The Role of Ginkgo biloba Extract as Monotherapy in Improving the Outcomes of Patients with Metabolic Syndrome: A Pilot Comparative Study with Metformin

Tavga A. Aziz*

*Department of Pharmacology and Toxicology, College of Pharmacy, University of Sulaimani, Kurdistan, Iraq

Abstract

The present study evaluates the effects of Ginkgo biloba extract as monotherapy on the glycemic status, insulin resistance (IR), body mass index (BMI), and visceral adiposity index (VAI), in addition to the inflammatory markers, oxidative status and leptin level in patients with metabolic syndrome in comparison with metformin.

The study is a randomized, double-blind pilot study conducted during the period May to September, 2020. Fifty patients were recruited in the study and they were allocated into two groups (25 per each group): Ginkgo biloba and Metformin groups, they received (120 mg Ginkgo biloba extract/capsule) and (500 mg Metformin/capsule) respectively; orally as a single dose for 90 days. Blood samples were taken at zero time and after 90 days and utilized for analysis of blood glucose, HbA1c, insulin and leptin levels, lipid profile, TAOS, hsCRP, TNFα and IL-6. Additionally, hematological markers, liver and kidney function tests also measured. Body mass index, waist circumference (WC), IR, and VAI were determined at baseline and after 90 days of GKB extract and metformin treatment.

Ginkgo biloba significantly decreased IR (4.3±2 vs 8±6.4), (P=0.047), BMI (30.7±2.7 vs 31.5±2.2) (P<0.048), VAI (183.7±101 vs 245.7±104.5), (P=0.036) and leptin level (4976±1803 vs 7317 ± 2807), (P=0.037) compared with baseline value. However, no significant decrease was observed on HbA1c and insulin level. GKB also significantly decreased IL-6 level (19.8±19 vs 28±22), (P=0.018) and TNFα level (130.6±33.7 vs 182.8±36.6), (P=0.001) with significant increase in HDL level (41.3±11.6 vs 30.7±4.8), (P=0.01) and TAOC (52.8±27 vs 37.9±15.5), (P=0.01) compared to the baseline values. Metformin led to a significant decrease (12.9±6 vs 27 ±19 µIU/ml) in insulin level (P= 0.032) and IR (6.7±5 vs 12.8±9), (P=0.039), with significant increase in HDL level (49.2±4.4 vs 38.0±3.8), (P=0.001) compared with the pre-treatment value.

The use of 120mg GKB as monotherapy was effective in improving the outcomes of metabolic syndrome suggesting it as a good candidate to be used in the clinical setting with a larger sample size and for a longer period of time.

Keywords: Ginkgo biloba, Metabolic syndrome, Glycemic status, Visceral adiposity index, Inflammatory markers.
Introduction

Metabolic syndrome (MetS) is a debatable clinical body characterized by metabolic disturbances. The etiology of the disease contributes to several factors upon which genetic and environmental factors have a critical role in the disposition of the disease. There are some risk factors such as obesity, insulin resistance, dyslipidemia, and hypertension that contribute to the pathogenesis of the disease. Improper management of MetS may end up with cardiovascular events and type 2 diabetes. Obesity is considered a pandemic and the prevalence has increased pronouncedly. Large bodies of evidence proved the relation between body weight, hyperlipidemia, metabolic syndrome and type 2 diabetes. In addition to the pivotal role of obesity in the development of insulin resistance, weight reduction is the first non-pharmacological strategy in the management of MetS, however people are not willing to adhere with a restricted low calories diet for a long period of time. Additionally, Some inflammatory markers are known to increase in patients with MetS. However, the relationship between inflammation and metabolic syndrome are not clear. One of the theories that explain this link could be the fact that obese peoples with MetS have high level of adipose tissue that contribute in the release of proinflammatory cytokines directly into the circulatory system. The increase in the levels of the inflammatory markers do not resemble that of acute or chronic inflammation since it is not associated with infection or serious tissue damage, it is a low grade of inflammation mainly known as meta-inflammation. The multifactorial etiologies of MetS render the management of the disease to be difficult because we need more than one medication to control the symptoms of the disease like hyperglycemia, hypertension, and dyslipidemia with truncal obesity. Polypharmacy is usually associated with increasing incidence of non-adherence, adverse reactions and drug interactions. Therefore, the search for new medication that possesses more than one mechanism to control the disease is of value. Medicinal plants have a long history in the management of various metabolic illnesses. Ginkgo biloba L. leaf extract (GKB extract), is among the nutraceuticals that gained great attention by the researchers because of its numerous biologically active constituents that may modify insulin action and/or production, the plant is known for its antioxidant, anti-inflammatory and hypolipidemic activity. Furthermore, ginkgo biloba proved to be effective in improving glycemic status and insulin sensitivity. Recently GKB was shown to be effective as add-on therapy with metformin in patients with T2DM and MetS, suggesting it as a good candidate to be tested as monotherapy in these diseases. Accordingly, the present study was designed to evaluate the effect of GKB alone on the outcome of metabolic syndrome.

