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COMPREHENSIVE REVIEW OF THE THERAPEUTIC POTENTIAL OF *MOMORDICA CHARANTIA* (BITTER MELON) IN DIABETES MANAGEMENT

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ABSTRACT

Diabetes mellitus, particularly type 2 diabetes (T2DM), is a global health problem with hyperglycemia, insulin resistance, and progressive β-cell dysfunction. Current antidiabetic therapies with limitations of adverse effects, high costs, and poor glycaemic control in certain patients, have limited their efficacy in the clinical scenario. Medicinal plants and natural products have therefore been the focus of interest as complementary approaches in diabetes management. One such plant with a long history in traditional medicine for the treatment of diabetes is *Momordica charantia* (bitter melon). A rich phytochemical profile consisting of saponins, polypeptides, flavonoids, and triterpene glycosides, gives it its therapeutic potential, which is attributed to its enhancing insulin secretion and sensitivity, inhibiting carbohydrate digesting enzyme action, its influence on lipid metabolism and its antioxidant and anti-inflammatory properties. Bitter melon was critically reviewed in the context of ethnopharmacological background, phytochemical constituents, molecular mechanisms, preclinical and clinical evidence, formulation strategies, and safety considerations in the management of diabetes. We also produce six summary tables that combine selected study data. While we have good evidence here, there are important additional trials of standardized extract preparations with fixed doses and duration needed to establish the best dosing and long-term safety. Overall, *Momordica charantia* has great potential as a complementary agent in the integrative management of T2DM.

Keywords: *Momordica charantia*, bitter melon, diabetes mellitus, hypoglycemic, phytochemicals, complementary therapy, insulin resistance

1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that affects millions worldwide and is of considerable morbidity and mortality **[33]**. T2DM is a disease characterized by insulin resistance, insulin deficiency, chronic hyperglycemia, and subsequent associated complications including, cardiovascular disease, neuropathy, and nephropathy. However, metformin, sulfonylureas, DPP-4 inhibitors, GLP1 receptor agonists, and insulin are conventional pharmacological therapies that are effective for many patients, but they also have side effects, high costs, and inadequacy of glycemic control in the patients **[33, 26]**. For this reason, alternative and complementary approaches to diabetes management are being actively explored.

Momordica charantia, also known as bitter melon or bitter gourd, is a tropical vine rich in tradition in traditional medicine as an agent for the treatment of diabetes and other metabolic disorders **[1, 7]**. Bitter melon contains a complex phytochemical composition including saponins, polypeptides, flavonoids, and cucurbitane-type triterpene glycosides, whose therapeutic offing is bitter melon bitters **[9, 15, 17]**. In recent decades, the hypoglycemic, antihyperglycemic, and antidyslipidemic effects and the molecular mechanisms of action of this plant have been increasingly investigated by scientific investigations.

