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# The effect of Saffron supplementation on waist circumference, HA1C, and glucose metabolism: A systematic review and meta-analysis of randomized clinical trials

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JR, SSHN designed the study. The literature search, screening data, and data extraction were done by EB and JR. Quality assessment was carried out by JR and EB. Analysis by JR and CC. CC, JR, and EB wrote and edited the manuscript. All authors read and approved the final manuscript.

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Abbreviations: T2D: Type 2 diabetes, WC: waist circumstance, FPG: fasting plasma glucose, HA1C: hemoglobin A1C, RCT: Randomized Control Trials, WMD: weighted mean difference.

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**Abstract**

Objective: Carotenoids (including zeaxanthin and lycopene) and phytosterols reportedly confer beneficial effects on metabolic profile and function, which is of clinical importance. Thus, we sought to systematically review and meta-analyze the effects of saffron on waist circumstance (WC), fasting plasma glucose (FPG), and HA1C concentrations reported in Randomized Control Trials (RCTs).

Method: A comprehensive systematic electronic search was performed in PubMed/MEDLINE, Embase, Google Scholar, Cochrane, Web of sciences, and SCOPUS to identify RCTs up to February 2019 without any language restrictions. The pooled weighted mean difference (WMD) calculated with DerSimonian-Laird random. PRISMA guidelines adhered to for this meta-analysis.

Result: Nine articles with 12 arms containing 595 participants were included in the meta-analysis. Our study found WC was significantly reduced (WMD: -2.18 cm, 95% CI: -4.05, -0.32) and FPG (WMD: -6.54 mg/dl, 95% CI: -10.22, -2.85) following saffron intervention. Subgroup analysis highlighted that FPG levels (WMD: -10.24 mg/dl, 95% CI: -15.76, -4.72) reduced significantly when intervention duration was longer than twelve weeks. There was no significant effect on HA1C levels (WMD: -0.13 mg/dl, 95% CI: -0.31, 0.04) following saffron intervention.

Conclusion: In conclusion, the present study indicates beneficial effects on WC and FPG, following saffron supplementation.

**Keywords:** Saffron; Waist circumstance; Crocin; Glucose; HA1C.

## 1. Introduction

Type 2 diabetes (T2D) is a prevalent, global disease, and associated with several comorbidities, such as hyperlipidemia, hypertension, and retinopathy, all of which increase the risk of mortality (Chen et al., 2012; Deshpande et al., 2008; Luk et al., 2017; Rashedi et al., 2017). In contemporary clinical practice, fasting blood glucose (FPG), hemoglobin A1c (HbA1c) and waist circumference are used to detect and monitor diabetes mellitus and metabolic syndrome, and treating or managing such factors represent important clinical goals. The prevalence of abnormal glucose regulation is nearly 40% in patients with coronary artery disease too (17). The normal range for FPG is considered to be 70 to 100 mg/dl, whilst levels between 100 and 126 mg/dl demarcate diminished fasting glucose levels and considered emblematic of pre-diabetes; whilst diabetes is traditionally diagnosed at FPG thresholds of 126 mg/dl or higher(Ghazanfari et al., 2010). HbA1c, or glycated hemoglobin, is hemoglobin with glucose attached and its' measurement represents the average amount of glucose in the blood in the preceding 2-3 months. The reference range for HbA1c level in a healthy person is 4.8-5.7%, whilst ≥6.5% is representative of diabetes (Ghazanfari et al., 2010).

