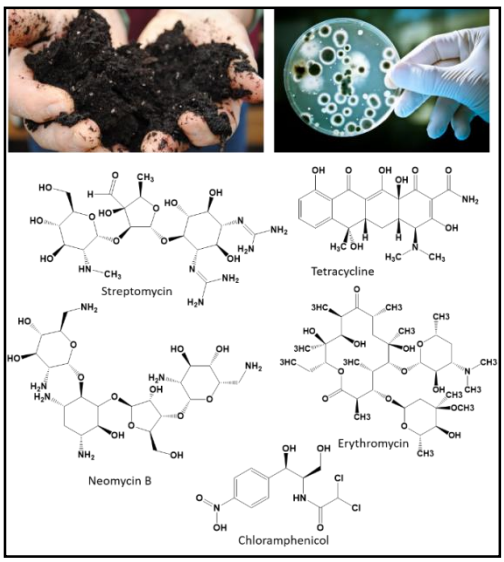

Figure 4: Bacteria isolated from soil are prolific producers of antibacterial compounds. Soil photo by: Pam Dumas. Available at: Flicker, Soil bacteria photo by: Alexander Raths

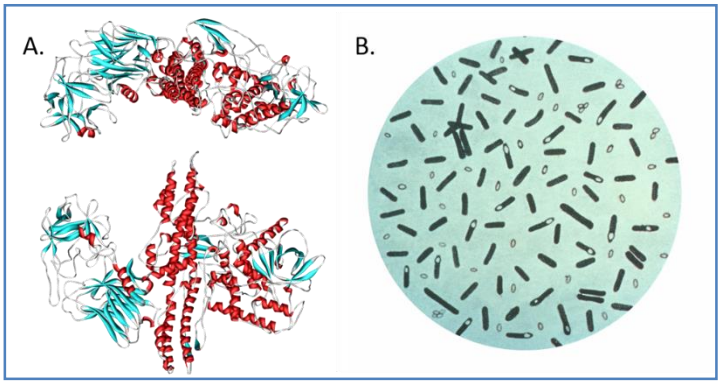

Fig. 5: Botulinum toxin. (A) Diagram of botulinum toxin A. Consuming food products tainted with the neurotoxin produced by (B) the bacterium Clostridium botulinum can cause paralysis and death

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ARCHAEA

The researchers Carl Woese and George E. Fox made the discovery of organisms that are now designated as Archaea in 1977. This discovery is considered to be relatively recent in the annals of human history. A different branch of ancient prokaryotic creatures separated at an early period in the history of life on Earth, as demonstrated through the use of genetic sequencing to establish that this event occurred. Therefore, based on these genetic differences, Woese proposed classifying prokaryotic species into two primary groups: bacteria and archaea. It is interesting to note that many Archaea have evolved to life in harsh settings such as the polar regions, hot springs, acidic springs, alkaline springs, salt lakes, and the tremendous pressure of deep ocean water. This ability allows them to survive in a wide variety of environments. Extremophiles is another name for these particular Archaea species.

Before Woese and Fox made their finding, scientists believed that prokaryotic extremophiles were bacteria that had descended from more common bacterial species that are more familiar to us. Now, there is evidence to imply that these lifeforms have been there for a very long time, and they may have strong evolutionary ties to early life forms that were on Earth. The research that Woese conducted on Archaea is crucial because of the implications it has for the hunt for life on other planets. Extremophiles may be hardy enough to survive in the harsh circumstances that are found on faraway worlds. Due to the fact that many archaea have adapted to living in harsh settings, they also possess enzymes that are active under conditions that are relatively rare. Because biotechnological processes commonly entail high temperatures, extremes of pH, high salt concentrations, and/or high pressure, these enzymes may find use in the food, chemical, and pharmaceutical industries. For instance, Pyrococcus furiosus is an archaeal species that thrives in extremely harsh environments (Fig. 6.6). Because it grows best in extremely high temperatures, which are significantly higher than the temperatures that are preferred by thermophiles, it can be categorised as a hyperthermophile. It is renowned for having a growth temperature that is optimal for boiling water, which is 100 degrees Celsius (a temperature that would destroy most living organisms). Recently, the research group led by Dr. Tang was successful in isolating a thermostable enzyme from this species that is capable of breaking down lactose, a disaccharide sugar that can be found in milk (Fig. 6.6). People who suffer from lactose intolerance are more likely to avoid dairy products because the condition causes digestive problems and prompts them to steer clear of dairy altogether. Because milk is the primary source of both calcium and vitamin D, individuals who are lactose intolerant frequently do not consume appropriate amounts of both nutrients, which can lead to unfavourable effects in terms of their health. Lactose-free milk can be produced, but doing so

necessitates the use of lactase derived from microorganisms, and it also raises the risk of contamination. Nevertheless, this method offers a viable solution to the issue. This problem can be solved by using thermostable lactase enzymes, which continue to do their job even after being subjected to the conditions of pasteurisation. Initial investigations of this enzyme indicate that it reaches its maximum level of activity at 100 degrees Celsius and that it can remain active even when subjected to temperatures of 110 degrees Celsius (Fig-6).

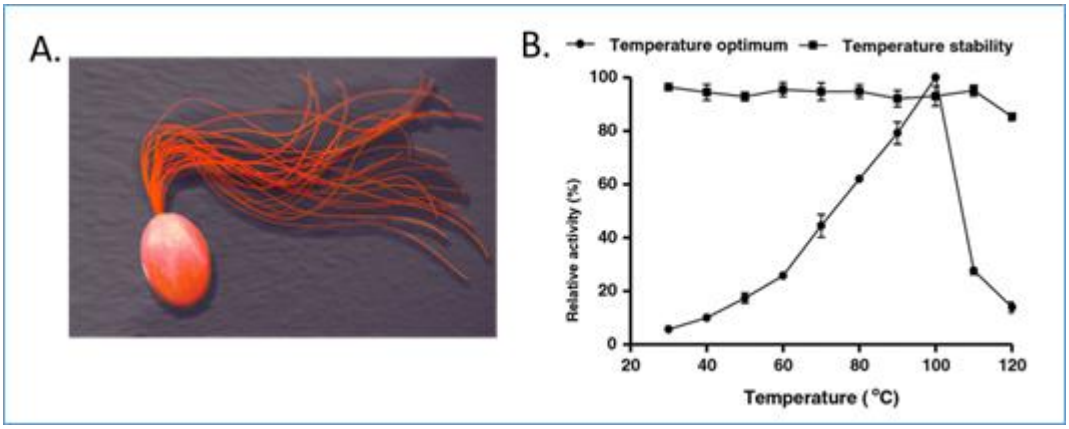


Fig. 6: The Extremophile Pyrococcus furiosus. (A) Shows a computer recreation of P.furiosus (B) Shows the effects of temperature on the stability of the lactase enzyme, β-glucosidase. (A) Recreation of P. furiosus by: Fulvio314
(B) Effects of temperature figure on P.furiosus lactase activity and text adapted from: Li, *et al.*, (2013) BMC Biotechnol. 13:73.

EUKARYOTIC ORGANISMS

The Protista, Fungi, Plantae, and Animalia are the four primary kingdoms that are comprised of eukaryotic creatures (Fig -7). Fungi are eukaryotic creatures that can be either single-celled or multicellular and are mostly responsible for decomposition in their surrounding environment. Fungi are heterotrophic. Heterotrophs are organisms that are unable to manufacture their own nourishment and must rely on external sources instead. Autotrophic, or the ability to produce one's own sustenance, is a characteristic shared by multicellular eukaryotic creatures, such as plants. In addition to this, plants are distinguished by the presence of real roots, stalks, and leaves. Animals are multicellular, eukaryotic, heterotrophic organisms that are distinguished by their ability to move at some point throughout their lives. It is common practise to refer to all eurkaryotic creatures that do not belong in the kingdoms of Fungi, Plantae, or Animalia as Protista (or occasionally Protoctista), a term that can also be used interchangeably. On the other hand, this classification is not perfect because it lumps together protists that have characteristics similar to animals, plants, and fungi under the same heading. Instead of using the more traditional protist categorization, several researchers find that it is more useful to categorise the protist kingdom into subgroupings of similar organisms based on phylogenetic data. In point of fact, the evolutionary categorization of Kingdom Protista given by Carl Woese divides the kingdom's inhabitants into three distinct primary classes: the ciliates, the flagellates, and the microsporidia (Fig-3). In the following part of this article, we are going to concentrate on some natural product examples derived from the kingdoms of fungi, plants, and animals. Bear in mind, however, that a great many protists are also important producers of a wide variety of fascinating natural products.

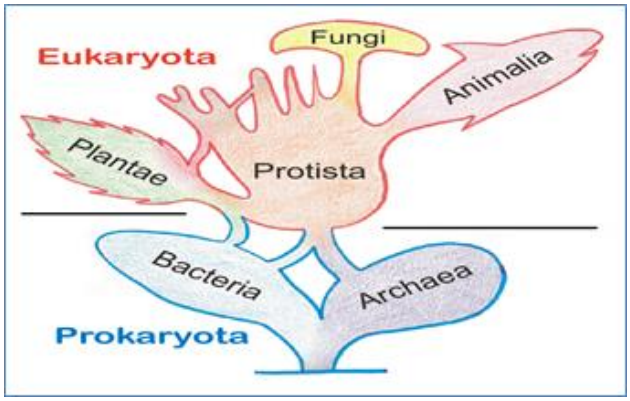
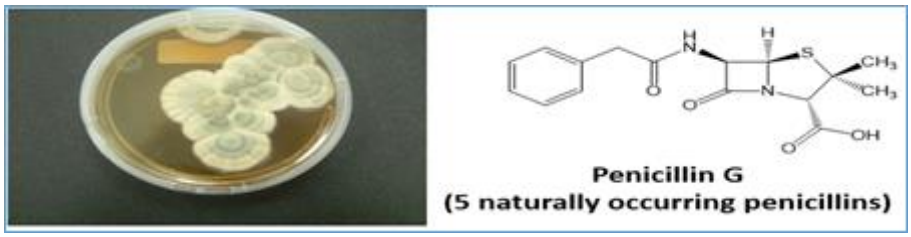


Fig. 7: Major Domains and Kingdoms of Life

FUNGI

As was discussed before, fungi are eukaryotic creatures that are heterotrophic and largely function as decomposers in their surrounding environment. They range from single-celled organisms like yeast and mould to multicellular species with fruiting bodies like mushrooms. Yeast and mould are examples of unicellular organisms. Fungi are responsible for the production of a diverse array of secondary natural products. Some of them are extremely poisonous, which is how they got their popular names like "death cap," "destruction angel," and "fool's mushroom." Others have discovered that medicine can be of tremendous benefit. For instance, several anti-infective medications have been derived from fungi. These include the penicillins, the cephalosporins, and griseofulvin. The penicillins are antibacterial drugs derived from Penicillium chrysogenum, and the cephalosporins are antibacterial drugs derived from Cephalosporium acremonium (Fig-8, parts A-C). Another medicinally helpful fungal metabolite is lovastatin, which comes from the fungus Aspergillus terreus. Lovastatin was the lead for the statins, which are a group of medications that are typically utilised to bring cholesterol levels down (Fig-8, part D).



