

Pharmacology of *Ficus religiosa*- A review

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Abstract:- Chemical analysis showed that *Ficus religiosa* contained tannins, phenols, saponins, sugars, alkaloids, methionine, terpenoids, flavonoids, glycosides, proteins, separated amino acids, essential and volatile oils and steroids. Previous pharmacological studies revealed that *Ficus religiosa* possessed antimicrobial, anti-parasitic, anti-Parkinson's, anticonvulsant, anti-amnesic, anticholinergic, antidiabetic, antiinflammatory, analgesic, cytotoxic, anti-ulcer, wound healing, antioxidant, anti- asthmatic, reproductive, hepato-, nephro- and dermato- protective effects. The current review highlights the chemical constituents and pharmacological effects of *Ficus religiosa*.

Keywords: chemical constituents, pharmacological effects, pharmacology, *Ficus religiosa*

I. INTRODUCTION:

Herbal medicine is the oldest form of medicine known to mankind. It was the mainstay of many early civilizations and still the most widely practiced form of medicine in the world today. The World Health Organization (WHO) estimates that 4 billion people, 80 percent of the world population, presently use herbal medicine for some aspect of primary health care[1]. Plants generally produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of many pharmaceutical drugs [2-50]. *Ficus religiosa* contained tannins, phenols, saponins, sugars, alkaloids, methionine, terpenoids, flavonoids, glycosides, proteins, separated amino acids, essential and volatile oils and steroids. Previous pharmacological studies revealed that *Ficus religiosa* possessed antimicrobial, anti-parasitic, anti-Parkinson's, anticonvulsant, anti-amnesic, anticholinergic, antidiabetic, antiinflammatory, analgesic, cytotoxic, anti-ulcer, wound healing, antioxidant, anti- asthmatic, reproductive, hepato-, nephro- and dermato- protective effects. This review will highlight the chemical constituents and pharmacological effects of *Ficus religiosa*

Synonyms:

Ficus caudata Stokes, *Ficus peepul* Griff., *Ficus religiosa* var. *cordata* Miq., *Ficus religiosa* var. *rhynchophylla* Miq., *Ficus rhynchophylla* Steud., *Ficus superstiosa* Link, *Urostigma affine* Miq. and *Urostigma religiosum* (L.) Gasp [51].

II. TAXONOMIC CLASSIFICATION:

Kingdom: Plantae, **Subkingdom:** Viridiaeplantae, **Phylum:** Tracheophyta, **Subphylum:** Euphyllphytina, **Infraphylum:** Radiatopses, **Class:** Magnoliopsida, **Subclass:** Dilleniidae, **Superorder:** Urticanae, **Order:** Urticales, **Family:** Moraceae, **Genus:** *Ficus*, **Species** *Ficus religiosa* [52].

III. COMMON NAMES:

Arabic: teen mukadas, teen Asnam, shajarat bebal, *Ficus* abu lesan; **Chinese:** pu ti shu; **English:** botree, peepultree, sacred fig; **French:** arbre de Dieu, figuier de pagodes; **German:** bobaum, heiliger feigenbaum, indischer pepulbaum, pepulbaum; **India:** papal, pipul; **Italian:** fico del diavolo; **Portuguese:** figueira-dos-pagodes, figueira-religiosa; **Spanish:** higuera de agua; **Swedish:** tempelfikus [53].

IV. DISTRIBUTION:

It is native to the Asia-Tropical (Bangladesh; India, Nepal, Pakistan, China, Myanmar, Thailand, Vietnam and Iraq) and it is cultivated in wide tropical areas [53].

V. DESCRIPTION:

Trees, 15-25 m tall, d.b.h. 30-50 cm, epiphytic when young, crown wide when mature. Bark gray, smooth or longitudinally ± fissured. Branchlets grayish brown, sparsely pubescent when young. Stipules ovate, small, apex acute. Petiole slender, as long as or longer than leaf blade, articulate; leaf blade triangular-ovate, 9-17 × 8-12 cm, leathery, abaxially green, adaxially dark green and shiny, base broadly cuneate to ± cordate, margin entire or undulate, apex acute to caudate with a 2-5 cm cauda; basal lateral veins 2, secondary veins 5-7 on each side of midvein. Figs axillary on leafy branchlets, paired or solitary, red when mature, globose to depressed globose, 1-1.5 cm in diam., smooth; peduncle 4-9 mm; involucre bracts ovate. Male, gall, and female flowers within same fig.

Male flowers: few, near apical pore, sessile; calyx 2- or 3-lobed, margin revolute; stamen 1; filament short. Gall flowers: pedicellate; calyx 3- or 4-lobed; ovary globose, smooth; style short; stigma enlarged, 2-lobed. Female flowers: sessile; calyx 4-lobed, broadly lanceolate; ovary globose, smooth; style thin; stigma narrow [54].

