# Effects of *Ginkgo biloba* on Diseases Related to Oxidative Stress

Authors
Gabriela Achete de Souza[1], Sâmylla Vaz de Marqui[1], Júlia Novaes Matias[1], Elen Landgraf Guiguer[1,2], Sandra Maria Barbalho[1,2]

Affiliations
1 Department of Biochemistry and Pharmacology, School of Medicine, University of Marília (UNIMAR), Marília, São Paulo, Brazil
2 Department of Biochemistry and Nutrition, Faculty of Food Technology of Marília, (FATEC), Marília, São Paulo, Brazil

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Correspondence
Dr Sandra Maria Barbalho
Department of Biochemistry and Pharmacology, School of Medicine, University of Marília
Av. Higino Muzzi Filho 1001, Marília 17525-902, SP, Brazil
Phone: + 55 1 49 96 55 31 90, Fax: + 55 14 21 05 40 00
smbarbalho@gmail.com

## ABSTRACT

*Ginkgo biloba* (GB) is one of the most widely used phytotherapeutic products in the world, and its extract has beneficial properties for the treatment of several pathologies, such as diabetic cardiomyopathy, neurodegenerative diseases, cataracts, hearing loss, myocardial lesion, hippocampus neuronal lesions, morphometry testicular changes, and liver damage. This review aims to investigate the effects of GB on diseases related to oxidative stress. Databases such as MEDLINE/PUBMED and EMBASE were consulted, and PRISMA guidelines were used to build the review. This plant has antioxidant properties since it regulates the expression of antioxidant enzymes positively and reduces reactive oxygen and nitrogen species, contributing to the reduction of lipid peroxidation. It also exhibits anti-inflammatory properties, inhibiting the expression of pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-$\alpha$. In animal models, the use of GB can show positive effects on brain damage, neurodegenerative diseases, myocardial injury, and renal and liver damage. In humans, the positive effects were shown in diabetes, metabolic syndrome, and ischemic colitis. These effects are due to the presence of compounds such as bilobalide, isoramnetina, quercetin, kaempferol, and ginkgolides A, B, and C. For these reasons, GB can be a low-cost alternative to the therapeutic approach of several pathologies since it acts in the prevention, treatment, and inhibition of several complications of common comorbidities.

## Introduction

Oxidative stress is caused by destructive and progressive modifications in one or more body tissues, leading to dysfunction of organs, premature aging, and sometimes disease and death. It is a natural and fundamental process of the body, but it also involves the acceleration of destructive modifications over time, not only at the cellular level but also at the molecular level [1, 2].

On an ongoing basis, the cells produce oxygen (ROS) and nitrogen (RNS) reactive species as part of metabolic processes during stress exposure, radiation, infections, and smoke exposure. These substances cause significant damage in organic biomolecules (nucleic acids, lipids, and proteins), inducing alterations in DNA, which, in turn, affect homeostasis and can lead to several oxidative disorders related to stress, such as cardiovascular diseases and cancer. It is possible that the usage of phytotherapeutic products, such as *Ginkgo biloba* (GB), may delay this process [3, 4].

GB belongs to the Ginkgoceae family, and it is one of the oldest living species on the planet. The leaves and seeds of this plant have been used for medicinal purposes in China for centuries, initially being used for asthma and problems in the digestive system. In Europe and the USA, they have been sold since the sixties, and now they represent one of the most popular phytotherapeutic products in the world [5–12].

Therefore, this study aimed to review the effects of GB on oxidative processes.

## Methodology

### Data source

To carry out this review, we used the MEDLINE–PubMed (National Library of Medicine, National Institutes of Health) and EMBASE databases to retrieve studies from May 2013 to October 2019), fol-

lowing the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). This review was conducted to answer the following question: What are the effects of GB on diseases related to oxidative stress?

### Research

This research includes placebo-controlled randomized clinical trials, case-control retrospective studies, and prospective transversal studies. Experimental model studies were also conducted. The combinations of used terms for this research were *Ginkgo biloba* and *oxidative stress*, and *Ginkgo biloba* and *inflammation*. These combination of terms resulted in a list from which we selected 58 articles that were used to build ▶ **Table 1**. The flowchart shows the selection of articles, as well as the inclusion and exclusion of studies (▶ **Fig. 1**). Other studies about GB, inflammation, oxidative stress, and antioxidants were used in the discussion section.

### Eligible criteria and study selection

This research includes quantitative and qualitative studies that reported the usage of GB in the treatment of diseases caused by oxidative stress and inflammation. All the articles relating to GB and oxidative stress and GB and inflammation published in the last 5 y were included, except for revisions, communication letters, and non-English articles.

### Data extraction

Data extraction was performed by 3 authors who used the pre-defined data above. The data was extracted from articles that included the date, author, specimen size, gender, diseases related to oxidative stress and inflammation, and the usage of GB extract (EGB761). Disagreements between the above reviewers were evaluated and resolved by a third reviewer.

Only original articles were selected. The exclusion criteria for this research were revisions, non-English studies, case reports, not full-text articles, editorials, and poster presentations. Revisions were used to help in the discussion but were not included in ▶ **Table 1**.

## Results

In the last 5 y, 54 studies showed the potential of EGB761 and its components in animal models. Most of them were performed on mice of varying species (Wistar, Sprague-Dawley, C57BL, Balb/c, ICR, hairless), and remaining studies were conducted on humans. All the research studies were developed in universities and health care centers, and the articles are summarized in ▶ **Table 1**.

