GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Pharmacognosy, phytochemistry, pharmacology and clinical application of *Ginkgo biloba*

Manisha P. More [1], Anuja S. Motule [1], Prajakta N. Dongare [1], Prerna A. Patinge [1], Rahul D. Jawarkar [1], Ravindra L. Bakal [1] and Jagdish V. Manwar [2,*]

[1] *IBSS's Dr. Rajendra Gode Institute of Pharmacy, Mardi Road, Amravati-444 602, MS, India.*
[2] *IBSS's Dr. Rajendra Gode College of Pharmacy, Mardi Road, Amravati-444 602, MS, India.*

GSC Biological and Pharmaceutical Sciences, 2021, 16(02), 229–240

Publication history: Received on 19 July 2021; revised on 24 August 2021; accepted on 26 August 2021

Article DOI: https://doi.org/10.30574/gscbps.2021.16.2.0249

Abstract

In the present review, we are highlighted various pharmacognostic and pharmacological aspects of the different parts of plant *Ginkgo biloba*. Leaves are mainly potential source of phytochemical constituents. The plant encompasses variety of pharmacological activities namely antioxidant, hypolipidemic, antibacterial, etc. The pharmacological profile of plant is mainly attributed to the presence of chemicals such as Ginkgolide A, Ginkgolide B, Ginkgolide C, Bilobalide, Ginkgotoxin, ginkgolides and bilobalide are the major constituents. The pills with the highest concentration of plant extract (100 mg) allow the intake of the highest antioxidants concentration. It is also used along with 5-flurouracil in cancer treatment. There is need to explore more activities of the plant.

Keywords: *Ginkgo biloba*; Pharmacognosy; Ginkgolide A; Tinnitus

1. Introduction

Herbal medicines have been used for over 5000 years and they are one of the most promising sources of new medicines. *Ginkgo biloba* is one the medicinal plants wifely used in treatment of various diseases and disorders [1]. *Ginkgo biloba* has identity as a valuable plant for mankind since more than 2000 years. The name *Ginkgo* is derived from a wrong transcription of the Japanese name Yin-Kwo (silver fruit), while the epithet *biloba* refers to the bilobed shape of leaves; the English name "maidenhair tree" is due to a resemblance of the leaf shape and veins to maidenhair fern [2-4].

2. Geographical distribution

The G. *biloba* tree, which is native to China, Japan, and Korea, is distributed through cultivation in many parts of Europe, America, and the temperate regions of New Zealand, Argentina, and India [5-6]. Tree also found in other regions (Table 1).

3. Taxonomy

Plant taxonomy is the science that finds, identifies, describes, classifies, and names plants. Taxonomy of *Ginkgo biloba* is given in Table 1. *Ginkgo biloba* is both the Latin binomial and common name of the species. It is also known as "maidenhair tree," owing to its resemblance to the maidenhair fern. The phylum Ginkgophyta catagorizes seed pollen-bearing deciduous plants lacking flowers and fruiting structures. The seed is only found on the female plant, and is surrounded by a fleshy covering. *Ginkgo* is derived from the Chinese and Japanese name for the plant, meaning "silver

* Corresponding author: Jagdish V Manwar
IBSS's Dr. Rajendra Gode College of Pharmacy, Mardi road, Amravati-444 602, MS, India.

apricot," or "silver fruit," referring to the female seed structure. *Ginkgo* is a translation error; it should be *Ginkyo*. *biloba* is Latin for "two-lobed," referring to the leaf shape [5-7] (Table 2).

Table 1 Geographical distribution

Country	Region
China	Zhejiang province, Guangxi, Guizhou, Sichuan province, etc
Japan	Tsukuba, Ibaraki, Okayama, Tokyo, Fukuoka
Korea	Seoul, Incheon
Netherlands	Utrecht
Austria	Vienna University
France	Montpellier
Germany	Hannover
Italy	Padua
North America	Pennsylvania
India	Uttarakhand

Table 2 Taxonomy of *Ginkgo biloba*

Classification	Name
Botanical name	*Ginkgo biloba L.*
Kingdom	Plantae
Division	Pinophyta
Phylum	Ginkgophyta
Class	Ginkgoopsida
Order	Ginkgoales
Family	Ginkgoaceae
Genus	Ginkgo
Species	*Biloba*
Plant part	Leaf
Common names	Fossil tree, Kew tree, Maidenhair tree.

4. Morphology

The plant body of *Ginkgo biloba* is sporophytic, and the sporophyte resembles several conifers in general habit. The trees have a pronounced ex-current habit of growth and attain a height up to 30 meters. The branches are dimorphic i.e. bear long shoots which are of unlimited growth with scattered leaves and dwarf shoots which are short branches of limited growth. A dwarf shoot of 2-3 cm length may be several years old.

4.1. Leaves

Leaves may be pale yellow, golden yellow or dark green in colour. Foliar epidermis also exhibits some distinguishable characters in *Ginkgo biloba*. The leaves are hypostomatic (i.e., bear stomata only on the lower surface of the leaf). The *Ginkgo biloba* tress has long and short branches growing at right angles. The leaves grow alternate on the long branches

during spring. They are fan-shaped, leathery and smooth. They are often deeply grooved in the middle of the leaf, producing two distinct lobes, hence the name *Ginkgo biloba* (two lobes) (Fig. 1).