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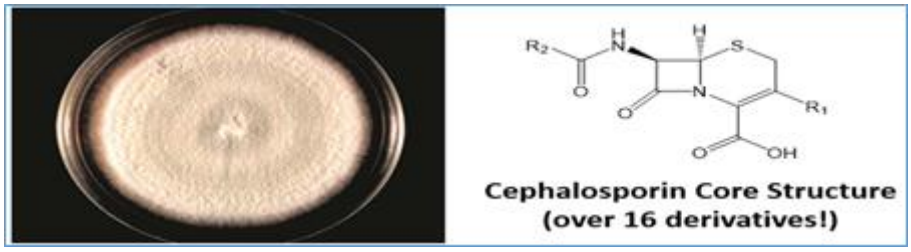

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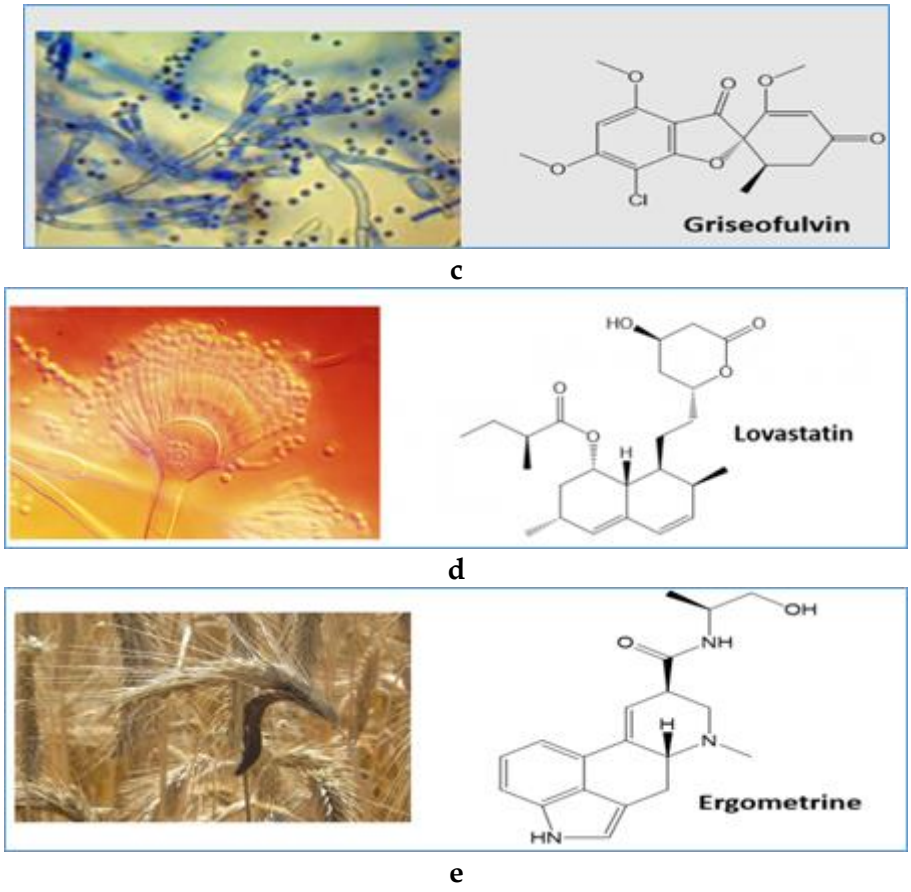


Fig. 8: Examples of fungal secondary metabolites.

Ergometrine, which comes from the genus Claviceps, is a vasoconstrictor and is used immediately upon childbirth to stop any bleeding that may occur (Fig -8, part E). The snapshot of Claviceps spp. shows that this species of fungi typically grows on grain crops like wheat and barley. You will notice this fact when you examine the photograph. If large numbers of these fungi are consumed by humans, it is possible that they could become poisoned as a result of the contamination of grain crops by these fungus. Ergotism is the medical term for this form of poisoning, which can result in convulsions. Ergometrine's vasoconstrictive actions can potentially lead to gangrenous side effects if the drug is consumed in such quantities to be considered hazardous. The first areas to be impacted are the distal parts, such as the fingers and toes that have a less developed circulatory system. This can lead to a loss of feeling in the periphery, as well as edoema, and, ultimately, the death and loss of the affected tissues.

Cyclosporin is yet another incredible example of a fungal metabolite that has significant consequences for medicinal practise. A cyclic peptide structure is formed by the assembly of amino acid building blocks to produce the alkaloid known as cyclosporin (Fig-9). The primary biological effect it has is to dampen the activity of the immune system. As a result, it is a common medication provided to patients after organ transplants in order to assist in lowering the risk of the transplanted organ being rejected. Tolypocladium inflatum was the source of the fungus that led to the discovery of cyclosporin in 1971. (Fig-9). In 1983, following a period of twelve years during which it was investigated in laboratories and tested in clinical settings, the FDA gave their blessing for it to be used. It is considered one of the drugs that are the most efficient as well as safe to use, which is why

the World Health Organization included it on their list of essential medicines. Notably, T. inflatum is the asexual, single-celled form of a fungus that can also take on a sexually reproducing multicellular life stage, in which it is known as the fungi Cordyceps subsessilis. In this sexually reproducing life stage, the fungus is known as Cordyceps subsessilis (Fig-9). The fact that cyclosporin can only be produced while the organism is in its asexual life stage is evidence that the expression of genes can change dramatically within an organism depending on the organism's life stage or on other factors that are present in the environment in which the organism is found.

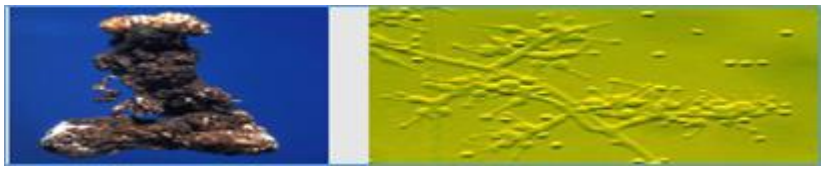
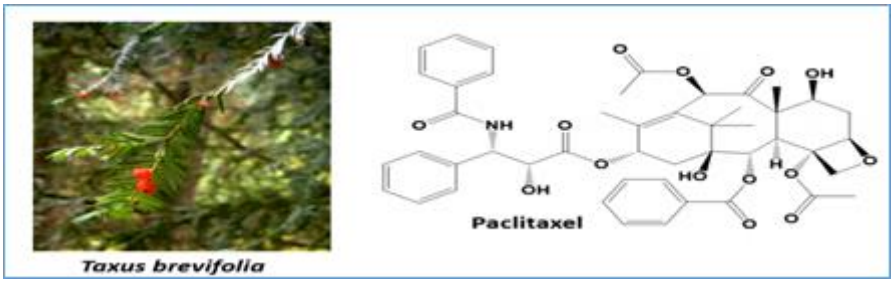


Fig. 9: Fungal Production of Cyclosporin.
(A) Multicellular life-stage of the fungus, known as Cordyceps subsessilis,
(B) Unicellular life-stage of the fungus, known as *Tolypocladium inflatum*

PLANTS

The term "plant" refers to multicellular, eukaryotic organisms that are capable of autotrophy, or the ability to produce their own food. These life forms are categorised into the "Kingdom of Plants." They do this using a process known as photosynthesis, which involves utilising the light energy provided by the sun to convert carbon dioxide and water into simple sugars. This process allows them to manufacture their own food. Oxygen is produced as a by-product when this reaction is carried out. As a result, plants constitute a significant portion of the oxygen supply on the globe. There are probably between 250,000 and 300,000 unique species of plants on this planet, according to some estimates. Plants are a key source of secondary metabolites that are both extremely complex and highly structurally diverse. In addition to providing oxygen and being used as a source of food, plants are also a major source of these secondary metabolites. This structural variety can be partially ascribed to natural selection, which favours species that are able to produce powerful chemicals that discourage herbivory (feeding deterrents). Despite the limited number of plant species that have been subjected to in-depth research, a large number of naturally occurring substances that exhibit pharmacological activity have been isolated and are now utilised in the practise of modern medicine. Clinically useful examples include the anticancer agents paclitaxel and vinblastine, which are derived from the plants Taxus brevifolia and Catharanthus roseus, respectively; the antimalarial agent artemisinin, which is derived from Artemisia annua; the opioid analgesic drug morphine, which is derived from Papaver somniferum; and galantamine, which is derived from Galanthus spp., which is used (Fig- 9).



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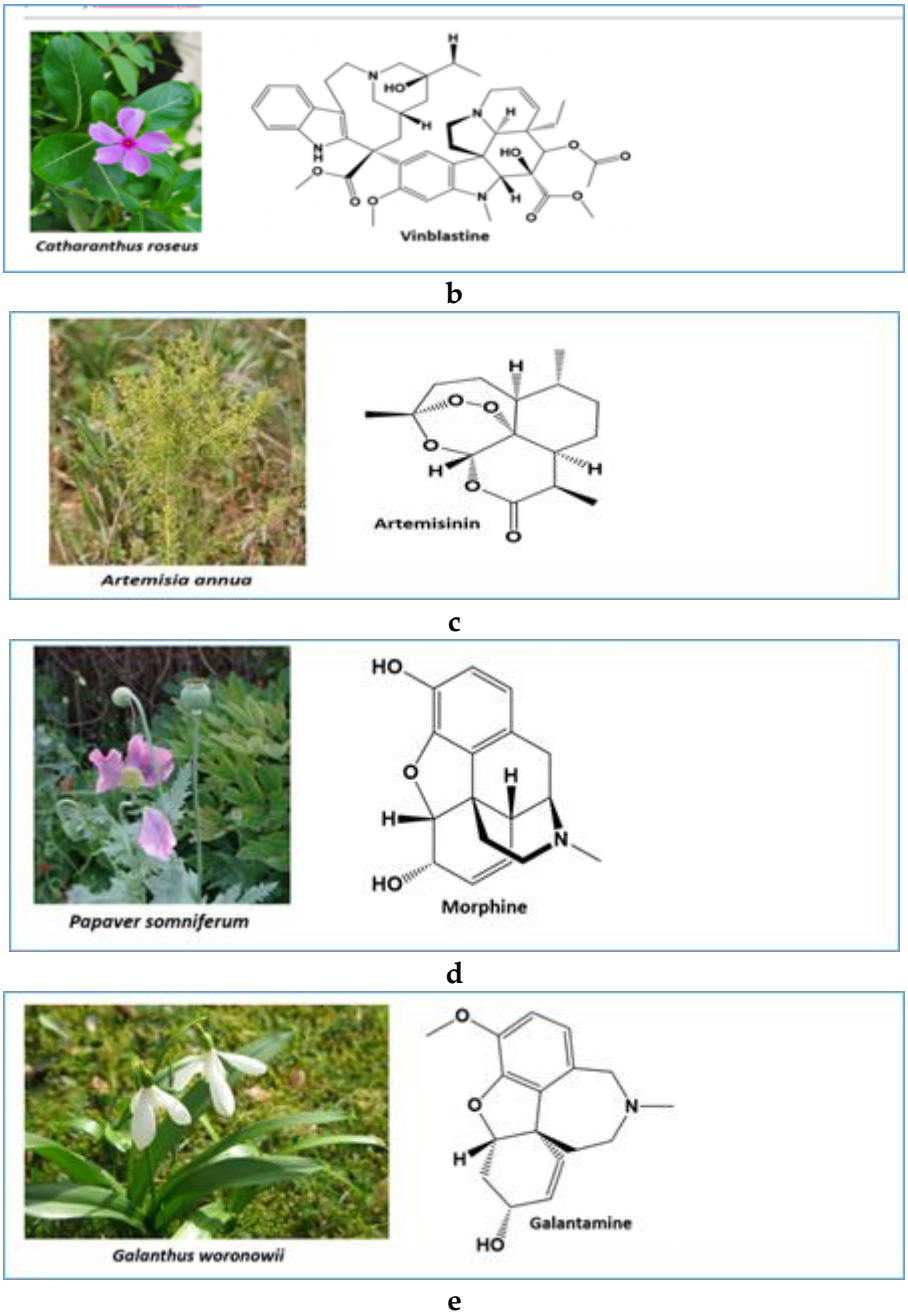

