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A Comprehensive Review On Phytoconstituents, Bioactivities, And Clinical Studies On *Ficus Carica L.* (Moraceae) And Its Role In Human Health And Disease Management

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Abstract:
Many studies have been published about the chemical compounds produced by *Ficus carica* Linn. and benefits toward the health. *F. carica* used since ancient time and widely for medicinal purpose, the leaves decoction was consumed as a tea. The benefits of *F. carica* components are still under investigation by many researchers around the globe. This review provides a summary of the constituents of the chemical compounds and toxicity studies, clinical studies and biological activities conducted on *F. carica* fruit, leaves, latex, bark, and root. Approximately 125 biochemical compounds of *Ficus carica Linn* were identified and classified under eight categories: triterpenoids, volatile ingredients, coumarins, furanocoumarins, flavonoids, hydroxybenzoic acids, hydroxycinnamic acids, as well as miscellaneous. Numerous scientific studies have demonstrated its antimicrobial, anticholinesterase, anti-diabetic, hepatoprotective, renoprotective, antioxidant, anti-inflammatory, and anticancer properties. We know our review will be a valuable for those looking for scientific evidence resource that support *F. carica* leaves medicinal properties, as well as the research gaps that need to be filled to enhance the economic value and medical benefits of the *F. carica* leaf. In this review, extensive literature research was conducted to reveal the benefits of *F. carica* for human health.

Introduction:

F. carica (*teen* in Arabic) is belongs to the family Moraceae and is one of the largest genera of medicinal plants, and over 750 species. It is also mentioned in the Qur'an as one of the titles of the letters, Surat Al-Tin, indicating its health benefits (Lansky, 2010; Mawa et al., 2013; Uddin, 2021; Jagtap & Bapat, 2019). *Ficus carica* It is likewise tiny in size and sweet in flavor and grows in Taif areas such as Ash-Shaf among villages of the Sufyani tribe, particularly in Al-Khadra land, and south of Saudi Arabia, and is known as "Al-Hamat" there. As a result, so the figs, particularly those found in Taif, have not been investigated, we anticipate discovering more about the therapeutic benefits of this wonderful plant. Moreover, phytochemical research on figs has revealed that the pulp, fruit, leaves, peel, latex, bark, and root contain a total of 125 bioactive compounds and chemical constituents including phytosterols, phenolic compounds such as Quercetin-3-O-rutioside in Entire figs, as well as exhibited the highest concentrations citric acid, cyanidin-3-rutinoside, and epicatechin in pulp, leaves, peel.(Teruel-Andreu et al., 2021) Also the twelve furanocoumarins, anthocyanins, six triterpenoids, six coumarins such as psoralen and bergapten (Figure 1), and thirty-eight volatile compounds such as hydrocarbons, hydroxybenzoic acids, chlorogenic acids, hydroxycinnamic acids, thirty-four flavonoids

