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*Ginkgo biloba*L.: Phytochemical components and antioxidant activity

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Curative effects of *Ginkgo biloba* L. have been recognized for centuries, dating back to traditional Chinese medicine which used crushed leaves to treat several health problems. Although *G. biloba* L. has several known and investigated activities, the antioxidant activity of its extract (EGb 761) is particularly relevant because reactive oxygen (ROS) and reactive nitrogen (RNS) species are constantly produced in aerobic organisms. Currently, the exploitation of the antioxidant activity of *G. biloba* extract Egb 761 has been of particular pharmacological importance because oxidative stress may be harmful to cells and may trigger the development of many disorders. The antioxidant activity of the EGb extract against oxidative stress has been associated with several therapeutic effects and currently, Egb761 is indicated to treat labyrinthitis, headache, memory disturbance, intermittent claudication, dementia, Alzheimer's disease, glaucoma, cardiovascular disorders, cerebral ischemia, increased libido and sexual activity, and psychiatric diseases, such as depression. This study is a review of basic and clinical studies related to antioxidant properties of *G. biloba* L.

Key words: *Ginkgo biloba* L., EGb 761, antioxidant activity, phytotherapic drug.

INTRODUCTION

Although medicinal plants have provided biologically relevant products for centuries, they still serve as a source for new medicines (Czelusniak et al., 2012; Albuquerque and Hanazaki, 2006). *Ginkgo biloba* L. is a widely used plant in popular medicine; its popular names are Ginkgo Japan, tree-fern, or simply *ginkgo.* Traditional Chinese medicine uses dry and mashed leaves of ginkgo to treat health problems such as asthma, bronchitis, hearing loss, tuberculosis, cognitive dysfunction, stomach pain, skin problems, and anxiety (Almeida, 2009).

Other current uses, such as arteriosclerosis, thrombus formation, ischemic heart disease, and the prevention of diabetes mellitus have also been reported (D'ippolito et al., 2005; Zhao e al., 2015). Recently, *G. biloba* extract associated with extracts from grape seed and skin, green tea, resveratrol, quercetin and bilberry

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was reported to decrease diastolic pressure in hypertensive subjects (Biesinger et al., 2015).

Several authors (Kose et al., 1997; He et al., 2014; Sarikcioglu et al., 2004) have reported that the *G. biloba* L.(EGb 761) extract has antioxidant action. Because reactive oxygen (ROs) and reactive nitrogen (RNs) are constantly produced in aerobic organisms, the ability of EGb 761 to act as a free radical scavenger is significantly relevant (Vasconcelos et al., 2007; Boligon et al., 2013). Of potential therapeutic significance, the combination of EGb 761 with other plant extracts can increase synergistically the antioxidant properties of the combinations (Wang et al., 2015).

Free radical species (FRs) are highly unstable and can react with cellular components. Under normal conditions, the production of these species is balanced by the presence of a sophisticated defense mechanism consisting of enzymatic and non-enzymatic components (Barbosa et al., 2006; Imai and Nakagawa, 2006) such as superoxide dismutases (SOD), catalases (CAT), glutathione peroxidases (GPx), and other components (Spadiene et al., 2012).

Eventually, however, some endogenous or exogenous factors can induce an increased production of ROs and RNs, or trigger depletion in antioxidant mechanisms, leading to an unbalance known as oxidative stress. This condition affects biomolecules and cellular structures and leads to several harmful effects on cells (Rover et al., 2001). These effects may lead to the development of several diseases, particularly pathologies related to the central nervous system (Alok et al., 2014; Pereira et al., 2014). Because the EGb 761 extract has known antioxidant activity against oxidative stress, it may be effective in both treatments and prophylaxis of chornic degenerative diseases (Diamond et al., 2000; Puppo and Silva, 2008; Jager et al., 2006; Berigan and Page, 2000; Forlenza, 2003; Gauthier and Schlaefke, 2014; Siegel et al., 2014; Cheng et al., 2015; Montes et al., 2015; Solfrizzi and Panza, 2015).

This article reviews information related to antioxidant properties of *G. biloba* L. described in basic and clinical studies.

MATERIALS AND METHODS

This study is an integrative literature review of the effects related to the antioxidant properties of *G. biloba* L. in studies published between 1991 and 2015, surveyed in Pubmed, Scientific Eletronic Library Online (SciELO) and Sience Direct.

Ginkgo biloba L. characterization

G. biloba L. is a species from the Ginkgoaceae family cited in Chinese therapeutics around 2,800 years B.C. This is a primitive, deciduous, high and robust plant, with fan-shaped disposed leaves and irregularly lobed; these plants can reach up to 40 m in height (Almeida, 2009; Lorenzi and Matos, 2000; Lorenzi et al., 2003). *G. biloba* L. was the first species to germinate after the atomic bomb explosion in Hiroshima, in 1946. The species is highly resistant to insects, microorganisms, and environmental toxins and conditions (Lima and David, 2006; Raven et al., 2001).

