



GINKGO BILOBA L.: AN EXCEPTIONAL MEDICINAL PLANT

Ruchi¹, Kushi Tehri², Monika Kalia³, Savita Rani⁴, Rekha Sharma⁵, Sonika Kalia^{6*}, Anjali Rawat⁷, Divyesh Suvedi⁸, Anu Verma⁹

Abstract

Ginkgo biloba L. is a living fossil, a hardy plant species that has survived through glaciations, climate change, biotic and abiotic stresses. *Ginkgo* has the reputation of being listed in high demand as a medicinal plant as well as an ornamental plant. This plant shows a variety of therapeutic uses in various diseases and owing to this quality. *Ginkgo* has been used as a medicinal plant in traditional Chinese medicine for a long time. *Ginkgo* offers a large number of pharmacological activities including antidiabetic, antioxidant, antidementia, antihypertensive, antidepressant, antiaging, anti-inflammatory, anticancerous, hepatoprotective, neuroprotective, respiratory system supporting activities and many more, enabling it to be utilized in various medications for cerebral disorders, peripheral circulatory problems and a variety of uses. This review has provided a summary of major components found in *Ginkgo biloba* and their medicinal properties other commercial products developed from *Ginkgo*.

Keywords: Extract of *Ginkgo biloba* (EGb), flavonoids, terpenoids, antioxidant, neuroprotective, anti-inflammatory.

^{1, 2, 6*, 7, 7, 8, 9}Department of Biotechnology, School of Applied and Life Sciences, Uttarakhand University, Dehradun, 248001

^{6*}Department of Agricultural Biotechnology, CSKHPKV, Palampur, Himachal Pradesh, 176062

³Department of Entomology, CSKHPKV, Palampur, Himachal Pradesh, 176062

⁴School of Agricultural Sciences, Baddi University of Emerging Sciences & Technology, Solan, Himachal Pradesh, 173205

⁵School of Bioengineering and Food technology, Shoolini University, Solan, Himachal Pradesh 173229

***Corresponding author:** - Sonika Kalia

*Department of Biotechnology, School of Applied and Life Sciences, Uttarakhand University, Dehradun, 248001, E-mail:- sonikakalia.266@gmail.com, Mobile: 8988336168

DOI: - 10.48047/ecb/2023.12.si5a.0338

INTRODUCTION

Ginkgo biloba L. is a member of ginkgoaceae family and commonly known as maidenhair tree. It is also known as a living fossil due to the fact that it is the only living member of its family and a seed plant of one of the oldest origin [1]. In Chinese culture the use of *Ginkgo* seeds was there from very early time in their traditional medicine system and later on the leaves were also used for medicinal purposes [2]. *Ginkgo biloba* is a plant that has immense importance as a medicine and being used since ages for the treatment of various diseases especially in the treatment of diseases of central nervous system e.g. Alzheimer's disorder [3] and cardiovascular diseases [4]. *Ginkgo* L. has been successful in surviving extinction due to its resilient nature attributed to its secondary metabolites especially ginkgolides and bilobalide [5]. It has also survived through the adverse effects of atomic bomb blast of Hiroshima as it was the first plant species that had germinated after the bomb blast in the contaminated area proving its high tolerance to abiotic stress [1]. This plant is also grown as ornamental purpose in European and Asian countries [6].

GEOGRAPHICAL DISTRIBUTION

China, Korea and Japan are the native countries of *Ginkgo biloba*, apart from these countries it is also cultivated in other parts of the world like in New Zealand, Argentina, North America and India [7]. The wild distribution of *Ginkgo* population is restricted to some provinces of China, e.g. in the west mountains of Tienmushan, Anhui province, Zhejiang province and Dabieshan mountains [8]. This plant is listed under the

International Union for Conservation of Nature and Natural Resources' endangered category (Endangered B1+2c ver 2.3. Year Published: 1998).

