

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

SJIF Impact Factor: 5.273

A REVIEW ON SCREENING OF THE LEAVES OF FICUS RELIGIOSA LINN (PEEPAL TREE) FOR ITS ANTIDIABETIC ACTIVITY

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Received on: 14/03/2020	ABSTRACT				
Revised on: 04/04/2021	Diabetes is contemplated as one of the most common chronic diseases internationally.				
Accepted on: 24/04/2021	It is an extensive pancreatic disease affecting large amount of the community glob				
	This is growing authentication that grows manufacturing and/or unsuccessful				
*Corresponding Author	scavenging of ROS (Reactive Oxygen Species) may play a censorious part in chronic				
Sunil Singh	diseases. Lipid can be produced by peroxidation highly responsive ROS which control the chemical changes in close to all cellular integrant, leading to production of ROS and disorder in antioxidant protect system in diabetic thing has been reported. The antioxidants are used to treat and decrease the complications (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, myocardial infarction, and atherosclerosis) of diabetes mellitus. Herbal medications have been used for the treatment of variety of				
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	ailments among which Ficus religiosa belonging to the family Moraceae is the vital				
	one. As mentioned in the herbal medicine system, F. religiosa have the potential to				
	treat disorders including hyperglycemia, diarrhea, inflammatory disorders, epilepsy,				
	and stomach problems, sexual and infectious diseases. There are countless studies on the reaction of antioxidants in the modulation of diabetes. The aim of this study was to abstract the middle role of oxidative stress in the pathogenesis of diabetes and the				
	approaching role of antioxidants to overcome lipid peroxidation through their				
	radicals clearance properties.				
KEYWORDS: Antidiabetic, <i>Ficus religiosa</i> , antioxidant, Phyt Pharmacological action.					

INTRODUCTION

Diabetes mellitus (DM), endocrine metabolic disorder is outcome of lack of insulin or decreased insulin activity resulting in elevated glucose levels known as hyperglycemia. Improper carbohydrate, protein and fat metabolism are other associated issues with DM.53 With incidence of 5% in common population worldwide, DM has became an epidemic. Lack of physical exercise, unhealthy food habits, obesity and stressful lifestyle remains to be the major factors for prevalence of DM.57 Type-I or Insulin dependent diabetes mellitus and (Type-II) or Non Insulin dependent diabetes mellitus are two categories of DM. Due to complete pull down of β islets cells, production of insulindecreases which is the characteristic feature of type 1. This causes difficulty in maintaining blood glucose levels to normal values. Type I DM was observed both in adult as well as child patients where elevated glucose levels were recorded in fasting and post prandial blood.54Peripheral vascular resistance, change in blood flow rate causing cardiac disease, diabetic retinopathy, neuropathy, nephropathy and hypertension are also the complications commonly

associated in DM. Also a micro-vascular and macrovascular complication arising out of DM has increased the morbidity and mortality rate in the recent years.55 The World Health Organization reported that 30 million people were diagnosed with diabetes in 1985. That number increased to 135 million people in 1995, and approximately 300 million people are estimated to be affected by the year 2025 (WHO, 2016). The number of diabetes mellitus cases is steadily increasing throughout the world, and its major complications (disability and hospitalization) are posing a significant financial burden (Adams, 2011).

Presently, different kinds of synthetic drugs, such as incretinmimetics, meglitinides, biguanides, sulfonylureas, thiazolidinediones, α -glucosidase inhibitors, dipeptidyl peptidase-IV inhibitors and sodium/glucose co-transporter 2 (SGLT2) inhibitors, are available for diabetes mellitus management. While antidiabetics provide some promising results, they also produce various adverse effects (Gacche and Dhole, 2011). Therefore, it remains necessary to search for novel antidiabetic drugs to control diabetic disorders

without any side effects (Dhawan et al., 2002.