Ginkgo biloba L. phytochemistry

G. biloba L. therapeutic uses were based on macerated plant leaves, which contain known active compounds (Table 1). However, not all these components were useful as therapeutic compounds; Western medicine started using *Ginkgo* extracts in 1965 (Lima and David, 2006). The percentage of each constituent in the extract can vary according to the country where it was produced and the season in which the plant was harvested (Silva et al., 2010). In an effort to standardize this product that has been sold for more than two decades (Kock, 2005; Schulz et al., 2002), Egb761 was extracted from dry and mashed leaves. The flavonoid fraction in this extract stops lipid peroxidation, acting as free-radical scavenger, and helping in the prevention of oxidative stress (Silva et al., 2002). In addition, flavonoids increase the release and reuptake of serotonin (Ahlemeyer and Kriegelsteins, 1998), stop the reduction of cholinergic muscarinic receptors related to age, and stimulate its reuptake in the hippocampus (Defeudis, 1991; Blumenthal et al., 1998). Ginkgolide B is another important active principle in the EGb 761 extract that acts as an antagonist of the platelet-activating factor (PAF) receptor, and thus, inhibits platelet aggregation and improves cognitive and memory function (Luo, 2001; Smith and Luo, 2004). The active compounds, bilobalide (1), ginkgolide A (2), and ginkgolide B (3) (Figure 1) found in the EGb 761 extract have been reported to induce the reduction of peripheral benzodiazepine receptors, that are involved in many biological processes, however, with unknown functions (Amri et al., 1996).

Antioxidant activity

The antioxidant activity in the *G. biloba* L. extract is played by its flavonoids (Mckenna et al., 2001; Macarenco et al., 2001) protecting cellular membranes from oxygen reactive species, chelating transition metals, and acting on the expression of protein antioxidant molecules or leading to an increase in antioxidant metabolites (Smith and Luo, 2004). The literature reports several studies with *G. biloba* L. demonstrating its antioxidant activity. Yoshikawa et al. (1999) showed that the EGb 761 extract has a relaxing effect on vascular walls improving microcirculation and blood flow. Therefore, it could be used in the prevention and treatment of chronic oxidative damage, ischemic heart disease, cerebral infarction, and chronic inflammation (Yoshikawa et al., 1999). Beek (2000) reports that the extract inhibits the activity of xanthine oxidase, which uses molecular oxygen as an electron acceptor to produce superoxide ions and hydrogen peroxide. Hence, the extract activity inhibits the formation of these oxygen reactive species and prevents cellular damages. In the same vein, EGb 761 has been reported to blunt the high-glucose-induced oxidative DNA damage in human umbilical vein endothelial cells (HUVECs) (He et al., 2014) and to inhibit the aggregation of β-amyloid peptide *in vitro* (Xie et al., 2014). Moreover, the EGb 761 extract has the capacity to directly minimize FRs or recycling tocopherol radicals in both cases, sparing the vitamin E present in the membrane. The presence of tocopherol in membranes is important beyond the protection of phospholipids in the lipid bilayer of membrane units against the attack of reactive oxygen species. In addition to antioxidant activity, the EGb 761 extract inhibits the phospholipase A2, which hydrolyzes the ester bonds in phospholipids releasing the substrate for the cyclooxygenase that catalyzes the formation of endoperoxides and giving an

Table 1. Main chemical constituents of *Ginkgo biloba L*.

Metabolite class	Substance	Reference
Flavonoids	Quercetin Kaempferol Isorhamnetin Glycosides	He et al. (2008)
Terpenoids	Bilobalide	He et al. (2008)
	Ginkgolide Ginkgolide B Ginkgolide C Ginkgolide J	Banov et al. (2006)
Biflavones	Bilobetina Ginkgetina	Schneider et al. (2007)
	Ginkgolic acid	Banov et al. (2006)
Organic acids	Shikimic acid Kynurenic acid Ascorbic Acetate 3-Methoxy-4-acid hydroxybenzoic acid 4-hydroxybenzoic acid 3,4-diidroxibenzoic 6-hydroxyquinurenic acid	Schneider et al. (2007)
Other substances	Glucose Ramanose Sterols Aliphaticketones Alcohols Diterpenes Phenylpropanoids Carotenoids	Schneider et al. (2007)

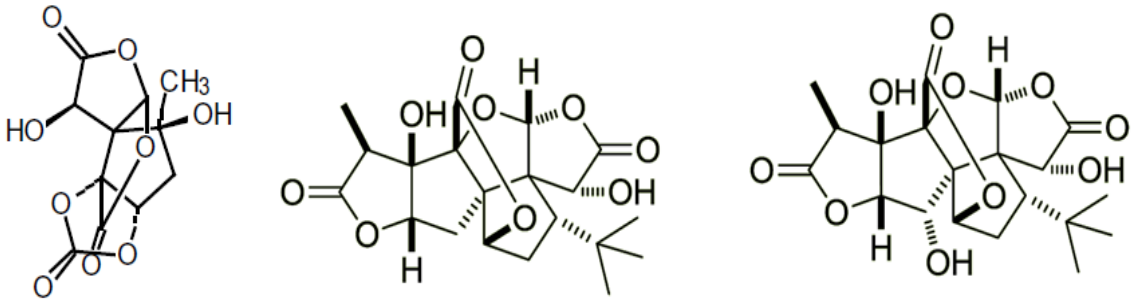

Figure 1. Chemical structure of some active compounds found in *Ginkgo biloba L*.: bilobalide (1) ginkgolide A (2), and ginkgolide B (3).

antithrombotic activity to the plant (Kusmic et al., 2004).