## Discussion

The increase in chronic degenerative diseases has led to a growing interest in phytotherapeutic products since they are low-cost options and normally do not have important adverse effects. In that context, EGB761 presents an essential relevance for its antioxidant and anti-inflammatory properties [9–11].

EGB761 has been used for the treatment of a series of comorbidities related to oxidative stress and, due to its antioxidant nature, it can decrease oxidative processes and neutralize lipid peroxidation. Among the bioactive components of EGB761, we can highlight flavonoids (about 28%) such as quercetin, kaempferol isorhamnetin, lipoxygenase, phospholipase A2, and terpenic lactones (2.8–3.4% of ginkgolídeos A, B, and C and 2.6–3.2% bilobalide) (▶ **Table 2**) [9, 13, 14].

### GB and inflammation

A lesser known property of EGB761 is its anti-inflammatory action both in human and animal models and *in vitro* studies. Currently, it is known that its components, mainly ginkgolide A, can suppress cyclo-oxygenase-2 (COX-2) and 5-lipo-oxygenase (5-LOX), which are limiting enzymes for the conversion of arachidonic acid to prostaglandin and leukotrienes particularly, and it also can reduce endoplasmic reticulum stress, which would be responsible for boosting the inflammation. It was found that EGB761 can inhibit the effects of the lipopolysaccharide (LPS) by improving the action of transforming growth factor (TGF), thus reducing the gene expression of Interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-$\alpha$) (▶ **Fig. 1**), resulting in down-regulation of the inflammatory processes. It is also known that ginkgolide B can inhibit platelet-activating factor (PAF), which plays a large part in the inflammation of the airways [12, 13, 15–20]. Although the reduction of pro-inflammatory cytokines has been identified in the studies, little is known about the mechanism of this reduction. The most known mechanism is illustrated in ▶ **Fig. 2**.

EGB761 is very well-known for its neuroprotective activity and for promoting memory improvement. Both factors are directly related to its antioxidant properties. The components of EGB761 perform several actions in the regulation of oxidative stress, and among these actions, the main mechanisms are the capture of free radicals and the indirect inhibition of free radicals formation [13].

Each of the components shows specific actions on proteins and specific metabolic pathways, thus contributing to oxidative stress attenuation, according to ▶ **Table 2**.

Besides the specific actions of each component, other advantages have been attributed to EGB761. As an example, its usage in neurology can improve circulation because it can reduce the peroxide level in cerebellar neurons and protect the cortical neurons from iron-induced injuries. It also reduces ROS and RNS, hydroxyl radicals (OH), peroxyl radicals (ROO), anion superoxide radical (O2−), nitric oxide, and hydrogen peroxide radical ($H_2O_2$). It positively regulates the expression of RNAm of antioxidant enzymes, such as mitochondrial superoxide dismutase (MnSOD) and glutathione peroxidase (GPx) [10, 13, 21, 22]. ▶ **Fig. 3** presents the effects of GB on inflammation and oxidative stress.

### GB and oxidative stress

Many diseases are related to oxidative stress, such as hearing loss, where there is observed a critical increase of ROS in the cochlea blood flow; this same excess in the eyes may lead to cataracts. Oxidative stress leads to lipid peroxidation, protein oxidation, and DNA mutation, causing damage to nerve cells and being responsible for neurological disorders [23–27].

Besides being related to the origin of diseases, oxidative stress also has an impact on the aggravation of other pathologies, as in

▶ **Table 1** EGB761 and diseases related to oxidative stress and inflammation.