Traditional uses:

Traditionally, the leaf juice was used in the treatment of asthma, cough, sexual disorders, diarrhoea, haematuria, ear-ache, toothache, migraine, eye troubles, gastric problems and scabies. The leaf decoction was used as in toothache. The fruits were used in the treatment of asthma and other respiratory disorders and scabies. The stem bark was used in gonorrhoea, bleeding, paralysis, diabetes, diarrhea, bone fracture, as antiseptic, astringent and antidote [52].

Physicochemical characteristics:

Physicochemical analysis of *Ficus religiosa* fruit powder showed: loss on drying 8.99%, total ash 5.88%, acid insoluble ash 0.60%, water soluble 33.10 % and alcohol soluble extractive 28.80% [55].

Chemical constituents:

The preliminary phytochemical analysis revealed that the plant contained tannins, phenols, saponins, sugars, alkaloids, methionine, terpenoids, flavonoids, glycosides and steroids [56-61]. The total phenol content present in one milligram of aqueous and ethanolic extracts of the bark was 497.77 and 375.23 μ g, respectively [62]. The total phenolic contents of absolute ethanol, absolute methanol, aqueous ethanol (ethanol: water, 80:20 v/v) and aqueous methanol (methanol: water, 80:20 v/v) extracts was 3.13 \pm 0.19, 5.34 \pm 0.36, 2.67 \pm 0.16 and 4.11 \pm 0.18 (GAE g/100 g of DW) by shaking extraction technique and 2.12 \pm 0.09, 4.93 \pm 0.28, 2.26 \pm 0.10 and 4.13 \pm 0.21 (GAE g/100 g of DW) by reflux extraction technique respectively [63]. However, chemical analysis showed that *Ficus religiosa* was rich in flavonoids, quercetin was most abundant 1.428 \pm 0.5 - 4.29 \pm 0.4 mg/Kg and myricetin was also present in good amounts 0.08 \pm 0.3-1.0 \pm 0.5 mg/kg [64]. The barks of *Ficus religiosa* contained bergapten, bergaptol, lanosterol, β -sitosterol, stigmasterol, lupen-3-one, β -sitosterol-d-glucoside (phytosterolin), vitamin k1, tannin, wax, saponin, leucoanthocyanidin, leucoanthocyanin, leucocyanidin-3-0- β -D-glucopyranoside, leucopelargonidin- 3-0- β -D-glucopyranoside, leucopelargonidin-3-0- α -L- rhamnopyranoside, lupeol, ceryl behenate, lupeol acetate and α -amyrin acetate [65-69]. Fruits contained protein 4.9%, amino acids, isoleucine, phenylalanine, asparagine, tyrosine, flavonols (kaempferol, quercetin, and myricetin), undecane, tridecane, tetradecane, (e)- β -ocimene, α - thujene, α -pinene, β -pinene, α -terpinene, limonene, dendrolasine, dendrolasine α -ylangene, α -copaene, β -bourbonene, β -caryophyllene, α -trans bergamotene, aromadendrene, α -humulene, alloaromadendrene, germacrene, bicyclogermacrene, γ -cadinene and δ -cadinene 65, 67, 70-71].

The major components of *Ficus religiosa* leaf oil were identified to be Eugenol (27.0%), Itaconic anhydride (15.4%), 3-Methylcyclopentane-1,2-dione (10.8%), 2-Phenylethyl alcohol (8.0%), and Benzyl alcohol (4.2%). However, the leaf contained 44 compounds including (%): (3Z)-Hexenol 1.1, (2Z)-Hexenol 0.7, *n*-Hexanol 0.7, Phenol 0.7, Adipoin 0.6, 3-Methylcyclopentane-1,2-dione 10.8, Itaconic anhydride 15.4, Benzyl alcohol 4.2, Salicylaldehyde 1.5, Phenylacetaldehyde 0.6, Allyl caproate 3.5, Linalool 0.3, *n*-Nonanal 0.3, 2-Phenylethyl alcohol 8.0, Benzeneacetonitrile 1.2, (2E,6Z)-Nonadienal 0.4, (2E)-Nonen-1-ol 0.5, (2E,6Z)-Nonadienol 0.5, (E)-Linalool oxide 0.5, Catechol 1.1, Coumaran 3.4, (E)-Cinnamyl alcohol 0.6, *p*-Vinylguaiaicol 1.1, (3Z)-Hexenyl tiglate 0.6, Eugenol 27.6, (2E)-Hexenyl (3Z)-hexenoate 0.3, (E)- β -Ionone 1.6, Dihydroactinidiolide 0.4, α -Copaene-11-ol 0.4, (3Z)-Hexenyl benzoate 0.5, *epi*- γ -Eudesmol 0.5, γ -Eudesmol 0.4, *epi*- α -Cadinol 1.0, β -Eudesmol 1.8, α -Eudesmol 1.0, α -Cadinol 0.7, Pentadecanal 0.7, Palmitic acid 0.7 and Phytol 0.7% [72].

