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Review Article

Ficus benghalensis: A plant with potential pharmacological properties, from tradition to pharmacy

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Abstract

Purpose: *To undertake an overview of the potential pharmacological properties of Ficus benghalensisis.*
Methods: *Data were acquired from several online sources, including Scopus, Elsevier Science Direct, PubMed, and Sci-Hub, using the keywords "Ficus benghalensis", "medicinal plants", "anti-oxidant", "anti-inflammatory", and "anti-cancer".*
Results: *Ficus benghalensis has valuable secondary metabolites including terpenoids, ketones, coumarins, oentacyclic, furocoumarin, flavonols, flavonoids, sterols, esters, carbohydrates, carboxylic acid, and polycyclic aromatic hydrocarbons. Due to its phytochemical profile, it is regarded as a plant with potential pharmacological properties such as anti-diarrheal, anti-inflammatory, anti-cancer, anti-oxidant, anti-bacterial, anti-diabetic, anti-tumor, immunomodulatory, anthelmintic, and anti-angiogenic. This review highlights the phytochemistry, traditional uses and pharmacological potential of Ficus benghalensis.*
Conclusion: *Ficus benghalensis has potentials for treating several ailments. However, further research, including in vivo studies and preclinical trials, is necessary to ascertain its biological and pharmacological uses accurately.*

Keywords: *Medicinal plants, Ficus benghalensisis, Anti-cancer, Anti-oxidant, Immunomodulatory*

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INTRODUCTION

Over time, natural products obtained from plants gained importance for treating various diseases [1]. Plants-based natural products provide a vast array of chemical compounds to be experimented with as new drug candidates [2]. The first written record of traditional drug systems from plants was found around 2600 BC. This system had about 1000 substances extracted from plants, a few of which were predominantly utilized for oil extraction in Mesopotamia. Egyptian medicine is as old as 2900 BC, but the most famous record dates back to 1500 BC and is known as "Ebers Papyrus",

with about 700 drugs basically derived from plants [3].

Presently, plant products are integral components of healthcare systems in many parts of the world. The reason behind using herbal products is the low price of plant-derived traditional medicines [4]. Bioactive compounds are generally secondary metabolites, i.e., steroids, alkaloids, tannins, and phenolic compounds are isolated from plants. Various plant-based natural products are used as direct chemotherapeutic agents, while many others decrease the severe effects experienced due to chemotherapy [5].

Ficus benghalensis, commonly known as the Banyan tree, is a traditional medicinal plant belonging to the Moraceae family. A Swedish naturalist, Carolus Linnaeus was the first to publish his work on genus Ficus in "Systema Naturae" in 1735. Ficus is the dominant genus in angiosperms, with about 2000 varieties, 40 genera and 800 species [6].

The plant parts of the genus *Ficus* are useful as astringent, haemostatic, anti-septic, anti-inflammatory, anti-oxidant, and anti-cancer agents. They are also important for treating various harmful diseases such as liver enlargement, leucorrhoea, cough, piles, asthma, diarrhea, ulcers, gonorrhea, menorrhagia, deficient lactation, rheumatism as well as skin and heart diseases [7-9].

The vital pharmaceutical compound anthocyanin was first extracted from *Ficus benghalensis* and is renowned for its anti-angiogenic activity. Furanocoumarins are phytotoxins reported in many species of the genus Ficus. The methanol extract of *Ficus benghalensis* exhibits various anti-bacterial, wound healing, pollution inhibitory, and fungicidal effects [7].

This review article focused on some of the bioactive constituents extracted from *Ficus benghalensis* and several pharmacological and biological properties, including anti-oxidant, anti-cancer, anti-angiogenic, anti-bacterial, anthelmintic, anti-inflammatory, anti-diarrhoeal, anti-diabetic, anti-tumor, and immunomodulatory (Figure 1). Data has been acquired from several online sources, including Scopus, Elsevier Science Direct, PubMed, and Sci-Hub, using the keywords "Ficus benghalensis", "medicinal plants", "anti-oxidant", "anti-inflammatory", and "anti-cancer".