Evaluation of plants with potential therapeutic activity was recommended by WHO (1980) as an alternative where safety is a major concern with modern drugs. For the treatment and management of DM many researchers have worked on number of plants and plant materials with various experimental techniques.66Approximately 200 pure bioactive compounds from different chemical groups (e.g., phenolic acids, flavonoids, triterpenoids, alkaloids and carbohydrates) have been isolated from these medicinal plants and possess strong antidiabetic properties as exhibited by their regulation of glucose levels in the blood (Misbah et al., 2013). It is believed that the drugs from natural resources significantly increases secretion of insulin, enhances uptake of glucose by adipose tissues and reduce production and absorption of glucose by liver and intestinal mucosa respectively.67 Traditional medicine recommends a huge number of plant species, especially for management of diabetes. There is a need to compile the knowledge of these plants in a scientific manner, research and develop it for more effective therapeutic benefit.

This review is focused on prevention or treatment of diabetes and its complications by using different parts including bark aerial roots, leaves, fruits and roots of Ficus religiosa and their bioactive components. This review includes antidiabetic effects of Ficus religiosa that will lead to discover more scientific knowledge about the diabetes; a global problem for developed, developing and under developed countries.

Different mechanisms of Diabetic mellitus

Ficus religiosa

The quality of human life for thousands of years has been improved by Plants and its components. Herbal medicine is based on the plants and its natural physiological active components that can improve the health and alleviate illness by maintaining human health and environment. The available information on F. religiosa has been divided into four sections, which are ethno-pharmacology, morphology, phytochemistry and pharmacological studies. Ficus religiosa Linn (Moraceae) commonly known as 'Peepal tree' is a widely branched tree with leathery, heart-shaped, long tipped leaves on long slender petioles and purple fruits growing in pairs. It has got mythological, religious and medicinal importance in Indian culture since ancient times [Ghani et al, 1998, Prasad et al, 2006].

In India, it is known by several vernacular names, the most commonly used ones are as follows:

- Asvatthah (Sanskrit),
- Sacred fig (Bengali), Peepal (Hindi),
- Arayal (Malayalam),
- Ravi (Telgu) and
- Arasu (Tamil) [Warrieret al, 1996].

Taxonomy

- Domain: Eukaryota
- Kingdom: Plantae
- Subkingdom: Viridaeplantae
- Phylum: Tracheophyta
- Subphylum: Euphyllophytina
- Infraphylum: Radiatopses
- Class: Magnoliopsida
- Subclass: Dilleniidae
- Superorder: Urticanae
- Order: Urticales
- Family: Moraceae
- Tribe: Ficeae
- Genus: Ficus
- Specific epithet: Religiosa Linnaeus
- Botanical name: Ficus religiosa Roxb

Habitat

F. religiosa is known to be a native Indian tree, and thought to be originating mainly in Northern and Eastern India, where it widely found in uplands and plane areas and grows up to about 1650 meters or 5000 ft in the mountainous areas. It is also found growing elsewhere in India and throughout the subcontinent and Southern Asia, especially in Buddhist countries, wild or cultivated. It is a familiar sight in Hindu temples, Buddhist monasteries and shrines, villages and at roadsides. People also like to grow this sacred tree in their gardens. F. religiosa has also been widely planted in many hot countries all over the world from South Africa to Hawai and Florida but it is not able to naturalize away from its Indian home, because of its dependence on its pollinator wasp, Blastophagaquadraticeps. An exception to this rule is Israel where the wasp has been successfully introduced.

Description

a. Macroscopic characteristics

Leaves: The first appearance of is red-pinkish colour and after growth they becomes dark green in colour and length is about 12 to 18 cm long. The leaves are present as alternate to each other and heart-shaped, shiny with an elegant tail-like tip which is often called a "drip-tip", monitoring water efficiently down to the soil. The leaves are framed as 5-7 pairs of side-veins and further divided into very fine veins8.

Bark: Barks are present in the form of flat or slightly curved pieces, varying from 1.0 - 2.5 cm in size. External surface of bark is brown or ash colored and inner surface is smooth and brownish. The fractures are fibrous. The taste of the bark is as astringent8.

Flowers: The colour of flower is red, appear in February. For settling of seeds, pollinator wasps play important role like *Blastophaga quadraticeps*8.

Fruit: The fruits are grows as small flat-topped figs in May/June, which Are present in pairs on the twigs. At

first the basal stalk are green and appears blackish purple after ripening and are three in number 8.