Leaves also contained aspartic acid, glycine, threonine, alanine, proline, tryptophan, tryosine, methionine, valine, isoleucine, leucine, *n*-nonacosane, *n*-hentricontanen, hexa-cosanol and *n*-octacosan 73-74]. HPLC analysis of the methanolic extract showed the presence of high amounts of serotonin (2.89%, w/w) [75]. A serine protease (religiosin) was purified from the decolorized latex of *Ficus religiosa*. It was a glycoprotein with a molecular mass of 43.4 kDa by MALDI-TOF [76].

Pharmacological effects:

Antimicrobial effect:

Ethanol extracts of the *Ficus religiosa* was screened for antibacterial activity against *Enterococcus faecalis*, *Proteus vulgaris*, *Staphylococcus saprophyticus*, *Shigella flexneri*, *Shigella sonnie* and *Shigella dysenteriae*. The minimum inhibitory concentrations against these bacteria were within the range of 250-500 μ g/ml [77]. The MIC of *Ficus religiosa* leaves ethanolic extract against ampicillin and vancomycin resistant native strain of *Staphylococcus aureus* was 3.91 \pm 0.43 mg/ml [78]. The various solvents extract like aqueous, methanol, chloroform, petroleum ether and hexane of the bark of *Ficus religiosa* were screened for antibacterial activity against Enterotoxigenic *E. coli* isolated from diarrhoeal patients, at 200mg/ml concentration by disc diffusion method. The methanol extracts exhibited good activity compared to chloroform and aqueous extracts. Petroleum ether and hexane extracts did not show any activity [79].

A combination of hot alcoholic extracts of *Ficus infectoria*, *Ficus religiosa* and *Piper betel* were found to be effective against resistant and sensitive strains (Gram negative resistant *Klebsiella* strains, sensitive *Klebsiella* strains, resistant *Enterobacter* strains, sensitive *Enterobacter* strains, resistant *Escherichia coli* strains, resistant *Pseudomonas* strains, sensitive *Pseudomonas aeruginosa* strains and standard *Pseudomonas aeruginosa* ATCC 2862) and (Gram positive resistant *Staphylococcus* strains, sensitive *Staphylococcus* strains, resistant *Micrococcus* strain and standard *Staphylococcus aureus* ATCC 2901), isolated from skin and soft tissue infections. The ointment showed bactericidal activity within 2 h against the resistant strain of *Pseudomonas* spp [80]. Effect of ethanolic extract of *Ficus religiosa* fruits extract was studied against two Gram positive bacteria (*Staphylococcus epidermidis* and *Staphylococcus aureus*) and two Gram negative bacteria (*P. vulgaris* and *Klebsiella pneumonia*). The minimum inhibitory concentration of extract against *Staphylococcus epidermidis* and *Klebsiella pneumonia* was 15 mg/ml, while the minimum inhibitory concentration against *Staphylococcus aureus* and *P. vulgaris* was 30 mg/ml. At 15 mg/ml concentration of extract *K. pneumonia* showed more sensitivity (21 mm) than *S. epidermidis* (19 mm). At 30 mg/ml concentration *P. vulgaris* showed more sensitivity (12 mm) than *S. aureus* (9 mm) [81]. Bark of *Ficus religiosa* was dissolved in 67% ethanol. Extract was then subjected to antimicrobial efficacy tests against primary plaque colonizers and periodontal pathogens. *Ficus religiosa* showed antibacterial activity against primary plaque colonizers at 48 h with mean zone of inhibition of 2.6 ± 0.54 mm [82]. The antimicrobial activity of methanol and diethyl ether extracts of bark and leaves of *Ficus religiosa* (100, 200, 300 and 400 mg/ml) was investigated against two Gram negative bacteria (*E. coli* and *Pseudomonas aeruginosa*), and one Gram positive bacteria (*Staphylococcus aureus*). The methanol extracts of leaves and bark showed antimicrobial activity, a higher activity was recorded at 400 mg/ml concentration against the three tested bacteria. Both leaf and bark methanol extracts gave zone of inhibition of 2.8 and 2.2 mm against *S. aureus*, 2.4 and 1.8 mm against *E. coli* and 2.2 and 1.1 mm against *P. aeruginosa* respectively [83]. The antimicrobial activity of the aqueous extract of bark, leaf, stem, fruit of *Ficus religiosa* was determined by disc diffusion method against *Escherichia coli*, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, *Aeromonas hydrophila*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Aspergillus niger* and *Candida albicans*. The highest zone of inhibition (10-15 mm in diameter) was observed in 100 mg/ml concentration in all tested microbes [61]. The acetone, methanol, ethylacetate extracts (25-100 µg/ml) of *Ficus religiosa* bark were evaluated for antibacterial activity against *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus vulgaris*, *Bacillus subtilis* and *Staphylococcus aureus*. The growth of *Bacillus subtilis* was significantly inhibited by acetone extract of *Ficus religiosa*. Higher concentrations of the same extract were required to inhibit *E. coli*. Methanol extract of the plant was very active against all the tested bacterial pathogens except *P. aeruginosa*. Ethyl acetate extract was not active against all the bacterial species [57]. High antibacterial activity was possessed by aqueous extract of *Ficus religiosa* against *B. subtilis* with about 24 mm inhibition zone. It also exerted antibacterial activity against multi drug resistant *P. aeruginosa* [84]. The antiviral activity of *Ficus religiosa* was investigated against RSV and HRV *in vitro* by plaque reduction and virus yield assays, and the major mechanism of action was investigated by virus inactivation and time – of – addition assays. *Ficus religiosa* methanol bark extract was most active against HRV with an EC₅₀ of 5.52 µg/ml. This extract inhibited late steps of replicative cycle. Water bark extract was the most active against RSV with an EC₅₀ between 2.23 and 4.37 µg/ml. Partial virus inactivation and interference with virus attachment were both found to contribute to the anti-RSV activity. Replication of both viruses was inhibited in viral yield reduction assays [85]. The oil leaf of *Ficus religiosa* was screened for antimicrobial activity against *Aspergillus niger*, but was inactive (MIC = 2500 µg/ml). The antibacterial effect of leaf oil was studied against *Pseudomonas aeruginosa*, *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*. It was marginally active (MIC = 625 µg/ml) [72].

