

A Review on Anti-Osteoporotic Potential of *Ficus religiosa* Fruit and its Constituents

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Abstract

Ficus religiosa or commonly known as “Peepal” is a large deciduous or semi-evergreen tree that has been remarkably and indigenously utilized due to its immense pharmacological importance in the cure of disorders of Central Nervous System, endocrine system, Gastrointestinal system, reproductive system, respiratory system and various infectious diseases etc. Its Fruits are rich in mineral content like calcium, phosphorous, zinc which induces osteoblastic differentiation and bone turnover rate. The high content of flavanoids (Quercetin, myricetin, Kaempferol) possess antioxidant ability which can be utilized to treat osteoporosis by reducing the oxidative stress caused by reactive oxygen species. Moreover high serotonin content in ficus fruits also alters bone remodeling physiology on the basis of its site of availability. This review might provide a platform to those who will be interested in studying further this fruit, either for analyzing phytochemical profiling or its anti-osteoporotic usage.

Keywords: *Ficus religiosa* fruit, Osteoporosis, Antiosteoporotic potential

1. Introduction

Humans have been fortunate enough to extract, obtain and use every bit of plants from thousands of years in the form of medicines, beverages, cosmetics, seasonings and dyes. These herbal medicines from every plant species provides natural constituents which has the ability to uplift health and reduces ailments. Currently plant research is increasing day by day focusing on natural potential of medicinal plants used among various traditional systems due to which researchers interest have been increasing every minute in the use of herbal medicines [1]. *Ficus religiosa* possess a vital role among herbal plants as every parts of this mythological tree in the form of its leaves, barks, fruits or seed bears therapeutic properties due to its abundance in several important bioactive compounds such as flavonoids, alkaloids,

tannins, saponins etc. Every part of this tree is considered valuable by the modern pharmacological industry on the account of its anti-convulsant, antimicrobial, anti-inflammatory, analgesic and wound healing abilities [2].

Ficus religiosa or commonly known as “Peepal” is a large deciduous or semi-evergreen tree with 30 meters height and 3 meter width which massively grow as a boulevard along the roadside or as a mythological figure in the temples which are considered sacred among various religions of Hinduism, Buddhism and Jainism [3]. The Ficus tree or ‘fig’ grows and originates in the regions of Northern and Eastern India along with some neighbouring countries like Pakistan, Nepal, China, Sri Lanka. *Ficus religiosa* tree has been remarkably and indigenously utilized in Ayurveda, Unani, Homeopathy and Siddha system of medicines due to its immense pharmacological importance in the cure of disorders of Central Nervous System, endocrine system, Gastrointestinal system, reproductive system, respiratory system and various infectious diseases etc. [4]. Phytochemical investigation on entire parts of *Ficus religiosa* has provided the beneficial presence of phenolic components like tannins and flavonoids along with phytosterols, amino acids, hydrocarbons, furanocoumarins, volatile components and many more secondary metabolites [5]. According to the Ministry of Ayush, the dried fruits like figs, raisins or prunes are enriched with fiber and a well developed fig with succulent flesh are naturally enriched with antioxidants, phytonutrients, vitamins and minerals. Thus, this review focuses the potential traditional and pharmacological ability of *Ficus religiosa* fruits along with its relevance in bone health or osteoporosis. The ripe fruits of *F. religiosa* are comestible and good source of proteins and mineral [3]. Fruits are rich in phytochemicals like flavonoids, terpenoids, glycosides etc. which cures asthma and digestive disorders [1].

However, the scientific information of *Ficus religiosa* fruit is not in the proper documentation for reference, and also existence of scientific knowledge is limited. Therefore, this review might provide a platform to those who will be interested in studying further this fruit, either for analyzing phytochemical profiling or its anti-osteoporotic usage.

1.1 Botanical description

Ficus religiosa is a massive deciduous tree which grows upto the height of 35m and bears either single or paired figs on the lateral side of the leafy branchlets along with many small flowers. The fruits are usually smooth, depressed or globose in shape and about 2-3 cm in diameter which are green in color when unripe and finally turns purple when ripe with sweet taste. Although the fruits are available throughout the year but they are harvested during May and June [3].