Fig. 10: Examples of biologically active metabolites from plants

ANIMALS

Eukaryotic, multicellular organisms that belong to the kingdom Animalia are called animals. Animals are heterotrophic organisms that, in addition to being mobile at some point in their lifecycle, are distinguished by the fact that they consume other organisms' waste products. In a general sense, animals can be split up into two categories: vertebrates and invertebrates. Vertebrates are animals that have a backbone or spine (also called the vertebral column), and they make up less than five percent of all animal species that have been described. Fish, amphibians, reptiles, birds, and mammals are all included in this group. Invertebrates, which do not have a backbone, make up the rest of the animal kingdom. Molluscs, which include clams, oysters, octopuses, squid, and snails; arthropods, which include millipedes, centipedes,

insects, spiders, scorpions, crabs, lobsters, and shrimp; annelids, which include earthworms and leeches; nematodes, which include hookworms and liver flukes; flatworms, which include tapeworms and liver flukes; Zoology is the scientific name for the study of animal life. In addition to being a source of bioactive natural compounds, animals also include. Specifically, poisonous species including snakes, spiders, scorpions, caterpillars, bees, wasps, centipedes, ants, toads, and frogs have garnered a lot of interest in recent years. [Citation needed] This is due to the fact that the components of venom, including as peptides, enzymes, nucleotides, lipids, and biogenic amines, among other things, frequently have very specific interactions with a macromolecular target in the body. This biological activity, like plant feeding deterrents, is linked to natural selection. Organisms that are capable of killing or paralysing their prey and/or defending themselves against predators are more likely to live and reproduce than those that are incapable of doing so.

Chlorotoxin is an example of a peptide that blocks small-conductance chloride channels. It is composed of 36 amino acids and may be found in the venom of the deathstalker scorpion (Leiurus quinquestriatus) (Fig. 11). It renders its prey helpless by injecting its poison into it. Glioma brain cancer cells are the ones that chlorotoxin adheres to most strongly in humans. This is a remarkable finding. Gliomas are a subtype of tumour that can develop in either the spinal chord or the brain. It is not uncommon for it to develop into a malignant form of cancer, which is characterised by a poor prognosis and a high risk of metastasis (the spread of disease to other parts of the body). Surprisingly, chlorotoxin forms bonds solely with the cells of the tumour and not with the normal tissue of the brain. Because of this property, new approaches have been developed to diagnose, treat, and eradicate various distinct kinds of cancer. For instance, a clinical trial for TM-601, which is a synthetic analogue of chlorotoxin and is currently in phase II, is currently being conducted. It is possible to treat malignant glioma by attaching radioactive iodine-131 to TM-601 and using this combination. TM-601 is able to pass through both the blood-brain barrier and the tissue barrier in order to connect to cancerous brain tumour cells while leaving healthy tissue unharmed. Iodine will be drawn directly to the tumour when TM-601 is coupled to the radioactive iodine-131, and once there, it will be able to kill tumour cells more effectively than normal cells.

Fig. 11: Chlorotoxin from the deathstalker scorpion (*Leiurus quinquestriatus*)

A ribbon diagram of the chlorotoxin protein is shown on the right. Photo of the deathstalker scorpion.

CONCLUSION

Interest in the biological activity of natural products derived from a variety of organisms, particularly for the purpose of the discovery of helpful medications, has been a significant driving factor in the development of concepts and laboratory procedures in the field of organic chemistry.

Natural products can be broken down into two primary categories: primary metabolites, which are essential for an organism's continued existence, and secondary metabolites, which are not essential for an organism's continued existence but do, in most cases, provide the organism with some kind of growth or survival advantage within its environment. Primary metabolites and secondary metabolites both fall under the category of natural products. Major structural characteristics are frequently used as the basis for categorising natural items. The alkaloids, the phenylpropanoids, the polyketides, and the terpenoids are the four major classes of natural products. The alkaloids are organic molecules that contain nitogen; the phenylpropanoids are derived from the amino acids phenylalanine or tyrosine; the polyketides are derived from acetate and malonate; and the terpenoids are derived from the building block isoprene, which has The process of searching for and discovering new natural products all over the world is referred to as bioprospecting, and the academic field that elucidates the structure of natural products and studies their biological activity is referred to as pharmacognosy. Bioprospecting and pharmacognosy both play an important role in the pharmaceutical industry.

Natural products with biologically active properties can be discovered in every type of living thing on the planet. There are two primary categories of organisms that can be found in the natural world: prokaryotic organisms and eukaryotic organisms. Prokaryotic organisms are unicellular and do not contain any membrane-bound organelles, while eukaryotic organisms can either be unicellular or multicellular and contain a nucleus as well as other membrane-bound organelles. Bacteria and archaea are the two major life domains that biologists use to classify the different types of prokaryotic organisms. All eukaryotic species can be found in the third domain, which is called Eukaryota. Animalia, Plantae, Fungi, and Protista are the four primary kingdoms that fall under the umbrella of the domain Eukaryota. There are those in the scientific community who divide the Kingdom Protista into numerous subcategories. The discovery of natural products from organisms in all of the major domains of life has produced significant contributions to western medicine that will last for a long time.

Michel Chevreul's work on the research of soaps is considered to be among the earliest examples of inquiries into organic chemistry and the explication of structures. Saponification is the process of generating soaps from fatty acids and alkalis, both of which are considered basic compounds. An alkali base, such as sodium hydroxide, is utilised in the saponification reaction. This causes an ester bond to be hydrolyzed, resulting in the formation of an alcohol and the salt of a carboxylic acid (in this case, the fatty acid). These preliminary research as well as studies

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Chapter 16

MEMBRANE SCIENCE AND SEPARATION TECHNOLOGY

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ABSTRACT

This chapter describes membrane science, membrane technology, membrane separation processes, membrane materials, and membrane characterization techniques have been discussed. Synthetic membranes are widely used in various fields, including desalination of sea and brackish water, ultrapure water, wastewater treatment, hemodialysis, blood oxygenators, and controlled drug delivery have also been discussed.

KEYWORDS: Membrane science, Membrane technology, Membrane separation processes, Membrane materials, Membrane characterization.

INTRODUCTION

The word "membrane" is defined as a thin layer that acts as a selective barrier between two adjacent phases, such as liquid, gas, vapour, and regulates their transportation. The membrane is considered as a molecular sieve fabricated in the form of a thin layer from more than one layered material with small pores to enable the separation of tiny particles. Membranes can be used to separate solute-solvent, solute-solute, particle-solute, and particle-solvent mixtures.

This definition is based on a macroscopic level, but it should be taken care that the separation is at the microscopic level. Accordingly, it can be said that a membrane process is a combination of both bulk and momentum transfer. A membrane can be homogeneous or heterogeneous in nature, symmetric or asymmetric in nature; it can carry a positively or negatively charged or be neutral or bipolar. The flow or diffusion of individual molecules through a membrane can be influenced by an electric field or a concentration, pressure, or temperature gradient. The thickness of the membrane might range from 100 microns to several millimetres.

Membrane separation has become more popular than other traditional separation technologies like crystallization, distillation, and others, especially in small-scale operations. The important advantages of membranes are their low capital cost, low energy requirement, high separation efficiency, compact design, easy organization with other separation processes, and no requirement of secondary separation processes. The properties of a membrane mainly depend on factors like porosity, pore diameter, pore size distribution, particle size distribution of the solutes, and the affinity between the feed and the membrane material for solubility/diffusivity. In the membrane, the separation process, a particle mixture is achieved by passing one or more particles through the membrane (permeate fractions) and rejecting the other particles of the membrane (retentate fractions). The retentate is called concentrate, as it is a concentrated media of rejected substances as presented in Fig. 1.

This chapter discusses membrane separation technology, we will provide some information about the membrane science and technology, membrane preparation, the characterization of membranes, and their various applications.

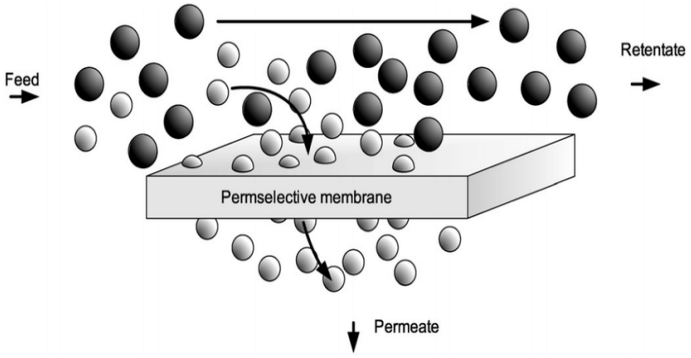

Fig. 1: The ideal concept of membrane process

MEMBRANE SCIENCE

Membrane science is a field concerned with the development of materials for membrane design and process performance. Material selection, membrane preparation, membrane characterization, membrane transport phenomena, membrane module design, and process performance are therefore clearly categorizable in membrane science [1-3]. Each of these categories relates with permeation and permeable media, which is the membrane, to some extent [4]. The important categories of membrane science appear in Fig. 2.

