Protective Impact Of Ginkgo Biloba Extract Against Thioacetamide Induced Hepatotoxicity In Albino Rats

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ABSTRACT

The purpose of this study to investigate the protective and therapeutic effect of Ginkgo biloba leaves extract (GbE) against hepatotoxicity induced by thioacetamide (TAA) in male albino rats.

Rats were injected intraperitonially by TAA in a dose of 200 mg/kg b.wt. twice every week for 28 days (TAA treated group). GbE was orally administered in a dose 100mg/kg b.wt. for 7 days before the first dose of TAA treatment and during exposure period (Gb protected group) and also after the last dose of TAA treatment for 28 days (Gb treated group). The gained results revealed a significant increases in MDA and NO concentrations in blood and liver of TAA group with concomitant decrease in GSH, GSH-px, SOD and CAT activities. DNA fragmentation percentage, TNF-α concentration, hydroxyproline content and tissue transglutaminase activity were also increased. Serum transaminases, ALP and GGT activates as well as bilirubin content were increased. This study showed that Ginkgo biloba extract has a potential activity against thioacetamide. Induced hepatotoxicity and suggested that the chemical constituents of Ginkgo biloba are effective in modulation of oxidative stress induced by thioacetamide.

INTRODUCTION

Oxidative stress, characterized by the overproduction of reactive oxygen species (ROS), which overwhelm the levels of antioxidants, has been suggested as the pathogenic factor of a number of human diseases and was reported to cause tissue damage (1). ROS can damage DNA, impair protein function and increase lipid peroxidation (2). Exogenous sources of free radicals include tobacco smoke, certain pollutants and organic solvents, anesthetics, hyperoxic environments and pesticides. Some of these compounds as well as certain medications are metabolized to free radical intermediate products that have been shown to cause oxidative damage to the target tissues (3). Thioacetamide (TAA, CH3-C[S] NH2), a known fungicide used to control fruits decay (4), was shown to be oxidized at the thioamide group to TAA sulfoxide (CH3- C[SO] NH2) and subsequently di-Soxide (CH3-C[SO2] NH2) in the liver. The reactive intermediates in this pathway covalently bind to hepatic macromolecules and eventually cause liver injury (5,6), whereby free radical mediated lipid peroxidation contributes to the development of TAA induced liver fibrosis (7,8), Among various hepatotoxins, TAA is known to be the most potent because of its rapid elimination and cumulative injury (9). The biochemical and morphological changes observed in TAA induced rat liver injury resemble to a large extent human liver disease and could serve as a suitable model for studying the causes of human liver fibrosis and cirrhosis (10). Herbal medicine is increasingly gaining acceptance from the public and medical professionals due to advances in the
understanding of the mechanisms by which herbs positively influence health and quality of life (11). Ginkgo biloba (maidenhair tree) is one of the oldest herbal medicines that have been used as a therapeutic agent in modern pharmacology. Ginkgo biloba has been a popular remedy in traditional Chinese medicine for over 4000 years, and it has been a common herbal medicine in Europe since the 1730's (12). GbE is a mixture mainly of flavonoid glycosides (24%) and terpenoides (6%) (ginkgolides and bilobalide), has been shown to exhibit a variety of pharmacological actions (13). So, the present study was aimed to evaluate the beneficial action of Ginkgo biloba extract on hepatotoxicity induced by TAA administration in male albino rats.

MATERIAL AND METHODS

Animals and Treatment

Fifty male locally bred strain albino rats weighing 120 ± 10 g were used in the current study. They were maintained on a balanced diet and water ad libitum. Animals were classified into five equal groups, 10 rats each. The 1st group served as control, the 2nd group was given GbE orally in a dose of 100mg/kg b.wt. (14) daily for 28 days. The 3rd group was injected intraperitoneal by TAA in a dose of 200 mg/kg b.wt. twice weekly for 28 days (15). The 4th group received the same dose of GbE 7 days before the first dose of TAA injection and continued during the exposure period (28 days). The 5th group was given the same dose of GbE after the last dose of TAA treatment and continued for 28 days. At the end of experiment the animals were scarified. Blood, serum and liver samples were taken for biochemical and histopathological examination. Blood and liver samples were used for determination of MDA concentration (16), nitric oxide concentration (17), GSH concentration (18), GSH-px activity (19), SOD activity (20) and CAT activity (21). Serum samples were used for estimation of AST,ALT activities (22), ALP activity (23), GGT activity (24) and bilirubin (Total, direct and indirect) (25). DNA fragmentation percentage was determined to the method of Perandones (26). TNF-α concentration (27), hydroxyproline content (28) and iTG activity (29), were estimated in liver samples.

