REVIEW ARTICLE

THERAPEUTIC POTENTIAL OF SITAGLIPTIN AND *CAMELLIA SINENSIS* IN DIABETES MANAGEMENT

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Abstract:

This review explores the synergistic potential of combining sitagliptin with *Camellia sinensis* for the management of type 2 diabetes mellitus (T2DM). Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, enhances incretin activity, improving glycemic control. *Camellia sinensis* (green tea) is rich in bioactive compounds like catechins and flavonoids, offering antihyperglycemic, antioxidant, and anti-inflammatory effects. The combination leverages complementary mechanisms: sitagliptin prolongs incretin activity, while green tea polyphenols improve β-cell function and enhance glucose uptake. Preclinical studies in diabetic rat models demonstrate that *Camellia sinensis* improves glucose tolerance and insulin release. Combining it with sitagliptin further enhances the inhibition of DPP-4 and reduces oxidative stress. Clinical evidence, though limited, indirectly supports this combination, showing improved lipid profiles and insulin sensitivity with green tea supplements. By addressing the multifactorial pathophysiology of T2DM, this dual approach presents a holistic strategy for improved glycemic control and reduced complications.

Keywords: Sitagliptin, *Camellia sinensis*, DPP-4 inhibitors, Diabetes management, Combination therapy, Antioxidant properties.

Introduction:

Diabetes mellitus (DM) is a chronic metabolic disorder that has emerged as a significant global health challenge, affecting millions of individuals worldwide. It is characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both. Among the various forms of diabetes, Type 2 diabetes mellitus (T2DM) is the most prevalent, accounting for over 90% of all diabetes cases. T2DM is closely associated with obesity, chronic inflammation, oxidative stress, and genetic predisposition. The rising prevalence of T2DM is alarming, with projections estimating that over 783 million people will be affected by 2045, posing a substantial burden on healthcare systems globally.

Conventional treatment strategies for T2DM typically involve a combination of lifestyle modifications and pharmacotherapy. Commonly prescribed medications include metformin, sulfonylureas, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin. Sitagliptin, in particular, has gained prominence due to its ability to enhance endogenous incretin activity, thereby improving glycemic control with a minimal risk of hypoglycemia. However, despite the efficacy of these synthetic drugs, long-term use is often associated with adverse effects, reduced therapeutic efficacy, and increased treatment costs. These limitations have prompted the exploration of alternative and adjunctive therapies that can complement conventional treatments and provide a more holistic approach to diabetes management. In recent years, natural products have garnered significant attention as cost-effective and accessible alternatives for managing diabetes. Among these, *Camellia sinensis* (commonly known as green tea) has emerged as a promising candidate due to its rich content of bioactive compounds, including catechins, epigallocatechin gallate (EGCG), and flavonoids. These compounds exhibit a wide range of pharmacological effects, including antioxidant, anti-inflammatory, and glucoselowering properties. Preclinical and clinical studies have demonstrated that *Camellia sinensis* extracts can enhance insulin secretion, inhibit DPP-4 activity, and improve glucose tolerance, making it a viable adjunctive therapy for diabetes management.

Camellia sinensis

Camellia sinensis, commonly known as the tea plant, is a species of evergreen shrub or small tree whose leaves and leaf buds are used to produce tea. It belongs to the genus

Camellia within the family Theaceae. Native to East Asia, particularly China and India, *Camellia sinensis* is widely cultivated in tropical and subtropical regions around the world. The plant is renowned for its role in producing various types of tea, including green tea, black tea, white tea, oolong tea, and pu-erh tea, depending on the processing methods applied to the leaves.

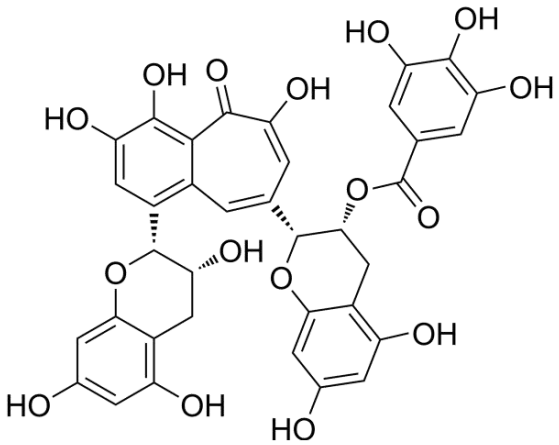

Figure 1: *Camellia sinensis* (L.) O. Ktze. extract | Natural Compounds

The therapeutic potential of *Camellia sinensis* has been recognized for centuries, particularly in traditional Chinese and Ayurvedic medicine. The plant is rich in bioactive compounds, primarily polyphenols, which include catechins, epigallocatechin gallate (EGCG), flavonoids, and other antioxidants. These compounds are responsible for the plant's wide range of pharmacological properties, including antioxidant, antiinflammatory, antihyperglycemic, and cardioprotective effects.

