Received: 24 April 2019 | Revised: 11 June 2019 | Accepted: 13 July 2019

DOI: 10.1002/ptr.6469

REVIEW

WILEY

Protective effects of *Ginkgo biloba* L. against natural toxins, chemical toxicities, and radiation: A comprehensive review

Seyedeh Farzaneh Omidkhoda[1] | BiBi Marjan Razavi[1,2] | Hossein Hosseinzadeh[1,3]

[1] Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

[2] Targeted Drug Delivery Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

[3] Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence
Hossein Hosseinzadeh, Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran.
Email: hosseinzadehh@mums.ac.ir

Nowadays in our developing and industrial world, humans' health or even their life is threatened by exposure to poisons. In this situation, detecting a protective compound could be helpful and interesting. In the present article, we collected and reviewed all studies, which have been conducted so far about the protective effects of *Ginkgo biloba* L. (GB), one of the most ancient medicinal tree species, against toxicities induced by chemical toxic agents, natural toxins, and also radiation. In overall, investigations showed that GB exerts the antioxidant, antiinflammatory, antiapoptotic, and antigenotoxicity effects in different toxicities. There are also some special mechanisms about its protective effects against some specific toxic agents, such as acetylcholine esterase inhibition in the aluminium neurotoxicity or membrane-bond phosphodiesterase activation in the triethyltin toxicity. Ginkgolide A was the most investigated active ingredient of G. *biloba* leaf extract as a protective compound against toxicities, which had the similar effects of total extract. A few clinical studies have been conducted in this field, which demonstrated the beneficial effects of GB against toxic agents. However, the promising effects of this valuable herbal extract will practically remain useless without carrying out more clinical studies and proving its effects on human beings.

KEYWORDS

antidote, *Ginkgo biloba*, natural toxin, radiation, toxic chemicals

1 | INTRODUCTION

Ginkgo biloba L. (GB; Ginkgoaceae family) is one of the most ancient medicinal tree species with useful applications in health, food, and supplements. It is native to China, Japan, and Korea and popularly known as living fossil. Nowadays, it is cultivated worldwide for beneficial using of its nuts and leaves (Mohanta, Tamboli, & Zubaidha, 2014). The main active components, which are thought to be responsible for the pharmacological properties of GB, include flavonoids (kaempferol, quercetin, myricetin, apigenin, isorhamnetin, luteolin,

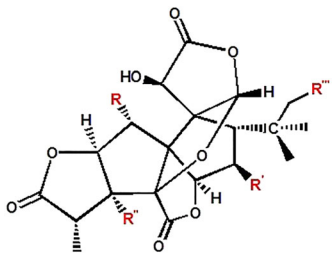
Abbreviation: AA, arachidonic acid; AChE, acetylcholine esterase; AD, Alzheimer's disease; AFB1, Aflatoxin B1; AKt, protein kinase B; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; Apaf-1, apoptotic protease activating factor 1; AP-1, activator protein-1; AST, aspartate aminotransferase; Bad, Bcl-2 agonist of cell death; Bax, Bcl2-Associated X Protein; Bcl-2, B-cell lymphoma 2; Bcl2-Xl, B-cell lymphoma-extra large; BUN, blood urea nitrogen; CAT, catalase; CCl_4, carbon tetrachloride; CO, carbon monoxide; COX-2, cyclooxygenase-2; cPLA2α, cytosolic phospholipase A2; Cr, creatinine; ERK, extracellular signal-regulated kinase; GB, *Ginkgo biloba* L; GP_X, Glutathione peroxidase; GSH, reduced glutathione; HO-1, Heme oxygenase-1; IκB, IκB kinase; IL-6, Interleukin-6; IL-1β, interleukin-1beta; iNOS, nitric oxide synthase; JNK, jun N-terminal kinase; LDH, lactate dehydrogenase; LPC, lysophosphatidylcholine; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MIP-2, macrophage inflammatory protein-2; MMP-9, matrix metalloproteinase-9; MN, micronuclei; mPGES-1, microsomal prostaglandin E synthase-1; MPO, myeloperoxidase; mTOR, mammalian target of rapamycin; NADPH, nicotinamide adenine dinucleotide phosphate; NF-KB, nuclear factor kappa beta; NO, nitric oxide; Nrf-2, nuclear factor (erythroid-derived 2)-like 2; PDE, phosphdiesterase enzyme; PGE-2, prostaglandin E2; PI3K, phosphatidylinositol-3-Kinase; PPAR-α, peroxisome proliferator-activated receptor α; ROS, reactive oxygen species; SAPK, stress-activated protein kinase; SGLT1, sodium-glucose linked transporter-1; SOD, superoxide dismutase; SREBP-1c, sterol regulatory element binding protein 1c; TBARS, thiobarbituric acid reactive substances; TET, triethyltin; TEWL, transepidermal water loss; TGF-β1, transforming growth factor beta; TLR-4, toll-like receptor-4; TNF-α, tumour necrosis factor; TNFR-1, tissue necrosis factor receptor 1; TP, total protein; TRAIL-1, tumour necrosis factor-related apoptosis-inducing ligand-1; TTP, tristetraprolin; 5-FU, 5-fluorouracil

and tamarixetin), terpene trilactones (ginkgolide A, ginkgolide B, ginkgolide C, ginkgolide J, ginkgolide M, ginkgolide K, ginkgolide L, ginkgolide P, ginkgolide Q, and bilobalide; Figure 1) and proanthocyanidins (van Beek and Montoro, 2009; Liao, Zheng, Li, & Peng, 2011). Leaves and seeds of GB have been used in Chinese, Japanese, and Indonesian traditional medicine for thousands of years (Singh, Barreto, Aliev, & Echeverria, 2017). Recently, GB leaf extracts (GBLEs) are being used very commonly as the phytomedicines all over the world (Tang et al., 2017). In this regard, there are a lot of commercial products of GBLEs that have been purchased and applied in approximately all studies reviewed here, except those we especially explained. These standardized forms that also named EGb 761 contain 24% of ginkgo flavone glycosides and 6% of terpene trilactones. According to the modern pharmacological studies, GBLE has been used in the treatment of several diseases including neurodegenerative diseases such as Alzheimer's disease (AD; Ihl et al., 2011), cerebral disorders (Saleem, Zhuang, Biswal, Christen, & Dore, 2008), vascular problems (Keheyan, Dunn, & Hall, 2011), age-related memory deficit (Stackman et al., 2003), and oxidative stress (Bernatoniene et al., 2011; Mohamed & Abd El-Moneim, 2017).

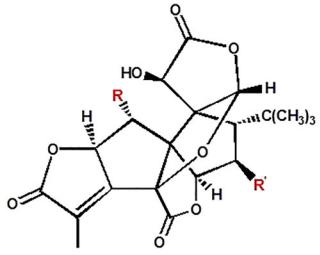
The extract or active ingredients of some important plants, such as *Curcuma longa* (Hosseini & Hosseinzadeh, 2018), *Berberis vulgaris* (Mohammadzadeh, Mehri, & Hosseinzadeh, 2017), *Nigella Sativa* (Tavakkoli, Ahmadi, Razavi, & Hosseinzadeh, 2017), *Cinnamomum zeylanicum* (Dorri, Hashemitabar, & Hosseinzadeh, 2018), *Silybum Marianum* (Fanoudi, Alavi, Karimi, & Hosseinzadeh, 2018), *Camellia sinensis* (Rameshrad, Razavi, & Hosseinzadeh, 2017), *Vitis vinifera* (Tabeshpour, Mehri, Shaebani, & Hosseinzadeh, 2018), and *Crocus sativus* (Razavi & Hosseinzadeh, 2015) have shown the beneficial effects against natural toxins and toxic chemicals. Several reviews exist about the protective effects of GB mostly on dementia and neurological disorders; however, no review has been written about its neutralizing effects against toxins and toxicities so far, and in regard to the various and useful applications and the effects of GB, which have been established up to now, it was necessary to collect and review the papers about the protective effects of this precious plant on toxicities developed via the exposure to natural toxins, chemical toxic agents, and also radiation (Figure 2).

2 | METHODS

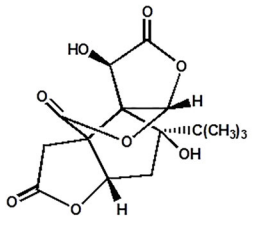
A comprehensive literature review was conducted using some keywords in combination of (*ginkgo biloba* or ginkgolide) and (toxicity or toxin or toxic or venom or poison or chemical or radiation or metal or pesticide). The most relevant titles were chosen among hundreds of articles. Following scientific databases were used to search (last accessed on: Scopus, PubMed, Web of science, and Google scholar). Studies were identified through electronic databases from their inception up to February 2019. No limitation was applied in the advanced searching. Non-English language articles, the topics in which some chemical substances were solely used to induce an animal model (to assess the mechanisms of a disorder not an intoxication or human intoxication with those substances was not possible), topics about



	R	R′	R″	R‴
Ginkgolides A	H	H	OH	H
Ginkgolides B	OH	H	OH	H
Ginkgolides C	OH	OH	OH	H
Ginkgolides J	H	OH	OH	H
Ginkgolides M	OH	OH	H	H
Ginkgolides P	H	H	OH	OH
Ginkgolides Q	OH	H	OH	OH



	R	R′
Ginkgolides K	OH	H
Ginkgolides L	H	H
Ginkgolides N	OH	OH



Bilobalide

FIGURE 1 Chemical structure of terpenoids in *G. biloba* leaf extract [Colour figure can be viewed at wileyonlinelibrary.com]

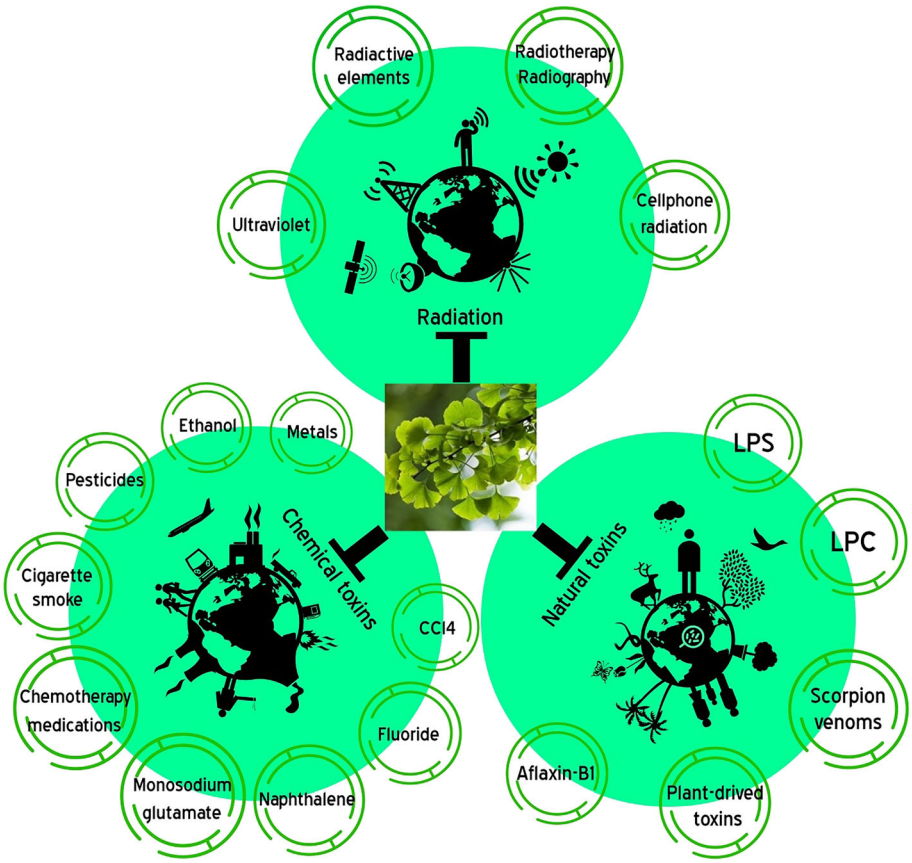


FIGURE 2 Protective effects of *G. biloba* extract against radiation, natural toxins and chemical toxicities [Colour figure can be viewed at wileyonlinelibrary.com]

the adverse reactions of nontoxic medications, and pathological disorders such as Alzheimer were excluded. The flow chart of the search process was shown in Figure 3. The contents were categorized into three main headings: natural toxins, chemical toxicities, and radiation. Figure 1 was drawn by ChemDraw software, ultra 7.0 version.

3 | NATURAL TOXINS

Natural toxins are chemicals that are naturally produced by living organisms, including scorpion or snake venom, mycotoxins, bacterial, and plant toxins. The antidotal effects of GBLE against natural toxins have been shown in the several studies.

3.1 | Scorpion venoms

Leiurus quinquestriatus scorpion venom induces cellular damages, which is associated to multiple organ failure (Amitai, 1998). In a study, GBLE (150 mg/kg/day, orally, for 2 weeks before venom) and aprotinin (nonselective protease inhibitor, 30 min before venom), significantly reduced venom-induced oxidative stress in the heart and lung tissues of rats. Results indicated that combination of GBLE and aprotinin potentiated the protective effects of GB on reduced glutathione (GSH), malondialdehyde (MDA), and lactate dehydrogenase (LDH) in the heart and lung tissues (Fatani et al., 2006). Therefore, a direct conclusion is that oxidative stress and proteases are involved in the venom-induced cellular damages; however, it is better to evaluate the protease inhibiting effects of GBLE in addition to its antioxidant power.

3.2 | Lipopolysaccharide

3.2.1 | Lung

Lipopolysaccharide (LPS), which is found in the outer membrane of Gram-negative bacteria, provokes the activity of immune cells and elicits inflammatory responses. The protective effects of GB against LPS-induced acute lung injury in mice (Huang et al., 2013; Lee et al., 2014; Wu et al., 2016; Yao et al., 2015) and D-galactose-aged rats (Sun, Zhang, Si, & Wang, 2002) have been shown.

To investigate the effect of GBLE on the acute lung injury induced by LPS in D-galactose-aged rats, GBLE was given 7 days before the experiment, once a day via intragastric administration. LPS-induced acute lung injury. In the LPS-treated rats, more inflammatory cells in the lung tissue were observed. Moreover, TNF-α, LDH, and myeloperoxidase (MPO) activities were increased in lung tissue of LPS-administrated rats compared with the control. GBLE could alleviate all changes induced by LPS in these animals (Sun et al., 2002).