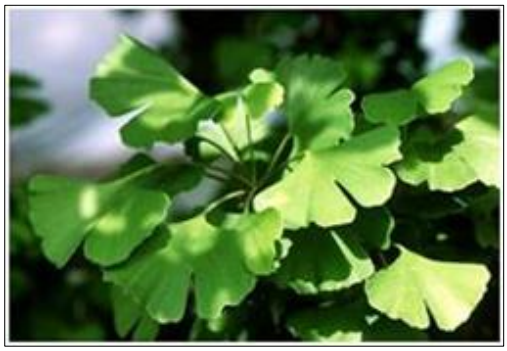

Figure 1 Leaves

Ginkgo leaf is also used orally for preventing acute mountain sickness and aging, regulating gastric acidity, improving liver and gallbladder function, regulating bacterial flora, controlling blood pressure. It is also used orally to treat asthma, allergies, bronchitis, and for various disorders of the central nervous system [8-9]

4.2. Trunk

A *Ginkgo biloba* tree can reach 30- 40m in height and a spread of 8meters. Trunk can become about 3-4 meters wide in diameter. It is straight columnar and sparingly branched. Young trees have usually a central trunk, pyramidal in shape, with regular, lateral, ascending, asymmetrical branching. It fissures rough furrows with the age [10] (Fig. 2).

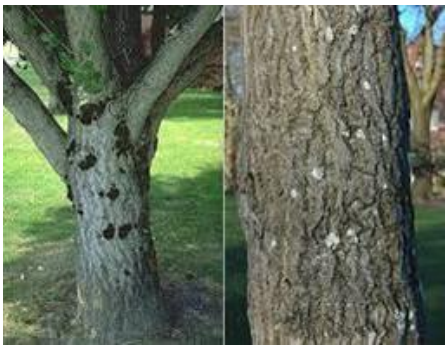

Figure 2 Trunk

4.3. Fruits

Female ginkgo tree bears oval to round, 2.5–3.5 × 1.6–2.2 cm fleshy fruits about the size of small jujube (Chinese date). Fruit is normally green when young turning to pale yellow when mature. Its outer, nasty smelling pulp (exocarp) is known botanically as sarcotesta.

Figure 3 Fruits

A single hard shelled seed enclosing edible embryo (kernel) is situated at the center of fruit. Ginkgo kernels measure about 1.5-2 cm in length and 1 cm in diameter and feature light jade green hue (Fig. 3).

4.4. Flowers

Female flower display an abundance of ovules in pairs on stalks each containing an egg cell, initially very green, but later turning greenish yellow, then orange and brown. The male flowers are ivory-colored, catkin-like pollen cones (microsporangia), 3–6 on each short shoot containing boat-shaped pollen sacs with widely gaping slit (Fig. 4).

Figure 4 Flowers

4.5. Seeds

The mature seed of Ginkgo is relatively large (20-30 mm x 16-24 mm) and consists of an embryo embedded in the tissue of the female gametophyte surrounded by a thick seed coat. This seed coat consists of a soft, fleshy outer layer (sarcotesta), a hard, stony middle layer, and a thin, membranous inner layer. The seed, devoid of the fleshy sarcotesta, is generally referred to as the Ginkgo "nut," with dimensions of 19-30 mm x'll-14 mm [9-14] (Fig. 5).

Figure 5 Seeds

5. Phytoconstituents of plant

The major bioactive compounds of Ginkgo are reported to be terpenoids, flavonoids, biflavonoids, organic acids, polyprenols, and many others. Of these, Ginkgolide A, Ginkgolide B, Ginkgolide C, Bilobalide, Ginkgotoxin, ginkgolides and bilobalide are the major constituents. Ginkgolides can be classified in five forms (A, B, C, J, and M), all having the same molecular geometrical skeleton but different numbers and geometric locations of hydroxyl functional groups. Ginkgolides A, B, and C, and bilobalide have been shown to increase circulatory perfusion, antagonize platelet activating factor (PAF), have neuroprotective effects, and serve as cognitive activators. The flavone glycosides possess antioxidant and mild platelet aggregation inhibiting activities [15-16].

A standardized leaf extract of *G. biloba*, known as EGb 761, contains 24% flavonoid glycosides, 6% terpenoids, 5%–10% organic acids, and other constituents, and are responsible for numerous health benefits. The flavonoids present primarily as glycosides. Major and minor flavonoids are described below. Standardized extracts of ginkgo leaves are frequently formulated to contain 24% flavonoids and 6% lactones. Other important constituents found in ginkgo include

biflavonoids and traces of alkylphenols, such as ginkgolic acids. Ginkgo also contains ginkgotoxin, which has been reported to be structurally related to vitamin B6 [17-18].

The main active ingredients of *Ginkgo biloba* extract (GbE) are flavones and flavone glycosides ginkgolides, catechin, diterpene, lactones, ascorbic acid, iron-based superoxide dismutase sesquiterpenes p-hydroxybenzoic acid.

