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The Role of *Trigonella foenum-graecum* as Antioxidant by Regulating Oxidative Stress in Type 2 Diabetes Mellitus: A Systematic Review

Icha Nadhirotul Izza Afida [1,*] and Savira Oktavia Ainiyati [2]

[1] *Department of Histology and Pathology Anatomy, Faculty of Medicine, University of Jember, Jember, East Java, Indonesia.*
[2] *Department of Microbiology, Faculty of Medicine, University of Jember, Jember, East Java, Indonesia.*

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Abstract

Diabetes mellitus is a chronic metabolic disease characterized by persistent hyperglycemia and often associated with increased oxidative stress, which contributes to the progression of diabetes complications. The use of herbal plants as complementary therapy is increasingly developing, one of which is fenugreek (*Trigonella foenum-graecum*), known to have antidiabetic and antioxidant activities. The aim of this study is to systematically evaluate the effects of fenugreek on oxidative stress in diabetic conditions based on available scientific evidence. This study employs a systematic literature review based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. The literature was searched from five databases: Google Scholar, PubMed, Nature, ScienceDirect, and Springer. A total of 5 articles met the eligibility criteria. All studies indicate that fenugreek has a protective effect on diabetic conditions through modulation of oxidative stress. The administration of fenugreek consistently correlates with a reduction in oxidative damage biomarkers and an increase in endogenous antioxidant capacity. Additionally, fenugreek also shows improvements in metabolic parameters and provides protective effects on target organs affected by diabetes complications, including the pancreas, liver, kidneys, and heart. Fenugreek shows promising potential as a complementary therapy in diabetes management, especially through its ability to modulate oxidative stress. Although the available results support the therapeutic effects of fenugreek, clinical research on humans with more robust methodological designs is still needed to confirm its efficacy and safety for clinical practice.

Keywords: Fenugreek; SOD; MDA; Type 2 Diabetes Mellitus; Phytochemical

1. Introduction

Diabetes mellitus (DM) is a major global health challenge that is increasing in the 21st century (1). It is a chronic metabolic disorder characterized by persistent hyperglycemia, where the body fails to regulate blood glucose levels effectively due to a deficiency in insulin secretion, insulin resistance, or both (2,3). This phenomenon is not only an individual clinical problem but has also significantly increased over the past few decades, burdening healthcare systems in terms of rising treatment costs, social burdens for families, and reduced quality of life for patients. The risk does not stop at higher mortality rates, as diabetes often serves as a risk factor for serious complications such as nephropathy, retinopathy, neuropathy, and cardiovascular disease, which gradually damage body functions and decrease life expectancy (4,5).

Understanding the pathogenesis of diabetes, especially type 2, means recognizing that this disease is not singular. Behind the widely known insulin resistance and pancreatic β-cell dysfunction, there is another central mechanism often overlooked, which is oxidative stress (6–8). Long-standing hyperglycemia is not just an abnormal number on blood test results. This condition triggers excessive production of reactive oxygen species (ROS) through various intersecting metabolic pathways. These include activation of the polyol pathway, formation of advanced glycation end-products

* Corresponding author: Icha Nadhirotul Izza Afida

(AGEs), and mitochondrial electron transport chain dysfunction. All of these converge on one problem: the accumulation of ROS that exceeds the capacity of endogenous antioxidant defenses. The consequences of this are damage to lipids, proteins, and DNA, leading to deeper insulin resistance, impaired endothelial function, and more progressive development of diabetes complications (9).

Amid this reality, conventional pharmacological therapy is indeed available in a variety of options. However, field practice shows that long-term effectiveness remains limited. Side effects that disrupt patient compliance, the continuously rising treatment costs, and phenomena of therapy saturation often reduce management success (10,11). Therefore, the focus of researchers and healthcare practitioners has gradually shifted toward natural substances that have the potential to become complementary therapies. Among the many plants that are on the radar, fenugreek (*Trigonella foenum-graecum* L.) attracts attention because of its long history of use in traditional medicine systems and its diverse bioactive compounds. Bioactive substances such as alkaloids, flavonoids, steroid saponins, soluble fiber, trigonelline, diosgenin, and 4-hydroxyisoleucine open up opportunities for non-monolithic metabolic manipulation (12,13).