Anti-parasitic effect:

Ficus religiosa bark methanolic extract showed 100% lethality for *Haemonchus contortus* worms using *in vitro* testing [86]. The stem and bark extracts of *Ficus religiosa* proved lethal to *Ascaridia galli in vitro* [87].

Anti-Parkinson's activity:

The anti-Parkinson's activity of petroleum ether extract of *Ficus religiosa* leaves was investigated in rats. The effects of *Ficus religiosa* (100, 200, and 400 mg/kg, po) were studied using *in vivo* behavioral parameters like catalepsy, muscle rigidity, and locomotor activity and its effects on neurochemical parameters (MDA, CAT, SOD, and GSH) in rats. Haloperidol was used to induce catalepsy and 6-hydroxydopamine (6-OHDA) to induce Parkinson's disease-like symptoms. The increased cataleptic scores (induced by haloperidol) were significantly ($p < 0.001$) reduced by petroleum ether extract of *Ficus religiosa* at a dose of 200 and 400 mg/kg (po). 6-OHDA significantly induced motor dysfunction (muscle rigidity and hypolocomotion) and significantly increased lipid peroxidation level and depleted superoxide dismutase, catalase, and reduced glutathione level. Daily administration of petroleum ether extract of *Ficus religiosa* (400 mg/kg) significantly improved motor performance and significantly attenuated oxidative damage [58].

Anticonvulsant effect:

The effect of flavonoid-rich ethyl acetate fraction of the crude extract of *Ficus religiosa* in combined with phenytoin was evaluated on seizure severity, depressive behavior, and cognitive deficit in pentylenetetrazol (PTZ)-kindled mice. Combined treatment of flavonoid-rich ethyl acetate fraction (2.5, 5, and 10 mg/kg; ip) with a subeffective dose of phenytoin (15 mg/kg; ip) in post kindled animals once daily for fifteen days showed a dose-dependent decrease in the seizure severity score, a decreased number of mistakes, increased step-down latency in passive shock avoidance paradigm, and decreased immobility time in the tail suspension test in comparison with the phenytoin only-treated group. Biochemical investigations of the brain tissue showed amelioration of thiobarbituric acid reactive substances, reduced glutathione levels, and reduced catalase and acetylcholinesterase activities [88]. The effect of the saponin-rich fraction of the extract of *Ficus religiosa* (SRF) was studied in pentylenetetrazol (PTZ) kindling mouse model and its associated depression and cognition deficit. Treatment with the SRF (1, 2 and 4 mg/kg; ip) for 15 days in kindled mice significantly decreased seizure severity on days 5, 10 and 15 when challenged with PTZ (35 mg/kg; ip). Marked protection against kindling-associated depression was also observed on days 10 and 15 in the SRF-treated groups when tested using the tail-suspension test. The SRF treatment failed to protect kindling-associated learning and memory impairments in the passive shock avoidance paradigm [89]. The anticonvulsant activity of figs extract (25, 50 and 100 mg/kg, ip) was studied in seizures induced by maximum electroshock (MES), picrotoxin and pentylenetetrazol (PTZ). Cyproheptadine, a nonselective 5HT_{1/2} serotonin antagonist (4 mg/kg, ip) was used to study the reversal of protective effect of extract in these models. Acute toxicity, neurotoxicity and potentiation of pentobarbitone induced sleep by extract were also studied. Extract showed no toxicity, potentiated pentobarbitone induced sleep and inhibited seizures induced by MES and picrotoxin in a dose dependent manner. Anticonvulsant effect of extract was comparable to clinically used antiepileptic drugs (phenytoin and diazepam). However, PTZ induced seizures were not inhibited. Animals pretreated with cyproheptadine showed inhibition of the anticonvulsant effect of extract which indicated the involvement of serotonergic pathways in the anticonvulsant activity of extract [90]. The anticonvulsant activity of the aqueous aerial root extract of *Ficus religiosa* (25, 50 and 100 mg/kg, po) was evaluated in chemo-convulsant-induced seizures in mice. The extract protected the animals in the strychnine and pentylenetetrazole tests in a dose-dependent manner. It was less potent in the picrotoxin and isoniazid induced seizures tests. The extract also exhibited dose-dependent potentiation of acetylcholine in rat ileum but failed to potentiate the effect of 5-HT in rat fundus strip preparation [91].