| Pathology | Model | Intervention | Main results of the use of EGB761 | Conclusion | References |
|---|---|---|---|---|---|
| Neurodegenerative diseases | ICR rats; Tau transgenic rats; Wistar rats; humans older than 75 y; C57BL/5 rats; ddY rats | Standardized GB extract at concentrations (mg/kg): 4, 50, 100, 200, 400, 500, 600, 800, and 1000. | Increase of the mitochondrial functions, and protective _effect due to an action as free radicals eliminator. Patients had an improvement in the Wechsler's scale of memory. | EGB761 improved the cognitive and motor functions, and its supporting role may prevent and treat Alzheimer's disease, Parkinson's, and other neurodegenerative diseases. | [25, 26, 29, 45–53] |
| Brain damage | Sprague-Dawley rats; C57BL/Wistar rats | Ginkgolide B extract at concentrations (mg/kg): 1, 2, 3.5, 4, and 12; ginkgolide K (mg/kg): 3.5, 7, and 14; and standardized GB extract (mg/kg): 50 and 100. | Significant reduction of the punctuation of brain deficit, concentration of IL-1$\beta$, IL-6, and IL-8, expression of ICAM-1, COX-2, iNOs, TNF-$\alpha$, ROS, CAT, SOD, NF-$\kappa$B, and IkBa, products of lipid peroxidation. Increased CBF, HIF-1$\alpha$, VEGF, improved blood flow, and stimulated angiogenesis. Improvement of perception and motor functions. | Results showed that EGB761 components had a protective role against the cerebral ischemia, and against cisplatin and damages, besides stimulating the angiogenesis. | [8, 54–58] |
| Myocardial injury | C57BL/6J rats; Sprague-Dawley rats | Standardized GB extract at concentrations (mg/kg): 20, 40, 100, 200, and 400. | Significant reduction of cardiac enzymes CK, AST, and LDH in plasma. The heart attack areas were significantly decreased, as well as glucose, LDL, cholesterol, triglycerides, IL-1$\beta$, TNF-$\alpha$, IL-6, IL- 1, collagen I and III, caspase-3/9, NF-$\kappa$B, MDA, SOD, CAT, GSH, TGF-$\beta$, protein p38, and BCL-2. There was an improvement in the contractility and a decrease of diastolic pressure. | EGB761 is able to attenuate the myocardial lesions in patients with and without diabetes, including the apoptosis of cardiomyocytes, interstitial fibrosis, and intramyocardial inflammation; it improves cardiac function, besides having a cardio-protective effect by several metabolic ways. | [12, 18–20, 59, 60] |
| Pulmonary diseases | Balb/c rats and ICR rats | Standardized GB extract at concentrations (mg/kg): 0.01, 0.1, 1, 10, and 40. Ginkgolide B was used at concentrations (mg/kg): 10, 20, and 40. | The extract of ethyl acetate of GB was able to suppress the expression of cytokines, attenuate the inflammation of the airways induced through allergens, and relieve pulmonary lesions. | The results showed that GB had a role in the improvement of the pulmonary lesion, which was induced through LPS, and in the reduction of signs and symptoms of pulmonary diseases caused by allergens. | [15, 32, 61] |
| Aortic rupture | C57BL/6 rats | Standardized GB extract containing 40 mg/kg of flavonoids and 10 mg/kg of ginkgolides. | EGB761 application prevented the aortic rupture in cases of abdominal aorta aneurysms. Individual use of EGB761 did not show a preventive effect. | EGB761 is helpful as a protective effect for abdominal aortic aneurysm, showing its endothelial protective effect. | [1] |
| Neuronal lesion | Sprague-Dawley rats | Standardized GB extract 12 mg/kg and 100 mg/kg | Improvement of the lesion induced through hypoxia and through neurotoxic component in the hippocampus, showing less apoptotic cells in CA1 area. Increase of SOD and GSH activity, and decrease of MDA, ROS, glial fibrillary acidic protein, NFkB, TNF-$\alpha$, IL-1$\alpha$, and IL-6. | EGB761 can protect the neuronal cells against acute hypoxia and improve cognitive functions through the improvement of neuronal lesion. | [8, 13] |
| Blood-brain barrier dysfunction | Wistar rats with induced neurotoxicity. | Standardized GB extract 120 mg/kg | GB application decreased the levels of $Ag^+$ and MDA, increased the activity of GPX, GST, CAT, and SOD, and lessened the expression of JP-1 and JAM-3. | The treatment with EGB761 is able to stabilize and maintain the integrity of the blood-brain barrier. | [37] |
| Hypertension by kidney damage | Wistar rats | Standardized GB extract 100 mg/kg. | EGB761 induced progressive reduction of the systolic, diastolic, and medium blood pressure, and improved lipid profile, the levels of GSH, and expression of eNOS. It reduced TNF-$\alpha$, IL-6, and IL-1$\beta$. | The results showed EGB761 has the capacity of protecting against hypertension by kidney damage and enhanced the effects of Losartan and Simvastatin. | [16] |