In another study EGb761 (0-1000μg/kg) was administrated 30 min before LPS in mice. After 6 hr, histopathological damages and arterial

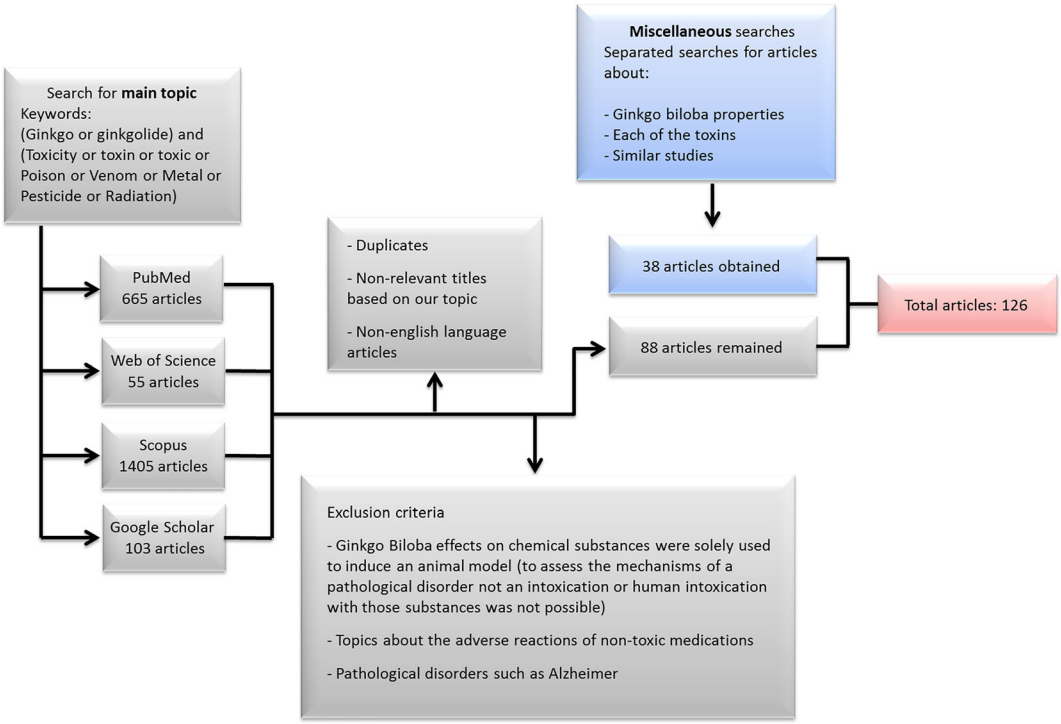


FIGURE 3 Flow chart of the search process, inclusion and exclusion criteria [Colour figure can be viewed at wileyonlinelibrary.com]

blood gas exchange were improved and overactivation of inflammatory response pulmonary edema and hyaline membrane formation were markedly reduced by EGb 761. Some molecular mechanisms including reduced production of proinflammatory cytokines and chemokines, such as TNF-α, IL-6, and MIP-2, reduced expression of COX-2 and iNOS, and reduced IκB kinase (IκB) phosphorylation and NF-κB activation are involved in the protective effects of EGb761 in LPS-induced acute lung injury. Down-regulation of Akt and JNK phosphorylation and down-regulation of ERK and MAPK phosphorylation are considered as the primary and as the secondary pathways, respectively (Lee et al., 2014).

In the investigation of Yao et al. (2015), a commercially available GB extract was analyzed by ultraperformance liquid chromatography-mass spectrometry chromatography and the presence of following ingredients was confirmed: (−)-epigallocatechin, (+)-catechin hydrate, (−)-epicatechin, quercetin 3-*O*-[6-*O*-(α-L-rhamnosyl)-β-Dglucoside], quercetin 3-*O*-β-D-glucoside, quercetin 3-*O*-[4-*O*-(α-L-rhamnosyl)-β-D-glucoside], quercetin 3-*O*-α-L-rhamnoside, bilobalide, bilobetin, ginkgolide C, ginkgolide B, ginkgolide A, luteolin, apigenin, kaempferol, isorhamnetin, and genkwanin. This extract (12 and 24 mg/kg in mice) significantly reduced the inflammatory cell numbers in the bronchoalveolar lavage fluid, decreased the expression of NF-κB p65 and COX-2, increased superoxide dismutase (SOD) activity, and inhibited MPO activity compared with the LPS group. The GB extract also improved the histological changes of the lungs induced by LPS (Yao et al., 2015). Huang et al. (2013) also assessed LPS-induced lung damages with and without EGb761 administration in different doses (0-1,000μg/kg) and separated groups by measurement of SOD and catalase (CAT) activity, MMP-9, MPO, MDA, GSH, NF-κB, and IκB level. They suggested that GB has noticeable improving and dose-dependent influence on all factors. Therefore, it can be concluded that the one of possible protection mechanisms of GBLE is the NF-κB pathway suppression via the revival of tissue antioxidant capacity (Huang et al., 2013).

Li et al. (2017) assayed ginkgolide A, as an active ingredient of GBLE. This compound attenuated the expression of proinflammatory mediators, such as COX-2 and NO as well as proinflammatory cytokines, including TNF-α, IL-6, and IL-1 in mouse peritoneal macrophages, mouse macrophage RAW264.7 cells, and differentiated human monocytes, which all cell types were intoxicated by LPS in vitro. These effects were partially attributed to the down regulation of NF-κB, P38 MAPK, and activation of AMPK signalling pathways. Moreover, ginkgolide A was able to inhibit the release of TNF-α and IL-6 induced by LPS in mice (Li et al., 2017). As it is reported above, the results obtained from the in vitro study on inflammatory cells support the outcomes of the in vivo research projects.

3.2.2 | Central nervous system/neurons

One of the systemic effects of LPS on central nervous system (CNS) is depression's development. An in vivo investigation was conducted to assess anhedonia as a main symptom of depressive disorders by sucrose preference test after injection of saline, LPS (100 μg/kg), EGb761 (50 mg/kg for 2 weeks), LPS, and EGb761 concomitantly in rats. This study showed that GBLE could significantly inhibit anhedonia induction in the animals and compensate the dopamine decrement, which was due to the LPS administration, but it was not able to increase the low level of serotonin significantly (Yeh et al., 2015).

EGb761 (10-500 μg/ml) showed the potential of neuroprotection via microglial cells, which were primarily isolated from rat brain. The extract of this herb inhibited the overgeneration of cytokines and inflammatory factors, such as IL-1β, IL-6, TNF-α, and PGE-2 induced by LPS. As shown in this study, the suppression of PGE-2 is the result of two general mechanisms that the first one is the inhibition of the production of AA, as a substrate of PGE-2 generation and the second one is the inhibition of enzymes, which is involved in the biosynthesis of this factor such as mPGES-1 and cPLA2α. However, GB failed to reduce the activity of COX-2, kappa B alpha, and multiple mitogen activated MAPKs. The authors declared that more studies on mTOR pathway might be helpful (Gargouri et al., 2018).

3.2.3 | Cardiovascular system:

Lin et al. (2007) clarified that TLR-4 mediates the proliferation of human aortic smooth muscle cells and in regard to the point that the stimulation of TLR-4 also leads to activate inflammatory signals, and LPS is able to increase the expression and stability of TLR-4 mRNA, then it is concluded that LPS results in both inflammation and proliferation, two considerable risk factors of atherosclerosis. It was proposed that GBLE (25-100 μg/ml) attenuated TLR-4-mediated proliferation via reducing the NADPH oxidase activity and inhibition of increased level of phosphorylated ERK1/2. Despite the fact that the SAPK/JNK pathway had a marked role in LPS-induced elevated TLR-4 expression, GBLE did not show a significant effect on this pathway (Lin et al., 2007). Another investigation, which was done in human coronary artery endothelial cells, suggests that ginkgolide A (10 and 20 μM) could hamper the release of inflammatory mediators and prevent higher activity of TLR-4 and NF-κB through regulation of PI3K/Akt upstream pathway (Zhaocheng et al., 2016).

3.2.4 | Immune system

There are some experiments were carried out in order to clarify the effect of GB on LPS-induced toxicity in mouse macrophage cells named RAW 264.7. Based on all these studies, totally, GB possesses notable antiinflammatory influences, which are at the transcriptional level and via NF-κB/AP-1, MAPKs, COX-2/PGE2, and iNOS/NO pathways (Ilieva et al., 2004; Jang et al., 2012; Park et al., 2006; Ryu et al., 2012; Wadsworth & Koop, 2001; Wadsworth, McDonald, & Koop, 2001). An additional pathway has been shown by Ryu et al. (2012) that the increment activity and expression of HO-1 as an antioxidant are mediated via the elevated level of its transcription factor, Nrf-2. In this research, the ethyl acetate extract of GB leaves, which was prepared by Ryu et al. (2012), was used. In their extraction method, all final fractions (ethyl acetate, n-butanol, and water) in 1-50 μg/ml were nontoxic, but only the ethyl acetate fraction possessed antiinflammatory effects (Ryu et al., 2012). Thus, the different pathways, which were shown in this study, can possibly be attributed to the different extract that they used, but unfortunately, it has not been determined and confirmed which compounds of the GB leaves have been entered into the active fraction and have these antiinflammatory influences.

The results of most studies were dose-dependent. The dose ranges of GBLE (commercially standardized) were 10-1,000 μg/ml (Ilieva et al., 2004) and 40-120 μg/ml (Park et al., 2006), and the dosage of ethyl acetate extract of GB leaves was lower, 1-20 μg/ml (Ryu et al., 2012). It is likely because of its different composition. Furthermore, a novel method was applied by one of these studies conducted by Jang et al. (2011) to minimize the environment-dependent genomic variations in the extract content by isolating a kind of stem cells of GB plant as a generating source of active ingredients. They cultured the cambial meristematic cells of the GB roots, which are the vascular stem cells and prepared the ethanolic extraction of the cells with a special protocol (Jang et al., 2012).

A similar research, but on monocytes (THP-1 cell line), represented that TLR-4 expression was reduced by GB in the condition of LPS-related inflammation through TTP and MAPKs regulation that these effects depended on duration of the exposure (Lee et al., 2011).

3.2.5 | Kidney

LPS can cause damages in renal tissue, which appear as tubular destruction due to the elevation of systemic lipid peroxidation and deterioration of renal antioxidant capacity in rats. Oral administration of 50 mg/kg of EGb 761 alleviated the renal histological injuries developed by intraperitoneal injection of 10 mg/kg LPS. Vitamin D was chosen as positive control in this study. The significant antioxidant effects of EGb 761 were comparable with vitamin D, and their effects were potentiated together (Coskun, Armutcu, Kanter, & Kuzey, 2005). More research projects are required to determine the mechanisms involved in nephroprotective effects of GB.

3.2.6 | Intestine

A research conducted by Zhang et al. (2012) revealed that equal feeding with the fermented form of GB leaves more than nonfermented form improved the disturbed intestinal absorptive function, inflammation, and improper morphologic changes induced by LPS (0.5 mg/kg IP) in chickens. Fermentation of the GB leaves was carried out by cultured *Aspergillus niger* under a controlled condition. After fermentation process, the content of total flavonoids, total ginkgolic acid, polysaccharides, protein, and amino acids of the fermented leaves and nonfermented ones were quantified and compared. The amount of total flavonoids and total ginkgolic acids were diminished by fermentation, and the biological activity of GB leaves became stronger. A hypothesis, which is expressed by authors, is that glycosyl group of flavonoids' structure may be separated by enzymes of *A. niger* in fermentation process; therefore, they biologically became more active (Zhang et al., 2013).

3.2.7 | Ear

In an experimental study, LPS was directly applied into the ear of the male guinea pigs to develop labyrinth toxicity. Degrees of hearing loss, structural hair cell damages, increased extravasation, and decreased cochlear blood flow were consequences of the LPS ototoxicity. About 20 μl of LPS in a concentration of 3 mg/ml was dropped intratympanicly. The animals were treated with 100 mg/kg of GB for 3 days. The results indicated that this herbal extract strongly inhibited the mentioned effects arose from LPS toxicity (Jang et al., 2011). The specific cellular and molecular mechanisms involved in GB protection against LPS-ototoxicity have not been investigated.

3.2.8 | Eye

Ilieva et al. (2004) evaluated the effects of GB on uveitis caused by LPS injection in rats, in addition to the cell culture assessment that it has been mentioned before. In the in vivo part of the study, 24 hr after 200 μg (100 μg/footpad) of LPS and 1, 10, and 100 μg of GB administration, the aqueous humour of the animals was separated. Protein, infiltrated cells, and NO level dramatically increased in LPS group and were significantly suppressed by GB. These results in concomitant with the findings of the cell culture assessment displayed the antioxidant capacity of GBLE (Ilieva et al., 2004).

Approximately all studies about LPS on animals or cells suggested that GB have significant antiinflammatory effects mostly via NF-κB, PGE-2, Cox-2, MAPKs, and in some cases via TLR-4 and HO-1. A summary of molecular mechanisms of GB protection against LPS toxicity was shown in Figure 4.

3.3 | Aflatoxin B1

Aflatoxin B1 (AFB1) is a common toxic member of the aflatoxins' family, which was considered as the toxic fungal secondary metabolite. Aflatoxins are produced by the fungi *Aspergillus flavus*, *Aspergillus parasiticus*, and *Aspergillus nominus*. It is estimated that about 4.5 billion people are at risk of chronic exposure to aflatoxins through contaminated food crops especially in developing countries (Cao et al., 2017). In vitro study showed that GBLE significantly inhibits the reduction of the cells viability and the increase of intracellular reactive oxygen species (ROS) level and MDA production induced by

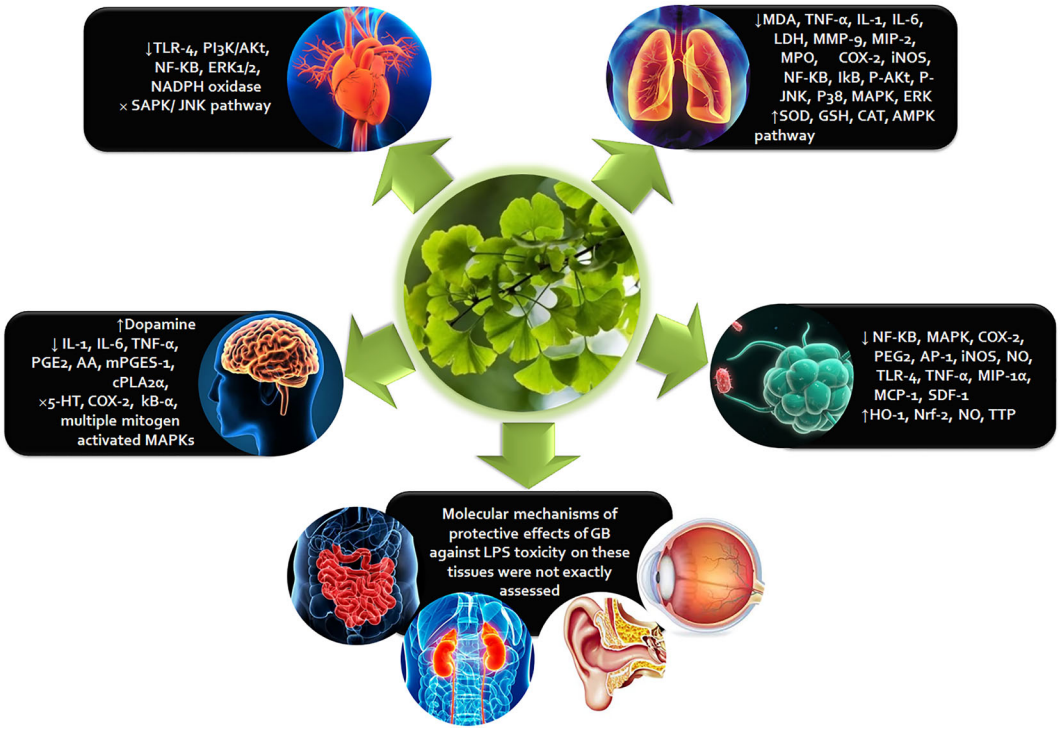


FIGURE 4 Summary of the mechanisms of *G. biloba* protection against Lipopolysaccharidelipopolysaccharide toxicity in different tissues. ↓ or ↑, respectively, shows a significant decrease or increase, and × shows no significant change in mentioned factors. AA: arachidonic acid; AKt: protein kinase B; AP-1: activator protein-1; CAT: catalase; COX-2: cyclooxygenase-2; cPLA2α: cytosolic phospholipase A2; ERK: extracellular signal-regulated kinase; GB: *Ginkgo biloba* L. ; GSH: reduced glutathione; HO-1: Heme oxygenase-1; IκB: IκB kinase; IL-6: interleukin-6; IL-1β: interleukin-1beta; iNOS: nitric oxide synthase; JNK: jun N-terminal kinase; LDH: lactate dehydrogenase; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; MCP-1: monocyte chemoattractant protein-1; MDA: malondialdehyde; MIP-2: macrophage inflammatory protein-2; MMP-9: matrix metalloproteinase-9; mPGES-1: microsomal prostaglandin E synthase-1; MPO: myeloperoxidase; NADPH: nicotinamide adenine dinucleotide phosphate; NF-KB: nuclear factor kappa beta; NO: nitric oxide; Nrf-2: nuclear factor (erythroid-derived 2)-like 2; PGE-2: prostaglandin E2; PI3K: phosphatidylinositol-3-Kinase; SAPK: stress-activated; SDF-1: stromal cell-derived factor 1, protein kinase; SOD: superoxide dismutase; TLR-4: toll-like receptor-4; TNF-α: Tumour necrosis factor; TTP: tristetraprolin. [Colour figure can be viewed at wileyonlinelibrary.com]

AFB1 in human hepatocytes (HepG2 cells) through antioxidant effects (Hao et al., 2008). Another study was carried out by the same authors on Wistar rats. They investigated the effects of EGb761 on liver cancer induced by intra-abdominal injection of 100-200 μg/kg AFB1. The tests including MDA, GSH levels, and histopathological evaluation showed that after 42th and 55th weeks, GB significantly reduced the size of the cancerous area and oxidative stress (Hao et al., 2009). It seems that the inhibition of cancer cannot only be due to the oxidative stress suppression; therefore, the other more specific mechanisms should be considered.

