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The Effect of Nettle (*Urtica dioica*) Supplementation on the Glycemic Control of Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract

Objectives: Type 2 diabetes mellitus (T2DM) is a major health problem, worldwide, that is associated with increased morbidity and mortality. Several randomized controlled clinical trials (RCTs) have investigated the effect of nettle (*Urtica dioica*) supplementation on markers of glycemic status in patients with T2DM, with conflicting results. Therefore, the present study assessed the effect of nettle on some glycemic parameters in patients with T2DM.

Methods: A comprehensive search was conducted in PubMed, Scopus, Cochrane Library, and Web of Science, from database inception up to June 2019, to identify RCTs investigating the effect of nettle supplementation on glycemic markers, including; fasting blood sugar (FBS) concentrations, insulin levels, homeostasis model assessment-estimated insulin resistance index (HOMA-IR), and glycosylated hemoglobin percentage in adults with T2DM. The Cochrane Collaboration tool was used to assess the methodological quality of the included studies. Results of this meta-analysis were reported based on the random effects model.

Results: Eight RCTs, comprising 401 participants, were included in the present systematic review and meta - analysis. Based on the Cochrane Collaboration Risk of Bias tool, 6 studies were considered as good quality, two were fair, and three studies were poor, respectively. The results of the meta - analysis revealed a significant reduction in FBS concentrations (WMD: -18.01 mg/dL, 95% CI: -30.04 to -5.97, P < 0.001, I^2=94.6%) following nettle supplementation. However, no significant reduction was observed in insulin levels (WMD: 0.83 Hedges' g, 95% CI: -0.26 to 1.92, P= 0.13, I^2=89.4%), HOMA-IR (WMD: -0.22, 95% CI: -0.83 to 0.40, P= 0.49, I^2=69.2%), or glycosylated hemoglobin percentage (WMD: -0.77%, 95% CI: -1.77 to 0.22, P= 0.12, I^2=83.0%).

Conclusion: The findings of the present study suggest that nettle supplementation may be effective in controlling FBS for T2DM patients. However, further studies are needed to confirm the veracity of these results.

Keywords: Nettle, Glycemic markers, Type 2 diabetes mellitus, Systematic review, Meta-analysis

Introduction

Type 2 diabetes mellitus (T2DM), as a chronic disease, is increasing in prevalence globally, and concurrently with other non-communicable diseases across all age groups (Chen et al., 2012). It has been reported that 190 million people were diagnosed as diabetic in 2008 and, according to estimates, this number will reach 366 million in 2030 (Zheng et al., 2017). There are various approaches available to combat T2DM prevalence in the community, including; lifestyle modifications, such as dietary change and exercise, as well as drug interventions (Inzucchi et al., 2012). Despite undeniable benefits, most of the drugs used in the treatment of diabetes also elicit serious side effects, which is why the use of alternative or adjunct therapies, which have little to no deleterious side-effects, is an important consideration for clinicians and other key-stakeholders (Hunt et al., 2000, Ryan et al., 2001, Bösenberg and van Zyl, 2008). Moreover, it is evident that herbal alternative therapies are cheaper and easier to administer (Rao et al., 2010, Covington, 2001), whilst Pandey et al (2011) year noted more than 800 herbal medicines which are, purportedly, capable of improving glycemic parameters (Pandey et al., 2011).

One example, Nettle (*Urtica dioica)*, which is a member of the *Urticaceae family*, is known for its wide range of biological activities and beneficial effects on human health (Chrubasik et al., 1997a). It contains chemical materials, including; flavonoids, silicic acid, butyric acid, potassium-ions, nitrates, volatile oil, histamine, serotonin, acetylcholine, formic acid and leukotriene's (Chrubasik et al., 2007, Namazi et al., 2012a, Joshi et al., 2014). The beneficial effects of this plant include anti-inflammatory (Riehemann et al., 1999a), anti-hyperglycemic (Bnouham et al., 2003), anti-proliferative (Durak et al., 2004), immunomodulatory (Ahmet Başaran et al., 1997a), diuretic (Tahri et al., 2000), anti-platelet aggregation (El Haouari et al., 2006b), anti-allergic (Mittman, 1990), antimicrobial, anti-oxidant, and anti-ulcer and analgesic activities (Gülçin et al., 2004).