- Major flavonoids

Major flavonoids are quercetin-3-β-D-glucoside, quercitrin and rutin, etc.

- Minor flavonoids

Minor flavonoids are Quercetin,Kaempferol and sorhamnetin

- Lactone components [19-22].

6. Nutritional value

Other than above phytoconstituents, the plant is rich in nutritional source (Table 3).

Table 3 Nutritional value of plant

Nutrition	Amount
Vitamin B3 (Niacin)	6 mg (37.50%)
Copper, Cu	0.274 mg (30.44%)
Carbohydrate	37.6 g (28.92%)
Vitamin B6 (Pyridoxine)	0.328 mg (25.23%)
Vitamin B1 (Thiamin)	0.22 mg (18.33%)
Phosphorus, P	124 mg (17.71%)
Vitamin C (Ascorbic acid)	15 mg (16.67%)
Tryptophan	0.071 g (16.14%)
Threonine	0.268 g (15.23%)
Vitamin B9 (Folate)	54 µg (13.50%)
Valine	0.283 g (13.40%)
Iron, Fe	1 mg (12.50%)
Isoleucine	0.209 g (12.50%)
Potassium, K	510 mg (10.85%)
Calories in (100g)	182 K cal

7. Pharmacological activities

The plant is reported to show a numerous pharmacological activity.

7.1. Alzheimer's disease

Ginkgo biloba extract (GBE) standardized to 24% Ginkgo flavon glycosides and 6% terpenoids shows great benefit in senility and AD; increases brain functional capacity; normalizes Ach receptors in hippocampus of aged animals, increasing cholinergic transmission. GBE helps reverse or delay mental deterioration only in early stages of AD; may help patient maintain normal life, avoid nursing home; improves Clinical Global Impressions score, stabilizes AD, and significantly improves mental function without side effects[23].

7.2. Hepatoprotective effects

In a *Gingko biloba* composite (GBC) was suggested that GBC was effective in halting the development of liver fibrosis of chronic hepatitis. *Gingko biloba* can also be used to protect the liver from carbon tetrachloride damage. Ginkgo has not been specifically linked to liver injury, either in the form of transient serum enzyme elevations or clinically apparent acute liver injury. Indeed, ginkgo is sometimes used to treat acute or chronic liver injury [24].

7.3. Acute pancreatitis

Acute pancreatitis is an inflammatory condition of the pancreas. The plant extract is demonstrated to be highly advantageous in case of acute pancreatitis. The extract reduces serum amylase as well as lipase level. This action of the extract is dependent on the free radical scavenging effect [25].

7.4. Antioxidants effects

Ginkgo contains high levels of flavonoids and terpenoids, which are compounds known for their strong antioxidant effects. Antioxidants combat or neutralize the damaging effects of free radicals. Free radicals are highly reactive particles that are produced in the body during normal metabolic functions, such as converting food to energy or detoxification [26-28].

7.5. Sexual dysfunction

G. biloba extract have shown positive result on sexual dysfunction. Extract is potent in treating sexual dysfunction which is induced due to intake of antidepressant drugs. The impotency is considered to be due to selective serotonin reuptake inhibitors (SSRI), serotonin and nor epinephrine reuptake inhibitors (SNRI), monoamine oxidase inhibitor (MAOIs), and tricyclics. On combination with sex therapy the extract was effective for sexual response arousal [29].

7.6. Glaucoma treatment

The extract elevates the ophthalmic artery end diastolic velocity and do not produce any effect on systemic arterial blood pressure, intra ocular pressure or heart rate. Flavonoids, often found in Ginkgo biloba, had a beneficial impact on glaucoma, particularly in terms of increasing ocular blood flow and potentially halting the progression of visual field loss. More quality research is warranted to determine the role in treating glaucoma [30-31].

7.7. Hypolipidemic activity

Gingko biloba extract can be used as hypolipidemic agent though not as effective as the cholesterol lowering agentlovastatin. The flavonoid content of the plant is assumed to be responsible for their hypolipidemic action and the plant is estimated for their hypolipidemic action and the plant is estimated to contain 24% flavonoids [32].

7.8. Antibacterial activity

The compounds of plant showed high antimicrobial activity against Gram-positive and Gram-negative bacteria, including several food-borne pathogens. In particular, compounds 5-7 and 8-10, containing phenolic acids and bilobols, respectively, were highly effective against *Salmonella enteric serovar Typhimurium, Listeria monocytogenes, Listeria innocua, Streptococcus pyogenes, Escherichia coli,* and *Shigella dysenteriae*. On the opposite, compounds 1-4, containing cardanols, showed little antibacterial activity [33-35].

7.9. Platelet activating factor antagonist

Platelet activating factor is a phospholipid which act as activator as well as a mediator in many leucocytes function, platelet aggregation and inflammatory process. Gingolide which is the terpene present in the plant has been reported with unique platelet activating factor antagonist activity [36-37].

7.10. Dementia and cognitive impairment

Ginkgo has been repeatedly evaluated for its ability to reduce anxiety, stress and other symptoms associated with Alzheimer's disease and cognitive decline associated with aging. Some studies show a marked reduction in the rate of cognitive decline in people with dementia using ginkgo, but others fail to replicate this result [38-39].