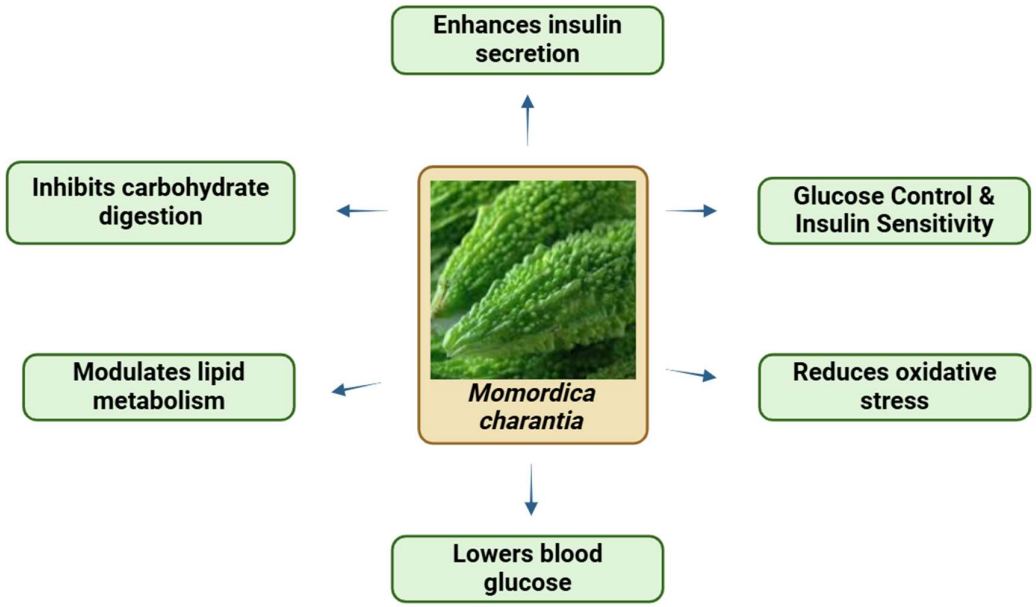

Figure 1: Advantages of Momordica charantia in relation to Diabetes Mellitus

Intending to give a complete overview of the therapeutic potential of *Momordica charantia* in diabetes management, this review aims to make a detailed review of the subject. Its ethnopharmacological background and phytochemical profile are first described, and then its anti-diabetic action's molecular mechanisms are discussed in detail. We then review preclinical and clinical studies of the efficacy and safety of this compound. We also present formulation strategies including polyherbal combinations and nutraceutical approaches as well as safety concerns and problems of quality control. Finally, we also identify current gaps in the research and point toward future directions.

2. Ethnopharmacology and Phytochemical Profile

2.1. Ethnopharmacological Background

Momordica charantia has been used in traditional medicine in many cultures. For example, bitter melon is used not only for its antidiabetic effects but also for the management of hypertension and other chronic conditions in Ghana **[1]**. For many years, traditional healers in Asia and Africa have known about its ability to lower blood sugar levels and many scientific investigations have been conducted on its efficacy in modern clinical settings **[7, 26]**. This is a sign that traditional knowledge should be validated by rigorous scientific research before its use in ethnomedicine.

2.2. Phytochemical Constituents

The medicinal properties of bitter melon are due to its rich content of bioactive compounds. The key phytochemical classes include:

Saponins: Characteristically, charantin, an assortment of steroidal saponins, was later demonstrated to address hypoglycemia by upgrading insulin thickness and improving glucose uptake **[15, 8, 17]**.

Polypeptides: Polypeptides: Polypeptide-p, also called an ‘insulin-like’ peptide, is believed to act like insulin and support glucose utilization **[9, 10]**.

Cucurbitane-type Triterpene Glycosides: Recent studies have shown Cucurbitane-type Triterpene Glycosides to possess hypoglycemic activity via multiple molecular pathways **[19]**.

Flavonoids and Phenolic Compounds: Bitter melon may contain flavonoids and Phenolic Compounds that act as potent antioxidants thus helping to protect pancreatic β cells from oxidative stress and lower inflammation **[9, 6]**.

Other Bioactives: Vicone and other compounds could act synergically to enhance metabolic homeostasis **[29, 15]**.

Table 1: Phytochemical Constituents of *Momordica charantia*

Phytochemical Class	Key Compounds	Reported Biological Activities	References
Saponins	Charantin	Hypoglycemic, insulin-sensitizing	[15], [17]
Polypeptides	Polypeptide-p	Insulin-like activity, enhanced glucose utilization	[9], [10]
Flavonoids & Phenolic Compounds	Various flavonoids, phenolics	Antioxidant, anti-inflammatory	[6], [9]
Cucurbitane-type Triterpene Glycosides	Cucurbitacins, triterpene glycosides	Hypoglycemic via multiple pathways	[19]
Other Bioactives	Vicine, others	Synergistic effects on glucose metabolism	[15], [29]

3. Mechanisms of Action in Diabetes Management

Momordica charantia has several interrelated mechanisms of antidiabetic effects. These mechanisms aim at important pathophysiological aspects of diabetes as insulin secretion, insulin sensitivity, enzyme inhibition, inflammation, and oxidative stress.

3.1. Enhancement of Insulin Secretion and β-Cell Function

The stimulation of insulin release and maintenance of ~ 15% of remaining pancreatic β cells is one of the main mechanisms. It has been shown in previous studies that bitter melon extracts stimulate the secretion of glucagon-like peptide I (GLP-I) and contribute to the function and viability of β–cells **[3, 13]**. In diabetic animal models, bitter melon treatment prevented the dedifferentiation of β-cells and promoted regeneration so that β-cells were able to regenerate and their endogenous insulin production increased.