STATUS OF CULTIVATION OF GINKGO PLANT FROM THE INDIAN PERSPECTIVE

In India, the mountains of Central Himalaya are the abode for *Ginkgo biloba* where this plant grows naturally at an elevation of 6000 ft. [9]. It is found in hilly areas of North-East and North-Western regions of the country [10]. It grows in Dehradun, Nainital, Mussoorie and Ranikhet of Uttarakhand, Shimla, Manali and Kalpa of Himachal Pradesh, Meghalaya, Punjab and West Bengal of India [11]. A research conducted in India documented approximately 30 trees that were growing naturally, around 60 percent of these plants were below the age of 35 and rest of the 40 percent were in semi arid conditions [12]. Owing to various medicinal uses and increasing demand for its bioactive compound, Indian government has also taken a step towards its conservation and cultivation and has sanctioned projects from National Medicinal Plant Board Government of India New Delhi.

BIOACTIVE COMPOUNDS

Several investigations have been made in order to collect the information about the prominent medicinal compounds in the *Ginkgo*. The various chemically active components in *Ginkgo* leaves include terpenoids, flavonoids [13], biflavonoids [14], polyphenols [15] and organic acids [16] etc (Figure 1).

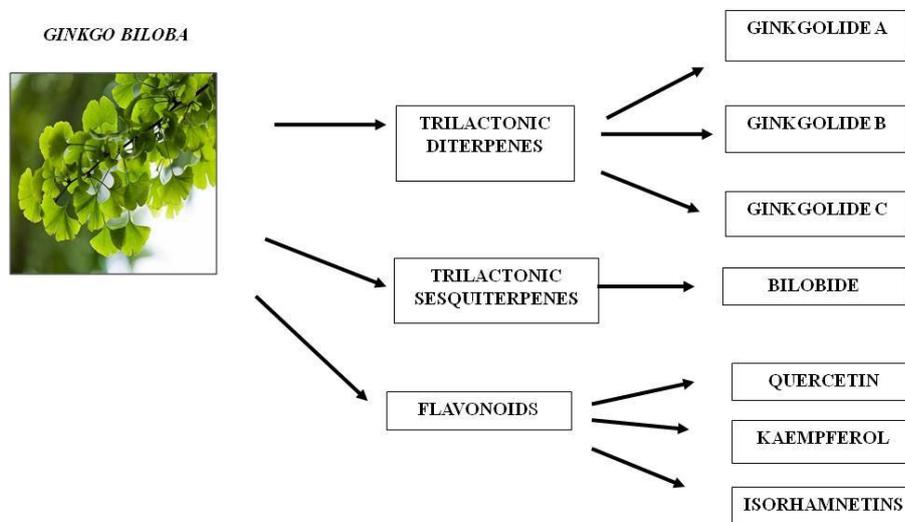


FIGURE 1: VARIOUS BIOACTIVE COMPOUNDS IN *GINKGO BILOBA*

FLAVONOIDS

Various flavonoids have been identified by using Liquid Chromatography, Mass Spectrometric technique. Approximately 110 flavonoids have been identified in *Ginkgo biloba* till this date. Major flavonoids found are kaempferol 3-O- α -[6000-P-coumaroyl (β -d)-glucopyranosyl(1,2)-rhamnopyranoside]-7-O- β -d-glucopyranoside and isorhamnetin 3-O- α -l-[6000-p-coumaroyl(α -d)-glucopyranosyl(1,2)-rhamnopyranoside], these two flavonoids when combined with different flavonol glycosides, exhibits antioxidant properties. these flavonol glycosides are quercetin 3-O- α -L-[6'''-p-coumaroyl-(β -D)-glucopyranosyl-(1,2)-rhamnopyranoside], quercetin 3-O- β -D-glucopyranoside, quercetin 3-O- β -rutinoside, quercetin 3-O- β -D-glucopyranosyl-(1-2)-alpha-L-rhamnopyranoside, quercetin 3-O- α -L-[6'''-p-coumaroyl-(β -D)-glucopyranosyl-(1,2)-rhamnopyranoside]-7-O- β -D-glucopyranoside, kaempferol 3-O- α -L-[6'''-p-coumaroyl-(β -D)-glucopyranosyl-(1,2)-rhamnopyranoside]etc.[17].

