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Chemical, Biological and Pharmacological Activities of *Ficus religiosa*: an Extensive Review

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Abstract

Herbal drugs are one of the world's oldest and most precious gifts. Medicinal herbs and plants have a prominent place in the healthcare system, with *Ficus religiosa*, being one of the most important. It is commonly known as fig, which is widely used in traditional medicinal systems as antiulcer, anticonvulsant, wound healing, antinephropathic, antiviral, analgesic, anti-inflammatory, antimicrobial, immunostimulant, antihyperlipidemic, antioxidant, antiasthmatic, parasympathetic modulatory, anti-acetylcholinesterase, anticancer and cognitive enhancing agents. Secondary metabolites isolated from the plant such as stigmasterol, methyl oleanolate, lanosterol, caffeic acid, bergenin, amides, lupin 3-one, β-sitosterol, n-octacosanol, and flavonoids are considered to be the principal bioactive compounds of *F. religiosa*. The purpose of this review was to outline the phytochemistry, pharmacology and toxicity profile of *F. religiosa.* Aside from plant morphology and phytochemistry, the application of the plant in the most recent discoveries and nanotechnology was also explored. Furthermore, the review addresses recent therapeutic breakthroughs and identifies areas for further research that should be addressed in future studies.

Key words: *Ficus religiosa*, phytochemistry, traditional medicine, pharmacology, toxicity, nanotechnology.

Introduction

In traditional and modern medicinal systems, many of the beneficial therapeutic agents are derived from plant sources (Pochhi and Muddeshwar, 2017). These plants, used as herbal medicines, hold great promise for the discovery of novel drug molecules for diseases for which current treatments are inefficient while exhibiting fewer adverse effects (Kukde *et al.*, 2021). The genus *Ficus* Linn. consisting of 750-1000 species, is the largest tracheophyte medicinal plants genus in the Moraceae family and is found in the tropical and subtropical regions (Hesami *et al.*, 2018a; Biju *et al.*, 2020). *F. religiosa,* commonly known as Peepal is a perennial, evergreen monoecious tree widely distributed in Bangladesh, India, Pakistan, Sri Lanka, Nepal, Myanmar, China, Iraq, and Iran and an important member of the genus having medicinal and religious values (Hesami and Daneshvar, 2018b; Chaudhary *et al.*, 2017). *F. religiosa* has been planted as an ornamental tree in various regions of South America, North America, Australia, Europe,

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the Middle East and Africa (Vianna Filho *et al.*, 2017). The term '*Ficus*' is Latin for fig, while the term '*religiosa*' indicates the religious significance of the tree. In the Indian subcontinent, it is known as the mythical 'World Tree' or the 'Tree of Life' which is the earliest depicted tree in literature and art (Gupta *et al.,* 2021). It is also called the 'Sacred Fig' as it is regarded sacred by the believers of Hinduism, Buddhism and Jainism (Hesami *et al.,* 2017; Patil *et al.,* 2020). It's a tall, highly branched tree with heart-shaped and leathery leaves with long pointed edges on long thin axils and purple figs that grow in pairs (Garg *et al.,* 2018). *F. religiosa* can propagate through seeding and vegetative methods and the seeds remain viable for a few months (Daneshvar, 2019; Parab *et al.,* 2021).

F. religiosa is a good source of proteins, carbohydrates, vitamins, minerals, dietary fibers, amino acids and nitrogen (Tahir *et al.*, 2020). The bark contains saponin gluanol acetate, β-sitosterol, tannins, lupeol acetate, lupeol, ceryl behenate, α-amyrin acetate, leucoanthocyanin and leucoanthocyanidin (Selvan and Chourasia, 2017). Among the plants of the *Ficus* genus, the fig of this plant contains the highest level of serotonin (Mamidisetti *et al.,* 2018). The air pollution tolerance index for *F. religiosa* is 10.73-9.39, indicating that the plant can be used as a pollution sink (Bashir *et al.,* 2021; Sastry and Barua, 2017; Agrahari *et al.*, 2018). It also has a rougher surface area, a denser canopy and a larger surface area than most other tropical trees, which contribute to its superior dust-capturing ability (0.82 mg/cm^2 and 0.88 mg/cm^2 in industrial and commercial locations) (Roy *et al.*, 2020). The tree is used worldwide as food, medicine, fodder, vegetable & fuel and the wood has been used in the construction of houses, furnishings, packaging, spoons, forks, bowls and other things (Thanomchat *et al.,* 2019; Subash *et al.,* 2019). Its medicinal value has been documented in the management of infectious diseases, microbiological disorders, inflammation, epilepsy, menstrual disorders, gastrointestinal difficulties, respiratory problems, arthritis, seizure, and stress (Aslam and Akhtar, 2019; Mamta *et al.,* 2021; Rajiv and Sivaraj, 2012).