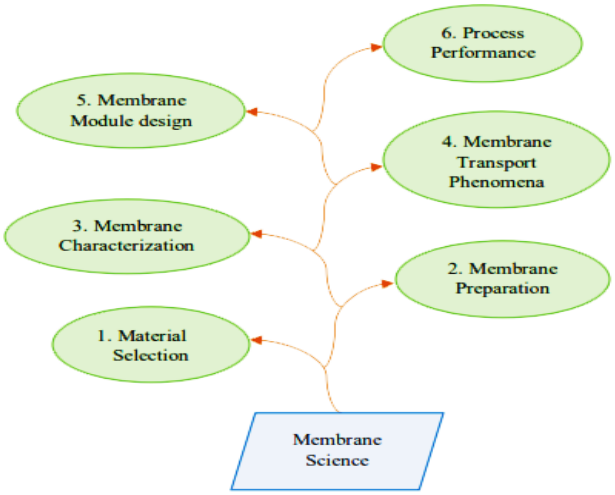

Fig. 2: Important categories of material science

MEMBRANE TECHNOLOGY

Membrane technology involves the related scientific and engineering methods for the transport of particles, species, or materials through or by membranes. Membrane technology is used to explain the mechanical separation processes for separating volatile organic compounds [5-6]. Several main steps in the development of membrane technology are listed in Fig. 3.

Membrane technology is used in several industrial and environmental applications, due to the advantages of membrane separation as a clean technology, saving energy, and it's potential to replace usual processes, including as filtration, distillation, ion exchange, and chemical treatment systems. Other advantages include its capacity to generate high-quality items and system design flexibility.

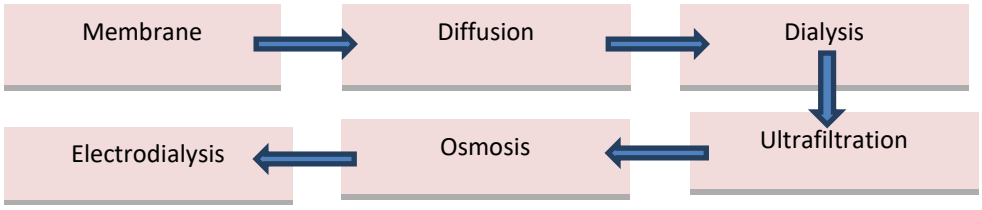

Fig. 3: Several main steps in progress of membrane technology

MEMBRANE SEPARATION PROCESSES

Membrane separation is a new separation method that has a high evaporation efficiency, low energy consumption, is simple to operate, and produces no pollution. The membrane also plays a vital function in changing the composition of a solution based on relative penetration rates. Membrane performance can be measured by the capacity of the synthetic membrane to prevent, regulate, or enhance the permeation. Various factors control the rate of permeation and the transport mechanism. These include the magnitude of the driving force and the size of the permeating molecule relative to the size of the available permanent. Membrane separation processes are classified by driving force, membrane type and configuration, and removal capabilities and procedures. By applying a driving force (pressure, temperature, concentration, or electrical potential) across the membrane, selected particles can be transported through the membrane.

The application of membrane separation processes in industry is mainly caused by innovations in membrane materials. Microfiltration [7, 8], Ultrafiltration [9, 10], Nanofiltration [11,12], Reverse Osmosis and Gas Separation [13,14] are only a few of the processes that use membrane materials (Fig. 4).

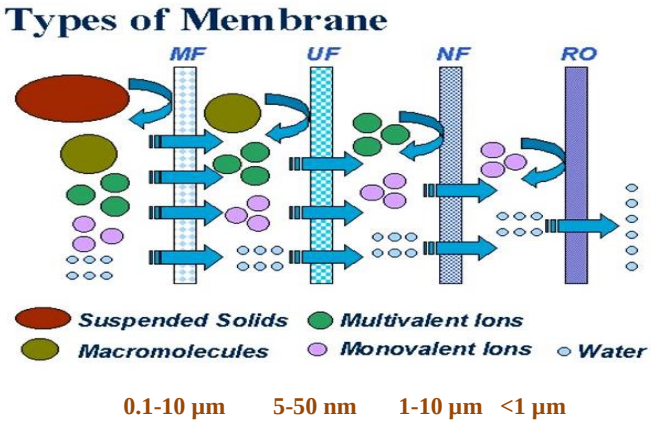

Fig. 4: Schematic diagram of filtration spectrum of related separation processes

MICROFILTRATION (MF) MEMBRANE

Microfiltration membranes are made up of homogeneous pores with as many as possible per unit area and the thinnest feasible layer where these pores are at their smallest. The quantitative separation of suspended particles in the 0.1–10 μm size range from liquids and gases is accomplished using MF membranes (Fig. 5). In cross-flow microfiltration tests, cellulose acetate, polyethersulfone, mixed ester, and polycarbonate membranes with three different pore sizes (0.40-0.45, 0.22, and 0.10 μm) were used [15].

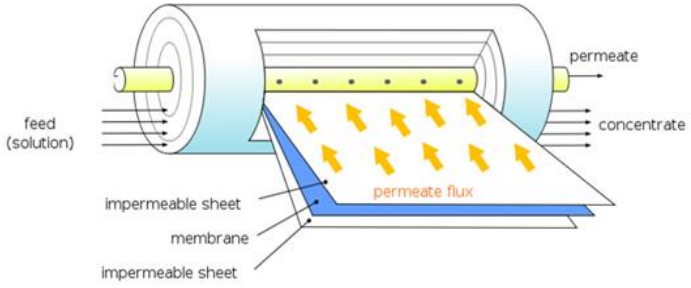

Fig. 5: Microfiltration membrane

ULTRAFILTRATION (UF) MEMBRANE

UF membranes usually have pore sizes in the range of 5–50 nm and retain species in the molecular range from 3000 to 500000 Da [16], while solvent (water) passes through the membrane. The skin layer of UF membranes is permeable. The membrane productivity (flux) and separation extent are the most essential UF membrane features (rejection of various feed components).

Microfiltration and ultrafiltration membranes can be considered porous membranes, where used in biotechnological applications, the pharmaceutical industry, and in food and beverage processing. Ultrafiltration of apple juice is a good example. These methods are also employed in the purification of water and the treatment of wastewater. (Fig. 6).

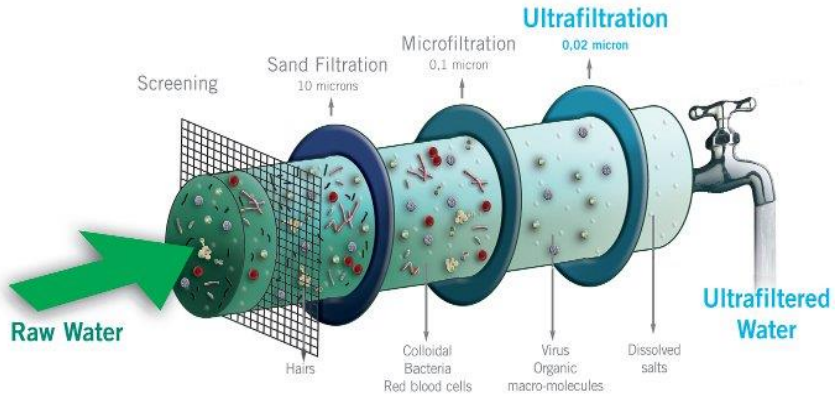

Fig. 6: Ultrafiltration membrane

NANOFILTRATION (NF) MEMBRANE

Nanofiltration is a new term for a filtration process that uses membranes with pore sizes ranging from 1 to 10 μm. Nanofiltration is a promising alternative to conventional water treatment for

achieving many water quality objectives, such as the removal of organic, inorganic, and microbiological contaminants [17-23]. Electrostatic repulsions are also used to separate inorganic salts that are much smaller than the pore size (Fig. 7.).

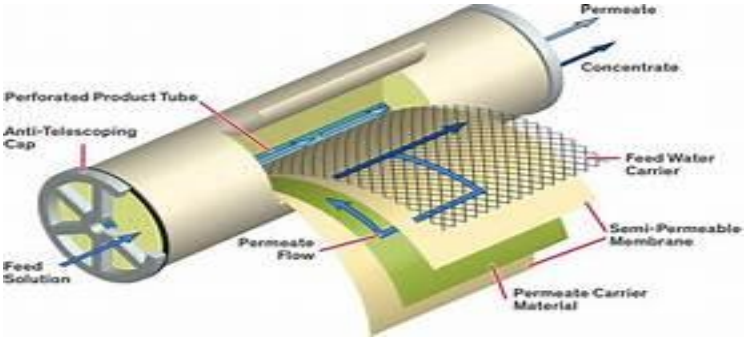

Fig. 7: Nanofiltration membrane

REVERSE OSMOSIS (RO) MEMBRANE

The osmotic flow is reversed when a higher pressure (than the osmotic pressure) is applied to the side with the lower concentration of solvent. This is known as reverse osmosis (RO). The pore radius of the RO membrane must be less than 1 μm. (Fig. 8). The polymeric RO membrane [24] is a dense, non-porous membrane made up of a polymer network in which solutes are dissolved. The first-generation reverse osmosis membrane is made of cellulose acetate (CA).

Fig. 8: Reverse osmosis membrane

The membranes MF, UF, NF, and RO are all pressure-driven membranes. Gas selective separation, pervaporation, and piezodialysis membranes are examples of pressure-driven membranes. A hydraulic or gas pressure is applied to speed up the passage of species through the membrane in these pressure-driven processes (porous or non-porous). The membrane hydrodynamic or gas permeability varies greatly depending on the component.

GAS SELECTIVE SEPARATION MEMBRANE

Non-porous membranes are commonly used for gas selective separation. It could be a composite or an asymmetric membrane with an elastomeric or glassy polymeric top layer (like silicone rubber and natural rubber). The selected layer's thickness ranges from 0.1 to a few microns (Fig. 9). The difference in dissolution and diffusion of the gas that permeates the membrane is used in the gas separation mechanism. For gas permeation, a gas or vapour is present on both the upstream and downstream sides of the membrane.

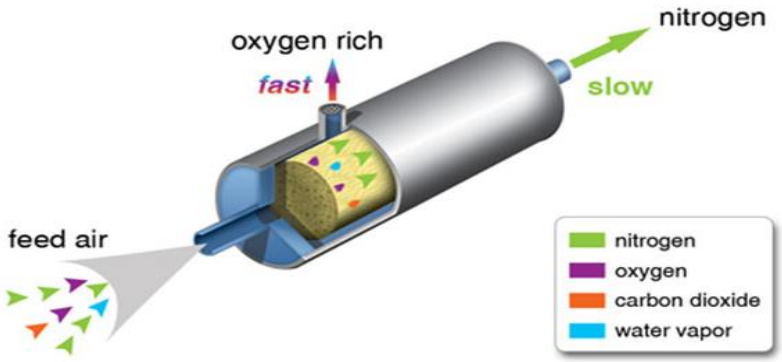

Fig. 9: Gas selective separation membrane

MEMBRANE MATERIALS

A significant element that requires more consideration is the selection of materials suitable for making a synthetic membrane for a certain purpose. The nature and amplitude of interactions between permeants and membranes can be controlled by choosing the right membrane material. It determines the polymer chains that constitute the solid sections of the membrane's packing density and segment mobility.