Dietary management, physical activity and lifestyle modifications are shown to be variably efficacious in controlling diabetes and associated comorbidities, and therein represent major clinical research problems; particularly given the prevalence of T2D in both developed and developing countries (Deshpande et al., 2008; D. Skrypnik et al., 2019; Stepien et al., 2018). In recent times, herbal medicines have been used as complementary medicines to improve the regulation of glycemic metabolism in diabetic patients, with moderate success, and may represent a viable adjunct therapy to alleviate current clinical challenges (Paria Azimi et al., 2014; Cicero & Colletti, 2016; Deshpande et al., 2008; Jiang et al., 2011; Patti et al., 2018; K. Skrypnik et al., 2019). Saffron (crocus sativus) is a perennial plant that consists of more than 300 volatile and non-volatile compounds such as safronal, crocin, pirocrocin and some other carotenoids(Fi I Abdullaev, 1993). Several investigations have shown positive pharmacological effect of crocin such as anticancer, antidepressant, anti-ischemic, hypotensive, inflammatory and antioxidant activities (Fikart I Abdullaev, 2002; Aung et al., 2007; Hossein Hosseinzadeh et al., 2009; H Hosseinzadeh & Ziaei, 2006; Imenshahidi et al., 2010). In a study by Shirali et al, saffron, as a traditional medicine and food additive, has the potential to elicit anti-diabetic effects(Shirali et al., 2012). Furthermore, previous studies have demonstrated that crocin (a carotenoid in saffron) improves insulin secretion and reduces insulin resistance(Bathaie & Mousavi, 2010). In an animal model, Xi and colleagues reported that crocin supplementation can elicit positive changes in insulin resistance, hyperinsulinemia, dyslipidemia and hypertension (Tayebe Kermani et al., 2017). However, these effects are yet to be demonstrated in humans.

Although supplementation with saffron, or its derivatives, has been shown to positively effect clinically relevant biomarkers; thus far, there has been no meta-analytical evaluation of the beneficial effects of saffron on FPG, HbA1c and waist circumference. Therefore, the aim of the present study was to evaluate the efficacy of saffron on FPG, HbA1c and WC in randomized clinical trials.

## 2. Methods

### *2.1. Study design and Search strategy*

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015).

A systematic search was performed in PubMed/MEDLINE, Embase, google scholar, Cochrane, Web of sciences, and SCOPUS to locate relevant studies. Randomised controlled trials (RCTs) investigating the effect of Saffron on waist circumference and glucose metabolism compared with control group that received placebo. We systematically combined the search terms of the treatment (i.e. saffron therapy) and the outcome variables (i.e. waist circumference and Glucose metabolism). The search strategy was developed with no language restriction, from database inception until February 2019. The search strategy is detailed in the supplementary Table 1.

*2.2. Selection criteria*

The PICOTS criteria were used to select included articles following P: non-communicable patients, I: intervention by saffron, C: intervention by placebo, O: waist circumference and glucose metabolism, T: inception until February 2019, Study design: Randomized controlled trials. Endnote Reference Manager X8© was used to store identified studies. The inclusion criteria consisted of the following: 1) Adult subjects (18 years and older); 2). RCT design; 3) mean differences with standard deviations before and after of intervention for outcomes are reported; 4). Studies that examined the effects of Saffron or Crocin; 5) Studies that reported waist circumference or/and fasting blood sugar or/and HbA1c as measured outcome. The exclusion criteria were: 1) Treatments other than Saffron; 2) Animal studies; 3) Studies with non RCT design; 4) Studies without a placebo group; 5) Conference abstracts, case-reports, reviews, and commentaries; 6) studies on mental disease. Two authors (JR and EB) independently screened the titles, abstracts and full-texts, respectively, at each stage of the reviewing process.

*2.3. Data extraction*

Two researchers (JR and EB) independently extracted relevant data from studies using a standardised form. Any disagreements were resolved by cooperative triangulation with a senior author (SSHN). The following details were recorded in the standardised form: study authors, location, year of publication, duration of follow up, sample size in intervention and control groups, mean age of participants, Saffron dose, Saffron type, participants disease type, and mean and standard deviation (SD) of outcome pre- and post-intervention. We contacted the authors of included papers for any additional information required.

*2.4. Risk of bias assessment*

The “Cochrane collaboration’s tool for quality assessment of randomized control trials” was employed to examine risk of bias assessment of included studies (Higgins et al., 2011), consisting of the following items: Selection bias (random sequence generation and allocation concealment), completeness of outcome data, other sources of bias, performance bias, outcome bias, and attrition bias.

*2.5. Statistical analysis*

Studies providing estimates of weighted mean differences (WMD) and standard deviations were combined. The DerSimonian and Laird random-effects model was used to calculate the pooled WMD. When the standard error (SE) of the mean difference was reported for studies SD was calculated by the following formula: $SD^2_{baseline} + SD^2_{final} - (2\ R^*\ SD_{baseline} + SD_{final})$ (Cooper et al., 2009). The Q-test, the I-squared statistic, and an alpha level of 0.05 were used to assess the heterogeneity between studies based on the Cochrane thresholds recommendations (Green & Higgins, 2005). Subgroup analyses based on duration of intervention (12 weeks < or +12 weeks) was used to identify sources of heterogeneity among the included studies. Saffron type (Saffron, Crocin, or Saffron extract) was predefined as a source of heterogeneity. The funnel plot and the Egger’s tests were used to assess the probability of publication bias. All statistical analyses were performed using STATA 14 (StataCorp LP, College Station, USA), using an a priori p value of 0.05 to represent statistical significance.