F. religiosa is a general ingredient in many formulations used in traditional medical systems such as Ayurveda, Siddha and Unani (Chavan *et al.,* 2019). The fig tree is widely used in traditional medicinal systems as an antidiabetic, antiulcer, anticonvulsant, wound healing, antinephropathic, antiviral, analgesic, anti-inflammatory, antimicrobial, immunostimulant, antihyperlipidemic, antioxidant, antiasthmatic, parasympathetic modulatory, anti-acetylcholinesterase, anticancer agent and cognitive enhancer (Utami *et al.,* 2020; Prakash *et al.,* 2017; Manorenjitha et al., 2013; Rathod *et al.,* 2018). In various Ayurvedic formulations namely, Nyagrodhadi churna, Nalpamaradi tailam, Saribadyasavam and Chandanasavam the bark of the tree is used (Raisagar *et al.,* 2019). '*F. religiosa* arishta' is an herbal hydro-alcoholic formulation from Ayurvedic pharmacopeia used in the treatment of inflammatory disorders (Jyothisree and Umadevi, 2020). The plant also shows anti-nephrotoxic and nephroprotective properties against a variety of nephrotoxic substances (Fang *et al.,* 2021; Chaure *et al.,* 2021). There have also been reports on the gender-specific adverse effects of oral administration of *F. religiosa* extracts (Akhtar *et al.,* 2020; Goyal, 2014). Even though several literature reviews on this plant have already been published, this one is presented to include all of the most recent scientific updates on its phytoconstituents and therapeutic effects studied through various approaches.

Materials and Methods

An extensive literature search was conducted on the phytochemical and pharmacological effects on *F. religiosa*. Research articles on phytochemical analysis, *in vivo, in vitro* and clinical trials were collected. All these papers were collected using bibliographic databases, search engines and journal websites, such as PubMed, Google Scholar, Nature, Researchgate and others.

Results and Discussion

Plant morphology: The matured ficus tree is thirty meters in height with dark barks. The

undeveloped leaves appear pink or red at first, then turn to deep green, and cordate in shape as mature. The heart-shaped and glossy leaves are 12-20 cm in length, 5-8 cm wide and have five to seven veins. They are joined to the stem with a 6 to 8 cm long petiole. The leaves have five to eight sets of transverse veins, as well as a system of extremely fine veins. They are oval in shape with a leathery, shiny surface, short, sheathing stipules, caudate-acuminate apex and pinnate venation. There are no trichomes in the plant (Sethuramani *et al.,* 2021). The bark is slightly arched or straight, with a thickness ranging from 1.0 to 3.0 cm (5 to 8 mm). It occurs in level or slightly bent sections ranging in thickness from 1.0 to 2.5 cm or more. In February, the little crimson flowers appear and the fruits appear from May to June as figs that are 12-13 mm or 1.5 inches wide (Patil *et al.*, 2020).

Figure 1. *Ficus religiosa* plant with unripe fruits.

Phytochemistry of F. religiosa: The alkaloids, phenolics, flavonoids, phytosterols, furanocoumarins, amino acids, volatile compounds and aliphatic and aromatic alcohols were extracted and identified from different extracts of *F. religiosa* (Hesami and Daneshvar, 2018c; Shaikh *et al.,* 2020). Several secondary metabolites, such as stigmasterol, methyl oleanolate, lanosterol, caffeic acid, bergenin, amides, lupin 3-one, β-sitosterol, n-octacosanol, and flavonoids, have been characterized, while many are still unidentified (Hesami *et al.*, 2018d; Nawaz *et al.*, 2020). Lupenyl acetate, lanosterol, piperlongumine,

piperine, quercetin, kaempferol, myricetin, and methyl piperate are the active ingredients having anti-inflammatory properties (Yueniwati *et al.*, 2021; Hesami *et al.*, 2019).