The effect of nettle supplementation on T2DM has been considered in several human-based randomized clinical trials (RCTs) (Khajeh-Mehrizi et al., 2014a, Dabagh and Nikbakht, 2016a, Ghalavand et al., 2017a, Korani et al., 2017a, Kianbakht et al., 2013a, Dadvar et al., 2016, Tarighat et al., 2012, Hassani et al., 2016); however, the results are equivocal at best. Some studies (Korani et al., 2017a, Khajeh-Mehrizi et al., 2014a, Dabagh and Nikbakht, 2016a, Ghalavand et al., 2017a, Kianbakht et al., 2013a, Tarighat et al., 2012) have reported significant improvements in biochemical outcomes, in T2DM patients, as a result of nettle supplementation, whereas others have reported no improvement (Hassani et al., 2016, Dadvar et al., 2016).

To the best of our knowledge, no unifying analysis has been conducted to summarize the effect of nettle supplementation on markers of glycemic control in T2DM patients. Therefore, the present study aimed to perform a comprehensive systematic review and meta-analysis of available RCTs to evaluate the efficacy of nettle (*Urtica dioica*) supplementation on markers of glycemic status in adults with T2DM.

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Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in the conduct of this study (Moher et al., 2009). The PICOS criteria (Population: patients with T2DM; Intervention: use of nettle; Comparator: placebo/no treatment group; Outcomes: fasting blood sugar [FBS] concentrations, insulin levels, homeostasis model assessment-estimated insulin resistance index [HOMA-IR], and glycosylated hemoglobin percentage; Study design: RCTs, was used to perform the systematic review. Our study protocol was not registered on any website, however it is available from the authors upon request.

Search strategy

An online search was carried out using the online databases; PubMed, Scopus, ISI Web of Science, and Cochrane library, from inception up to June, 2019, without any language or publication date restrictions. We used the following text words and medical subject headings (MeSH) to identify the potential interest articles: ("Nettle" OR "*Urtica dioica*") AND ("Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "Hyperglycemia" OR "Hemoglobin A, Glycosylated" OR "Insulin Resistance" OR "Metabolic Syndrome X" OR "Glucose Intolerance" OR "Prediabetic State" OR "HOMA-IR" OR "β-cell function" OR "insulin secretion" OR "impaired glucose tolerance" OR "impaired fasting glucose" OR "glycemic control" OR "insulin" OR "glucose" OR "diabetic" OR "HbA1c" OR "diabetes" OR "type 2 diabetes" OR "glycohemoglobin"). Electronic searches were complemented by hand searches of the reference lists of eligible articles, and email correspondences with authors for additional data, where relevant.

Study selection

Firstly, electronic and manual search results were exported to End-Note software, version X6 (Thomson Reuters) and duplicate publications were removed. Then, two investigators (A.Gh and A.H) selected eligible articles, independently, by reading the title, abstract, and, where required, the full-text version of remaining publications. Finally, all human RCTs (either parallel or cross-over designs) that examined the effects of nettle supplementation on adults (age≥18 years old) with T2DM were included. Studies were excluded if they: (1) supplemented nettle in combination with any other drugs, minerals, or botanicals (unless a separate arm controlled the effect of the mixed substance); (2) were publications with duplicate data; (3) contained trials with follow up duration less than 4 weeks; and (4) were studies without sufficient data. Disagreements regarding the study selection process were resolved by discussion with a third researcher (S.F).

Data extraction

The following data were extracted from the full-text of included studies using a pre-designed abstraction form: first author's last name, publication year, location of the study, study design, gender, mean age and body mass index (BMI) of participants, total sample size, study duration, dose of nettle supplementation, and main results. When the data were reported at multiple measurements, only the outcomes at the end of the intervention were included in the analysis. Data extraction was conducted by two authors, independently (A.Gh and A.H). Subsequently, full texts studies were assessed, and discrepancies were resolved through discussion with a third, independent researcher. In the case of multiple publications with duplicate/overlapped data for the same trial, the publication with comprehensive and complete data was selected.

