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AN INTEGRATIVE REVIEW OF PHARMACOLOGICAL ACTIVITY OF *FICUS CARICA* (MORACEAE)

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ABSTRACT

The common fig tree (*Ficus carica*) has long been associated with the treatment of various health problems such as inflammation, diabetes, gastrointestinal disorders and infectious diseases. Ficus carica belongs to the family named Moraceae family. The present systematic review describes the many possible pharmacological activities of the common fig tree and the role of flavonoids, phenolic compounds, terpenoids, alkaloids and coumarins for these activities. Ficus carica has emerged as a good source of traditional medicine for the treatment of various ailments such as anemia, cancer, diabetes, leprosy, liver diseases, paralysis, skin diseases, and ulcers. It is a promising candidate in pharmaceutical biology for the development/ formulation of new drugs and future clinical uses. The main pharmacological properties of Ficus carica are strong antioxidant properties; antibacterial properties against some oral bacteria; anti-inflammatory properties; antidiabetic properties (lowering blood glucose); anticancer properties (anti mutagenic and anti-angiogenic); hepatoprotective properties; antipyretic properties and neuroprotective properties.

KEYWORDS: *Ficus carica*, antioxidant, antidiabetic, anti-inflammatory, antibacterial activity.

1. INTRODUCTION

Ficus carica has been cultivated for a significant period of time. Due to the long history of cultivation, figs have great cultural and religious significance and have been a symbol of fertility in several ancient cultures. In the Qur'an, figs are referred to as one of the three fruits along with the olives and on Mount Sinai. God has sworn by His name in the Quran by the fig in the Surah Al-Tin. The fig is a member of one of 37 genera of the Moraceae family that includes 800 varieties of fig; many are genetically diverse. The fig tree is cultivated in areas that experience longer, warmer growing seasons, and produces two crops of figs per year. The fig fruit can be eaten as is, dried, used to make jam or fruit leather, or in other ways. Other parts of the fig tree (the leaves, latex, syrup, etc.) can also be used in ways other than as food; such as, the leaves are used for animal feed; the latex is used to coagulate milk and to form curds; and the syrup is used as an effective remedy for mild constipation.

From a nutrition perspective, *Ficus carica* represents many things that can promote a long life and this plant/fruit has many health-promoting properties due to their high level of calcium, potassium and iron. Figs are a good source of many important vitamins and diet-friendly fiber and contain no sodium or fat and no cholesterol. In addition to the minerals and vitamins in figs, *Ficus carica* also has a high concentration of phytochemicals (substances produced by plants that provide health benefits) and specifically, a number of flavonoids and phenolic acids such as chlorogenic acid and gallic acid both exist in fresh and dried figs. The levels of these bioactive compounds are determined by a number of factors including the variety of fig harvested, when it was harvested (harvest time), the maturity of the fig, and what part of the fig you are consuming.

Figs are commonly used in traditional medicine to treat conditions including respiratory illnesses, digestive problems, liver disorders, diabetes, leprosy, and ulceration. Figs have official recognition in the Western pharmacopoeias including the British and Spanish pharmacopoeias for therapeutic purposes; therefore, researchers have developed several methods of

preserving the benefits of figs, with drying being one of the most well-established methods. Modern preservation technologies such as freeze-drying and microwave-drying corresponding to different purposes are critical to being able to prepare timely and economically viable fig products.[15] (Ramadan, 2023a)

2. Taxonomy
2.1 Kingdom: Plantae,
2.2 Division: Magnoliophyta,
2.3 Class: Magnoliopsida,
2.4 Order: Urticales,
2.5 Family: Moraceae
2.6 Genus: *Ficus*
2.7 Species: *carica*

3. PLANT PROFILE

Figure: a) Ficus carica.

3.1 Synonyms: Ficus carica var. caprificus Risso,Ficus carica var. riparium Hausskn, Ficus carica var. rupestris Hausskn, Ficus colchica Grossh, Ficus communis Lam, Ficus deliciosa Gasp, Ficus globosa Miq, Ficus latifolia Salisb, Ficus silvestris Risso, Caprificus insectifera Gasp, Caprificus leucocarpa Gasp.