Evidence from experimental and clinical studies indeed continues to strengthen the position of fenugreek (14). However, what is interesting is that its mechanism of action is not unilinear. An increase in insulin sensitivity occurs simultaneously with the stimulation of insulin secretion, the inhibition of glucose absorption in the intestine occurs in parallel with improvements in the lipid profile, and the modulated inflammatory response appears to complement the overall picture (15,16). Recently, findings regarding its antioxidant activity have added another dimension. Polyphenols and flavonoids in fenugreek are reported to reactivate endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). At the same time, they suppress levels of malondialdehyde (MDA) as a marker of oxidative damage. This means that fenugreek not only reduces blood glucose levels but also has the potential to intervene more deeply, protecting tissues from damage mediated by oxidative stress (17,18).

However, it must be acknowledged that the available evidence landscape is still far from uniform. The variation in research results is quite significant. Some report impressive effects, while others are less conclusive. Differences in study design, participant characteristics, the form of fenugreek used (whole seeds, extract, or powder), dosage, intervention duration, and the parameters measured all contribute to the inconsistency. Moreover, the existing evidence is still scattered across individual publications, making it difficult to draw a comprehensive overview of how strong and reliable fenugreek is in the context of diabetes management. This is where the gap needs to be filled. A synthesis of evidence that not only gathers but also critically evaluates each existing finding is required. A systematic review approach with a systematic search, selection, and analysis protocol becomes a relevant tool to identify, select, and synthesize the existing literature. Through this method, the study aims to evaluate the effectiveness of *Trigonella foenum-graecum* supplementation in the diabetic population, focusing on glycemic control and oxidative stress biomarkers. The results are expected to provide a more solid scientific foundation for the position of fenugreek as a complementary therapy and also open avenues for more targeted future research.

2. Materials and methods

This study employs a systematic literature review as its research method. The data for this research were gathered from existing online studies (secondary data). The literature was sourced from five databases: Google Scholar, PubMed, Nature, ScienceDirect, and Springer. The search utilized a combination of keywords, including "fenugreek", "SOD", “MDA”, “*Trigonella foenum-graecum”,* "type 2 diabetes mellitus "phytochemical", and connected by the Boolean operators "OR" and "AND".

The inclusion criteria used in this systematic review was (a) article published between 2016-2026; (b) research conducted in any country; (c) publications written in English; (d) studies available in full-text and open-access format; (e) indexed in Scopus (Q1-Q4); (f) original research articles; (g) study that investigate fenugreek (*Trigonella foenum-graecum*) as potential herbal medicine for type 2 diabetes mellitus by regulating oxidative stress. While the exclusion criteria used in this study were (a) review articles; (b) studies without full-text access; (c) articles not relevant to the topic of interest.

The literature screening and eligibility assessment process for this review followed by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. The procedure involved the following stages: (a) defining the review topic; (b) formulating the research question; (c) Identifying relevant keywords; (d) Establishing inclusion and exclusion criteria; (e) Conducting database searches using the selected keywords; (f) Screening studies based on

titles, abstract and keywords; (g) Retrieving full-text articles relevant to the topic; and (h) synthesizing the eligible studies.

3. Results and discussion

A total of 5 articles were identified as meeting the predefined eligibility criteria and were subsequently included in the final analysis. These articles were selected following a systematic search across four electronic databases, which initially yielded many records. After removing duplicates and applying the inclusion and exclusion criteria, only studies directly addressing the antioxidant potential of *Trigonella foenum-graecum* in type 2 diabetes mellitus remained eligible. The study identification, screening, and selection process is presented in the PRISMA flowchart (Figure 1), which provides a transparent overview of how the final pool of articles was determined. To facilitate comparison and synthesis, the essential characteristics of the included studies, such as author, year of publication, country of origin, study design, and key findings are summarized in Table 1. These characteristics are further examined and discussed in detail within the discussion section, where each study's strengths, limitations, and relevance to the research objective are critically analyzed.