Microscopic characteristics: The shape of bark's h. T.S. appears as cubical to rectangular. The cork cells are thick walled and masses of stone cells are present in dead elements of secondary cortex: cork cambium distinct with rows of newly formed secondary cortex, mostly composed of stone cells towards periphery. Stone cells found scattered in rarely large groups, isolated; most of parenchymatous cells of secondary cortex contain numerous starch grains and few prismatic crystals of calcium oxalate; secondary phloem a wide zone, consisting of sieve elements, phloem fibers in singles or in groups of two and non lignified; numerous crystal fibers also present; in outer region sieve elements mostly collapsed while in inner region intact; phloem parenchyma mostly thickwalled; stone cells present in single or in small groups similar to those in secondary cortex; a number of ray-cells and phloem parenchyma filled with brown pigments; prismatic crystals of calcium oxalate and starch grains present in a number of parenchymatous cells; medullary rays uni to multiseriate, wider towards outer periphery composed of thick-walled cells with simple pits; in tangential section ray cells circular to oval in shape; cambium when present, consists of 2-4 layers of thin-walled rectangular cells .39

Phytochemical Screening

Ficus religiosa shows the presence of following phytochemicals:^[4]

• The bark of Ficus religiosa showed the presence of

- Leaves extract yield various compounds such ascampestrol, stigmasterol, isofucosterol, α-amyrin, lupeol, tannic acid, arginine, serine, aspartic acid, glycine, threonine, alanine, proline, tryptophan, tryosine, methionine, valine, isoleucine, leucine, nnonacosane, n- hentricontanen, hexa-cosanol and noctacosan.
- The fruit of *F.religiosa* contains chemical constituents such as asgaragine, tetradecane, tyrosine, undecane, tridecane, α-thujene, α-pinene, β-pinene, α-terpinene, limonene, dendrolasine α-ylangene, β-bourbonene, β-caryophyllene, α-trans bergamotene, aromadendrene, α-humulene, alloaromadendrene, germacrene, bicyclogermacrene, γ- cadinene and δ-cadinene. Alanine, threonine, and tyrosine.^[1]
- The crude latex of *Ficus religiosa* shows the presence of a serine protease called as religiosin. HPLC analysis of flavonoids as kaempferol, rhamnetin, myricetin, isorhamnetin and quercetin as standards. The study evaluated that quercetin was most potential constituent reported in *F. religiosa*.

Traditional Uses

F. religiosa is a common plant used in Ayurveda and uses are mentioned in the medicine system.^[11] The use of different parts of *F. religiosa* is mention in table (Table 1).

Plants Part	Traditional use		
	Antibacterial against Staphylococcus aureus, gonorrhoea, diarrhoea astringent, cooling,		
Bark	aphrodisiac, dysentery, haemorrhoids and anti-inflammatory, gastrohelcosis, burns [Warrier, et al,		
	1996] 50		
Bark Decoction	Cooling, gonorrhea, skin diseases, scabies, vomiting [Kapoor et al, 1999]. 51		
Leaves	Purgative, wounds, skin diseases [Warrier, et al, 1996].50		
Leaf juice	Asthma, cough, sexual disorders, diarrhea, haematuria, toothache, migraine, eye problems, gastric		
	problems, scabies [Warrier, et al, 1996]. 50		
Leaf decoction	Analgesic for toothache [Kunwar et al, 2006]. 52		
Dried fruit	Tuberculosis, fever, paralysis, hemorrhoids [Kunwar et al,2006].52		
Fruit	Asthma, laxative, digestive [Warrier, et al, 1996]. 50		

Table 2: List of medical plants used as anti-diabetic agents in Indian medicine.