3.2 BIOLOGICAL SOURCE: *Ficus carica.*

3.3 FAMILY: Moraceae.

3.4 CHEMICAL CONSTITUENTS
Figs are rich in bioactive compounds, including phenolics (such as chlorogenic acid, rutin, caffeoylquinic acid, and ferulic acid), flavonoids (such as quercetin 3-O-rutinoside), phytosterols (such as betulol, lupeol, β sitosterol, and amyrins) triterpenes, anthocyanins, organic acids, coumarins (such as psoralen and bergapten), and volatiles (including benzyl alcohol, linalool, eugenol, and germacrene D). In addition to containing a wide array of bioactive compounds, the latex of figs is also high in proteolytic enzymes, protein, and phenolic compounds; while most of the polyphenols and phosphorus found in figs come from the fruits and leaves.

3.5 USES
Figs have historically been used for treating wounds, diabetes, constipation, and inflammation; however, since the use of polyphenols extracted from figs have been shown in modern studies to exhibit antioxidant activity, anti-cancer activity, antimicrobial properties, and anti-diabetic properties, figs are also being researched for use as therapeutics. Figs are important elements of Mediterranean diets, as both edible fruits and ornamental plants, but may grow out of control in some regions.

4. PHARMACOLOGICAL ACTIVITIES
4.1 Anti-pyretic activity
The anti-pyretic potential of an ethanol leaf extract from *Ficus carica Linn.* using albino rats with yeast-induced pyrexia. The study found that 100 mg/kg and 200 mg/kg and 300 mg/kg oral doses led to body temperature reduction which occurred in a dose-dependent manner. The effect started one hour after treatment and lasted for five hours. The extract achieved results that matched Paracetamol, which serves as a standard anti-pyretic medication. The chemical analysis of the extract showed that it contained flavonoids and steroids and alkaloids and tannins, which together might produce these therapeutic effects.[1] (Patil V. R, n.d.)

4.2 Anti-inflammatory activity
*Ficus carica Linn.*leaves show strong anti-inflammatory effects against both acute and chronic inflammation tests. The study showed that ethanolic extracts (EE) produced greater effects than petroleum ether and chloroform extracts in their testing of rat paw edema which used carrageenan and cotton pellet granuloma methods. The ethanolic extract showed a 75.90% reduction of acute inflammation and a 71.66% decrease of chronic granuloma weight at the 600~mg/kg oral dosage with results that matched the standard drug Indomethacin. Flavonoids are the main reason for this pharmacological activity because they block the release of prostaglandins and kinins which cause inflammation. The scientific findings support the traditional use of this treatment for inflammatory disorders but researchers continue to study active components of the treatment.[2](Patil & Patil, 2011)

4.3 Anti-spasmodic activity
The common fig Ficus carica shows traditional medicinal properties for treating stomach-related medical conditions while it exhibits strong antispasmodic effects. The researchers used an aqueous-ethanol plant extract to study its medical effects on isolated rabbit jejunum samples and achieved verification of the extract's capacity to induce smooth muscle relaxation. The plant contains various biologically active chemical byproducts which include ferulic acid and coumarin and lupeol acetate and sitosterol that together create its medicinal properties.[3] (Jyotirmoy Das, n.d.)

4.4 Anti-platelet activity

The aqueous ethanol extracts (AEE) of ripe dried figs have demonstrated significant anti-platelet (AP) activity through their effects on human platelet aggregation (PA) induced by adenosine 5'-diphosphate (ADP) and epinephrine and anti-spasmolytic activity, thus supporting the traditional use of figs as a treatment for gut motility and inflammatory disorders. Furthermore, the latex of *Ficus carica* contains ficin, a proteolytic enzyme mixture that demonstrates hemostatic properties by activating coagulation factor X (CFX) in humans therefore shortening activated partial thromboplastin time and prothrombin time. Therefore, the protease components of figs could have the potential to develop into a new class of pharmaceuticals targeting antiplatelet agents.[4] (Badgujar et al., 2014)