Figure 1: Biological profile of *Ficus benghalensis*

Phytochemical investigations on *Ficus benghalensis*

Phytoconstituents encompassing terpenoids, triterpenes, ketones, tiglic acid, ester coumarins, oentacyclic, furocoumarins, flavonols, flavonoids, sterols, carbohydrates, and serine proteases with medicinal significance are present in different extracts of *Ficus benghalensis* [10].

Flavonols and flavonoids

Flavonols and flavonoids that have been found in the leaves of *Ficus benghalensis* possess potential anti-oxidant activities. Flavonols include quercetin-3-galactoside, rutin, bengalenosides i.e. 5,7 dimethyl ether leucoperalgonidin-3-0-α-L-rhamnoside and glycosides or flavonoids have been found in the leaves of *Ficus benghalensis*. Other flavonols and flavonoids including delphinidin-3-o-α-L rhamnoside, pelargonodin-3-o-α-L-rhamnoside, 3-0-alpha-D galactosyl, 5,7-trimethyl ether of delphinidin-3-0-a-L-rhamnoside, leucopelargonidin-3-0-α-L rhamnoside, and leucopelargonin glycoside of leucopelargonidin possess anti-oxidant properties [7, 11].

Terpenoids and alcohol

Terpenoids and alcohols including pentacyclic triterpenes [10], triterpenoids [10, 12], friedelin [10-12], 3-friedelanol [10], lupeol [7, 10, 11], betulinic acid [10], β-amyrin [7, 10], phytol, triacontanol, globulol, lanosterol, dihydrobrassicasterol, furostanol are present in ficus plants[13]. Others are sterols incorporating β-sitosterol [7, 10, 11, 14], ficosterol [12], taraxosterol [7, 11], 3-sitosterol [12], and stigmasterol have been extracted from ficus benghalensis [13].

Carboxylic acid and esters

The tiglic acid ester of ψ-traxasterol and carboxylic acids including quinic acid, ergosterol acetate, amyrin acetate, and lupenyl acetate have also been isolated from the heartwood from *Ficus benghalensis* [13].

Carbohydrates

The seeds and fruits of Ficus benghalensis have been involved to isolate a lectin (galactose) and purified on fetuinagarose through affinity repulsion chromatography. This lectin was named *Ficus benghalensis* agglutinin (FBA). The molecular mass of FBA was 33 kDa [7, 10].

Ficus benghalensis agglutinin (FBA) consists of galactose and it was first extracted from the seeds of this plant. Other carbohydrates were also extracted such as α-D-glucose, D-galactose, D-fructose [12], α-Dglucoside, and aglucoside [7].

Different compounds are isolated from aerial parts of Ficus benghalensis and they possess numerous pharmacological properties of interest as shown in Table 1 and Figure 2.

The extracts derived from different parts of Ficus benghalensis have a broad range of bioactive compounds which further need to be investigated for their potential pharmaceutical applications.

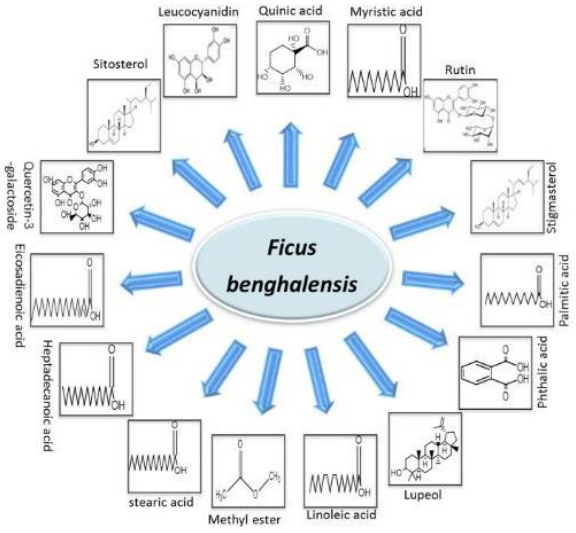

Figure 2: Some of biochemical active compounds present in *Ficus benghalensis*

Biological properties

Anti-cancer effect

Cancer has unfortunately been recognized as the second leading cause of death worldwide. More than, 200 various kinds of cancers that can affect the human body. Studies have reported that silver nanoparticles (AgNs) derived from the bark of *Ficus benghalensis* and *Azadirachta indica* exhibited anti-proliferative effects on osteosarcoma cancerous cells [17].