Plant name	Family	Reference
Abrusprecatorious L.	Fabaceae	Nwanjo et al., 2008
Andragraphispaniculata	Acanthaceae	Chakkaravarthy et al., 2009
Abutilon indicum .	Malvaceae	Krisanapun et al., 2009
Anthocleistadjalonesis	Loganiaceae	Okokon et al., 2012
Ficus retusa	Umbellifereae	Swapandeepet al., 2010
Aeglemarmelos (Linn.)	Rutaceae	Sabu and Kuttan, 2004
Aloe vera (L.). Burm. f.	Liliaceae	Vijayalakshmi et al., 2008
Acacia Arabica	Leguminoseae	Yasir et al., 2010

Cecropiaobtusifolia	Urticaceae	Cetto and WIedenfeld, 2011
Allium Cepa	Liliaceae	Ozougwu et al., 2011
Passifloramollissima	Passifloraceae	Edwin et al., 2007
Helicteresisora	Sterculiaceae	Suthar et al., 2009
Carica papaya Linn.	Caricaceae	Adeneye et al., 2009
Zea mays L.	Poaceae	Parekh et al., 2007
Cassia kleinii	Lauraceae	Babu et al., 2003
Cassia glauca	Caesalpiniaceae	Farswan et al., 2009
Phyllanthusfraternus	Euphorbiaceae	Garg et al., 2010
Acacia nilotica	Caesalpiniaceae	Zaman et al., 2008
Ichnocarpusfrutescens	Apocynaceae	Barik et al., 2008
Cocciniagrandis (L.). Voigt.	Cucurbitaceae	Dhanabal et al., 2004
Aloe barbedensis	Liliaceae	Okyar et al., 2001
Carumcarvi L.	Umbelliferae	Eidi et al.,2006
Micheliachampaca	Magnoliaceae.	Jaralad et al., 2008
Capparissepiaria	Capparidaceae	Selvamani et al., 2008
Allium porrum L.	Liliaceae	Aslan et al.,2010
Emblicaofficinalis (Gaertn.)	Euphorbiaceae	Mehta et al., 2009
Annonasquamosa	Annonaceae	Shirwaikar <i>et al.</i> , 2004.
Smallanthussanchifolius	Compositae	Sanchez et al., 2010
Sphaeranthusindicus	Asteraceae	Jha et al., 2010
Perseaamericana	Lauraceae	Anita et al., 2005
Merremiaemerginata	Conolvulaceae	Gandhi et al., 2012
Mangiferaindica	Anacardiaceae	Ganogpichayagra et al., 2017
MoringaoleiferaLamk	Moringaceae	Al-Malki et al., 2015
. Momordicacharantia	Cucurbitaceae	Josheph and Jini, 2013
Loranthusmicranthus L.	Loranthaceae	Ali et al., 2008
Rhododendrontomentosum	Ericaceae	Dampc&Luczkiewicz 2013
Paspalumscrobiculatum Linn.	Poaceae	Jain et al., 2010
Psidiumguajave Linn	Myrtaceae	Mazumdar et al., 2015
PterocarpusmarsupiumRoxb.	Fabaceae	Chakravarthy et al., 1980
Rauwolfia serpentine Linn.	Apoycynaceae	Quereshi et al., 2009
P. santalinus Linn.	Fabaceae	Kameswara et al., 2001
Rheum emodi Wall.	Polygonaceae	Arvindekar et al., 2015
Solanumnigrum Linn.	Solanceae	Maharana et al., 2010
Strychnospotatorum Linn. F	Loganiaceae	Biswas et al., 2014
SwertiachirataBuch-Hamm	Gentianaceae	Arya et al., 2011
SyzygiumalternifoliumWalp.	Myrtraceae	Badri&Rao, 2001
S. cumini Linn.	Myrtraceae	Rai, 1995
Tecomastansi (Linn.)	Bignoniaceae	Rahmatullah et al., 2010
Trigonellafoegnum –graceum Linn.	Fabaceae	Rai, 1995
T. chebula	Combretaceae	Sabu&Kuttan, 2002.
Tinosporacordifolia	Menispermaceae	Kinkar&Patil, 2015
Tribulusterestris (Linn.)	Zygophyllaceae	El-Shaibany et al., 2015