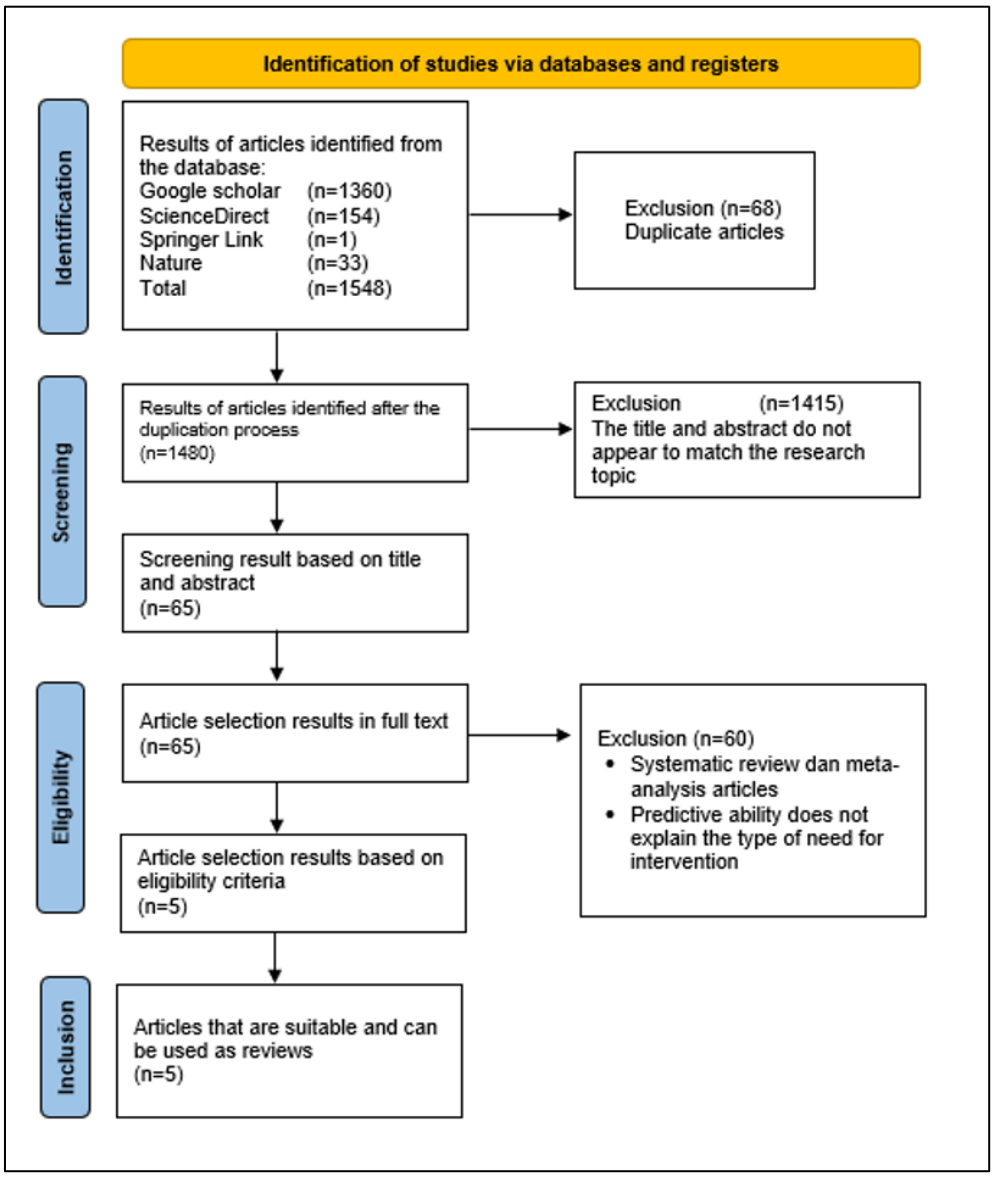

Figure 1 PRISMA Diagram of Article Search Process

Table 1 Characteristics of the included study

Author, Year	Study Design	Population/ Subject	Intervention	Comparator	Outcomes
Li et al., 2018 (19)	Experimental animal study	60 male C57BL/6J mice; Type 2 Diabetes Mellitus model induced with high-fat diet (HFD) + streptozotocin (STZ 100 mg/kg); divided into 6 groups (n=10/group)	Fenugreek extract in the form of high-dose (E1H) and low-dose (E1L) flavonoid extract, as well as high-dose (E2H) and low-dose (E2L) stilbene glycoside extract, was administered for 4 weeks.	Normal (standard diet + water) Diabetes group without treatment Diabetes group with standart treatment	Blood glucose levels decreased in the high-dose groups: E1H decreased by 19.2% and E2H decreased by 36.5% after 4 weeks. Oxidative stress biomarkers improved compared to the diabetes group: SOD increased (E1H: +27.6%; E2H: +25.0%), CAT increased (E1H: +39.0%; E2H: +40.6%), and MDA decreased (E1H: −37.9%; E2H: −36.6%). Histopathology showed improvement in fat degeneration in the liver, kidneys, and pancreas, especially in the E2H group (high-dose stilbene glycoside).
Bafadam et al., 2021 (20)	Experimental animal study	32 male Wistar rats, divided into 4 groups (n=8/group): control, diabetes, diabetes + metformin, diabetes + Fenugreek	Fenugreek seed powder 2 g/kg/day for 6 weeks after diabetes induction	Normal (standard diet + water) Diabetes group without treatment Diabetes group with standart treatment (metformin)	Compared to the diabetes group, fenugreek significantly reduces blood glucose, ROS, and cardiomyocyte apoptosis. Antioxidant activity increases through the reduction of myocardial oxidative stress. The expression of apoptosis proteins (Bax, caspase-3) decreases, while Bcl-2 increases.
Alsieni M et al., 2021 (21)	Experimental animal study	36 male albino mice; Diabetes Mellitus model induced with streptozotocin (STZ	Extraction of fenugreek seed water 200 mg/kg body weight (group G4); also,	Normal (standard diet + water) Diabetes group	There was a decrease in blood glucose and HbA1c levels.

		65 mg/kg); divided into 6 groups	there is fenugreek leaf extract 200 mg/kg body weight (G3)	without treatment	Reduction in lipid peroxidation (MDA) Increase in antioxidant enzymes (SOD, CAT, GSH, GST) compared to diabetic controls. The histological structure of the liver and testes also improved, approaching normal.