such as rutin, two of steroids, and seven of fatty acids such as stearic acid ethyl ester, linolenic acid methyl ester and linoleic acid ethyl ester (Figure 1). also have magnesium, potassium, fiber, vitamin C, vitamin A, and calcium (Badgujar et al., 2014; Duke, 2002; Lansky, 2010; Mawa et al., 2013; Saif et al., 2020; Jagtap & Bapat, 2019). In brief, *F. carica* has antiulcer ,anticancer, immunological, dermatological, antispasmodic, hypolipidemic, antioxidant, antiparasitic, antiviral, antibacterial, antimutagenic, anti-inflammatory, anti-angiogenic, antidiabetic, antipyretic, reproductive, antiplatelet, endocrine, nootropic, antidiarrheal, hepato/nephron-protective, and anti-wart effects. In addition, the fruit is anti-oxidative, anti-spasmodic, and nephroprotective, while the stem is both antioxidant and anti-inflammatory. The leaf is anti-inflammatory, anti-pyretic, anti-diabetic, hepato-protective, anti-angiogenic, immunomodulatory, and antinematicidal, and it is used to treat ischemia and reperfusion injuries. The latex is anti-cancer, anti-bacterial, anti-angiogenic, antiviral, and anthelmintic. Furthermore, the bark of the fig tree has anti-diabetic properties. The purpose of this review is to delve into some major research on the active compounds and pharmacological activities of *Ficus carica* (Duke, 2002; Lansky, 2010; Li et al., 2021; Saif et al., 2020; Shahrajabian et al., 2021; Jagtap & Bapat, 2019). With the spread of incurable diseases and new epidemics spreading globally, as well as with the increasing causes of morbidity and mortality, the need for novel drugs is increasing. Furthermore, the latex of *F. carica* acts as a source of SARS-CoV-2 inhibitory compounds such as lupeol, alpha-amyrin, and luteolin. *Ficus carica* can be used to combat the COVID-19 pandemic, which has killed 5 million people globally in the last two years. In addition, alkaloids, for example, have anti-HIV potential and can be used to treat acquired immunodeficiency syndrome (AIDS) (M. C. Ali et al., 2020; Behl et al., 2021; WHO, 2021; Tsang et al., 2020). In this context, research is required to document medicinal plants used to treat chronic diseases such as diabetes in several in vivo investigations, *F. carica* extracts dramatically increased insulin release and, as a result, blood glucose levels have been lowered.(Deepa et al., 2018) And as a co-therapy for high blood pressure with impotence caused by the adverse effects with long-term use of calcium channel blockers (perhexiline), centrally acting alpha-agonist hypotensive medicines (clonidine), diuretics (hydrochlorothiazide, spironolactone), and beta blockers (carvedilol/metoprolol).(Ajeigbe et al., 2021) Thus, new medicines extracted from figs must be identified which are effective and safe and can be used alone or in combination with other medicines, can overcome the threats and upcoming risks of multidrug-resistant bacteria, for example, methicillin-resistant *Staphylococcus aureus,* which is resistant to penicillin, or can protect against the side effects of cancer medicine due to their lack of specificity towards to cancer cells. This review highlights on the various effects of *F. carica* compounds in development control of MDR in microbes and against untraceable virus mutations and as a good alternative to some medicines that have serious short- or long-term side effects. In particular, it is important to study *F. carica* and other unexplored plants to identify novel medications for global health benefits (Alam et al., 2021; Behl et al., 2021).

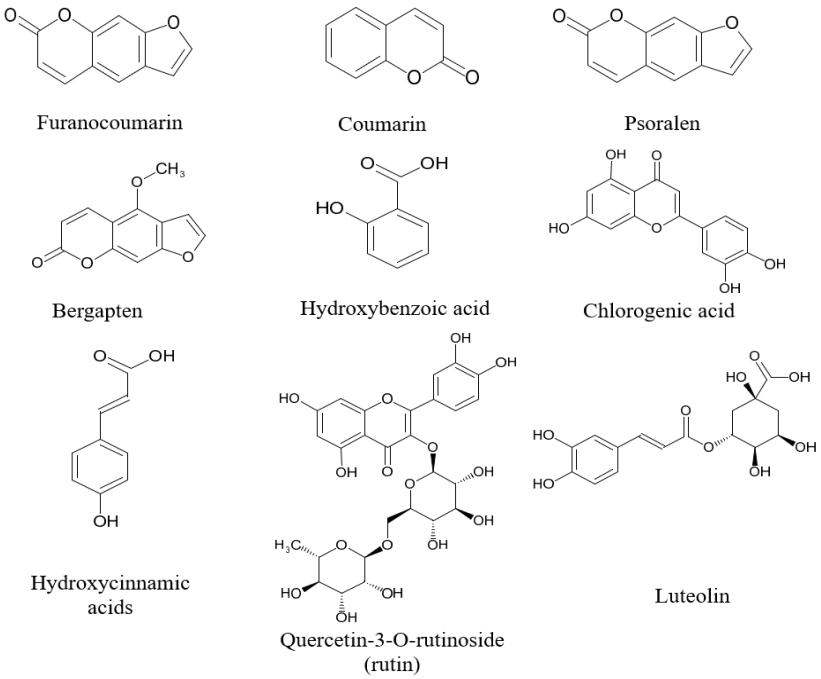

Figure 1 Most dominant bioactive compounds in F. carica.