Patients, Materials and Methods

Patients

The study protocol was approved by the Ethical Committee of the College of Medicine/University of Sulaimani (certificate no 507/1024), and has been approved in Iranian Registry of Clinical Trials with registration reference IRCT20200803048285N1. The study was carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000 (A set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association). Written informed consent was obtained from each participant prior to enrollment in this pilot study.

Materials

Ginkgo biloba extract, as a standardized powder (EGb761), was obtained from Apollo Healthcare Resources, Singapore; metformin (Met) tablets (500 mg, Merck Sante S.A.S., France) were obtained from the verified and licensed pharmacy.

Methods

Study design and patient treatment

The study was a randomized, double-blinded pilot study conducted between May to September 2020 at the Center of Diabetes and Endocrine Glands, Directory of Health/ Sulaimani city. The patients were recruited from public hospitals and private clinics according to the selection criteria. According to the inclusion criteria, patients of both sexes with the age range of 25-65 years, diagnosed by a specialist physician as having metabolic syndrome depending on the guideline of metabolic syndrome. The exclusion criteria included pregnancy, ischemic heart disease, cardiac arrhythmias, glucose-6-phosphate dehydrogenase (G6PD) deficiency, bleeding disorders, seizures, and known hypersensitivity to any component of the trial drugs (GKB extract and Metformin). Moreover, patients on supplements that contain multivitamins and polyphenols were also excluded. Sixty patients were originally screened for eligibility; only 50 were eligible and randomized into two groups (25 patients each) as follows: Metformin (500 mg tablet) group and GKB group received GKB extract (120 mg/capsule) as a single dose for 90 days. The GKB capsules were prepared in the laboratory of pharmaceutics, College of Pharmacy, University of Sulaimani. Patient follow-up was performed on monthly base to ensure patient compliance.
Unfortunately, only 39 patients; 19 patients from the first group and 20 patients from the second group were completed the study and included in the final data analysis (Figure 1).

### Anthropometric outcomes

Anthropometric measures were evaluated at baseline and after 90 days at the end of the treatment. Height and weight were measured by an electronic scale and a wall-mounted stadiometer. Waist circumference was measured by a tape measure. Each measurement was taken twice, and the average values were recorded. In addition, the body mass index (BMI) was calculated according to the following formula:

\[
BMI = \frac{\text{weight (kg)}}{\text{height}^2 \text{ (m}^2)}
\]

Visceral adiposity index (VAI) was also measured. The VAI is an empirical mathematical model, which is gender specific and based on simple anthropometric (BMI and WC) and functional parameters (TG and HDL-c), which is an indicator of body fat distribution and function. Calculation of VAI was according to the formula given by Amato et al. The formula is a linear equation derived by extrapolation from the relationship between BMI and WC in a healthy normal/overweight population. Distribution mode of adipose tissue was corrected for TG and HDL-c levels to determine the VAI as follows:

- **Female VAI** = \((\frac{WC}{36.58} + (1.88 \times BMI)) \times (\frac{TG}{0.81}) \times (1.52/HDL)\)
- **Male VAI** = \((\frac{WC}{39.68} + (1.89 \times BMI)) \times (\frac{TG}{1.03}) \times (1.31/HDL)\)

Where WC is expressed in cm, BMI in kg/m2, TG in mmol/L, and HDL in mmol/L.