Table 1: Some of chemical Compounds isolated from Ficus benghalensis with pharmacological profile

Plant Part	Chemical Compounds	Pharmacological Profile	References
Aerial part and root	Anthocyanins	Anti-angiogenesis activity	[15, 16]
Leaf	Friedelin, β-sitosterol, Rutin, CuNFs, Quercetin-3-galactoside	Anti-diarrhoeal activity, pollution inhibitory activity, CuNFs synthesis activity, nanomaterial synthesis activity	[13, 29]
Heart wood	Esters, taraxasterol, benzoate tiglic Acid		[8,15-17]
Fruit and seed	Carbohydrates lectin, *Ficus benghalensis* agglutinin (FBA)	Anti-microbial activity, anti-tumor activity, carbohydrates binding activity of *Ficus benghalensis* agglutinin (FBA), cooling effect	[14-16]
Stem and bark	Leucocya-nidin delphinidin-3-O-α-L rhamno of Leucocyanidin-3-O-β-D-Galactosyl rhamnoside Keto-n-cosanyl Strearate Palmitate	Anti-cancer activity, anti-diabetic activity, ulcer pain inhibitors, free radical scavenging activity	[14-17]
	α-sitosterol-α-6-Hepta triacontene-10-one penta triacontan-5-one meso-inositol phenyl tetra decanyl oleiate	Larvicidal Activity (methanol extracts), free radical scavenging activity	[8, 13, 17]

Molecular targets involved in anti-cancer activity are transcription factors (API, NF-κB, NRF2), growth factors (EGF, FGF, PDGF), cell cycle proteins (cyclin D, CDK1, CDK2, p53, p27, p21), pro-apoptotic proteins (caspases and Bax), anti-apoptotic proteins (bcl-2, TRAFI and survivin), and protein kinases (PKA, PKC, MAPK and TyK2) [18] (Table 2).

Furthermore, the molecular mechanism of action of Ficus benghalensis against HepG2 and MCF-7 carcinoma cells has not been clearly understood. However, phytochemical analysis demonstrated that anti-cancer agents are present in various parts of this plant particularly in the leaves (β-sisterol, lupeol and psoralen). It has been reported that triterpenes possess inhibitory effects on apoptotic proteins, growth factors and many cell cycle regulatory proteins [19, 20].

Experiments were performed on green leaves, fruits and woody branches of *Ficus benghalensis* to test anti-cancer effects on six cancer cell lines i.e, AGS, MCF-7, SW-742, SLKC-6, A-375, and PLC/PRF-5 [21] (Figure 3).