3.4 | Lysophosphatidylcholine

Lysophosphatidylcholine (LPC) is an important lipid molecule in mammalian tissues and possesses different proinflammatory and atherogenic effects (Matsumoto, Kobayashi, & Kamata, 2007). In vitro study on H9c2 cell line showed that protective effect of GBLE against LPC-induced myocyte damage is partly attributed to the induction of HO (an antioxidant enzyme which can mediate the adaptive cellular response to oxidative stress and is responsible for regulating the intracellular level of heme). The induction of HO was not observed by GB terpenoids such as ginkgolide B and bilobalide. The induction of gene expression and activity of HO by GBLE may be due to the alteration of intracellular glutathione level (Chen, Zeng, Chen, Su, & Lai, 2001).

3.5 | Toxins derived from plants

3.5.1 | Lantadene

Latadenes (pentacyclic triterpenoides) are major toxic compounds found in the leaves of the red flower variety of *Lantana camara* Linn., which belongs to *Verbenaceae* Family. Camara damages liver and kidneys and also induces photosensitization in ruminants. Among nonruminant animals, guinea pigs show the most typical symptoms comparable to those observed in ruminants. It has been documented that the methanolic leaf extract of GB was able to protect against lantadene-induced hepatic damage in guinea pigs. So that the elevated levels of serum ALT, AST, and ALP induced by lantadenes were significantly decreased by methanolic GBLE dose-dependently. The increased levels of lipoperoxids and decreased levels of SOD, GSH and catalase were markedly restored to that of control by methanolic GBLE; moreover, the induction of apoptosis induced by lantadene was suppressed in GB treated animals. The hepatoprotective effect of GB was comparable to silymarin (Parimoo et al., 2014).

3.5.2 | Cassava

Cassava (*Manihot esculenta* Crantz) is an edible tuber due to its high carbohydrate content. Cassava contains cyanogenic glycosides such as linamarin and lotaustralin; so, long term consumption of cassava, an improper processing, and a low protein diet have been associated with neurodegenerative and neurological diseases. A study showed the protective effect of GBLE (160 mg/kg/day, for 28 days, orally) on disturbed locomotor activity and neuronal damage in hippocampus induced by cassava juice (linamarin, 0.30 mg/kg) in rats. According to the results of the study, in cassava-treated rats, crossing and rearing in the open field test and number of damaged neurons in the hippocampus were increased as compared with the vehicle group from day 14 of treatment. Moreover, an uncoordinated swim characterized by the lateral swim in the swim test was observed. GBLE attenuated both behavioral and neuronal damages induced by cassava juice administration possibly due to the high flavonoid content of GBLE (Rivadeneyra-Dominguez, Vazquez-Luna, Rodriguez-Landa, & Diaz-Sobac, 2013), because it is reported that flavonoids have the potential of neuroprotection via multiple mechanisms, such as PI3K/Akt and MAPK pathway regulation (Spencer, 2009).

3.5.3 | Gossypol

Pigment-producing glands of the cotton seed contain a polyphenolic compound known as gossypol, which can cause toxicity. Ingestion of gossypol in high concentrations or for a long time decreases fertility rate in ruminants and nonruminants probably because of increased production of prooxidants and decreased antioxidant concentrations (Santana et al., 2015). The protective effect of GBLE against gossypol-induced apoptosis in human lymphocytes was investigated. Results showed that the level of apoptosis was decreased to 17.5% and 20% following pretreatment of lymphocytes with 10 μg/ml EGb 761 for 30 min or 1 hr. Moreover, EGb 761 treatment (25-150 μg/ml) reduced the percentage of apoptosis between 8 and 10% of the control levels (Ergun, Yurtcu, & Ergun, 2005).

4 | CHEMICAL TOXICITIES

4.1 | Metals

4.1.1 | Aluminium

As aluminium (Al) is broadly distributed in the environment, exposure to it is very common during daily life. Al and its salts are daily used in drinking water, in our diets, food additives, and some beverages (Lione, 1983). It is a well-documented neurotoxicant due to its easy access to the central nervous system and high accumulation in the brain (Lakshmi, Sudhakar, & Prakash, 2015).

Several studies reported the beneficial effect of GBLE in Al-induced memory and learning impairments and oxidative stress in the brain (Abd-Elhady, Elsheikh, & Khalifa, 2013; Gong et al., 2006; Gong, Wu, Huang, Sun, & Shi, 2005; Mohammadzadeh et al., 2017). Learning and memory deficit were induced by both intragastric administration and drinking of $AlCl_3$ solution for 3 (Gong et al., 2006) or 5 months (Gong et al., 2005). GBLE administration (50, 100, 200 mg/kg/day) for 2 months after $AlCl_3$ intake ameliorated learning and memory deficit through inhibition of the AChE expression in hippocampus (Gong et al., 2006) or by reduction of the levels of amyloid precursor protein and caspase-3 in hippocampus of Al-treated rats

dose-dependently (Gong et al., 2005). The improvement of memory and learning by GB in the animals was confirmed by Morris water maze test in both studies, so that GB caused significantly lower escape latency and searching distance in comparison with $AlCl_3$-treated rats (Gong et al., 2005; Gong et al., 2006). In another study, oral administration of $AlCl_3$ (10 mg/kg) for 3 months significantly increased TBARS and decreased GSH, CAT, and SOD in the brain. Furthermore, $AlCl_3$ reduced the levels of some neurotransmitters in brain tissue such as noradrenaline, dopamine, and serotonin. Decrease in the amounts of serum Zn, Cu, and Mg along with a significant increase in serum Fe was observed in rats administered $AlCl_3$. ALP and acid phosphatase were increased by $AlCl_3$. $AlCl_3$ induced some degenerative changes in rat brain tissues. These biochemical and histological changes were improved by GB (200 mg/kg, orally for 3 months), which may be due to its antioxidant effects (Mohammadzadeh et al., 2017). In the study of Abd-Elhady et al. (2013), rats were treated with 10 mg/kg of aluminium lactate intraperitoneally for 28 days in order to induce the aluminium toxicity. In this group, Al level was significantly raised in serum, hippocampus, cortex, and whole brain; memory function in the passive avoidance task test was disrupted; and AChE activity was diminished. Twenty-eight-day oral administration of 200 mg/kg of hydro-alcoholic (50:50) GBLE caused a higher level of AChE activity and memory function without any changes in Al levels in serum or brain of the animals. GBLE also increased the reduced form of glutathione and decreased MDA level (Abd-Elhady et al., 2013).

4.1.2 | Lead

Lead, which is chemically named Pb, is one of the most important toxic heavy metals that have been concentrated in the earth via human industrial activities. This element can cause infertility, psychotic and degenerative disorders, high blood pressure, renal dysfunction, and interrupted zinc-related functions in the body (Maret, 2017).

In an investigation, 50 and 100 mg/kg GBLE were used orally to evaluate its possible effects on oxidative stress induced by 500 ppm of lead acetate in drinking water (rats were treated with lead acetate for 4 weeks). In this study, frontal cortex, cerebellum, hippocampus, and brain stem of sacrificed animals were prepared and the content of factors, including free radicals, MDA, and antioxidant enzymes were measured. The findings demonstrated that GB dose-dependently protected the brain tissue from high levels of oxidative stress, which is caused by lead acetate intoxication (Yallapragada & Velaga, 2015).

4.1.3 | Cadmium

This metal is a toxic element, which enters into the body through inhalation and ingestion. The smoke of cigarette reported as a major source of exposure to cadmium in humans (Bernhoft, 2013).

In the original study of Predes et al. (2010), the single dose injection of 3 μmol/kg cadmium chloride, after 56 days, resulted in decreased volume of rat leydig cells, their cytoplasm, and nucleus; however, it did not induce any significant changes in the blood testosterone level, the size of each testicular parenchyma component, and the number of leydig cells. Fifty-six-day treatment of animals with oral administration of GB extract (a commercial product containing 19.2 mg/ml ginkgo flavonoids and 4.8 mg/ml terpenelactone) with the dose of 100 mg/kg prevented the cellular histomorphological alterations. The authors declared that the relation of these protective effects of GB to its antioxidant properties needs to be confirmed with more investigations (de Souza Predes, Monteiro, Matta, Garcia, & Dolder, 2011).

4.1.4 | Mercury

There is mercury (Hg) in the three forms of elemental, organic, and salts (mono or divalent). Pharmacokinetic characteristics, toxicity magnitude, and target organs of mercury depend on the form to which humans are exposed (Bernhoft, 2012).

The effect of antioxidant activity of GB on mercury intoxication was evaluated in an animal study. To develop the mercury toxicity, rats were administered 5 mg/kg of $HgCl_2$ as a single dose. Mercury injection significantly elevated the blood level of BUN, Cr, ALT, AST, TNF-α, and LDH activity associated with increased MPO activity, free radical overgeneration, and decreased GSH amount in kidney, liver, brain, and lung tissues. Intraperitoneally injection of 150 mg/kg of the GBLE for 5 days was considerably capable of restoring all these changes (Çavuşolu, Yapar, & Yalçin, 2009).

4.1.5 | Heavy metal-contained wastewater

This kind of water is often found nearby to industrial centres. Waters, which consist of the high amount of heavy metals, can endanger the life of its surrounding animals and plants. Cavusoglu et al. (2008) analyzed the wastewater, which is discharged into the Melet River in the terms of heavy metals and evaluated its effects on germination and growth of the *Vicia faba* L. seeds with and without exposure to GBLE. The levels of MDA and micronuclei (MN) were also measured in the plant roots. The analysis of the polluted water showed that the heavy metals from the most to the least concentration, respectively, were Pb, Al, Ni, Cr, Fe, Cu, Zn, and Cd. The number of germinated seeds, which were fed with wastewater, was much less than those were fed with the tap water. In the presence of the GBLE (10, 20, and 30 μM in the river water) germination percentage was significantly raised in a dose-dependent manner. The effects of polluted water and GB on the root lengths and weights were similar to their effects on germination percentage. GB also had significant alleviative influence on increased MDA and MN level induced by waste water feeding (Cavusoglu et al., 2010).

4.1.6 | Triethyltin

This neurotoxic agent is the organic form of tin atom, which is attached to three ethyl groups. It is demonstrated that GBLE could inhibit the deleterious effects of triethyltin (TET) in rats, so that there was no change in electrolyte and water balance of the brain in the animals, which were dosed GBLE (10 ml/kg of drinking water consists of

100 mg/kg GB) accompanying with TET (0.002% in drinking water) for 14 days, and TET administration was associated with significant destructive cerebral oedema and histological damages in comparison with normal animals (Otani, Chatterjee, Gabard, & Kreutzberg, 1986). The other study focused on the possible molecular mechanism of GB related to these protective effects. The results of this study clarified that GBLE was able to restore the activity of the membrane-bound form of the PDE, which was reduced by TET administration, but it did not affect on the soluble form. The performers showed that this modulating effect of GBLE is not because of the formation of complex with TET and it possibly had a direct or indirect activating effect. PDE activation prevents the cyclic-AMP accumulation in the cells and its toxic effects on cellular metabolisms (Macovschi, Prigent, Nemoz, & Pacheco, 1987).

In view of the effects of GBLE against neurotoxicity induced by some metals, such as Al and Pb or the other toxic agents, it is interesting to clarify the active ingredients of this herbal extract which is effectively able to cross the brain-blood barrier.

4.2 | Ethanol

Ethanol is one of the alcoholic compounds that is widely used and abused in all over the world. Exposure to long term or high concentrations of ethanol can lead to chronic or acute toxicity. The liver is the major organ that affected by ethanol, because this substance is metabolized mostly in the liver, although a lot of tissues are susceptible to its adverse effects (Rusyn & Bataller, 2013). The results of Chan and Hsuuw research (2007) revealed that the ethanol in a concentration range of 50-400 mM for 36 hr significantly decreased Hep G2 cell viability and increased the cellular apoptosis and ROS generation. When ginkgolide B was added up to 25 mM to the cells, which were treated with 100 mM of ethanol, cell viability, apoptosis percentage, and ROS production were dose-dependently improved; however, the higher concentrations (50 and 100 mM) of ginkgolide B with the concomitant of 100 mM of ethanol induced more apoptosis and ROS generation. The effect of the concurrent use of ginkgolide B with ethanol on caspase-3 level and JNK/AP-1 activity in hepatic cells was the same as the results obtained from cell viability assay (Chan & Hsuuw, 2007); thus, it indicates that the hepatocellular protective effects of ginkgolide B can be associated with suppression of caspase-3, oxidative stress, and regulation of JNK/AP-1 pathway.

Yao et al. (2007, 2009) in two different studies exhibited the role of HO-1 in mediating antioxidant effects of GB on liver oxidative injuries induced by ethanol. In the first study, animals were treated with 2.4 mg/kg of oral ethanol solution for 90 days in order to induce liver toxicity, and in two separated groups, animals pretreated with 48 and 96 mg/kg of GBLE 1 hr before ethanol administration. In the next step, after the sample preparation, serum ALT and AST level, MDA, GSH, SOD, glutathione peroxidase (GP_X), CAT level, and HO-1 gene expression in the liver tissue were measured. The ethanol administration resulted in much higher level of ALT, AST, and MDA than the control group and significant reduction in tissue antioxidant enzymes and HO-1 expression. GB reversed all consequences of ethanol ingestion to the normal level in a dose-dependent manner (Yao et al., 2007). In the second study, the effect of quercetin, one of the active ingredients of GB and also a lot of other herbal extracts, on ethanol-associated hepatocyte toxicity via the HO-1 pathway was assessed. It was demonstrated that carbon monoxide (CO), an outcome of the heme metabolism with HO-1 activity rather than other metabolites, is effective in the protective pathways of quercetin. It was clarified that CO inhibited the ethanol-induced CYP_2E_1 up-regulation, an enzyme involved in oxidative stress. Therefore, quercetin can attenuate the oxidative damages of ethanol through the up-regulation of HO-1 and then its metabolite, CO (Yao et al., 2009).