TERPENOIDS

A number of terpene compounds are present in the roots, seeds and leaves of *Ginkgo*; the most significant are ginkgolides (diterpenes) and bilobalides (sesquiterpenes). A research carried out by Zhang et al. (2015) revealed that the bilobide and ginkgolide are present in every parts of *Ginkgo* seeds. High amounts of these four compounds were found in embryos and endosperms. Processing methods reduce these compounds in the seeds [18]. Ginkgolides are the

antagonists of Palate Activating Factors thus they have the ability to cure the central nervous system related disorders[19]. Bilobides are of immense importance as anti-edema activity of EGB 761[20]. It is neuroprotective in nature hence shows effectiveness in the treatment of neurodegenerative diseases[21]. It has also been reported that bilobides inhibits the decrease in ATP levels of endothelial cells that is induced due to hypoxia[22]. Bilobides shows anti-inflammatory properties[23] and they are able in the suppression of the brain membrane breakdown caused by hypoxia [24].

THERAPEUTIC EFFECTS OF GINKGO

The use of *Ginkgo biloba* in China is dated back to around 2000 years[10]. It has been used for the cure of asthma, bronchitis [25] tuberculosis, cognitive dysfunction, stomach pain, [26], heart issues, skin infections, infection in bladder, alcohol abuse, etc. (Figure 2)[26]. To find the efficacy of *Ginkgo biloba*, several tests have been conducted and so many claims have been found true hence it has now established as a well known medicinal plant with therapeutic potential and as an organic source of supplement. It is clinically tested and approved as a medication for treating Alzheimer's disease[27], neurological disorders [28] and cardiovascular disorder. Studies also suggest that it has potential to cure problems related to cerebro-vascular ailments, stroke epilepsy and disease related to peripheral vascular system [29, 30].