The presence of flavonoids, alkaloids, carbohydrates, saponins, glycosides, and tannins in various extracts of *F. religiosa* leaf was discovered in qualitative phytochemical investigations (Ghadigaonkar *et al.*, 2021; Utami *et al.*, 2021). Significant amounts of total phenolic contents (19.97-62.93 g gallic acid equivalents/mg) and total flavonoid contents (29.88-135.95 g QE/mg) were found in leaf extract (Ghadigaonkar *et al.*, 2021). The leaves contain 0.4-0.75 mg/g ascorbic acid that contribute to its high tolerance towards air pollution (Bashir *et al.*, 2021). Among the forty-four compounds identified in the leaf oil, eugenol (27%), 2-Phenylethyl alcohol (8%), 3-Methylcyclopenetane-1,2-dione (10.8%) and itanoic anhydride (15.4%) are the four main constituents of the leaf extract. The other components include *n*-hexanol, phenol, adipoin, *n*-nonanal, 2-phenylethyl alcohol, benzeneacetonitrile, (*E*)-linalool oxide, catechol, coumaran, (*E*)-cinnamyl alcohol, *p*-vinylguaiacol, eugenol, dihydroactinidiolide, α-copaene-11-ol, β-eudesmol, α-eudesmol, α-cadinol, pentadecanal, palmitic acid, and phytol (Al-Snafi, 2017). Thirty-one volatile compounds have been identified in the dry leaves including palmitic acid (hexadecanoic acid), propionic acid, stearic acid (octadecanoic acid), citric acid, aspartic acid, and phenylalanine (Suriyakalaa *et al.*, 2021). Religiosin B and C enzyme glycoproteins, also known as serine proteases are found in the decolorized latex of *F. religiosa* (Al-Snafi, 2017; Murugesu *et al.*, 2021). Furanocoumarin derivatives (bergapten and begaptol), flavonoids, phenols, phytosterols, alkaloids, tannins, vitamin K, lanosterol, lupen-3-one, methyl oleanolate, and steroids have been found in the aqueous extract of bark (Devanesan *et al.*, 2018). On the other hand, the petroleum ether extract contained 35 compounds including 13 saturated fatty acids (31.19%), 8 unsaturated fatty acids (59.24%), 1.76% alkene, 6.02% alkane, 0.97% fatty alcohols, and 0.82% cyclic fatty acid esters (Ali *et al.*, 2017a).

Recently, a new β-steryl naphthyl ester and two novel fatty acids have been characterized in a phytochemical screening of the methanolic extract of the stem bark for the first time (Ali *et al.*, 2017b). Other recent phytochemical studies led to the discovery of a novel lanostane type-triterpenic ester and a novel naphthyl-substituted phytosterol from the bark and the extraction of a new fiber with 55.58% cellulose content from the root of *F. religiosa* (Ali *et al.*, 2020; Moshi *et al.*, 2020a and Moshi *et al.*, 2020b). The fruit of *F. religiosa* contains substantial amounts of flavonoid (1111.1 ± 33.3 mg/kg dry matter) and phenolic contents (Jawanjal *et al.*, 2021; Sultana and Anwar, 2008). The seeds contain amino acids, phytosterols, fatty matter, glycoside, carbohydrates, coloring matter, and β-sitosterol (Devanesan *et al.*, 2018). Endophytes, including actinomycetes, bacteria, and fungi live inside the plant tissue and create secondary metabolites that are similar to those produced by plants (Tiwari *et al.*, 2017). Figure 2 depicts the distinct phytocompounds discovered in *F. religiosa*.

Pharmacological activities: *F. religiosa* is a magical plant with various medicinal activities and uses. It contains different secondary metabolites in different parts, such as leaves, roots, bark and stems. These complex chemical substances play role in different pharmacological activities. Different systems like the endocrine system, central & peripheral nervous systems, reproductive system and digestive system are affected by the chemical compounds of *F. religiosa*. A wide spectra of *in vivo* and *in vitro* studies is conducted to ensure pharmacological activities, like, nephroprotective effect, bronchoconstriction effect, astringent effect, anti-hyperlipidemic effect, antimicrobial effect and so on. These pharmacological effects with mechanism, assay and proper dose are described below.