Al Hunduwan et al., 2024 (22)	Experimental animal study	Male albino rat model of Diabetes Mellitus induced by streptozotocin (STZ); divided into 5 groups: control, STZ, STZ+ZnO NPs, STZ+Fenugreek (TFG), STZ+TFG+ZnO NPs	Fenugreek (TFG) seed extract in the STZ+TFG group; also the combination of TFG + zinc oxide nanoparticles (ZnO NPs)	Normal (standard diet + water) Diabetes group without treatment Diabetes group with ZnO NPs	TFG increases antioxidant biomarkers: GSH increases (2.84 → 13.08 ng/mL), SOD increases (85.02 → 184 U/mL), CAT increases (84.22 → 121.6 MU/L). MDA decreases (2.266 → 0.734 nmol/mL) ($p<0.001$). TFG also improves kidney function (reduces BUN, creatinine, uric acid), lipid profile, and histological kidney damage.
Vishwakarma et ak., 2024 (23)	Experimental animal	24 male Albino Wistar rats (10–12 weeks old, 180–220 g), divided into 3 groups (n=8/group), diabetes model induced with STZ + high-fat diet	Extract of fenugreek seed ethanol 500 mg/kg body weight/day orally for 28 days in the diabetic group	Normal (standard diet + water) Diabetes group without treatment	Blood glucose levels significantly decreased in the intervention group (day 7: 441.1 ± 42.81, day 28: 216.6 ± 13.92 mg/dL). Oxidative stress biomarkers improved: MDA decreased (4.36 vs 5.73), SOD increased (33.3 vs 9.12), and Catalase increased (52.4 vs 15.75) compared to the diabetic control ($p=0.001$).)

3.1. Taxonomy and botanical view of *Trigonella foenum-graecum*

Fenugreek or *Trigonella foenum graecum* L. is a short-lived herbaceous plant from the Fabaceae family, widely known as a spice plant as well as a medicinal plant. In Indonesia, this plant is not as popular as ginger, turmeric, or temulawak, but its use is beginning to increase, especially in the fields of herbal medicine, nutraceuticals, and pharmacological research, particularly related to metabolic diseases such as diabetes mellitus. Morphologically, *Trigonella foenum-*

graecum is a short perennial herbaceous plant, approximately 30 to 60 cm tall. Its stem grows upright, with fine branches, and is light green in color. The root system consists of a taproot with several well-developed lateral roots, which is a common characteristic of members of the Fabaceae family (24,25).