### Biochemical and hematological tests

Patients were informed to be fasted for exactly 12 h, then about 10 mL blood was taken from each patient at zero time (before starting treatment) and after 90 days’ treatment by vein puncture. From which, about 2.0 mL was drawn in EDTA containing tubes and utilized for analysis of hematological markers fasting blood glucose (FBG) and HbA1c using colorimetric methods (Roche-cobas C 311, Roche Diagnostics GmbH, Mannheim, Germany). Insulin resistance calculated using HOMA-IR (22). The remainder 8.0 mL was drawn in plain tubes and left to clot, then centrifuged at 3000 rpm for 20 min to obtain serum. The serum was stored at -20°C unless analyzed immediately. The serum insulin content was measured using an immunoassay method (Roche-Cobas e 411; Hoffman-La Roche Ltd.). The serum was used for analysis of leptin 34, total lipid profile 35 using colorimetric methods (Roche-cobas C 311, Roche Diagnostics GmbH, Mannheim, Germany). TNFα and IL6 were measured using human TNFα and human IL6 ELISA Kit respectively by a colorimetric method 36, 37 (Visible Spectrophotometer 721, China). Liver 40 and kidney functions test 41, 42 and hematological markers 43 were determined calorimetrically using ready-made kits (Randox, London, UK) according to the manufacturer’s instructions.

### Statistical analysis

The statistical analysis was performed using the GraphPad Prism 5.1 software (GraphPad Software, Inc., La Jolla, CA, USA). Descriptive statistics was utilized to compare the patient’s characteristics between the two groups. Paired t-test was utilized to evaluate the difference between the pretreatment mean and post treatment mean of the same group. Unpaired t-test was utilized to evaluate the differences between post treatment mean of the different groups. Two-way analysis of variance, supported by Bonferroni’s post hoc analysis, and analysis of covariance were used to determine the difference between the mean of independent samples at P-value < 0.05.

### Results

The baseline data of the MetS patients were shown in Table 1. There were no statistically significant differences (P>0.05) in all parameters between the Metformin and GKB groups including the age, gender, weight, WC, BMI and HbA1c. After 90 days of treatment, FBG levels of both GKB treated group and metformin treated group were non-significantly decreased (125±17 mg/dl vs 126 ±30) and (135±11 mg/dl vs 141 ±17) respectively, (P>0.05) compared with baseline values (Figure 2 A). Regarding the effects on insulin, 90 days’ treatment with GKB extract non-significantly decreased (20.6±17 µIU/ml vs 36.7 ±28) level (P= 0.07) compared with baseline values, while treatment with metformin led to a significant decrease (12.9±6µ IU/ml vs 27 ±19) in insulin levels compared with baseline values (P= 0.032) (Figure 2 B). Concerning the level of HbA1c, GKB treated
group produced a non-significant decrease (7±0.8% vs 7.2±1%) compared to the baseline value (P=0.6) with no significant change produced by metformin (Figure 2 C). Regarding Insulin resistance, there was a significant decrease after 90 days of treatment with each of GKB extract and metformin compared with the pre-treatment value (4.3±2 vs 8±6.4), (6.7±5 vs 12.8±9), (P=0.047) and (P=0.039) respectively (Figure 2 D).

**Figure 2**: Effect of Gingko biloba extract (GKB) on the serum level of (A) Fasting Glucose (B) Insulin (C) HbA1c (D) Insulin Resistance of patients with metabolic syndrome. Values were presented as mean ± S.D; * significantly different compared with baseline values (paired t-test, P<0.05). Values with non-identical letters (a, b, c) were significantly different among each other (ANOVA, P<0.05).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Metformin n=19</th>
<th>GKB n=20</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44.15±9.5</td>
<td>45.7±7.8</td>
<td>0.25</td>
</tr>
<tr>
<td>Male (%)</td>
<td>4 (21%)</td>
<td>5 (25%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.46±13.46</td>
<td>80.7±17</td>
<td>0.18</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32 ±7</td>
<td>31.5±2.2</td>
<td>0.56</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>97.6±10.2</td>
<td>102.2±5.5</td>
<td>0.23</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7±0.95</td>
<td>7.2±1</td>
<td>0.68</td>
</tr>
</tbody>
</table>