3.2. Improvement of Insulin Sensitivity

A hallmark of T2DM is insulin resistance, and bitter melon seems to alleviate this condition. Bitter melon extracts have been demonstrated in studies in diabetic rats to regulate the expression of proteins, suppressors of cytokine signaling 3 (SOCS-3), and c-Jun N-terminal kinase (JNK), key mediators of insulin resistance **[14]**. Bitter melon improves overall glycemic control by boosting insulin sensitivity and is of benefit in both lowering fasting blood glucose levels and improving overall control of glycemia.

3.3. Inhibition of Carbohydrate-Digesting Enzymes

It slows down carbohydrate digestion by inhibiting important digestive enzymes such as α-amylase and α-glucosidase **[6, 23]**. This mechanism is particularly important for the management of postprandial hyperglycemia, a major challenge in the management of T2DM.

3.4. Antioxidant and Anti-inflammatory Effects

Oxidative stress and chronic inflammation play significant roles in the development and progression of diabetes. Bitter melon possesses potential antioxidants (flavonoids and phenolics) that act as free radical

scavengers, and prevent oxidative damage to pancreatic β cells **[6, 9]**. In addition, bitter melon regulates inflammatory cytokine production reduces systemic inflammation, and improves insulin signaling **[4, 7]**.

3.5. Modulation of Lipid Metabolism

Dyslipidemia is commonly associated with T2DM. It has been shown that bitter melon reduces plasma cholesterol and triglyceride levels and improves lipid profiles **[2, 30]**. In addition, improved lipid metabolism provides glycemic control but also decreases the risk of cardiovascular complications.

3.6. Inhibition of Advanced Glycation End Products (AGEs)

Non-enzymatic glycation of proteins and lipids leads to the formation of AGEs and diabetic complications. Bitter melon may prevent the formation of AGEs and thus reduce tissue damage and complications of diabetes **[18]**.

Table 2: Proposed Mechanisms of Action of *Momordica charantia* in Diabetes Management

Mechanism	Description	Key References
Enhancement of Insulin Secretion	Stimulates GLP-I secretion and improves β-cell function, enhancing endogenous insulin production.	[3], [13]
Improvement of Insulin Sensitivity	Modulates insulin signaling pathways (e.g., SOCS-3, JNK) to reduce insulin resistance.	[14], [16]
Inhibition of Carbohydrate-Digesting Enzymes	Inhibits α-amylase and α-glucosidase, reducing carbohydrate digestion and postprandial glucose spikes.	[6], [23]
Antioxidant and Anti-inflammatory Effects	Reduces oxidative stress and inflammation via flavonoids, protecting β-cells and improving insulin action.	[4], [7], [9]
Modulation of Lipid Metabolism	Lowers plasma cholesterol and triglyceride levels, improving overall lipid profiles.	[2], [30]
Inhibition of AGEs Formation	Prevents the formation of advanced glycation end products, reducing diabetic complications.	[18]

4. Preclinical Evidence

In a large function of pre-clinical studies, *Momordica charantia* has been studied for its antidiabetic effects in various animal models, and for revealing mechanism and efficacy data.

4.1. Glucose Homeostasis

Bitter melon extracts have, over and again, been demonstrated in animal studies to improve glycemic control. For example, aqueous extracts from Bhat *et al*. **[3]** demonstrated that aqueous extracts increased GLP-I secretion in both Wistar rats, which are lean and Wistar rats with diabetes resulting in better glycemic control. Like Ma *et al*. **[14]**, bitter melon was also reported to ameliorate insulin resistance in T2DM rat models by regulating key insulin signaling pathways. Bitter melon seems to improve the measure of glucose tolerance or lower fasting plasma glucose levels in these studies.

4.2. Lipid Profile Improvement

Bitter melon has also been studied in several preclinical studies regarding its effects on lipid metabolism. Bitter melon extract mixed with ethanol also increased lipid profiles in mice that exhibited type II

diabetes-like symptoms, decreasing both hyperglycemia and dyslipidemia, Baek *et al*. **[2]**. Koopmans *et al* **[10]** reported that bitter melon fruit reduction of plasma fructosamine in diabetic minipigs would indicate improved long-term glycemic control.