In another research, Qiu et al. (2015) investigated the effects of a triple mixed herbal formulation named SGR on fatty liver developed by chronic ethanol consumption. This formulation consists of three herbs: Semen Hoveniae extract: 80%, GBLE: 10%, and *Rosa roxburghii* Tratt extract: 10%. After mixing prepared Semen Hoveniae extract with other two purchased extracts, the content analysis was carried out by chromatography, and it illustrated the presence of dihydromyricetin, dihydroquercetin, quercetin, and flavonoids. Findings of this study represented that ethanol elevated the triglyceride level in serum and liver tissue of mice through the decreased expression level of adiponectin, peroxisome proliferator-activated receptor (PPAR-α) and AMPK-β, and increased expression level of TNF-α and sterol regulatory element binding protein 1c (SREBP-1c). SGR administration for 30 days had the potential of regulating the expression of adiponectin, PPAR-α, TNF-α, SREBP-1c, and the level of phosphorylated AMPK-β, instead of the total expression of AMPK-β (Qiu et al., 2015). In the studies, which are conducted on a combination of several herbs, there is an uncertainty in making conclusion about the effects of every herbal component, unless some treated groups with the isolated or purified herbal extracts are added.

4.3 | Carbon tetrachloride (CCl_4)

This compound is chemically a member of the haloalkanes that nowadays their uses have been minimized or forbidden because of their toxic effects. The liver is the most important target organ of CCl_4 (Weber, Boll, & Stampfl, 2003). CCl_4 interaction with CYP_2E_1 leads to $\dot{CCl}_3$ radical, which reacts with oxygen and generates the CCl_3O free radical. The formation of this radical, possibly, is the onset of the consequent injuries like lipid peroxidation, cell membrane dysfunction, calcium homeostasis disturbances, cellular enzymatic leakage, DNA damage and genotoxicity, hepatic fibrosis, cellular proliferative changes, and finally liver cancer (Manibusan, Odin, & Eastmond, 2007).

There are four similar studies about the effects of GB on CCl_4 hepatotoxicity in rats with the differences in dosing administration of CCl_4 and GBLE. These studies were summarized in Table 1. In the study of Shenoy et al. (2001), CCl_4 was intraperitoneally injected at the dose of 0.5 mg/kg for 7 days, and in another group 50 mg/kg/day of GBLE (with 0.24 mg of ginkgo flavonglycosides per gram of dry extract) was simultaneously administered (IP) with CCl_4. Oral silymarin (200 mg/kg) was given as a positive control. After treatments, the level of ALT, AST, ALP, total protein (TP), and albumin (Alb) in the serum and

TABLE 1 Protective effects of G. *biloba* leaf extract against carbon tetrachloride

CCl_4 and GBLE dosing	Evaluated tissue	G. *biloba* effects	References
CCl_4: 0.5 ml/kg/day, 7 days, IP GBLE: 50 mg/kg/day, 7 days	liver	↓ALT, ↓AST, ↓ALP, ↑TP, ↑Alb in the blood ↓MDA, ↑GSH in the liver Histopathological improvement	Ashok et al. (2001)
CCl_4: 1 ml/kg/day of 50% (v/v) CCl_4 solution in olive oil, 7 days, IP GBLE: 25 and 50 mg/kg/day, 10 days (3 days before the start of CCl_4 injection), IP	liver	↓ALT, ↓AST, ↓ALP, ↑TP, ↑Alb in the blood ↓MDA, ↑GSH, ↑SOD, ↑CAT, ↑GP_X in the liver Histopathological improvement	Naik and Panda (2007)
CCl_4: 0.25 ml/kg of 50% CCl_4 suspension in corn oil, single dose, PO GBLE: 4 mg/kg/day, 5 days before CCl_4 administration, PO	liver	↓ALT, ↓AST, ↑Alb in the blood ↓MDA, ↑TNF-α and ↑IL-6 mRNA level in the liver Histopathological improvement	Chavez-Morales et al. (2011)
CCl_4: 5 ml/kg of 40% (v/v) CCl_4 solution in olive oil for the first time, then 3 ml/kg every 4 days, SC GBLE: 10, 40 and 160 mg/kg/day, 6 weeks	liver	↓ALT, ↓AST, ↓ALP, ↑TP, ↑Alb, ↓hyaluronic acid, ↓laminin, ↓triglyceride, ↓total cholesterol in the blood ↓MDA, ↑GSH, ↑SOD in the liver Histopathological improvement	Yang et al. (2011)
CCl_4: 0.25 ml of 50% CCl_4 suspension in corn oil, single dose, PO GBLE: 4 mg/kg/day, 5 days before CCl_4 administration	Kidney	↓TP and ↓glucose in the urine ↓MDA in the kidney Histopathological improvement	Chavez-Morales et al. (2017)

Note. ↓ or ↑, respectively, shows a significant decrease or increase in comparison with CCl_4-treated group.

the amount of MDA and GSH in the liver tissue were measured. Moreover, the histopathological assessment of the livers was also performed (Ashok et al., 2001). Other three researches were conducted according to the protocols mentioned in the table below (Table 1). Based on all four studies, we can totally conclude that carbon tetrachloride elevated the level of MDA and therefore caused the cellular membrane damage that the rise in the blood level of hepatic enzymes is the evidence of that. Drop in the level of albumin was an indicator of the liver dysfunction due to the CCl_4 administration, and the histopathological assessment showed the tissue necrosis and fatty infiltration to some extent. Treatment of animals with GBLE preserved the liver from being harmed by CCl_4 intake (Ashok et al., 2001; Naik & Panda, 2007; Chavez-Morales et al., 2011; Yang, Wang, Ye, & Li, 2011). It should be noted that isolated and purified polyphenols of GB leaves have been used in the study of Yang et al., 2011; therefore, the polyphenols in addition to flavone glycosides and terpenoids of GB leaves are effective at least on CCl_4-developed hepatic toxicity. Moreover, the study of Naik and Panda (2007) has been the only study in which the phytosomes of *G. biloba* extract (Ginkgoselect) were used. These phytosomes also consist of flavone glycosides, terpenoids, tannins, and proteins.

One of the effects of CCl_4 on the liver tissue in the study of Chavez-Morales et al. (2010) is the elimination of the TNF-α expression in comparison with control (Chavez-Morales et al., 2011). This effect is in the vise versus line of some studies (Weber et al., 2003). The authors believe that this result is due to the inhibition of protein expression by CCl_4 in the liver and the restoring effect of GBLE in this case was expressed as a modulating influence (Chavez-Morales et al., 2011). Another experiment of Chavez-Morales et al. (2017) demonstrated that neither of renal functional factors, including urine flux, clearance of inulin, and p-aminohippurate was influenced by CCl_4, but it significantly increased proteinuria, MDA level, and induced tubular necrosis more in the inner cortex of the kidneys. GBLE administration significantly alleviated these injuries (Chavez-Morales et al., 2017).

Although the mechanisms of CCl_4 toxicity have partly been determined, in all mentioned studies, only the general oxidation or inflammation-related parameters were evaluated in GB protective effect on CCl_4. It would be more valuable that the effects of GB on specific pathways involved in CCl_4 toxicity, including CYP_2E_1 expression or DNA damage, were also assessed.

4.4 | Pesticides

4.4.1 | Insecticides

Methamidophos

Finkler, Silveira, Munaro, and Zanrosso (2012) investigated the possible effect of EGb 761 on the ototoxicity induced by methamidophos (0.3 and 3 mg/kg/day for 7 days) as an organophosphorus pesticide. The structure of the main part of cochlea including hair cells, named organ of corti, in guinea pigs was analyzed by means of the electron microscopy and the results indicated that GBLE (100 mg/kg/day, 90 min before methamidophos administration) prevented the organ of corti structural deformation (Finkler et al., 2012).

Diazinon

Diazinon is the other insecticide, which is applied for agricultural purposes. Several investigations demonstrated the diazinon genotoxicity or its toxic effects on the animal vascular system, heart, and liver. These toxicities were limited by herbal active ingredients (Lari et al.,

2015; Razavi, Hosseinzadeh, Abnous, & Imenshahidi, 2014; Razavi, Hosseinzadeh, Abnous, Khoei, & Imenshahidi, 2016; Razavi, Hosseinzadeh, Movassaghi, Imenshahidi, & Abnous, 2013; Zeinali, Meybodi, Rezaee, Rafatpanah, & Hosseinzadeh, 2018). Considering that this substance and the other similar compounds may enter the waters and threat the marine animal lives, a study has been conducted about its toxic effects on the immune system of Rainbow trout fishes, one of the most cultured fish species. The immunomodulatory and immunoprotective effects of GB were assessed on this toxicity. The findings exhibited that 1 and 2 g of dried hydro-alcoholic GB extract per 1 kg of fish diet were able to restore the serum total immunoglobulin level, peroxidise, and lysosome activity, which had been suppressed by diazinon (0.287 mg/l). These two doses of GB also inhibited the rise of renal transforming growth factor beta (TGF-β1) and IL-1β level due to the diazinon exposure. The immunomodulatory effects of GB did not appear in doses of 0.5 and 4 g/kg diet. The authors have declared that GB in higher doses probably has immunotoxic effects in this model, because it was observed that 4 g/kg of GB lessened total immunoglobulins, complement activity, peroxidise, and lysosome activity with and without diazinon in comparison with control (Hajirezaee, Rafieepour, Shafiei, & Rahimi, 2019).

4.4.2 | Rodenticides

Bromethalin is a potent rodenticide, and it is used in the resistant cases to anticoagulant poisons (DeClementi & Sobczak, 2018). The mechanism of its toxic effects in the brain as a major target organ is by reducing cellular ATP level following the uncoupling of mitochondrial oxidative phosphorylation. A decreasing in the ATP production leads to dysfunction of the Na/K ATPase pump and finally the accumulation of the Na and water (Peterson, 2013). Bromethalin was administered with the dose of 1 mg/kg. After 24 hr, MDA, Na and water level in the brain were determined. In the other group, rats were treated with bromethalin with concurrent administration of 100 mg/kg of GBLE. This herbal extract could hamper the accumulation of the excessive amounts of Na and water and the overgeneration of MDA in the brain tissue of bromethalin-treated rats. Furthermore, GBLE significantly attenuated the neurotoxic signs, which were consequences of the cerebral oedema and injuries (Dorman, Cote, & Buck, 1992).

4.4.3 | Herbicides

Glyphosate

GBLE was also used to be checked that whether it has any effect on glyphosate toxicity. To reach this, Cavusoglu, Yapar, Oruc, and Yalcin (2011) orally administered 50 and 150 mg/kg of GBLE with intraperitoneal single injection of glyphosate (50 mg/kg) in mice. In the animals, which received only glyphosate, ALT, AST, BUN, Cr, and MDA levels in the liver and kidney significantly elevated in comparison with the control group. In addition, genotoxicity was markedly developed in this group. It was evaluated through the measurement of the related factors, including MN frequency in red blood cells, mitotic index, and chromosome aberrations in bone marrow cells. GB possessed the protective effect on all these abnormalities likely via its antioxidant properties (Cavusoglu et al., 2011).

Paraquat

Mostly, an accidental exposure to high doses of paraquat can lead to toxicity and even death. The major target organ of this herbicide is lung (Kurisaki, 1989); however, it may have neural toxicity.

The original study of Kang, Chen, Xu, Li, and Wang (2007) demonstrated that GBLE (10, 20, and 40 μg/ml) dose-dependently reduced the injuries in PC12 cells treated with paraquat. Following the cell incubation with paraquat, cell viability and B-cell lymphoma 2 (Bcl-2) level significantly decreased and apoptosis-related parameters increased (Kang et al., 2007). Nevertheless, one cell culture study is not valid enough to verify the protective effects of GB against paraquat-induced toxicity.

4.4.4 | Fungicides

Topsin

In the investigation of Sakr, Mahran, and Abdel-Maksoud (2011), GB was considered for its antioxidative activity in the case of ovarian toxicity via exposing to dimethyl 4, 4,-(o-phenylene) bis (3-thioallophanate), a chemical fungicide, which is commercially named topsin. It is often used as a plant seed preservative. The findings of this study suggested that topsin (oral dose of 0.1 LD50 for 8 weeks) caused pathologic alterations in the ovary components, including epithelial cells, blood vessels, the structure, and the number of follicles. In addition to histological changes, follicle-stimulating hormone and luteinizing hormone level were significantly diminished and serum estradiol level obviously increased. The elevation of serum MDA level and the significant reduction in serum SOD and CAT enzymes indicated that topsin toxicity can be mediated through oxidative stress and overgeneration of ROS. Remarkable efficacy of GBLE (40 mg/kg/day for 4 weeks after topsin administration), as a powerful antioxidant, in the improvement of topsin toxicity confirmed this hypothesis (Sakr et al., 2011).

4.5 | Cigarette smoke

In two separated assays of Wang et al. (2010 and 2011), GBLE was utilized alone and with cobalt porphyrin in cigarette filter to minimize the toxicity of its smoke. After preparing the GB-contained cigarettes, a system was applied to produce and trap the cigarette smoke in order to test its free radical contents, in vivo acute and chronic toxicity in the animals. The condensed form of cigarette smoke was also tested for mutagenicity potential. Both modified versions of cigarettes had less toxicity and mutagenicity than non-modified cigarette and the animals, which were exposed to GB-contained cigarette experienced milder toxicity-related complications, so it means that GB lowered the toxic effects of cigarette smoke. On the other hand, there were much lower amounts of solid and gas-phase free radicals related to modified version in comparison with non-modified one (Wang et al.,

2010; Wang et al., 2011). Therefore, the protective effects of GB might originate from its radical scavenging and antioxidant activity.

4.6 | Monosodium glutamate

This compound is a food additive, which is widely applied in the processed food industry. The adverse effects of monosodium glutamate (MSG) intoxication appear mostly in CNS, liver, and reproductive system (Husarova & Ostatnikova, 2013).

An investigation represented that oral 1.5 mg/kg of MSG, twice a week for a month, was attributed to dysfunction of the liver and kidney in rats. About 80 mg/kg of GBLE, along with MGS administration, markedly attenuated the liver enzymes, BUN, Cr, and MDA levels. These findings demonstrated that the oxidative stress plays a crucial role in the MSG toxicity (Elatrash & Abd El-Haleim, 2015).

4.7 | Naphthalene

Naphthalene is broadly used in the industry as a precursor to produce chemical compounds. Acute exposure to toxic amounts of this substance can result in hemolytic anaemia. Toxic effects of naphthalene are mostly because of increased oxidative stress. A study revealed that 30-day administration of 100 mg/kg of naphthalene induced overproduction of free radicals, serum TNF-α and IL-β, and significantly suppressed antioxidative capacity of lung, liver, and kidney of mice. Furthermore, the histopathological evaluation of the animal lung, kidney, and liver clarified that naphthalene harmed the structure of these tissues. Most importantly, the oral treatment of naphthalene-injected animals with 150 mg/kg of GB prevented all of the mentioned injuries (Tozan et al., 2007).

4.8 | Fluoride

Fluoride is one of the important trace elements for the human body, but in the optimum level. In fact, consumption of the larger amounts of this ion can lead to fluorosis and neural damage.