Effects of *Camellia sinensis* on glucose diffusion *in vitro*

Leaf extract of *C. sinensis* (mg/ml) significantly reduced glucose diffusion in concentration-dependent manner by 9–27 % ($P < 0{\cdot}05$–$0{\cdot}001$.

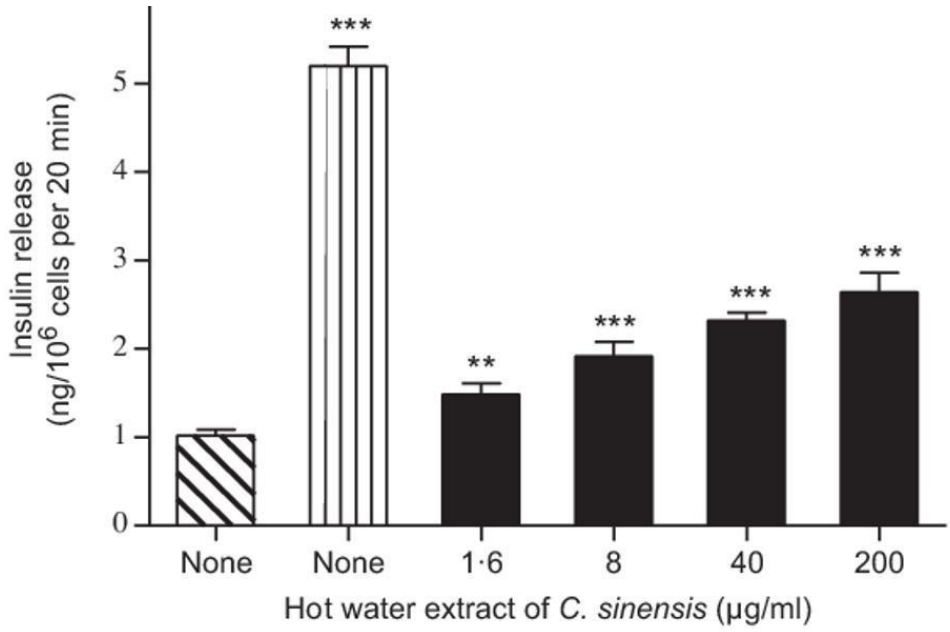

Figure 2: Effects of *Camellia sinensis* on glucose diffusion *in vitro*

Effects of *Camellia sinensis* on dipeptidyl peptidase-4 enzyme activity *in vitro*

As shown in, sitagliptin, an established inhibitor, decreased *in vitro* DPP-IV enzyme activity by 15–98 % ($P < 0{\cdot}01$–$0{\cdot}001$) at 1×10^{-3}–10 μ **M**. *C. sinensis* extract inhibited DPP-IV activity by 5–59 % at 40–5000 μg/ml ($P < 0{\cdot}05$ and $P < 0{\cdot}001$.