Histopathology

Samples from livers were kept in 10 % formalin for histopathological examination.

Statistical analysis

The SPSS (version 10) was used in data analysis. Data were analyzed with one-way analysis of variance (ANOVA) followed by a post hoc test (LSD alpha) for multiple comparisons. The data were expressed as mean ± standard deviation (SD). P values < 0.05 were considered to be statistically significant.

RESULTS

Administration of GbE to rats, by force-feeding, for a period of 28 days, did not show significant changes in all the studied parameters, indicating that the extract did not affect lipid peroxidation and liver function test (Tables 1-5).

TAA induced significant decreases in blood and liver GSH concentration, SOD, GSH-px and CAT activities which were parallel to significant increases in MDA and NO contents (Tables 1,2).
Table 1. Effect of GBE on erythrocytic MDA, GSH, NO levels, CAT, GSH-px and SOD activities in different experimental groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Gb</th>
<th>TAA</th>
<th>Gb protected</th>
<th>Gb treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA µg/ml</td>
<td>80.07 ± 1.94&lt;sup&gt;c&lt;/sup&gt;</td>
<td>79.47 ± 1.45&lt;sup&gt;c&lt;/sup&gt;</td>
<td>91.86 ± 1.68&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>81.44 ± 1.22&lt;sup&gt;c&lt;/sup&gt;</td>
<td>83.45 ± 2.19&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>NO µm/ml/ml</td>
<td>17.80 ± 0.62&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17.86 ± 0.32&lt;sup&gt;c&lt;/sup&gt;</td>
<td>21.97 ± 0.36&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>17.19 ± 0.88&lt;sup&gt;c&lt;/sup&gt;</td>
<td>19.72 ± 0.35&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>GSH mg/dl packed RBCs</td>
<td>120.38 ± 2.57&lt;sup&gt;c&lt;/sup&gt;</td>
<td>124.21 ± 1.39&lt;sup&gt;c&lt;/sup&gt;</td>
<td>92.09 ± 2.94&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>105.37 ± 4.86&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>93.59 ± 2.76&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>GSH-px µg oxidized GSH/min/ml packed RBCs</td>
<td>231.85 ± 21.23&lt;sup&gt;c&lt;/sup&gt;</td>
<td>225.31 ± 9.92&lt;sup&gt;c&lt;/sup&gt;</td>
<td>133.75 ± 5.45&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>207.04 ± 12.46&lt;sup&gt;c&lt;/sup&gt;</td>
<td>214.11 ± 3.44&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>CAT µmol/ml packed RBCs</td>
<td>320.04 ± 7.76&lt;sup&gt;c&lt;/sup&gt;</td>
<td>135.07 ± 5.95&lt;sup&gt;c&lt;/sup&gt;</td>
<td>291.85 ± 3.00&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>321.33 ± 2.03&lt;sup&gt;c&lt;/sup&gt;</td>
<td>322.44 ± 1.49&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>SOD µg/ml packed RBCs</td>
<td>10.94 ± 0.41&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11.23 ± 0.65&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.70 ± 0.38&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>10.78 ± 0.33&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.75 ± 0.44&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Results are given as mean ± S.D. for 10 rats a: significantly different from control. b: significantly different from Gb. c: significantly different from TAA.