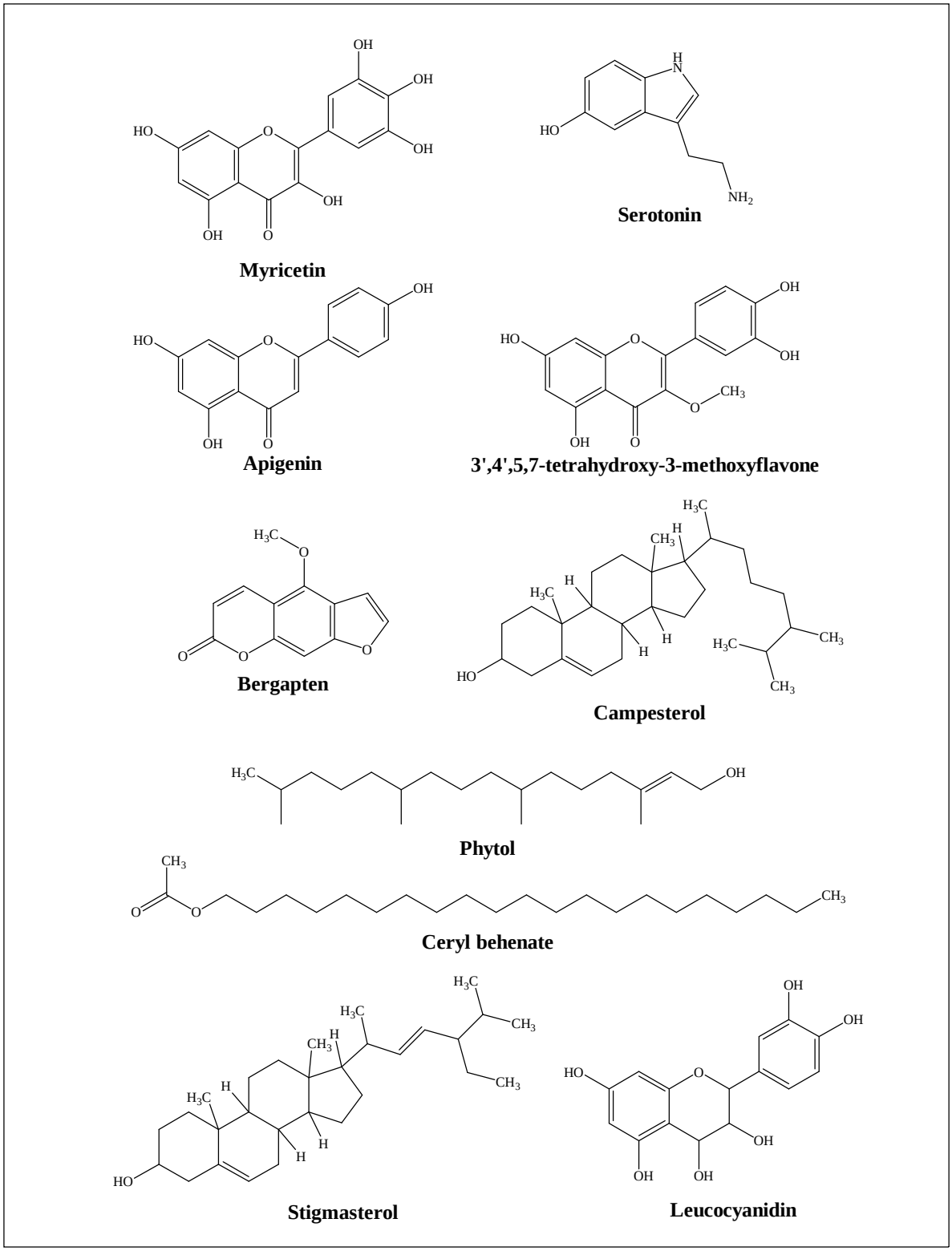

Figure 2. Chemical structures of bioactive compounds of *F. religiosa.*

Table 1. Microorganisms found in *F. religiosa* and their therapeutic activities.

Microorganism	Species	Compounds isolated	Therapeutic activity	References
Bacteria	*Azoarcus nasutitermitis*			Lin *et al.*, 2020
	Azoarcus rhizosphaerae			
Endophytic fungi	*Curvularia lunata*	1-Eicosane	Antimicrobial, antidiabetic and cytotoxic properties	Murugesu *et al.*, 2021
	Aspergillus sp.	Naphthaquinone antibiotic herbarin, herbaridine A	Antidiabetic, antiinflammatory effect	
	Aspergillus aculeatus, *Penicillium* sp., *Cephaliophora irregularis*, *A. sydowii*, *Diaporthe* sp., *A. quadrilineatus*, *A. flavus*, *A. versicolor*		Anti-oxidant and anti-diabetic activities	Jayant and Vijayakumar, 2021
Nematode	*Parasitodiplogaster religiosae*			Zeng *et al.*, 2018
Rhizobacterium	*Bacillus safensis*			Asif, 2019

(i) Antioxidant activity: Tannins, flavonoids and polyphenols are mainly responsible for antioxidant activities. Some assays justify this statement that aqueous extract at a dose of 100 and 200 mg/kg shows antioxidant effect in streptozotocin-induced diabetic rats by decreasing superoxide dismutase [for 100 mg/kg] and by enhancing catalase (CAT) and glutathione peroxidase (GSH-Px) activity (Kirana *et al.*, 2009). In the case of methanolic extract 11.75, 50.65, 400 µg shows activity by bleaching 1,1 diphenyl-2-picrylhydrazyl (DPPH) radical (Anandjiwala *et al.*, 2008). Ethanolic extract at 200 µg/mL to 1000 µg/mL shows antioxidant effect by increasing H_2O_2 in the DPPH method (Zaidi *et al.*, 2009).