Quality assessment of studies

The Cochrane risk of bias tool (Higgins and Altman, 2008) was used for quality assessment as follows: sequence generation, allocation and concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. According to the Cochrane guideline handbook, the words "yes," "no," and "unclear" corresponded to low, high, and unknown risk of bias, respectively. Quality assessment was also undertaken by two authors (AH and A.Gh) separately, and any discrepancies were resolved through discussion with a third, independent researcher.

Statistical analysis

All analyses were performed using STATA software version 12 (STATA corp, College Station, TX, USA). The weighted mean difference (WMD) and the standard deviation (SD) of the FBS, glycosylated hemoglobin, insulin level, and HOMA-IR index between the intervention and control groups were applied to calculate overall effect size. In studies in which mean change was not directly reported in intervention and control groups, it was calculated by the minus of the post-intervention data from the baseline value. Besides, if only SD for the baseline and final values were provided, the SD for the net changes were imputed according to the method of

Follmann et al. (Follmann et al., 1992) using a correlation coefficient of 0.5. Due to the fact that included RCTs were carried out in different settings, a random effects model was used to conduct all meta-analyses. The heterogeneity between studies was examined by the I-squared (I^2) index. Heterogeneity was considered statistically significant if $P < 0.01$ or $I^2 > 50\%$ (Higgins and Green, 2006). We conducted subgroup analysis based on gender of participants, baseline BMI, and participants mean age to assess the impact of these variables on outcomes. Sensitivity analyses were performed using the leave-one-out method (i.e. deleting one trial at a time and re-calculating the effect size), to explore the extent to which inferences might depend on a particular study or group of studies. The publication bias was investigated by both graphical (funnel plots) and test method (Egger's regression test) (Egger et al., 1997). A P-value <0.05 was accepted as statistically significant, unless otherwise specified.

Results

Search results and study selection

The initial literature search yielded 456 articles from all the databases, and 210 articles remained following removal of duplicates. The titles and abstracts of these articles were screened, and 193 abstracts were deemed to be potentially irrelevant for the meta-analysis. In the next step, 9 papers were excluded based on the full-text review. These exclusions were due to the following reasons: administered nettle in combination with other components (n=4), duplicate dataset (n=2), contained no placebo group (n=1), studies that did not provide sufficient data for outcomes (n=2). Finally, 8 trials (Dabagh and Nikbakht, 2016a, Dadvar et al., 2016, Ghalavand et al., 2017a, Hassani et al., 2016, Khajeh-Mehrizi et al., 2014a, Kianbakht et al., 2013a, Korani et al., 2017a, Tarighat et al., 2012) were included in this meta-analysis. Of these, 6 trials (Dabagh and Nikbakht, 2016a, Dadvar et al., 2016, Ghalavand et al., 2017a, Kianbakht et al., 2013a, Korani et al., 2017a, Tarighat et al., 2012) reported the effect of Nettle on FBS, 3 articles (Kianbakht et al., 2013a, Korani et al., 2017a, Tarighat et al., 2012)

on glycosylated hemoglobin, 3 articles (Hassani et al., 2016, Khajeh-Mehrizi et al., 2014a, Tarighat et al., 2012) on HOMA-IR, and 3 trials (Khajeh-Mehrizi et al., 2014a, Korani et al., 2017a, Tarighat et al., 2012) on insulin. The process of study identification is presented in Fig.1.

Characteristics of the included studies

The main characteristics of eligible trials are summarized in Table 1. These studies were published between 2012 and 2017. The design of all the included trials was parallel and all were carried out in Iran. Participants age ranged from 41 to 57 years. Two studies (Dabagh and Nikbakht, 2016a, Ghalavand et al., 2017a) were conducted exclusively on males, and two (Dadvar et al., 2016, Hassani et al., 2016) on females, whilst the other four trials were performed on both genders. Nettle dose ranged from 1.5 to 10 g/day, and intervention duration ranged from 8 to 12 weeks. Baseline BMI of participants in each study indicated that all trials examined overweight and obese subjects.