Table 2. Effect of GBE on hepatic MDA, GSH, NO levels, CAT, GPx and SOD activities in different experimental groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Gb</th>
<th>TAA</th>
<th>Gb protected</th>
<th>Gb treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA µg/g tissue</td>
<td>105.107 ± 1.73&lt;sup&gt;c&lt;/sup&gt;</td>
<td>104.243 ± 1.65&lt;sup&gt;c&lt;/sup&gt;</td>
<td>162.990 ± 3.09&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>112.661 ± 2.14&lt;sup&gt;c&lt;/sup&gt;</td>
<td>114.437 ± 6.94&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>NO µm/g tissue</td>
<td>70.65 ± 1.50&lt;sup&gt;c&lt;/sup&gt;</td>
<td>74.29 ± 1.43&lt;sup&gt;c&lt;/sup&gt;</td>
<td>87.28 ± 4.77&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>81.02 ± 2.70&lt;sup&gt;c&lt;/sup&gt;</td>
<td>79.90 ± 4.55&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>GSH mg/g tissue</td>
<td>158.10 ± 3.69&lt;sup&gt;c&lt;/sup&gt;</td>
<td>162.42 ± 3.45&lt;sup&gt;c&lt;/sup&gt;</td>
<td>136.66 ± 3.86&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>150.74 ± 2.36&lt;sup&gt;c&lt;/sup&gt;</td>
<td>156.71 ± 4.43&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>GSH-px µg oxidized GSH/min/g tissue</td>
<td>333.45 ± 7.48&lt;sup&gt;c&lt;/sup&gt;</td>
<td>345.02 ± 6.62&lt;sup&gt;c&lt;/sup&gt;</td>
<td>162.84 ± 8.62&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>348.00 ± 7.04&lt;sup&gt;c&lt;/sup&gt;</td>
<td>341.96 ± 6.73&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>CAT µg/g tissue</td>
<td>365.04 ± 5.32&lt;sup&gt;c&lt;/sup&gt;</td>
<td>373.93 ± 6.26&lt;sup&gt;c&lt;/sup&gt;</td>
<td>270.81 ± 17.32&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>352.74 ± 10.61&lt;sup&gt;c&lt;/sup&gt;</td>
<td>357.89 ± 3.93&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>SOD µg/g tissue</td>
<td>11.10 ± 0.33&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11.76 ± 0.41&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.92 ± 0.17&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>9.71 ± 0.35&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>9.32 ± 0.55&lt;sup&gt;abc&lt;/sup&gt;</td>
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</table>

Results are given as mean ± S.D. for 10 rats a: significantly different from control. b: significantly different from Gb. c: significantly different from TAA.

The pre-treated group with GBE showed a significant reduction of oxidative stress parameters. On the other hand, post-treatment with GBE not ameliorated neither the increases of NO content nor the depletion of GSH content and SOD activity in blood. In addition pre and post-treatment didn't ameliorated NO content in the liver.

Significant increases of serum ALT, AST, ALP and GGT activities were observed in rats that received TAA. Pre-treatment with GBE ameliorated these increases while post-treatment didn't ameliorated the increases in ALT and GGT activities Table 3.
Table 3. Effect of GBE on ALT, AST, ALP and GGT activities in the sera of different experimental groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Gb</th>
<th>TAA</th>
<th>Gb protected</th>
<th>Gb treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (U/l)</td>
<td>12.40 ± 0.76c</td>
<td>11.63 ± 0.97c</td>
<td>18.30 ± 1.46ab</td>
<td>14.87 ± 0.74c</td>
<td>12.07 ± 1.07c</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>13.30 ± 0.93c</td>
<td>13.00 ± 0.92c</td>
<td>19.90 ± 1.53ab</td>
<td>13.43 ± 1.07c</td>
<td>16.80 ± 1.25b</td>
</tr>
<tr>
<td>ALP (U/l)</td>
<td>198.33 ± 14.50c</td>
<td>187.67 ± 18.00c</td>
<td>337.00 ± 18.50ab</td>
<td>288.67 ± 10.41ab</td>
<td>244.67 ± 11.57ab</td>
</tr>
<tr>
<td>GGT (U/l)</td>
<td>43.00 ± 3.28c</td>
<td>43.00 ± 3.61c</td>
<td>104.67 ± 8.37ab</td>
<td>58.33 ± 3.93abc</td>
<td>79.00 ± 1.53ab</td>
</tr>
</tbody>
</table>

Results are given as mean ± S.D. for 10 rats a: significantly different from control. b: significantly different from Gb. c: significantly different from TAA.

Significant increases in the content of total, direct and indirect bilirubin were observed in the rats injected with TAA. Pre-treatment with GbE ameliorated these increases. On the other hand, post-treatment with GbE not ameliorated these increases Table 4.