In an animal study, it is observed that the level of MDA and GSH and the activity of SOD and CAT in fluoride-treated mice (50 mg/L in drinking water for 30 days) were significantly higher than both normal mice (with 0.04 ppm fluoride in drinking water) and fluoride-treated mice, which concomitantly received 20 mg/kg/day of EGb 761 for 30 days. Moreover, tissue staining of hippocampus for the histopathological assessment showed considerable neural degeneration in the intoxicated animals, in comparison with control and EGb 761 plus fluoride-treated group (Atmaca, Aksu, Yıldırım, & Atmaca, 2014). Totally, it is concluded that EGb 761 is a protective agent against oxidative stress induced by high concentration of fluoride.

4.9 | Chemotherapy medications

The effects of GB leaf extract have been investigated on different toxicities developed by anticancer drugs including cisplatin, doxorubicin, bleomycin, 5-fluorouracil (5-FU), and oxaliplatin. All studies, which have been performed in this field up to now, were summarized in Table 2. Overall, this valuable herbal extract illustrated its antioxidant, antiapoptotic, and antiinflammatory effects; however, it also possessed the other special influences. This extract even alleviated the structural and functional changes in the evaluated tissues, and in some cases, it influenced even at the protein expression level. In most of these studies the measurement of oxidative stress-associated parameters was in common (Abd-Ellah & Mariee, 2007; Amin et al., 2012; Astolfi, Simoni, Ciorba, & Martini, 2008; Daba et al., 2002; Erdogan et al., 2006; Esen et al., 2018; Hauns, Haring, Kohler, Mross, & Unger, 2001; Huang, Whitworth, & Rybak, 2007; Khafaga & Bayad, 2016; Liu et al., 2008; Marshall et al., 2004; Naidu, Vijay, Krishna, Sundaram, & Singh, 2002; Yeh et al., 2009).

All of the studies in the table below (Table 2) were carried out on the cells or animals with the exception of two studies conducted on humans by Hauns et al. (2001) and Marshall et al. (2004). The results of Hauns et al. clinical trial in which 44 patients with colorectal cancer were involved demonstrated that GBLE could even enhance the efficacy of chemotherapy with 5-FU, in addition to the reduction of the drug toxic effects and the increment of patient tolerability (Hauns et al., 2001). The limited number of cases in this study is a weakness point of it. Another clinical study also suggested the positive effect of GBLE on treatment efficacy and its alleviative influence on oxaliplatin-induced neurotoxicity (Marshall et al., 2004).

About 50-200 mg/kg of GBLE or EGb 761 were given to the animals in most studies; however, a very lower dose of this extract (5 mg/kg/dose) was used to assess its antidotal effects on doxorubicin cardiotoxicity and reproductive toxicity and it was significantly effective (Liu et al., 2008; Yeh et al., 2009). Because a similar study on doxorubicin-induced cardiotoxicity was done using 100 mg/kg of GB (Abd-Ellah & Mariee, 2007), the only conclusion is that the lower doses of EGb 761 than the usual doses have also enough potency to influence at least on doxorubicin toxicities.

5 | RADIATION

Based on previous studies, which have been mentioned below, GB has some protective effects on damages induced by different kinds of radiation to which humans are exposed in their lifetime, such as waves produced by cell phones and radioactive elements or scattered during radiotherapy, radiography, or even sunshine.

5.1 | Cell phone

Gevrek, Aydin, Ozsoy, Aygun, and Bicer (2017) demonstrated that intraperitoneal injection of 100 mg/kg/day of EGb761 reversed high testicular apoptotic index and the testis histomorphological changes and disturbances related to animal fertility, such as decreased sperm numbers and testosterone hormone level induced by cell phone

TABLE 2 Protective effects of G. *biloba* leaf extract against anticancer drugs

Drug	Investigated case/drug toxicity	Drug and GBLE dosing	G. *biloba* effects	References
Cisplatin	Wistar albino rat/ Ototoxicity	Cis.: 12 mg/kg, single dose, IP GBLE: 100 mg/kg/day, for 10 days, orally	Hearing enhancement (by Distortion product otoacoustic emission test) Histopathology improvement (in cochlea)	Esen et al. (2018)
	Albino rats/Reproductive toxicity	Cis.: acute: 24 mg/kg, single dose, IP Sub chronic: 6 mg/kg, once a week for 4 weeks GBLE: 150 mg/kg/day, totally for 30 days, orally	↑Motility (%), ↑number and ↓abnormal morphology of sperms (%) ↑Total weight of reproductive components ↑Serum testosterone level ↓MDA and ↑GSH peroxidase in acute toxicity and ↓ in sub-chronic toxicity (in testis) Mild histopathological improvement more in acute toxicity (in testis, epididymis, prostate)	Khafaga and Bayad (2016)
	Wistar rats/Reproductive toxicity	Cis.: 10 mg/kg, single dose, IP GBLE: 50, 100 and 150 mg/kg/day, for 5 days, orally	↑Motility (%) and ↑number of sperms In testis tissue: ↓MDA level, ↑CAT, ↓SOD and ↓MPO activity Histopathological improvement (in testis) ↓Apoptosis (by TUNEL test)	Amin et al. (2012)
	OCK-3 cell line/Ototoxicity	Cis.: 13 μM for 48 hours GBLE: Pre-treatment with 12.25, 25, 50, 100, 150, 200, 300 μg/ml for 2 and 24 hours	↓Apoptosis ↓DNA fragmentation No toxic effects by GB in Cell viability assay	Astolfi et al. (2008)
	Wistar rats/Ototoxicity	Cis.: 13 mg/kg, single dose, IP GBLE: 200 mg/kg, single dose, IP	reversion of the threshold shift in Auditory brain stem response ↑Endocochlear potential Intact Structure of the cochlea (by electron microscopy assessment)	Huang et al. (2007)
Doxorubicin	Sprague–Dawley rats/ reproductive toxicity	Dox.: 3 injections of 3 mg/kg, every 2 days, IP GBLE: 3 injection of 5 mg/kg, every 2 days, IP, a day before Dox injection	↑Sperm count ↑Body and testicular weight ↑Number and diameter of seminiferous tubules Histopathological improvement In testis tissue: ↓MDA and ↑GSH, ↑SOD, ↑GPX and ↓caspase-3 activity ↑Cu/Zn-SOD, ↑Bcl-2/Bcl2-Associated X Protein (Bax), ↓Apoptotic Protease Activating Factor 1 (Apaf-1) ↓Apoptosis (by TUNEL test) No sig. change in Fas receptor, tissue necrosis factor receptor 1(TNFR-1), tumour necrosis factor-related apoptosis-inducing ligand-1 (TRAIL-1), Bid, caspase-8 activity ↓Cytochrome-c release from mitochondria to cytoplasm ↑Testicular cell population by flow cytometry In serum: ↑Cu/Zn-SOD level and expression and ↑Mn-SOD level	Yeh et al. (2009)
	Sprague–Dawley rats/ myocytes/ cardiotoxicity	Dox.: animals: 3 injections of 3 mg/kg, every 2 days, IP Cells: 1μM for 24 hr GBLE: animals: 3 injections of 5 mg/kg, every 2 days, IP, a day before Dox injection Cells: 25μg/ml for 24 hr	In rat primary cultured myocytes: ↑Cell viability ↓Apoptosis (by flow cytometry analysis) Restoring the mitochondrial membrane potential ↓Cytochrome-c release from mitochondria to cytoplasm ↓Expression of P53 No sig. change in Fas receptor and Fas ligand expression (by RT-PCR) In both primary cells and heart tissue: ↓Apoptosis (by TUNEL test) ↑Bcl-2/Bax, ↓Bcl-2 agonist of cell death (Bad) ↓Caspase-3 activity	Liu et al. (2008)

(Continues)

TABLE 2 (Continued)

Drug	Investigated case/drug toxicity	Drug and GBLE dosing	G. *biloba* effects	References
	Sprague–Dawley rats/ hyperlipidemic nephrotoxicity	Dox.: 5 mg/kg, single dose, IV GBLE: 100 mg/kg/day, for 35 days, orally	In urine: ↓Total protein, ↓*N*-acetyl-*β*-D-glucosaminidase, ↓nitrite, ↑creatinin clearance In serum: Lipid profile improvement, ↓urea, ↑total protein In kidney: ↓MDA and ↑GSH level, ↑SOD and CAT activity,↓ nitrite	Abd-Ellah and Mariee (2007)
	Swiss Albino mice/ cardiotoxicity	Dox.: 4 mg/kg, once a week for 4 weeks, IP GBLX:100 mg/kg/day, for 4 weeks, orally	Enhancement of cardiac function (by Electrocardiography) Morphological improvement of myocytes (by electron microscopy assessement) ↓MDA level, ↑SOD and ↑CAT activity (in heart) ↑Total antioxidant activity (in heart and plasma)	Naidu et al. (2002)
Bleomycin	Sprague–Dawley rats/ plasma oxidative injuries	Ble.: 2.5 U/kg, single dose, intratracheal injection GBLE:100 mg/kg/day, for 14 days, orally	In serum: ↓MDA and ↓nitric oxide level ↑SOD, ↑GPx and ↓XO activity	Erdogan et al. (2006)
	Wistar albino rats/lung fibrosis	Ble.: 15 mg/kg, 3 times a week for 4 weeks, IP GBLE: 100 mg/kg, 3 times a week for 4 weeks, orally, a day after Bleomycin administration	↓tension of pulmonary arterial rings in response to serotonin ↓TNF-α in serum ↓MDA and collagen level in lung tissue	Daba et al. (2002)
5-Fluorouracil	Humans with advanced progressive colorectal cancer	5-FU: 500 mg/m^2/day, on day 2-6 in every course which was every 3 weeks, IV infusion for 30 min GBLE: 350 mg/day, on day 1-6 in every course which was every 3 weeks, IV infusion for 30 min before 5-FU injection	↑Treatment efficacy ↑Treatment tolerability ↑overall quality of life (EORTC-QLQ-C30 questionnaire)	Hauns et al. (2001)
Oxaliplatin	Humans with metastatic colorectal cancer/ neuropathy	OX.: FOLFOX or CAPEOX chemotherapy regimens GBLE: 120 mg/kg, 2 times a day, orally	↓Severity and duration of acute neuropathy (Neuropathy monitoring by Ox-specific neurotoxicity grading scale)	Marshall et al. (2004)

Note. ↓ or ↑, respectively, shows a significant decrease or increase in comparison with CCl_4-treated group. Cis.: cisplatin; Dox: doxorubicine; Bleo.: bleomycin; 5-FU: 5-Fluorouracil; Ox.: oxaliplatin.

electromagnetic radiation (0.96 W/kg for six weeks and 4 hr/day; Gevrek et al., 2017). Another study showed that long-term exposure of rats' brain to the cell phone radiofrequency increased cell apoptotic markers in the hippocampus region and GB decreased cell mortality (Gevrek, 2018). EGb761 has successfully been used as a preventive agent against morphological and structural destruction of genome, cytoplasm, and membrane of human lymphocytes exposed to simulated radiofrequency waves like cell phone radiation (1.8 GHz; Esmekaya et al., 2011).

5.2 | Radiotherapy/Radiography

Radiotherapy is the other source of radiation that may have some side effects or complications. In a study, radiotherapy was conducted with the dose of 36 Gy by means of cobalt-60 induced dermatitis in Wistar rats. Intraperitoneal administration of 100 mg/kg/day of EGb761 for 5 days significantly increased GSH and decreased MDA and NO levels in comparison with the control group. In addition, the percentage of animals with dermatitis- diminished from 100% in radiated group to 13% in EGb761-treated group. Thus, these changes supposed to be developed through inhibiting oxidative stress and free radicals by antioxidant effects of GBLE (Yirmibesoglu et al., 2012). Two similar studies displayed the antioxidant effect of oral GBLE (40 mg/kg/day) in the lens of rats exposed to cobalt gamma radiation of 5 Gy (Ertekin et al., 2004; Okumus et al., 2011). Ismail and El-Sonbaty (2016) showed that the fermentation of GB leaves can improve its bioactivity. Their fermentation method was based on indicated previous study of Zhang et al. (2012) by *A. niger*. The methanolic extraction of fermented and nonfermented GB leaves was analyzed by gas chromatography–mass spectrometry.

Comparison between contents of these two types of leaves demonstrated that all GB constituents were raised or even some compounds were produced after fermentation process, except isokaempferide, which was disappeared. In this research, rats were treated with GB leaves and its fermented form (50 mg/kg/day, intragastric), from 15 days before a single dose of gamma radiation (6 Gy). MDA, SOD, GPx, and GSH as antioxidant agents; catecholamines as the stress-related hormones; IL-1β and TNF-α gene expression as inflammatory signals; and DNA Fragmentation analysis were measured. The results exhibited that fermented form had more antiinflammatory, antiapoptotic, and antioxidative effects than intact form against radiation injuries; however, both types were significantly effective (Ismail & El-Sonbaty, 2016).

Technetium-99m as another gamma irradiating element has been used to induce the model of lens injury in rats. The oral administration of GBLE (0.11 mg/kg for 7 days before radiation) could compensate the lens-related oxidative injuries induced by intravenous injection of 1 mCi of ^{99}mTc-sestamibi (Khedr, Shafaa, Abdel-Ghaffar, & Saleh, 2018). Raafat et al. (2012) conducted another research with the similar method, but on the rat liver. The findings demonstrated that GBLE has the potential of protecting hepatocytes against oxidative stress, histopathological damages, and programmed cell death due to the Technetium-99m injection (Raafat, Saleh, Shafaa, Khedr, & Ghafaar, 2013).

Furthermore, the effect of GBLE on patients who treated with radioactive iodine-131 to ablate their thyroid tumour was assessed. It was mentioned that the iodine-131 can lead to genotoxicity associated with the generation of free radicals and ROS, which is identified by clastogenic factors and MN in peripheral blood lymphocytes. The increment of these factors was inhibited in a group of patients received GBLE (120 mg/day of Tanakan for 3 days before, up to one month after thyroid ablation) in concomitant with the main treatment (with the dose of 3.7 GBq or 100 mCi), and there was no detection of any side effects and changes in clinical outcome. Although, the authors declared as their study weakness point, that the dose of iodine therapy was twofold or higher than the standard amount (Dardano et al., 2012).

5.3 | Radioactive elements

The injection of 5 mg/kg of uranium developed toxicity in the liver and kidney of mice. It has been indicated that this toxicity is due to the oxidative stress because it increases MDA content and decreases GSH level. Two evaluated doses of GBLE (50 and 150 mg/kg/day for 5 days) had dose-dependent alleviative effects on hepatic and renal markers such as, AST, ALT, BUN, Cr, and reduced oxidative damages (decreased MDA and increased GSH; Yapar, Cavusoglu, Oruc, & Yalcin, 2010).

In Cavusoglu et al. (2009) investigation, an oral GBLE pretreatment (50 and 150 mg/kg/day) had antidotal effects against DNA damages and oxidative stress induced by uranium injection in mice (5 mg/kg; Çavuşolu et al., 2009).

5.4 | Ultraviolet

There is some evidence of protective effects of GBLE on topical injuries caused by ultraviolet (UV) radiation on skin.