Fenugreek leaves are compound trifoliate, meaning each leaf stalk consists of three leaflets. The leaf shape tends to be oval to lanceolate with slightly serrated edges. The surface of the leaves is smooth and light green in color. This leaf structure plays an important role in photosynthesis and is also one of the parts of the plant that contains bioactive compounds, including flavonoids and polyphenols. Fenugreek flowers are small, with a pale yellowish-white to pale cream color. The flowers usually appear solitary or in pairs in the leaf axils. As a member of the legume family, the flower shape resembles a papilionaceous flower with a distinctive structure consisting of a standard, wings, and a keel. The fenugreek fruit is a slender, elongated pod measuring about 10 to 15 cm in length. Each pod can contain 10 to 20 seeds. Fenugreek seeds are the most utilized part of the plant for pharmacological and nutritional purposes. The seeds are small, hard, yellowish-brown in color, and have a strong, distinctive aroma due to the presence of volatile compounds and alkaloids (26–28).

The taxonomic position of *Annona muricata* is as follows, according to the Integrated Taxonomic Information System (2025) (29):

Kingdom : Plantae

Division : Magnoliophyta

Class : Magnoliopsida

Order : Fabales

Family : Fabaceae

Genus : Trigonella

Spesies : *Trigonella foenum-graecum* L.

3.2. Role of *Trigonella foenum-graecum* as Antioxidant in Type 2 Diabetes Mellitus

The synthesis results from five studies analyzed indicate that *Trigonella foenum-graecum* or fenugreek has a consistent potential as an antidiabetic agent primarily through the modulation of oxidative stress. All of the reviewed studies used animal models of induced diabetes, mainly through streptozotocin (STZ) or a combination of high-fat diet and STZ, which are widely used experimental models to replicate conditions of chronic hyperglycemia, insulin resistance, and diabetes complications (30). Although all available evidence comes from animal studies and cannot yet be directly generalized to the human population, the emerging pattern of results shows a strong biological consistency regarding the role of fenugreek in reducing oxidative stress in diabetic conditions (31).

Oxidative stress is one of the central mechanisms in the pathogenesis of diabetes mellitus and its complications (32). Chronic hyperglycemia leads to increased formation of reactive oxygen species (ROS) through various metabolic pathways, including activation of the polyol pathway, formation of advanced glycation end products, activation of protein kinase C, and mitochondrial dysfunction (33). Excessive ROS production causes an imbalance between free radicals and the body's endogenous antioxidant defense systems. This condition triggers lipid peroxidation, protein damage, cell membrane dysfunction, and DNA injury, ultimately worsening insulin resistance and accelerating damage to diabetes target organs (34,35).

One of the most consistent findings from the five studies is fenugreek's ability to reduce oxidative stress biomarkers, particularly malondialdehyde (MDA). MDA is a final product of lipid peroxidation commonly used as an indicator of oxidative damage to cell membranes. An increase in MDA levels reflects high damage caused by ROS in tissues. A study by Vishwakarma et al. (2024) showed that administration of ethanol extract of fenugreek seeds significantly decreased MDA levels compared to the diabetes group without therapy (23). Similar results were also reported by Alsieni et al. (2021), Al Hunduwan et al. (2024), and Li et al. (2018), all of whom found a significant reduction in MDA after fenugreek intervention. The consistency of these findings suggests that fenugreek can suppress the increased lipid peroxidation caused by hyperglycemia (19,21,22).

In addition to lowering MDA, fenugreek has also been proven to enhance endogenous antioxidant system activity. Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPx) play a crucial role in neutralizing ROS and protecting cells from oxidative damage . In diabetic

conditions, the activity of these enzymes generally decreases due to excessive consumption of antioxidants to combat ROS. In the study by Vishwakarma et al. (2024), SOD and CAT activities significantly increased after administration of fenugreek. Alsieni et al. (2021) reinforced these findings by showing increased levels of SOD, CAT, GSH, and GST in diabetic rats given fenugreek extract. This indicates that fenugreek not only acts as a direct free radical scavenger but also contributes to restoring endogenous antioxidant capacity (36).