4.3. Enzyme Inhibition and Antioxidant Activity

Protein extracts from bitter gourd leaves have been shown to inhibit activities of both α amylase and β glucosidase in vitro **[6, 23]**. Such inhibition results in slower carbohydrate digestion and lower postprandial hyperglycemia. At the same time, studies have demonstrated that bitter melon has strong antioxidant activity, an important protective mechanism against oxidative stress in pancreatic β cells **[7, 8]**.

4.4. Inflammatory Modulation

Bitter melon has been shown to have anti-inflammatory properties in animal models. The bitter melon extracts can reduce proinflammatory cytokine levels, as well as modulate the immune response and concomitantly mitigate chronic inflammation implicated in T2DM **[4, 7]**. Improvement of insulin signaling and metabolic control are associated with these effects.

Table 3: Summary of Key Preclinical Studies

Study (First Author, Year)	Animal Model/Method	Intervention Details	Main Findings	Reference
Bhat *et al*., 2018	Wistar rats (healthy and diabetic)	Aqueous extract of M. charantia	Increased GLP-I secretion; improved glycemic control	[3]
Ma *et al*., 2017	T2DM rat model	Bitter melon extracts	Improved insulin sensitivity; modulated SOCS-3 and JNK pathways	[14]
Baek *et al*., 2018	Type II diabetes-mimicking mice	Ethanol extract mixture (including M. charantia)	Reduced hyperglycemia; improved lipid profiles	[2]
Chokki *et al*., 2020	In vitro enzyme assays	Protein extracts from M. charantia leaves	Inhibited α-amylase and β-glucosidase activities	[6]
Koopmans *et al*., 2024	Diabetic obese Göttingen Minipigs	Bitter melon fruit vs. stems/leaves	Reduced plasma fructosamine; modulated plasma insulin levels	[10]
Deng *et al*., 2023	Diabetic mice	Saponins from M. charantia	Hypoglycemic effect via multiple pathways	[8]

5. Clinical Evidence

While clinical studies of *Momordica charantia* are fewer than preclinical studies, several clinical trials and systematic reviews have been conducted to evaluate its efficacy and safety in human subjects.

5.1. Clinical Trials in Prediabetes and T2DM

Bitter melon has been evaluated in several clinical trials in people with prediabetes or T2DM for its hypoglycemic effects. Bitter gourd has been shown to reduce fasting plasma glucose levels in prediabetic patients in Tanzania by Krawinkel *et al*. **[11]** in an intervention study. Studies by Peter *et al*. **[21]** have also developed protocols to assess the safety and efficacy of bitter melon in

prediabetic and diabetic patients. However, these studies provide promising reductions in glycemic indices, but the results are heterogeneous.

5.2. Systematic Reviews and Meta-Analyses

Systematic reviews and meta-analyses give a broader view of the clinical outcome. In a systematic review and meta-analysis of randomized clinical trials, Laczkó-Zöld *et al*. **[12]** failed to demonstrate definitively the metabolic effects of bitter melon owing to discrepancies in extract preparations, dosing regimens, and study designs. Overall Zhuang and al. registered improvements in glycemic control, and lipid profile, but also showed considerable heterogeneity in studies **[34]**.

5.3. Safety and Tolerability

In clinical settings, bitter melon is well tolerated, with the most common adverse effects occurring in the gastrointestinal tract, with mild flu-like symptoms **[7, 21]**. Although the extracts that have been used in clinical trials have varying quality and standardization, these make the assessment of long-term safety and efficacy more challenging.

Table 4: Summary of Clinical Studies

Study (First Author, Year)	Population	Intervention (Formulation & Duration)	Main Outcomes	Reference
Krawinkel *et al*., 2018	Prediabetic patients (Tanzania)	Bitter gourd intervention; oral administration for 12 weeks	Significant reduction in fasting plasma glucose levels	[11]
Laczkó-Zöld *et al*., 2023	T2DM patients	Various bitter melon extracts; RCTs with variable durations	Inconclusive metabolic effects; significant heterogeneity in outcomes	[12]
Zhang *et al*., 2024	T2DM patients	M. charantia supplementation (oral) for 6-12 weeks	Improvement in glycemic control and lipid profiles	[34]
Peter *et al*., 2018	Prediabetes and T2DM patients	Protocol for systematic review/meta-analysis across multiple RCTs	Highlighted need for standardized interventions and dosing	[21]

5.4. Additional Observational Studies

Similarly, it has been shown, in observational studies, that consuming bitter melon is associated with improved glycemic control (largely as a result of reducing fasting glucose levels) and lower incidence of diabetes related complications. Supportive evidence for these studies is obtained **[26, 27]**, however, they remain sorely lacking in their nonrandomized design and confounding factors.