Figure 1. Fruits of *Ficus religiosa*

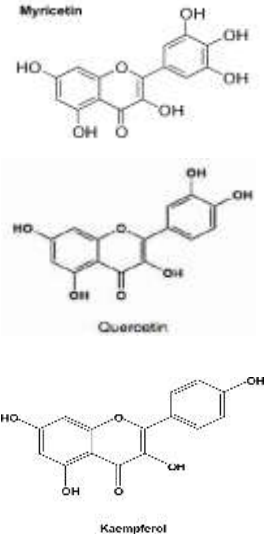
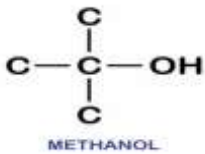
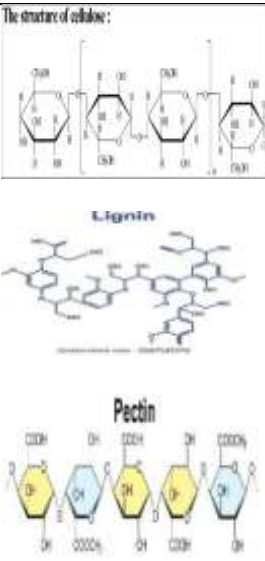
2. Phytochemistry and medicinal attributes

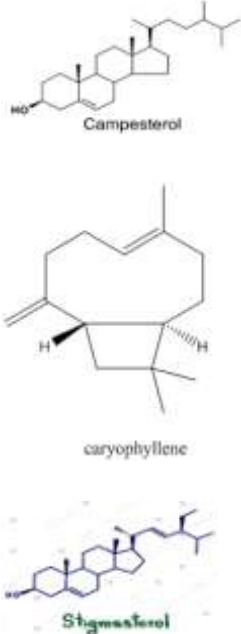
The sacred fig or *Ficus religiosa* is not being marketed commercially, but it is commonly used by ayurveda practitioners for treating various ailments. It is also consumed fresh for its dehydration properties. Various studies have shown that figs of *Ficus religiosa* are a great source of various compounds such as phenolics, flavonoids, antioxidants, carbohydrates, proteins and fibres. The preliminary phytochemical screening of *ficus religiosa* fruit under standard procedure divulged the presence of phenolic compounds and amino acids in aqueous and 90% methanol extract, steroids in petroleum ether (60-80°C) extract and carbohydrates in aqueous extract [6]. Fruits of *ficus religiosa* contains major and considerable amount of flavonoids and various other phenolic components [7]. The Reverse Phase High Performance Liquid Chromatographic (RP-HPLC) with UV detection observed that Fruit of *ficus religiosa* contains myricetin (694 mg/kg), quercetin (256.3 mg/kg) and kaempferol (160.8 mg/kg). Generally, higher extract yields, better antioxidant activity, and higher total phenolic contents were obtained using organic solvents such as 80% hydro-methanol compared to absolute organic solvents. The analgesic and anti-inflammatory activity shown by the extract of *Ficus religiosa* fruits through inflammatory paw edema test are attributed individually or collectively to the flavonoids, phenols, terpenoids and glycosides present in it [8]. *F. religiosa* fruits are a brilliant source of fiber as the ripe fruits constitute hemicellulose (19.0%), cellulose (40.3%), lignin (34.9%) and pectin (5.8%) [9]. Immature fruits contain a significant amount ADF (Acid detergent fibre), NDF (Neutral Detergent Fibre) and ADL (Acid Detergent lignin) [10].

The fruit pulp contains asparagine and tyrosine, which are the most abundant amino acids. It also has alanine, aspartic acids, glycine, and norvaline [5]. The fruit of sacred figs contains various volatile compounds, such as simple aliphatics (undecane, tridecane, tetradecane), acyclic monoterpenes ((e)- β -ocimene, perillene), cyclic monoterpenes (α -pinene, β -pinene, camphene, α -terpinene and Limonene) and sesquiterpenes (β caryophyllene, β -bourbonene, δ -cadinene, α -copaene, α -ylangene). The high concentration of serotonin content in fruit extract of *ficus religiosa* exhibited anticonvulsant activities. [11]. The dried powder of sacred fig was added to make candies with phytochemical, nutritional, antioxidant and antimicrobial properties [3]. The main compounds detected by GC-MS in the extract of *Ficus religiosa* were Campesterol, Caryophyllene, Stigmasterol, β and α Amyrin. Stigmasterol is known to be a precursor in the formation of semi-synthetic progesterone hormone [12]. Campesterol has anti-microbial and antioxidant

properties that reduces the risk of heart diseases by lowering the saturated fat and cholesterol [13].