P-value consider significant if P<0.05.
Figure 3 A clearly shows that the use of 120mg GKB extract, as a single oral dose for 90 days, significantly decreased BMI (30.7±2.7 vs 31.5±2.2) ($P<0.048$) compared with baseline values, while administration of metformin resulted in a non-significant decrease (32.4±6.9 vs 32.8±7) in BMI compared with baseline values. Moreover, GKB-treated patients showed a non-significant decrease in waist circumference values (99.6±5.5 vs 102.2±5.5) ($P=0.06$) compared with baseline values, while metformin did not significantly affect this parameter after 90 days (Figure 3 B). Regarding the effect on visceral adiposity index (VAI), (Figure 3 C) shows that in GKB treated group, there was a significant decrease (183.7±101 vs 245.7±104.5) in VAI after 90 days of treatment compared with the baseline value ($P=0.036$); meanwhile, a non-significant decrease (158±77.8 vs 195.6±145.5) in VAI was observed after 90 days of treatment with metformin ($P=0.26$) compared with the pre-treatment value. GKB also resulted in a significant decrease (4976±1803 vs 7317 ± 2807) in the level of leptin after 90 days’ treatment ($P=0.037$); compared with the pretreatment value with no significant change (6169±2414 vs 7176 ± 2812) observed with the use of metformin ($P=0.22$) (Figure 3 D).

After 90 days of treatment total cholesterol, triglyceride and serum LDL were non-significantly changed with each of GKB extract and metformin compared with the pre-treatment value (Figure 4 A, B and C). While serum HDL levels was significantly increased after 90 days of treatment with each of GKB extract (41.3±11.6 vs 30.7±4.8), ($P=0.01$) and metformin (49.2±4.4 vs 38.0±3.8), ($P=0.001$) compared with the pre-treatment value (Figure 4D).
Figure 4. Effect of Ginkgo biloba extract (GKB) on the serum level of (A) Total cholesterol (B) Triglycerides (C) LDL and (D) HDL of patients with metabolic syndrome. Values were presented as mean ± S.D; * significantly different compared with baseline values (paired t-test, *P*<0.05).

Regarding TNFα there was a significant decrease after 90 days of treatment with GKB extract (130.6±33.7 vs 182.8±36.6), (*P*<0.001) compared with the pre-treatment value and (130.6±33.7 vs 181.3±74), (*P*<0.05) compared with metformin treated group (Figure 5 A). While the use of 500 mg metformin produced no significant change compared with the baseline value. Ninety days’ treatment with GKB extract also produced a significant decrease in the level of IL6 (19.8±19 vs 28±22), (*P*=0.018) compared with the pre-treatment value with non-significant decrease produced by group treated with metformin (Figure 5 B). Moreover, hs-CRP was non-significantly decreased in GKB treated group and non-significant increase produced by metformin treated group (Figure 5 C). Serum TAOC was significantly increased after 90 days of treatment with GKB extract (52.8±27 vs 37±19.5), (*P*=0.01); compared with the pre-treatment value.

Figure 5. Effect of Ginkgo biloba extract (GKB) on the serum level of (A) TNF-α (B) IL6 (C) hs-CRP of patients with metabolic syndrome. Values were presented as mean ± S.D; * significantly different compared with baseline values (paired t-test, *P*<0.05). Values with non-identical letters (a,b) were significantly different among each other (ANOVA, *P*<0.05).
Metformin also increased the level of TAOC however it was statistically not significant (Figure 6). All the biochemical analyses regarding the liver functions indicated no alteration of values after 90 days of GKB treatment (Table 2), except serum ALP where significant decreases were reported in each of GKB and metformin treated groups compared with baseline values (P=0.02) and (P<0.001) respectively. For the kidney function tests; serum creatinine levels were significantly elevated compared with baseline values in the metformin-treated group (P=0.014) but still within the normal range, with no significant change in blood urea level in both treated groups (Table 3). Regarding the hematological markers; (Table 4) reveals significant increase (P=0.038) in Hb concentration in the GKB-treated patients after 90 days compared with baseline values. Meanwhile, platelet count significantly decreased in GKB treated group (P=0.014) and metformin treated group (P=0.011).