*continued*

▶ **Table 1** *Continued*

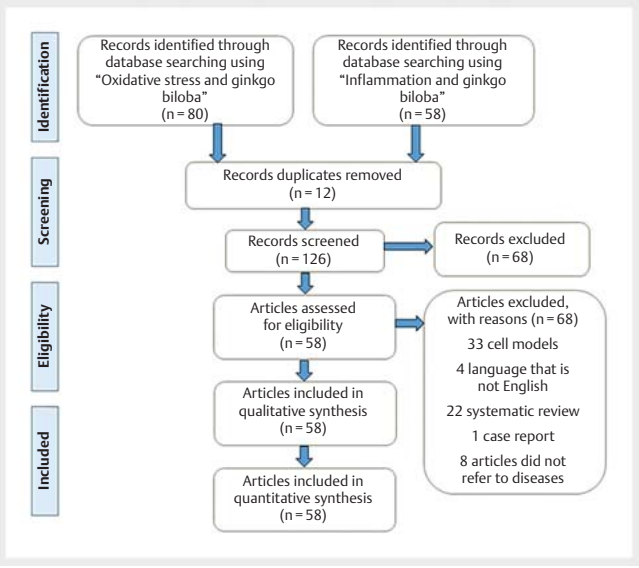
| Pathology | Model | Intervention | Main results of the use of EGB761 | Conclusion | References |
|---|---|---|---|---|---|
| Diabetes mellitus | Wistar rats; Humans with DM2; C57BL/6 rats | Standardized GB extract at concentrations (mg/kg): 50 and 110, and used 2 tablets pills containing 9.6 mg of flavonoid and 2.4 mg of terpenoid lactones. | EGB761 decreases the body weight and triglycerides both in DM1 and DM2, besides improving the DM2 induced through streptozotocin and the pancreatic lesions. It also decreased CML and of 8-isoprostane. | The results showed that EGB761 has an anti-inflammatory effect on the pancreas, decreasing the serum glucose in DM1, induced through streptozotocin. Besides that, it improves DM2 induced through a high-fat diet. | [38, 39, 62] |
| Metabolic syndrome | Humans with diagnosis of SM; Wistar rats. | Standardized GB extract at concentrations (mg/kg): 120, 240, and 500. | Reduction of glycemia during fast, glycated hemoglobin, BMI, serum levels of leptin, total cholesterol, LDL, MPO, food intake and weight gain, and the level of TNF-$\alpha$. There was an increase of SOD, GPx, cAMP, cGMP; and reduction of NF-$\kappa$B. | The results showed that the adjuvant use of EGB761 significantly improved glucose control, body adiposity, lipid profile, and inflammatory processes. It may be beneficial to avoid the progression of metabolic imbalance and avoid the insulin resistance related to obesity. | [33–35] |
| Renal damage | C57BL/6 rats | Ginkgetin aglycone 200 mg/kg. | Ginkgetin lessened the inflammatory markers and the renal damage induced through LPS, inhibited renal cell apoptosis, increased SIRT1, and decreased NF$\kappa$B. | The use of ginkgetin showed a protective effect on the inflammatory answer induced by LPS, preventing renal damage. | [22] |
| Liver damage | Wistar rats; C57BL/6 rats; Sprague-Dawley rats | Standardized GB extract at concentrations (mg/kg): 15, 25, 30, 200, and 600. | It decreased triglycerides, LDL, cholesterol, AST, ALT, FASN, ACC, body weight, adipose tissue, oxidase diamine, endotoxins, D-lactic acid, TNF-$\alpha$, liver damages, and the necroinflammatory answer. It reduced the expression of p65 protein, iNOS, COX-2, p38 protein, MAPK, NF-$\kappa$B/i$\kappa$B$\alpha$ and BCL-2/Bax. | EGB761 is able to reduce the free radicals, showing a hepatoprotective effect to steatosis, hepatic fibrosis, and to alcoholism. It is able to inhibit the lipogenesis and the cell inflammation, helping against hepatitis. | [14, 63–66] |
| Testicular damage | Wistar rats with hypertension | Standardized GB extract at concentrations (mg/kg): 50, 100, and 200. | Improvement of the testicular damages and led to a rising of testosterone levels, spermatocytes, and lymphocytes. It also showed a decrease of mitochondrial tissue NAD+, of TNF, of plasmatic IL-1, and the levels of TBARS, of ALP and ACP; it increased SOD, CAT, and GSH, besides normalizing the seminiferous tubes and the spermatogenesis. | The results suggest that EGB761 can be a protective and therapeutic agent against the male reproductive toxicity induced through electromagnetic radiation and through aluminum, besides lessening the alterations caused by ischemia in the testicular tissue, helping to treat the infertility in such cases. | [28, 67, 68] |
| Colorectal cancer | Sprague-Dawley rats | Standardized GB extract at concentrations (mg/kg): 675 and 1350. | The use of EGB761 decreased the levels of TGF-$\beta$, BCL-2, serum EGF, CEA, CCSA-4, and MMP-7. It modified the expressions of p-catenin, K-ras, and C-myc and decreased COX-2, cyclin D1, and immunopositive cells from the colon tissue. | The results showed that EGB761 has anti-tumor activity, and it can help to prevent the progression of the colorectal cancer. | [40] |
| Acute ischemic colitis | Hospitalized humans with ischemic colitis | Adjuvant treatment with EGB761 | The adjuvant treatment with EGB761 improves the cessation of symptoms in 89% of the cases with abdominal pain and cramps and 93% for the cases with hematochezia | EGB761 exhibited protection against ischemic colitis, and it can have an effective therapeutic potential for prevention of ischemic lesion of the colon. | [36] |
| Cataract | Sprague-Dawley rats and Wistar rats | Standardized GB extract at concentrations (mg/kg): 100, 110, and 200. | Improvement of the antioxidant capacity (decrease of MDA and the aldose reductase activities); normalized the activities and concentrations of CAT and SOD. | The results showed efficiency of EGB761 for the treatment of cataract (reduction of cataractogenesis). | [9, 24, 69] |

*continued*

▶ **Table 1** *Continued*

| Pathology | Model | Intervention | Main results of the use of EGB761 | Conclusion | References |
|---|---|---|---|---|---|
| Depression | C57BL/6J rats | Dipertene ginkgolides meglumine injection (DGMI) 4.06 and 12.18 mg/kg. | Upregulation of phosphate, kynurenic acid, inosine, aminobutyric acid, n-oleoyldopamine, l-glutamine, l-cysteine, glycine, ethanolamine, and pyrophosphate and regulated the lactic acid, pyroglutamic acid, alanine, asparagine, O-phosphoethanolamine, N-acetyl-L-aspartic acid, d-glycerol-1-phosphate and N-acetyl-beta-alanine. | DGMI showed antidepressive effect by the reversion of alterations on the biosynthesis of glutamate, on the metabolism of aspartate and lipids, and alterations in oxidative stress. | [41] |
| Hearing loss | Sprague-Dawley rats | Standardized GB extract at concentrations (mg/kg): 90, 100, and 180. | Significant attenuation of oxidative stress in the cochlear cells. | EGB761 protected the neural tube cochlear cells, reducing oxidative stress, initiating the apoptosis, leading to prevention of hearing loss related to oxidative stress. | [23, 27, 70] |
| Medullar ischemia | Sprague-Dawley rats | For this study they used the standardized GB extract 100 mg/kg. | EGB761 better preserved the structures of the spinal medulla (in form, extension and cytoplasmatic characteristic). | EGB761 had a protective effect on medullar tissue lesion by ischemia. | [42] |