7.11. Vertigo

Ginkgo biloba extract could reduce the intensity, frequency, and duration of vertiginous syndrome compared (47% in the EGb group compared to 18% in the placebo group). Another randomized controlled trial in 2014 showed that there

was no statistically significant difference in vertigo treatment outcomes between Ginkgo biloba versus betahistine group though EGb had a better tolerance profile. Again, due to the lack of strength of the evidence, more studies are necessary to establish the efficacy of Ginkgo biloba in treating vertigo.

7.12. Tinnitus

Gingko biloba was effective in patients with a primary complaint of tinnitus. GB extracted data from systematic reviews concluded the use of *Ginkgo biloba* did not alleviate the severity of tinnitus or improve the quality of life of patients [40-42].

8. Analysis of plant's extract

There are many analytical tools that are used for the analysis of various pharmaceutical and herbal formulations, crude drugs and their extracts [43-65]. These methods include UV-spectrophotometry, gas chromatography, HPLC, HPTLC, etc [65-110]**.**

9. Conclusion

Thus, the plant could be used as an herbal remedy to treat many conditions. It may be best known as a treatment for dementia, Alzheimer's disease, and fatigue. It's often used to treat mental health conditions, Alzheimer's disease, and fatigue. Other conditions it's used to treat are: anxiety and depression, schizophrenia, insufficient blood flow to the brain, blood pressure problems, altitude sickness, erectile dysfunction, asthma, neuropathy, cancer, premenstrual syndrome, attention deficit hyperactivity disorder (ADHD), macular degeneration.

Compliance with ethical standards

Acknowledgments

We express our sincere thanks to Shri. Yogendraji Gode and Dr. Yogeshji Gode, IBSS's Dr. Rajendra Gode Institute of Pharmacy, Amravati and Dr. Rajendra Gode College of Pharmacy, Amravati (India).

Disclosure of conflict of interest

The author declares no conflict of interest.

References

[1] Hori T, Ridge RW, Tulecke W, Del Tredici P, Tremouillaux Guiller, Tobe JH. Ginkgo biloba- A global treasure. From biology to medicine. Springer, Tokyo. 1997.

[2] Singh B, Kaur P, Gopichand, Singh RD, Ahuja PS. Biology and chemistry of Ginkgo biloba, Fitoterapia. 2008; 79: 401-418.

[3] Yang G, Wang Y, Sun J, Zhang K, Liu J. Ginkgo biloba for Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Curr Top Med Chem. 2016; 16(5): 520-8.

[4] Chan PC, Xia Q, Fu PP. Ginkgo biloba leave extract: biological, medicinal, and toxicological effects. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2007; 25(3): 211-44.

[5] Hori T, Ridge RW, Tulecke W, Del Tredici P, Tremouillaux-Guiller J, Tobe H. editors. Ginkgo biloba-A Global Treasure. Tokyo: Springer-Verlag. 1997; 173-81.

[6] Isah T. Rethinking Ginkgo biloba L.: Medicinal uses and conservation. Pharmacogn Rev. 2015; 9(18): 140-148.

[7] Razna K, Sawinska Z, Ivanisova E, Vukovic N, Terentjeva M, Stricik M, Kowalczewski PL, Hlavackova L, Rovna K , Ziarovska J, Kacaniova M. Properties of Ginkgo biloba L.: Antioxidant Characterization, Antimicrobial Activities, and Genomic MicroRNA Based Marker Fingerprints. Int. J. Mol. Sci. 2020; 21: 3087.

[8] Gilman EF, Watson DG. Ginkgo biloba Maidenhair Tree. Fact Sheet. 1993; ST-273: 1–3.

[9] Yoshikawa T, Naito Y, Kondo M. Ginkgo biloba leaf extract: review of biological actions and clinical applications. Antioxid Redox Signal. 1999; 1(4): 469-80.

[10] Gunkle JE, Thimann KV, Wetmore RH. Studies of development in long shoots and short shoots of Ginkgo biloba L., part IV. Growth habit, shoot expression and the mechanism of its control. Am J Bot. 1949; 36: 309–16.

[11] Holt B, Rothwell G. Is Ginkgo biloba (Ginkgoaceae) really an oviparous plant? Am J Bot. 1997; 84: 870.

[12] Lang F, Hoerr R, Noeldner M, Koch E. Ginkgo biloba extract EGb 761®: From an ancient Asian plant to a modern European herbal medicinal product. Wagner H, Ulrich-Merzenich G, editors. Vienna: Springer. 2013; 431-70.

[13] Van Beek TA. J Chromatogr A. Chemical analysis of Ginkgo biloba leaves and extracts. 16 Aug 2002; 967(1): 21-55.

[14] Prajapati, Purohit, Sharma, Kumar. A handbook of medicinal plants A complete source book, Updesh Purohit for Agrobios, Section II. 252 – 253.

[15] AR. Mullaicharam. A Review on Evidence Based Practice of Ginkgo biloba in Brain Health AR. Mullaicharam. 2013; 1(1): 24-30.

[16] Ahlemeyer B, Krieglstein J. Neuroprotective effects of Ginkgo biloba extract. Cell Mol Life Sci 2003; 60(9): 1779-1792.

