Anti-diabetic Properties of *Melissa officinalis* and Saffron: Recent Advances and Discoveries

Melissa officinalis ve Safranın Anti-diyabetik Özellikleri: Son Gelişmeler ve Keşifler

Behnam Sadigi[1,2], Reza Yarani[3], Nikolaj Travica[4], Zahra Yousefi[5], Seyed Kazem Shakouri[6], Alireza Ostadrahimi[7]
Majid Mobasseri[8], Fateme Tahmasbi[1], Sarvin Sanaie[9*], Mostafa Araj-Khodaei[9*]

[1] Student research committee, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Department of Persian Medicine, Faculty of traditional medicine, Tabriz University of medical sciences, Tabriz, Iran
[3] Translational Type 1 Diabetes Research, Department of Clinical Research, Steno Diabetes Center Copenhagen, Gentofte, Denmark
[4] Deakin University, IMPACT – the Institute for Mental and Physical Health and Clinical Translation, Food & Mood Centre, School of Medicine, Barwon Health, Geelong, Victoria, Australia
[5] Research Center of Psychiatry and Behavioral Sciences, Aging research institute, Tabriz University of medical sciences, Tabriz, Iran
[6] Physical Medicine and Rehabilitation Research Center, Aging research institute, Tabriz University of medical sciences, Tabriz, Iran
[7] Department of Clinical Nutrition, School of Nutrition and Food Sciences, Tabriz University of medical sciences, Tabriz, Iran
[8] Department of Internal Medicine, School of Medicine, Tabriz University of medical sciences, Tabriz, Iran
[9] Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran
* Equally contributed

ABSTRACT

Aim: Diabetes mellitus is a chronic medical condition characterized by an accumulation of glucose in the bloodstream. Specifically, type 2 diabetes occurs when the body's cells are unable to efficiently respond to insulin, the hormone responsible for transporting circulatory glucose into cells. In the advanced stages of the disease, the body may also not produce sufficient amounts of insulin. As the disease progresses, the symptoms become more severe and potentially lead to a series of comorbidities. Although several medications are used to treat and control type 2 diabetes, these medications may have serious side effects. Hence, the use of herbal medicine to alleviate type 2 diabetes has been studied and has attracted widespread interest. Our major goal is to examine these herbs' effectiveness and related mechanisms of action in treating type 2 diabetes.
Method: We studied worldwide traditional medicines, old texts, and published literature for anti-diabetic effect of *Melissa officinalis* and saffron. Electronic databases comprising PubMed, Web of Science, Science Direct, Scopus and Google Scholar were searched to collect articles published between 1990 and 2022 years.
Results: We confirmed that a variety of herbal therapies, including saffron and lemon balm (Melissa officinalis), had anti-diabetic activities based on the findings of various research.
Conclusion: Saffron and *Melissa officinalis* have anti-diabetic properties.

Keywords: Type 2 diabetes, Herbal medicine, Saffron, Melissa officinalis, Nutrition

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ÖZET

Amaç: Diabetes mellitus, kan dolaşımında glikoz birikimi ile karakterize kronik bir tıbbi durumdur. Özellikle tip 2 diyabet, vücut hücreleri dolaşımdaki glikozun hücrelere taşınmasından sorumlu hormon olan insüline etkili bir şekilde yanıt veremediğinde ortaya çıkar. Hastalığın ileri aşamalarında vücut yeterli miktarda insülin de üretemeyebilir. Hastalık ilerledikçe semptomlar daha şiddetli hale gelir ve potansiyel olarak bir dizi komorbiditeye yol açar. Tip 2 diyabeti tedavi etmek ve kontrol altına almak için çeşitli ilaçlar kullanılsa da, bu ilaçların ciddi yan etkileri olabilir. Bu nedenle, tip 2 diyabeti hafifletmek için bitkisel ilaçların kullanımı araştırılmış ve yaygın bir ilgi görmüştür. Başlıca amacımız, bu bitkilerin tip 2 diyabet tedavisindeki etkinliğini ve ilgili etki mekanizmalarını incelemektir.
Yöntem: *Melissa officinalis* ve safranın anti-diyabetik etkisi için dünya çapında geleneksel ilaçları, eski metinleri ve yayınlanmış literatürü inceledik. PubMed, Web of Science, Science Direct, Scopus ve Google Scholar'dan oluşan elektronik veri tabanları taranarak 1990 ve 2022 yılları arasında yayınlanmış makaleler toplandı.
Bulgular: Çeşitli araştırmaların bulgularına dayanarak safran ve melisa (*Melissa officinalis*) dahil olmak üzere çeşitli bitkisel tedavilerin anti-diyabetik aktivitelere sahip olduğunu doğruladık.
Sonuç: Safran ve Melissa officinalis anti-diyabetik özelliklere sahiptir.