A wide range of organic, inorganic, and polymeric materials are used to make membranes. Barium, carbons, alumina, iron, and zeolites are examples of inorganic materials. The majority of commercial membranes, on the other hand, are made of polymers and liquids. Cellulose nitrate, cellulose acetate, and polyamide are examples of organic compounds. These materials are utilized to make membranes that have great mechanical strength, thermal stability, and chemical resistance, as well as long-term separation stability. Synthetic membranes can be made using a variety of different ways.

MEMBRANE CHARACTERIZATION

Various advanced techniques were used to characterise the fabricated membrane, revealing its morphology, crystallographic structure, physical properties, existence of groups and bonds in materials, loss by materials, and exothermic or endothermic nature of materials, among other things. These are the methods:

SCANNING ELECTRON MICROSCOPY (SEM)

SEM is a type of electron microscope that scans a sample with a focused beam of electrons to make images of it. The electrons interact with the atoms in the sample, producing a variety of signals that may be detected and contain information about the surface topography and composition of the sample. Specimens can be studied in high vacuum, low vacuum, moist circumstances (in environmental SEM), and at a variety of cryogenic and higher temperatures. The SEM characterization was carried out at a 20 kV accelerating voltage. To reduce charging, the sample was mounted on a copper stub and sputter coated with gold. This technique is used to estimate morphology, topography, surface flaws, and inclusions, among other things. In 1937, Manfred von Ardenne invented a genuine scanning microscope with great magnification. A demagnified and precisely focused electron beam is used in this very small raster.

TRANSMISSION ELECTRON MICROSCOPY (TEM)

TEM is a technique of microscopy in which a beam of electrons is passed through an ultra-thin object and interacts with it as it passes through. The interaction of electrons passed through the specimen creates a micrograph. Light microscopes are not capable of imaging at the same resolution as TEM. TEM is a popular analytical technique in a variety of scientific fields, including physical and biological sciences. TEM analysis was performed with ultra-high resolution optics for characterization which provides maximum performance and productivity for biological and material sciences applications. Max Knoll and Ernst Ruska designed the first TEM in 1931.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FT-IR)

The infrared spectrum of absorption, emission, photoconductivity, or Raman scattering of a solid, liquid, or gas is obtained using the FT-IR technique. An FT-IR spectrometer collects high spectral resolution data over a large spectral range at the same time. The Perkin-Elmer Infracord, introduced in 1957, was the first low-cost spectrophotometer capable of recording an infrared spectrum. The wavelength range covered by this instrument was 2.5μm to 15μm. The sample compartment of a particular type is 200 mm wide, 290 mm deep, and 255 mm high. The sample chamber's entrance and exit beams are sealed with a coated KBr window, and the sample chamber is sealed from the outside with a hinged cover.

THERMO GRAVIMETRIC ANALYSIS (TGA)

TGA is a thermal analysis method that measures changes in the physical and chemical properties of materials as a function of increasing temperature or time. Physical phenomena such as second-order phase transitions, such as vaporization, sublimation, absorption, adsorption, and desorption, can be studied using TGA. TGA is widely used to assess specific properties of materials that have lost or gained mass due to decomposition, oxidation, or volatile loss.

DIFFERENTIAL THERMAL ANALYSIS (DTA)

DTA, like differential scanning calorimetry, is a thermal analytical technique. The substance under investigation and an inert reference are subjected to similar thermal cycles in DTA, with any temperature differences between the sample and the reference being recorded. In comparison to the inert reference, changes in the sample, whether exothermic or endothermic, can be recognized. A DTA curve thus offers information on transformations such as glass transitions, crystallization, melting, and sublimation that have occurred.

X-RAY DIFFRACTION ANALYSIS (XRD)

X-ray crystallography is a technique for determining the atomic and molecular structure of a crystal by causing a beam of incident X-rays to diffract in numerous directions due to the crystalline atoms. A crystallographer can create a three-dimensional image of the density of electrons within the crystal by measuring the angles and intensities of these diffracted beams. The mean locations of the atoms in the crystal, as well as their chemical bonds, disorder, and other information, may be deduced using this electron density. The primary method for determining the atomic structure of novel materials is still X-ray crystallography.

ENERGY DISPERSIVE X-RAY ANALYSIS TECHNIQUE (EDX)

Energy dispersive X-ray analysis technique is a tool and techniques used for characterization of analysis of chemical composition of sample. In this tool, identification of samples is done by electromagnetic radiation and matter interaction. In this technique, when a X-ray radiation is fall on

matters, each element shows characteristics structure and element atomic structure can be determined uniquely for each element. So, each element present in sample has s specific atomic structure and this phenomenon was used in EDX characterization tool. A high energetic beam of charged particles are used for stimulate the emission of the characteristic X-ray from the material or specimen. These high energy beams are focused with the sample used for the study. In the rest mode, atoms of the sample are in ground state level. Electrons in discrete energy levels or electron shells bound to the nucleus. When incident beam is applied, then electrons are excited in the inner shells, ejecting it from the shell while an electron hole is created at the place of ground electron.

APPLICATIONS OF SYNTHETIC MEMBRANES

Synthetic membranes are widely used today in a variety of precise and commercially important separation processes, including desalination of sea and brackish water, purification of bio products and food, and gas and vapour separation. They also play a crucial role in energy conversion and storage systems, as well as synthetic organs and medicine delivery systems. Gas separation, pervaporation, and membranes in medical devices, as well as energy storage and conversion systems, have all become increasingly significant in recent times.

Membranes and their processes are applied in four different applications:

- in molecular and particulate mixture separation
- in the release of active agents in a regulated manner
- in membrane reactors and synthetic organs and
- in systems for energy storage and conversion

The transport properties of a membrane for distinct components in a mixture dictate its role in a separation process. The separation method does not require any chemicals, operates at low temperatures, and consumes very little energy [25]. Membranes are also the most environmentally friendly branch of separation technology due to its nontoxic content.

TREATMENT OF WATER

The primary market for membranes will continue to be water treatment, as it has been in the past. There are numerous types of water treatment available:

DESALINATION OF BRACKISH OR SEAWATER

The desalination of brackish or seawater accounts for almost half of all RO systems now installed [26]. (Fig. 10). The salinity of brackish water is higher than that of fresh water but lower than that of seawater. Technically, brackish water comprises between 0.5 and 30 g of salt per litre (0.5 to 30 parts per thousand), and the costs of the primary desalination processes are proportional to the salt content. Other competing desalination techniques include ion exchange, electrodialysis, and multi-effect evaporation. The use of these three methods, on the other hand, is dependent on the amount of salt present. The WHO recommends a salt concentration of 500 mg/1 in drinking water. As a result, brackish water must frequently be de-salted to remove up to 90 percent of the salt. One of the first applications of reverse osmosis was a cellulose acetate membrane, which easily satisfies this criteria. The salt concentration in seawater is 3.2-4.0 percent, hence membranes with stronger salt rejection are desirable. Salt rejection of 97-99 percent is achieved by cellulose acetate membranes, which is slightly lower than expected.

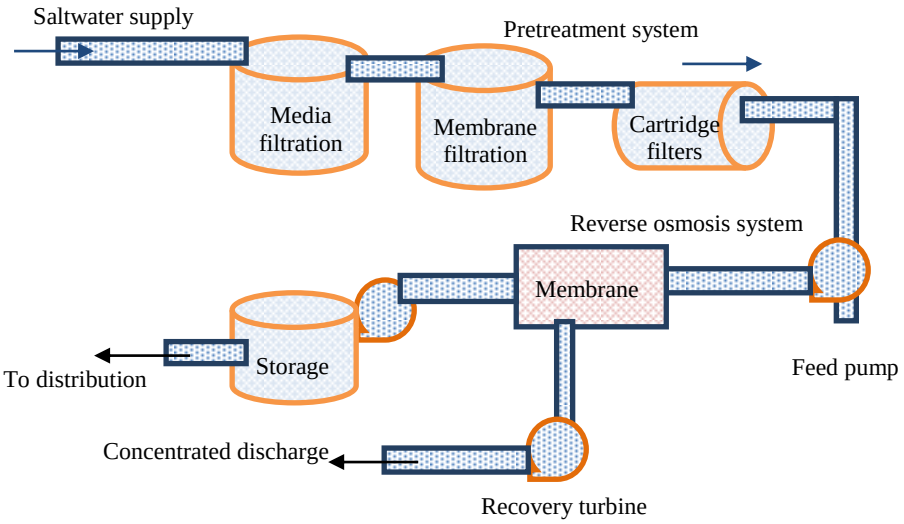

Fig. 10: A simplified basic scheme of water treatment by RO

ULTRAPURE WATER

For washing integrated circuit chips and other devices, the semiconductor and electronics industries require a reliable supply of high-quality water. Pure water is required for tissue culture media, bacteriological media, buffer solutions, analytical solvents, formulation aids, medication and intravenous solutions, standards and reagents, and equipment cleaning in pharmaceuticals and biotechnology.

WASTEWATER TREATMENT

One of the most important applications of membranes is wastewater treatment. Industrial UF was first created to remove particle and macromolecular contaminants from waste fluids and sewage. Chemical addition (aluminium sulphate, polymers, and lime), coagulation, flocculation, sedimentation, filtration, and disinfection (typically with chlorine) are all examples of traditional wastewater treatment. Regrettably, if a chlorine-sensitive RO or NF procedure is performed afterwards, chlorine must be eliminated. Trihalomethanes (THM) and synthetic organic compounds may be subject to additional requirements. MF and UP are very effective at removing bacteria that could pose a health risk.

BIOMEDICAL APPLICATIONS

In the medical field, synthetic membranes are quite popular. There are perhaps too many instances of membrane uses in this subject. Only three of these areas will be discussed briefly: Hemodialysis (artificial kidney), blood oxygenators (artificial heart/lung), and controlled release medicines are all examples of artificial kidneys.

(i) HEMODIALYSIS

Hemodialysis is required for those whose kidneys have failed and they can no longer control their waste disposal. When the kidneys' ability to eliminate hazardous wastes fails, blood pressure may rise, the body may retain too much fluid, and red blood cells may not be produced in sufficient quantities. Dialysis can remove waste products and restore electrolyte and pH levels by replacing parts of the kidney's functions. The patient's blood is pumped through a semipermeable dialysis membrane that is submerged in a saline bath with salt, potassium, and calcium concentrations that

are identical to those in the blood. As a result, urea and other low-molecular-weight metabolites migrate through a concentration gradient across the membrane to the dialysate.