6. Formulation and Synergistic Approaches

6.1. Polyherbal and Nutraceutical Combinations

Bitter melon is often used in combination with other medicinal plants to enhance its antidiabetic effects. For instance, Chattopadhyay *et al*. **[5]** showed that the Ayurvedic polyherbal formulations consisting bitter melon and other herbs were more effective to enhance glycemic

parameters as compared to bitter melon. Also similarly, Lu *et al*. **[13]** looked at mixing red yeast rice, bitter melon and chromium in db/db mice resulting in improved pancreatic β cell function and glycemic control.

6.2. Formulation Strategies and Standardization

One of the main obstacles to bitter melon research translation to the clinic is variability in extract preparation and dosage. Standardization of bitter melon extracts is necessary to have the same levels of bioactive compounds including charantin, polypeptide-P and cucurbitane glycosides. Development of quality control procedures and standardized formulations has begun that are reliable in clinical trials **[7, 17]**.

Table 5: Formulation Strategies and Synergistic Effects

Study (First Author, Year)	Combination/Product	Model/Subjects	Outcome	Reference
Chattopadhyay *et al*., 2022	Ayurvedic polyherbal formulations (including bitter melon)	T2DM patients	Improved glycemic control and safety profile	[5]
Lu *et al*., 2020	Nutraceutical combination (red yeast rice, bitter melon, chromium)	db/db mice	Alleviation of β-cell dedifferentiation; improved glycemic control	[13]
Perumal *et al*., 2022	Polyherbal combination (Taraxacum officinale and bitter melon)	Rat models	Synergistic antidiabetic activity observed	[20]
Koopmans *et al*., 2024	Comparative study of different plant parts of bitter melon	Göttingen Minipigs	Differential effects on plasma fructosamine and insulin levels	[10]

7. Safety, Quality Control, and Tolerability

7.1. Safety Profile

The safety of *Momordica charantia* has been evaluated in both preclinical and clinical studies. Overall, bitter melon is well tolerated when administered at therapeutic doses. Mild gastrointestinal disturbances, such as nausea or diarrhea, have been reported but are generally transient and resolve with continued use **[7, 21]**. However, because of the variability in extract composition, adverse effects may be more pronounced with non-standardized preparations.

7.2. Quality Control Issues

Quality control is a critical concern in the use of botanical extracts. The concentration of bioactive compounds in bitter melon can vary depending on factors such as the plant's geographic origin, harvest time, and extraction methods **[7, 17]**. Standardization of extracts is necessary to ensure consistent efficacy and safety. Regulatory guidelines and rigorous quality control protocols are needed for commercial formulations intended for diabetes management.

Table 6: Safety and Quality Control Data

Study (First Author, Year)	Study Type	Safety/Tolerability Findings	Quality Control/Standardization Notes	Reference
Bhat *et al*., 2018	Animal study (Wistar rats)	No significant adverse effects observed	Aqueous extract; quality not standardized	[3]
Laczkó-Zöld *et al*., 2023	Clinical meta-analysis	Generally well tolerated; mild GI disturbances reported	High heterogeneity due to variable extract preparations	[12]
Krawinkel *et al*., 2018	Clinical intervention study	Mild adverse effects in a minority of subjects	Extract formulation details vary; need for standardization	[11]
Chattopadhyay *et al*., 2022	Systematic review of Ayurvedic formulations	Safe with no major adverse events reported	Emphasis on quality control in polyherbal products	[5]

8. DISCUSSION

8.1. Integration of Evidence

Momordica charantia has extensive preclinical and emerging clinical evidence of multifactorial antidiabetic effects. These are preclinical studies demonstrating consistently its ability to improve glycemic control, improve insulin sensitivity, modify lipid profiles, inhibit digestive enzymes, and anti-inflammatory and antioxidant actions **[2, 3, 8, 14]**. Heterogeneous clinical studies of the product generally provide modest benefits in lowering fasting plasma glucose and improving lipid profiles in prediabetic and diabetic patients **[11, 12, 34]**. Taken together, these findings suggest that bitter melon may be therapeutically useful as an adjunct in diabetes management.