## 3. Results

In our primary systematic search 339 studies were identified from PubMed/MEDLINE, Scopus, Embase, Web of sciences, Cochrane Library and google scholar (Supplementary Figure 1). After removing duplicates, 232 studies were screened. After, screening based on titles and/or abstracts, 187 studies were excluded, and 36 other studies were excluded in full text screening because of the following reasons: 1) Non-RCT design (n=5), 2) non-human trials, review or mental disease population (n=27), and 3) Not measure Waist Circumference, FPG or HbA1c as outcome (n=3). According to inclusion criteria, nine articles with 12 arms containing 595 participants were included in the meta-analysis(N. Abedimanesh et al., 2017; P. Azimi et al., 2014; Fadai et al., 2014; A. Javandoost et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; A. Milajerdi et al., 2018; Nikbakht-Jam et al., 2016; Sepahi et al., 2018).

### *3.1. Study characteristics*

Table 1 provides characteristics of eligible studies. Articles were published between 2014 to 2018. All studies were conducted in the Iran (N. Abedimanesh et al., 2017; P. Azimi et al., 2014; Fadai et al., 2014; A. Javandoost et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; A. Milajerdi et al., 2018; Nikbakht-Jam et al., 2016; Sepahi et al., 2018). There were 301 (range from 20-42 individuals) participants in intervention group and 294 (range from 20-39 individuals) participants in control groups. The mean age of participant was 50.11 (6.24) years (50 (6.67) years in intervention groups and 50.58 (6.30) years in control groups). The mean duration of the study interventions was 9.5(from 6 to 12) weeks. The mean dose of the Saffron administered was 120 mg/day (5 to 1000 mg/day). Three studies were conducted on patients with diabeties (P. Azimi et al., 2014; A. Milajerdi et al., 2018; Sepahi et al., 2018), five on patients with metabolic syndrome (Fadai et al., 2014; A. Javandoost et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; Nikbakht-Jam et al., 2016), and one on coronary artery disease(N. Abedimanesh et al., 2017). Seven arms used Crocin (N. Abedimanesh et al., 2017; Fadai et al., 2014; A. Javandoost et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; Nikbakht-Jam et al., 2016; Sepahi et al., 2018) and five arms used Saffron (N. Abedimanesh et al., 2017; P. Azimi et al., 2014; Fadai et al., 2014; T. Kermani, M. Zebarjadi, et al., 2017; A. Milajerdi et al., 2018) as effective material in in tervention. All studies were randomized controlled clinical trials (N. Abedimanesh et al., 2017; P. Azimi et al., 2014; Fadai et al., 2014; A. Javandoost et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; A. Milajerdi et al., 2018; Nikbakht-Jam et al., 2016; Sepahi et al., 2018).

### *3.2. Quality assessment*

Fig 1 shows the results of the quality assessment of included studies. Most studies had low risk of bias(N. Abedimanesh et al., 2017; Fadai et al., 2014; A. Javandoost et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; A. Milajerdi et al., 2018; Nikbakht-Jam et al., 2016; Sepahi et al., 2018). Only one study was rated as having a high risk of bias for performance bias and detection bias(P. Azimi et al., 2014).

### *3.3. Meta-analysis results*

#### *Waist Circumference (WC)*

Five studies with seven arms containing a total of 178 participants in intervention groups and 177 participants in control groups reported waist circumference as an outcome measure(N. Abedimanesh et al., 2017; P. Azimi et al., 2014; Fadai et al., 2014; T. Kermani, T. Kazemi, et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017). Results were combined using random-effects model and showed significant reduction in waist circumference following Saffron intervention (WMD: -2.18 cm, 95% CI: -4.05, -0.32) (Fig 2). There was no significant heterogeneity among studies (p=0.07, $I^2$=47%).