4.5 Anthelmintic Activity

The latex of this plant is used directly as an anthelmintic, while its leaves are historically have been used as a vermicide to remove worms. Research has demonstrated that the latex is a rich source of the hydrolytic enzyme ficin (cysteine protease), which is effective at eliminating gastrointestinal nematodes from rodents. Studies on the anthelmintic activity of four different leaf extract solvents (aqueous, methanol, chloroform, and petroleum ether) against Pheretimaposthuma (Indian earthworms) showed that these extracts caused paralysis and death of the parasites as well as standard products such as mebendazole. The anthelmintic activity of this plant works by either starving the worms to death or immobilizing them so they can be expelled from the host's GI tract.[5] (Shruti Gaikwad, n.d.)

4.6 Hepatoprotective Activity

Hepatoprotective properties of an extract from the leaves of the fig *(Ficus carica)* plant were demonstrated by the extensive recovery of hepatotoxic effects induced by rifampicin on rat livers from the in vivo administration of the fig extract. The use of the extract resulted in a significant decrease in the levels of two liver enzyme markers, namely SGOT (Serum Glutamate Oxaloacetate Transaminase) and SGPT (Serum Glutamate Pyruvate Transaminase) which had been elevated because of rifampicin treatment, as well as in the level of bilirubin resulting from that same rifampicin treatment. The administration of the fig extract was found to return the weight of the liver back to normal levels. The extract also restored elevated pentobarbital sleeping times secondary to rifampicin treatment back to normal levels. Histological studies have also confirmed the hepatoprotective effects of Ficus carica leaf extract by demonstrating the regeneration of damaged liver cells and the restoration of the normal cytoarchitecture of the rat liver. The results of this research strongly support the continued use of Ficus carica in traditional medicine for the treatment of liver disease (e.g., jaundice).[6]

4.7 Anticonstipation Activity

Ficus carica's ethanolic fruit extract has been found to have strong anti-constipation effect by increasing digestive tract movement and by improving fecal condition as seen in animal testing. Studies having used loperamide to induce constipation in animals show that high doses of the extract greatly enhanced peristaltic activity and returned fecal water content to an almost normal level. This effect is believed to be due to an interaction with serotonin signaling within the gastrointestinal tract, wherein the extract lowers the level of serotonin transporter or (SERT) in the colon and thus stimulates release of serotonin, resulting in overall increased colonic motility. In addition, high levels of soluble cellulose and phenolic compounds found throughout the fruit play a role in increasing total fecal bulk and in modulating gut-microbiota, lending further support to the use of this product as a natural laxative.[7] (Lalitha et al., n.d.)

4.8 Hypoglycemic Activity

The aqueous extract from *Ficus carica* leaves shows pronounced hypoglycemic effects when tested in streptozotocin-induced diabetic rats. The extract was administered to diabetic animals daily for three weeks, and plasma glucose concentrations were significantly reduced without any stimulation of insulin secretion. Furthermore, plasma insulin levels decreased in normal rats treated with the extract, suggesting an increase in insulin sensitivity or a more economical use of insulin. The mode of action of this plant extract appears to be a peripheral effect rather than a pancreatic one. Observations from hindquarter perfusion studies demonstrated that the plant extract promotes glucose uptake by skeletal muscle cells in an insulin-independent manner, indicating a direct tissue effect similar to that of insulin.[8] (Pérez et al., 2000)

4.9 Hypocholestremic Activity

The effects of dried fig consumption on hypercholesterolemic (high cholesterol) rats show that it has a substantial hypocholesterolemia effect and lowers blood lipids (blood fat) in rats with high cholesterol and a high-fat diet. Fig fruit is also full of important antioxidants like vitamins A and C, polyphenols (total) and flavonoids, which are beneficial to heart health. When researchers add three different levels of dried figs to the diet (2%, 4%, and 6%) of rats on a high-cholesterol diet, results came back showing a decrease in total cholesterol, triglycerides and low-density lipoprotein (LDL) cholesterol and at the same time it increased high-density lipoprotein (HDL) cholesterol (sometimes called "good" cholesterol), which will improve the total lipid profile. The bioactive properties within figs appear to prevent or limit the effects of hypercholesterolemia and oxidative stress and regulate (alter) lipid metabolism.[9] (Salem et al., 2022).