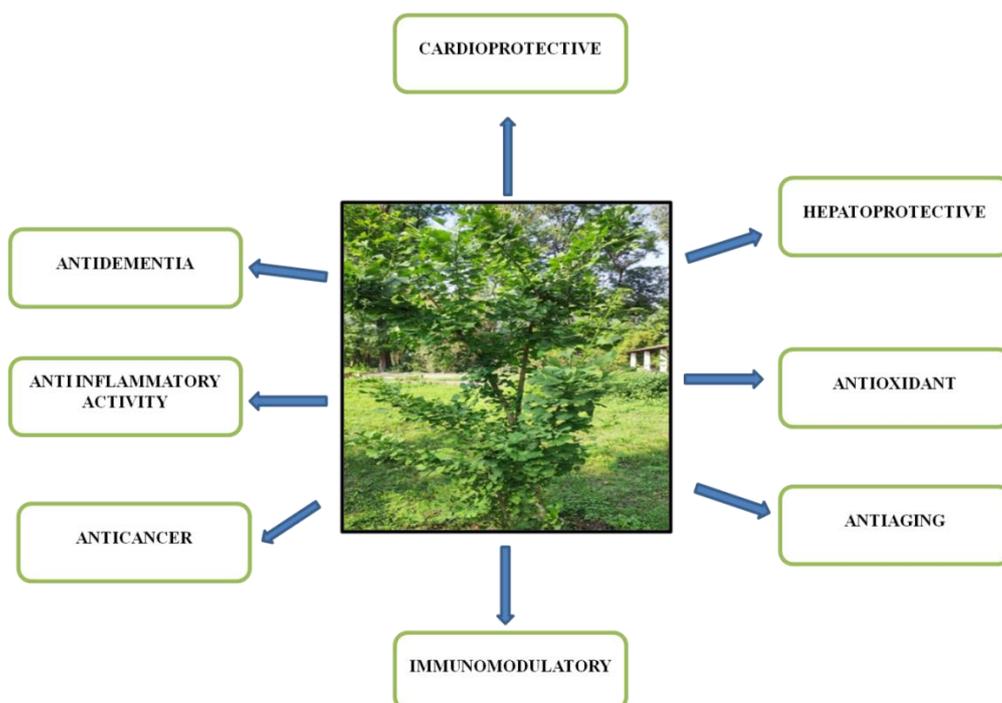


FIGURE 2: VARIOUS PHARMACOLOGICAL ACTIVITIES OFFERED BY GINKGO BILOBA

ANTIOXIDANT

A number of compounds having antioxidant properties are observed in *Ginkgo biloba* owing to the presence of bioactive compounds like terpenes, biflavonoids and flavonoids etc. These bioactive compounds exhibit antagonistic actions for the reactive oxygen species (ROS) - oxyferyl, hydroxyl, peroxy, NO and super oxides etc. and as a result it provides protection from various diseases and damage to the cells caused by ROS. These reactive oxygen species are produced in cellular metabolic process that leads to aging, diseases and cell death. *Ginkgo biloba* leaf extract (EGb) inactivates oxygen free radicals as well as enhances the activity of enzyme glutathione peroxidase and inhibits peroxidation of lipids [31], increases the activity of superoxide dismutase (SOD) resulting in the reduction of rate of apoptosis in diabetic vascular cells [32]. *Ginkgo biloba* extract (EGb) consists ginkgo flavones, ginkgolide, procyanidins and organic acids etc and the DPPH scavenging ability of these compounds has been confirmed and the order of their activity is procyanidins > ginkgo flavones > organic acids > ginkgolides [33].

NEUROPROTECTIVE EFFECT

Studies have suggested that the bioactive components like terpenoids and flavonoids in *Ginkgo biloba* seed have positive effects in the improvement of cerebral blood flow and the improved blood flow in brain could have preventive effects on the neurodegenerative disorders [34]. Extracts of *Ginkgo biloba* leaves have therapeutic effects on various problems like brain ischemia, AD – a cognitive impairment, neurological disease [35, 36]. EGB 761 shows effectiveness in the cure of Alzheimer's disease at a daily dose dependent manner and the dose that has been found effective is 240 mg/kg/day [28]. *Ginkgo biloba* is consumed as a supplement to improve memory and cognitive powers. A test conducted by Winter et al reported that in mice, 4-8 week of oral consumption of 100 mg/kg/day showed the betterment in memory and learning power during apatite operant conditioning [37].

PROTECTIVE EFFECTS FROM RESPIRATORY DISEASE

In the treatment of respiratory diseases the responsible bioactive compounds in *Ginkgo* are – extract of ginkgo leaves, biflavones, ginkgetin [38], ginkgolides [39]. Various studies have revealed that the ginkgolide B provides

protection to the lungs from the injuries caused by asthma and infections [40].

ANTICANCEROUS EFFECTS

Studies have been conducted to test the effectiveness of methanolic extract of *Ginkgo biloba* leaves on the treatment of Wister rats having hepatocellular carcinoma and it was found that the *Ginkgo biloba* extract is effective in the betterment of histological quality of liver tissues. Administration of the extract of *Ginkgo biloba* leaves reduced the level of serum alphaprotein (AFP), carcinoembryonic antigen (CEA), and glypican-3 (GPC-3) and also downregulated the expression level of foxp-1 and upregulates the expression of ING-3 gene that indicates the regressive effects of *Ginkgo biloba* extract on hepatocellular carcinoma because of its antiproliferating and apoptotic qualities [41]. Another research revealed that extract of ginkgo leaves exhibits inhibitory effects on the proliferation of human gastric carcinoma SGC7901 cells in a dose and time dependent manner where in the strongest inhibition was observed with the dose more than 300mg/L for 48 and 72 hours. The extract of *Ginkgo* leaves down regulates the expression of C-myc genes and cyclin D1 that results in the inhibition of gastric carcinoma cell proliferation [42].