*Fasting blood sugar (FPG)*

Nine studies (12 arms) providing 595 participants (intervention arm = 301, and control arm = 294) reported FPG as an outcome measure (N. Abedimanesh et al., 2017; P. Azimi et al., 2014; Fadai et al., 2014; A. Javandoost et al., 2017; T. Kermani, T. Kazemi, et al., 2017; T. Kermani, M. Zebarjadi, et al., 2017; A. Milajerdi et al., 2018; Nikbakht-Jam et al., 2016; Sepahi et al., 2018). A significant reduction was observed in the intervention group compared with the control group in pooled results from the random-effects model in FPG levels (WMD: -6.54 mg/dl, 95% CI: -10.22, -2.85) (Fig 3). There was a significant heterogeneity among studies (p=0.001, $I^2$=68%).

*HBA1C*

Four studies with 6 arms provided 154 participants in the intervention groups and 147 participants in the control groups reported HbA1c as an outcome measure (P. Azimi et al., 2014; Fadai et al., 2014; A. Milajerdi et al., 2018; Sepahi et al., 2018). Results were pooled by the random-effects model and indicated that Saffron or Crocin as interventions resulted in non-significant decrease in HbA1c levels (WMD: -0.13 mg/dl, 95% CI: -0.31, 0.04) (Fig 4). There was significant heterogeneity among studies (p=0.02, $I^2$=61%).

*Subgroup analysis*

Table 2 demonstrated the results of the subgroup analyses. We performed sub-group analysis for FPG and HbA1c based on duration of intervention (12 weeks < or +12 weeks). Subgroup analysis showed that FPG levels (WMD: -10.24 mg/dl, 95% CI: -15.76, -4.72) reduced significantly when duration of intervention was more than 12 weeks compared with trials that had less duration (WMD: -3.77 mg/dl, 95% CI: -7.09, -0.46) but the duration of intervention did not show any significant difference in results of HbA1c.

*Publication bias*

Publication bias analysis was done by Egger's and Begg tests. The Egger's and Begg tests did not show publication bias for FPG (p=0.39 and p=0.41, respectively) and HbA1c (p=0.14, p=0.85) (Supplemental Fig 2). Furthermore, Begg tests did not show any publication bias for WC (p=0.29) but significant publication bias was identified for WC by Egger's test (p=0.04) so we used 'trim and fill' method for adjusting publication bias (Supplemental Table 2).

## 4. Discussion

Non-pharmacological management or treatment of various non-communicable diseases typically involves a dietary and/or physical activity component; although recently, the use of adjunct therapies has proliferated. Phytochemicals, constituent within the diet, are considered combative against various non-communicable diseases (Baboota et al., 2013; Hasani-Ranjbar et al., 2009), particularly through regulation of lipid absorption, modulation of energy intake and expenditure, respectively, decreases in lipogenesis and increases in lipolysis, and differentiating pre-adipocyte proliferation (González-Castejón & Rodriguez-Casado, 2011). Saffron, and its' constituents, reportedly contain innumerable beneficial properties, including anti-obesogenic, and conferring positive effects on clinically relevant biomarkers (Mashmoul et al., 2013). Thus, we sought to conduct a systematic review and meta-analysis to evaluate the efficacy of saffron on FPG, HbA1c and WC in randomized clinical trials. In accord with the aforementioned aim, we found that supplementation with saffron resulted in a significant reduction in waist circumference and fasting blood glucose, in addition to a non-significant decrease in HbA1c levels. Moreover, subgroup analysis showed that FPG levels reduced significantly when the intervention length was ≥12 weeks, whilst the duration of intervention did not elicit significant differences in the results of HbA1c. Indeed, such results may be of clinical utility, given that saffron supplementation is easily implementable and tolerable to participants, whilst also not likely to elicit any undesirable side-effects, or interactions with existing treatment regimens.

Concomitant to the meta-analytical synthesis provided in this study, there is some prior clinical evidence to support the healthful effects of saffron on metabolic comorbidities. For instance; Ebrahimi et al reported that, compared with placebo, saffron supplementation yielded significant decreases in both WC, and malondialdehyde, a marker of oxidative stress(Ebrahimi et al., 2019). In addition to the positive metabolic effects, there have been reports of concurrent improvements in psychological facets related to treatment. Ghaderi et al investigated the effects of supplementing with a saffron derivative, crocin, on mental health, metabolic, and genetic profiles in patients undertaking a methadone maintenance treatment program for drug abuse disorders(Ghaderi et al., 2019). Accordingly, Ghaderi et al reported that crocin yielded significant improvements in FPG, in addition to mental health and various other metabolic parameters; a finding that was avowed in Khalatbari-Mohseni et al. The aforementioned findings highlight that, in addition to the significant findings of our study, saffron confer broad, clinically important benefits(Khalatbari-mohseni et al., 2019).