In studies by Dabagh et al. (Dabagh and Nikbakht, 2016a), Ghalavand et al. (Ghalavand et al., 2017a), Hassani et al.(Hassani et al., 2016), and Dadvar et al. (Dadvar et al., 2016), there were three intervention groups (Nettle, Nettle + aerobic training, aerobic training + placebo) and one placebo group. We considered the result of the nettle and placebo groups as one study and the result of the nettle + aerobic training and placebo + aerobic training groups as another study.

Quality assessment

The details of quality assessment are shown in Table 2. Although all included studies were randomized, only 5 trials (Dadvar et al., 2016, Khajeh-Mehrizi et al., 2014a, Kianbakht et al., 2013a, Korani et al., 2017a, Tarighat et al., 2012) reported their respective methodology of randomization. Two studies were double-blinded (Khajeh-Mehrizi et al., 2014a, Kianbakht et

al., 2013a), two (Korani et al., 2017a, Tarighat et al., 2012) were single-blinded, and the remaining trials did not report any blinding procedure. All included studies reported no significant participant withdrawal. Among the included studies in this meta-analysis, the quality of 2 studies (Dabagh and Nikbakht, 2016a, Ghalavand et al., 2017a) was low, whilst 6 studies (Dadvar et al., 2016, Hassani et al., 2016, Khajeh-Mehrizi et al., 2014a, Kianbakht et al., 2013a, Korani et al., 2017a, Tarighat et al., 2012) had high quality.

Effect of nettle supplementation on FBS

Overall, 6 eligible studies (Dabagh and Nikbakht, 2016a, Dadvar et al., 2016, Ghalavand et al., 2017a, Kianbakht et al., 2013a, Korani et al., 2017a, Tarighat et al., 2012) with 9 treatment arms, including a total of 306 participants, examined the effect of nettle supplementation on FBS. Combining their findings, based on the random effects model, we found that FBS was significantly reduced after nettle supplementation (WMD: -18.01 mg/dL, 95% CI: -30.04 to -5.97, $P < 0.001$) compared to the control group, with a significant between-study heterogeneity (I^2=94.6%, $P < 0.001$) (Fig. 2). The mean age and BMI of study participants did not explain this heterogeneity. However, the gender of study participants could explain the heterogeneity. Studies that were conducted on both sexes (WMD: -40.71 mg/dL, 95% CI: -60.85 to -20.58) revealed a greater reduction in FBS than those performed on men (WMD: -7.91 mg/dL, 95% CI: -12.08 to -3.74) or women (WMD: -8.61 mg/dL, 95% CI: -14.17 to -3.05) separately (Table 2). Furthermore, the removal of the studies, one by one, did not significantly change the effect of nettle consumption on FBS.

Effect of nettle supplementation on glycosylated hemoglobin

Overall, 3 clinical trials (Kianbakht et al., 2013a, Korani et al., 2017a, Tarighat et al., 2012), including a total of 186 subjects, reported the effect of nettle consumption on glycosylated

hemoglobin. Pooled effect size did not show any significant effect of nettle supplementation on glycosylated hemoglobin (WMD: -0.77%, 95% CI: -1.77 to 0.22, P= 0.12) (Fig. 3). Although between-study heterogeneity was significant (I^2=83.0%, P < 0.001), we could not perform subgroup analysis due to a lack of eligible studies. The sensitivity analysis showed that overall estimates were not affected by elimination of any individual study.

Effect of nettle supplementation on HOMA-IR

The pooled estimate from the random-effects model that performed on 3 studies (Hassani et al., 2016, Khajeh-Mehrizi et al., 2014a, Tarighat et al., 2012) (4 treatment arms) including 145 participants showed that nettle had no significant effect on HOMA-IR index (WMD: -0.22, 95% CI: -0.83 to 0.40, P= 0.49) (Fig. 4). Although between-study heterogeneity was significant (I^2=69.2%, P < 0.02), we could not perform subgroup analysis due to a lack of eligible studies. The sensitivity analysis showed that removing any of the studies did not substantially change the effect of nettle supplementation on HOMA-IR index.