(ii) BLOOD OXYGENATORS

When the patient's lungs cannot function generally during surgery, blood oxygenators are employed. The 1930s saw groundbreaking progress on these devices. This mechanical device was created to imitate the functions of the heart and lungs, allowing heart and great vascular surgery to be performed. The entire exchange membrane capacity between blood capillaries and air sucked in and out in the human lung is approximately 80 m^2. The human lung membrane is around 1 μm thick, and the lung's total exchange capacity is significantly greater than what is generally necessary. Silicone rubber membranes were utilised in the early membrane oxygenators, but microporous polyolefin fibres are now employed instead.

(iii) CONTROLLED DRUG DELIVERY

A synthetic membrane is used to control the rate of drug distribution to the body in controlled drug delivery systems. The membrane in certain devices regulates drug penetration from a reservoir in order to obtain the desired medication delivery rate. Other systems rely on the osmotic pressure created by water diffusion through a membrane to power tiny pumps. In other devices, the medicine is embedded in the membrane material, which dissolves or degrades over time in the body. Diffusion and biodegradation are then used to regulate drug distribution.

CONCLUSION AND FUTURE PROSPECTS

In this chapter, we have discussed membrane science, membrane technology, membrane separation processes, membrane materials, and membrane characterization techniques. Synthetic membranes have various applications related to separation and membrane technology, water treatment, and biomedical sciences.

In several applications, today's membranes and processes are perfectly enough, while in others, there is a clear need for additional advancements in both membranes and processes. For reverse osmosis desalination of sea and brackish water, for example, there are membranes available today that are quite satisfactory in terms of flux and salt rejection, and the procedures have been demonstrated over many years of operation. Hemodialysis and hemofiltration work in the same way. These applications are only expected to see minor changes in the near future. Membrane separation processes are also applied to the advanced areas of space and space exploration programs. Also, research based on the development of novel nanomaterial with specific properties and structures holds great promise for the development of membrane science.

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Chapter 17

THE IMPORTANCE OF QUALITY SEEDS AND THEIR PRODUCTION

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ABSTRACT

The Formulation Development and Technology Transfer of generic Lacosamide oral syrup was the primary goal of this research, by using the reference product of VIMPAT. Lacosamide was used as an adjunctive treatment of refractory partial-onset seizures. The Formulation developmental studies, optimization studies for sweetening agents, viscosity modifier (carmellose sodium and macrogol) and preservative efficacy test were performed. All the parameters were evaluated and found within the limit. The Process developmental studies and Process optimization studies were carried out for large scale manufacturing. Based on the outcome of the Process optimization batch, a similar manufacturing condition is recommended for the future Exhibit batches. From this study, it can be concluded that generic Lacosamide oral syrup can be prepared and able to transfer its technology to large scale manufacturing. Further studies are required to verify the stability and process development optimization studies. Long term pharmacokinetic and pharmacodynamic investigations in humans are needed to evaluate the drug's effectiveness and safety.

KEYWORDS: Lacosamide, Partial-onset seizures, Process development studies, Exhibit batch.

INTRODUCTION

The term "seed" can be defined as "structurally, a real seed is a fertilised developed ovule, consisting of an embryonic plant, a store of food, and a protective seed coat," where the "store of food" refers to the cotyledons and endosperm that are contained within the seed. However, from the perspective of seed technology, a seed can be a mature ovule that was formed sexually and consists of a complete embryo, endosperm, and/or cotyledon with a covering (seed coat). It also refers to the propagating materials utilised for production, such as healthy seedlings, tubers, bulbs, rhizomes, roots, cuttings, setts, slips, and all sorts of grafts, as well as vegetatively propagating materials. Planting high-quality seed is one of the strategies to boost output without significantly expanding the area of land that is already being farmed. Seed is therefore the most important and essential input for crop development.

This chapter gives an overview of seeds, including their characteristics, the significance of seeds, and how they are produced. The biological and economic significance of seeds cannot be overstated. They have a high concentration of protein, carbohydrate, and oil reserves, all of

which are beneficial to the early phases of a plant's growth and development. Because of these reserves, several types of grains and legumes are considered to be primary food sources for a significant number of people all over the world.

In the event that seed-borne infections and early season insects are not treated in a timely manner, the results can be catastrophic. Because seeds are the starting point for the cultivation of ninety percent of all food crops, they are an essential component of agricultural production and productivity that must be maintained over time [1]. In developing countries like India, where a significant portion of the population and GDP (gross domestic product) are dependent on agricultural production, the part that seeds play in the agricultural industry is of the utmost significance [2]. The goal of agriculture in the modern era is to maximise output while minimising the use of resources like land, water, and labour. Sanitation, crop rotation, mixed cropping, adjustment of date of sowing, fallowing, summer ploughing, green manuring composting, and other environmentally friendly disease management practises [3] to combat plant pathogens have already lost their acceptability and are being reevaluated as a component of integrated pest management. [4]. The use of chemicals to control pests through soil or foliar application has a number of drawbacks, including high cost, selectivity, effect on target organisms, development of pest resistance, resurgence of pests, contamination of food and feed, potential health risks, toxicity toward plants and animals, environmental pollution, and so on [5]. In spite of the significant progress that has been made in the field of plant genetic engineering, the rate of resistant variety generation and the longevity of these varieties have been slow and unpredictable [6].

In light of these constraints and a rising global population, there has been a growing interest in the development of such management practises and tools that, by themselves or in combination with other practises, could bring about a reasonably good degree of reduction of inoculum potential and, at the same time, ensure the sustainability of production, cost effectiveness, and a healthy ecosystem. One of these tools is known as "seed treatment," and it is one of the management practises that can bring about this reduction [3]. Seed treatment is analogous to a new born being cared for by their mother [7], and it can range from a simple dressing through coating and pelleting [8,9]. Seed treatment is the process of exposing seeds to various agents, whether they be physical, chemical, or biological in nature. These agents are not used to make the seeds free of pests or diseases; rather, they are used to treat seeds so that they can provide the possibility of pest and disease control in the event that it is required during the germination and emergence of young plants as well as the early growth of the plant [10]. As can be seen throughout the course of human history, the application of seed treatments has been and continues to be an essential component of environmentally responsible agricultural practise. Seed treatments have been beneficial to the production of a wide variety of crops because they offer protection against pre- and post-emergent pests and diseases, as well as the assurance of a uniform stand in a wide range of soil types, cultural practises, and environmental conditions. This has led to an increase in crop yields. Seed treatments are a cost-effective agricultural input that are placed directly on the seed using cutting-edge technology. This results in increased crop yields [11]. In addition, alternative methods of crop protection are currently being

supplanted by seed treatments because of the residual systemic efficacy that seed treatments possess [1] Different methods for application have been suggested from time to time, and it is necessary to develop even more sophisticated methods that provide greater control of plant diseases while having the least negative impact on seed health [12, 13].

Characteristics/attributes of quality seed;

It must be genetically pure:

a) Breeder/nucleus: 100 %
b) Foundation seeds: 99.5%
c) Certified seeds varieties: 98%
d) Certified hybrid seeds:95%
e) Certified hybrid cotton: 90%
f) Certified hybrid castor: 85%

1. It should have required level of physical purity:

a) All crops: 98%
b) Carrot: 95%
c) Ragi: 97%

1. Free form other crop seeds (number/kg): designated inseparable crop seeds are plants seeds cultivated crops found in the seed fields and whose seeds are so similar to crop seed that it is difficult to separate them economically by mechanical means. This causes physical admixtures with the crop seeds only when these crops mature approximately at the same time when seed crop matures. Oats and wheat seeds are examples of what can be found in barley [14].

2. Not contaminated with undesirable weed seeds, which are the seeds of weed species that are damaging in one or more of the following ways:

3. Due to the fact that the size and shape of weed seeds are comparable to those of agricultural seeds, it is difficult to distinguish between the two using mechanical means.

4. The development pattern of weeds is of a determinate nature, and they compete with crops for all available resources.

5. Some components of weed plants can be harmful or even lethal to humans and other animals.

6. Weed plants can also act as alternate hosts for several kinds of insects and diseases.

Ex. Bersem: chicory

PADDY

Wild paddy (Oryza sativa var. fatua), Cucurbits: Wild cucurbits spp., Lettuce: wild lettuce, Bhendi: wild Abelmoscous spp, Wheat: Convolvulus arvensis (Hirankuri) Free from diseases that have been designated: this relates to the illnesses that have been indicated for the seed certification and that have the potential to cause contamination of seed lot.

Ex: loose smut of wheat (Ustilago tritici), Kernal smut of sorghum (Sphacelotheca sorghi), Grain smut of pearl millet (Tolyposporium penicillariae), Ergot of bajra (Claviceps

microcephala), Early blight of tomato (Alternaria solani), little leaf of brinjal (Datura virus-2) etc.

High germination and vigour

Optimum moisture content

Cereals: 10-12 %, Pulses: 7-9%, Oilseeds: 6-7%

Since the beginning of time, people have understood how crucial it is to have high-quality seeds. According to the ancient text known as Manu Smriti, "Subeejam Sukshetre Jayate Sampadyathe," or "good seed in good soil yields abundantly," can be translated as "good seed in good soil yields abundantly." Because of its significance in the development of agriculture and agrarian cultures, the quality of seeds has always been held in a revered position. The Rigveda, which dates back to 2000 BC, has references to the value placed on mother earth and seeds. In the 5th century, Kautilya Artha Shasthra, surapalas vrikshayurveda discussed the significance of seeds and provided information on how to properly handle seeds to promote healthy germination. In order to shield the seed while it germinates, a seed dressing containing milk, vidanga, cowdung, and honey can be applied [15].

Despite the fact that ancient agricultural practises acknowledged the significance of seeds, it wasn't until the beginning of the 20th century that the requirement for organised seed production became apparent. This was when the Royal commission on Agriculture (1925) recommended the dissemination of improved varieties and seed distribution.

IMPORTANCE OF QUALITY SEED

1. Seed is an essential input in crop production;

2. It is the least expensive input in crop production and the most important factor in the development of agriculture;

3. The crop status is largely dependent on the seed materials that are used for sowing; 4. The response of other inputs in crop production depends on the seed material that is used.

2. The number of seed that must be purchased in order to cultivate a crop is fairly low, and its price is significantly lower in comparison to that of other inputs.

3. This highlights the need for increasing the areas that are devoted to the production of quality seed.

4. It is predicted that using seeds of high quality in combination with enhanced varieties can contribute approximately 20-25 percent to an improvement in production.

The advent of modern plant breeding methods and biotechnological advances in seed industry plays a significant role in developing of high yielding varieties and hybrids.