In an in vivo experiment, 5-day oral administration of GBLE (100 mg/kg/day) was able to increase SOD activity after its decline in the dorsal animal skin by a single dose of 0.24 J/cm^2 of UV-B, which was irradiated to the back of mice for 8 min. It also increases Zink level, but it was not significant (Aricioglu et al., 2001). Dal Belo, Gaspar, and Maia Campos (2011) formulated a topical combination of glycolic extract of *G. biloba*, and green tea to evaluate its efficacy against subsequent outcomes of UV-A/UV-B radiation generated by a solar simulator in the animal skin, such as sunburn, skin thickness, erythema, transepidermal water loss (TEWL), and also dermohistological changes. These findings show that this combination possesses significant positive effects on all above-mentioned factors, and in some aspects like TEWL and erythema index, GB was more active than green tea and even the combination of both herbs. It was suggested that these two herbs did not have absorption of UV A/B and the effects are due to the antioxidant activity (Dal Belo et al., 2011). In addition, there is another research about GB topical formulation in combination with vitamins and red algae extract in order to assess their photoprotective capacity. This formulation had notable antiapoptotic and antiinflammatory influences in the skin of mice exposed to UV-A/B. Nevertheless, we cannot infer that how much of the favourable effects are caused by GB (Mercurio et al., 2015). In overall, based on reviewed articles, GB is a promising candidate for enhancing or preventing the injuries developed by radiation exposure mostly via reinforcement of tissue antioxidant capacity and prevention of DNA damage and apoptosis.

6 | CONCLUSION

Taken together, the effectiveness of GBLE was established against various types of intoxications, which were developed through exposure to some natural toxins, such as LPS, LPC, scorpion venom, lantadenes, cassava, gossypol, aflatoxin B1, and chemical toxic agents, such as metals, ethanol, pesticides, CCl_4, cigarette smoke, naphthalene, and monosodium glutamate and also the deleterious outcomes of different kinds of radiations. It is worthwhile to indicate that the fermentation of GB leaves increased its bioactivity in two studies.

In brief, GBLE attenuated the LPS toxicity in lung, CNS, cardiovascular system, kidney, intestine, ear, and eye via pathways of NF-κB, PGE-2, Cox-2, MAPKs, TLR-4, and HO-1. Refer to the most studies, the beneficial effects of this extract against almost all of the toxins are possibly exerted by its antioxidant capacity (decreasing of lipid peroxidation and restoring of GSH, GP_x, SOD, and CAT) and its antiinflammatory effects. The increment of HO, as a new antioxidant pathway, by GBLE was suggested in LPS, LPC, and ethanol toxicities. GBLE also has an AChE inhibiting effect in the cognitive disorder induced by Al in addition to its antioxidative influences. GBLE through regulation of JNK/AP-1 pathway and apoptosis also reduces the

toxicities of some agents. PDE is another target of GBLE to improve TET-induced cerebral oedema.

It is worthwhile to indicate that the bi-phasic pharmacological effect is a typical phenomenon in antioxidative substances, such as vitamin C, vitamin E, green tea polyphenols, and GBLE. The diverse effects might also be attributed to different concentrations, different cell types tested, different experimental conditions, etc. (Hou et al., 2008). By the way, antioxidant substances such as GB are often pro-oxidant in high doses (Lin et al., 2014).

Considering that the assessment of the possible injuries may be developed by substances under investigation is critical in addition to their beneficial effects; it is important to be mentioned that the International Agency for Research on Cancer has recently been reported that GBLE is in the Group 2B classification, which is referred to possible human carcinogens (Mei et al., 2017). Moreover, there are studies that were performed with the purpose of toxicological evaluation of GBLE in the animals, mice, and rats, in different GB doses, exposure duration, and animal sex. The results of the study of Rider et al. (2014) showed that the injuries in the liver, thyroid, and nose of animals were dose-, time-, and sex-dependent so that the serious destructive changes including tissue necrosis and atrophy developed in higher doses than 250 mg/kg in 3-month assessments. However, these kinds of severe injuries appeared in lower doses in 2-year assessments (Rider et al., 2014). Based on studies that focused on protective effects of GB, almost all protective doses of GBLE used in animals were lower than 250 mg/kg for several days or weeks. It demonstrates that in order to exploit the GB benefits, we should choose the optimum dose and duration of treatment.

However, a few clinical studies have been conducted about the present subject; the promising effects of this valuable herbal extract will practically remain useless without carrying out more clinical studies and also proving the predomination of its protective effects on its possible toxic effects in human beings.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

ORCID

Seyedeh Farzaneh Omidkhoda https://orcid.org/0000-0003-0049-906X

BiBi Marjan Razavi https://orcid.org/0000-0002-7450-9286

Hossein Hosseinzadeh https://orcid.org/0000-0002-3483-851X

REFERENCES

Abd-Elhady, R. M., Elsheikh, A. M., & Khalifa, A. E. (2013). Anti-amnestic properties of *Ginkgo biloba* extract on impaired memory function induced by aluminum in rats. *International journal of developmental neuroscience*, *31*(7), 598–607. https://doi.org/10.1016/j.ijdevneu.2013.07.006

Abd-Ellah, M. F., & Mariee, A. D. (2007). *Ginkgo biloba* leaf extract (EGb 761) diminishes adriamycin-induced hyperlipidaemic nephrotoxicity in rats: Association with nitric oxide production. *Biotechnology and Applied Biochemistry*, *46*(1), 35–40.

Amin, A., Abraham, C., Hamza, A. A., Abdalla, Z. A., Al-Shamsi, S. B., Harethi, S. S., & Daoud, S. (2012). A standardized extract of *Ginkgo biloba* neutralizes cisplatin-mediated reproductive toxicity in rats. *Journal of biomedicine & biotechnology*, *2012*, 362049.

Amitai, Y. (1998). Clinical manifestations and management of scorpion envenomation. *Public health reviews*, *26*(3), 257–263.

Aricioglu, A., Bozkurt, M., Balabanli, B., Kilinc, M., Nazaroglu, N. K., & Turkozkan, N. (2001). Changes in zinc levels and superoxide dismutase activities in the skin of acute, ultraviolet-B-irradiated mice after treatment with *Ginkgo biloba* extract. *Biological trace element research*, *80*(2), 175–179. https://doi.org/10.1385/BTER:80:2:175

Ashok, S. K., Somayaji, S. N., & Bairy, K. L. (2001). Hepatoprotective effects of *Ginkgo biloba* against carbon tetrachloride induced hepatic injury in rats. *Indian Journal of Pharmacology*, *33*(4), 260–266.

Astolfi, L., Simoni, E., Ciorba, A., & Martini, A. (2008). *In vitro* protective effects of *Ginkgo biloba* against cisplatin toxicity in mouse cell line OCk3. *Audiological Medicine*, *6*(4), 251–258. https://doi.org/10.1080/16513860802527930

Atmaca, N., Aksu, D., Yıldırım, E., & Atmaca, H. T. (2014). *Ginkgo biloba* extract (EGb 761) protects the mice brain against fluoride-induced oxidative stress. *Fresenius Environmental Bulletin*, *23*, 1790–1794.

Bernatoniene, J., Majiene, D., Peciura, R., Laukeviciene, A., Bernatoniene, R., Mekas, T., … Kopustinskiene, D. (2011). The effect of *Ginkgo biloba* extract on mitochondrial oxidative phosphorylation in the normal and ischemic rat heart. *Phytotherapy research*, *25*(7), 1054–1060. https://doi.org/10.1002/ptr.3399

Bernhoft, R. A. (2012). Mercury toxicity and treatment: A review of the literature. *Journal of environmental and public health*, *2012*, 460508.

Bernhoft, R. A. (2013). Cadmium toxicity and treatment. *Scientific World Journal*, *2013*, 394652.

Cao Z., Shao B., Xu F., Liu Y., Li Y., Zhu Y. (2017). Protective effect of selenium on aflatoxin B1-induced testicular toxicity in mice. *Biological trace element research*, *180*(2): 233-238, Protective Effect of Selenium on Aflatoxin B1-Induced Testicular Toxicity in Mice, DOI: https://doi.org/10.1007/s12011-017-0997-z.

Cavusoglu, K., Yapar, K., Kinalioglu, K., Turkmen, Z., Cavusoglu, K., & Yalcin, E. (2010). Protective role of *Ginkgo biloba* on petroleum wastewater-induced toxicity in Vicia faba L. (Fabaceae) root tip cells. *Journal of environmental biology*, *31*(3), 319–324.

Cavusoglu, K., Yapar, K., Oruc, E., & Yalcin, E. (2011). Protective effect of *Ginkgo biloba* L. leaf extract against glyphosate toxicity in Swiss albino mice. *Journal of medicinal food*, *14*(10), 1263–1272. https://doi.org/10.1089/jmf.2010.0202

Çavuşolu, K., Yapar, K., & Yalçin, E. (2009). Antioxidant potential of *Ginkgo biloba* leaf extract against uranium-induced genotoxicity and oxidative stress in albino mice. *Fresenius Environmental Bulletin*, *18*(9), 1551–1558.

Chan, W. H., & Hsuuw, Y. D. (2007). Dosage effects of ginkgolide B on ethanol-induced cell death in human hepatoma G2 cells. *Annals of the New York Academy of Sciences*, *1095*, 388–398. https://doi.org/10.1196/annals.1397.042

Chavez-Morales, R. M., Jaramillo-Juarez, F., Posadas del Rio, F. A., Reyes-Romero, M. A., Rodriguez-Vazquez, M. L., & Martinez-Saldana, M. C. (2011). Protective effect of *Ginkgo biloba* extract on liver damage by a single dose of CCl(4) in male rats. *Human & experimental toxicology*, *30*(3), 209–216. https://doi.org/10.1177/0960327110371698

Chavez-Morales, R. M., Jaramillo-Juarez, F., Rodriguez-Vazquez, M. L., Martinez-Saldana, M. C., Del Rio, F. A. P., & Garfias-Lopez, J. A. (2017). The *Ginkgo biloba* extract (GbE) protects the kidney from damage produced by a single and low dose of carbon tetrachloride in adult

male rats. *Experimental and toxicologic pathology*, *69*(7), 430–434. https://doi.org/10.1016/j.etp.2017.04.003

Chen, J. X., Zeng, H., Chen, X., Su, C. Y., & Lai, C. C. (2001). Induction of heme oxygenase-1 by *Ginkgo biloba* extract but not its terpenoids partially mediated its protective effect against lysophosphatidylcholine-induced damage. *Pharmacological research*, *43*(1), 63–69. https://doi.org/10.1006/phrs.2000.0753

Coskun, O., Armutcu, F., Kanter, M., & Kuzey, G. M. (2005). Protection of endotoxin-induced oxidative renal tissue damage of rats by vitamin E or/and EGb 761 treatment. *Journal of Applied Toxicology*, *25*(1), 8–12. https://doi.org/10.1002/jat.1002

Daba, M. H., Abdel-Aziz, A. A. H., Moustafa, A. M., Al-Majed, A. A., Al-Shabanah, O. A., & El-Kashef, H. A. (2002). Effects of L-carnitine and *Ginkgo biloba* extract (EGb 761) in experimental bleomycin-induced lung fibrosis. *Pharmacological Research*, *45*(6), 461–467. https://doi.org/10.1006/phrs.2002.0985

Dal Belo, S. E., Gaspar, L. R., & Maia Campos, P. M. (2011). Photoprotective effects of topical formulations containing a combination of *Ginkgo biloba* and green tea extracts. *Phytotherapy research*, *25*(12), 1854–1860. https://doi.org/10.1002/ptr.3507

Dardano, A., Ballardin, M., Caraccio, N., Boni, G., Traino, C., Mariani, G., … Monzani, F. (2012). The effect of *Ginkgo biloba* extract on genotoxic damage in patients with differentiated thyroid carcinoma receiving thyroid remnant ablation with iodine-131. *Thyroid*, *22*(3), 318–324. https://doi.org/10.1089/thy.2010.0398

de Souza Predes, F., Monteiro, J. C., Matta, S. L., Garcia, M. C., & Dolder, H. (2011). Testicular histomorphometry and ultrastructure of rats treated with cadmium and *Ginkgo biloba*. *Biological trace element research*, *140*(3), 330–341. https://doi.org/10.1007/s12011-010-8702-5

DeClementi, C., & Sobczak, B. R. (2018). Common rodenticide toxicoses in small animals. The Veterinary clinics of North America. *Small animal practice*, *48*(6), 1027–1038. https://doi.org/10.1016/j.cvsm.2018.06.006

Dorman, D. C., Cote, L. M., & Buck, W. B. (1992). Effects of an extract of *Gingko biloba* on bromethalin-induced cerebral lipid peroxidation and edema in rats. *American journal of veterinary research*, *53*(1), 138–142.

Dorri, M., Hashemitabar, S., & Hosseinzadeh, H. (2018). Cinnamon (*Cinnamomum zeylanicum*) as an antidote or a protective agent against natural or chemical toxicities: a review. *Drug and chemical toxicology*, *41*(3), 338–351. https://doi.org/10.1080/01480545.2017.1417995

Elatrash, A. M., & Abd El-Haleim, S. Z. (2015). Protective role of *Ginkgo biloba* on monosodium glutamate: Induced liver and kidney toxicity in rats. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, *6*(1), 1433–1441.

Erdogan, H., Fadillioglu, E., Kotuk, M., Iraz, M., Tasdemir, S., Oztas, Y., & Yildirim, Z. (2006). Effects of *Ginkgo biloba* on plasma oxidant injury induced by bleomycin in rats. *Toxicology and industrial health*, *22*(1), 47–52. https://doi.org/10.1191/0748233706th245oa

Ergun, U., Yurtcu, E., & Ergun, M. A. (2005). Protective effect of ginkgo biloba against gossypol-induced apoptosis in human lymphocytes. *Cell biology international*, *29*(8), 717–720. https://doi.org/10.1016/j.cellbi.2005.04.005

Ertekin, M. V., Kocer, I., Karslioglu, I., Taysi, S., Gepdiremen, A., Sezen, O., … Bakan, N. (2004). Effects of oral *Ginkgo biloba* supplementation on cataract formation and oxidative stress occurring in lenses of rats exposed to total cranium radiotherapy. *Japanese journal of ophthalmology*, *48*(5), 499–502. https://doi.org/10.1007/s10384-004-0101-z

Esen, E., Ozdogan, F., Gurgen, S. G., Ozel, H. E., Baser, S., Genc, S., & Selçuk, A. (2018). *Ginkgo biloba* and lycopene are effective on cisplatin induced ototoxicity? *The journal of international advanced otology*, *14*(1), 22–26. https://doi.org/10.5152/iao.2017.3137

Esmekaya, M. A., Aytekin, E., Ozgur, E., Guler, G., Ergun, M. A., Omeroglu, S., & Seyhan, N. (2011). Mutagenic and morphologic impacts of 1.8GHz radiofrequency radiation on human peripheral blood lymphocytes (hPBLs) and possible protective role of pre-treatment with Ginkgo biloba (EGb 761). *The Science of the total environment*, *410-411*, 59–64. https://doi.org/10.1016/j.scitotenv.2011.09.036

Fanoudi, S., Alavi, M. S., Karimi, G., & Hosseinzadeh, H. (2018). Milk thistle (*Silybum marianum*) as an antidote or a protective agent against natural or chemical toxicities: a review. *Drug and chemical toxicology*, 1–15. https://doi.org/10.1080/01480545.2018.1485687

Fatani, A. J., Al-Zuhair, H. A., Yaquob, H. I., Abdel-Fattah, A. A., El-Sayed, M. I., & El-Sayed, F. A. (2006). Protective effects of the antioxidant *Ginkgo biloba* extract and the protease inhibitor aprotinin against *Leiurus quinquestriatus* venom-induced tissue damage in rats. *Journal of Venomous Animals and Toxins including Tropical Diseases*, *12*, 255–275.