Effect of nettle supplementation on insulin

The effect of the nettle supplementation on insulin concentration was examined in 3 clinical trials (Khajeh-Mehrizi et al., 2014a, Korani et al., 2017a, Tarighat et al., 2012) (143 subjects). Overall, our meta-analysis did not demonstrate any beneficial effect of nettle supplementation on insulin levels (WMD: 0.83 Hedges' g 95% CI: -0.26 to 1.92, P= 0.13) (Fig. 5). Although between-study heterogeneity was significant (I^2=89.4%, P < 0.001), we could not perform subgroup analysis due to a lack of eligible studies. The sensitivity analysis showed that overall estimates were not affected by the elimination of any study.

Publication bias

Evaluation of publication bias by visual inspection of funnel plot demonstrated no evidence of publication bias in the meta-analysis of nettle supplementation on FBS, glycosylated hemoglobin, HOMA-IR, and insulin **(Supplemental Figure 1**). Egger's linear regression test also revealed the same result (FBS: P= 0.44, glycosylated hemoglobin*:* P= 0.40, HOMA-IR: P= 0.73, and insulin: P= 0.10).

Discussion

Recently, a contemporary interest has emerged towards utilizing nettle supplements as a hypoglycemic agent (Jacob and Narendhirakannan, 2019). Consequently, the aim of this study was to evaluate the efficacy of nettle supplementation on markers of glycemic status in adults with T2DM.

To the best of our knowledge, our study is the first meta-analysis on this topic, and the results indicate that nettle supplementation may significantly reduce FBS levels, but elicits no significant effects on glycosylated hemoglobin percentage, insulin concentrations, and HOMA-IR index. Importantly, these results were influenced by between-study heterogeneity, where subgroup analyses for FBS levels indicated that gender represented a viable source of between-study heterogeneity; whereas the lack of a sufficient number of eligible studies rendered subgroup analyses impossible for glycosylated hemoglobin, insulin concentrations, and HOMA-IR index.

The beneficial effects of nettle are attributable to its various phytochemicals. Nettle leaves are rich in flavonoids (mainly quercetin, kaempferol, rutin, and their 3-rutinosides and 3-glycosides, catechin, epicatechin and epigalocatehin-gallate), in addition to organic acids, essential oils, phenolic compounds, carotenoids, lectins, chlorophylls, tannins, vitamins and minerals. The root contains lectins, polysaccharides, phytosterols, lignans, coumarines (scopoletin), and high amounts of fatty acids. The main constituents of nettle stems are

flavonoids and anthocyanins, whilst their flowers contain high amounts of β-sitosterol and 7 flavonoid glycosides (Said et al., 2015, Upton, 2013, El Haouari and Rosado, 2019b).

Numerous *in vitro* and *in vivo* animal studies have reported the hypoglycemic activity of nettle, and speculated the mechanistic action (El Haouari and Rosado, 2019a). It is suggested that nettle affects glucose absorption in the intestine, as well as glucose uptake in peripheral tissues (Bnouham et al., 2003, Said et al., 2008, Domola et al., 2010, Kadan et al., 2013a). Nettle purportedly inhibits key carbohydrate digestive enzymes, including α-amylase and α-glucosidase, and, accordingly, decreases the intestinal absorption of glucose (Rahimzadeh et al., 2014, Önal et al., 2005, Bnouham et al., 2003, Said et al., 2008). Nettle has insulin-mimetic, insulin-sensitizing, and insulin-secretagogue properties; moreover, it forms unique glucose-permeable pores in lipid bilayers, activates the peroxisome proliferator-activated receptor-γ, and modulates the translocation of glucose transporter-4 from the cytoplasm (Di Virgilio et al., 2015) to the skeletal muscle (Domola et al., 2010, Rau et al., 2006, Farzami et al., 2003a, Qujeq et al., 2011, Kadan et al., 2013a). Furthermore, nettle can proliferate insulin-producing β-cells of the pancreatic islets of Langerhans and protect them from oxidative damage (Golalipour et al., 2010b, Golalipour and Khori, 2007). Additionally, this plant can, reportedly, increase the activity of some important metabolic enzymes, such as acetyl-CoA carboxylase and nucleoside-diphosphate kinase (Qujeq et al., 2011). Is has been reported that oxidative and endoplasmic reticulum stress play a key role in beta-cell dysfunction in diabetes (Gerber et al., 2017, Hasnain et al., 2016). Due to its anti-inflammatory, anti-oxidant and free radical scavenging properties, nettle is considered to exert a noticeable ameliorating impact on oxidative stress-induced beta-cell damage (Di Virgilio et al., 2015). Also, it has been suggested that nettle is able to protect the liver from oxidative damage in type 2 diabetes, which is attributable to its antioxidant effects (Golalipour et al., 2010a).