(ii) Wound healing activity: Flavonoids, terpenoids, sterols, alkaloids and saponin β-sitosteryl-D-glucoside are responsible for wound healing activity. In Wistar albino rats, 300 mg/kg dose of leave extract increases wound healing/closure rate, whereas 10% ointment (in case of roots) decreases epithelialization period and increases hydroxyproline content (Zaidi *et al.*, 2009).

(iii) Nephroprotective effects: Nephroprotective effects refer to the protection of the nephron or kidney from harm. Alkaloids, glycosides, amino acids, flavonoids and tannins show nephroprotective activities. Methanolic extracts of latex 200 mg/kg dose show this effect in Wistar rat models by decreasing levels of urea and creatinine (Yadav and Srivastava, 2013).

(iv) Anti-asthmatic activity: Asthma is a condition that narrows airways and creates difficulty in breathing. Flavonoids, terpenoids, tannins, phenols and sterol help in the maintenance of asthma. Aqueous extract of leaves at a dose of 150 and 300 mg/kg of body weight in guinea pigs delay histamine-induced pre-convulsion dyspnea (Kapoor *et al.*, 2011).

(v) Anti-acetylcholinesterase activity: Steroids, alkaloids, flavonoids, phenols, saponins, tannins, glycosides and sterols are responsible for this activity. Methanolic extract of stem bark at a dose of 73.69 µg/mL prolongs the half-life of acetylcholine by hindering acetylcholinesterase (Vinutha *et al.*, 2007).

(vi) Broncho-constriction effect: Histamin and acetylcholine has significant effects in broncho-constriction. Glycosides, terpenoids, flavonoids, serotonergic content are key components that shows broncho-constriction effect. Methanolic extract of fruits at various doses such as 0.5, 1 and 2 mg/ kg are effective, this assay is conducted in histamine and acetylcholine induced guinea pig and these doses affect the EC(50) doses of both histamine and acetylcholine (Ahuja *et al.,* 2011).

(vii) Astringent activity: Components present in *F. religiosa* steroids, flavonoids, alkaloids, phenol content, glycosides, tannins, saponins, polyphenolic compounds, sterols, terpenoids, serotonergic content are responsible for astringent activity. Using tannic acid as standard, entire mature fruit and inner bark shows 0.6% astringency compared to tannic acid (fruit) in bovine serum albumin assay with remazol brilliant blue (Ahuja *et al.,* 2011).

(viii) Anti-fertility activity: Flavonoids, serotonergic content, terpenoid, glycosides show anti-fertility activity. Methanolic extract of fruits of *F. religiosa* gives anti-fertility activity, for example- 1% anti-fertility effect was seen on uterus of goats when methanolic extraction is given. It reducues diameter of uterine glands and myometrium thickness of uterus of goats and increased activity (Sharma *et al.,* 2013).

(ix) Anti-inflammatory activity: Anti-inflammatory activities are shown by steroids, flavonoids, alkaloids, phenol content, glycosides, tannins, saponins, polyphenolic compound, sterols. Ethanolic extract of bark at a dose of 100 mg/kg when administrated in carrageenan induced golden Syrian hamsters expresses anti-inflammatory action. Mainly production of reactive oxygen species is responsible for anti-inflammatory activity (Murugesan *et al.,* 2012).

(x) Anti-ulcer activity: Flavonoids, terpenoids, tannins, phenols, sterols, Steroids, alkaloids, phenol content, glycosides and saponins show anti-ulcer activity. Ethanolic bark extract at 200 and 400 mg/kg doses in reduces the amount of gastric acid and hyper acidity in Wistar rats. On the other hand, ethanolic leaf extract at a dose of 2000 mg/kg in albino mice decreases gastric secretion (Gregory *et al.,* 2013; Khan *et al.,* 2011).

(xi) Hepatoprotective activity: Alkaloids, glycosides, amino acids, flavonoids and tannins show hepatoprotective activity. Methanolic extracts of latex at a dose of 300 mg/kg in cisplatin-induced liver injury in Wistar rats degenerate inflammatory infiltrate (Yadav, 2015).

(xii) Analgesic effect: Flavonoids, phenols, terpenoids and glycosides are mainly responsible for analgesic activity. Methanolic extract of fruits in acetic acid writhing test (in mice) causes inhibition of cyclo-oxygenases and shows an analgesic effect at 200 and 400 mg/kg doses (Mamidisetti *et al.,* 2018).