[17] Vasseur M, Jean T, Defeudis FV, Drieu K. Effects of repeated treatments with an extract of Ginkgo biloba (EGb 761), bilobalide and ginkgolide B on the electrical activity of pancreatic β cells of normal or alloxan-diabetic mice: an ex vivo study with intracellular microelectrodes. Gen. Pharmacol. 1994; 25(1): 31–46.

[18] Augustin S, Rimbach G, Augustin IL, Schliebs R, Wolffram S, Cermak R. Effect of a short-and longterm treatment with Ginkgo biloba extract on amyloid precursor protein levels in a transgenic mouse model relevant to Alzheimer's disease. Arch Biochem Biophys. 2009; 481(2): 177-1782.

[19] Shi C, Liu J, Wu F, Yew DT. Ginkgo biloba extract in Alzheimer's disease: from action mechanisms to medical practice. Int J Mol Sci. 2010; 11(1): 107-23.

[20] Shenoy KA, Somayaji SN, Bairy KL. Evaluation of hepatoprotective activity of Ginkgo biloba in rats.Indian Journal of Physiology and Pharmacology. 01 Apr 2002; 46(2):167-174.

[21] Xiao-Wu Xu, Xiao-Min Yang, Yong-Heng Bai, Yan-Rong Zhao, Gong-Sheng Shi, Jian-Guo Zhang, Yi-Hu Zheng. Treatment with Ginkgo biloba extract protects rats against acute pancreatitis-associated lung injury by modulating alveolar macrophage. 2014; 9(1): 43–48.

[22] Smith JV, Luo Y. Studies on molecular mechanisms of Ginkgo biloba extract. Appl. Microbiol. Biotechnol. 2004; 64: 465-472.

[23] Ellnain-Wojtaszek. M, Kruczy nski Z, Kasprzak J. Analysis of the content of flavonoids, phenolic acids as well as free radicals from Ginkgo biloba L. leaves during the vegetative cycle. Acta Pol. Pharm. 2001; 58: 205–209.

[24] Torres de Pinedo A, Peñalver P, Morales JC. Synthesis and evaluation of new phenolic-based antioxidants: Structure–activity relationship. Food Chem. 2007; 103: 55–61.

[25] Cohen AJ, Bartlik B. Ginkgo biloba for antidepressant-induced sexual dysfunction. Journal of Sex and Marital Therapy. 1998; 24: 139–143.

[26] Harris A, Gross J, Moore N, et al. The effects of antioxidants on ocular blood flow in patients with glaucoma. 2018;96(2):237-241.

[27] Park JW, Kwon HJ, Chung WS, et al. Short-term effects of Ginkgo biloba extract on peripapillary retinal blood flow in normal tension glaucoma. Korean J Ophthalmol. 2011; 25: 323–328.

[28] Arunkumar Dubey, Ahalya Devi, Gopalankutty, Ravi Pathiil Shankar. Hypolipidemic activity of standardized Gingko biloba extract 761 in wistar rats, Iranian journal of pharmacology and therapeutics. 2005; 4(1): 9-12.

[29] SC Sati, Savita Joshi. Antibacterial activities of Gingko biloba L. leaf extracts, the scientific world journal. 11 2011; 2237- 2242.

[30] Kauraman Deep, Nain parminder, Nain jaspreet. *In vitro* antimicrobial and anti oxidant study of gingko biloba bark extract, IJRP. 2012; 3(6): 116-119.

[31] Carraturo A, Raieta K, Tedesco I, Kim J and Russo GL. Antibacterial Activity of Phenolic Compounds Derived from Ginkgo biloba Sarcotestas against Food-Borne Pathogens. Microbiology Research Journal International. 2014; 4(1): 18-27.

[32] Braquet. P, Hosford. D, Ethno pharmacology and the development of natural PAF antagonists as therapeutic agents, J. Ethnopharmacol. 1991; 32: 135-138.

[33] Birkle DL, Kurian P, Braquet P, Bazan NG. Plateletactivating factor antagonist BN52021 decreases accumulation of free polyunsaturated fatty acid in mouse brain during ischemia and electroconvulsive shock, Journal of Neurochemistry. 1988 Dec; 51(6): 1900-1905.

[34] Herrschaft H, Nacu A, Likhachev S, Sholomov I, Hoerr R, Schlaefke S. (Ginkgo biloba extract EGb 761(R) in dementia with neuropsychiatric features: A randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240mg. 2012; 46: 716-723.

[35] Weitbrecht WU, Jansen W. Primary degenerative dementia: therapy with Ginkgo biloba extract. Placebo-controlled double-blind and comparative study. 1986; 104: 199–202.

[36] Sokolova L, Hoerr R, Mishchenko T. Treatment of Vertigo: A Randomized, Double-Blind Trial Comparing Efficacy and Safety of Ginkgo biloba Extract EGb 761 and Betahistine. International Journal of Otolaryngology. 2014; 682439.

[37] Hallak B, Schneider A, Güntensperger D, Schapowal A. Standardized Ginkgo biloba Extract in the Treatment of Vertigo and/or Tinnitus: A Review of the Literature. 2021; 10(02).