The exact mechanistic action of the bioactive compounds constituent within nettle are not fully elucidated; however, a number of these compounds are proposed to have anti-diabetic properties. It has been suggested that one of the active components of nettle, Urtica Dioica-1 (UD-1), contains insulino-mimetic properties, and via its special structure (cyclical peptides) and by forming glucose permeable pores, enhances glucose uptake (Farzami et al., 2003b, Wang et al., 2001). In addition, lectin, a glycoprotein in nettle, functions by increasing the pancreatic secretion of insulin from β-cells, concomitant to mimicking insulin actions (Peumans et al., 1984).

Based on the pooled effect sizes observed in the present analysis, it seems that nettle supplementation does not significantly affect HOMA-IR index, glycosylated hemoglobin percentage and insulin production. It is important to note that the number of studies included in the meta-analysis of the aforementioned outcomes was small, and this fact may represent a viable reason for their statistically non-significant effect sizes. In addition, we speculate that the intervention dose and duration, as well as the type of the nettle product which has been used, may influence the results. For example, accumulating evidence suggests that it takes at least 3 months for significant changes in glycosylated hemoglobin concentrations to manifest (Li et al., 2009), however, the intervention period of nearly all studies (Dabagh and Nikbakht, 2016a, Dadvar et al., 2016, Ghalavand et al., 2017a, Hassani et al., 2016, Khajeh-Mehrizi et al., 2014a, Korani et al., 2017a, Tarighat et al., 2012) included in the present analysis was less than 3 months. In fact, in a study conducted by Kianbakht *et al*, in which nettle leaf extract has been used for 3 months and combined with the conventional oral anti-hyperglycemic drugs, the blood levels of glycosylated hemoglobin decreased significantly, compared with placebo arm (Kianbakht et al., 2013b).

With regards to the effect of nettle supplementation on insulin concentrations and insulin resistance, the dose and type of the supplement seem to be influential. For instance, Khaje-

Mehrizi *et al*, investigated the effects of 100mg/kg/day extract of nettle on 60 diabetic patients for 8 weeks, and reported the significant effects of intervention on insulin level, as well as insulin resistance indices (Khajeh-Mehrizi et al., 2014b). While Korani *et al*, who administered 60 mg/kg/day of hydro-alcoholic nettle extract for 8 weeks on 60 diabetic patients, reported no significant impact on insulin level. The authors suggested that the duration of study may not have been sufficient to enhance the AMP-activated protein kinase (AMPK) activity adequately, and therefore, insulin secretion (Korani et al., 2017b).

Nettle appears to reduce the complications of diabetes mellitus through its anti-inflammatory, immunomodulatory, anti-platelet aggregation, antioxidant, free radical scavenging, analgesic, natriuretic, calcium channel blocking, nitric oxide-mediated vasodilatory, and antihyperlipidemic properties (Riehemann et al., 1999a, Ahmet Başaran et al., 1997b, Rovira et al., 1999, El Haouari et al., 2006a, El Haouari et al., 2007, Gülçin et al., 2004, Swanston-Flatt et al., 1989, Tahri et al., 2000, Qayyum et al., 2016, Das et al., 2011).