Anti-amnesic effect:

The effect of the methanol extract of *Ficus religiosa* was investigated in scopolamine-induced anterograde and retrograde amnesia in mice. Transfer latency (TL) to the preferred niche in the elevated plus-maze (EPM) and learning avoidance of passive behavior to avoid punishment in the modified passive avoidance paradigm (MPA) were used as behavioral models for the assessment of memory. Scopolamine (1 mg/kg, ip) was administered before training for induction of anterograde amnesia and before retrieval for induction of retrograde amnesia in both models. The methanol extract of *Ficus religiosa* (10, 50, and 100 mg/kg, ip), treatment resulted in significant improvement of memory, as it attenuated the scopolamine-induced anterograde and retrograde amnesia dose-dependently. While, cyproheptadine pretreatment significantly reversed the anti-amnesic effect of the methanol extract of *Ficus religiosa* [92]. Ethanol extract of *Ficus religiosa* leaves was evaluated for memory enhancing activities in Wistar albino rats and Swiss albino mice using elevated-plus maze, step through passive avoidance test, sodium nitrite intoxication, Hebb-Williams Maze and radial arm maze. Scopolamine (1mg/kg, ip) and sodium nitrite (95mg/kg, sc) were used as inducing agent in elevated-plus maze and sodium nitrite intoxication respectively. The extract significantly improved memory and reversed the amnesia induced by scopolamine, and hypoxia induced by sodium nitrite [93].

Acetylcholinesterase inhibitory effect:

Methanolic extract of the stem bark of *Ficus religiosa* inhibited the acetylcholinesterase enzyme, accordingly this indicated that the plant was beneficial in Alzheimer's diseases treatment [94].

Hepato-, nephro- and dermato- protective effects:

The hepatoprotective effect of methanolic extract of *Ficus religiosa* (100, 200 and 300mg/kg bw, po) was studied in isoniazid-rifampicin and paracetamol induced hepatotoxicity in rats. All the treatment protocols followed 21 days for INH+RIF model and seven days for paracetamol model. Administration of methanolic extracts of *F. religiosa* significantly prevented isoniazid-rifampicin and paracetamol induced elevation in the levels of serum liver marker enzymes and TBARS level in experimental groups of rats. Total protein and reduced glutathione levels were significantly ($P < 0.001$) increased in treatment group. The effect of extract was comparable with a standard drug, Liv 52. The biochemical effects were further confirmed by histological results [95].

The hepatoprotective effects of *Ficus religiosa* latex in cisplatin induced liver injury was investigated in Wistar rats. Cisplatin-treated animals showed significant increase in serum alanine amino transferase, aspartate amino transferase, alkaline phosphatase and hepatocytes cells degeneration, inflammatory infiltrate and necrosis, these changes were significantly ($p < 0.01$) alleviated by *Ficus religiosa* latex [56]. Alcohol extract of *Ficus religiosa* stem bark was evaluated for nephro-protective effects, it reduced the blood urea nitrogen level close to normal value against the toxic effects induced by rifampicin and isoniazid in rabbits. The histopathological studies of kidney of untreated rabbit showed severe degree of infiltration in the glomerulus without renal tubular space between the glomerulus, congestion in the renal parenchyma, necrosis and condensed nucleus. The rabbits treated with extract show normal appearance of the nuclei with no condensed nucleus without any necrosis but at some places there was mild congestion. Kidney tubular cells structure was normal in appearance [96]. The dermatoprotective effects of ethanolic extract of *Ficus religiosa* was studied by topical application of the extract to the backs of rabbits daily for 4 days, against known irritants such as sodium dodecyl sulfate, atrazine, and petrol. Skin was examined after 24, 48, and 96 h for erythema. Skin biopsies were taken on 5th day for microscopic examination. Erythema produced by irritants reduced significantly with the simultaneous application of *Ficus religiosa* extracts. The mean \pm SEM epidermal thickness (micrometer) with sodium dodecyl sulfate was 45.40 ± 1.89 and *Ficus religiosa* + sodium dodecyl sulfate was 18.60 ± 0.51 . Similar findings were revealed after using plant extracts with atrazine and petrol. The results indicated that *Ficus religiosa* demonstrated the potential to block the dermatotoxic effects of topical irritants and could be used successfully to prevent skin toxicity [97].

