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Saffron and *Melissa officinalis* (Lemon Balm) on Glycemic Markers

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Abstract

Background: Metabolic control is a major concern for the prevention of metabolic disorders. Saffron and *Melissa officinalis* are natural sources of antioxidants that can reduce the risk of metabolic diseases. This study aimed to identify and highlight the effects of saffron and *Melissa officinalis* on glycemic markers. **Methods:** Four research sources were examined in randomized controlled trials on the effects of saffron and *Melissa officinalis* on glycemic markers. Several studies have explored the effects of saffron and *Melissa officinalis* (lemon balm) on glycemic markers and their antidiabetic properties. Some studies have shown positive effects, such as decreased serum levels of FPG in patients with type 2 diabetes. Other studies have shown significant reductions in triglyceride and glycated hemoglobin levels, but no significant difference in glycemic control. Studies have also investigated the effects of saffron with concurrent training, resistance training, aerobic training, or both. **Conclusion:** Research shows that saffron and *Melissa officinalis* L significantly affect glycemic markers, including FPG, HbA1c, HOMA-IR, and insulin resistance, providing valuable insights for patients with diabetes. Future research should explore the effects of saffron and *Melissa officinalis* L on glycemic markers, involving *in vitro* and *in vivo* studies and larger randomized controlled trials.

Keywords

Crocus sativus L, Saffron, *Melissa officinalis*, Lemon Balm, Herbal Medicine, Metabolic Syndrom

1. Introduction

Metabolic disorders such as diabetes and insulin resistance are the main causes of mortality worldwide and pose a threat to health. Therefore, prevention and treatment of these diseases are important [1]. Medicinal plants are used to treat various disorders worldwide [2]. Saffron (*Crocus sativus* L) is a perennial stemless herb of the Iridaceae family that grows extensively in Iran and other countries such as Spain, India, and Greece. Its active components have demonstrated beneficial pharmacological properties, including anticonvulsant, antidepressant, anti-inflammatory, anti-tumor, radical scavenger, learning- and memory-improving, and antidiabetic effects [3]. The most expensive spice is referred to as "Red Gold." Saffron stigmas include crocin, picrocrocin, crocetin and safranin. Crocin is responsible for the reddish color of saffron [4] and several studies have indicated its potential to enhance blood sugar levels [5]-[7]. *Melissa officinalis* (MO), also known as lemon balm, is a perennial herbaceous plant that belongs to the mint family Lamiaceae [8]. MO is thought to contain a variety of active chemical components found in the leaves and essential oils, as well as polyphenolic and terpene chemicals. MO has been extensively used in folk medicine for various medical applications. Owing to its pleasant odor, it is employed in the culinary and aromatherapy sectors. Notably, only aerial plant components are commonly exploited, with the roots receiving less attention [9]. This herb, which contains a high concentration of phenolic chemicals, can be used to prevent and treat disorders such as hyperlipidemia, type 2 diabetes, and CVD [10]. Several studies have shown that MO is a possible treatment for a wide range of ailments including central nervous system disorders, anxiety, infections, and high blood pressure. However, further clinical trials are required to confirm our results [9]. MO is a source of active phytochemicals such as triterpenes, flavonols, and phenolic acids. In traditional Asian medicine, MO is used to treat numerous ailments including rheumatoid arthritis, gastrointestinal illnesses, and neurological disorders [8]. The main purpose of this review was to examine the effects of saffron and *Melissa officinalis* on glycemic markers.

1.1. Antioxidants in Saffron and *Melissa officinalis*

Proposed Mechanisms of Action

Saffron contains active compounds, such as crocin, safranal, and crocetin, which are believed to influence glycemic control through several biological pathways. Crocin, for example, improves insulin sensitivity by enhancing GLUT4 translocation and stimulating AMP-activated protein kinase (AMPK) activity in muscle cells. Safranal has antioxidant properties that reduce oxidative stress, a key factor in insulin resistance. Similarly, *Melissa officinalis* is rich in flavonoids, rosmarinic acid, and other phenolic compounds that may influence carbohydrate metabolism. Its antidiabetic properties may be mediated by the increased expression of hepatic glucokinase, upregulation of GLUT4 transporters, and improved insulin signaling. Both herbs also possess anti-inflammatory properties that may further contribute to glycemic regulation by modulating systemic inflammatory markers associated with metabolic dysfunction [11] [12].

