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Article

Gingko biloba extract improves the lipid profile, inflammatory markers, leptin level and the antioxidant status of T2DM patients poorly responding to metformin: A double-blind, randomized, placebo-controlled trial

Saad Abdulrahman Hussain[1,*], Tavga Ahmed Aziz[2], Taha Othman Mahwi[3], Zheen Aorahman Ahmed[2]

[1]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Rafidain University College, Baghdad, Iraq, [2]Department of Pharmacology and Toxicology, College of Pharmacy, University of Sulaimani, Kurdistan Region, Iraq, [3]Department of Medicine, College of Medicine, University of Sulaimani, Kurdistan Region, Iraq

The present study aims to evaluate the effects of *Ginkgo biloba* (GKB) extract as "add-on" therapy with metformin on the lipid profile, inflammatory markers, leptin and the total antioxidant capacity (TAOC) of patients with type 2 diabetes mellitus (T2DM). It is a multi-center, randomized, placebo-controlled double-blinded clinical study. Sixty patients were allocated into two groups: control and treatment groups; they received orally either 120 mg starch/capsule or 120mg GKB/capsule, respectively as an adjuvant with metformin for 90 days. Blood samples were obtained at zero time and after 90 days. The blood was utilized for analysis of the lipid profile, inflammatory markers, leptin, and TAOC. The GKB extract produced a significant decrease in the levels of TG, LDL-c, and CRP, with a significant increase in HDL-c compared to baseline values. There were no significant changes reported in the placebo-treated group. It also produced a significant decrease in the concentrations of IL-6, TNF-α, and leptin compared to baseline values and placebo-treated groups with a significant increase in TAOC compared to baseline values. In conclusion, GKB extract, as an adjuvant with metformin, decreases inflammatory mediators, leptin level and improves the antioxidant status and lipid profile of T2DM patients improperly managed with metformin.

Keywords: *Ginkgo biloba*. Uncontrolled T2DM. Inflammatory markers. Leptin. Antioxidant status.

INTRODUCTION

Diabetes mellitus is a metabolic disorder with life-threatening complications. It is characterized by chronic hyperglycemia and impaired carbohydrates, lipids, and proteins metabolism caused by complete or partial insufficiency of insulin secretion and/or insulin action (Ding *et al*., 2014). Genetic and environmental factors contribute to the etiology of type 2 diabetes mellitus (T2DM) (Gastaldelli, 2011; Ismail-Beigi, 2012). Both genetic and environmental factors, such as nutrition, sedentary lifestyle, smoking and stress are having their roles in inducing chronic inflammation. Many studies have proved the association between low-grade inflammation and T2DM. Moreover, interventional studies have confirmed the role of inflammation in the pathogenesis of T2DM and vascular complications (Zozulinska, Wierusz-Wysocka, 2006). Many studies demonstrated that insulin resistance could be attributed to oxidative stress through insulin signals inhibition and dysregulation of the adipokines TNF-α and leptin. On the other hand, oxidative stress characterized by the generation of various

***Correspondence:** S. A. Hussain. Department of Pharmacology and Toxicology. Faculty of Pharmacy. Al-Rafidain University College. Baghdad, Iraq. Phone: +9647901712624. E-mail: saad.hussain@ruc.edu.iq
ORCID: https://orcid.org/0000-0002-1909-417X