Table 1: Phytochemistry and Medicinal Attributes of *Ficus religiosa* Fruit

Compound	Constituents	Structure	Uses	Reference
Flavonols	Myricetin, Quercetin and Kaempferol	 <p>Myricetin</p> <p>Quercetin</p> <p>Kaempferol</p>	Antioxidant activity	[7]
Phenol	80%Hydro-methanol	 <p>METHANOL</p>	Anti-inflammatory activity	[7]
Fiber	Hemicellulose (19.0%), cellulose (40.3%), lignin (34.9%) and pectin (5.8%)	<p>The structure of cellulose:</p>  <p>Lignin</p> <p>Pectin</p>	Hypolipidemic activity	[9]
Phytosterol	Campesterol, Caryophyllene, Stigmasterol, β and α		Campesterol has anti-microbial and antioxidant properties	[12]

	Amylin.	 <p>Campesterol</p> <p>caryophyllene</p> <p>Stigmasterol</p>	Stigmasterol is known to be a precursor in the formation of semi-synthetic progesterone hormone	
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3. Traditional and contemporary uses

Ficus religiosa is one of the ancient religious tree with traditional therapeutic vitality in Indian customs. The famous sacred text of Hinduism, Atharaveda considers its therapeutic characteristics with holy medicinal herbs like Soma and Kustha [4]. Each and every parts of *Ficus religiosa* such as its roots, barks, fruits, leaves, seeds and even latex have been used either alone or in combination with other medicinal plants in overcoming various ailments. Currently research is at its peak to validate the ethnomedicinal utility of *Ficus religiosa* fruits.

TABLE 2: Traditional uses of *Ficus religiosa* fruit

Region/ System of medicines	Traditional activity	Part / preparation used	References
Ayurveda	Cardiac disorders	Riped fruits	[14], [15]
Unani	Laxatives and purgatives	Fruits	[14]
Unani	Aphrodisiac	Root bark and fruits	
Sonaghati, Sonbhadra, UP and Karnataka, India	Asthma and cough	4-6gm of fruit powder	[16]
Kali gandaki, watersheds, Nepal Mizoram, India	Respiratory disorders	Fruits Fruit juice (5ml, 3-5 times daily)	[17]
Bangladesh	Paralysis	Dried fruits	

Bangladesh	Fever	Dried fruits	[18]
Bangladesh	Tuberculosis	Dried fruits	
Bangladesh	Hemorrhoids	Dried fruits	

Osteoporosis is the most emerging metabolic disorder of the bone that affects mostly women at some point in their lives prominently due to fall or cease in ovarian estrogen formation after menopause which leads to high bone turnover rate in creates imbalance in bone remodeling that is, disturbance in rate of bone formation and bone resorption [19]. Alteration in calcium homeostasis causes imbalance in calcium regulating hormones such as parathyroid hormone and calcitonin which also causes increase in bone turnover [20].

In the recent study conducted among various age group people in Eastern Ghats of Andhra Pradesh during a period of 2014-2019, it was observed that out of total 77 species, ripen fruits of *Ficus religiosa* possess best and affordable potential in curing osteoporosis. According to the information collected from among the tribal doctors/ Gurus/ Vaidyas or local healers, riped and sun dried powdered fruits of *Ficus religiosa* when mixed with 500 gms of powdered organic jaggery and 10 gms of this powdered mixture is consumed with hot cow milk twice daily for 3 months helped in curing and treating osteoporosis and joint pain. Apart from this fruits also helped in regulating productive working of endocrine glands in the body [21]. Thus this review emphasizes the possible connection of *Ficus religiosa* fruit in the cure or prevention of osteoporosis based on its phytoconstituent importance.