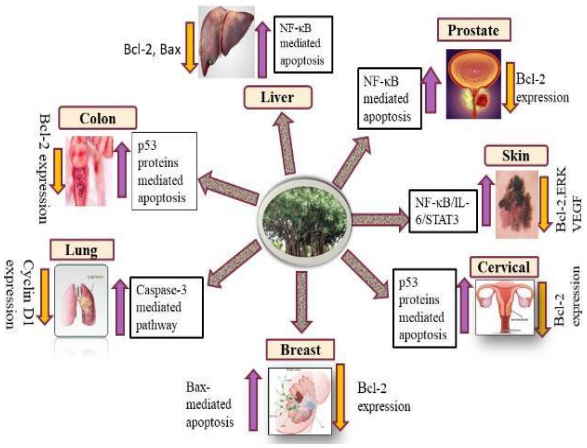

Figure 3: Anti-cancer effects of ficus plant against different cancer types

Anti-angiogenic effect

The anti-angiogenetic potential of pelargonidin, an anthocyanin compound obtained from Ficus bengalensis was evaluated in an *in vivo Danio rerio* animal model. Pelargonidin significantly reduced the aortic development which clearly declares that pelargonidin have potential anti-angiogenetic properties [15]. The anti-cancer mechanism of action of pelargonidin proceeds via decreased levels of H_2O_2 and TNFα-induced VEGF, VEGF inhibition or down-regulation of VEGF receptor expression. Anti-carcinogenic activity might be ascribed to its antioxidant properties transmitted by phenolic moieties in its structure [15, 16].

Anti-tumor effect

The fruit extracts of ficus species showed antitumor property in the potato disc bioassay (% tumor inhibition > 20 %) interestingly with no toxicity in Brine Shrimp test. However, further researches are clearly required to explore the molecular mechanism underlying anti-tumor potential of these traditional medicinal plants [22].

Anti-Inflammatory effect

The anti-Inflammatory potential of ficus bengalensis was evaluated by administration of the aqueous and methanolic extracts on carrageenan-induced hind paw edema rat models, both these extracts inhibited the expression of malondialdehyde and myeloperoxidase. Furthermore, it inhibited the production of the serum marker enzymes AST, ALT and ALP. These results demonstrate that anti-inflammatory potential of MEFB could be attributed to its antioxidant properties [23]. Oral administration of AEFB resulted in a dose-dependent inhibitory action against inflammation in a carrageenan-induced rat paw oedema model [24]. The summary of anti-inflammatory effect of Ficus benghalensis is provided in the Table 2.

Antioxidant effect

Excessive production of free radicals during various metabolic reactions is dangerous and harmful for living systems. Antioxidants are free radical scavengers having capability to hinder these free radical chains reactions, protecting the biological systems from the adverse impacts of oxidative stress. One study stated that phytochemicals such as phenolic compounds show inhibitory action on ROS/RNS and ameliorate the production of free radicals [28]. One study reported that methanolic extract of Ficus benghalensis was subjected to DPPH free radical scavenging activity for the evaluation of its antioxidant effect. Phytochemical analysis affirmed that free radical scavenging effect of Ficus benghalensis was shown because of presence of polyphenolic and flavonoid profile [29].

Anti-diabetic effect

Diabetes mellitus has been considered a group of diseases caused by the deficit of insulin production or insulin resistance.

Table 2: Anti-inflammatory properties and molecular targets of the *Ficus benghalensis* in various animal models

Assay type	Organism tested	Dose/conc.	Molecular targets	Ref
Anti-inflammatory bowel disease	Adult albino (wistar strain) rats	AEFB(250mg/kg/b.w) AEFB(500mg/kg/b.w)	PGs↓, Nitric oxide (NO) synthase ↓ SOD↓, iNOS↓	[25, 26]
TNBS-induced inflammatory bowel disease	Rats	AEFB(250mg/kg) AEFB(500mg/kg)	iNOS↓, SOD↓, PGE2↓, MPO↓	[23]
SOD, MDA and NO content, and mast cell degranulation in TNBS	Rats	AEFB(250mg/kg) AEFB(500mg/kg)	PGE2⊥, COX-2 NO↓,MDA↓, SOD↓	[26]
Anti-inflammatory and analgesic activity in animal model on carrageenan induced hind paw edema	Wistar rats	MEFB(200mg/kg, Po) MEFB(400mg/kg, Po)	ROS⊥	[23]
Cotton-pellet granuloma	Rats	MEFB(200mg/kg, Po) MEFB(400mg/kg, Po)	PGs↓, MPO↓, MDA↓	[23]
Acetic acid induced vascular permeability	Swiss albino mice (20-25g)	MEFB(200mg/kg, Po) MEFB(400mg/kg, Po)	NO↓, iNOS⊥, SOD↑, **PGE2 ⊥, MPO ↓**	[23]
Carrageenan-induced paw edema experiment	Rats	Ethanolic (300mg) petroleum ether extracts (600 mg/kg/day)	MPO↓, SOD↑	[27]