inflammatory mediators including adhesion molecules and interleukins (Tangvarasittichai, 2015) may adversely impact the development and progression of diabetic complications. Moreover, excessive FFA and glucose can initiate inflammatory cascades through the oxidative stress and depletion of endogenous antioxidants (Houstis, Rosen, Lander, 2006; Kaul *et al*., 2010). Accordingly, ameliorating inflammatory response and boosting the antioxidant system could be of value in improving the outcome of T2DM. Medicinal plants have provided biologically relevant products for centuries; they still serve as a valuable source for new medicines (Czelusniak *et al*., 2012). Among these plants, *Ginkgo biloba* extract (GKB) has taken great attention by the researchers for its various pharmacological activities, and it is one of the most widely used herbal medicines worldwide (Diamond, Bailey, 2013). The main ingredients of the extract contain 24% flavone glycosides and 6% terpenoids. The plant is inexpensive with minimal adverse reactions. GKB has many pharmacologic effects; it acts as an antioxidant, anti-inflammatory agent and modulates the functions of the immune response. Moreover, GKB showed beneficial effects in many central nervous system disorders, such as memory loss, dementia, fluctuations in mood, and psychiatric disorders such as schizophrenia and Alzheimer's disease (Diamond, Bailey, 2013; Montes *et al*., 2015). The plant extract is effective in acute pancreatitis and myocardial ischemia/reperfusion injury which are associated with the expression of the inflammatory mediators (Zhou *et al*., 2006; Kusmic *et al*., 2004). Traditional Chinese medicine uses dry and mashed leaves of ginkgo to treat health problems such as asthma, bronchitis, hearing loss, tuberculosis, cognitive dysfunction, stomach pain, skin problems, and anxiety (Zhou *et al*., 2016). << Please, Insert 3 authors >> Other current uses, including arteriosclerosis, thrombus formation, ischemic heart disease, and the prevention of diabetes mellitus have also been reported (Zhao, Gao, Cui, 2015). Additionally, GKB recently demonstrated a significant decrease in food intake, body weight gain and visceral adiposity in diet-induced obesity in rats (Hirata *et al*., 2015; Banin *et al*., 2014). Our previous study has revealed a significant role of GKB in improving glycemic status and insulin resistance in patients with T2DM (Aziz *et al*., 2018). Accordingly, the present study aims to evaluate the effects of GKB extract, when used as an "add-on" therapy with metformin, to improve the lipid profile, leptin level, and inflammatory and antioxidant status of patients with uncontrolled T2DM.

MATERIAL AND METHODS

Ethical consideration

The study protocol was approved by the local Research Ethics Committee of the College of Medicine, University of Sulaimani and carried out in accordance with the principles of the Helsinki Declaration as revised in 2000. Written informed consent was obtained from each participant before enrollment in this placebo-controlled randomized double-blind study. None of the enrolled patients were taking any medications that influence glycemic control other than metformin.

Study Protocol

The study is a multi-center, randomized, placebo-controlled double-blinded clinical trial conducted from December 2016 to October 2017 at the Center of Diabetes and Endocrinology, Directory of Health, Sulaimani city. The patients were recruited from public hospitals or private clinics according to the selection criteria. Eighty patients were originally screened for eligibility; sixty were eligible and randomized into two groups (30 patients each) as follow: the first group received their commonly used dose of metformin with a placebo formula; while the second group received their commonly used dose of metformin with 120 mg GKB extract (single daily oral dose). Only 20 patients from the first group and 27 patients from the second group completed the 90-day trial and were included in the final analysis. The most common reasons for the volunteers to quit the study during or after the first intervention arm include the loss of interest in continuing participation and loss follow-up, among others (Figure 1). The inclusion criteria required that the patients were of both sexes with an age range of 25-65 years; diagnosed as having T2DM for not less than 1 year and their glycemic

status was uncontrolled (pre-specified HbA1c ≥ 7.0% at baseline) by the use of metformin as a monotherapy. The exclusion criteria were type 1 DM patients, pregnant patients, patients with ischemic heart disease, cardiac arrhythmias, deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD), bleeding disorders, seizures, known hypersensitivity to any component of the trial drugs (*Gingko biloba* extract, metformin, or placebo), and patients on supplements that contain multivitamins and polyphenols. Body weights, waist circumferences, body mass index (BMI) were recorded for each patient both at baseline and the end of treatment. The placebo formula (120 mg starch/capsule) or the GKB formula (120mg *Ginkgo biloba* extract/capsule) was used as an "add-on" therapy with metformin and administered orally as a single dose for 90 days.