Antibacterial properties:

The dried fruit of Algerian *F. carica* exhibits antibacterial action against Gram +ve bacteria including *Bacillus subtilis* sp. Spizizenii*, Staphylococcus aureus,* and *Enterococcus faecalis* as well as Gram -ve bacteria including *Enterobacter cloacae*, *Salmonella enterica* , *Escherichia coli* , and *Pseudomonas aeruginosa.* (Debib et al., 2014). Debib et al. (2014) used amoxicillin (25 mg), gentamicin (15 mg) and erythromycin (15 UI) as the positive controls. They determined antibacterial activity by scaling the zone of inhibition by Vernier scale in millimeters if reached to 14 mm or more it will consider it has high activity. Thus, *F. carica* was deemed to have significant antimicrobial efficacy (Philip et al., 2009). Also , a lot of studies approved the methanolic extracts of *F. carica* exhibit a strong antimicrobial effect (Aref et al., 2010; Lazreg-Aref et al., 2012). Research of Jeong et al., 2009 was showed that a Methanol (MeOH) combination extracts obtained from dried leaves of *F. carica* demonstrated significant antibacterial activity against *Prevotella intermedia, Aggregatibacter actinomycetemcomitans, Streptococcus gordonii, Streptococcus anginosus*, and *Porphyromonas gingivalis* [minimum inhibitory concentration (MIC): 0.16–0.63 mg/ml; minimum bactericidal concentration (MBC): 0.31–0.63 mg/ml] A methanol extract in combination with gentamicin as well as ampicillin exhibited synergistic effects against oral bacteria, resulting in a 4-8-fold decrease in MIC, and against *Streptococcus sanguinis, Streptococcus sobrinus,* and *Porphyromonas gingivalis* (Jeong et al., 2009). Kamal et al. (2020) the effect of *F. carica* extracts was investigated against pathogenic bacteria that affect human and isolated from the intestine and urinary tract, including *Enterobacter aerogenes, Pseudomonas aeruginosa , Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Klebsiella* sp, and *Shigella* sp. and consider a useful for treating intestine and urinary tract infections , The effects of three different volumes of *F. carica* (300, 400, and 500 mg/ml) against the three bacteria were tested, and as a positive control, various antibiotics were used depending on pathogenic bacteria. Agsint *Klebsiella sp*., 400 and 500 mg/ml of *F. carica* ethanol extract showed substantial antibacterial activity ($p \leq 0.05$) which was superior to those of ciprofloxacin, penicillin, clindamycin, trimethoprim, amoxicillin, and tetracycline. *F. carica* extracted with acetone solvents at 500 mg/ml showed substantially superior activity ($p \leq 0.05$) over the same medicines. Furthermore, *F. carica* extracted with a chloroform solvent at 300, 400, and 500 mg/ml showed substantial superiority ($p \leq 0.05$) over the other studied antibacterials. The flavonoids exert their mechanism by inhibiting energy metabolism, nucleic acid synthesis, and cytoplasmic membrane function and by causing bacterial membrane damage. In another study, Nafis et al., 2019 used clinical yeast and various pathogenic bacteria (*Micrococcus luteus*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Klebsiella pneumoniae* clinical isolates). In addition, four therapeutically relevant yeast species were used for making *F. carica* essential oils, the main constituents of the oil being bergapten (6.1 %), caryophyllene oxide (9.0%), and ficusin (32.8%) (Nafis et al., 2019). Antimicrobial tests revealed the essential oil of *F. carica* effective against all bacteria tested, showing MICs from 4.75 mg/mL to 38 mg/mL. In addition, when *F. carica* essential oils were combined with conventional antibiotics, a synergistic effect was observed, especially against gram +ve bacteria, with fractional inhibitory concentration index values ranging from 0.312 to 0.750. Surprisingly, the oil of *F. carica* leaf was reduced the antibiotic MICs by approximately 16 fold (Nafis et al., 2019). They also showed that this oil had an antibacterial synergic activity mostly with ciprofloxacin mainly against *Micrococcus luteus, Staphylococcus aureus,* and *Bacillus subtilis* (Nafis et al., 2019). Further studies demonstrated *F. carica* exhibits good activity against *Staphylococcus aureus, Bacillus cereus*, *Escherichia coli* and *Pseudomonas aeruginosa*. *Staphylococcus aureus* was extremely sensitive to chloroform *F. carica* extract, with 74 mm diameter of zone of inhibition, whereas *E. coli* was extremely sensitive to metabolic *F. carica* extract, with 82 mm zone of inhibition (Shafique et al., 2021).