4. Relevance of *Ficus religiosa* fruit in osteoporosis

4.1 Minerals and osteoporosis.

Verma and Gupta, (2015)[3] determined the minerals and heavy metal content in dried powdered figs of *Ficus religiosa* and concluded that the fig contains 4.8mg/100gm of Aluminium, 1.6mg/100gm of Boron, 848mg/100gm Calcium, 0.12mg/100gm Copper, 224mg/100gm of Mangesium, 165mg/100gm Phosphorous, 1.1mg/100gm Zinc, 6mg/100gm of Iron and many other contents such as Strontium, Titanium, Barium and Manganese. Minerals provide fruitful effects in human bones and body. According to the study conducted by United States Department of Agriculture, Boron showed productive role in suppression of postmenopausal osteoporosis by reducing the calcium excretion by 44% and activating VIT D. Half of the total manganese content of the body is located in bones wherein it promotes bone cell proliferation and functions. Magnesium allows effective absorption of calcium and together with calcium it maintains normal bone physiology and shares its role in formation of bone matrix and hydroxyapatite that offers bone rigidity. Deficiency of magnesium halts bone growth, reduction in osteoblastic activity and rise in oxyradicals that induces osteoclastic bone resorption [22]. Copper is a necessary mineral for bone development and maintenance as it plays a role in crosslinking of collagen and elastin. Zinc promotes osteoblastic formation and provides anabolic effect to bone [23].

4.2 Antioxidants and osteoporosis

Oxidative stress is the state where alteration in antioxidant activity and excessive accumulation of free radicals or reactive oxygen species (ROS) results in oxidative

damage of the cells thereby causing dysfunction of biological system [24]. The reactive oxygen species performs twofold functions in bone metabolism depending upon the physiological and pathological conditions. Under physiological condition the osteoclast produces ROS which degrades calcified bone tissues and participates in bone remodeling [25]. ROS being active inducers of cytokines and TNF are strongly involved in the bone loss related with estrogen deficiency. Thus, deficiency in estrogen promotes bone resorption by osteoclast since estrogen promotes oxidant defenses [24].

Reactive oxygen species such as hydroxyl radicals [OH·], superoxide anion radical [O²⁻·], hydrogen peroxide [H₂O₂] and nitric oxide [NO] often causes enzyme oxidation, protein oxidation and degradation but these effects are counterinteracted by the antioxidants such as superoxide dismutase [SOD], glutathione peroxidase [GPx] and catalase, since intake of antioxidants might protect bones from osteoporosis and speeds up fractured bone healing. Unfortunately no exact mechanism of free radicals and oxidative stress can be linked with osteoporosis but the study has shown that nitric oxide (NO) radical alters bone remodeling and bone loss as the paracrine and autocrine mediator of bone cells with regards to various stimuli such as pro-inflammatory cytokines, mechanical strains and sex hormones [24]. *Ficus religiosa* both possess antioxidant activities which may support the study since in osteoporotic patients, the lipid peroxidation level gets elevated and antioxidant enzymes gets reduced and oxidative stress condition occurs. The antioxidant activity of dried fruit extract of *Ficus religiosa* was determined against free radical 1, 1-diphenyl-2-picrylhydrazyl (DPPH) which assess the scavenging activities of many natural constituents such as anthocyanins, crude extracts of plants or phenolic compounds by donating a hydrogen ion and forming the reduced DPPH-H•. It was observed that in 0.05mg/ml of ethanolic extract of dried fruit of had the highest scavenging activity, i.e. 94.40%, followed by a methanolic extract of dried fruit of sacred fig which is 91.24% [3].

The study conducted by [26] (Sultana, Anwar and Ashraf, 2009) concluded that the antioxidant potential of the plant extract depends upon the extracting methods and solvent of extraction and it was perhaps proved by subjecting the fruit powder of *Ficus religiosa* to shaking and refluxing with different solvent such as absolute methanol and ethanol, 80% hydro-methanol and hydro-ethanol in order to determine the DPPH scavenging and percent inhibition of linoleic acid. Out of all solvents, 80% hydro-methanolic extract of *Ficus religiosa* fruits received by refluxing contained the highest amount of antioxidant components such as phenols and flavonoids and gives maximum antioxidant potential.