[38] J Grassmann. Terpenoids as plant antioxidants. 2005; 72: 505-35.

[39] Bruce J Diamond, Samuel C Shiflett, Nancy Feiwel, Robert J Matheis, Olga Noskin, Jennifer A. Richards, Nancy E. Schoenberger, PhD Ginkgo biloba extract: Mechanisms and clinical indications. 2000; 81(5) : 668-678.

[40] Attella MJ, Hoffman SW, Stasio MJ, Stein DC. Ginkgo bilobu extract facilitates recovery from penetrating brain injury in adult male rats. Exp Neurol. 1989; 105: 62-71.

[41] Janssens D, Michiels C, Delaive E, Eliaers F, Drieu K, Remacle J. Protection of hypoxia-induced ATP decrease in endothelial cells by Ginkgo bilobu extract and bilobalide. Biochem Pharmacology. 1995; 50: 991-9.

[42] More MP, Dongare PN, Patinge PA, Bakal RL, Motule AS. An overview on phytoconstitute and utilisation of Lepidium sativum linn (Garden Cress). World Journal of Pharmacy and Pharmaceutical Science. 2021; 10(1): 710-719.

[43] Dongare PN, Motule AS, et al. An Overview on anticancer drugs from Marine source. World Journal of Pharmaceutical Research. 2021; 10(1): 950-956.

[44] Badukale NA, et al. Phytochemistry, pharmacology and botanical aspects of Madhuca indica: A review. Journal of Pharmacognosy and Phytochemistry. 2021; 10(2): 1280-1286.

[45] Gudalwar BR, et al. Allium sativum, a potential phytopharmacological source of natural medicine for better health. GSC Advanced Research and Reviews. 2021; 06(03): 220–232.

[46] Manwar J, Mahadik K, Paradkar A. Plackett–Burman design: A statistical method for the optimization of fermentation process for the yeast Saccharomyces cerevisiae isolated from the flowers of Woodfordia fruticosa. Fermentation Technology. 2013; 2: 109.

[47] Wadekar AB, et al. Morphology, phytochemistry and pharmacological aspects of Carica papaya, an review. GSC Biological and Pharmaceutical Sciences. 2020; 14(03): 234-248.

[48] Manwar J, et al. Isolation, biochemical and genetic characterizations of alcohol-producing yeasts from the flowers of Woodfordia fruticosa. J Young Pharm. 2013; 5(4): 191-194.

[49] Manmode R, et al. Effect of preparation method on antioxidant activity of ayurvedic formulation kumaryasava. J Homeop Ayurv Med. 2012; 1: 114.

[50] Manmode R, et al. Effect of preparation method on antioxidant activity of ayurvedic formulation kumaryasava. J Homeop Ayurv Med. 2012; 1: 114.

[51] Manwar J, et al. Comparative antioxidant potential of Withania somnifera based herbal formulation prepared by traditional and non-traditional fermentation processes. Integrative Medicine Research. 2013; 2: 56–61.

[52] Khadatkar SN, et al. *In-vitro* anthelmintic activity of root of Clitoria ternatea linn. 2008; 4(13): 148-150.

[53] Khadatkar SN, et al. Preparations and evaluation of microcapsules of capsaicin. International Journal of Chemical Sciences. 2007; 5(5): 2333-2341.

[54] Malode GP, et al. Phytochemistry, pharmacology and botanical aspects of Murraya Koenigii in the search for molecules with bioactive potential - A review. GSC Advanced Research and Reviews. 2021; 06(03): 143–155.

[55] Padgilwar S, et al. Traditional uses, phytochemistry and pharmacology of Oroxylum Indicum: A Review. International Journal of Pharmaceutical and Phytopharmacological Research. 2014; 3(6): 483-486.

[56] Nikhare AM, et al. Morphological, Phytochemical and pharmacological aspects of Syzigium Cumini. International Journal of Medical, Pharmaceutical and Biological Sciences. 2021; 1(1): 1-11.

[57] Padgilwar SS, Manwar JV. Relative Influence of adrenergic β-agonist and antagonist on the inflammation and their interaction with aspirin. European Journal of Experimental Biology. 2013; 3(1): 467-472.

[58] Parbat AY, et al. Ethnopharmacological review of traditional medicinal plants as immunomodulator. World Journal of Biology Pharmacy and Health Sciences. 2021; 06(02): 043–055.

[59] Sahare AY, et al. Antimicrobial activity of Pseudarthria viscida roots. Asian Journal of Microbiology Biotechnology & Environmental Sciences. 2008; 10(1): 135-136.

[60] Sahare AY, et al. Hypericum perforatum: A Medicinal plant. Plant Archives. 2007; 7(2): 463-468.

[61] Malode LL, et al. Potential of medicinal plants in management of diabetes: An updates. GSC Advanced Research and Reviews. 2021; 08(01): 149-159.

[62] Nimbalwar MG, Gudalwar BR, Panchale WA, Wadekar AB, Manwar JV, Wadkute SK, Bakal RL. Pharmacognostic and Nootropic Aspects of Withania Somnifera: A Potential Herbal Drug as Memory Enhancer International Journal for Research in Applied Science & Engineering Technology (IJRASET). 2021; 9 (VIII): 1075-1081.