Table 2. Effect of Gingko biloba extract (GKB) on the liver function markers of patients with metabolic syndrome.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Metformin (n=19)</th>
<th>GKB (n=20)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline after 90 days</td>
<td>baseline after 90 days</td>
</tr>
<tr>
<td>Serum AST (U/L)</td>
<td>20.21±7.25*</td>
<td>19.12±4.82*</td>
</tr>
<tr>
<td>Serum ALT (U/L)</td>
<td>17.11±8.2*</td>
<td>15.7±5.2*</td>
</tr>
<tr>
<td>Serum ALP (U/L)</td>
<td>75.4±25.5*</td>
<td>64.6±20.2*</td>
</tr>
</tbody>
</table>

Values were presented as mean±S.D; n: number of patients; * significantly different compared with baseline values (paired t-test, P<0.05); values with different superscripts (a,b) within each parameter were significantly different (ANOVA, P<0.05).

Table 3. Effect of Gingko biloba extract (GKB) on the renal function markers of patients with metabolic syndrome.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Metformin (n=19)</th>
<th>GKB (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Urea (mg/dL)</td>
<td>25±6.5*</td>
<td>25.6±8.4*</td>
</tr>
<tr>
<td>Serum Creatinin (mg/dL)</td>
<td>0.65±0.12*</td>
<td>0.75±0.12*</td>
</tr>
</tbody>
</table>

Values were presented as mean±S.D; n: number of patients; * significantly different compared with baseline values (paired t-test, P<0.05); values with different superscripts (a,b) within each parameter were significantly different (ANOVA, P<0.05).

Table 4. Effect of Gingko biloba extract (GKB) on the hematological markers of patients with metabolic syndrome.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Metformin (n=19)</th>
<th>GKB (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>12.9±1.2</td>
<td>13.4±1.5</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>37.9±3.8</td>
<td>39.4±4.6</td>
</tr>
<tr>
<td>RBC count x10⁶ (cells/µL)</td>
<td>4.4±0.5</td>
<td>4.6±0.5</td>
</tr>
<tr>
<td>WBC count x10⁶ cells/µL</td>
<td>8.5±2.3</td>
<td>8.1±1.6</td>
</tr>
<tr>
<td>Platelets count x10⁹ cells/L</td>
<td>257±50</td>
<td>223±57*</td>
</tr>
</tbody>
</table>

Values were presented as mean±S.D; n: number of patients; * significantly different compared with baseline values (paired t-test, P<0.05).
Discussion

The first step in the treatment of metabolic syndrome is modification of lifestyle via avoiding sedentary lifestyle and this includes decreasing food intake and increasing physical activity, however unfortunately only a few patients are willing to modify their lifestyle without the aid of medications. In the present study, GKB for the first time has been used as a monotherapy in patients with MetS; and it was effective in modifying and improving some of the components of MetS such as insulin resistance, BMI, VAI and HDL in addition to the inflammatory markers and the antioxidant status. Similarly, many studies have shown the effectiveness of GKB in improving insulin sensitivity (23, 44, 45). The glycemic status have been improved by the use of GKB in the current study however, the change was statistically not significant which could be attributed to the small dose and/or the short period of treatment, additionally, the exact effect of the plant cannot judge on such a small sample size. Moreover, it was effectively enhanced insulin sensitivity and this finding was in tune with other studies (44, 24). Obesity secondary to high fat food produces alterations in the regulation of peripheral metabolism and food intake, subsequently decreasing insulin sensitivity, enhancing weight gain, and other metabolic disorders (46, 47). In many countries, obesity is considered as a major health problem and the primary goal is how to decrease the prevalence of obesity (48); and in spite of the efforts for minimizing obesity, still non-pharmacological interventions are inadequate to achieve satisfaction (9, 49, 4), and because of the high risk associated with obesity in developing insulin resistance (5), additional medications are required to accomplish the necessity in the treatment of obesity. Nutraceutical recognized from traditional medicinal plants may represent a good choice for the development of new medications targeting obesity. In the current study, GKB extract successfully decreased BMI and WC; and this effect could be attributed to the terpenoid component of the plant that have the ability to inhibit the activity of pancreatic lipase (PL), which may in part give some clues about the reduction of body fat mass. Moreover, GKB was found to significantly inhibit PL (50), which may attribute to the reduction of BMI in the current study. While metformin did not affect BMI and WC which could be due to the small dose used in the study and relatively short period of treatment (51). GKB was effective in decreasing VAI and this finding was consistent with other study which demonstrated that prolonged treatment with GKB stimulated a noticeable visceral adiposity loss, improvement of insulin sensitivity via stimulation of insulin signaling cascade in gastrocnemius muscle (52).