Finkler, A. D., Silveira, A. F., Munaro, G., & Zanrosso, C. D. (2012). Otoprotection in guinea pigs exposed to pesticides and *Ginkgo biloba*. *Brazilian journal of otorhinolaryngology*, *78*(3), 122–128. https://doi.org/10.1590/S1808-86942012000300020

Gargouri, B., Carstensen, J., Bhatia, H. S., Huell, M., Dietz, G. P. H., & Fiebich, B. L. (2018). Anti-neuroinflammatory effects of *Ginkgo biloba* extract EGb761 in LPS-activated primary microglial cells. *Phytomedicine*, *44*, 45–55. https://doi.org/10.1016/j.phymed.2018.04.009

Gevrek, F. (2018). Histopathological, immunohistochemical, and stereological analysis of the effect of *Ginkgo biloba* (Egb761) on the hippocampus of rats exposed to long-term cellphone radiation. *Histology and histopathology*, *33*(5), 463–473.

Gevrek, F., Aydin, D., Ozsoy, S., Aygun, H., & Bicer, C. (2017). Inhibition by Egb761 of the effect of cellphone radiation on the male reproductive system. *Bratislavske lekarske listy*, *118*(11), 676–683. https://doi.org/10.4149/BLL_2017_128

Gong, Q. H., Wu, Q., Huang, X. N., Sun, A. S., Nie, J., & Shi, J. S. (2006). Protective effect of Ginkgo biloba leaf extract on learning and memory deficit induced by aluminum in model rats. *Chinese journal of integrative medicine*, *12*(1), 37–41.

Gong, Q. H., Wu, Q., Huang, X. N., Sun, A. S., & Shi, J. S. (2005). Protective effects of *Ginkgo biloba* leaf extract on aluminum-induced brain dysfunction in rats. *Life sciences*, *77*(2), 140–148. https://doi.org/10.1016/j.lfs.2004.10.067

Hajirezaee, S., Rafieepour, A., Shafiei, S., & Rahimi, R. (2019). Immunostimulating effects of *Ginkgo biloba* extract against toxicity induced by organophosphate pesticide, diazinon in rainbow trout, Oncorhynchus mykiss: innate immunity components and immune-related genes. *Environmental science and pollution research international.*, *26*, 8798–8807. https://doi.org/10.1007/s11356-019-04327-7

Hao, Y. R., Yang, F., Cao, J., ou, C., Zhang, J. J., Duan, X. X., et al. (2008). Protective effect of *Ginkgo biloba* extract on cytotoxicity induced by aflatoxin B1 in HepG2 cells. 15, 1796–1799.

Hao, Y. R., Yang, F., Cao, J., Ou, C., Zhang, J. J., Yang, C., … Su, J. J. (2009). *Ginkgo biloba* extracts (EGb761) inhibits aflatoxin B1-induced hepatocarcinogenesis in Wistar rats. *Journal of Chinese medicinal materials*, *32*(1), 92–96.

Hauns, B., Haring, B., Kohler, S., Mross, K., & Unger, C. (2001). Phase II study of combined 5-fluorouracil/*Ginkgo biloba* extract (GBE 761 ONC) therapy in 5-fluorouracil pretreated patients with advanced colorectal cancer. *Phytotherapy Research*, *15*(1), 34–38. https://doi.org/10.1002/1099-1573(200102)15:1<34::AID-PTR755>3.0.CO;2-2

Hosseini, A., & Hosseinzadeh, H. (2018). Antidotal or protective effects of *Curcuma longa* (turmeric) and its active ingredient, curcumin, against natural and chemical toxicities: A review. *Biomedicine & pharmacotherapy*, *99*, 411–421. https://doi.org/10.1016/j.biopha.2018.01.072

Hou, R. R., Chen, J. Z., Chen, H., Kang, X. G., Li, M. G., & Wang, B. R. (2008). Neuroprotective effects of (−)-epigallocatechin-3-gallate (EGCG) on paraquat-induced apoptosis in PC12 cells. *Cell Biology International*, *32*, 22–30. https://doi.org/10.1016/j.cellbi.2007.08.007

Huang, C. H., Yang, M. L., Tsai, C. H., Li, Y. C., Lin, Y. J., & Kuan, Y. H. (2013). Ginkgo biloba leaves extract (EGb 761) attenuates lipopolysaccharide-induced acute lung injury via inhibition of oxidative stress and NF-kappaB-dependent matrix metalloproteinase-9 pathway. *Phytomedicine*, *20*(3-4), 303–309. https://doi.org/10.1016/j.phymed.2012.11.004

Huang, X., Whitworth, C. A., & Rybak, L. P. (2007). *Ginkgo biloba* extract (EGb 761) protects against cisplatin-induced ototoxicity in rats. *Otology & neurotology*, *28*(6), 828–833. https://doi.org/10.1097/MAO.0b013e3180430163

Husarova, V., & Ostatnikova, D. (2013). Monosodium Glutamate Toxic Effects and Their Implications for Human Intake: A Review. *JMED Research*, *2013*(2013), 1–12.

Ihl, R., Bachinskaya, N., Korczyn, A. D., Vakhapova, V., Tribanek, M., Hoerr, R., … Napryeyenko O, GOTADAY Study Group (2011). Efficacy and safety of a once-daily formulation of *Ginkgo biloba* extract EGb 761 in dementia with neuropsychiatric features: A randomized controlled trial. *International journal of geriatric psychiatry*, *26*(11), 1186–1194.

Ilieva, I., Ohgami, K., Shiratori, K., Koyama, Y., Yoshida, K., Kase, S., … Ohno, S. (2004). The effects of Ginkgo biloba extract on lipopolysaccharide-induced inflammation *in vitro* and in vivo. *Experimental eye research*, *79*(2), 181–187. https://doi.org/10.1016/j.exer.2004.03.009

Ismail, A. F., & El-Sonbaty, S. M. (2016). Fermentation enhances *Ginkgo biloba* protective role on gamma-irradiation induced neuroinflammatory gene expression and stress hormones in rat brain. Journal of photochemistry and photobiology. *B, Biology*, *158*, 154–163.

Jang, C. H., Cho, Y. B., Kim, J. S., Cho, S. W., Yang, H. C., Jung, K. H., … Kang, S. I. (2011). Effect of Ginkgo biloba extract on endotoxin-induced labyrinthitis. *International journal of pediatric otorhinolaryngology*, *75*(7), 905–909. https://doi.org/10.1016/j.ijporl.2011.04.003

Jang, S. H., Lee, E. K., Lim, M. J., Hong, N. J., Oh, I. S., Jin, Y. W., … Jang, Y. S. (2012). Suppression of lipopolysaccharide-induced expression of inflammatory indicators in RAW 264.7 macrophage cells by extract prepared from Ginkgo biloba cambial meristematic cells. *Pharmaceutical biology*, *50*(4), 420–428. https://doi.org/10.3109/13880209.2011.610805

Kang, X., Chen, J., Xu, Z., Li, H., & Wang, B. (2007). Protective effects of *Ginkgo biloba* extract on paraquat-induced apoptosis of PC12 cells. *Toxicology in vitro*, *21*(6), 1003–1009. https://doi.org/10.1016/j.tiv.2007.02.004

Keheyan, G., Dunn, L. A., & Hall, W. L. (2011). Acute effects of *Ginkgo biloba* extract on vascular function and blood pressure. *Plant foods for human nutrition*, *66*(3), 209–211. https://doi.org/10.1007/s11130-011-0234-4

Khafaga, A. F., & Bayad, A. E. (2016). Impact of *Ginkgo biloba* extract on reproductive toxicity induced by single or repeated injection of cisplatin in adult male rats. *International Journal of Pharmacology*, *12*(4), 340–350. https://doi.org/10.3923/ijp.2016.340.350

Khedr, M. H., Shafaa, M. W., Abdel-Ghaffar, A., & Saleh, A. (2018). Radioprotective efficacy of Ginkgo biloba and Angelica archangelica extract against technetium-99m-sestamibi induced oxidative stress and lens injury in rats. *International journal of radiation biology*, *94*(1), 37–44. https://doi.org/10.1080/09553002.2018.1407463

Kurisaki, E. (1989). Lung toxicity of Paraquat. *Eisei kagaku*, *35*(4), 261–272. https://doi.org/10.1248/jhs1956.35.261

Lakshmi, B. V., Sudhakar, M., & Prakash, K. S. (2015). Protective effect of selenium against aluminum chloride-induced Alzheimer's disease: Behavioral and biochemical alterations in rats. *Biological trace element research*, *165*(1), 67–74. https://doi.org/10.1007/s12011-015-0229-3

Lari, P., Abnous, K., Imenshahidi, M., Rashedinia, M., Razavi, M., & Hosseinzadeh, H. (2015). Evaluation of diazinon-induced hepatotoxicity and protective effects of crocin. *Toxicology and industrial health*, *31*(4), 367–376. https://doi.org/10.1177/0748233713475519

Lee, C. Y., Yang, J. J., Lee, S. S., Chen, C. J., Huang, Y. C., Huang, K. H., & Kuan, Y. H. (2014). Protective effect of *Ginkgo biloba* leaves extract, EGb761, on endotoxin-induced acute lung injury via a JNK- and Akt-dependent NFkappaB pathway. *Journal of agricultural and food chemistry*, *62*(27), 6337–6344. https://doi.org/10.1021/jf501913b

Lee, Y. W., Lin, J. A., Chang, C. C., Chen, Y. H., Liu, P. L., Lee, A. W., … Lin, F. Y. (2011). *Ginkgo biloba* extract suppresses endotoxin-mediated monocyte activation by inhibiting nitric oxide- and tristetraprolin-mediated toll-like receptor 4 expression. *The Journal of nutritional biochemistry*, *22*(4), 351–359. https://doi.org/10.1016/j.jnutbio.2010.03.002

Li Y., Wu Y., Yao X., Hao F., Yu C., Bao Y., Wu Y., Song Z., Sun Y., Zheng L., Wang G., Huang Y., Sun L., Li Y. (2017). Ginkgolide A ameliorates LPS-induced inflammatory responses *in vitro* and in vivo. *International Journal of Molecular Sciences*, *18*(4): 794, Ginkgolide A Ameliorates LPS-Induced Inflammatory Responses In Vitro and In Vivo, DOI: https://doi.org/10.3390/ijms18040794.

Liao, H. J., Zheng, Y. F., Li, H. Y., & Peng, G. P. (2011). Two new ginkgolides from the leaves of *Ginkgo biloba*. *Planta medica*, *77*(16), 1818–1821. https://doi.org/10.1055/s-0030-1271153

Lin, F. Y., Chen, Y. H., Chen, Y. L., Wu, T. C., Li, C. Y., Chen, J. W., & Lin, S. J. (2007). *Ginkgo biloba* extract inhibits endotoxin-induced human aortic smooth muscle cell proliferation via suppression of toll-like receptor 4 expression and NADPH oxidase activation. *Journal of agricultural and food chemistry*, *55*(5), 1977–1984. https://doi.org/10.1021/jf062945r

Lin, H., Guo, X., Zhang, S., Dial, S. L., Guo, L., Manjanatha, M. G., … Mei, N. (2014). Mechanistic evaluation of *Ginkgo biloba* leaf extract-induced genotoxicity in L5178Y cells. *Toxicological Sciences*, *139*(2), 338–349. https://doi.org/10.1093/toxsci/kfu037

Lione, A. (1983). The prophylactic reduction of aluminium intake. *Food and chemical toxicology*, *21*(1), 103–109. https://doi.org/10.1016/0278-6915(83)90277-6

Liu, T. J., Yeh, Y. C., Ting, C. T., Lee, W. L., Wang, L. C., Lee, H. W., … Lai, H. C. (2008). *Ginkgo biloba* extract 761 reduces doxorubicin-induced apoptotic damage in rat hearts and neonatal cardiomyocytes. *Cardiovascular Research*, *80*(2), 227–235. https://doi.org/10.1093/cvr/cvn192

Macovschi, O., Prigent, A. F., Nemoz, G., & Pacheco, H. (1987). Effects of an extract of Ginkgo biloba on the 3',5'-cyclic AMP phosphodiesterase activity of the brain of normal and triethyltin-intoxicated rats. *Journal of neurochemistry*, *49*(1), 107–114. https://doi.org/10.1111/j.1471-4159.1987.tb03401.x

Manibusan, M. K., Odin, M., & Eastmond, D. A. (2007). Postulated carbon tetrachloride mode of action: A review. *Journal of environmental science and health. Part C, Environmental carcinogenesis & ecotoxicology reviews*, *25*(3), 185–209. https://doi.org/10.1080/10590500701569398

Maret, W. (2017). The bioinorganic chemistry of lead in the context of its toxicity. *Metal ions in life sciences*, *17*.

Marshall J., Zakari A., Hwang J.J., Papadopoulos V., Rosenberg A., Silver C. (2004). Ginkgo Biloba (GB) extract as a neuroprotective agent in oxaliplatin (Ox)-induced neuropathy. *Journal of Clinical Oncology*, 22(14_suppl): 3670-3670.

Matsumoto, T., Kobayashi, T., & Kamata, K. (2007). Role of lysophosphatidylcholine (LPC) in atherosclerosis. *Current medicinal chemistry*, *14*(30), 3209–3220. https://doi.org/10.2174/092986707782793899

Mei, N., Guo, X., Ren, Z., Kobayashi, D., Wada, K., & Guo, L. (2017). Review of *Ginkgo biloba*-induced toxicity, from experimental studies to human case reports. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*, *35*(1), 1–28. https://doi.org/10.1080/10590501.2016.1278298

Mercurio, D. G., Wagemaker, T. A., Alves, V. M., Benevenuto, C. G., Gaspar, L. R., & Maia Campos, P. M. (2015). In vivo photoprotective effects of cosmetic formulations containing UV filters, vitamins, *Ginkgo biloba* and red algae extracts. *Journal of photochemistry and photobiology. B, Biology*, *153*, 121–126. https://doi.org/10.1016/j.jphotobiol.2015.09.016

Mohamed, N. E., & Abd El-Moneim, A. E. (2017). *Ginkgo biloba* extract alleviates oxidative stress and some neurotransmitters changes induced by aluminum chloride in rats. *Nutrition*, *35*, 93–99. https://doi.org/10.1016/j.nut.2016.10.012

Mohammadzadeh, N., Mehri, S., & Hosseinzadeh, H. (2017). Berberis vulgaris and its constituent berberine as antidotes and protective agents against natural or chemical toxicities. *Iranian journal of basic medical sciences*, *20*(5), 538–551. https://doi.org/10.22038/IJBMS.2017.8678

Mohanta, T. K., Tamboli, Y., & Zubaidha, P. K. (2014). Phytochemical and medicinal importance of *Ginkgo biloba* L. *Natural product research*, *28*(10), 746–752. https://doi.org/10.1080/14786419.2013.879303

van Beek T.A., Montoro P. (2009). Chemical analysis and quality control of *Ginkgo biloba* leaves, extracts, and phytopharmaceuticals. *Journal of chromatography. A*, *1216*(11): 2002-2032.

Naidu, M. U. R., Vijay, K. K., Krishna, M. I., Sundaram, C., & Singh, S. (2002). Protective effect of *Gingko biloba* extract against doxorubicin-induced cardiotoxicity in mice. *Indian Journal of Experimental Biology*, *40*(8), 894–900.