4.3 Flavonoids and osteoporosis

Aqueous organic solvent extract of *ficus religiosa* yields appreciable amount of total phenolic and total flavonoidal content as compared to absolute organic solvent. [7](Sultana and Anwar, 2008) determined the concentrations of flavonols namely myricetin, quercetin and kaempferol in *Ficus religiosa* fruit when extracted with acidified methanol and analysed by reverse phase high performance liquid chromatographic (RP-HPLC) with UV detection and observed that Fruit of *ficus religiosa* contains myricetin (694 mg/kg), quercetin (256.3 mg/kg) and kaempferol (160.8 mg/kg). Flavonoids derived from food especially

flavones such as quercetin, myricetin and kaempferol conducts various biological activities such as anti-inflammatory, anti-oxidant, anti-microbial, anti-thrombotic, anti-allergic, anti-atherogenic, cardioprotective and vasodilatory.

Kaempferol is a natural flavanoid used to ameliorate post menopausal symptoms and osteoporosis in Chinese woman. It is considered as an “ideal candidate flavanoid” for osteoporosis management since it inhibits bone resorption *in vitro* by inhibiting RANKL mediated differentiation of osteoclastic cells [27]. RANKL induces osteoclastic differentiation and activation which resorbs bone cellular matrix and leads to development of osteoporosis. Moreover the study conducted *in vitro* states that kaempferol might lowers the casualty of development of estrogen-dependent cancers more effectively in comparison with Hormone replacement therapy during osteoporosis treatment since kaempferol is an estrogen related receptor α and γ inverse agonist [28]. Owing to the above stated research on kaempferol in accordance with bone health, it was proved that 5mg/kg of kaempferol showed improvement in histomorphological parameters of bone such as B Pm, BV/TV, B Ar. And effectively ameliorates post- menopausal osteoporosis.

Quercetin- Quercetin is the member of naturally occurring flavanoid family which has shown marked antiosteoporotic activity *in vivo* as well as *in vitro*. Oral administration of quercetin and its subsequent derivatives are efficient in enhancing bone pathology and its biochemical parameters such as serum osteocalcin, alkaline phosphatase, and estradiol. Quercetin and its derivatives aids in reversing the osteopenia in animal models of osteoporosis likely through its antioxidant and anti-inflammatory activity along with its ability to promote osteogenesis and inhibits osteoclast activity. Such investigations suggest the incidence of developing Quercetin and its derivatives as a drug candidate or an active diet addition in the treatment and management of osteoporosis [29]. In *in vitro* study on mouse cell line RAW264.7 cells, Quercetin and its conjugate, quercetin-3-O-beta-D-glucuronide inhibits osteoclast differentiation and expression induced by the receptor activator of nuclear factor-kappa B ligand (RANKL) without affecting the uterus in ovariectomized mice. Thus, the study shows that dietary quercetin prevents bone loss but does not show estrogenic activity through estrogen receptor [30]. Moreover due to its antioxidant and estrogenic nature, quercetin can be a productive substitution for alendronate in Retinoic acid induced osteoporosis in which quercetin enhances bone mineral density along with calcium and phosphorus content.

Myrcetin is another essential flavanoidal component that confers promotion of bone mass, osteogenic differentiation and inhibition of osteoclastic activity which was proved both *in vivo* and *in vitro* through glucocorticoid-induced osteoporosis. The results concluded mechanistically that With reference to the activities of alkaline phosphatase (ALP), osteocalcin, and type I collagen enzyme-linked immunosorbent assay (ELISA), myrcetin manifests differentiation in MG-63 and hFOB human osteoblasts cells through enhancement of Bone Morphogenetic Protein (BMP-2) formation and activation of SMAD1/5/8 and p38 MAPK [31].