Medical plants are rich in biologically active substances. These plants can provide raw components for synthesis of novel or semisynthetic medications, found in many sections of the plants and can be obtained from any part of the plant like seeds, roots, leaves, flowers or the entire plant. Most medicinal plants have direct or indirect therapeutic effects [13]. *Melissa officinalis* contains polyphonic acid, flavonoids, triterpenes, and volatile chemicals. M. officinalis has many qualities and is effectively used in many diseases, including depression, anxiety, stress, and digestive, neurological, and cardiovascular disorders [14]. M. officinalis prefers plants in the medical field because of their edible, aromatic, and particularly characteristic characteristics. The therapeutic benefits of MO have been demonstrated using many secondary metabolites including terpenes, phenolic acids, and flavonoids. Eo contains harammin, citrate, hexenol, octin, octinone, eugenol, and octinol [15]. Saffron, as well as an example of a medicinal herb, has been used medicinally for more than 2500 years and has been used in traditional medicine for the treatment of various diseases, including cardiovascular diseases, asthma, and sleeplessness. Saffron has several beneficial effects on several active compounds including safranal, crocetin, and crocins [16]. Over 150 compounds that generate aroma found in saffron, saffron essential oil has a prominent compound called safanal, it's a substance formed in saffron via the hydrolysis of picrocrocin during the drying and storage of saffron, also includes many volatile active ingredients like carotenoids (zeaxanthin, lycopene, and many α- and β-carotenes) [17]. Crocin helps reduce blood sugar levels through different ways by activating certain cells in the pancreas called langerhans islets also makes the muscles in the body respond better to insulin, additionally crocin has strong antioxidant properties because of the existence of carotenoids and is more effective than safranal, the combined of all the Bioactive components gives saffron excellent antioxidant properties [18].

2. Methods

A structured literature search was conducted up to 2024 across four major databases: PubMed, Google Scholar, ScienceDirect, and the Central Register of Controlled Trials. The objective was to identify randomized controlled trials (RCTs) that investigated the effects of *Crocus sativus* L. (saffron) and *Melissa officinalis* (lemon balm) on glycemic control.

Keywords used during the search included: "saffron", "lemon balm", "*Crocus sativus*", "*Melissa officinalis*", "diabetes", "glycemic markers", "HbA1c", "insulin", and "fasting plasma glucose". Studies were screened for relevance based on titles, abstracts, and full texts, focusing exclusively on human clinical trials with outcomes related to glycemic parameters.

Inclusion Exclusion Criteria

Only human clinical studies were searched in the previous databases, and animal studies were excluded. However, only relevant studies have been conducted.

3. Results

Several randomized controlled trials have investigated the effects of saffron and *Melissa officinalis* (lemon balm) on glycemic markers, as summarized in **Table 1**.

Both botanicals are recognized for their antidiabetic properties [9]. The findings, however, are mixed—some studies reported significant improvements, while others observed minimal or no effects.

Table 1. The studies that examined the effects of saffron and *Melissa officinalis* on glycemic markers.

Study (Year)	Study design	Sample size	Ganders	Population	Dose	Intervention/ Groups	Duration	Outcomes
Milajerdi *et al.* 2018	Randomized, triple-blinded	54	Female/male	T2DM	15 mg saffron twice a day	saffron placebo	8 weeks	After 8 weeks the saffron group showed significant decrease in serum FBS. There was no significant difference in HbA1c.
Ebrahimi *et al.* 2019	Randomized, double-blind	80	Female/male	T2DM	100 mg/day	saffron placebo	12 weeks	There was no significant changes in serum insulin, fasting blood glucose, HbA1c, and insulin sensitivity.
Giannoulaki *et al.* 2024	Randomized, double-blind	61	Female/male	DMT-1	84 mg/day	Saffron Placebo	6 months	The saffron group showed significant changes in HbA1c, serum triglycerides, and diabetes distress.
Hooshmand Moghadam *et al.* 2022	Randomized, double-blind	60	Male	T2DM	100 mg/day	Saffron supplementation placebo concurrent training + saffron supplementation concurrent training + placebo	12 weeks	In all three groups (CT, CTS, S) showed significant decrease in FPG, HOMA-IR, HbA1c, and insulin concentrations. But the CTS group was the most significant compared to other groups.
Karimi-Nazari *et al.* 2019	Randomized, double-blind	75	Female/male	Prediabetic	15 mg/day	saffron placebo	8 weeks	After 8 weeks the saffron group showed significant effects in FBS, and HbA1c.
Kotanidou *et al.* 2023	Randomized, double-blind	74	Female/male	prediabetic	60 mg/day of saffron 1000 mg/day of metformin.	saffron metformin placebo	12 weeks	The metformin group showed significant decrease in fasting glucose, fasting insulin, fasting cholesterol and HOMA-IR. The saffron group showed no significant decrease except fasting triglycerides.