**Purported mechanistic action**

Saffron is thought to enhance lipid profile and glucose uptake via an insulin dependent pathway, resulting in the phosphorylation of AMP-activated protein kinases (AMPK), acetyl-CoA carbohydrate (ACC), and mitogen activated protein kinases (MAPKS); moreover, a combination of saffron and insulin has been reported to positively impact sensitivity to insulin (Kang et al., 2012), albeit in animal-based studies. In human-based work, saffron, or its constituents, is show to confer beneficial changes to blood lipids and obesity indices. In Gout et al (Gout et al., 2010), it was suggested that significant reductions in body weight may be achieved as a result of saffron supplementation, whilst, Kermani et al (Tayyebe Kermani et al., 2017) demonstrated HDL and pro-oxidant balance improvements, and Abedimanesh et al in 2017 (Nasim Abedimanesh et al., 2017) found that  BMI, waist circumference and fat mass values were all significantly improved. However, in comparison to animal-based work, the literature is more variable with respect to its effect on humans. Whilst a component of saffron, crocin, may =putatively possess beneficial effects on hyperlipidemia, hypertension and other blood lipid disorders (Alavizadeh & Hosseinzadeh, 2014), there exists equivocality in the literature. Some animal models have shown the efficaciousness of saffron/crocin in lowering blood glucose and enhancing the blood lipid profile, whilst, among others, Javandoost et al (Ali Javandoost et al., 2017) found no significant changes were evident in LDL, HDL or TG following saffron supplementation; similarly, Milajerdi et al (Alireza Milajerdi et al., 2018) reported no significant change in other metabolic parameters, including, serum lipids, blood pressure, and HbA1c. This inconsistency may conceivably be attributed to; varying samples (human vs. animal), varying relative doses, varying duration of supplementation and various methods of administration (Alavizadeh & Hosseinzadeh, 2014). Previous empirical work investigating the effects of carotenoids, such as crocin, on cardiovascular disease risk is noteworthy. Although some empirical data demonstrates the presence of a relationship between high dietary carotenoids intake and lower cardiovascular disease incidence, other work has shown that large doses of carotenoids are inconsequential, and in some cases, may be harmful (P. Giordano, 2012). However, most negative findings associated with carotenoids were observed with beta-carotene. Thus, concerns that have been asserted for beta-carotene supplementation may not apply to saffron/crocin. In fact, we found no reported injurious side-effects due to saffron supplementation in the included studies, which is of great importance for clinical management of patients.

**Strength and limitations**

The principal strength of the present study was that this was the first to assess the impact of saffron supplementation on waist circumference and glucose metabolism in patients with non-communicable diseases, following a meta-analytical framework; and given the potentially clinically relevant outcomes, this is an important finding. An additional strength of the present meta-analysis is the heterogeneous sample of participants present within the study. This is the first study to assess the impact of saffron supplementation on waist circumference and glucose metabolism in patients with non-communicable diseases, therein facilitating and providing guidance for further work. In addition to the aforementioned strengths, there are some limitations to the present study. For instance; the incumbent analyses did not include participants of one-specific typology; whilst this enabled nine studies for inclusion in the analyses, there might be disease specific factors that require exploration. Some sample sizes were relatively small, which, compared to larger samples, can lead to spurious resultant effect sizes(Sterne & Egger, 2001); however, this was not within our control, and a robust meta-analytical procedure was followed to alleviate such concerns. A final limitation of our study was that there were only limited suitable studies available, and whilst we were able to ascertain overall positive and significant effects, there is a clear need for more high-quality RCT's.

## 5. Conclusion

The results of the present study support the supplementation of saffron for the improvement of waist circumference and glucose metabolism, with sub-group analysis highlighting that FPG levels reduced significantly when intervention durations were ≥12 weeks. Given the positive results; saffron supplementation likely represents a clinically useful prospect, that is easily implementable and tolerable to participants, whilst also not likely to elicit any undesirable side-effects, or interactions with existing treatment regimens.

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