ACC: acetyl-CoA carboxylase; ACP: acid phosphatase; Akt: protein kinase B; ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; Bax: BCL-2-associated X protein; BCL-2: B-cell lymphoma 2; BMI: body mass index; cAMP: cyclic adenosine monophosphate; CAT: catalase; CBF: cerebral blood flow; CCSA-4: colon cancer-specific antigen-4; CEA: carcino-embryonic antigen; cGMP: cyclic guanosine monophosphate; CK: creatine kinase; CML: plasma carboxymethyl lysine; COX-2: cyclooxygenase-2; CT: total cholesterol; DM1: type 1 diabetes mellitus; DM2: type 2 diabetes mellitus; EGF: epidermal growth factor; eNOS: nitric oxide synthases endothelial; FASN: fatty acid synthase; GPx: glutathione peroxidase; GSH: glutathione; GST: glutathione S-transferase; HIF: hypoxia-inducible factor; HIF-1-$\alpha$: hypoxia-inducible factor 1-alpha; ICAM-1: intercellular adhesion Molecule 1; IkBa: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; IL: interleukin; IMC: body mass index; iNOs: nitric oxide synthases inducible; JAM-3: junctional adhesion molecule 3; JP-1: junction protein; LDH: lactate dehydrogenase; LDL:; low-density lipoprotein; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; MDA: malondialdehyde; MMP-7: matrix metalloproteinase-7; MPO: myeloperoxidase; NAD: nicotinamide adenine dinucleotide; NF-$\kappa$B: NF-kappa-B-inducing kinase; ROS: reactive oxygen species; SIRT1: sirtuin 1; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances; TG: triglyceride; TGF-$\beta$: transforming growth factor $\beta$; TNF-$\alpha$: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor




▶ **Fig. 1** Flow diagram for the literature search (based on PRISMA, 2009).

the case of diabetes, in which hyperglycemia leads to oxidative stress, resulting in cardiomyopathy. The same happens after partial hepatectomy, in which the free radicals harm liver regeneration. In addition to those cases, oxidative stress can reduce the total number of moving sperm cells and induce lesions to the myocardium during the heart reperfusion [12, 14, 28–30]. In all these cases, it is possible to use EGB761 (▶ **Table 1**).

To investigate the effects of EGB761 on cognitive functions, Belviranli and Okudan [25] performed research on Wistar mice and found out that, with the supplementation of EGB761, there was significant improvement not only in the locomotor activity but also in anxiety, spatial learning, and memories. Another important discovery of this research was that in older rats, there was an improvement of the oxidative damage in cerebral tissue. Beyond this research, there were 11 more experimental studies in which it is possible to realize the positive impact of EGB761 in degenerative diseases.

According to Tang et al. [12], the free radicals derived from oxygen are known for playing a critical role in the genesis of heart tissue injury. Under normal conditions, cells can suppress free radicals. However, the unbridled formation of free radicals promotes an imbalance. Pathological conditions, such as ischemic-reperfusion, may cause this imbalance. This study showed that the administration of EGB761 in mice inhibited the signaling pathways of toll-like receptor-4 and nuclear factor-$\kappa\beta$ (NF-$\kappa\beta$), showing protective effects against the ischemic-reperfusion lesion because of its anti-inflammatory effects.

According to Tao et al. [15], the administration of EGB761 showed significant decreases in the release of IL-4, IL-5, IL-6, IL-8, IL-13, and TNF-$\alpha$ in allergic mice. EGB761 was also responsible for adjusting the leukocyte elastase, an active protein in blood coagulation disorders, chronic bronchitis, and pulmonary injury. The components of EGB761 were able to reduce airways inflammation. Wu et al. [31] showed that ginkgolides play a vital role in the alleviation of LPS-induced pulmonary injury. Similarly, Lee et al. [32] concluded that the expression of pro-inflammatory mediators, such as TNF-$\alpha$, IL-6, macrophage inflammatory protein (MIP)-2, nitric oxide synthase (NOS) and COX-2, was suppressed in adult mice. EGB761 also reduced the activation of NF-kappa-B-inducing kinase (NF$\kappa$B) and the phosphorylation of NF-kappa-B inhibitor (I$\kappa$B).

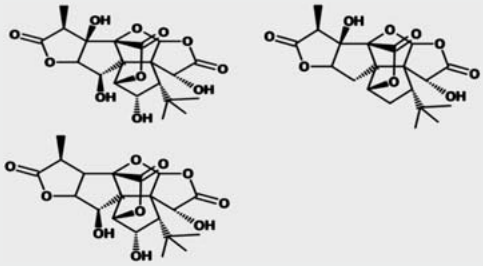
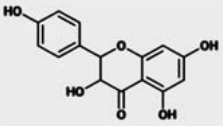
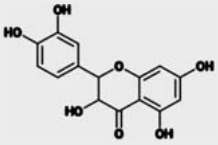
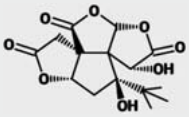
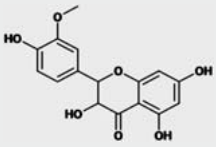
The study performed by Aziz et al. [33] evaluated the effects of EGB761 (120 mg a day) in patients taking Metformin for 90 days, comparing them to a placebo group. It was possible to conclude that the administration of EGB761 decreased the levels of HbA1c, glycemia, insulin, insulin resistance, abdominal circumference, serum leptin, and inflammatory markers. It did not cause liver, renal, and hematopoietic system damage but showed significant improvement in patients with metabolic syndrome. Regarding metabolic syndrome, Hirata et al. [34] showed that the administration of EGB761 in obese mice (500 mg/kg) promoted a significant decrease in feed intake and decreased weight in comparison controls, showing that EGB761 is an option for treatment of obese patients who are resistant to nutritional education treatment. The work of Siegel et al. [35], even with a small number of participants, showed the capacity of EGB761 in diminishing the homeostatic model assessment of insulin resistance (HOMA-IR), the C-reactive protein (CRP), and IL-6, concluding that EGB761 can be used as a complementary drug with preventive potential for cardiovascular diseases, a common cause of death in patients with metabolic syndrome.