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Mobasseri *et al.* 2020	Randomized, double-blind	60	-	T2DM	100 mg/day	saffron placebo	8 weeks	After 8 weeks the saffron group significantly reduced the FBG levels.
Moravej Aleali *et al.* 2019	Randomized, double-blind	64	Female/male	T2DM	15 mg two pills per day	saffron placebo	3 Months	After 3 months there was significant difference between two groups in FPG, Cholesterol, and HbA1c. But there was no significant difference in TG.
Rajabi *et al.* 2024	Randomized, double-blind	44	Famale	T2DM	200 mg daily	Saffron + training Placebo + training saffron supplementation placebo	12 weeks	There was significant reduction in body weight in the PT, ST, SS group. There was decreased in body fat percentage and BMI in the PT, ST, and SS group. The PT, ST, and SS group showed significant decreases in glucose levels and insulin resistance.
Tajaddini *et al.* 2021	Randomized, double-blind	70	Female/male	T2DM	100 mg/day	saffron placebo	8 weeks	After 8 weeks statistic analysis of saffron group showed significant reduction in FPG, insulin, and TG.
Asadi *et al.* 2019	Randomized, double-blind	62	Female/male	T2DM	700 mg twice daily	M. officinalis placebo	12 weeks	There was significant difference in serum FBS, HbA1c, and TG. But there was no significant change in insulin or HOMA-IR.
Nayebi *et al.* 2020	Randomized, double-blind	37	Female/male	T2DM	Two 500 mg capsules daily	M. officinalis Placebo	3 months	After 12 weeks of intervention, M. officinalis group showed reduction in TG levels, and also in FBS and HbA1c. The P group indicated slightly decrease of the overall serum glucose levels

Continued

Sadighi *et al.* 2024	Double-blind	90	Female/male	T2DM	250 mg capsules every 12 hours	M. officinalis Saffron Placebo	3 months	After three months treatment, significant differences in FBS levels in the saffron group and M. officinalis group, significant reductions in HbA1c. The M. officinalis group showed significant changes in insulin resistance levels in both groups of saffron and M. officinalis showed reduction in triglyceride levels.

For instance, Sadigi *et al.* demonstrated that saffron hydroalcoholic extract significantly reduced fasting plasma glucose (FPG), total cholesterol, and HbA1c in patients with type 2 diabetes [9]. Similarly, Milajerdi *et al.* reported that saffron extract decreased serum FPG levels in type 2 diabetic patients [19].

Giannoulaki *et al.* observed a significant reduction in triglycerides and HbA1c in patients with type 1 diabetes following saffron supplementation, although no substantial changes were seen in glycemic control overall [5].

Some trials examined saffron in combination with exercise interventions. Rajabi *et al.* found that aerobic training, with or without saffron supplementation, led to significant reductions in insulin resistance and blood glucose in women with type 2 diabetes [11]. Likewise, Hooshmand Moghadam *et al.* investigated saffron combined with both resistance and aerobic training in obese men with type 2 diabetes and reported reductions in FPG, HOMA-IR, HbA1c, and serum insulin levels [6].

Regarding *Melissa officinalis*, Asadi *et al.* found improvements in FPG, HbA1c, HOMA-β, and triglycerides after supplementation [20]. Nayebi *et al.* also reported favorable outcomes in glycemic parameters among diabetic patients treated with M. officinalis [21].