Antifungal properties:

Candida albicans was the most sensitive to *F. carica*, with greater than 22 mm diameter of zone of inhibition and MIC values greater than 32 µg/ml (Debib et al., 2014). Moreover, sensitive to various extracts such as flavonoids and phenolic compounds, as well as dried figs of the Algerian taamriout variety, which show pronounced antimicrobial activity with MIC 32–128 mg/ml (Debib et al., 2014). Another study demonstrated the *F. carica* exhibits good activity against two fungal species—*Aspergillus niger* and *Aspergillus oryzae*.

Chloroform extracts have a high diameter of zone of inhibition against *A. oryzae* (55 mm), and methanolic extracts have a high diameter of zone of inhibition against *A. niger* (79 mm) (Shafique et al., 2021).

Antiviral properties:

The *F. carica* latex fruit has strong resilience to stress situations and a high natural therapeutic value; in particular, it contains phenolic compounds, including ferulic acid (Figure 2), which is a main compound in hexanoic extract (P2) and hexane-ethyl acetate extract (P3). These are the two extracts that are being evaluated as possible herbal with antiviral against *Echovirus type 11* (ECV-11), *Adenovirus* (ADV), and *Herpes simplex type 1* (HSV-1)(Adamson, 2020; Lazreg Aref et al., 2011). Furthermore, these compounds at all concentrations from pure to the maximum dilution concentration 78 mcg/ml have a mechanism that suppress the replication of both DNA viruses for HSV-1 and ADV and RNA viruses for ECV-11 by interfering with the receptors of these viruses and block the adsorption and entry human cells of the viruses into. Thus, the viral effect suppressed. In addition, a virucidal test (which measures the efficacy of virucidal disinfectants) proved the antiviral activity (Lazreg Aref et al., 2011). Thus, developing viral entry inhibitors that can be utilized as innovative antivirus medicines to suppressing the replication of ADV, ECV-11, and HSV-1 and this step essential because it allow to the virion to penetrates the host cell (Lin et al., 2002; Moore & Stevenson, 2000).

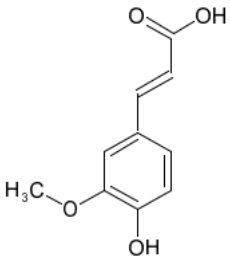

Figure 2 Ferulic acid

Avian influenza virus subtype H9N2 immunogenicity was improved when include the fig oil hexanoic extract in the vaccine formulation instead of mineral oil. Quercetin and chlorogenic acid especially act as anti-influenza agents (Najjari et al., 2015). *Ficus carica* contains active compounds such as lupeol, alpha-amyrin, and luteolin and these compounds has the highest binding affinity to the SARS-CoV-2 main protease and cause interaction with the catalytic residues His 41 and Cys 145. Amyrin have a strong inhibitory effect on the SARS-CoV-2 main protease and consider the most stable phytochemicals. Amyrin and lupeol when compared to the known SARS-CoV-2 main protease (Mpro) in inhibiting the α-ketoamide they have the higher superior binding free energies. They suggest that we can use *Ficus carica* as drug against SARS-CoV-2 (M. C. Ali et al., 2020).