Table 4. Effect of GBE on Serum bilirubin total, direct and indirect concentrations in different experimental groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Gb</th>
<th>TAA</th>
<th>Gb protected</th>
<th>Gb treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin total (mg/ml)</td>
<td>0.537±0.009c</td>
<td>0.513±0.041c</td>
<td>0.907±0.043ab</td>
<td>0.720±0.023abc</td>
<td>0.800±0.047ab</td>
</tr>
<tr>
<td>Bilirubin direct (mg/ml)</td>
<td>0.237±0.018c</td>
<td>0.253±0.020c</td>
<td>0.473±0.041ab</td>
<td>0.387±0.012abc</td>
<td>0.407±0.024ab</td>
</tr>
<tr>
<td>Bilirubin indirect (mg/ml)</td>
<td>0.290±0.015c</td>
<td>0.260±0.031c</td>
<td>0.433±0.007ab</td>
<td>0.33±0.035</td>
<td>0.400±0.026</td>
</tr>
</tbody>
</table>

Results are given as mean ± S.D. for 10 rats a: significantly different from control. b: significantly different from Gb. c: significantly different from TAA.

As shown in Table 5, TAA significantly increased liver hydroxyproline content, rTG activity, DNA fragmentation percentage and TNF-α concentration. Pre and post-treatment with GbE significantly ameliorated these increases Table 5.
on CCl₄-induced liver fibrosis in Wistar male rats. They found that the liver fibrosis rats treated with GbE had decreased serum bilirubin. Finally, GbE induced striking improvement of liver function (47).

In the present study the biomarkers for liver fibrosis showed a significant increases in liver tTG activity, TNF-α concentrations and hydroxyproline content in TAA treated group. Several researchers have suggested that part of hepatocellular injury induced by TAA is mediated through oxidative stress caused by the action of cytokines through lipid peroxidation (84,85). Free radicals activate the hepatic stellate cells (HSC) and increase the deposition of extracellular matrix (ECM) components. Also, the fibrogenesis appears to involve several events mediated by proinflammatory and cytotoxic cytokines, such as tumor necrosis factor (TNF), interleukins and transforming growth factor (TGF) (86,87). Other studies, have documented the association between fibrogenesis and the excessive deposition of collagen, elastin, laminin (88) and hyaluronan (89), in the ECM. Additionally, factors involved in stabilization or degradation of these proteins may play a potential role in the progression or reversibility of fibrosis.

Kupffer cells are the major source of mitogens, such as TNF-α in the liver (90,91). TNF-α is a multifunctional cytokine (92), that acts as mediator of the acute phase response in the liver and is a cytotoxic agent in many types of hepatic injury. Some authors have suggested that TNF-α may be necessary for hepatic proliferation (92). Elevation of TNF-α concentration after TAA treatment is involved in the programming of liver damage product of the inflammatory response (93).

Hydroxyproline is an amino acid unique to all of the collagens and represents 12% of amino acids in the major fibrillar collagen types I and III. Therefore, the measurement of hydroxyproline content serves as an excellent standard of fibrosis (86). In TAA treated group an increase in liver hydroxyproline content may be related to an incomplete post-translational maturation of collagen fibrils which involves the synthesis of hydroxyproline residues by prolyl 4-hydroxylase; these residues are needed to stabilize the collagen triple helix (94).

Tissue transglutaminase (tTG) is liver derived enzyme which stabilize the scar formation. The increase in tTG activity in TAA treated group may be attributed to the increased binding of the nuclear factor-kappaB (NF-κB) to the NF-κB motif of the tTG promoter, where tTG gene expression increases during hepatic injury and fibrosis (95). The concomitant increase of both hepatic collagen and tTG activity may be explained by the dual effect exerted by the NF-κB, which is induced by oxidative stress (96). Nevertheless, the association between tTG activity and fibrosis may involve other factors such as the factor beta (TGF-β), major fibrogenic growth factors, where tTG activates the latent TGF-β1, which in turn leads to de novo synthesis of tTG (97). The increase of tTG activity may also be a consequence of GSH depletion and mitochondrial dysfunction (98).

These results are consistent with previous studies which demonstrated that TAA treatment possessed hepatotoxic effect, increasing tTG activity (99,100), TNF-α concentration (95,103-105). And decreasing hydroxyproline content in liver (104-106).

Finally, reduced hepatic antioxidant function has also been suggested as one of the mechanism of TAA induced hepatotoxicity where, TAA decreases the level of some endogenous antioxidants including α-tocopherol (107).

In the present study, TAA treatment induced dramatically elevation in DNA fragmentation percentage. These increase may be a result of interaction of ROS with biological molecules, producing toxic free radicals that cause cellular DNA or protein damage and lipid-peroxidation (108,109).

Results obtained in the present investigation agree with previous study by Duthie et al. (110) who reported that TAA treatment resulted in chromosome breakage or abnormal DNA methylation. In addition
nucleic acids can be attacked and subsequent damage to DNA can cause mutations which may be carcinogenic (3).