Naik, S. R., & Panda, V. S. (2007). Antioxidant and hepatoprotective effects of *Ginkgo biloba* phytosomes in carbon tetrachloride-induced liver injury in rodents. *Liver international*, *27*(3), 393–399. https://doi.org/10.1111/j.1478-3231.2007.01463.x

Okumus, S., Taysi, S., Orkmez, M., Saricicek, E., Demir, E., Adli, M., & al, B. (2011). The effects of oral *Ginkgo biloba* supplementation on radiation-induced oxidative injury in the lens of rat. *Pharmacognosy magazine*, *7*(26), 141–145. https://doi.org/10.4103/0973-1296.80673

Otani, M., Chatterjee, S. S., Gabard, B., & Kreutzberg, G. W. (1986). Effect of an extract of *Ginkgo biloba* on triethyltin-induced cerebral edema. *Acta neuropathologica*, *69*(1-2), 54–65. https://doi.org/10.1007/BF00687039

Parimoo, H. A., Sharma, R., Patil, R. D., Sharma, O. P., Kumar, P., & Kumar, N. (2014). Hepatoprotective effect of *Ginkgo biloba* leaf extract on lantadenes-induced hepatotoxicity in guinea pigs. *Toxicon*, *81*, 1–12. https://doi.org/10.1016/j.toxicon.2014.01.013

Park, Y. M., Won, J. H., Yun, K. J., Ryu, J. H., Han, Y. N., Choi, S. K., & Lee, K. T. (2006). Preventive effect of *Ginkgo biloba* extract (GBB) on the lipopolysaccharide-induced expressions of inducible nitric oxide synthase and cyclooxygenase-2 via suppression of nuclear factor-kappaB in RAW 264.7 cells. *Biological & pharmaceutical bulletin*, *29*(5), 985–990. https://doi.org/10.1248/bpb.29.985

Peterson, M. E. (2013). Bromethalin. *Topics in companion animal medicine*, *28*(1), 21–23. https://doi.org/10.1053/j.tcam.2013.03.005

Qiu, P., Li, X., Kong, D. S., Li, H. Z., Niu, C. C., & Pan, S. H. (2015). Herbal SGR formula prevents acute ethanol-induced liver steatosis via inhibition of lipogenesis and enhancement fatty acid oxidation in mice. *Evidence-based Complementary and Alternative Medicine*, 2015.

Raafat, B. M., Saleh, A., Shafaa, M. W., Khedr, M., & Ghafaar, A. A. (2013). *Ginkgo biloba* and *Angelica archangelica* bring back an impartial hepatic apoptotic to anti-apoptotic protein ratio after exposure to technetium 99mTc. *Toxicology and industrial health*, *29*(1), 14–22. https://doi.org/10.1177/0748233711433938

Rameshrad, M., Razavi, B. M., & Hosseinzadeh, H. (2017). Protective effects of green tea and its main constituents against natural and chemical toxins: A comprehensive review. *Food and chemical toxicology*, *100*, 115–137. https://doi.org/10.1016/j.fct.2016.11.035

Razavi, B. M., & Hosseinzadeh, H. (2015). Saffron as an antidote or a protective agent against natural or chemical toxicities. *Daru*, *23*, 31. https://doi.org/10.1186/s40199-015-0112-y

Razavi, B. M., Hosseinzadeh, H., Abnous, K., & Imenshahidi, M. (2014). Protective effect of crocin on diazinon induced vascular toxicity in subchronic exposure in rat aorta ex-vivo. *Drug and chemical toxicology*, *37*(4), 378–383. https://doi.org/10.3109/01480545.2013.866139

Razavi, B. M., Hosseinzadeh, H., Abnous, K., Khoei, A., & Imenshahidi, M. (2016). Protective effect of crocin against apoptosis induced by subchronic exposure of the rat vascular system to diazinon. *Toxicology and industrial health*, *32*(7), 1237–1245. https://doi.org/10.1177/0748233714554941

Razavi, B. M., Hosseinzadeh, H., Movassaghi, A. R., Imenshahidi, M., & Abnous, K. (2013). Protective effect of crocin on diazinon induced cardiotoxicity in rats in subchronic exposure. *Chemico-biological interactions*, *203*(3), 547–555. https://doi.org/10.1016/j.cbi.2013.03.010

Rider, C. V., Nyska, A., Cora, M. C., Kissling, G. E., Smith, C., Travlos, G. S., … Chan, P. C. (2014). Toxicity and carcinogenicity studies of Ginkgo biloba extract in rat and mouse: Liver, thyroid, and nose are targets. *Toxicologic pathology*, *42*(5), 830–843. https://doi.org/10.1177/0192623313501235

Rivadeneyra-Dominguez, E., Vazquez-Luna, A., Rodriguez-Landa, J. F., & Diaz-Sobac, R. (2013). Neurotoxic effect of linamarin in rats associated with cassava (*Manihot esculenta* Crantz) consumption. *Food and chemical toxicology*, *59*, 230–235. https://doi.org/10.1016/j.fct.2013.06.004

Rusyn, I., & Bataller, R. (2013). Alcohol and toxicity. *Journal of hepatology*, *59*(2), 387–388. https://doi.org/10.1016/j.jhep.2013.01.035

Ryu, E. Y., Park, A. J., Park, S. Y., Park, S. H., Eom, H. W., Kim, Y. H., … Lee, S. J. (2012). Inhibitory effects of Ginkgo biloba extract on inflammatory mediator production by Porphyromonas gingivalis lipopolysaccharide in murine macrophages via Nrf-2 mediated heme oxygenase-1 signaling pathways. *Inflammation*, *35*(4), 1477–1486. https://doi.org/10.1007/s10753-012-9461-6

Sakr, S. A., Mahran, H. A., & Abdel-Maksoud, A. M. (2011). Suppressive effect of ginkgo biloba extract (egb 761) on topsin induced ovarian toxicity and oxidative stress in albino rats. *Journal of Applied Pharmaceutical Science*, *1*(4), 46–54.

Saleem, S., Zhuang, H., Biswal, S., Christen, Y., & Dore, S. (2008). Ginkgo biloba extract neuroprotective action is dependent on heme oxygenase 1 in ischemic reperfusion brain injury. *Stroke*, *39*(12), 3389–3396. https://doi.org/10.1161/STROKEAHA.108.523480

Santana, A. T., Guelfi, M., Medeiros, H. C. D., Tavares, M. A., Bizerra, P. F. V., & Mingatto, F. E. (2015). Mechanisms involved in reproductive damage caused by gossypol in rats and protective effects of vitamin E. *Biological research*, *48*(1), 43–43. https://doi.org/10.1186/s40659-015-0026-7

Singh, S. K., Barreto, G. E., Aliev, G., & Echeverria, V. (2017). *Ginkgo biloba* as an alternative medicine in the treatment of anxiety in dementia and other psychiatric disorders. *Current drug metabolism*, *18*(2), 112–119. https://doi.org/10.2174/1389200217666161201112206

Spencer, J. P. (2009). Flavonoids and brain health: Multiple effects underpinned by common mechanisms. *Genes & nutrition*, *4*(4), 243–250. https://doi.org/10.1007/s12263-009-0136-3

Stackman, R. W., Eckenstein, F., Frei, B., Kulhanek, D., Nowlin, J., & Quinn, J. F. (2003). Prevention of age-related spatial memory deficits in a transgenic mouse model of Alzheimer's disease by chronic Ginkgo biloba treatment. *Experimental neurology*, *184*(1), 510–520. https://doi.org/10.1016/S0014-4886(03)00399-6

Sun, R., Zhang, H., Si, Q., & Wang, S. (2002). Protective effect of Ginkgo biloba extract on acute lung injury induced by lipopolysaccharide in D-galactose aging rats. *Chinese journal of tuberculosis and respiratory diseases*, *25*(6), 352–355.

Tabeshpour, J., Mehri, S., Shaebani, B. F., & Hosseinzadeh, H. (2018). Protective effects of Vitis vinifera (grapes) and one of its biologically active constituents, resveratrol, against natural and chemical toxicities: A comprehensive review. *Phytotherapy research*, *32*(11), 2164–2190. https://doi.org/10.1002/ptr.6168

Tang, Y., Zhou, G., Yao, L., Xue, P., Yu, D., Xu, R., … Duan, J. A. (2017). Protective effect of Ginkgo biloba leaves extract, EGb761, on myocardium injury in ischemia reperfusion rats via regulation of TLR-4/NF-κB signaling pathway. *Oncotarget*, *8*(49), 86671–86680. https://doi.org/10.18632/oncotarget.21372

Tavakkoli, A., Ahmadi, A., Razavi, B. M., & Hosseinzadeh, H. (2017). Black seed (Nigella Sativa) and its constituent thymoquinone as an antidote or a protective agent against natural or chemical toxicities. *Iranian journal of pharmaceutical research*, *16*(Suppl), 2–23.

Tozan, A., Sehirli, O., Omurtag, G. Z., Cetinel, S., Gedik, N., & Sener, G. (2007). *Ginkgo biloba* extract reduces naphthalene-induced oxidative damage in mice. *Phytotherapy research*, *21*(1), 72–77. https://doi.org/10.1002/ptr.2027

Wadsworth, T. L., & Koop, D. R. (2001). Effects of *Ginkgo biloba* extract (EGb 761) and quercetin on lipopolysaccharide-induced release of nitric oxide. *Chemico-biological interactions*, *137*(1), 43–58. https://doi.org/10.1016/S0009-2797(01)00208-3

Wadsworth, T. L., McDonald, T. L., & Koop, D. R. (2001). Effects of *Ginkgo biloba* extract (EGb 761) and quercetin on lipopolysaccharide-induced signaling pathways involved in the release of tumor necrosis factor-alpha. *Biochemical pharmacology*, *62*(7), 963–974. https://doi.org/10.1016/S0006-2952(01)00734-1

Wang, C., Dai, Y., Feng, G., Yang, W., He, R., Zhou, X., … Tan, L. (2011). *Gingko biloba* extract and cobalt porphyrin additive to remove harmful components from cigarette smoke and reduce its toxicity. *Toxicological and Environmental Chemistry*, *93*(10), 2111–2122. https://doi.org/10.1080/02772248.2011.626419

Wang, C. G., Dai, Y., Li, D. L., & Ma, K. Y. (2010). *Ginkgo biloba* leaf extract action in scavenging free radicals and reducing mutagenicity and toxicity of cigarette smoke in vivo. *Journal of Environmental Science and Health - Part A Toxic/Hazardous Substances and Environmental Engineering*, *45*(4), 498–505.

Weber, L. W., Boll, M., & Stampfl, A. (2003). Hepatotoxicity and mechanism of action of haloalkanes: Carbon tetrachloride as a toxicological model. *Critical reviews in toxicology*, *33*(2), 105–136. https://doi.org/10.1080/713611034

Wu, F., Shi, W., Zhou, G., Yao, H., Xu, C., Xiao, W., … Wu, X. (2016). Ginkgolide B functions as a determinant constituent of Ginkgolides in alleviating lipopolysaccharide-induced lung injury. *Biomedicine & pharmacotherapy*, *81*, 71–78. https://doi.org/10.1016/j.biopha.2016.03.048

Yallapragada P.R., Velaga M.K. (2015). Effect of *Ginkgo biloba* extract on lead-induced oxidative stress in different regions of rat brain. *Journal of environmental pathology, toxicology and oncology*, *34*(2): 161-173, Effect of Ginkgo biloba Extract on Lead-Induced Oxidative Stress in Different Regions of Rat Brain, DOI: https://doi.org/10.1615/JEnvironPatholToxicolOncol.2015013095.

Yang, L., Wang, C. Z., Ye, J. Z., & Li, H. T. (2011). Hepatoprotective effects of polyprenols from *Ginkgo biloba* L. leaves on CCl4-induced hepatotoxicity in rats. *Fitoterapia*, *82*(6), 834–840. https://doi.org/10.1016/j.fitote.2011.04.009

Yao, P., Hao, L., Nussler, N., Lehmann, A., Song, F., Zhao, J., … Nussler, A. (2009). The protective role of HO-1 and its generated products (CO, bilirubin, and Fe) in ethanol-induced human hepatocyte damage. *American journal of physiology. Gastrointestinal and liver physiology*, *296*(6), G1318–G1323. https://doi.org/10.1152/ajpgi.00555.2007

Yao, P., Li, K., Song, F., Zhou, S., Sun, X., Zhang, X., … Liu, L. (2007). Heme oxygenase-1 upregulated by *Ginkgo biloba* extract: Potential protection against ethanol-induced oxidative liver damage. *Food and Chemical Toxicology*, *45*(8), 1333–1342. https://doi.org/10.1016/j.fct.2007.01.016

Yao, X., Chen, N., Ma, C. H., Tao, J., Bao, J. A., Zong-Qi, C., … Li-Yan, M. I. (2015). *Ginkgo biloba* extracts attenuate lipopolysaccharide-induced inflammatory responses in acute lung injury by inhibiting the COX-2 and NF-kappaB pathways. *Chinese journal of natural medicines*, *13*(1), 52–58. https://doi.org/10.1016/S1875-5364(15)60006-1

Yapar, K., Cavusoglu, K., Oruc, E., & Yalcin, E. (2010). Protective role of *Ginkgo biloba* against hepatotoxicity and nephrotoxicity in uranium-treated mice. *Journal of medicinal food*, *13*(1), 179–188. https://doi.org/10.1089/jmf.2009.0028

Yeh, K. Y., Shou, S. S., Lin, Y. X., Chen, C. C., Chiang, C. Y., & Yeh, C. Y. (2015). Effect of *Ginkgo biloba* extract on lipopolysaccharide-induced anhedonic depressive-like behavior in male rats. *Phytotherapy research*, *29*(2), 260–266. https://doi.org/10.1002/ptr.5247

Yeh, Y. C., Liu, T. J., Wang, L. C., Lee, H. W., Ting, C. T., Lee, W. L., … Lai, H. C. (2009). A standardized extract of *Ginkgo biloba* suppresses doxorubicin-induced oxidative stress and p53-mediated mitochondrial apoptosis in rat testes. *British Journal of Pharmacology*, *156*(1), 48–61. https://doi.org/10.1111/j.1476-5381.2008.00042.x

Yirmibesoglu, E., Karahacioglu, E., Kilic, D., Lortlar, N., Akbulut, G., & Omeroglu, S. (2012). The protective effects of *Ginkgo biloba* extract (EGb-761) on radiation-induced dermatitis: An experimental study. *Clinical and experimental dermatology*, *37*(4), 387–394. https://doi.org/10.1111/j.1365-2230.2011.04253.x

Zeinali, M., Meybodi, N. T., Rezaee, S. A., Rafatpanah, H., & Hosseinzadeh, H. (2018). Protective effects of chrysin on sub-acute diazinon-induced biochemical, hematological, histopathological alterations, and genotoxicity indices in male BALB/c mice. *Drug and chemical toxicology*, *41*(3), 270–280. https://doi.org/10.1080/01480545.2017.1384834

Zhang, X., Zhao, L., Cao, F., Ahmad, H., Wang, G., & Wang, T. (2013). Effects of feeding fermented *Ginkgo biloba* leaves on small intestinal morphology, absorption, and immunomodulation of early lipopolysaccharide-challenged chicks. *Poultry science*, *92*(1), 119–130. https://doi.org/10.3382/ps.2012-02645

Zhaocheng, J., Jinfeng, L., Luchang, Y., Yequan, S., Feng, L., & Kai, W. (2016). Ginkgolide A inhibits lipopolysaccharide-induced inflammatory response in human coronary artery endothelial cells via downregulation of TLR4-NF-kappaB signaling through PI3K/Akt pathway. *Die Pharmazie*, *71*(10), 588–591.

How to cite this article: Omidkhoda SF, Razavi BBM, Hosseinzadeh H. Protective effects of *Ginkgo biloba* L. against natural toxins, chemical toxicities, and radiation: A comprehensive review. *Phytotherapy Research*. 2019;1–20. https://doi.org/10.1002/ptr.6469