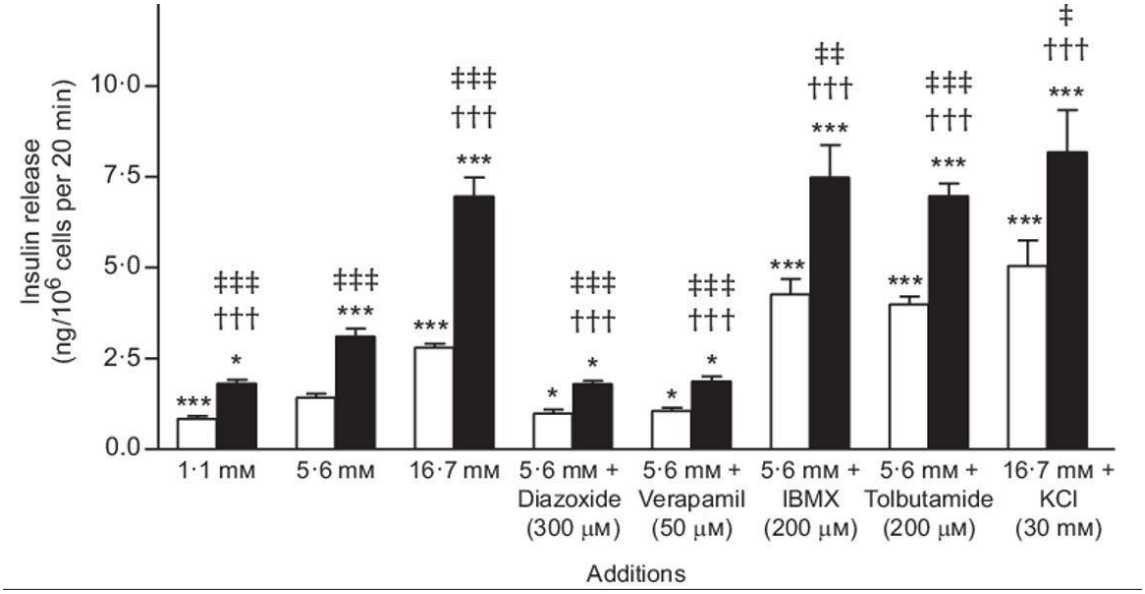

Figure 3: Effects of *Camellia sinensis* on dipeptidyl peptidase-4 enzyme activity *in vitro*

Effects of *Camellia sinensis* on insulin release from BRIN-BD11 cells

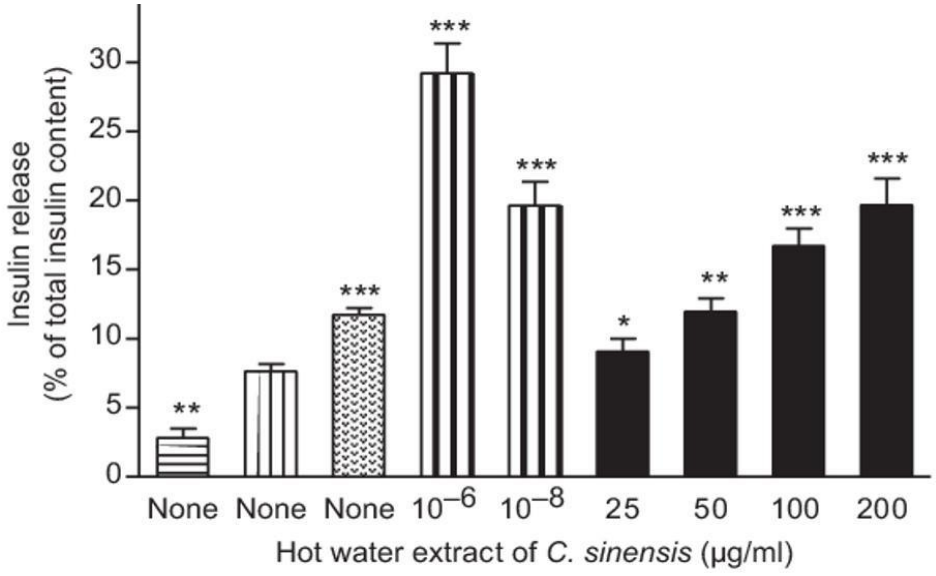

Figure 4: Effects of *Camellia sinensis* on insulin release from BRIN-BD11 cells

Concentration-dependent effects of *C. sinensis* (1·6–200 µg/ml) extract on insulin release are shown in. Alanine (10 mM) and KCl (30 mM) were used as positive controls. The extract produced dose-dependent increase in insulin secretion by 1·5–2·6fold in comparison with 5·6 mM or 16·7 mM glucose controls ($P < 0·05$–$P < 0·001$).

Cells were viable at up to 200 µg/ml concentrations, but LDH release was increased by 20–75 % at higher concentrations indicating loss of cellular viability.

Results and Discussion:

Preclinical Evidence:

- In animal models (e.g., high-fat-fed rats and streptozotocin-induced diabetic rats), *Camellia sinensis* demonstrated significant antihyperglycemic effects:
- Improved glucose tolerance and reduced fasting plasma glucose levels.
- Increased insulin secretion and reduced DPP-4 activity.
- Enhanced GLP-1 levels, which are crucial for glucose regulation.
- When combined with sitagliptin, the synergistic effects were observed:
- Greater inhibition of DPP-4 activity, leading to prolonged GLP-1 action.
- Increased antioxidant capacity, reducing oxidative stress and improving β-cell function.
- Reduced lipid peroxidation, which is associated with diabetic complications.