(xiii) Anti-epileptic activity: Bark extract of ethanol in Swiss albino mice shows an epileptic effect at 200 and 400 mg/kg doses. This is because high saponin content block voltage-dependent Na^+ channels and NMDA receptors and thus delay the onset of convulsion and reduce the duration of convulsion (Sapkota *et al.,* 2021).

(xiv) Antiarthritic activity: Flavonoids and terpenoids are mainly responsible for the antiarthritic activity. Methanolic bark extract in the case of Freund's adjuvant-induced arthritis in rats causes suppression of inflammatory mediator (Garg *et al.,* 2018).

(xv) Antihyperlipidemic effect: Aqueous extract of leaves at a dose of 250 mg/kg in alloxan-induced diabetic rats shows anti-hyperlipidemic activity by improving serum lipids, lipoproteins concentration and lipid metabolizing enzymes activity such as - lipase, HMG CoA reductase, LCAT (Lecithin cholesterol acyl transferase) (Pochhi and Muddeshwar, 2017).

(xvi) Anti-cancer activity: Some assays justify the anti-cancer activities of *F. religiosa*. Chloroform extract of leaves at a dose of 110 µg/mL in trypan blue exclusion dye test shows anti-cancer activity. Besides, chloroform extract at various doses such as 62.5, 125, 250, and 500 µg/mL in MDA-MB-231 breast cancer cell line through SRB assay shows oxidative stress and causes retardation of cell growth (Kumaresan *et al.,* 2018). Polyphenol dichloroacetic

acid present in *F. religiosa* shows cytotoxic effect. Combined crude extract of *F. religiosa* and *F. benghalensis* at a dose of 100 µg/mL in mitochondrial reduction assay against HeLa (human cervical cancer cell line) shows a cytotoxic effect. Through depolarizing polyphenol, dichloroacetic acid affects the proliferation of tumor cells and causes apoptosis in glioblastoma cancer (Kumaresan *et al.,* 2018).

(xvii) Antidiabetic effect: Sterols, β-sitosterol-D-glucoside, alkaloids, flavonoids and tannins present in *F. religiosa* are responsible for the antidiabetic effect. Aqueous extract of root, bark, leaves and ethanolic extract of bark in normal fasted male albino rabbits show positive results. Phytosterols present in bark decreases blood glucose level. Besides the antioxidant effect of tannin, flavonoids and polyphenols are suggested as possible mechanisms for anti-diabetic effects. For leaf extract, it reduces plasma glucose levels in a time and dose-dependent manner both in normal and alloxan-treated diabetic mice (Brahmachari and Augusti, 1962; Pandit *et al.,* 2010; Singh *et al.,* 2011).

(xviii) Antimicrobial activity: 70% ethanolic extract of bark shows activity against *H. pylori* in pylori plates and strains from antral biopsies patients (Zaidi *et al.,* 2009). Ethanolic extract of bark at a concentration of 10 g of powdered bark gives anti-microbial activity against *B. cereus* and *S. agalactiae* in agar disc diffusion and disc diffusion method (Nair and Chanda, 2006). Aqueous and ethanolic extract of bark at a concentration of 10 g of powdered bark is active against *B. cereus* in agar disc diffusion (for aqueous extract) and agar well-diffusion (for ethanolic extract) (Nair and Chandra, 2007). Aqueous, methanol and chloroform extract of bark show activity against *E. coli* in disc diffusion method where three enterotoxigenic *E. coli* were isolated from diarrhoeal patients (Uma *et al.,* 2009). 80% ethanolic extract of leaves is active against *E. coli*, *P. aeruginosa*, *S. aureus,* and *B. subtilis* in agar dilution method (Valsaraj *et al.,* 1997).

70% ethanolic extract of leaves at a dose of 100µL of 100 mg/mL extract shows antimicrobial activity against *S. aureus, S. paratyphi, S. dysenteriae, S. typhimurium, E. coli, S. typhi* and *C. albicans* in agar well diffusion method (Aqil and Ahmad, 2007). Aqueous, ethanol and methanolic extract of leaves for 0.5 mL of extract from 10g powder of leaf with 100 mL of solvent are active against *B. subtilis, P. aeruginosa, E. coli,* and *S. typhi* in agar plate method (Preethi *et al.,* 2010). Chloroform extract of fruits at a dose of 0.5 mg (in acetone) with a disc of 6.35 mm diameters is active against *A. chroococcum, B. cereus, B. megaterium, S. faecalis, S. lactis* and *K. pneumonia* in filter paper disc diffusion method (Mousa *et al.,* 1994). Phenolic compounds, such as phenols, flavanols, alkaloids show anti-fungal effect. N-butanol fraction of stem bark at a dose of 0.125 and 2 mg/mL shows anti-fungal activity while used in antifungal assay (through agar dilution method adopted by Javaid and Sammad) (Shahid *et al.,* 2016).