Pharmacological Effect

Antibacterial activity

Aqueous and ethanolic extracts of *F. religiosa* leaves showed antibacterial effect against *Staphylococcus aureus, Salmonella paratyphi, Shigella dysenteriae, S. typhimurium, Pseudomonas aeruginosa, Bacillus subtillis, S. aureus, Escherichia coli, S. typhi.* In another study, chloroform extract of fruits showed antimicrobial effect against *Azobacter chroococcum, Bacillus cereus, B. megaterium, Streptococcus faecalis, Streptomycin lactis, and Klebsiella pneumonia.* The ethanolic extract of leaves showed antifungal effect against *Candida albicans.* Aqueous, methanol, and chloroform extracts from the leaves of *F. religiosa* were completely screened for antibacterial and antifungal activities.^[17,19]

Anthelmintic activity

F. religiosa bark methanolic extract was 100% lethal for

Haemonchus contortus worms. The stem and bark extracts of *F. religiosa* proved lethal to *Ascaridia galli in vitro*. The latex of some species of *Ficus* (Moraceae), i.e., *Ficus inspida*, *F. carica* was also reported to have anthelmintic activity against *Syphacia obvelata*, *Aspiculuris tetraptera*, and *Vampirolepis nana*. It has been accepted that anthelmintic activity is due to a proteolytic fraction called ficin. It is evident from above that methanolic extracts of *F. religiosa* possibly exerted anthelmintic effect because of ficin.^[2,17]

Immunomodulatory activity

The immunomodulatory effect of alcoholic extract of the bark of *F. religiosa* (moraceae) was investigated in mice. The study was carried out by various hematological and serological tests. Administration of extract remarkably ameliorated both cellular and humoral antibody response. It is concluded that the extract possessed promising

immunostimulant properties.^[2]

Antioxidant activity

The literature showed that the antioxidative properties of the extract of *F. religiosa* fruit and bark were done using different solvents. They were evaluated on the basis of oil stability index together with their radical scavenging ability against 1, 1-diphenyl-2-picrylhydrazyl (DPPH). The oxidative stress and oxidative damage to tissues are common end points of chronic diseases such as diabetes, atherosclerosis, and rheumatoid arthritis. Oxidative stress in diabetes coexists with a reduction in the antioxidant status, which can further increase the deleterious effects of free radicals. The aqueous extract of F. religiosa reduces oxidative stress in experimentally induced type 2 diabetes rats. Type 2 diabetic rats gained relatively less weight during the course of development as compared to normal rats. Decrease in uptake of glucose, free fatty acids from circulation, and accelerated β-oxidation in adipose tissue lead to weight loss in diabetes. The aqueous extract of F. religiosa improved the body weight of diabetic rats.[8]

Aqueous extract of *F. religiosa* modulated the superoxide dismutase (SOD) activity in the diabetic rats dose dependently and also decreased catalase (CAT) activity.

The methanolic extract of *F. religiosa* leaf inhibits the production of nitric oxide and proinflammatory cytokines in lipopolysaccharide (LPS) stimulated microglia via the mitogen activation protein kinase (MAPK) pathway by using cell viability assay, nitric oxide assay, and enzyme-linked immunosorbent assay (ELISA).^[1] The extract exerts strong anti-inflammatory properties in microglial activation. It is likely that extract has a neuroprotective effect against inflammation by inflammatory mediators such as nitric oxide and cytokines.

Recently, the methanolic extract of *F. religiosa* has been reported to have neurotrophic effects and acetylcholinesterase inhibitory activity.

Wound-healing activity

The effect of hydroalcoholic extract of *F. religiosa* leaves on experimentally induced wounds in rats using different wound models results in dose-dependent wound-healing activity in excision wound, incision wound, and burn wound. A formulation of leaves extract was prepared in emulsifying ointment at a concentration of 5% and 10% and applied to the wounds. The result suggests that leaf extract of *F. religiosa* (both 5% and 10%) applied topically possess dose- dependent wound-healing activity.^[8]

Analgesic activity

The analgesic activity of stem bark of F. religiosa is explored by Sreelekshmi et al. using the acetic acid induced writhing (extension of hind paw) model in mice.

It showed dropping in the number of writhing of 71.56 and 65.93%, respectively at a dose of 250 mg/kg and 500 mg/kg body weight. Thus, it can be concluded that extract showed the analgesic effect probably by inhibiting synthesis or action of prostaglandins.