[63] Dongare PN, et al. An Overview on herbal cosmetics and cosmoceuticals. Int J Pharm Sci Rev Res. 2021; 68(1): 75-78.

[64] Sakhare TN, Dongare PN, Patinge PA, More MP, Motule AS, Bakal RL, Sawarkar HS. Review: Extraction of phytoconstituents by modern methods of extraction. Asio journal of Pharmaceutical and herbal medicine. 2021; 7(2): 06-15.

[65] Motule AS, et al. Development and physicochemical evaluation of bilayered transdermal patches of ondansetron hydrochloride Journal of Innovations in Pharmaceutical and Biological Sciences. 2021; 8(3): 17-23.

[66] Chaudhari KD, et al. Floating drug delivery system: An update of preparation and classification of formulation. Ijppr.Human. 2021; 21(1): 207-220.

[67] Chaudhari KD, et al. Comprehensive review on characterizations and application of gastro-retentive floating drug delivery system. GSC Advanced Research and Reviews. 2021; 07(01): 035-044.

[68] Dhamankar AK, et al. The novel formulation design of O/of ketoprofen for improving transdermal absorption. Int J of Pharm Tech Res. 2009; 4(1Suppl): 1449-1457.

[69] Jain CM, et al. Review on approaches for development and evaluation of extended-release tablets. Review on approaches for development and evaluation of extended-release tablets. World Journal f Pharmacy and Pharmaceutical Sciences. 2021; 10(4): 542-554.

[70] Kadam CY, et al. Design and *In vitro* characterization of phase transition system using rivastigmine tartrate for nasal drug delivery system. World Journal of Pharmaceutical Research. 2018; 8(1): 815-829.

[71] Malode GP, et al. Formulation and evaluation of a novel floating in situ gel system for the treatment of peptic ulcer. World Journal of Pharmacy and Pharmaceutical Sciences. 2021; 10(4): 416-1433.

[72] Manwar J, Kumbhar DD, Bakal RL, Baviskar SR, Manmode RS. Response surface based co-optimization of release kinetics and mucoadhesive strength for an oral mucoadhesive tablet of cefixime trihydrate. Bulletin of Faculty of Pharmacy. Cairo University. 2016; 54: 227–235.

[73] Manwar JV, et al. Diclofenac Sodium Loaded Nanosized Ethosomes: An Investigation on Z-Average, Polydispersity and Stability. J Pharm Res. 2017; 1(3): 000115.

[74] Nimbalwar MG, et al. A brief review on principle, preparation and properties of proniosomes: A provesicular drug delivery system. World J Pharm Sci. 2021; 9(5): 149-162.

[75] Nimbalwar MG, et al. Fabrication and evaluation of ritonavir proniosomal transdermal gel as a vesicular drug delivery system. Pharmacophore. 2016; 7(2): 82-95.

[76] Patil SS, et al. Ultrasound-Assisted Facile Synthesis of Nanostructured Hybrid Vesicle for the Nasal Delivery of Indomethacin: Response Surface Optimization, Microstructure, and Stability. AAPS PharmSciTech. 2019; 20(3): 97.

[77] Pophalkar PB, et al. Development and evaluation of ondansetron medicated jelly. World Journal of Pharmaceutical Research. 2018; 7(19): 1252-1263.

[78] Shubham Garibe, et al. Bioequivalence study of test formulations T1 and T2 Nadolol tablets USP with reference formulation in healthy adult, human subjects under fed conditions. Ijppr.Human. 2021; 20(2): 20-28.

[79] Suroshe RS, et al. Development and characterization of osmotic drug delivery system of model drug. World Journal of Pharmaceutical Research. 2018; 7(18): 1158-1171.

[80] Vaidya VM, et al. Design and in vitro evaluation of mucoadhesive buccal tablets of terbutaline sulphate. Int J PharmTech Res. 2009; 1(3): 588-597.

[81] Vohra M, et al. Bioethanol production: Feedstock and current technologies. Journal of Environmental Chemical Engineering. 2014; 2 (1): 573-584.

[82] Gulhane CA, Motule AS, et al. An Overview On Nail Drug Delivery System: A Promising Application for Various diseases. European Journal of Biomedical and Pharmaceutical Sciences. 2021; 8(2): 104-110.

[83] Dongare PN, Motule AS, et al. Recent development in novel drug delivery systems for delivery of herbal drugs: An updates. GSC Advanced Research and Reviews. 2021; 8(08): 008-018.

[84] Mankar SS, Motule AS, et al. Progress in development of herbal cosmeceuticals: An current status and prospects. International Journal of Medical, Pharmaceutical and Biological Sciences. 2021; 1(2): 1-11.

[85] Bakal RL, et al. Spectrophotometric estimation of amitriptyline HCl and chlordiazepoxide in pharmaceutical dosage form. Indian Journal of Pharmaceutical Education and Research. 2008; 42: 23–26.

[86] Bakal RL, et al. Spectrophotometric estimation of amitriptyline HCL and chlordiazepoxide in tablet dosage form. International Journal of Chemical Sciences. 2007; 5(1): 360–364.