IMMUNOMODULATORY EFFECTS

A research conducted on fish models revealed that *Ginkgo biloba* in powdered form has increased levels of monoamine neurotransmitter and exhibited altering effects on the glyphosate-induced hepatotoxicity, genotoxicity, lipid peroxidation and nephrotoxicity, resulting in increased immunity at 1-2 gm/kg diet [43]. Another research found that the administration of *Ginkgo biloba* seed extract on 28 day old BALB/c mice (in vivo), decreased the inflammation of airways and the mechanism involved in it was that the ginkgetin shows reduction in the expression of m RNA MUC5AC and stimulates HNE which results in the inhibition of airway inflammation [38].

GINKGO BILOBA BASED COMMERCIAL PRODUCTS

Several kinds of commercial products, developed from *Ginkgo biloba* are available in the market as dietary supplements and cognitive power and memory power boosters (Table 1)

TABLE: 1 COMMERCIALY AVAILABLE GINKGO BILOBA PRODUCTS				
NAME OF THE PRODUCT	TYPE	FORM OF PRODUCT	BRAND	QUALITIES
GINKGO BILOBA WITH BRAHMI	Dietary supplement	Capsule	Simply herbal	Supports healthy brain function, improves cognition power memory & focus
GINKGO BILOBA 120 mg	Dietary supplement	Capsule	Nature's Bounty	Mental alertness, improves brain power
GINKGO BILOBA 120mg	Dietary supplement	Capsule	Now foods	Improves alertness
ARJUNA CARDIAC WELLNESS	Dietary supplement	Capsule	Himalaya	Regulates blood circulation
BRAIN TEA	Tea	Tea bags	Nutri herbs	Sharpens memory , boosts immune system
GINKGO BILOBA LEAVES	Tea	Loose leaves	One herb	Improves memory, focus sharpening

CONCLUSION

The use of organic supplements and plant based medicines is gaining popularity around the globe due to the less harmful effects it poses to the human body as compared to allopathic medicines. Extensive research is conducted to derive the maximum benefit out of these plants having medicinal and nutritional properties. *Ginkgo biloba* is one of such plants that offer a vast array of therapeutic properties. It contains bioactive compounds such as terpenes (ginkgolides A, B, C, bilobides) and flavonoids (quercetin, kaempferol, isorhamnetins) etc. that are responsible for its various therapeutic activities and make the plant commercially desirable. There is still a gap in the knowledge about various effects and mechanisms behind its bioactivity that needs to be addressed for use of this plant to its fullest extent.

REFERENCES

- Mohanta T.K., Occhipinti A., Zebelo S.A., Foti M., Fliegmann J., Bossi S., Maffei M.E., Berteau C.M. 2012. Ginkgo biloba responds to herbivory by activating early signaling and direct defenses. *PLoS One* 7 (3), e32822
- Mahadevan S., Park Y. 2008. Multifaceted therapeutic benefits of Ginkgo biloba L.: chemistry, efficacy, safety, and uses. *Journal of Food Science* 73, 14–19
- Chan P.C., Xia Q., Fu P.P. 2007. Ginkgo biloba leave extract: biological, medicinal, and toxicological effects. *Journal of Environmental Science and Health C* 25 (3), 211–244
- Vellas B., Coley N., Ousset P.J., Berrut G., Dartigues J.F., Dubois B., Grandjean H., Pasquier F., Piette F., Robert P., Touchon J. 2012. Long-term use of standardized Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial. *Lancet Neurology* 11 (10), 851–859.
- Zhao Y.P., Fan G., Yin P-P., Sun S., Li N., Hong X., Hu G., Zhang H., Zhang F.M., Han J.D., Hao Y.J., Xu Q., Yang X., Xia W., Chen W., Lin H.Y., Zhang, J Chen, Zheng, SM X.M., Lee Y., Lee J., Uehara K., Wang J., Yang H., Fu C.X., Liu X., Xu X., Ge S. 2019. Resequencing 545 ginkgo genomes across the world reveals the evolutionary history of the living fossil. *Nature Communications* 10, 4201
- Murakami M., Abe M., Kakumoto Y., Kawano H., Fukasawa H., Saha M., Takada H. 2012. Evaluation of ginkgo as a biomonitor of airborne polycyclic aromatic hydrocarbons. *Atmospheric Environment* 54, 9–17
- Huh H., Staba E.J. 1992. The botany and chemistry of Ginkgo biloba L. *Journal of Herbs, Spices and Medicinal Plants* 1, 91–124
- Li HL. 1956. A horticultural and botanical history of Ginkgo. *Bull Morris Arboretum* 7:3–12
- Bitencourt J., Zuffellato-Ribas KC., Koehler HS. 2010. Ginkgo biloba L. cutting using three substrates. *Revista Brasileira de Plantas Medicinai* 12(2), 135–140
- Singh B., Kaur P., Gopichand., Singh R.D., Ahuja P.S. 2008. Biology and chemistry of Ginkgo biloba. *Fitoterapia* 79, 401–418
- Roychoudhury N., Mishra R.K. 2016. Ginkgo biloba Linn: A promising species of potential importance. *Van Sangyan* 3(7), 35–37
- Gopichand., Singh R.D., Kumat A., Meena R.L., Ahuja P.S. 2009. Current status of