ROLE OF IMPROVED SEEDS

1. The bearer of recent technological advances

2. A fundamental component of a safe food supply

3. The primary method for increasing crop yields in areas with fewer favourable production conditions

4. A medium for the speedy restoration of agricultural land following the occurrence of natural calamities.

ADVANTAGES TO USE HIGH-QUALITY SEEDS

1. Their genetic material has not been tainted in any way (true to type).
2. If the seed is of high quality, it will result in a high return per acre of land that is cultivated since the crop's genetic potential will be utilised to its utmost extent.
3. A lessening in the quantity of weed seed in addition to other types of agricultural seed that infests the soil.
4. A lower chance of contracting an infection and being invaded by insects
5. The decrease in the ratio of seeds to seedlings, which is also referred to as the rapid and even emergence of seedlings.
6. They have excellent health and are free of all diseases and parasites of any type.
7. They can easily adjust to the severe weather patterns and agricultural practises of the region in which they are used.
8. The great seed responds favourably to the application of various fertilisers and nutrients because of its superior quality.
9. The plant population and maturity level are the same throughout the entire area.
10. A crop that had great seed to grow from will have an attractive appearance when it is harvested.
11. The longevity of a variety can be increased by using high-quality seed.
12. Estimating the yield of a crop is not a difficult task at all.
13. The operations that take place after the harvest won't be tough to manage at all.
14. The procedures that are used to prepare the finished products have also been refined to make them more efficient.
15. Points for having a high product value and the ability to sell them on the market.

SEED PRODUCTION:

It is widely acknowledged that having access to high-quality seeds of improved cultivars is one of the most important factors in determining whether or not cultivars will be successfully adopted in a variety of agricultural and climatic settings. It is well recognised that an improvement in seed quality alone can account for an increase in output of at least 10–15 percent (ICAR 1993). On the other hand, a lack of quality seed continues to be one of the most significant obstacles in the way of closing the enormous yield gap. Therefore, the production and distribution of excellent seed is crucial if one want to approach the potentially realisable yield that a cultivar is capable of. The characteristics listed below should be present in seeds of high quality:

- Purity and uniformity of the genetic material, as well as compliance with the criteria established for the particular cultivar.
- Disease free, viable seeds.
- Unadulterated, meaning that it does not include any admixtures of other crop seeds, weeds, or inert stuff.
- Sufficient consistency with regard to the dimensions of size and shape as well as the hue.

The process of systematically cultivating plants is referred to as seed production. When it comes to seed production, suitable attention is provided at every stage, beginning with the

acquisition of seeds and continuing through the harvest with the adoption of appropriate seed and crop management practises. Producing one's own seed might result in increased income as well as improved seed quality for subsequent plantings.

SCOPE AND IMPORTANCE OF SEED PRODUCTION

Over the past half century, the agricultural sector in India has seen significant advancements. The production of food grains has increased significantly from 1947, when it stood at 50 million tonnes and reached 212 million tonnes in 2003-04. The nation has progressed from a state of food insecurity and the need to import supplies to one of food security and surpluses that can be sold abroad.

The Green Revolution in India has received praise from all corners of the globe for being a productive collaboration between the country's farmers, its scientists, and its government. Landmark achievements in agriculture during the 1960s and 1970s were the result of a combination of inputs including the introduction of high yielding varieties, increased fertiliser use, expansion of irrigation facilities, massive extension efforts, improved farm practises, and most importantly, ingenuity and industry on the part of the Indian farmers. The growth of the agriculture sector, on the other hand, has been unable to keep up with the growth of the population and has levelled out. In addition to having major repercussions for the nation's overall food security, the unsatisfactory growth of agriculture has been having a negative impact on the rate at which the economy of the nation is expanding. In order to meet the requirements of the imperatives of national food security, nutritional security, and economic development, an approach that is very concentrated and determined is required to increase agricultural productivity and production. Because it is doubtful that the total area that is being farmed will rise by a large amount, the focus will have to be placed on increasing the amount of production that can be obtained from each acre of farmed land [16].

A number of elements, including inputs like fertilisers, irrigation and plant protection measures, and adequate agronomic techniques, are responsible for the substantial improvement in yield and quality of crops that can be achieved. However, the utilisation of seed of a high quality is critically important to the production of crops for this reason. The use of seeds of low quality renders useless any and all agricultural methods as well as any and all other inputs that are administered to the crop, regardless of how generously these practises and inputs are utilised. In terms of the overall cost of production, the expense of the seed accounts for only a relatively small portion of the total. "What are known as the seeds of hope may turn into seeds of frustration" is how Sindhur Sen (1974) defines the significance of seed quality. If the seeds are not of high quality, "what are known as the seeds of hope may turn into seeds of frustration." Because of this, it is essential to utilise the seed that satisfies the specified specifications in terms of high levels of genetic purity, physical purity, physiological quality, and health quality. Since ancient times, most Indian farmers have relied on traditional kinds of crops; as a result, most of their seed requirements have been satisfied by farm-saved seeds. The usage of conventional plant kinds in conjunction with seeds that were preserved from previous harvests, the quality of which could not be verified, led to a precipitous drop in productivity.

Seed is the most important factor in agricultural production, and its success is directly related to how well other factors, such as labour and capital, perform. The availability of high-quality seeds that are suited to a variety of agroclimatic conditions, in adequate quantity, and at reasonable prices is necessary in order to increase agricultural production. The availability of quality seeds and their application are not one-time events. A sustainable rise in agricultural production and productivity must, by necessity, involve the ongoing creation of new and superior types of crops as well as the establishment of an effective system for the production and distribution of seeds to agriculturalists [17].

According to the National Seeds Policy 2002, which makes this point abundantly clear, "It has become evident that in order to achieve the food production targets of the future, a major effort will be required to enhance the seed replacement rates of various crops." [Citation needed] "It has become evident that in order to achieve the food production targets of the future, a major effort will be call for a significant increase in the number of high-quality seeds that are produced.

The National Seeds Policy from 2002 stipulates what the thrust areas should be.

i) Varietal Development.
ii) Seed Production.
iii) Seed Replacement Rate Enhancement.
iv) Primary responsibility for production of breeder seed to be that of the ICAR/State Agriculture Universities.
v) An effective seed production programme.
vi) Popularization of new varieties.
vii) Availability of newly developed varieties to farmers with minimum time gap.
viii) Provision of incentives to domestic seed industry to enable it to produce seeds of high yielding varieties and hybrid seeds at a faster pace to meet the challenges of domestic requirements.

Following the establishment of the National Seed Program, the National Seed Evaluation and Standards Committee, and private seed enterprises, these entities have begun producing certified and foundation seeds.

The seed industry in India is the eighth largest in the world, with an estimated value of INR 49 billion (USD 1.06 Billion) and a growth rate of between 12 and 13 percent on an annual basis. Because of favourable monsoon conditions, the industry has experienced robust expansion over the course of the past two years. The expansion of the private seed industry is no longer limited to the simple manufacturing and sale of seeds. It has successfully acquired the technological strength necessary to meet the varied requirements of the future. In recent years, Indian farmers have embraced tactics of intensive farming in order to meet the expanding demand for agricultural produce. This trend has occurred in tandem with the industrialization of India.

Table 1: Crop/Season-wise Requirement and Availability of Certified/Quality Seeds in India (2008-2009) (Indiastat.com)

Crop	Requirement	Availability
Cereals Total	13343953	16964189
Pulses Total	1749254	1829974
Oil Seed Total	4814665	5349716
Fibre Total	302279	361151
Patato	430000	430000

The development of high-quality seeds is helped along by a number of factors in India, including the country's diverse agroclimatic conditions and zones, its experienced and devoted farmers, its viable seed business, and several laws. Nevertheless, there is an immediate requirement for consolidating all of our strengths in order to overcome our limitations.

STRENGTHS

A network of 20 seed certification agencies and more than 96 notified seed testing laboratories to legally assure the quality seeds moving in the seed market. A large number of varieties in various vegetable crops are available that are suited to a variety of agro climatic conditions. Because of this, the selection process for beginning manufacturing in a specific region is simplified.

Our county is endowed with a variety of agro-climatic conditions, which means that they can be utilised for seed production of vegetables at any time of the year in one or another part of the nation. These conditions can be found in one or other part of the country.

A very rapid expansion of private seed enterprises, which are beneficial to the process of bridging. The disparity between the demand for vegetable seeds in the country and the supply of those seeds.

WEAKNESSES

- The country's vegetable seed production has historically been susceptible to the whims of the weather, which has led to the production of seeds of inferior quality.
- It is improper to have availability of true data on actual area under vegetable and requirements of vegetable seeds.
- The upkeep of an appropriate distance for isolation. It is sometimes difficult to maintain the recommended isolation distance because our system does not place any restrictions on the planting of specific vegetable crops in specific areas. This makes it difficult to plant isolation distances between crops.
- Indications of interest in newly developed better varieties that are extremely low or non - existent as a result of a lack of knowledge on their performance.
- The seed production chain suffers from a lack of sufficient nucleus and breeder seeds.
- Difficulties in lifting generated seeds when there are indents present.

Demand-influencing factors and conditions It is essential to make a distinction between what is actually demanded, what is seen to be demanded, and what the government anticipates the

farmers will buy. It is possible that the entire amount of certified or labelled seed that has been sold represents only a very small part of the overall demand.

When measuring and projecting demand, there are a lot of different elements that need to be addressed. Among them are the following:

- Cropping pattern and intensity
- Type of seed used Climate
- Demand for crop products
- Market scenario
- Disposable farm income
- Rate or level of adoption of new technology
- Government policy
- Crop cycles
- Habits and tradition
- Product performance
- Competitiveness
- Price
- Promotion

When an individual company or organisation is estimating the market share that may be gained by its own products, the most important factors that need to be taken into consideration are product performance, competitive positioning, price, and promotion. These factors are listed in the order of importance from most important to least important. This will serve as the foundation upon which sales projections and production plans are built.

DEMAND FORECASTING OF SEED

The failure of a seed firm to accurately estimate both demand and the repercussions of either overproduction or underproduction can have significant adverse effects on the company's finances. A shortage of seed results in a loss of revenue and is a source of irritation for the sales team and the dealer network. On the other hand, having an excessive number of carryovers and stock write-offs will prove to be quite costly. Because of this unique confluence of characteristics within the seed sector, providing an accurate estimate of consumer demand is of the utmost importance. Some of these characteristics include:

Longer period of time for the development of new products from breeding programmes

- Seasonality of production
- Production subject to variables like agro climatic conditions that are outside the control of management
- Statutory controls and quality standards
- Existence of a generation system – whereby the production in one year is the progenitor the next year
- Limited shelf like and loss of germination
- Longer period of time for the development of new products from breeding programmes • Seasonality of production
- Production subject to variables like agro

The rate at which farmers purchase new seeds rather than relying on their own stock to produce new plants is referred to as the seed replacement rate.

SEED REPLACEMENT RATE OF SELECT CROPS: 2005-06.

The first thing that needs to be done when doing demand forecasting is to compute the existing requirement multiplied by the percent bought seed. This represents the amount of commercial seed that farmers have purchased. When determining how many seeds are needed, it is important to take into account the seed's potential for reproduction. The rate at which the seed multiplies is referred to as the Seed Multiplication Ratio.