Another parameter that screened in this study is leptin; leptin is increasingly being involved in the etiology of metabolic disorders. It is one of the vital hormones expressed by the adipose tissue, and it has a critical role in regulating food consumption and energy production through its action on the hypothalamic nucleus. It has been reported that leptin shares the same signaling pathway with insulin (53, 54). Mutation in leptin or its receptor results in improper leptin signaling and eventually increases food consumption and attenuates energy liberation in humans and experimental animals in spite of obesity (55). In the present study, GKB significantly decreased the serum levels of leptin and the exact mechanism of such finding is unclear. However, the previously reported decrease in visceral adiposity (18), could be of value in explaining the changes in serum leptin. Additionally, GKB might exert a positive anti-inflammatory effect on the hypothalamus, with a consequent reduction of the levels of orexigenic peptide and/or increasing anorexigenic peptide levels, which may promote weight loss via suppressing the appetite (24). In the present study, GKB as monotherapy in patients with MetS was effective in modifying and improving some of the components of MetS such as HDL and metabolic inflammation. Many studies have shown the effectiveness of GKB in improving glycemic status (23, 44, 45), and ameliorating the inflammatory response (56, 24). Recently, the role of the oxidative stress and the pro-inflammatory mediators have been proved 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 (57). The anti-inflammatory effect of GKB demonstrated through attenuating the inflammatory markers; the study showed a pronounced decrease in the level of TNF-α which demonstrates a significant change with the baseline value and with the group treated with metformin. GKB also produced a significant decrease in the serum level of IL6 compared to the baseline value. This anti-inflammatory effect could be attributed to the modulating effect on the expression of many inflammatory mediators and the ability of the plant to downregulate nitric oxide level and prostaglandin E2 formation along with decreasing pro-inflammatory cytokines and upregulating NF-kB factor (24, 58, 59).
The relationship between oxidative stress and inflammation is greatly documented \(^{(60, 61)}\). Evidence from many studies proved the role of reactive species in the pathology of many chronic inflammatory diseases \(^{(62, 63)}\). Among the inflammatory cytokines that modulate the inflammatory response is TNF-α which has a pivotal role in the generation of reactive species and enhance the expression of other inflammatory cytokines. Targeting TNF-α may participate in the downregulation of the inflammatory responses \(^{(64)}\). The current study revealed a potent antioxidant capacity exhibited by GKB; many mechanisms are proposed for this effect such as chelation of transition metals, scavenging of reactive oxygen species and enhancing the production of antioxidant molecules \(^{(65)}\). Furthermore, GKB has been reported to attenuate oxidative damage in previous studies \(^{(19-65)}\).

Moreover, the plant exerted no deleterious effect on the liver, kidney and the hematological markers. Taking all these findings together suggests GKB as a good candidate to be tested on a larger sample size of MetS patients and for a longer period of time to explore the exact beneficial effect of the plant in this respect.

**Limitations**

The major limitations of this study are the small sample size and the relatively short duration of treatment. Therefore, future studies are warranted to determine the long-term effect of GKB extract by following up a larger study population.

**Conclusion**

The use of 120mg GKB as monotherapy was effective in improving the outcomes of metabolic syndrome through decreasing insulin resistance, BMI, VAI, and leptin levels, and it was also effective in decreasing the inflammatory markers and increasing the antioxidant capacities in comparison with metformin suggesting it as a good candidate to be used in the clinical setting with a larger sample size and for a longer period of time.

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**Disclosure**

The author reports no conflicts of interest in this work.

**References**