A more recent study by Sadighi *et al.* assessed both saffron and M. officinalis and found significant reductions in fasting blood sugar (FBS) and HbA1c in both treatment groups. Additionally, M. officinalis demonstrated beneficial effects on insulin resistance [12].

4. Discussion

4.1. Critical Analysis of the Evidence

While several RCTs have demonstrated the beneficial effects of saffron and *Melissa officinalis* on glycemic markers, the overall evidence remains inconsistent.

For instance, some studies reported significant improvements in FPG and HbA1c levels, whereas others reported no changes in insulin sensitivity or glycemic control [22] [23]. These discrepancies may stem from differences in dosage, treatment duration, and study population characteristics.

For example, studies using saffron in combination with exercise have shown greater improvement, indicating a possible synergistic effect [6] [11]. However, not all studies accounted for lifestyle or dietary habits, which could have confounded the results. Additionally, some studies had small sample sizes or short follow-up periods, limiting their statistical power and generalizability. Despite these limitations, collective evidence suggests a potential role for saffron and lemon balm in managing glycemic control, although further standardization in trial design is needed [20].

4.2. Risk of Bias and Study Quality Assessment

To evaluate the reliability of the included studies, several methodological aspects were assessed, including randomization, blinding, sample size, intervention duration, and control for confounding factors. Most studies were randomized and double-blind, suggesting a low risk of selection and performance bias. However, several trials had small sample sizes ($n < 60$), limiting the statistical power.

Moreover, only a few studies have clearly reported on dietary or lifestyle controls, which increases the risk of confounding bias. The duration of the interventions varied from 8 weeks to 6 months, with longer studies generally yielding more consistent findings. Attrition bias has seldom been addressed and compliance rates have not always been reported. Overall, the methodological quality of most studies ranged from moderate to high; however, heterogeneity in design and reporting practices limits the strength of the conclusions that can be drawn. The methodological quality and risk of bias across the included RCTs are summarized in **Table 2**.

Table 2. Risk of bias and study quality assessment.

Study	Randomized	Blinded	Sample Size	Duration	Confounding Control	Overall Quality
Milajerdi *et al.* (2018)	Yes	Triple	54	8 weeks	No	Moderate
Ebrahimi *et al.* (2019)	Yes	Double	80	12 weeks	No	Moderate
Giannoulaki *et al.* (2024)	Yes	Double	61	6 months	Partial	High
Hooshmand Moghadam *et al.*	Yes	Double	60	12 weeks	Yes	High
Karimi-Nazari *et al.* (2019)	Yes	Double	75	8 weeks	No	Moderate
Kotanidou *et al.* (2023)	Yes	Double	74	12 weeks	Yes	High
Mobasseri *et al.* (2020)	Yes	Double	60	8 weeks	No	Moderate
Moravej Aleali *et al.* (2019)	Yes	Double	64	3 months	Partial	Moderate
Rajabi *et al.* (2024)	Yes	Double	44	12 weeks	Yes	High
Tajaddini *et al.* (2021)	Yes	Double	70	8 weeks	No	Moderate
Asadi *et al.* (2019)	Yes	Double	62	12 weeks	Yes	High
Nayebi *et al.* (2020)	Yes	Double	37	3 months	No	Low
Sadighi *et al.* (2024)	Yes	Double	90	3 months	Yes	High

This review included 13 RCTs that investigated the effects of saffron and *Melissa officinalis* on glycemic markers. In particular, FBG and HbA1c levels, and insulin resistance were observed. Although the primary outcomes were comparable, these trials exhibited variations in design, duration, population, and saffron dosage.