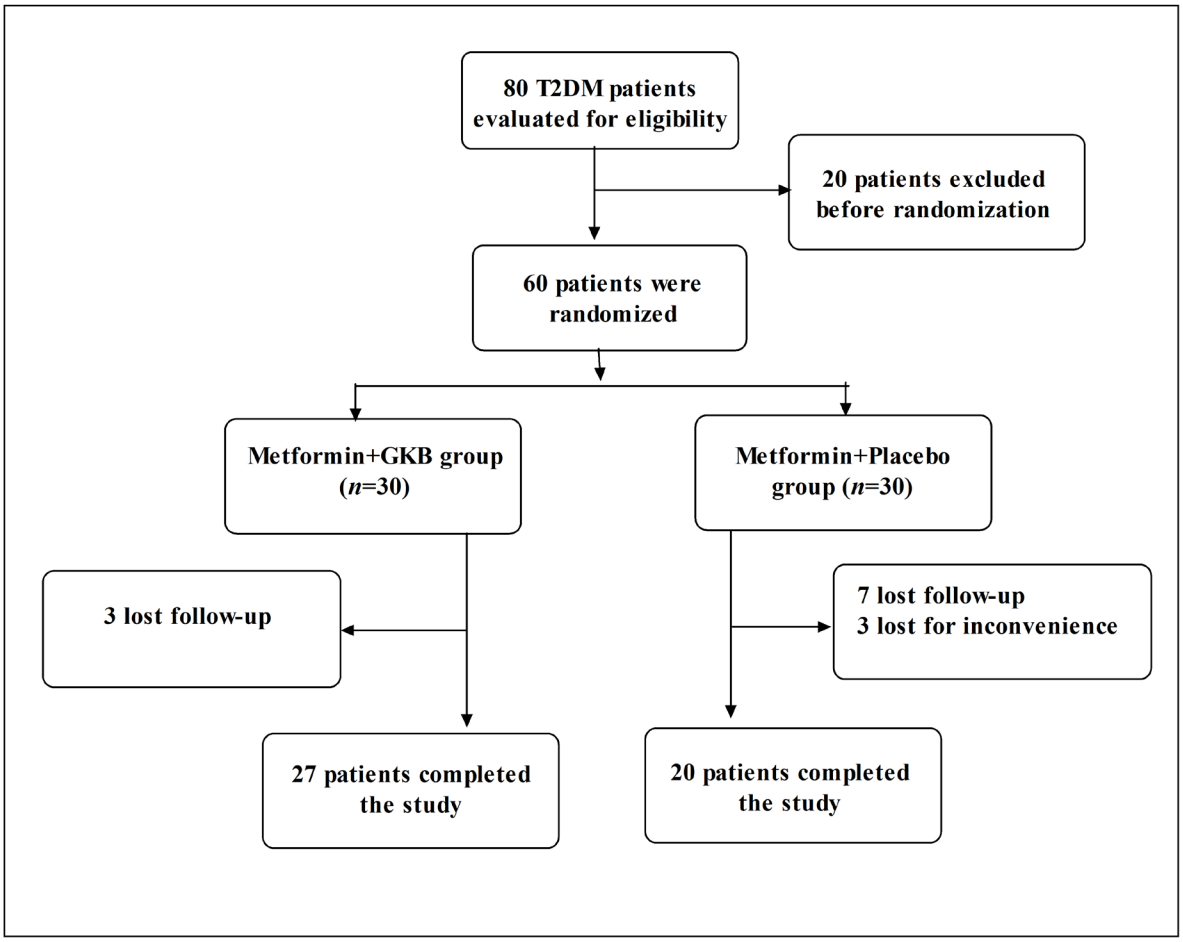

FIGURE 1 - Flowchart shows the screening, recruitment, and randomization of patients. T2DM, type 2 diabetes mellitus; GKB, *Ginkgo biloba*; *n*, number of subjects.

Preparation of samples and analysis

After 12 hr fasting, blood samples (10 ml) were taken from each patient at zero time (before starting treatment) and after 90 days by vein puncture, 8 ml aliquot was kept in plain tubes and left to clot and centrifuged at 3000 rpm for 20 min to obtain the serum. The serum was used for the analysis of leptin, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c), total

antioxidant capacity (TAOC), in addition to the serum levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) utilizing ready-made kits according to the manufacturers' specifications. The serum was stored frozen at (– 20°C) unless analyzed immediately.