Antiplatelet:

Human platelet-rich plasma in vivo was tested with dried ripe *F. carica* fruit against adrenaline (activation of α2-adrenergic) and adenosine 5-diphosphate (ADP; P2Y1 and P2Y12 receptors activating), which both caused platelet aggregation; research findings indicate that *F. carica* with 0.6 and 0.12 mg ml^{-1} dosages inhibit adrenaline-induced human platelet aggregation and ADP (Gilani et al., 2008).

Antispasmodic:

Research shows that the dried ripe fruit of *F. carica* relieves spasmolytic activity (smooth muscle spasms) in isolated rabbit jejunum, probably mediated by activate ATP-sensitive potassium channels (K+ATP), along with antiplatelet activity, which explains some of its therapeutic applications in disorders related to the motility of the intestinal and antiplatelet effect, also an anti-inflammatory (Gilani et al., 2008). *Ficus carica* fully suppresses contractions that induced by the low potassium (25 mM) at low doses (0.1–3.0 mg/mL) with an EC50 value of 0.37 mg/mL; while, it cause a mild-effect contractions that was induced by the high potassium (80 mM) at high dose of *Ficus carica* (1–10 mg/mL) compared to cromakalim (a vasodilator that opens

potassium channels), which produced similar results on low potassium and high potassium; and glibenclamide (a specific blocker of the K+ATP channels), which produced similar results on low potassium (Escande et al., 1988; Franck et al., 1994; Anwarul Hassan Gilani et al., 2008). Verapamil, on the other hand, being a calcium antagonist, suppresses the contractions induced in case of high and low potassium similarly (Anwar H Gilani et al., 2005; Anwarul Hassan Gilani et al., 2008).

Cardioprotective:

Ficus carica fruit acts against cardiotoxicity of numerous chemotherapic agents which are irreversible toxins resulting in the apoptosis of cardiac myocytes, which leads to myocardial fibrosis and heart disease. Anthracyclines, particularly doxorubicin (DOX), are the most common toxins; the mechanism of doxorubicin cardiotoxicity has not yet been fully understood it might be powerfully inducing the expression of death receptors in humans, inducing pluripotent stem cells derived from cardiomyocytes, increasing the generation of mitochondrial reactive oxygen types (ROS), and generating superoxide radicals, thus causing mitochondrial swelling. Moreover, the lipid peroxidation in biological processes typically has significant effects on ROS and oxidative stress production. The reduction of cardiotoxic doxorubicin impacts is a major challenge. Close monitoring and advisory and dose-adjustment parameters are required. Therefore, some herbal medicines, such as the fruit of *F. Carica*, are cardioprotective (Gholami et al., 2017; Thomas, 2017; Zhao & Zhang, 2017). This theory highlights strategies to protect the heart without affecting the efficacy of DOX. Crucial part of the pharmacotherapy can be in the bioactive plant constituents in dietary supplements, traditional herbs, and foods. Most herbal medicines investigated are beneficial due to antioxidant mechanisms, with a few also being helpful via other main routes such as DOX-induced cardiotoxicity, apoptosis, and iron mediation. The cardiotoxicity effect of DOX can be reduced by different compounds extracted from fig, such as proanthocyanidins, epigallocatechin-3-gallatoes, S-allylylcysteines, reseveratrol, and rutosides. Therefore, several herbal medicines have been discussed, including *F. carica*, that can be evaluated as combination therapies in the future for the prevention of cardiotoxicity caused by DOX through mechanisms other than antioxidants (M. A. Khan et al., 2014).