- Ginkgo biloba L. in India. *The Indian Forester* 135(11),1588-1593
13. Tarun Belwal R. S. R., Giri L., Amit B., Tariq M., Kewlani P. 2019. Ginkgo Biloba
 14. M. Li., B. Li., Xia and Z. M. 2019. Anticancer effects of five biflavonoids from Ginkgo biloba L. Male flowers in vitro. *Molecules* 24(8), 1496
 15. Tao R., Wang C., Ye J., Zhou H., Chen H. 2016. Polyphenols of Ginkgo biloba Enhance Antibacterial Activity of Five Classes of Antibiotics. *BioMed Res. Int.* 2016, 4191938
 16. Baek S. H., Lee J. H., Kim C., Ko J. H., Ryu S. H., Lee S. G. 2017. Ginkgolic acid C 17:1, derived from Ginkgo biloba leaves, suppresses constitutive and inducible STAT3 activation through induction of PTEN and SHP-1 tyrosine phosphatase. *Molecules* 22(2), 276
 17. Hasler, Gross G.A., Meier B., Sticher O. 1992. Complex flavonol glycosides from the leaves of Ginkgo biloba. *Phytochemistry* 31(4),1391–1394
 18. Zhang Q.Q., Zhang X.L., Li H.F., Meng Y., Liang X. 2015. Comparison on contenting of four kinds of terpene lactones in different parts of ginkgo semen and its different processed products. *J. Liaoning University TCM* 17, 45–47
 19. Guinot P., Braquet P. 1994. Effects of the PAF antagonists, ginkgolides (BN52063, BN 52021), in various clinical indications. *J. Lipid Mediat. Cell Signal* 10, 141–146
 20. Chatterjee S.S., Gabard B.L., Jaggy H.E.W. 1986. Pharmaceutical compositions containing bilobalide for the treatment of neuropathies. US patent No. 4,571,407 Feb 18
 21. Israel, M., Lesbats, B., 1982. Application to mammalian tissues of the chemiluminescent method for detecting acetylcholine. *J. Neurochem.* 39, 248–250
 22. Thompson, C.B., 1995. Apoptosis in the pathogenesis and treatment of disease. *Science* 267, 1456–1462
 23. Goldie M., Dolan S. 2013. Bilobalide, a Unique Constituent of Ginkgo Biloba, Inhibits Inflammatory Pain in Rats. *Behav. Pharmacol.* 24 (4), 298–306
 24. Klein J., 1997. Phospholipid breakdown and choline release under hypoxic conditions: Inhibition by bilobalide, a constituent of Ginkgo biloba. *Brain Res.* 755, 347–350.
 25. F. Eisvand, B. M. Razavi, and H. Hosseinzadeh 2020. “The effects of Ginkgo biloba on metabolic syndrome: a review,” *Phytotherapy Research*, vol. 34, no. 8, pp. 1798–1811,.
 26. Almeida E.R. 2009. Plantas adaptógenas e com ação no sistema nervoso central. Biblioteca, São Paulo. 24
 27. Herrschaft H., Nacu A., Likhachev S., Sholomov I., Hoerr R., Schlaefke S. 2012. Ginkgo biloba extract EGb 761® in dementia with neuropsychiatric features: a randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. *Journal of Psychiatric Research* 46 (6), 716–723.
 28. Kleijnen J., Knipschild P. 1992. Ginkgo biloba for cerebral insufficiency. *British Journal of Clinical Pharmacology* 34 (4), 352–358
 29. Sasaki Y., Noguchi T., Yamamoto E. 2002. Effects of Ginkgo biloba extract (EGb 761) on cerebral thrombosis and blood pressure in stroke-prone spontaneously hypertensive rats. *Clinical and Experimental Pharmacology and Physiology* 29, 963–7
 30. Napryeyenko O., Borzenko I., 2011. Ginkgo biloba special extract in dementia with neuropsychiatric features. *Arzneimittel forschung/ Drug research* 57(1), 4-11
 31. Goh L.M., Barlow P.J., Yong C.S. 2003. Examination of antioxidant activity of Ginkgo biloba leaf infusions. *Food Chemistry* 82, 275–282
 32. Zhao M., Wang X.X., Wan W.H. 2012. Effects of the Ginkgo biloba extract on the superoxide dismutase activity and apoptosis of endothelial progenitor cells from diabetic peripheral blood. *Genetics and Molecular Research* 13(1), 220-227
 33. Zhang L., Zhu C., Liu X., Su E., Cao F., Zhao L. 2022. Study on synergistic antioxidant effect of typical functional components of hydroethanolic leaf extract from Ginkgo biloba in vitro. *Molecules*, 27(2), 439
 34. Wang H. Y., Zhang Y. Q. 2019. The main active constituents and detoxification process of Ginkgo biloba seeds and their potential use in functional health foods. *Journal of Food Composition and Analysis* 83(6), 103247
 35. W. Zuo, F. Yan, B. Zhang, J. Li, and D. Mei. 2017. Advances in the studies of Ginkgo biloba leaves extract on aging-related diseases. *Aging and disease* 8(6),812–826
 36. Budni J., Bellettini-Santos T., Mina F., Garcez M. L., Zugno A. I. 2015. The involvement of BDNF, NGF and GDNF in aging and Alzheimer's disease. *Aging and Disease* 6:331–41.
 37. Winter E. 1991. Effects of an extract of Ginkgo biloba on learning and memory in mice. *Pharmacology Biochemistry and Behavior* 38 (1), 109–114