8.2. Mechanistic Complexity

Bitter melon acts through multiple, complementary mechanisms. Its direct mechanism of action on stimulating the secretion of GLP-I and improving pancreatic β cell function rectifies the deficiency of insulin and β cell dysfunction in T2DM **[3, 13]**. Carbohydrate-digesting enzyme inhibition is a means to control postprandial hyperglycemia **[6, 23]**. Also, its anti-inflammatory and antioxidant properties are critical to stave off oxidative stress, one of the most relevant contributing factors of insulin resistance and diabetic complications **[4, 7]**. Common in diabetic patients, further reducing the cardiovascular risk is also the modulation of lipid metabolism **[2, 30]**. This mechanistic complexity is consistent with the expected potency of bitter melon when used as a part of an integrative treatment strategy.

8.3. Clinical Implications

Momordica charantia has great potential in the management of diabetes, especially for patients who are looking for complementary or alternative therapies. Due to its low cost, wide availability, and favorable safety profile as compared to conventional medications, the drug is an attractive option, especially in areas with restricted access to the medication **[1, 26]**. Despite this variability in clinical outcomes resulting

from variation in extract preparation, dosage, and study design, a standardized formulation and larger well-controlled trial is needed.

8.4. Formulation and Standardization Challenges

A major barrier to translating bitter melon's antidiabetic potential into the clinic is a lack of standardization. However bioactive compounds concentration can differ much between preparations and the efficacy and safety are affected **[7, 17]**. However, to achieve standardized extraction methods and implement quality control protocols, bitter melon-based products need to continue to deliver therapeutic benefits.

8.5. Limitations and Future Directions

Despite the promising evidence, several limitations remain:

- **Studies:** The activity is supported by preclinical vs. clinical evidence, and many studies have been done in animal models, which do not necessarily fully mirror human physiology.
- **Heterogeneity in Clinical Trials:** Variability in study design, extract preparation, and dosing Countervailing Heterogeneity: The lack of uniformity in clinical trial design, extraction for dosing regimen, patients attending, and so on, often impedes clear conclusions.
- **Safety and Quality Control:** Although bitter melon seems safe, no long-term safety data or standardized quality control determinations exist.
- **Mechanistic Understanding:** There has been more than one putative mechanism but work is needed to provide extra detail regarding these molecular pathways.

Future research should focus on:

1. As small-scale randomized controlled trials of standardized bitter melon preparations would not be suitable for assessing such effects, conducting large-scale multicenter randomized controlled trials of these preparations would additionally be necessary.
2. Explores further the molecular mechanisms using advanced omics technologies.
3. Polyherbal and nutraceutical combinations that can be combined to use a similar effect.
4. The long-term safety and quality control aspects of bitter melon extracts are investigated.
5. Pharmacokinetic properties evaluations and build of the best dosing guidelines.

9. CONCLUSION

Momordica charantia is a promising complementary approach to the

management of diabetes mellitus. The antidiabetic potential of its rich phytochemical profile and antagonistic, as well as the multifaceted mechanisms, including increased insulin secretion, improved insulin sensitivity, inhibited digestive enzyme, anti-inflammatory and antioxidant effect, and modulated lipid metabolism may help explain its contributions to antidiabetic potential. Its efficacy is supported by robust preclinical data, partial clinical data show modest improvements in glycemic control and lipid profiles in patients with prediabetes and type 2 diabetes. Despite these challenges, bitter melon cannot be fully integrated into conventional diabetes management protocols until issues of extract standardization, study heterogeneity, and safe usage are addressed.

Optimization of bitter melon formulations and dosing strategies will require further research, including well-designed randomized controlled trials and mechanistic studies. *Momordica charantia* is a cheap, accessible, and safe adjunct to the integrative management of diabetes mellitus, which may improve outcomes and reduce the burden of this chronic disease.

Declarations

Author contributions

DB and LS: Conceptualization, Formal analysis, writing—original draft, writing—review & editing. LS: Supervision. Both authors wrote, read, and approved the study for publication, provided their critical feedback, and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Registration and Protocol

Not registered

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Availability of Data

All datasets for the study are available in the manuscript.

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