EGB761 presents an option for the treatment of acute ischemic colitis patients, according to Fang et al. [36]. The study was performed by selecting acute ischemic colitis patients, who were separated into 2 groups: the EGB761 group (n = 30) and the routine group (n = 17). The members of the EGB761 group received a routine of intravenous injections with EGB761. EGB761 decreased abdominal pain and hematochezia and promoted a significant attenuation of macroscopic and histological damages in the patient's colon. There was an increase in the levels of superoxide dismutase (SOD) and a decrease in the levels of malondialdehyde (MDA), TNF-$\alpha$, and IL-6. However, the number of patients in this study was small. Thus, it would also be viable if further research were done in order to enable this treatment in a noninvasive way, because the administration of intravenous injections might impede the compliance of patients with limited access to health services to receive the treatment.

An abdominal aortic aneurysm is a vascular disease characterized by a luminal pathological dilatation, and one of its fatal consequences is the aortic rupture. To evaluate the therapeutic effect of EGB761 on the aortic rupture, Huang et al. [1] administered angiotensin II (Ang II) in mice for 28 days, causing abdominal aortic aneurysm, and then administered EGB761 (100 mg/kg/day) for 56 days. It was possible to conclude that EGB761 prevents an aortic rupture in hypercholesterolemic mice, which were infused with Ang II, but only in the initial stage, restricting the protective range of this treatment in the mentioned comorbidity.

According to Ekici, Muhtaroğlu and Bedirli [14], after partial hepatectomy and liver transplant, the liver regeneration is awaited, for it is a vital process. After hepatectomy, the free radicals that are released by the peroxidation cause damage to tis-

▶ **Table 2** Components of *Ginkgo biloba* and their respective actions related to oxidative stress.

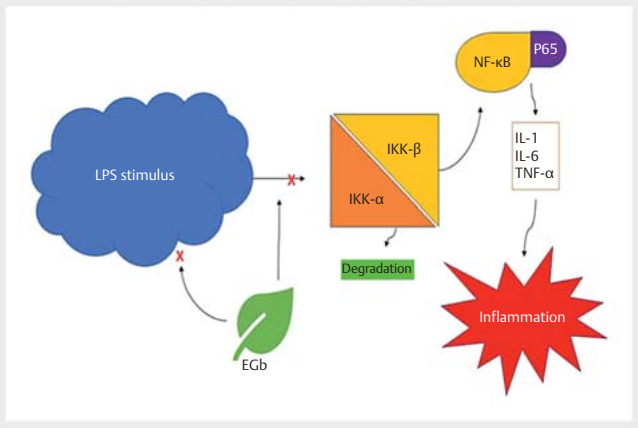
| Compound | Action | References |
|---|---|---|
| Ginkgolides A, B and C.  | Decrease the level of ROS, the release of LDH, TNF-$\alpha$, IL-1$\beta$ and IL-6 and the expression of c-fos and c-jun mRNA; inhibits activation factor of platelets and of signaling pathway NIK/IKK $\alpha$/IkB/NF-$\kappa$B; increases cellular proliferation, activity of free radicals capture, activation of the p42/p44 (ERK) MAPK pathways, levels of mRNA and the protein from the HIF-1$\alpha$. | [71–74] |
| Kaempferol  | Increase of the expression of GCLC, BDNF, BCL-2, and GSH; inhibits serotonin degradation by MAO, liberation of the Cytochrome C, activity of Caspase-3, fragmentation of the internucleosome DNA, NADH, activation of p53 protein, p65 protein, NF-$\kappa$B and apoptosis; decrease in the neurotoxicity induced through 3-NP and the elevation of BAX through ROS; elimination of free radicals; and upregulation of HMOX-1. | [43, 74, 75] |
| Quercetin  | Increase the level of BDNF; inhibition of degradation of serotonin by MAO, apoptosis; transcription of TNF-$\alpha$; activation of ERK, phosphorylation, and activation of JNK; decrease of lipid peroxidation in the plasma and phosphorylation of IkB$\beta$; upregulation of HMOX-1; and elimination of free radicals. | [43, 74, 76, 77] |
| Bilobalide  | Decrease in the expression of reactive species induced through $H_2O_2$; the elevation of BAX induced through ROS, the c-myc and p53proteins; upregulation of BCL-2, of the sub-unit III from the cytochrome c oxidase, of the sub-unit ND1 from the NADH dehydrogenase, and of the CREB-BDNF pathway. Inhibition of the degradation of membrane phospholipids; activity of the caspase-3. Increase of cellular proliferation of neurons of the hippocampus. | [30, 73, 74, 78] |
| Isorhamnetin  | Decrease of cellular death and fragmentation of DNA. Inhibition of apoptosis, liberation of cytokines from the mitochondria, and cleavage of PARP, the ERK pathway, and the activation of p53 protein. Upregulation of genes related to BCL-2; downregulation of BH3 gene and genes related to BAX. Elimination of ROS. | [74] |