Anahtar Sözcükler: Tip 2 diyabet, Bitkisel ilaç, Safran, Melissa officinalis, Beslenme

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ORCID IDs: B.S. 0009-0007-5211-2572R.Y.0000-0002-9892-1937,N.T.0000-0003-1841-3017,Z.Y.0000-0002-8708-6358,S.K.S.0000-0003-3815-4091,A.O.0000-0002-1058-1481,M.M. 0000-0002-8108-5979,F.T.0000-0002-0652-7693,S.S.0000-0003-2325-5631,M.A-K. 0000-0002-2590-8467

Address for Correspondence / Yazışma Adresi: Sarvin Sanaie, Faculty of Medicine, Golgasht Street, Azadi Boulevard, Tabriz, Iran E-mail: sarvin_so2000@yahoo.com

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INTRODUCTION

The use of herbal medicine has continuously increased over the past decades. One century ago, natural herbs were an essential therapy for treating human diseases (1). It has been predicted that more than 20% of modern medications are made from plants previously used medicinally (1). Importantly, the observed safety of herbal interventions has prompted the investigation of their efficacy in several conditions (2).

More than 410 million people live with diabetes worldwide, and an estimated 190 million have undetected diabetes (3). Type 2 diabetes accounts for more than 90% of patients with diabetes and leads to macrovascular and microvascular problems that cause profound physical and psychological distress, placing a profound burden on healthcare systems (3, 4). Type 2 diabetes predominantly occurs due to insulin resistance, a condition whereby body cells cannot recognize insulin. (5) As cells fail to recognize insulin, the pancreas recompenses by producing more insulin. Over time, the pancreas is unable to sustain the elevated production of insulin. (6) The exact reason for the occurrence of insulin resistance is mysterious, but could be attributed to a combination of genetic and lifestyle factors. (7) Primary treatment of type 2 diabetes involves lifestyle alterations that target diet, increasing physical activity, and exercise as well as reducing body weight.(8) Notably, herbal interventions have specifically been implemented in the management and potential treatment of Type 2 diabetes.(9-11) A wide variety of herbs are used to treat type 2 diabetes, with two promising interventions including saffron and *Melissa officinalis*. (12-17) Despite the medicinal importance of these plants in treating type 2 diabetes, no review has summarized the findings to date. As such, the main purpose of this review is to explore the efficacy and associated mechanisms of action of these herbs in type 2 diabetes.

Herbal medicine for Type 2 diabetes

Persian Medicine (PM) is one of the most ancient medical schools mostly known by manuscripts of Persian scientists such as The Canon of Medicine by Avicenna and The Great Continens by Rhazes (18). Additionally, PM owes several other scientists with precious manuscripts regarding anatomy and physiology, disease diagnosis, surgery instruments, and single and compound natural medicines (19). Persian medicine (PM) is a traditional form of medicine, comprising several hundred years of history. PM consists of numerous medicinal plants that have been used in the treatment of diabetes (20). For example, one study revealed that ethanol extract of Squash skin (Cucurbita pepo) altered serum lipid and blood glucose in alloxan-induced diabetic rats (21). Numerous studies have been evaluated the anti-diabetic effects of urtica dioica and the results showed that nettle supplement can control fasting blood glucose in patient with type 2 diabetes mellitus (22). Moreover, pomegranate is a fruit derived from a tree belonging to the Punicaceae family and growing in several regions of Iran, has shown anti-diabetic properties (23). Lettuce or milkweed is a plant belonging to the Compositae family that has demonstrated significant reductions in blood glucose (24). Oxidative stress is the causative agent augmenting diabetic problems in many organs by producing a toxic amount of free radicals (25). Findings revealed that the traditional plant, *Tinospora cordifolia,* produces an anti-diabetic effect by modifying oxidative stress, stimulating insulin secretion, inhibiting glycogenolysis and gluconeogenesis, and regulating overall blood glucose (26). Glabridin is a polyphenolic flavonoid (phytochemical found in plants) that is a bioactive component in licorice, which has shown multiple pharmacological activities, including anti-diabetic properties (27, 28). Evidence has suggested anti-oxidant effects of glabaridine (29, 30), for instance, oxidation of low-density lipoprotein was reduced by twenty percent after oral administration of licorice-root ethanol extract for six months. (31) Due to its therapeutic potential, *Stevia rebaudiana Bertoni* is a herbal medicine used by the Brazilian and Guarani Indians of Paraguay to treat diabetes (32, 33). Studies have suggested antioxidant potentials for Stevia as well. (34, 35) *Tinosporacordifolia* Miers (Menispermaceae) is a herbal medicine frequently found in hedgerows and is native to different areas (36, 37). *Tinosporacordifolia* has been extensively used in folk medicine in India as a tonic and therapy for metabolic disorders such as diabetes mellitus (37).
Findings have revealed that *Trigonella stellata* can alleviate diabetes mellitus by impacting drug-metabolizing enzymes, oxidative stress, and antioxidant enzyme activities (38). Furthermore, prepared garlic extract exhibited anti-diabetic properties in diabetes mellitus by inhibiting DPP-4 (dipeptidyl peptidase-4) (39).