[87] Gulhane CA, et al. UV- Visible Spectrophotometric estimation of azithromycin and cefixime from tablet formulation by area under curve method. World Journal of Pharmaceutical Sciences. 2021; 9(6): 163-168.

[88] Manwar JV, et al. Development of newer RP-HPLC method for simultaneous estimation of cefiximeand linezolide in bulk drugs and combined dosage form. International Journal of Pharmacy and Life Sciences. 2021; 12(1): 26-31.

[89] Gulhane CA, et al. Liquid chromatographic method for simultaneous estimation of thiocolchicoside and etoricoxib from tablet formulation. Asian Journal of Pharmaceutical Analysis. 2021; 11(2): 118-122.

[90] Manwar JV, et al. Application of simultaneous equation method for the determination of azithromycin and cefixime trihydrate in tablet formulation. Research Journal of Pharmacy and Technology. 2017; 10(1): 108-112.

[91] Bagade SB, et al. Simultaneous high performance thin layer chromatographic estimation of methocarbamol and nimesulide in combined dose tablet. Journal of Pharmaceutical Research. 2006; 5(4): 137-140.

[92] Manwar J, Mahadik K, Paradkar A, et al. Gas chromatography method for the determination of non-ethanol volatile compounds in herbal formulation. International Journal of Analytical and Bioanalytical Chemistry. 2013; 3(1): 12-17.

[93] Panchale WA, et al. Concurrent analysis of ambroxol HCl and salbutamol sulphate from tablet formulation by RP-HPLC. GSC Biological and Pharmaceutical Sciences. 2020; 13(03): 197-202.

[94] Panchale WA, et al. RP-HPLC method for simultaneous determination of escitalopram oxalate and flupentixol HCl in tablet dosage form. GSC Biological and Pharmaceutical Sciences. 2021; 14(01): 169-174.

[95] Panchale WA, et al. RP-HPLC method for simultaneous determination of metformin hydrochloride and linagliptine in pharmaceutical dosage form. World Journal of Pharmaceutical and Medical Research. 2021; 7(5): 234- 238.

[96] Panchale WA, et al. Simultaneous estimation of salbutamol sulphate and ambroxol HCl from their combined dosage form by UV-Vis spectroscopy using simultaneous equation method. GSC Biological and Pharmaceutical Sciences. 2020; 13(03): 127-134.

[97] Sabhadinde AF, et al. Novel RP-HPLC method for simultaneous analysis of chlorthalidone and telmisartan from combined dosage form. Ijppr.Human. 2020; 20(1): 491-502.

[98] Manwar JV, et al. Experimental design approach for chromatographic determination of ketorolac tromethamine from bulk drug and tablet formulation. Global Journal of Pharmacy & Pharmaceutical Sciences. 2017; 3(2): 38-47.

[99] Manwar JV, et al. Rapid RP-HPLC method for estimation of zidovudine from tablet dosage form. Der Chemica Sinica. 2011; 2(5): 152-156.

[100] Manwar JV, et al. Response surface based optimization of system variables for liquid chromatographic analysis of candesartan cilexetil. Journal of Taibah University for Science. 2017; 11: 159–172.

[101] Manwar JV, Mahadik KR, Paradkar AR, et al. Determination of withanolides from the roots and herbal formulation of Withania somnifera by HPLC using DAD and ELSD detector. Der Pharmacia Sinica. 2012; 3: 41–46.

[102] Nimbokar SW, et al. Development and validation of RP-HPLC method for determination of zonisamide from tablet formulation. World Journal of Pharmaceutical and Medical Research. 2021; 7(2): 196-200.

[103] Panchale WA, Bakal RL. First-order derivative spectrophotometric estimation of gemifloxacin mesylate and ambroxol HCl in tablet dosage form. GSC Biological and Pharmaceutical Sciences. 2021; 14(2): 029-036.

[104] Manmode RS, et al. Stability indicating HPLC method for simultaneous determination of methocarbamol and nimesulide from tablet matrix. Der Chemica Sinica. 2011; 2(4): 81-85.

[105] Panchale WA, et al. Chromatographic analysis of famotidine, paracetamol and ibuprofen from tablet formulation. Research Journal of Pharmacy and Technology. 2019; 12: 231-263.

[106] Motule AS, et al. Ethnopharmacological relevances of herbal plants used in cosmetics and toiletries preparations. Biological and Pharmaceutical Sciences. 2021; 16(2).

[107] Nimbalwar MG, et al. An overview of characterizatons and applications of proniosomal drug delivery system. GSC Advanced Research and Reviews. 2021; 07(02): 025-034.

[108] Prajakta N. Dongare, Ravindra Bakal, Manisha More, Prerana Patinge. Review: Carbon nanotubes in Cancer therapy. International journal of Pharmacy and Pharmaceutical research. Dec 2020; 20(1): 759-765.

[109] Bartere SA, Malode LL, et al. Exploring the potential of herbal drugs for the treatment of hair loss. Biological and Pharmaceutical Sciences. 2021; 16(02), 212–223.

[110] Gulhane CA, et al. Black phosphorus nanosheet-based new drug delivery system for the anticancer agents: A review. 2021;16(02):014–027.