3-NP: 3-nitropropionic acid; BAX: BCL-2 associated protein X; BCL-2: B-cell lymphoma protein 2; BDNF: brain-derived neurotrophic factor; BDNF: brain-derived neurotrophic factor; c-fos: gene c-fos; c-jun: gene c-jun; CREB: cAMP response element-binding protein; ERK: extracellular signal–regulated kinases; GCLC: glutamate-cysteine ligase catalytic subunit; GSH: glutathione; HIF-1$\alpha$: hypoxia-inducible factor 1-alpha; HMOX-1: Heme oxygenase 1; IkB: NF-kappa-B inhibitor; IkB-$\beta$: NF-kappa-B inhibitor beta; IKK $\alpha$: IκB kinase $\alpha$; IL: interleukin; JNK: c-Jun N-terminal kinase; LDH: lactate dehydrogenase; MAO: monoamine oxidase; MAPK: mitogen-activated protein kinase; mRNA: RNA messenger; NADH: dinucleotide of de nicotinamide and adenine; NF-$\kappa$B: NF-kappa-B-inducing kinase; NIK: NF-kappa-B-inducing kinase; PARP: poly adenosinediphosphate ribose; ROS: reactive oxygen species; TNF-$\alpha$: alpha tumoral necrosis factor

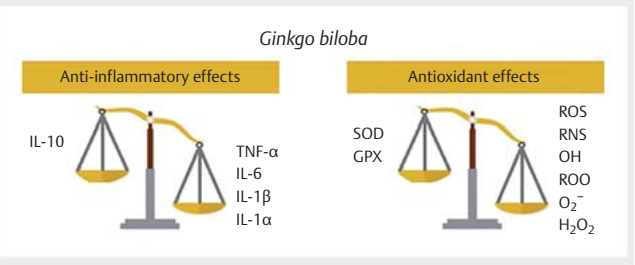
sues, and inactivation of the free radicals makes possible anti-inflammatory effects and speeds up the regeneration process. This study showed positive results with the intraperitoneal administration of EGB761 due to antioxidant and anti-inflammatory effects, as well as raising in the mitotic index.

According to Kaur, Sharma, and Nehru [13], neurotoxic disorders are one of the significant causes of death and tissue lesions. The trimethyl-tin (TMT), known for being a powerful neurotoxic product, was used to evaluate the protective effects against neuronal damage in the hippocampus of mice administrated with EGB761. This study showed a significant cognitive improvement, as well as a decrease of free radicals and pro-inflammatory cytokines, demonstrating that EGB761 is an effective agent against neuronal damage of the hippocampus inducted through TMT.

To evaluate the capacity of EGB761 to maintain the integrity of the hematoencephalic barrier, Lebda et al. [37], administrated 50 mg/g of AgNPs (silver nanoparticles) in mice by intraperitoneal route, inducing neurotoxicity. After the administration of EGB761 (120 mg/kg), the authors observed that EGB761 was able to neutralize the adverse effects of AgNPs, stabilizing the integrity of the




▶ **Fig. 2** EGB761 acts on the LPS, which unleashes events of transduction of serial signal including activation of NF-κB, which regulates the production of pro-inflammatory cytokines. LPS: lipopolysaccharide; EGB761: *Ginkgo biloba* extract; IKK-*β*: inhibiting nuclear factor kappa-B kinase subunit *β*; IKK-*α*: ihibiting nuclear factor kappa-B kinase subunit kinase subunit *α*; NF-κB: nuclear factor kappa-B; P65: transcription fFactor p65; IL: interleukin; TNF-*α*: tumoral necrosis factor *α*.




▶ **Fig. 3** Effects of *Ginkgo biloba* on inflammatory processes and oxidative stress. IL-10: interleukin 10; TNF-*α*: tumoral necrosis factor *α*; IL-6: interleukin 6; IL-1*β*: interleukin 1-beta; IL-1*α*: Interleukin 1-alpha; SOD mitochondrial: superoxide dismutase; GPx: glutathione peroxidase; ROS: oxygen reactive species; RNS: nitrogen reactive species; OH: hydroxyl radicals; ROO: peroxyl radicals; $O_2^-$: Superoxide Anionic Radical; $H_2O_2$: hydrogen peroxide.

hematoencephalic barrier by its anti-inflammatory, antioxidant, and anti-apoptotic properties, and by the improvement of protein of the tight junction.

Several studies have been done to analyze the action of EGB761 in the treatment of type 2 diabetes mellitus (DM2). According to the study of Zayed et al. [38], the administration of EGB761 in mice with inducted DM2 resulted in the reduction of glycemia in a very significant way and reduced the levels of urea and creatinine in comparison to diabetic mice that were not treated. The work of Rhee et al. [39] induced type 1 diabetes mellitus (DM1) and DM2 in mice and showed that the use of EGB761 reduced glycemia and levels of insulin. They also showed higher levels of hepatic lipoprotein lipase (LPL) and peroxisome proliferator-activated receptor alpha (PPAR-*α*), while Interleukin 1-beta (IL-1*β*) and the TNF-*α* were reduced. In the model in which DM2 was simulated, the mice that received EGB761 showed lower levels of triglycerides, higher levels of hepatic LPL and PPAR-*α*, and a decrease in body weight. Therefore, it is possible to conclude that EGB761 can have protective effects on patients with DM1 and DM2. However, there is still a lack of study models in human beings to corroborate such effects, which once proved, can be used by the population to prevent DM complications.