Other studies investigated the neuroprotective effects of *G. biloba* L. in mice through treatment with EGb 761 extract, before or after the administration of MPTP (1-metil-4-fenil- 1,2,3,6-tetrahydropiridine), which is a substance that causes irreversible symptoms of Parkinson disease. According to these authors, mice pre-treated with the EGb 761 extract showed protection against the MPTP toxicity. Protection against oxidized substances occurs through the inhibition of the MAO B enzyme that is responsible for the conversion of MPTP in MPP+. It was concluded that the extract prevents the entrance of oxidized MPTP in the dopaminergic tract obstructing the formation of FRs and, consequently, providing antioxidant protection (Wu and Zhu, 1999).

In addition to the neuroprotection against the natural production of FRs EROS, there are studies that link the protective activity of *G. biloba* L. against the induced production of these oxygen species. Ilhan et al. (2004) induced oxidative stress in mice using a system created with mobile phones and anechoic cameras; the treatment of these mice with dry powder of *G. biloba* L.showed that the SOD and GPx enzyme activities were preserved in the brain tissue.

Another study evaluated the activities of catalase, superoxide dismutase, and glutathione peroxidase in cerebral structures (hippocampus, striatum, and substantia nigra) in mice. The animals were orally treated with *G. biloba* L. extract in the dose of 100 mg/kg of body weight during 14 days. The results showed a meaningful increase in the activities of catalase and superoxide dismutase, decreased lipoperoxidation in the hippocampus, and no alterations in the activity of glutathione peroxidase. The authors emphasize that this protective effect might exploited in the development of new drugs to prevent, delay, or improve symptoms related to neurodegenerative diseases such as Alzheimer's disease (Bridi et al., 2001).

Toxicity in the EGb 761 extract

It is noteworthy to emphasize that tests performed with the EGb 761 extract revealed low toxicity to chronic or acute administration (Blumenthal et al., 1998; Blumenthal, 2000) but no mutagenic or teratogenic effects (Mills and Bone, 2000), or negative effects on the reproduction and development in the tested Wistar mice (Castro et al., 2005). Currently, there are many marketed phytotherapeutic products from *G. biloba* L. with indicated use for disorders and symptoms related to impaired cerebral blood flow, such as memory problems, cognitive function, dizziness, headache, vertigo, tinnitus, early stages of dementia, peripheral circulatory disorders, and retina problems. These medicinal products are in compliance with the current legislation (Colombo, 2011).

RESULTS AND DISCUSSION

A significant increase in the use of medicinal plants and herbal medicines has been observed as the result of new scientific information about the molecular mechanisms underlying the therapeutic action of some natural products. Natural products are mainly used by adults and elderly people who have chronic diseases and seek for alternative phytotherapeutic treatment options. These usages are often based on self-medication and in popular and traditional use of the plant extracts, generally without scientific support (Ekor, 2014). In the case of *G. biloba,* fortunately, the traditional use of the plant extracts has been supported by both experimental and epidemiological studies (Yang et al., 2014; Alok et al., 2014; Chen et al., 2015; Montes et al., 2015; Siegel et al., 2014). Of particular importance, *G. biloba* extracts have been proven to be safe for human consumption, particularly the EGb 761 standardize extract. It now is clear that *G. biloba* has antioxidant properties in a variety of *in vitro* and *in vivo* models and that the antioxidant components of the EGb 761 extract can be involved in the therapeutic efficacy of this secular plant. However, we still have scanty information if the modulation of oxidative stress by *G. biloba* extracts is the primary mechanism of the therapeutic properties of this plant. Thus, more studies are needed to establish if oxidative stress is the cause or the consequence of therapeutic properties of *G. biloba* extracts. For instance, *G. biloba* extracts have anti-inflammatory properties in different *in vitro* and *in vivo* models (Apetz et al., 2014; Siegel et al., 2014; Tisato et al., 2013; Chen et al., 2014; Hirata et al., 2015) and the inhibition of inflammatory response can decrease the oxidative stress. In short, the complex interplay between primary cellular responses and oxidative stress in chronic degenerative diseases and the modulation of this interaction by plant extracts need more detailed studies.

Conclusion

There are many studies in the literature demonstrating the powerful antioxidant action and the low toxicity of the EGb 761 extract, confirming the efficiency and the safety of *G. biloba* extracts secular use by the population worldwide.

Conflicts of interest

Authors have none to declare.

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