In the current situation in India, the manufacturing of seeds can either be undertaken as a cottage industry or as work done under contract for other seed firms. Both of these options are available. In either case, the production of seeds offers a significant opportunity to improve financial returns.

SCOPE FOR SEEDS EXPORT

There is a lot of potential for marketing of seed by Indian seed companies in countries lying between 300 North and South latitudes, which have comparable agro-climatic situations. The varieties that are bred in India are suitable, and they are comparable to varieties that are produced in the European Union (EU), the United States of America, and Japan, among other places. In addition, salary rates and patterns of spending in those places are analogous to the situation in India. India has the capability of exporting the seed to countries including Indonesia, Bangladesh, China, Sri Lanka, and other African nations. South and Central America, as well as the markets of more industrialised countries The Indian cotton hybrids are well suited for use in African nations because of the relatively low wage rates for hand picking undetermined varieties of cotton. Producing hybrid seeds of paddy, cotton, maize, sorghum, pearl millet, and sunflower, as well as producing varietal seeds of paddy, vegetables (tomatoes, brinjals, gourds, and bhendi), at a cheaper cost for export in AP is possible.

EXPORT OPPORTUNITIES

The potential for international trade can be divided up into two primary areas.

i. The cultivation of vegetable seeds on an individual basis (including hybrid vegetables)

ii. Export of branded seed products

i. The cultivation of vegetable seeds on an individual basis (including hybrid vegetables) The development of hybrid vegetable seed requires a significant amount of manual labour. There has been an increase in the amount of competition, which has led to the majority of the major global companies outsourcing their seed production to countries with lower labour costs. These countries include China, Thailand, Vietnam, Chile, and India, among others. Several Indian companies have established a good reputation over the course of the past 10 years by supplying good quality seed under contract production. We also have labour that is both experienced and skilled, allowing us to undertake this endeavour on a larger scale. If we take a look at the production capacity, we can see that seventy percent of India's seed sales come from seeds that were bred by farmers, twenty-six percent come from seeds that were bred in institutions that were publicly financed, and only four percent come from hybrids that were the result of research. The market for domestic hybrid seeds is estimated to be worth INR 4.9 billion and is

expanding at a pace of 10 percent each year, which compares well to the growth rate of 5 percent seen globally.

ii. The export of seeds with a branded name

Over the course of the past 15–20 years, the seed industry in India has developed into a thriving research-based enterprise (in vegetable as well as field crops). In order to cater to the wide range of agro-climatic conditions present in Indian agriculture, a number of cutting-edge, superior goods have been produced. It has been stated that Indian germplasm and seeds can adapt extremely well in countries that are failing in the region that is 300 kilometres north or south of the equator. This would encompass the markets of a number of developing nations located in Central and South America, Africa, and Asia. By the way, both Africa and Asia are currently the markets that are expanding at the quickest rate. The Indian seed business, with its enormous germplasm base and educated manpower, has the potential to become a significant supplier of technology for countries like these.

AGRI –EXPORT ZONES

Agriculture and agricultural exports are two areas in which India possesses a natural competitive advantage. Now that these policies have been tightened, the government's liberalisation and privatisation policies, as well as the positive clauses in the World Trade Agreement, India can be poised to double its agro exports to Rs.200 billion by 2007.

The idea of Agri Export Zones (AEZ) was conceived with the intention of fostering an increase in the quantity and value of agricultural goods that are shipped out of the country, as well as providing farmers with more lucrative opportunities over time. These zones have been established in order to facilitate the end-to-end development necessary for the export of particular items originating from a geographically contiguous region.

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Chapter
18

EFFECT OF PESTICIDES

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ABSTRACT

Pesticides are chemical substances that are meant to kill pests. In general, a pesticide is a chemical or a biological agent such as a virus, bacterium, antimicrobial, or disinfectant that deters, incapacitates, kills, pests. By their nature, pesticides are potentially toxic to other organisms.

KEYWORDS: Pesticides, Biological agent, Disinfectant, Toxic.

INTRODUCTION

Pesticides are chemicals that contain oxygen, sulfur, chlorine, nitrogen, phosphorus, and bromine as well as heavy metals such as copper, arsenic, sulfates, lead, and mercury. Pesticides are chemical substances that are meant to kill pests.

Pesticides are substances that are meant to control pests. Also used as substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport.

This includes herbicide, insecticide, nematicide, molluscicide, piscicide, avicide, rodenticide, bactericide, insect repellent, animal repellent, microbicide, fungicide, and lampricide. The most common of these are herbicides which account for approximately 80% of all pesticide uses.

DISCUSSION

In general, a pesticide is a chemical such as carbamate or biological agent such as a virus, bacterium, or fungus that deters, incapacitates, kills, or otherwise discourages pests. Target pests can include insects, plant pathogens, weeds, molluscs, birds, mammals, fish, nematodes (roundworms), and microbes that destroy property, cause nuisance, or spread disease, or are disease vectors.

TYPES OF PESTICIDES: These are grouped according to the types of pests which they kill.

1. Insecticides – insects
2. Herbicides – plants
3. Rodenticides – rodents (rats & mice)
4. Bactericides – bacteria
5. Fungicides – fungi
6. Larvicides – larvae

Pesticides can be classified by target organism, chemical structure and physical state. Biopesticides include microbial pesticides and biochemical pesticides. Plant-derived pesticides, or "botanicals", have been developing quickly. These include the pyrethroids, rotenoids, nicotinoids, and a fourth group that includes strychnine and scilliroside. Many pesticides can be grouped into chemical families. Prominent insecticide families include organochlorines, organophosphates, and carbamates Systemic insecticides, which poison pollen and nectar in the flowers, may kill bees and other needed pollinators. Pesticides are not recent inventions. Many ancient civilizations used pesticides to protect their crops from insects and pests. Ancient Sumerians used elemental sulfur to protect their crops from insects. Whereas, medieval farmers experimented with chemicals using arsenic, lead on common crops.

The Chinese used arsenic and mercury compounds to control body lice and other pests. While the Greeks and Romans used oil, ash, sulfur, and other materials to protect themselves, their livestock, and their crops from various pests. Meanwhile, in the nineteenth century, researchers focused more on natural techniques involving compounds made with the roots of tropical vegetables and chrysanthemums. In 1939, Dichloro-Diphenyl-Trichloroethane (DDT) was discovered, which has become extremely effective and rapidly used as the insecticide in the world. However, twenty years later, due to biological effects and human safety, DDT has been banned in almost 86 countries.

Examples of pesticides are fungicides, herbicides, and insecticides. Examples of specific synthetic chemical pesticides are glyphosate, Acephate, Deet, Propoxur, Metaldehyde, Boric Acid, Diazinon, Dursban, DDT, Malathion, etc

EFFECT OF PESTICIDES:

PESTICIDES THAT ARE RELATED TO THE TYPE OF PESTS ARE:

Sr.No.	Pesticides type	Action of Pesticides
1	Algicides	Control algae in lakes, canals, swimming pools, water tanks, and other sites
2	Antifouling	Kill or repel organisms that attach to underwater surfaces, such as boat bottoms
3	Antimicrobials	Kill microorganisms (such as bacteria and viruses)
4	Attractants	Attract pests (for example, to lure an insect or rodent to a trap).
5	Biopesticides	Biopesticides are certain types of pesticides derived from such natural materials as animals, plants, bacteria, and certain minerals
6	Biocides	Kill microorganisms
7	Disinfectants and sanitizers	Kill or inactivate disease-producing microorganisms on inanimate objects
8	Fungicides	Kill fungi (including blights, mildews, molds, and rusts)
9	Fumigants	Produce gas or vapor intended to destroy pests in buildings or soil
10	Herbicides	Kill weeds and other plants that grow where they are not wanted

11	Insecticides	Kill insects and other arthropods
12	Miticides	Kill mites that feed on plants and animals
13	Molluscicides	Kill snails and slugs
14	Nematicides	Kill nematodes (microscopic, worm-like organisms that feed on plant roots)
15	Ovicides	Kill eggs of insects and mites
16	Pheromones	Biochemicals used to disrupt the mating behavior of insects
17	Repellents	Repel pests, including insects (such as mosquitoes) and birds
18	Rodenticides	Control mice and other rodents
19	Slimicides	Kill slime-producing microorganisms such as algae, bacteria, fungi, and slime molds

The toxic chemicals in these are designed to deliberately release into the environment. The industrialization of the agricultural sector has increased the chemical burden on natural ecosystems. Pesticides are agrochemicals used in agricultural lands, public health programs, and urban green areas in order to protect plants and humans from various diseases. However, due to their known ability to cause a large number of negative health and environmental effects.

EFFECT OF PESTICIDES ON SOIL AND WATER POLLUTION

The presence and bio-availability of pesticides in soil can adversely impact human and animal health, and beneficial plants and soil organisms. Pesticides can move off-site contaminating surface and groundwater and possibly causing adverse impacts on aquatic ecosystems. A single teaspoon of healthy soil holds billions of soil microorganisms, including bacteria, fungi and other tiny life forms. These networks help plants access nutrients like nitrogen and phosphorus from the soil in exchange for a steady flow of carbon in the form of carbohydrates the plant photosynthesizes from the air. Soil microbes and plants make enzymes that catalyze biochemical transformation; these enzymes are the drivers of carbon and nutrient cycling. The flow of carbon to the soil depends on this partnership between plant roots and soil Why Reducing Pesticide Use is Central to Regenerative Agriculture We know more about the movement of celestial bodies than about the soil underfoot. But toxic pesticides can damage this microbial bridge.

Farmland is often well drained and natural drainage is often enhanced by land drains. Water from excessive rainfall and irrigation cannot always be held within the soil structure. Therefore, pesticides and residues (also nitrates and phosphates) can be quickly transported to contaminate ground water and freshwater supplies over a large geographical area. Some pesticides are considered carcinogenic in large doses, and as a result, the United States Environmental Protection Agency (EPA) has issued health standards defining maximum allowable contamination levels for 26 pesticides. Contaminated groundwater that resurfaces also affects no targeted plants, birds, or aquatic organisms (some of which are endangered) in the environment. Due to several years of control efforts, the share of pollution from point sources, such as discharges from sewage treatment plants or industrial sources, appears to be lessening. According to the EPA, the non-point source pollution resulting from agricultural tillage, pesticide application, and urban development sites is the chief cause of surface water

degradation today. Water pollution is one form of pollution that is caused by the improper use of pesticides. As a result, they alter the state of such water bodies by changing to its physical, chemical or biological conditions, thereby making it toxic, contaminated and unsuitable for use.

CONCLUSION

Apply pesticides at the lowest effective level. Avoid unnecessary pesticide treatments. Use Integrated Pest Management. Follow all label instructions. Apply proper rates and times as label indicates. Calibrate application equipment. Apply formulations that minimize drift. Use safety equipment when handling. Store and dispose of pesticide containers properly. Use biological controls when appropriate. Alter farming or cropping systems to control pests. Use disease and insect resistant crop varieties.

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