According to Gevrek et al. [28], radiation produced by electromagnetic mobile phones can lead to oxidative stress, being responsible for causing testicular morphometry damages, decreasing the number of moving spermatozoids, and decreasing testosterone levels. This study showed beneficial results after the administration of EGB761 in mice that were subjected to radiation–reducing the toxic effects, reverting the damage to the testicular tissue, and restoring spermatogenesis and hormonal levels–suggesting that EGB761 is a protective and therapeutic agent against male reproductive toxicity induced by radiation.

In the study by Abdel-Zaher et al. [16] hypercholesterolemia hypertension in mice was induced through methyl ester, nitro arginine, and food with 1% cholesterol. EGB761 was able to decrease hypertension caused by liver damage induced through hypercholesterolemia, reducing the expression of eNOS (endothelial nitric oxide synthase) and raising the expression of iNOS (inducible nitric oxide synthase), TNF-*α*, IL-6, and IL-1*β*.

The use of EGB761 for the treatment of colorectal cancer was evaluated during the study of Ahmed et al. [40]. Colorectal cancer was induced in mice through the administration of N-methyl nitrosourea by rectal route, 3 times a wk, for 5 wks, followed by treatment with EGB761 in a dose of 1.35 g/Kg. It was observed that the mice that received EGB761 had suppression of the proliferation of tumor cells, as well as a promotion of apoptosis. The study highlighted that the improvement of this condition may be attributed to the inhibition of the signaling module Wnt/*β*-Catenin. The results suggest that EGB761 is an alternative treatment approach to this type of cancer.

To analyze the effectiveness of GB for the treatment of kidney damage, Zhang et al. [22] used ginkgetin aglycone (GA), a new EGB761 with higher liposolubility and a higher antioxidant effect. The administration of GA protected against acute kidney damage induced through LPS and helped in relieving the inflammatory process, the kidney damage, and the tubular apoptosis. The GA avoided the kidney damage and activated Sirtuin 1 (SIRT1) by the inactivation of the signaling route of NFkB.

In another study, Cao et al. [24] divided the mice into a control group, group II–mice that received selenite (nontreated)–and group III–mice that received selenite + EGB761. The groups II and III received 19 mmol/kg of selenite, and group III received, in addition to it, 0.35% 100 mg/kg of EGB761 Selenite, which was used to decrease cataractogenesis. When examining both eyes of the mice, it was possible to notice that 83% of the mice of group II showed dense opacification of the lens (grade +++), while in group III, only 25% showed a light opacification (grade +). All mice in the control group showed full transparency of the lens (grade 0). These results show that the use of EGB761 can decrease the cataractogenesis process.

The effect of EGB761 on the treatment of depression was studied by Liang et al. [41]. The study analyzed the effects of diterpene ginkgolide (DG), an essential class of EGB761 components. The results showed that there were significant alterations in metabolism levels of neurotransmitters, oxidative stress, glutathione (GSH) metabolism, lipid metabolism, energetic metabolism, and kynurenic acid in the hippocampus. DG can exert an antidepressive role by the reversion of the alterations in the biosynthesis of glutamate, aspartate metabolism, oxidative stress, neural inflammation, and lipid and energy metabolism of the hippocampus. DG also raised the levels of gamma-aminobutyric acid (GABA), inosine, and kynurenic acid. As the levels of depression have been exponentially rising all around the world, it is of utmost importance that further research on this topic is done aiming at a more diverse range of treatments for this comorbidity.

Wang and Wang [23] investigated the use of EGB761 for the protection of cochlear neural stem cells (NSCs) and showed that this compound raises the cell viability, decreasing the oxidative stress-induced through $O_2$, beyond preventing mitochondrial depolarization and, as a consequence, apoptosis.

Park et al. [27] carried out a study to investigate the effects of renexin (a drug made of the combination of Cilostazol and EGB761) on the injury caused to the Corti organ by noise and to the medial olivocochlear system of mice, and showed that the treatment may lead to the recovery of the injuries caused by the noise.

The work of Badem et al. [42] evaluated the effect of EGB761 in medullar ischemia. For that, researched clamped the infrarenal abdominal aorta in mice, which were divided into groups, and values of MDA, SOD, GSH, and GPx tissue, as well as tissue from spinal cord samples, were analyzed. The mice that received the EGB761 showed a smaller medullar lesion in comparison to other groups. However, it was not possible to demonstrate a uniform effect of the action of EGB761 on the biochemical markers of ischemia/reperfusion lesion.

In all the studies of this review, it was possible to verify that no significant adverse effects are observed after the use of EGB761. However, research carried out by Jiang et al. [11] showed that a high level of ginkgolic acid could be hepatotoxic.

Besides the diseases related above, other comorbidities show an improvement with the use of EGB761, such as psychiatric disorders, vitiligo, chronic alcoholic myopathy, glaucoma, and renal hypertension [16, 43, 44].

To the best of our knowledge, this is the first review showing the effects of GB on diseases related to oxidative stress.

## Conclusion

GB, as well as its extract, has beneficial properties for the promotion and management of health because of its wide-ranging anti-inflammatory and antioxidant properties. Considering that diseases that are caused by oxidative stress have reached epidemic proportions worldwide, it is necessary to find accessible and effective alternatives that may minimize the risk factors for these diseases and contribute to the treatment.

More studies are necessary to enlighten the GB properties and applications in the pharmaceutical industry, as well as more information about doses, the best administration route, and pharmaceutical formulation in order to provide validation for its medicinal use.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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