A study by Al Hunduwan et al. (2024) provides stronger evidence regarding the antioxidant effects of fenugreek on specific organ complications, particularly the kidneys. In a diabetic rat model, fenugreek significantly increased levels of GSH, SOD, and CAT, accompanied by a decrease in MDA. These improvements correlated with better kidney function, as indicated by reductions in blood urea nitrogen, creatinine, and uric acid levels. These findings suggest that the antioxidant effects of fenugreek have broader clinical implications, namely protection against diabetic nephropathy. In other words, the reduction of oxidative stress by fenugreek not only improves laboratory biomarkers but also contributes to structural and functional protection of the organs (37).

The protective effects of fenugreek are also observed in other organs such as the liver, pancreas, and cardiovascular tissues. Li et al. (2018) reported that flavonoid extract and stilbene glycoside from fenugreek can repair histopathological damage to the liver, kidneys, and pancreas in a type 2 diabetes model. Interestingly, the group receiving a high dose showed a decrease in blood glucose levels accompanied by an increase in SOD and CAT, as well as a significant decrease in MDA. This indicates a close relationship between glycemic control and oxidative stress. The reduction in blood glucose likely decreases ROS production triggered by hyperglycemia, thereby indirectly reducing oxidative tissue damage.

Studi Bafadam et al. (2021) expands the understanding of the antioxidant mechanism of fenugreek by evaluating heart tissue. Diabetes is known to increase the risk of diabetic cardiomyopathy through mechanisms involving inflammation, apoptosis, and oxidative stress. In this study, fenugreek decreased ROS levels in the myocardium and reduced cardiomyocyte apoptosis. The reduction in proapoptotic protein expression such as Bax and caspase 3, along with an increase in the antiapoptotic protein Bcl-2, indicates that fenugreek can modulate cell death pathways triggered by oxidative stress. These findings are very important because they show that the benefits of fenugreek are not limited to metabolic control but also extend to cardiovascular protection (38,39).

The antioxidant effects of fenugreek are likely related to the content of active phytochemicals within its seeds. Fenugreek is known to be rich in flavonoids, polyphenols, steroid saponins such as diosgenin, alkaloids like trigonelline, as well as a unique amino acid called 4-hydroxyisoleucine. Flavonoids and polyphenols have the ability to donate electrons to neutralize free radicals, thereby reducing the accumulation of ROS. Diosgenin is known to have anti-inflammatory and antioxidant activities through modulation of cellular signaling pathways. Meanwhile, trigonelline has been reported to contribute to improved glucose metabolism and protection of pancreatic beta cells. The combination of these various bioactive compounds likely explains why fenugreek exhibits relatively consistent antioxidant activity across all studies (40).

However, there are some limitations in the available evidence. First, all the reviewed studies are animal studies, so the level of evidence is still lower compared to randomized clinical trials in humans. The biological response in animals does not always match the response in humans, especially regarding pharmacokinetics and effective doses. Second, there is heterogeneity in the forms of fenugreek preparations used, ranging from ethanol extracts, water extracts, seed powders, to flavonoid and stilbene glycoside isolates. This variation can affect the bioavailability of active compounds and the magnitude of antioxidant effects. Third, the duration of intervention and doses across studies vary quite a bit, which limits direct comparisons between the studies. Overall, the synthesis of these five studies indicates that *Trigonella foenum-graecum* has a strong antioxidant effect on diabetic conditions through three main mechanisms: reducing ROS production, inhibiting lipid peroxidation marked by decreased MDA, and enhancing endogenous antioxidant defense systems such as SOD, CAT, and GSH. These effects consistently correlate with improved glycemic control and protection of diabetes target organs such as the pancreas, kidneys, liver, and heart. These findings support the potential of fenugreek as a promising complementary therapy in diabetes management, particularly for suppressing complications mediated by oxidative stress. However, clinical studies on humans are still needed to confirm the effectiveness and safety of fenugreek in clinical practice.

4. Conclusion

Fenugreek shows promising potential as a complementary therapeutic agent in the management of diabetes mellitus, particularly through its ability to modulate oxidative stress, which plays a crucial role in the pathogenesis and progression of diabetes complications. Based on the analyzed studies, fenugreek contributes to improvements in

metabolic status and provides protective effects against tissue damage caused by diabetes. These findings reinforce the potential of fenugreek as a phytotherapy candidate that can support more holistic diabetes management. However, clinical studies on humans with more robust methodological designs are needed to confirm its effectiveness and safety for use in clinical practice.

Compliance with ethical standards

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Disclosure of Conflict of interest

The authors declare no conflicts of interest.

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