As can be seen in Figure 1, the primary anti-diabetic mechanism of medicinal plants is related to enzymatic activity, especially oxidative stress.

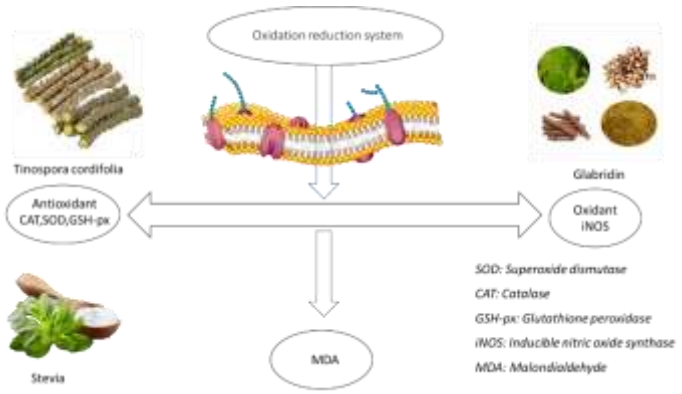


Figure.1. Schematic illustration of the mechanisms associated with herbal medicine in diabetics

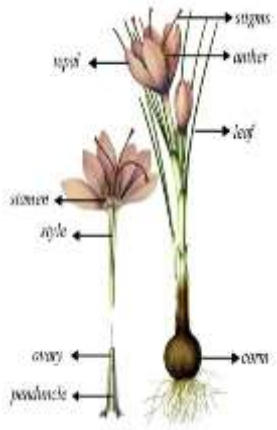
Saffron and *Melissa officinalis* in traditional medicine

Saffron and *Melissa officinalis (MO)* are widely used plants in traditional medicine. Studies show that these plants have a variety of medicinal properties. For instance, Saffron and its related carotenoid constituents have been widely studied for their biomedical properties(40). These have particularly been explored in cancer during the past decade. Saffron and its constituents play a crucial role in the inhibition of different disorders(40). Since saffron has various constituents and components, it has many applications that relate to foods and beverages, pharmaceuticals, various chemicals, and supplements(40, 41). Given that saffron is a relatively newly studied therapeutic agent, it could provide a promising medicinal intervention. Available literature has indicated anti-cancer and anti-tumor activity derived from saffron (42). Accordingly, malignant cells are more sensitive to the inhibitory effects of saffron on RNA and DNA synthesis than normal cells, while protein synthesis is not affected (43). Results from a study based on a cohort with mental health disorders have shown that saffron can positively reduce depression and anxiety (44). A double-blind comparative study showed the influence of saffron on both, depression and lipid profiles (45). A randomized, double-blind, placebo-controlled study revealed the efficacy of a combination of curcumin and saffron in managing depression (46). In general, the results of several studies indicate that saffron is effective in neurological and neurodegenerative diseases such as Alzheimer's and Parkinson's. However, numerous studies are underway to elucidate the exact mechanism of action.As can be deduced from Table 1,2, different parts of the saffron plant have important medicinal and therapeutic properties. In addition, saffron and *Melissa officinalis* have anti-diabetic properties, which are discussed below.

Table 1. Medicinal properties and active constituents of saffron.