Antidiabetic effect:

Aqueous extract of *Ficus religiosa* at a dose of 100 and 200 mg/kg orally decreased the fasting blood glucose in streptozotocin induced type 2 diabetic rats. *Ficus religiosa* modulated the enzymes of antioxidant defence system to combat oxidative stress. As a result, it reduced glutathione (GSH-reduced form) and inhibited the formation of malondialdehyde. Higher dose (200 mg/kg) had more pronounced effect [98]. The hypoglycemic effect of aqueous extract of *Ficus religiosa* bark at the doses of 25, 50 and 100mg/kg was studied in normal, glucose-loaded and STZ-diabetic rats. The three doses caused significant reduction in blood glucose levels in both models. The effect was more pronounced in 50 and 100mg/kg than 25mg/kg. The aqueous extract of *Ficus religiosa* bark also showed significant increase in serum insulin, body weight and glycogen content in liver and skeletal muscle of STZ-induced diabetic rats, with significant reduction in the levels of serum triglyceride and total cholesterol. The aqueous extract of *Ficus religiosa* bark also showed significant antilipidperoxidative effect in the pancreas of STZ-induced diabetic rats. The antidiabetic effect of *Ficus religiosa* was comparable with glibenclamide [99]. The effect of *Ficus religiosa* was studied on STZ-induced diabetic cardiomyopathy in rats. Streptozotocin (90 mg/kg i.p.), administered to 2 days old neonates (10–12 g), resulted in significant increase in fasting blood glucose, HbA1c, cardiac hypertrophic index, TGF- β 1, TNF α , malondialdehyde, LDH, CK-MB, BNP and caspase-3. It caused significant reduction in plasma insulin, heart rate and superoxide dismutase. The eight-week treatment of *Ficus religiosa* started after induction of six weeks of diabetes, significantly improved diabetic markers, oxidative stress, inflammatory and cardiac markers [100]. The effect *Ficus religiosa* on elevated glucose and inflammatory marker (tumor necrosis factor (TNF- α) was evaluated in streptozotocin-induced type 2 diabetic rats. Aqueous extract of *Ficus religiosa* at a dose of 100 and 200 mg/kg was given orally for a period of 4 weeks. After 4 weeks treatment, fasting blood glucose, postprandial blood glucose and TNF- α in serum were analyzed. Aqueous extract of *Ficus religiosa* at both dose levels decreased the elevated glucose and TNF- α in type 2 diabetic rats. The extract at 200 mg/kg had more pronounced effect [101].

Antiinflammatory and analgesic effects:

The aqueous extract of bark of *Ficus religiosa* was investigated for its anti-inflammatory effect and for its protective effect on mast cells against degranulation. A significant anti-inflammatory effect was observed in both acute and chronic models of inflammation. The extract also protected mast cells from degranulation induced by various degranulations [102]. The effect of a methanol extract of *Ficus religiosa* leaf was studied in lipopolysaccharide (LPS)-induced production of NO and proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-beta (IL-1beta) and IL-6 in BV-2 cells, a mouse microglial line. Methanol extract of *Ficus religiosa* leaf inhibited LPS-induced production of NO and proinflammatory cytokines in a dose-dependent manner. Methanol extract of *Ficus religiosa* leaf also attenuated the expression of mRNA and proteins of inducible nitric oxide synthase (iNOS) and proinflammatory cytokines. The molecular mechanism of methanol extract of *Ficus religiosa* leaf-mediated attenuation included down-regulation of the extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) signaling pathway, and suppression of the nuclear factor kappaB (NF-kappaB) activation [103]. Different fractions of dried leaves of *Ficus religiosa* were evaluated for analgesic and anti-inflammatory activity using different models of pain and inflammation. The analgesic activity of *Ficus religiosa* carried out using acetic acid-induced writhing in mice and tail flick test in rats. The anti-inflammatory activity was evaluated using carrageenan-induced rat paw edema and cotton pellet-granuloma formation in rats. Five different fractions (FRI, FRII, FRIII, FRIV and

FRV) of *Ficus religiosa* at the dose level of 20 and 40 mg/kg, po were tested. The fraction FRI (40 mg/kg, po) and FRIII (40 mg/kg, po) were found to be more effective ($P < 0.01$) in preventing carrageenan induced rat paw edema, cotton pellet granuloma formation, and acetic acid induced writhing compared to the other fractions. FRI (20 mg/kg, po) and FRIII (20 mg/kg, po) were also found to be more effective in increasing latency period in tail flick method [104].