Antiulcer activity

The ethanol extract of stem bark of Ficus religiosa extract (EBFR) exhibited potential antiulcer activity. The antiulcer activity of Ficus religiosa was evaluated in vivo against indomethacin and cold restrained stress induced gastric ulcers and pylorus ligation assay. The determination of antiulcer effect was based upon the reduction of ulcer index.^[14] The extract (100, 200 & 400 mg/kg) significantly reduced the ulcer index in all assay used. The hydroalcoholic extract of leaves of Ficus religiosa also exhibited antiulcer activity .The activity of extract was evaluated against pylorus ligation-induced ulcers, ethanol-induced ulcers and aspirin-Induced ulcers. Determination of antiulcer effect was based upon ulcer index and oxidative stress. Administration of Ficus religiosa significantly reduced the ulcer index (Saha and Goswami, 2010).

Anticonvulsant activity

Methanolic extract of figs of *F. religiosa* had anticonvulsant activity against maximum electroshock (MES) and picrotoxin-induced convulsions, with no neurotoxic effect, in a dose- dependent manner.^[1] The *F. religiosa* extract increased the threshold of MES and picrotoxin- induced convulsions with no neurotoxic effects, in a dose-dependent manner. Inhibition of antiepileptic effect of extract by cyproheptadine pretreatment showed that the extract might be mediating its effect via modulating serotonin-dependent GABAergic and/or glutamatergic neurotransmission.^[4,7,8]

Hypolipidemic activity

Dietary fiber content of food namely peepalbanti (*F. religiosa*), cellulose, and lignin were predominating constituents in peepalbanti, fed at 10% dietary level to rats, induced a greater resistance to hyperlipidemia than cellulose. The most pronounced hypocholesterolemic effect that appeared to operate through increased fecal excretion of cholesterol as well as bile acids. Dietary hemicellulose showed a significant negative correlation with serum and liver cholesterol and a significant positive correlation with fecal bile acids. The dietary fiber influenced total lipids, cholesterol, triglycerides, and phospholipids of the liver to varying extents.

Hypoglycemic activity

 β -Sitosterol-D-glycoside was isolated from the root bark of *F. glomerata and F. religiosa*, which has a peroral hypoglycemic activity. Oral administration of *F. religiosa* bark extract at the doses of 25, 50, and 100mg/kg was studied in normal, glucose-loaded, and STZ (streptozotocin) diabetic rats. The three doses of bark extract produced significant reduction in blood glucose levels in all the models. The effect was more

pronounced in 50 and 10mg/kg than 25mg/kg. *F. religiosa* also showed significant increase in serum insulin, body weight, and glycogen content in liver and skeletal muscle of STZ-induced diabetic rats, while there was significant reduction in the levels of serum triglyceride and total cholesterol. *F. religiosa* also showed significant antilipid peroxidative effect in the pancreas of STZ-induced diabetic rats. The results indicate that aqueous extract of *F. religiosa* bark possesses significant antidiabetic activity.^[16]

Anti-inflammatory activity F. religiosa has found to be potential anti-inflammatory & analgesic property. The mechanism underlying the effect is the inhibition of PG's synthesis. It was found that the leaf extract of F. religiosa has potential anti-inflammatory activity against carrageenan induced paw oedema. The inhibitory activity was found due to inhibition of release of histamine, serotonin (5HT), Kinins and PGs.^[8]

CONCLUSIONS

Medicinal plants are the local heritage with the global importance. World is endowed with a rich wealth of medicinal plants. Medicinal plants also play an important role in the lives of rural people, particularly in remote parts of developing countries with few health facilities. The present review reveals that *F. religiosa* contains several phytoconstituents like β -sitosteryl-D- glucoside, vitamin K, n-octacosanol, kaempeferol, quercetin, and myricetin. The plant has been studied for their various pharmacological activities like antibacterial, antifungal, anticonvulsant, immunomodulatory, antioxidant, hypoglycemic, hypolipidemic, anthelmintics, and wound healing activities.

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