Part of plant	Effect	Ref
Crocin	- Prevent the loss of learning and memory as well as the oxidative stress damage to the hippocampus induced by chronic stress - Aphrodisiac properties - Induce recognition and spatial memory - Inhibition of LPS-induce nitric oxide (NO) release from cultured rat	(59, 60)
Saffron extract	- Prevent or delay angiogenesis and progression of tumors - Inhibit the formation of skin papillomas in animals - Cardio-protective effect by preserving hemo- dynamics and left ventricular functions	(61-63)
Crocetin	- Inhibition of induced postsynaptic potentials and glutamate induced membrane depolarization - Neuroprotection by reducing the production of various neurotoxic molecules from activated microglia	(64, 65)
Safranal	- Protective effects on different markers of oxidative damage in rats - Saffron odor significantly decreased cortisol levels and increased testosterone level - Reduce diazinon hematological toxicity	(66, 67)

Table 2. Medicinal properties and active constituents of saffron



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Melissa officinalis (MO) is permanent aromatic rosemary commonly known as a honey balm and lemon balm (47). MO is considered a source of a range of active chemical compounds that are found in leaves or essential oil, and different polyphenolic and terpene compounds. MO has been widely used in folk medicine for various medical purposes (48). As such, it is used in the food industry and aromatherapy due to its fresh smell. Notably, only aerial plant components are conventionally used, with their roots attracting less consideration. Several studies have revealed that MO is a potential source for treating a varied range of diseases, particularly central nervous system disorders, anxiety, infections, high blood pressure, and others; however, assenting trials are necessary to validate these effects in clinical settings (49). Figure 2 illustrates the medicinal properties and active constituents of *Melissa officinalis.*

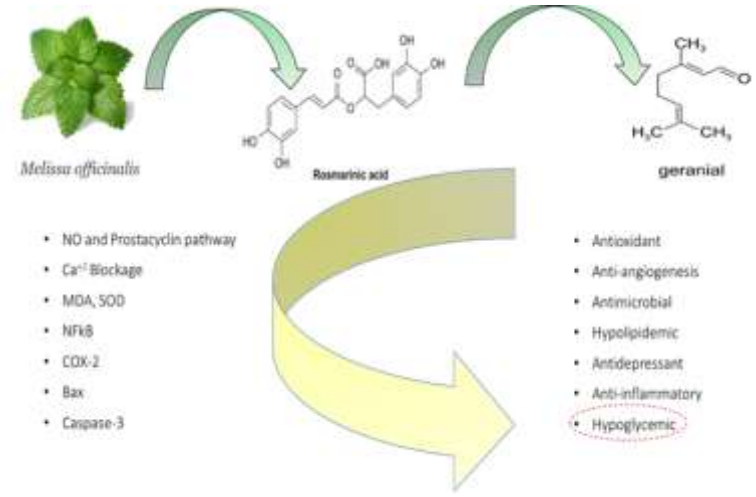

Figure 2. Medicinal properties and active constituents of *Melissa officinalis*.

Figure 2. continued.

Saffron and *Melissa Officinalis* in type 2 diabetes (T2D)

Diabetes mellitus typically includes lipid irregularities such as raised circulating levels of low-density lipoprotein (LDL-C), triglycerides (TG), total cholesterol (TC) and is accompanied by reduced circulating levels of high high-density protein (HDL) particles. Throughout diabetes, persistent hyperglycemia causes elevated production of free radicals, particularly reactive oxygen species (ROS) (50). These free radicals react with lipids by undergoing peroxidation to form lipid peroxides (50). The growth in the level of ROS in diabetes may be due to the decreased production and enzymatic and non-enzymatic destruction of catalase, increased production of superoxide dismutase (SOD), in addition to reduced antioxidants such as glutathione (GSH) (50, 51). Medicinal plants have a number of unique features implicated in the management and treatment of T2D, among which saffron and *Melissa officinalis* are of great importance.