Clinical Insights:

- While clinical trials directly investigating the combination of sitagliptin and *Camellia sinensis* are limited, indirect evidence supports their combined use:
- Sitagliptin is well-documented for its glycemic efficacy and safety profile, with minimal risk of hypoglycemia.
- *Camellia sinensis* supplements are widely recognized for their metabolic benefits, including improved insulin sensitivity, lipid profiles, and antioxidant effects.

- The combination of sitagliptin and *Camellia sinensis* is proposed to address the multifactorial pathophysiology of T2DM, including insulin resistance, β-cell dysfunction, oxidative stress, and chronic inflammation.

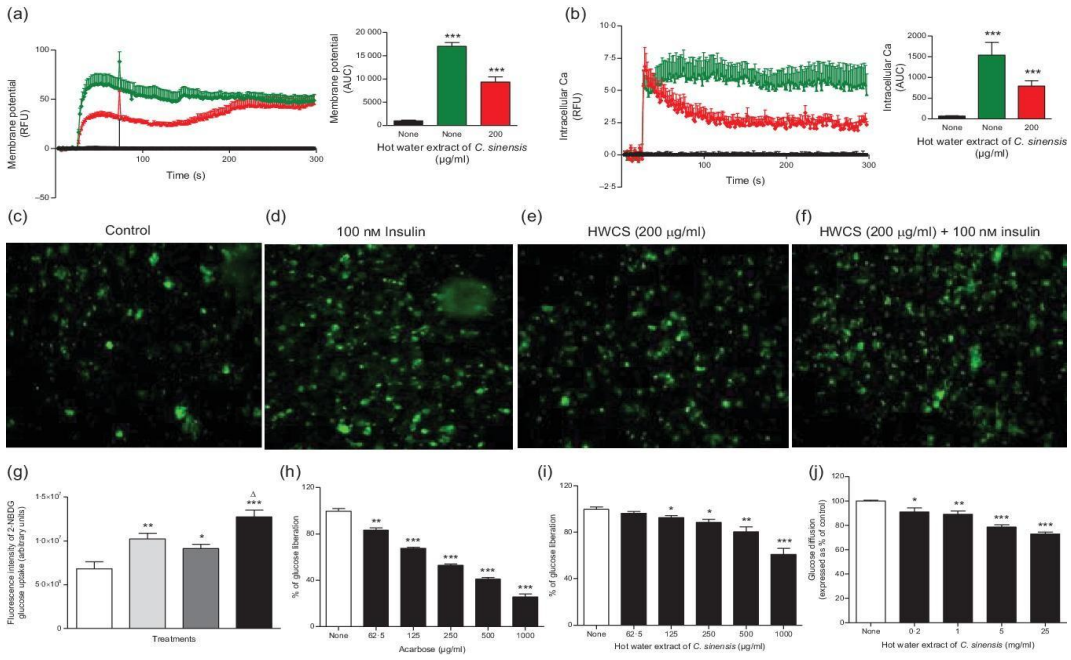

Figure 5: Effects of *Camellia sinensis* on BRIN-BD11 cell membrane depolarisation and intra-cellular calcium concentration

Future Prospects:

- The combination of sitagliptin and *Camellia sinensis* offers a novel and holistic approach to diabetes management:
- It leverages complementary mechanisms of action to improve glycemic control.
- It reduces the risk of diabetic complications by addressing oxidative stress and inflammation.
- It may provide a cost-effective and sustainable alternative to conventional pharmacotherapy, particularly for long-term management of T2DM.

Key Takeaways:

- The combination of sitagliptin and *Camellia sinensis* works through complementary mechanisms to improve glycemic control.
- Preclinical studies show synergistic effects, including enhanced DPP-4 inhibition, improved insulin secretion, and reduced oxidative stress.
- Clinical evidence, though limited, supports the metabolic benefits of both sitagliptin and *Camellia sinensis*, suggesting their combined use could be a promising strategy for T2DM management.
- Future research should focus on clinical trials to confirm the efficacy, safety, and longterm benefits of this combination therapy.

Conclusion:

Camellia sinensis is a versatile plant with a rich history of use in traditional medicine and a growing body of scientific evidence supporting its therapeutic benefits. Its bioactive compounds,

particularly catechins and flavonoids, offer a natural and holistic approach to managing chronic conditions like diabetes. When combined with conventional pharmacotherapy, such as sitagliptin, *Camellia sinensis* presents a promising strategy for improving glycemic control and reducing the risk of diabetic complications. This dual approach not only addresses the multifactorial nature of T2DM but also provides a sustainable and cost-effective solution for long-term diabetes management.

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