4.10 Anti-Cancer Activity

The latex of common fig *(Ficus carica)* has potent anti-cancer and antiproliferative properties against triple-negative breast cancer (TNBC) cell lines (MDA-MB-231). As demonstrated in in vitro studies, the brand latex has been shown to have a dose- and time-dependent inhibition of cancer cell proliferation, with a significant reduction in the number of viable cancer cells at concentrations as low as 0.1%. MDA-MB-231 cells treated with latex show morphological signs of apoptosis, including cytoplasmic vacuolation, cell blebbing, and cell shrinkage. In addition to its pro-apoptotic effects, the latex of *Ficus carica* has demonstrated its ability to inhibit metastasis by significantly reducing the migration rates of cancer cells, an important factor for preventing tumor metastasis. Molecular analysis has demonstrated that this anti-metastatic mechanism is due to the downregulation of three major signaling pathways, namely ERK2, CREB, and AKT2, which are all critical for cancer cell growth and survival.[10] (AlGhalban et al., 2021)

4.11 Cytotoxicity

The latex extracts from *Ficus carica* demonstrate their ability to kill vero cells at most tested concentrations because they show minimal to no cytotoxic effects. The microscopic examination results indicated that the methanolic (P1) hexanoic (P2) hexane-ethyl acetate (P3) and ethyl acetate (P4) extracts maintained cellular viability between 90% and 100% range. The methanolic extract showed a proliferative effect at 50\mu g mL^{-1} because it allowed cells to grow beyond their normal 100% viability level. The chloroform extract (P5) is the only extract that showed weak cytotoxic effects because its high concentration of 100~mg~ml caused cellular viability to drop below 80%.[11] (Lazreg Aref et al., 2011).

4.12 Anti-Viral Activity

The ability of *Ficus carica* latex to inhibit the growth of three specific viruses, including adenovirus, echovirus 11, and herpes simplex virus 1. Because the hexanoic (P2) and hexane-ethyl acetate (P3) extracts showed full antiviral activity, including virucidal action, cell pretreatment, and intracellular replication inhibition tests, the study concluded that they were very effective. At concentrations as low as 78~\mu g mL, the extracts showed their ability to prevent viral replication. Researchers found viral cytopathic effects at all tested concentrations, indicating that the methanolic (P1), ethyl acetate (P4), and chloroform (P5) extracts had no antiviral effects against the strains under investigation. Because the effective extracts attach to cellular receptors to prevent viruses from entering cells and from replicating internally, they exhibit strong activity.[11] (Lazreg Aref et al., 2011)

4.13 Anti-mutagenic activity

Ficus carica's anti-mutagenic qualities serve as a basic and crucial defence mechanism that keeps genetic materials stable against alterations brought on by chemical mutagens and environmental pollutants. Studies employing plant extracts to lessen mutagen exposures from two potent mutagenic substances, sodium fluoride and N-methyl-N'-nitro-N-nitrosoguanidine, have shown that they can lessen mutagenic effects. Rat bone marrow cells and Vicia faba plant cells were used in an analysis of the reduction and prevention of mutagenic activity with the herb Ficus carica, which showed a decrease in the damaging effect on DNA. Polyphenolic, flavonoid, and coumarin compounds—like psoralen and bergapten—are what give the plant system its protective qualities. They guard against free radicals and stop pro-mutagen activation, which can cause cancer.[12] (Ramadan, 2023)

4.14 Antiangiogenic activity

The effects of *Ficus carica* latex extract on Human Umbilical Vein Endothelial Cells (HUVECs) have provided compelling evidence of its anti-angiogenic activity. Studies show that the latex extract, especially in the concentration range of 100-400~\mu g/ml, inhibits both the proliferation and the formation of new capillary-like structures in a dose-dependent manner. This is important for cancer treatment because angiogenesis, the process of creating new blood vessels to feed the tumour, is a major factor in tumour growth and metastasis. Crucially, tests revealed no cellular damage up to 450~\mu g/ml, indicating that this inhibitory effect happens at concentrations that are not cytotoxic to the cells.[13] (Mostafaie & Mohammadi-Motlagh, n.d.)