In this study, Milajerdi *et al.* showed a significant difference in FBS after treatment with 15 mg of saffron (two pills per day) hydroalcoholic extract. This study measured glucose in the serum but did not assess insulin resistance or serum insulin concentration, which could ensure a more comprehensive understanding of metabolic control [19]. Aleali *et al.* showed a significant decrease in FPG and HbA1c levels after treatment with 15 mg of saffron (two pills per day) hydroalcoholic extracts [22]. Saffron has been shown to affect insulin concentration and reduce blood glucose levels positively. Furthermore, saffron supplementation improved glycemic indices in overweight prediabetic patients [7], and Karimi-Nazari *et al.* found significant changes in FBS and HbA1c levels in overweight prediabetic patients after supplementation with 15 mg saffron for eight weeks [7]. Mobasseri *et al.* reported a significant decrease in FBG levels after treatment with 100 mg/day in patients with type two diabetes for eight weeks. This study could not confirm which bioactiv compounds that are responsible for the effects because the use of whole plants extracts [23]. Tajaddini *et al.* reported a significant reduction in FPG and insulin levels after administration of 100 mg/day saffron supplements for eight weeks in patients with type two diabetes. This study while indicates important results, does not delve into the fundamental mechanisms through which saffron extract its effects [24]. Kotanidou *et al.* reported no significant differences in glycemic markers. While saffron showed positive effects they were less significant compared to metformin, this study included relatively small samples size which affected the generalisation of the results [25]. Ebrahimi *et al.* reported no significant differences in insulin, blood glucose, or HbA1c levels. Despite some positive findings there were no statistically significant differences, short duration which may not observe long term effects of saffron [26]. Giannoulaki *et al.* found that after six months, the group that was treated with three sachets a day containing 28 mg of C. sativus extract diluted in 200 ml showed significant changes in HbA1c and triglycerides in patients with type one diabetes [5]. Hooshmand Moghadam *et al.* this study investigates the effects of saffron combined with training in obese men with type two diabetes after 12 weeks with 200 mg of saffron powder the group that takes the saffron supplement and training showed the most significant decrease in FPG, HbA1c, HOMA-IR, and insulin concentration. There are potential interaction effects from combining resistance training and aerobic training, may complicate the interpretation of the results [6]. And Rajabi *et al.* study that investigated the effects aerobic training with or without saffron supplements in women with type two diabetes after 12 weeks of the study the group that did aerobic training and took the saffron supplements showed significant improvement in insulin resistance and serum levels of glucose. Some mechanisms of saffron action linked to saffron supplements activating the AMP-activated protein kinase pathway, contributes to regulating glucose metabolism and insulin sensitivity [11]. Nayebi *et al.* showed a reduction in FBS and HbA1c levels after 500 mg twice a day of *Melissa officinalis* for three months in patients with type two diabetes. In this study M. O showed antioxidant effects that may help reduce oxidative stress [21]. Asadi *et al.* showed that after the duration of this study, there was significant variation in serum FBS, HbA1c, and TG levels and no changes in insulin level or HOMA-IRi in patients with type two diabetes. This study includes the comprehensive assessment as dietary inputs and activity were evaluated at the beginning and middle and end of the study providing an understanding of factors that could influence the outcome [20]. To my knowledge, Sadighi *et al.* is the only recent study to examine the effects of saffron and *Melissa officinalis* and showed significant differences in FBS levels in the saffron and M. officinalis groups and significant reductions in HbA1c. The M. officinalis group showed a significant decrease in insulin resistance in both the saffron and M. officinalis groups. The mechanisms of saffron contain an important component called safranal, which is known for antioxidant which may help reduce oxidative stress, M. O helps lower blood sugar levels by increasing the production of hepatic glucokinase and GLUT4 transporter both of which are essential for glucose absorption in cells [12]. Herbal products may enhance antioxidant levels and hence reduce the pathogens associated with type two diabetes [27]. More studies are required to determine the beneficial effects of MO in human and laboratory models.

5. Recommendation for Future Studies

Future studies should consider the effects of saffron and *Melissa officinalis* L together. Additionally, *in vitro* and *in vivo* studies are required to investigate the underlying pathways of saffron and *Melissa officinalis* on glycemic markers, and larger randomized controlled trials are required to confirm the impact of saffron and *Melissa officinalis* on glycemic markers.

6. Conclusion

This review aimed to demonstrate the impact of saffron and *Melissa officinalis* on glycemic markers. By examining the effects of saffron and *Melissa officinalis* on glycemic index, this research highlights the significant impact on FPG, HbA1c, HOMA-IR, and insulin resistance. These findings provide valuable insights into individuals with diabetes and those at risk for insulin resistance. Future investigations are needed to explore the effects of *Melissa officinalis* and saffron on glycemic markers and the impact of *Melissa officinalis* on glycemic levels.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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