F. religiosa in recent scientific discoveries: Researchers have recently become interested in nanotechnology because of its cellular-level mechanisms that can benefit the pharmaceutical, nutraceutical and cosmetic industries. The application of plants for nanoparticle manufacturing has become increasingly popular in recent years. When compared to conventional methods, this process is far more ecologically acceptable and generates biodegradable waste. It has been found that the employment of *F. religiosa* extract in solid lipid nanoparticles increased the bioavailability and potency of the principal bioactive compounds (Priyanka *et al.,* 2017). Solid lipid nanoparticle form of *F. religiosa* shows greater potency and bioavailability and increases the plasma half-life of lupeol present in bark extract in male Wister rats (Priyanka *et al.,* 2017). Therefore, the utilization of solid lipid nanoparticles may result in a reduction in dose frequency, a longer duration of action, and improved therapeutic efficacy. Silver nanoparticle production employing plant extract is a fast, low-cost, environment-friendly, one-step biosynthesis technique that is also safe for medicinal uses (Rahman and Prasanna, 2018). Table 2 lists the nanoparticles produced with *F. religiosa* extracts and their therapeutic efficacy or use in different studies.

Natural sources such as *Ficus* provide a safer and more sustainable way to remove hazardous metal ions from industrial wastes than many other approaches (Tariq *et al.*, 2021; Tariq *et al.*, 2019). Senthilkumar *et al*. used organic *Ficus* Chlorophyll-a to synthesize a semi-organic Chl-a doped ADP (CHLAADP) single crystal with electrical and optical conductivity ideal for lenses, electronics, power grids, and sensors (Senthilkumar *et al.*, 2020; Senthilkumar and Manimekalai, 2020). According to theoretical and experimental investigations, *F. religiosa* can act as a green corrosion inhibitor due to the presence of campesterol, serotonin and myricetin, which reduces the erosion rate of steel at pH below seven (Haldhar *et al.*, 2018). Thus, it can serve as an excellent mild steel corrosion preventative agent in 0.5M H_2SO_4 owing to the abundance of aromatic rings and heteroatoms in the principal components (Haldhar *et al.*, 2018). The biomass carbon obtained from *F. religiosa* leaves could be a viable choice for potassium ion intercalating electrodes in energy-storing technologies (Rajkumar *et al.*, 2021).

Table 2. Application of *F. religiosa* in nanoparticle synthesis and their therapeutic effects.

Nanoparticles	Solution used	Plant part	Evaluated activity/ application	Result	Reference
Copper oxide nanoparticles	Cupric sulphate	Leaf	Anticancer activity	Apoptotic effect in cancer cells	Sankar *et al.*(2014)
CuO/C porous nanocomposite	Cupric sulphate	Leaf	Antimicrobial, antioxidant	Strong antimicrobial activity	Bhavyasree and Xavier (2021)
Silver nanoparticle	$AgNO_3$	Leaf	Antibacterial efficacy	Potent antibacterial efficacy	Kushare *et al.* (2020)
	$AgNO_3$	Leaf	Larvicidal activity	Reduced survival rate of larvae	Kantrao *et al.* (2017)
	$AgNO_3$	Leaf	Antitumor, antioxidant, antiangiogenic	Treatment of Dalton's ascites lymphoma	Antony *et al.* (2013)
SnO_2 nanoparticles	Tin chloride dihydrate	Leaf	Glucose detector	Successful detection of aquous glucose	Narayana *et al.* (2020)
Solid lipid nanoparticles	Glyceryl monosterate, poloxamer	Stem bark	Enhance bioavailability	Enhanced C_{max} and prolonged $t_{1/2}$ of lupeol	Priyanka *et al.* (2017)
	Lipid phase	Stem bark	Andiabetic effects	Decreased blood glucose level	Priyanka *et al.* (2018)
	Glyceryl monostearate	Stem bark	Andiabetic effects	Reduced blood glucose levels	Karunanidhi *et al.* (2021)
TiO_2 nanoparticles	$TiO(OH)_2$	Leaf	Larvicidal activity	Increased larvicidal activity	Soni and Dhiman (2020)
Zinc oxide nanoparticles	$ZnNO_3$ and NaOH	Leaf	Larvicidal activity	Increased larvicidal activity	
	$ZnNO_3$	Leaf	Antibacterial properties	Good antibacterial activity	Raghavendra *et al.* (2017)