Interestingly, concomitant to these beneficial biological activities, nettle has been shown devoid of toxicity when administered orally in animals (El Haouari and Rosado, 2019a), and was also concluded to be safe in a cellular toxicity test of L6 and HepG2 cell lines (Kadan et al., 2013b). Similarly, human-based studies have reported no significant adverse events or side effects from consumption of this plant (Dabagh and Nikbakht, 2016a, Dadvar et al., 2016, Ghalavand et al., 2017a, Hassani et al., 2016, Khajeh-Mehrizi et al., 2014a, Kianbakht et al., 2013a, Tarighat et al., 2012). In fact, only Korani et al.(Korani et al., 2017a) reported itching in one patient of the treatment group. However, allergic skin reactions (Contact urticaria and burning pain) and mild gastrointestinal adverse events have been observed following intake of commercial stinging nettle extracts; where it is asserted that histamine, acetylcholine, and serotonin, are responsible (Upton, 2013). With regards to drug interactions, no adverse interactions have been reported for nettle. Interestingly, consuming nettle products as an

adjunct to nonsteroidal anti-inflammatory drugs (NSAIDs) has been proposed to enhance clinical outcomes (Chrubasik et al., 1997b, Riehemann et al., 1999b). Overall, nettle is likely appropriate and safe for consumption in diabetic patients.

The majority of studies included in the present study did not provide sufficient details regarding how they controlled the intake of energy or macronutrients. Universally, studies only requested that participants not to change their habitual diet or physical activity during the intervention. Moreover, some trials exploring the effects of nettle on glycemic control used nettle preparation, either alone or in combination with a special training program)Dabagh and Nikbakht, 2016b, Ghalavand et al., 2017b, Kianbakht et al., 2013b), and has been suggested, by these studies, that the combination of regular training and nettle supplementation might be more effective, compared with using either intervention in isolation.

Considering the type of the nettle supplements, most of the included studies used the hydro-alcoholic nettle extract variant (Ali et al., 2016, Kianbakht et al., 2013b, Korani et al., 2017b, Namazi et al., 2012b). Two studies utilized dried nettle leaf powder (Dabagh and Nikbakht, 2016b, Dadvar et al., 2016), and a further two trials provided no details regarding the type or the preparation method for the extract which they have used)Ghalavand et al., 2017b, Khajeh-Mehrizi et al., 2014b). However, due to the limited number of eligible studies using the non-hydro-alcoholic nettle extract, we could not perform a subgroup analysis to reach a conclusive result about the difference between various types of nettle preparation, in the case of their impact on glycemic control.

The present meta-analysis has several limitations that should be taken into account when interpreting the findings. First, the number of studies included in this meta-analysis was not sufficient to draw definitive conclusions, however, this was out of the operational control of the study, and clearly demonstrates the necessity for further RCTs. Second, all of the included studies were conducted in the same country, i.e. Iran, which increases the internal validity of

the findings but reduces their global generalizability. Third, all of the potential sources of heterogeneity could not be accounted for by subgroup analyses, because they were not properly reported in the included studies. Forth, in terms of the effect of nettle on glycosylated hemoglobin and insulin concentrations and HOMA-IR, despite the significant between-study heterogeneity, the number of eligible studies was not sufficient to perform a subgroup analysis. Fifth, the nettle preparation varied between trials, six studies administered the extract and two studies used dried nettle leaves. It should be noted that these inconsistencies can affect the amount of active compounds within the nettle supplement, thus, this may conceivably have affected the results. Finally, the results of most studies were not adjusted for confounding factors such as dietary intake and physical activity. Therefore, more well-designed and well-reported randomized controlled trials with different ethnic populations are essential for future integration and consensus. Despite the above limitations, our study is the first to systematically review and meta-analyze the effect of nettle supplementation on glycemic control in patients with T2DM, and thus, provides valuable insights for future research in this field.

Conclusion

In summary, our findings tentatively support the use of nettle as an antidiabetic plant and suggest that nettle supplementation can be effective in controlling FBS in T2DM patients. Nevertheless, its holistic efficacy remains questionable, and further, larger, and longer duration trials are needed for clarification.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

None.

Author Contribution

AH, A.Gh, and S.F carried out the concept, design, and drafting of this study. AH, A.Gh and M.J.T searched databases, screened articles and extracted data. AH, A.GH, and S.F performed the acquisition, analysis, and interpretation of data. AH and C.C critically revised the manuscript. All authors approved the final version of the manuscript. AH and A.Gh are the guarantors of this study.

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