Hepatoprotective/spermoprotective:

In the research of Gond & Khadabadi, 2008 , the *F. carica* leaf was used to test its hepatoprotective effects with rifampin in rats. The rifampin dose was 50 mg/ kg, and the dose of *F. carica* leaf extract was 200 mg/100g. The rats that were not administered the *F. carica* leaf extract showed enlarged livers, which turned pale brown in color, but those treated with the *F. carica* leaf extract appeared normal and healthy when compared with normal rat liver. In addition, the histological study showed recovery of the damaged liver cells in the drug-treated group. Thus, petroleum ether extract of *F. carica* possesses liver-protective properties (Gond & Khadabadi, 2008). The hepatoprotective of the 500 mg/kg dose of methanolic extract of *F. carica* leaves has been investigated in rats given a carbon tetrachloride to induce liver damage and showed hepatoprotective effects. This might be attributed to reduce blood levels of aspartate aminotransferase, alanine aminotransferase, malondialdehyde equivalent, and total serum of the bilirubin, all of which are indicators of liver lipid peroxidation. It may also be due to an antioxidant effect or inhibition of cytochrome P450s, which impair the bioactivation of carbon tetrachloride (Mohan et al., 2007). Also, the ethanolic extract of *F. carica* leaves was dose-dependent to protect the liver (Mujeeb et al., 2011). A study found that after methanol intoxication, treatment with stem extract can protect mice from oxidative liver injury (Saoudi & El Feki, 2012). Studies have shown that *F. carica* relieves the destructive effects in the testes, liver, and bone marrow caused by cisplatin because it has high amounts of flavonoids which perform as antioxidants that is potent and inhibit lipid peroxidation and direct the scavenging of reactive oxygen species (ROS) to protect tissue and activate antioxidant enzymes. In addition, by acting as hydrogen donors, reducing agents, singlet oxygen quenchers, and free radical scavengers, phenolic substances work as antioxidants (Cirico & Omaye, 2006; Fahmy et al., 2020; Mawa et al., 2013), Cisplatin (CP) is a platinum-based standard antineoplastic drug that is used against different types of solid tumors and neoplasms. Cisplatin causes chromosomal abnormalities, micronuclei in polychromatic erythrocytes, and bone marrow damage. Cisplatin don’t have effect on spermatocyte chromosomes (germ cells) at dosages of 10 and 15 mg/kg. Furthermore, 15 mg/kg cisplatin induces increase

in the transcription frequency of these two hepatic genes—an inducible nitric oxide synthase (iNOS; its many functions include vasomotor tone control and cell attachment to the endothelium) and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB; type of transcription factor which widely expressed and controls the response to cellular stress)—as measured by polymerase chain reaction (PCR; lab test used to amplify DNA sequences). Thus, if *F. carica* was combined with cisplatin, the overall transcription frequency of the NF-kB gene was decreased at dosages of 400 and 600 mg/kg of *F. carica* as compared to cisplatin only. At the highest tested dose of the fig, it reversed increase in the transcription frequency of the iNOS gene to approximately the normal value (Fahmy et al., 2020). Aghel et al. (2011) shown the ethanolic extract of *F. carica* reduce the level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) under intoxication by carbon tetrachloride (CCl4). *F. carica* demonstrated a mild degree of lymphocyte infiltration, lipid alteration, and necrosis in the architecture of liver sections compared to the normal control group. At a dosage of 200 mg/kg, a hepatoprotective effect was observed. Furthermore, a prior study found that at 500 mg/kg of the methanolic extract of *F. carica* leaves showed a hepatoprotective effect (Mohan et al., 2007).

Renoprotective:

Gentamicin significantly increases ($p<0.001$) serum urea and creatinine levels, whereas these levels are significantly decreased ($p<0.001$) with a combination of gentamicin with extract of *F. carica* L. leaves. The extract of *F. carica* L. leaves was protect the kidneys of the albino mouse from gentamicin-induced morphological and anatomical alterations (Ghafoor et al., 2015).