Plant toxicity and biosafety: F. religiosa is considered to be safe as there is no evidence of its toxic effect from ancient traditional use. Even now the majority of studies done to determine toxicity show no sign of toxicity. Although the aqueous and alcoholic extract of leaves is considered to be safe, some extract shows toxicity varying on the dose. A table (Table 3) is given below regarding those extracts and the toxic effect with dose. Chloroform extract of fruits of *F. religiosa* shows toxicity with LC_{50} of 400 µg/mL, but having LC_{50} > 100 µg/mL is considered non-toxic. From this point of view, fruit

extract can be considered safe (Mousa *et al.*, 1994; Moshi *et al.*, 2010). Overall studies show that toxicity depends on therapeutic dose and type of extract and maximum extracts of *F. religiosa* are considered to be safe.

Table 3. Toxicity profile of *F. religiosa* and adverse effects in different animal models.

Plant extract	Toxic dose	Safe dose	Animal model	Adverse effects	Reference
Methanolic fruit extract	above 1000 mg/kg	25, 50 and 100 mg/kg	Rotarod	Neurotoxic effect	Singh and Goel, (2009)
Aqueous bark extract	above 2000 mg/kg	Up to 2000 mg/kg	Swiss female albino mice	Catharsis/allergies	Pandit *et al.* (2010)
Phytosterolin isolated from the bark	40-400 mg/kg	Not specified	Male albino rats	Increased motor activity and temperature, hyperirritability, piloerection, at last death after clonic convulsions	Balachandran and Govindarajan (2005)
Leaves with tannic acid	2 doses/day for 40 days	Leaves without tannic acid	In goats	Necrosis of the epithelial cells of both cortical and medullary regions of the renal tubule, vacuolar degeneration, myocardium congestion, focal hemorrhage, patchy degenerations with complete absence of epidermis	Tripathy *et al.* (1984)

Conclusions

In the Indian subcontinent, herbs have long been the primary means of treatment. The presence of diverse complex organic compounds of varying compositions identified as secondary plant metabolites confers therapeutic effects on medicinal plants (Chandrasekar *et al.*, 2010). Due to its therapeutic, aesthetic and religious value, *F. religiosa* L. is one of the most prominent plants in the Moraceae family and is recognized as a multifaceted forest tree (Hesami and Rahmati-Joneidabad, 2018e). It is an extensively used bark drug in traditional medicines and it's one of the five bark drugs in 'Panchavalkala' (Mallya *et al.*, 2018). It has been used in Bangladesh to treat a variety of ailments, including infectious infections, inflammation, and cancer (Bhalerao and Sharma, 2014). When administered in the recommended amount, it has no harmful effects on humans (Lakshmi HimaBindu *et al.*, 2013). The differing proportions of numerous phytochemicals, in selecting of suitable extracting solutions, could be one of the factors for the functions of these plant extracts (Abusufyan *et al.*, 2018). Its wide spectrum of secondary metabolites such as lanosterol, stigmasterol, caffeic acid, β-sitosterol, bergenin, methyl oleanolate, lupin-3-one, amides and flavonoids could be another factor behind its success as a traditional remedy (Hesami *et al.*, 2020). *F. religiosa* are important elements of tropical ecosystems because their wider canopy areas promote plants dispersed by frugivores and other species (Chakraborty *et al.*, 2021). Therefore, *F. religiosa* stem bark has future prospective to be used in a variety of ways. The antioxidant, anti-inflammatory, anticancer, antidiabetic, antibacterial, activities of the species were validated in the investigations, providing a scientific foundation for its use in herbal medicines. Antifertility, antiproliferative, anticancer, anti-stress, immunomodulatory and antimutagenic properties are a few potential therapeutic effects of *F. religiosa* that require further investigations. *In vivo* studies can be carried out in the future to assess the pharmacological actions demonstrated. Therefore, this review of phytochemicals and their therapeutic actions will provide forthcoming information on current studies, and therapeutic factors that may call for additional emphasis, as well as practical outcomes to be included in this plant species.

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Authors contribution

MSA has conceived the original idea. SAS and ST extensively consulted the literature. SAS, ST, and MSA prepared the initial manuscript and arranged the reference section. FA, JAC, AAC and SK critically reviewed the overall activities. MSA supervised the whole activity. All the authors read the review article meticulously and agreed to submit the article.

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Conflict of interest

There is no conflict of interest according to the authors.

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