Cytotoxic effect:

F. eligiosa fruit extract demonstrated activity in the brine shrimp test (*Artemia salina*). *F. eligiosa* fruit extract exhibited antitumor activity in the potato disc bioassay [105]. Ethanol extracts of the *Ficus religiosa* was also screened for cytotoxicity activity by using *in vivo* brine shrimp lethality assay. The percent mortality of shrimp was increased with the increase of the doses of the extracts. LC_{50} and LC_{90} values were found to 2.7 and 4.62 $\mu\text{g/ml}$. The oil leaf of *Ficus religiosa* was marginally active in the brine shrimp lethality test ($LC_{50} = 50 \mu\text{g/ml}$) and also showed *in vitro* cytotoxic activity against MCF-7 human breast tumor cell line ($80 \pm 5\%$ kill at 100 $\mu\text{g/ml}$) [77]. Extracts showed any marked inhibition on the uptake of calcium into rat pituitary cells GH4C1 [105]. The cytotoxic activity of aqueous and ethanolic preparations of *Ficus religiosa* bark was evaluated in cervical cancer cell lines, SiHa and HeLa. Both aqueous and ethanolic extracts of the bark showed significant cytotoxicity in cervical cancer cell lines SiHa (HPV16 positive) and HeLa (HPV18 positive) wherein ethanolic extract showed cytotoxicity at much lower doses compared to aqueous extract [62]. The anti-neoplastic potential of aqueous extract of *Ficus religiosa* bark was studied in human cervical cancer cell lines, SiHa and HeLa. The aqueous extract of *Ficus religiosa* altered the growth kinetics of SiHa (HPV-16 positive) and HeLa (HPV-18 positive) cells in a dose-dependent manner. It blocked the cell cycle progression at G1/S phase in SiHa that was characterized by an increase in the expression of p53, p21 and pRb proteins with a simultaneous decrease in the expression of phospho Rb (ppRb) protein. In HeLa, aqueous extract of *Ficus religiosa* induced apoptosis through an increase in intracellular Ca^{2+} leading to loss of mitochondrial membrane potential, release of cytochrome-c and increase in the expression of caspase-3. The aqueous extract of *Ficus religiosa* also reduced the migration as well as invasion capability of both cervical cancer cell lines accompanied with down-regulation of MMP-2 and Her-2 expression. In addition, it also reduced the expression of viral oncoproteins E6 and E7 in both cervical cancer cell lines [106]. Different fractions of *Ficus religiosa* [FR] were tested for *in vitro* anticancer activity using human MCF 7 and normal epithelial cell lines. The result showed that The IC_{50} value for FRI was found to be 160.3 μM , whereas the IC_{50} value for FRIII was found to be 222.7 μM in the normal epithelial cells [107]. The potential effect of acetone extract of *Ficus religiosa* leaf (FAE) in multiple apoptosis signaling was studied in human breast cancer cells. FAE treatment significantly induced dose and time dependent, irreversible inhibition of breast cancer cell growth with moderate toxicity to normal breast epithelial cells. Cell cycle analysis showed cell cycle arrest in G1 phase and induction of sub-G0 peak. FAE induced chromatin condensation and displayed an increase in apoptotic population. FAE stimulated the loss of mitochondrial membrane potential in multiple breast cancer cell lines when compared to normal diploid cells. Bax translocation to mitochondria was accompanied by the disruption of mitochondrial membrane potential and marked elevation in LEHDase activity (Caspase 9) [108]. *Ficus religiosa* leaf extract was proved as a good reducing agent to fabricate silver nanoparticles (AgNPs) by a simple, cost-effective and eco-friendly process in the treatment of Dalton's ascites lymphoma (DAL) in mice model [109].

Anti-ulcer effect:

Anti-ulcer activity of *Ficus religiosa* ethanolic extract (250 and 500 mg/kg body weight) was studied on stress induced ulcer animal models. Results showed that the extract treatments reduced ulcer area and gastric secretion in a dose-dependent manner [110]. The anti-ulcer potential of the ethanol extract of leaves of *Ficus religiosa* was investigated against *in vivo* aspirin induced ulcer and pylorus ligation assays. Gastric ulcers were induced in Swiss albino rats by oral administration of aspirin suspension and ligate the pylorus part of stomach. The results indicated that ethanolic extract significantly ($p < 0.001$) decreased the volume of gastric acid secretions, free acidity, total acidity and ulcer index [111]. The gastroprotective activity of hydroalcoholic extract leaves of *Ficus religiosa* was studied at two dose levels (250 and 500 mg/kg, oral) in rats against absolute ethanol (0.2 ml oral), aspirin (200 mg/kg) and pyloric ligation induced gastric ulcer. Administration of *Ficus religiosa* to rats significantly decreased the ulcer index value when compared with the control group [112]. The anti-ulcer potential of the ethanol extract of stem bark of *Ficus religiosa* was evaluated against *in vivo* indomethacin- and cold restrained stress-induced gastric ulcer, and pylorus ligation assays. The extract (100, 200 and 400 mg/kg) significantly ($P < 0.05$) reduced the ulcer index in all assays used. The extract also reduced the volume of gastric juice, free and total acidities [113]. 70% aqueous-ethanol extracts completely inhibited the growth of *Helicobacter pylori* at 500 $\mu\text{g/ml}$ in all used strains. Anti-*H. pylori* MBC value ranged from 125 to 250 $\mu\text{g/ml}$ [114].