Note: Up regulation↑, down regulation↓, inhibition ⊥, MEFB (methanol extract of *Ficus benghalensis*), AEFB (aqueous extract of *Ficus benghalensis*)

Now accessible antidiabetic drugs such as hypoglycemic drugs have limitations, arousing the need for selective and non-toxic antidiabetic drugs. Natural products have been reported as novel sources of bioactive antidiabetic entities. Treatment of AEFB at the dose concentration of 500 mg/kg/day potentially reduced the blood glucose level, serum electrolytes, glycolytic enzymes, lipid peroxides (LPO) and hepatic cytochrome (CYP) P-450 in streptozotocin-induced diabetic rats [27]. Ficus benghalensis extract tested at the dose concentration of 500mg/kg/day restored the normal levels of glycogen synthase (GS), lactate dehydrogenase (LDH), glucokinase (GK), succinate dehydrogenase (SD), and liver microsomal manooxygenase enzymes EROD, PROD, and PNPH [30]. AEFB with a dose of 300 mg/kg showed significant decrease in blood glucose levels in diabetic models. *Ficus benghalensis* inhibited the carbohydrate hydrolyzing enzymes and showed hypoglycemic activity *in vitro*. Aqueous extract of this plant has been reported to lower the glucose levels thus serving as hypoglycemic agent [31].

Antibacterial effect

The AEFB and MEFB showed antibacterial effects against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosae*, *E. coli*, and *Klebsiella pneumonia*. The Stem bark of Ficus benghalensis is used as anti-bacterial agent especially on wounds, abscess, and syphilitic ulcer. Hexane, chloroform and methanolic fractions of *Ficus benghalensis* presented antibacterial action against gram negative and gram positive bacteria [32].

Anti-diarrheal effect

Traditionally, *F. bengalensis*, *F. racemosa*, and *F. carica* were the most commonly used species for treatment of diarrhea. To test the efficacy of these plants' species, different experimental models were designed i.e., castor oil induced diarrhea, gastrointestinal motility test, and PGE2 induced-enteropooling. The results suggested that *F. bengalensis* and *F. carica* show significant inhibition against diarrhea at the concentrations of 400 and 600 mg/kg. Therefore, they can be regarded as potential candidates for antidiarrheal drugs. The tannins and flavonoids present in *Ficus* spp. might be responsible for its anti-diarrheal activity [33].

CONCLUDING REMARKS

This review presents the phytochemistry, traditional importance and pharmacological potential of *Ficus benghalensis*. This medicinal plant has various bioactive compounds such as lupeol, terpenoids, CuNFs, sitosterol, lanosterol, phytol, quinic acid, myristic acid, β-progesterone, enzymes proteases, and benghalensin. Several pharmacological effects have been reported from *Ficus benghalensis*, including anticancer, anti-inflammatory, anti-microbial, anti-oxidant, anti-diabetic and anthelmintic. Numerous in vitro and in vivo studies on this medicinal tree explicitly

show its anticancer effects. Further research and investigations are required on pharmacological compounds isolated from different parts of this plant. The bioactive constituents of Ficus bengalensis are effective against various cancer cell lines, but further investigations are needed to identify the molecular targets for these cancer cell lines (AGS, MCF-7, SW742, SLKC6, A375, and PLC/PRF/5). It is anticipated that these comprehensive facts will pave the way for researchers to discover promising candidates which will act as an anticancer, anti-microbial, anti-inflammatory, and anti-oxidant drug in the future.

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Ethical approval

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

Muhammad Mateen Tahir made substantial contribution in writing manuscript. Muhammad Mateen Tahir and Azhar Rasul contributed significantly to the design and preparation of the manuscript. Muhammad Mateen Tahir and Ammara Riaz contributed in the compilation of data. All authors read and approved final manuscript for publication.

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