Statistical analysis

Analysis of the data was performed utilizing the GraphPad Prism 5.1 software (GraphPad Software, Inc., La Jolla, CA, USA). Descriptive statistics was used to compare the patient's characteristics between the two groups. A paired *t*-test was performed to evaluate the difference between pre- and post-treatment means of the same group. An unpaired *t*-test was used to assess the differences between the post-treatment means of the different groups. One-way analysis of variance (ANOVA) supported by Bonferroni's *post hoc* analysis and analysis of covariance was used to determine the difference between the mean of independent samples at *P*-value <0.05.

RESULTS

The baseline data of the T2DM patients were shown in Table I. There were no statistically significant differences ($P>0.05$) in all parameters between the Met+placebo and Met+GKB groups, including duration of treatment with metformin (28±26.2 *vs*.40.9±38.4 months) and the mean daily doses (1.24±0.67 *vs*. 1.36±0.45 g/day). The main reported changes in the lipid profile during the study following treatment with GKB are shown in Table II. In the GKB-treated group, we reported a significant decrease in serum levels of triglycerides and LDL-c compared with the baseline value, with a nonsignificant decrease of total cholesterol. This was accompanied by a significant increase in HDL-c levels compared with baseline values and the placebo-treated group. Meanwhile, the placebo-treated group did not show significant changes in the lipid profile, except for the increase in HDL-c levels compared with the baseline level. Moreover, both treatment arms demonstrated a significant decrease in the TG:HDL-c ratio; however, the GKB-treated group has a significantly lower ratio compared with the placebo-treated group after 90 days. Meanwhile, a significant decrease in the LDL-c:HDL-c ratio was reported only in the GKB-treated group, compared with both the baseline values and placebo-treated group after 90 days (Table II). In Table III, the serum concentrations of hsCRP, TNF-α, and IL-6 were not significantly affected by the adjuvant use of the placebo formula with metformin after 90 days compared with baseline values. However, supplementation of GKB extract with metformin produced a significant decrease in the serum concentrations of hsCRP compared with baseline values. Meanwhile, serum IL-6 and TNF-α were found to be significantly lower ($P<0.001$) than baseline value and that reported in the placebo-treated group at the end of the treatment period. Additionally, the adjuvant use of GKB extract significantly decreased the serum leptin levels after 90 days compared with the baseline value, and this change was also significantly different ($P<0.05$) compared with that of the placebo-treated group after the same period of treatment. Meanwhile, the serum leptin level in the placebo group was changed significantly after 90 days of treatment (Table IV). Regarding the effects of GKB extract on the total antioxidant activity of T2DM patients, the results revealed a significant increase of TAOC in the group treated with GKB extract compared with the baseline value. However, the placebo-treated group did not show significant changes in the TAOC level after 90 days of treatment (Table IV).

TABLE I - Baseline characteristics of the T2DM patients enrolled in the study

Parameters	Met+Placebo *n*=20	Met+GKB *n*=27	*P* value
Age (yr)	48.2±10.3	48.7±9.6	0.85
Male (%)	3(15)	5(17.2)	0.42
Weight (kg)	83.4±12.2	82.7±17	0.88
BMI (kg/m^2)	34.2±6.2	33.9±6.0	0.8
WC (cm)	103.9±9.7	105.8±10.9	0.54
VAI	196.5±82.8	191.8±86.2	0.85
Diabetes duration (yr)	2.93±2.1	3.52±3.1	0.47
HbA1c (%)	8.8±2.3	8.6±1.6	0.69
Metformin therapy			
Duration of use (mo)	28±26.2	40.9±38.4	0.2
Daily dose (g)	1.24±0.67	1.36±0.45	0.45

Values are expressed as mean±SD and percentage. *n*: number of patients; Met: metformin: GKB: 120 mg *Ginkgo biloba* extract; BMI: body mass index; WC: waist circumference; VIA: visceral adiposity index; HbA1c: glycated hemoglobin.