Wound healing effect:

The wound-healing activity of *Ficus religiosa* extracts in ointment form (5 and 10%) was evaluated in incision and excision wound models in Wistar albino rats. Both 5 and 10% ointments of *Ficus religiosa* root extracts promoted the wound-healing activity significantly in all the wound models studied. They increased the rate of wound contraction, decreased the period for epithelialisation, increased skin breaking strength and increased hydroxyproline content [115]. The wound healing activity of *Ficus religiosa* hydroalcoholic leaf extracts ointment (5 and 10%) was studied in rats using excision and incision wound models. The healing of the wound was assessed by the rate of wound contraction, period of epithelialisation, skin breaking strength. Both (5% and 10% ointments) promoted the wound-healing activity significantly in both wound models. High rate of wound contraction, decrease in the period for epithelialisation, high skin breaking strength were observed in animals treated with 10% leaf extract ointment when compared to the control group of animals [116].

Antioxidant effect:

The antioxidant potential of aqueous and ethanolic preparations of *Ficus religiosa* bark was evaluated by oxygen radical absorbance capacity method. The aqueous and ethanolic extracts of the bark exhibited significant total antioxidant capacity, however the aqueous extract showed higher oxygen radical absorbance capacity than ethanolic extract. Both the extracts exhibited a significant increase in anti-lipid peroxidative activity with IC₅₀ values of 29.06 and 34.39 µg/ml for aqueous extract and ethanolic extracts, respectively [62].

Effect on asthma:

The anti-asthmatic activity of the aqueous extract of *Ficus religiosa* leaves was evaluated in histamine and acetylcholine induced bronchospasm in guinea pigs. Administration of the aqueous extract of *Ficus religiosa* leaves (150 and 300 mg/kg, ip.) produced significant effect on latency to develop histamine and acetylcholine induced pre-convulsive dyspnea. In the mast cell stabilizing model, the aqueous extract of *Ficus religiosa* leaves at 10, 20 and 30 µg/ml significantly increase the number of intact cells [117]. However, in another study, the administration of methanolic extract of *Ficus religiosa* fruits (125, 250 and 500 mg/kg, po) did not produced any significant effect on latency to develop histamine induced pre-convulsive dyspnea. While, in a dose of (0.5, 1 and 2 mg/ml), it possessed significant potentiation of the bronchoconstriction induced by both histamine and acetylcholine on guinea pig tracheal chain preparation [75].

Reproductive effects:

Effects of 1% methanol extract of *Ficus religiosa* fruits extract was studied on the goat uterus *in vitro* in exposure duration dependent manner (1, 4 and 8 hours). Effects on dimensions of uterine glands, surface epithelium, gland cell and myometrium were observed. The treatment induced a decline in uterine glands diameter which were crucial for implantation. The authors concluded that the extract exerted antifertility activity [118]. A clinical trial on 44 patients of erectile dysfunction (ED) were divided into two main groups: diabetic and non-diabetic, and were further divided into two subgroups as trial group and placebo group. In the trial group, Ashvattha prepared with 10 g powder of *Ficus religiosa* root bark, stem bark, fruit and tender leaf buds, was given twice a day. In both the diabetic and the non-diabetic subjects, Ashvattha provided encouraging results on ED as well as on seminal parameters in comparison to the placebo [119]. The potential benefits of three different antioxidants in reversing cadmium (Cd)-induced reproductive toxicity was studied in adult male rats. Treated groups received CdCl₂ (0.2 mg/kg), sulforaphane (25 µg/rat), vitamin E (75 mg/kg), and *Ficus religiosa* extract (100 mg/kg) for 15 days. Cadmium exposure caused significant decrease in final body weight ($p < 0.0001$). The plasma concentrations of Cd were significantly increased and Zn concentration decreased ($p < 0.0001$) in the Cd group as compared to the control group. The testicular concentrations of Cd were significantly increased and Zn concentration decreased ($p < 0.0001$) in the Cd group as compared to the control group. Cadmium exposure caused a significant decrease ($p < 0.0001$) in plasma testosterone concentrations and daily sperm production as compared to the control group. A significant effects were observed with Cd+ sulforaphane, Cd+ vitamin E, and Cd+ plant extract treated groups in slashing Cd-induced toxicity [120].

Toxicity:

Administration of 2000 mg/kg extract did not show any acute toxicity in albino mice [91, 112]. Orally administered dose ranged from 50–2000 mg/kg of extract did not produce any significant changes in the autonomic or behavior responses in rats [56]. In acute oral toxicity studies, the *Ficus religiosa* extract treated rats were observed for mortality up to 48 hrs. There was no mortality or any signs of behavioral changes observed after oral administration of methanol extract up to 5000 mg/kg body weight [95].

VI. CONCLUSION:

The current review highlights the chemical constituents and pharmacological effects of *Ficus religiosa* as a promising plant for many medical purposes as a results of effectiveness and safety.

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