Saffron has shown to considerably improve serum insulin concentrations and lower blood glucose levels in diabetic patients(52, 53). Crocin, due to its antioxidant capacity, calcium stabilization and antagonistic action may provide an efficient remedy for diabetic vascular complications. Various studies show that chemical and bioactive compounds found in saffron are its primary anti-diabetic agents. Hydroalcoholic extract of crocus sativus reduces blood glucose by decreasing fasting blood sugar in T2D patients, while no effect was observed on plasma lipid concentration and blood pressure reduction (54). Findings have shown that saffron controls glucose levels and inflammatory status in T2D by reducing the level of various inflammatory mediators (55). Saffron supplementation in T2D had favorable effects on serum malondialdehyde (MDA) levels (a marker of oxidative stress) and waist circumference. Conversely, saffron did not affect other estimated cardio-metabolic risk markers in diabetic patients (56). A systematic review discovered that saffron could be considered a valuable adjuvant therapy in the glycemic control of diabetic patients (57). Based on one clinical trial, +saffron reduced hyperlipidemia and hyperglycemia and enhanced liver function in patients with T2D (58). Moreover, saffron supplementation improved antioxidant and glycemic indices in overweight pre-diabetics, however, no useful effect was observed on anthropometric parameters and lipid profiles (59). Resistance and aerobic training with saffron ingestion was shown to effectively expand the antioxidant balance and peroxidase in men with T2D (60). In addition, low-intensity aerobic exercise with saffron supplementation improved the antioxidant capacity of diabetic rats (61). Specifically, Crocin supplementation has shown the ability to decrease insulin resistance and maintain glucose homeostasis in T2D, being suggested as an adjuvant to standard diabetic care (62). Conversely, the results of one study exhibited no improvement in antioxidant status, homocysteine levels and inflammatory biomarkers in T2D patients after treatment with saffron (63). Herbal products can increase antioxidant status and therefore decrease the pathologies associated with T2D(64).

In line with this, plants containing an abundance of antioxidant agents such as flavonoids exert protection against beta cell damage(64). Flavonoids are significant plant antioxidants that comprise of phenolic compounds, which act as free radical scavengers (65).

Findings have indicated the ingestion of a low concentration of MO to be an efficient anti-diabetic agent. This may be attributed to MO improving metabolism in the liver and adipose tissue, increasing glucose uptake and inhibiting gluconeogenesis in the liver (66). An important study has shown that *Melissa officinalis* essential oil (MOEO) administration resulted in significant anti-diabetic properties (67). Improvements in glycemic control, lipid profile, and a decrease in inflammation have followed the administration of MO with no side effects (68). It has further been shown that the hydro-alcoholic extract (HEMO) of the aerial components of MO initiated significant improvements on serum lipoprotein (17). At the same time, HEMO had no major effects on liver enzymes and lipids ratios (17). Consequently, MO extract could act as a safe intervention by modifying the organic markers and blood lipids in patients with T2D (17). Furthermore, HEMO had significant effects in reducing lipoprotein levels, serum lipids, blood sugar levels and increasing HDL levels. MO are further useful in reducing the serum TG level in dyslipidemia diabetic patients, although the underlying mechanism was unclear with the need of additional studies (15). Serum total lipids, cholesterol and liver enzyme levels were decreased significantly after oral administration of an aqueous extract of MO (69). One imperative study suggested that a MO extract presented with a hypo-lipidemic effect and protective effect on the liver of hyperlipidemic rats (70). Traditional medicine has demonstrated that MO administration could decrease liver enzymes and body weight and improve fatty liver grade in Non-Alcoholic Fatty Liver Disease (71). MO further has protective effects on the pancreatic beta cells against toxic chemicals such as streptozotocin (STZ). (72) More studies are required to examine the beneficial effects and possible adverse effects of MO in humans and laboratory models. According to one study, a decrease in TG and blood glucose levels, and an increase in HDL were observed in diabetic rats after consumption of hydroalcoholic extract present in the MO plant (73). Furthermore, the extract of MO has hypolipidemic effects that can consequently be effective in monitoring and inhibiting the pathologies associated with diabetes (74). In addition, blood sugar levels of diabetic rats were reduced in response to MO flavonoids, which have extensive antioxidant properties (75).

CONCLUSION

The present review aimed to highlight the importance of herbal medicines, particularly *Melissa officinalis* and saffron, in type 2 diabetes. Currently, data suggest that medicinal plants have several therapeutic properties that target type 2 diabetes, with minimal side effects. Notably, it has been distinguished that *Melissa officinalis* and saffron have numerous constituents that can be efficacious in patient with type 2 diabetes mellitus. Further biochemical and pharmacological investigations would clearly explain the mechanisms of action associated with *Melissa officinalis* and saffron and clarify their importance in diabetes research. Finally, large-scale trials that explore the active ingredients, varying dosages, long-term safety, and overall efficacy of saffron and *Melissa officinalis* in type 2 diabetes are required.

Conflict of interest

No conflict of interest was declared by the authors.

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