The present study showed that pre and post-treatment of GbE significantly reduced liver fibrosis as evidenced by significant decreases of tTG activity, TNF-α concentration and hydroxyproline content. These data go in hand with Harputluoglu et al., (111) who investigated that, GbE ameliorated the hepatic damage by TAA and suggested that the action of GbE may be due its free radical scavenging effects. Also Liu et al., (112) evaluated the effects of GbE on experimental liver fibrosis induced by CCl4 in rats and found that GbE was able to ameliorate liver injury through inhibiting the induction of NF-κB on HSC activation and the expression of TGF-β1.

Pre and post-treatment with GbE significantly reversed the damage of DNA induced in TAA treated rats. Min and Ebeler (113), suggested that quercetin which is the major component of flavonoid glycosides of GbE protects against cancer by inhibiting oxidative DNA damage as well as by enhancing DNA repair after oxidant challenge in colon cells.

Histological results were in agreement with the measured parameters and provided a supportive evidence for the biochemical analysis, in the liver sections of TAA treated group, showing distorted hepatic architecture and the dense bands of fibrous tissue which is radiating from the portal vein and dissecting the liver cells. The fibrous tissue shows proliferated bile ducts, proliferated capillaries and lymphocytic infiltration. Some large and multinucleated cells were seen.

Microscopic studies revealed that, liver section of rats receiving GbE after TAA treatment group, showed alleviation in liver fibrosis, preserved hepatic lobular architecture and marked improvement of the portal areas was seen.

Finally, hepatoprotective activity of GbE may be due to presence of compounds in this extract with high antioxidant capacity. Studies have shown that flavonoid (ginkgo-flavone glycosides) and terpenoid (ginkgolides and bilobalides) are the most important active substances in the GbE which have antioxidant effect (114,115).

In conclusion, the present study results demonstrated that GbE is effective in the prevention of TAA induced acute toxic effects in rats liver, which were proven by biological evaluation, biochemical analysis and further supported by the histological examinations in liver tissues. This hepatoprotective activity is both preventive (prophylactic) and curative (therapeutic).

REFERENCES


Hashim et al.,


التأثير الوقائي لمستخلص نبات الجنكيوبيلا على التسمم الكبريتي المحدث بعدها الثالوسيتاميد في الجرذان البيضاء الشهبة

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الغرض من هذه الدراسة هو التعرف على تأثير الوقائي والعلاجي من مستخلص أورق الجنكيوبيلا على التسمم الكبريتي الناجم عن مادة الثالوسيتاميد في ذكور الجرذان البيضاء الشهبة. تم حقن الفئران داخل الغشاء البركاني بمادة الثالوسيتاميد بجرعة 200 ملغ/كجم من وزن الفأر مرتين كل أسبوع لمدة 28 يوما (المجموعة التي تلقى مادة الثالوسيتاميد). مستخلص أورق الجنكيوبيلا أعطت عن طريق الفم بجرعة 100 ملغ/كجم من وزن الفأر قليل 7 أيام من الجرعة الأولى. من تلقى مادة الثالوسيتاميد والتي استمرت خلال فترة التعرض (المجموعة المجاورة بالجنكيوبيلا) وأيضا بعد آخر جرعة من مادة الثالوسيتاميد لمدة 28 يوما (الموثقة معالجة بالجنكيوبيلا) كشفت النتائج زيادة كبيرة في تركيز إنزيمات الملونين بالبيروكسيدات في الدم والكبد للمرحلة التي تلقى مادة الثالوسيتاميد مع مصباحية انخفاض في الجلودودين المختلط، الجليوتيانيون بروكسيداز، سوبار أكسيد الديماتيز وكالايترز. وزادت أيضا نسبة الجلودودين النераوح التنموي، وتركيز التيوبوريروزي التاء، محتوى الهيدروكسي بروتين ونشاط الترانزنجوليناز بنسبة الكبد. ونشط الترانزاميناز، الألكاينوس فوسفاتاز، وجلاموس جلودودينز انزهيراز وضلا عن زيادة محتوى البيليروبين.

أظهرت هذه الدراسة أن مستخلص الجنكيوبيلا لديه نشاط زائد ضد الثالوسيتاميد التي تسبب التسمم الكبريتي، والمفترض أن المكونات الكيميائية الجكوبيليا هي فعالة في تثبيط الضغط التأكسدي التي تسببها مادة الثالوسيتاميد.