TABLE II - Changes in the lipid profile of T2DM patients maintained on metformin and treated with Ginkgo biloba extract

Parameters	Met+placebo (*n*=20)		Met+GKB (*n*=27)	
	baseline	*90 days*	*baseline*	*90 days*
TG (mg/dL)	191.6±63.6	191.2±56.1	199.5±102.2	156.8±42.3*†
TC (mg/dL)	187.0±28.5	192.9±27.8	195.5±42.7	183.8±41.8^{NS}
LDL-c (mg/dL)	117.5±27.3	121.1±14.7	122.9±37.9	103.8±32.9*†
HDL-c (mg/dL)	36.6±10.5	43.3±8.5*	39.9±7.9	48.2±13.3*
TG/HDL-c	5.7±2.7	4.6±1.9*	5.3±3.1	3.5±1.3*†
LDL-c/HDL-c	3.6±1.5	2.9±0.6	3.2±1.3	2.2±0.8*†

Values are mean±SD; *n*: number of patients; * significantly different from baseline in each group (paired *t*-test, $P<0.05$); † significantly different from Met-placebo post-treatment (unpaired *t*-test, $P<0.05$); ANOVA: No significant differences between baseline values of all markers ($P>0.05$); Met: metformin: GKB: 120 mg *Ginkgo biloba* extract; TG: triglyceride; TC: total cholesterol; LDL-: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol.

TABLE III - Changes in the inflammatory markers of T2DM patients maintained on metformin and treated with *Ginkgo biloba* extract

Parameters	Met+placebo (*n*=20)		Met+GKB (*n*=27)	
	baseline	*90 days*	*Baseline*	*90 days*
hsCRP (mg/L)	5.9±4.8	6.2±4.9	7.0±5.2	5.4±3.8*
TNF-α (pg/mL)	127.2±69.8	136.0±69.3	117.8±80.7	55.1±43.1*†
IL-6 (pg/mL)	22.9±22.3	33.3±24.6	30.4±21.7	18.4±14.3*†

Values are mean±SD; *n*: number of patients; * significantly different from baseline in each group (paired *t*-test, $P<0.05$); † significantly different from Met-placebo post-treatment (unpaired *t*-test, $P<0.05$); ANOVA: No significant differences between baseline values of all markers ($P>0.05$); Met: metformin: GKB: 120 mg *Ginkgo biloba* extract; hsCRP: high sensitive C-reactive protein; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6.

TABLE IV - Changes in the serum leptin level and total antioxidant capacity (TOAC) of T2DM patients maintained on metformin and treated with *Ginkgo biloba* extract

Parameters	Met+placebo (*n*=20)		Met+GKB (*n*=27)	
	baseline	*90 days*	*Baseline*	*90 days*
Leptin (ng/ml)	7.8±2.0	6.2±2.2*	7.7±1.9	4.3±0.9*†
TOAC (U/ml)	47.9±17.8	46.4±20.0	37.6±18.1	50.0±20.1*

Values are mean±SD; *n*: number of patients; * significantly different from baseline in each group (paired *t*-test, $P<0.05$); † significantly different from Met-placebo post-treatment (unpaired *t*-test, $P<0.05$); ANOVA: No significant differences between baseline values of all markers ($P>0.05$); Met: metformin: GKB: 120 mg *Ginkgo biloba* extract.

DISCUSSION

Many studies have recognized dyslipidemia as an important risk factor for the emergence of vascular disorders in T2DM, and the efficacious and safe therapeutic options for diabetes-associated dyslipidemia are essential to interfere with the initiation and progression of vascular diseases in at-risk individuals (Schofield *et al*., 2016; Wu, Parhofer, 2014). Many studies focused on the health benefits of GKB extract, especially those related to its antioxidative properties in healthy subjects, but we aimed to evaluate its effect on T2DM patients with lipid profile complications. It is well-known that *Ginkgo biloba* leaves extract has powerful antioxidant effects (Lu *et al*., 2018; Ren *et al*., 2019); accordingly, we expected to report significant evidence regarding the improvement of lipid profile and increasing total antioxidant capacity of T2DM patients.