4.4 Dietary fibers and osteoporosis

The deficiency of estrogen in ovariectomized animals causes rise in energy consumption and increased body weight which ultimately leads to deposition of fat

shown by raised total cholesterol and triglyceride (TG) in serum [32]. Clinical studies have observed that dietary fibres alters the tissue and blood lipid levels on the basis of their nature and quantity. Being abundant in fiber content, fruits of *Ficus religiosa* were estimated for their hypolipidemic activity in male albino rats who were fed with hydrogenated oil rich semi-synthetic diet in order to induce hyperlipidemia along with the assimilation of 10% dietary fiber from the fruit powder. After treatment with the fruit powder, the decreased levels of serum cholesterol and phospholipids and decreased levels of total lipids and cholesterol in liver were observed along with increased fecal excretion of cholesterol and bile salts which proved negative influence of the *Ficus religiosa* fruit on the lipids absorption [9].

4.5 Serotonin and osteoporosis

According to the study, *F. religiosa* fruit contains highest amount of serotonin which could be applied in the study and treatment of various human cognitive disorder. The influence of serotonin on bone has been observed among diverse animal models through interaction with 5-HT (5-Hydroxy Tryptamine) receptors located in major types of bone cell such as osteoblasts, osteocytes, and osteoclast. Serotonin possess opposite effects on bone mass according to its site of origin, since central serotonin inhibits sympathetic output and shows negative regulator of bone mass accumulation that enhances bone formation. On the contrary, serotonin derived through gut inhibits bone formation by direct decrease in osteoblast proliferation yet, blocking the synthesis of both central and peripheral serotonin causes low bone mass composition. [33]. Thus, these findings suggest that overall decrease in level of serotonin reduces bone mass while increase serotonin levels results in bone mass accumulation, hence confirming that treatment with an antidepressant such as an SSRI (Selective Serotonin Reuptake Inhibitor) increases serotonin signaling that induces bone mass accumulation [34]. But at the same time administration of the SSRI in mice that antagonizes 5-HTT reduces bone mineral density (BMD) and alters trabecular architecture, irrespective of the effects of estrogen deficiency. Therefore, further exploration of the molecular basis for the role of serotonin in bone is necessary. This should include research into the roles of gut-derived and brain- derived serotonin in bone [35].

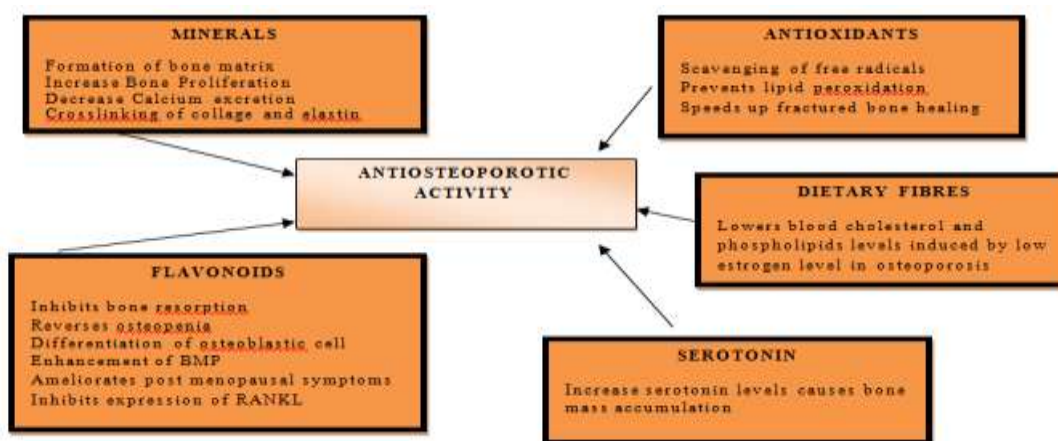


Figure 2. Antiosteoporotic activity of *Ficus religiosa* fruit

5. Conclusion

Ficus religiosa fruits possess basic pharmacological activities with reference to its antioxidant nature but still the current narrow literature available on *Ficus religiosa* fruits limits its exploration in the field of research. Thus, owing to its high flavonoidal, mineral and serotonin content the vast research exploration can be achieved in osteoporosis.

Conflict of interest

There is no conflict of interest

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