4.15 Hypolipidemic activity

The leaf and twig extracts of *Ficus carica*, or common fig, have been shown to have strong hypolipidemic activity, which is advantageous for controlling elevated blood lipid levels. The administration of these extracts resulted in a significant decrease in several important lipid parameters in experimental models that used Triton WR-1339 to cause hyperlipidaemia in mice. Serum levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and very-low-density lipoprotein cholesterol (VLDL-c) all significantly decreased because of the treatment.

On the other hand, high-density lipoprotein cholesterol (HDL-c), sometimes known as "good" cholesterol, significantly increased. The presence of bioactive substances like phenols, flavonoids, and anthocyanins, which may work in concert to improve the overall lipid profile, is responsible for this dual effect, which lowers harmful lipids while raising protective ones. According to these results, Ficus carica extracts may be useful natural treatments for hyperlipidaemia with a good safety record because acute toxicity tests revealed no death or adverse clinical symptoms, even at high dosages.[14] (Boukhalfa et al., 2018)

4.16 Antioxidant activity

Ficus carica (common fig) shows that its leaf and twig parts contain high antioxidant capacity because of their abundant phenolic compounds and flavonoids and anthocyanins. The research demonstrates that the extracts from these parts show effective free radical neutralization through their DPPH and ABTS radical scavenging testing results. The scientists measured the total phenolic content of the leaves and twigs to range from 12.84 to 19.78 mg gallic acid equivalents per gram which provided strong reducing power and protection against oxidative stress. The antioxidant capacity of this substance interacts with the plant's ability to reduce blood lipid levels because it protects cells from oxidative harm. The natural antioxidants provide a safer option than artificial treatments because they show no harmful effects at high dosage levels. The results of this study validate *Ficus carica's* traditional use as a medicinal plant for treating metabolic disorders and cardiovascular conditions.[14] (Boukhalfa et al., 2018)

5. CONCLUSIONS

Ficus carica Linn. (commonly called fig tree) is an active component of today ethinopharmaceuticals and continues to validate its valuable role as a medicine, based on pharmaceutical evidence demonstrating a multitude of medicinal uses/benefits, across cultures, through traditional medicine over the years. Numerous studies have corroborated the effectiveness of Ficus carica Linn. at treating pyrexia, inflammation, spasms or spasticity, inhibiting platelet aggregation, treating helminthic infections, liver damage, treating constipation, regulating blood glucose levels, lowering plasma cholesterol levels, cancer, treating viral infections, mutagenicity, angiogenesis, and oxidative stress – all comparable to established pharmacotherapeutic agents frequently used in clinical practice (e.g., paracetamol for fevers and pain, indomethacin for inflamed conditions, mebendazole for treating helminthic infections).

In summary, *Ficus carica'* bioactive compounds possess a wide range of biological activities due to synergistic effects of the phytochemicals and as such represent an attractive potential source of natural therapeutic agents. These studies provide a common link between ethnomedicine and modern pharmacology; thus, warranting additional clinical trials, isolation of active phytochemicals from *Ficus Carica* (fig tree), and formulation of safe and effective medicines that may effectively address the pathophysiological aspect of inflammation/metabolic syndromes/infections/cancers, may ultimately be substantiated by this research. Future studies will provide answers regarding the human efficacy and bioavailability of *Ficus carica*-derived medicines, while establishing the mechanism through which this low-cost nutritional food source can be utilized globally to improve the health of the population.

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