It has been reported that GKB extract has the potential to prevent hyperlipidemia-induced renal damage in both experimental animals and hypertensive patients, which was mostly attributed to the decrease in the oxidative and nitrosative stress and the inflammatory cascades initiated in the renal tissues (Abd-Ellah, Mariee, 2007; Abdel-Zaher *et al*., 2017). In tune with the results of the present study, it has been reported that GKB extract was effective in correcting dyslipidemia in the animal model of non-alcoholic fatty liver disease,

and the mechanism of action may be associated with the increase in total lipase activity, decrease free fatty acids (FFA) content of the liver, and the reduction of TG synthesis (Yang *et al*., 2016). Recent studies have proved the role of the oxidative stress and the pro-inflammatory mediators in the pathogenesis of insulin resistance; hence, attenuating the process of the inflammatory response is one of the therapeutic strategies to prevent the development and progression of insulin resistance (Rehman, Akash, 2016). Furthermore, the role of leptin is increasingly being involved in the etiology of T2DM. It has been reported that leptin shares the same signaling pathway with insulin (Khokhar, Sidhu, Kaur, 2013). Accordingly, the present study is the first randomized double-blind placebo-controlled trial that aimed to assess the effect of GKB extract, as "add-on" treatment to metformin, on the levels of hs-CRP and pro-inflammatory cytokines in patients with T2DM. The data presented in this study clearly showed that GKB was effective in decreasing the levels of the inflammatory mediators especially TNF-α, which demonstrates a significant change compared with the placebo group. This effect could be attributed to the modulating effect of GKB contents on the expression of many inflammatory mediators (Kaur, Sharma, Nehru, 2018). Moreover, targeting TNF-α may enhance the downregulation of the immune and inflammatory responses, because TNF-α plays a pivotal role in the stimulation of reactive oxygen species, expression of other pro-inflammatory mediators, activation of leucocytes, and eventually amplification of the inflammatory cascades (Zhou *et al*., 2006). In an *in vitro* study, GKB demonstrated pronounced efficacy in decreasing various cytokines including TNF-α production. The proposed mechanism was the down-regulation of the JNK-AP-1 signaling pathway (Cheng *et al*., 2003). Recently, we have reported that GKB extract improves the glycemic status and insulin resistance, reduces body mass index and visceral adiposity index in patients with T2DM poorly controlled with metformin (Aziz *et al*., 2018). In the current study, one of the targets was the screening of GKB effects on the level of leptin. Leptin is one of the important hormones expressed by the adipose tissue and found to play a pivotal role in the energy homeostasis. It is a cytokine liberated in proportion to body fat contents and acts on the hypothalamic nuclei to decrease food consumption and accelerate energy production (Friedman, Halaas, 1998). However, improper leptin signaling either due to a mutation in leptin or leptin receptor gene increases the consumption of food and limits the liberation of energy in humans and experimental animals despite obesity (Montague *et al*., 1997). In the present study, the GKB extract significantly decreases the serum levels of leptin in T2DM patients, and regarding this finding, there is no adequate evidence to explain the exact mechanism that contributes to such an effect. However, the previously reported decrease in visceral adiposity (Aziz *et al*., 2018) may be correlated with the changes in the serum leptin levels. Moreover, a 90-day treatment with GKB extract might exert a positive anti-inflammatory effect on the hypothalamus, with consequent reduction of the levels of orexigenic peptide and/or increasing anorexigenic peptides levels, which may promote weight loss via the suppression of the appetite (Hirata *et al*., 2015). The major limitations of the present study include the small sample size, the relatively short duration of treatment, and the requirement for dose-response effects for GKB extract when used alone or as an adjuvant to the antidiabetic drug. Therefore, future studies are recommended to clarify the long-term effect of GKB extract by following up with a larger study sample. Taking these findings together with our previous one on the BMI, waist circumferences, VAI and improving glycemic status and insulin sensitivity (Aziz *et al*., 2018), we can suggest the use of GKB extract as a promising candidate to be added as adjuvant therapy for diabetic patients poorly responding to metformin or other antidiabetic medications.

CONCLUSION

The use of GKB extract, as an "add-on" medication with metformin, was effective in decreasing the inflammatory mediators, leptin level and improving the antioxidant status and lipid profile of T2DM patients improperly managed with metformin alone. This finding may support the beneficial role of GKB extract as an "add-on" option to the treatment regimen of T2DM patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in this work.

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