38. Tao Z., Jin W., Ao M., Zhai S., Xu H., Yu L. 2019. Evaluation of the anti-inflammatory properties of the active constituents in *Ginkgo biloba* for the treatment of pulmonary diseases. *Food & Function* 10, 2209–2220
39. F. Wu, W. Shi, G. Zhou et al., 2016. Ginkgolide B functions as a determinant constituent of Ginkgolides in alleviating lipopolysaccharide-induced lung injury. *Biomedicine & pharmacotherapy* 81, 71–78
40. Luo Z.C., Huang Y., Qin K.X., Liang Z.X. 2009. Effect of ginkgolide B on NF- κ B expression in pulmonary tissue of mice with acute lung injury. *Acta Acad. Med. Mil. Tert.* 31, 1358–1361
41. Ahmed H.H., Shousha W.G., El-Mezayen H.A., El-Toumy S.A., Sayed A.H., Ramadan, A. R. 2017. Biochemical and molecular evidences for the antitumor potential of *Ginkgo biloba* leaves extract in rodents. *Acta Biochimica Polonica* 64(1), 25-33
42. Qian Y., Xia L., Shi W., Sun J. J., Sun, Y. Q. 2016. The effect of EGB on proliferation of gastric carcinoma SGC7901 cells. *Clinical and Translational Oncology* 18, 521-526
43. 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* 26(9): 8798–8807