Hyperthyroidism:

Antithyroid drugs such as carbimazole can be used to treat hyperthyroidism, but they induce hypothyroid disease, which is a problem associated with the use of carbimazole. Several investigations have demonstrated that the methanolic extract of F. carica leaves was helpful in treating carbimazole-induced hypothyroidism (Sharhan & Rasheed, 2018). There an experiment was done on rats and used antithyroid carbimazole as positive control (used for treating hyperthyroidism), and gave a leaves extract from *F. carica* (500 mg/kg BW) to cause a hypothyroidism, and then treatment with Thyroxin (100 mg) (Sharhan & Rasheed, 2018). They suggest we can use extract of *F. carica* leaves to regulate hypothyroidism through the presence of phytochemical components stimulate the thyroid follicle to elevate synthesis of high amounts of T3 and T4 for the treatment of hypothyroid animals (Sharhan & Rasheed, 2018). An additional study was done to assessed *F. carica* effect on thyroid regulation in albino rats and were given oral ethanolic extracts of *F. carica* leaves various dosages (125, 250, and 500 mg/kg). The standards for antithyroid and thyroid medicines were propylthyuracle 10 mg/kg were given subcutaneous injection and thyroxine 0.5 mg/kg were given intraperitoneal injection. The existence of tyrosine within leaf extract, although it was a precursor to T3 as well as T4 hormones, was demonstrated by phytochemical analysis (Saxena et al., 2012). In addition, another study has proven a therapeutic effect of *F. carica* fruits on hyperthyroidism in Algeria (Taïbi et al., 2021). Finally, another experimental rat study revealed that ethanolic extracts of *F. racemosa* bark have lowered effects on T3 and T4 levels, which increased with thyroxine. Extracts were also compared to the methimazole reference medicine (Azharuddin et al., 2015).

Osteoporosis management:

Among the world's most serious health issues are bone-related disorders such as osteoporosis and rheumatoid arthritis. Consuming products containing large amounts of calcium such as dairy, in general, can promote and maintain bone mineral density, which decreases with aging, eventually resulting in osteoporosis (Richards et al., 2008). Previous research reported that *F. carica* modulates bone remodeling (Choi et al., 2011). It has been observed that bone disorders including such rheumatoid arthritis or osteoporosis are caused by an imbalance throughout the bone remodeling process, which again is induced via osteoclast cell differentiation. (Park et al., 2008).

It was found that *F. carica* contains amounts of calcium like those in human milk. These researchers suggest that *F. carica* acts as a natural calcium supplement for preventing bone disorders (Gani et al., 2018; O'Brien

et al., 1998). *F. carica* controls the expression of osteoblast-specific genes including osteocalcin (OCN), bone morphogenetic protein 2 (BMP-2), and osteoprotegerin (OPG), and activate the nuclear factor kappa-b ligand (RANKL) pathway and this will suppress the generation of osteoclast (Liu et al. 2010; Raggatt et al. 2010).

Anti-inflammatory:

Research was done on the fruit of *F. carica* to test the inflammatory effects by testing its inhibitory effect on nitric oxide (NO) production. And was showed the para-disubstituted benzene in some isoflavone derivatives (Figure 3) to have more inhibitory effects against NO formation (Liu et al., 2019).

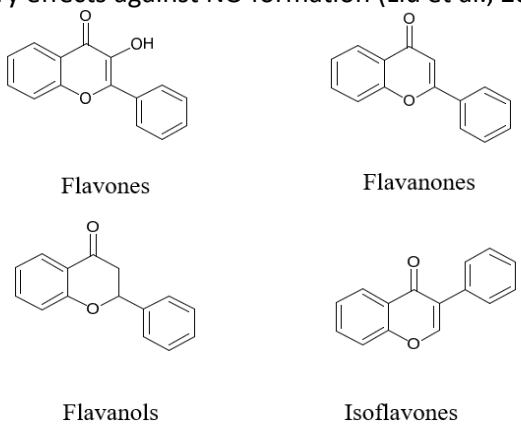

Figure 3 isoflavones derivatives

Additionally, in other research, rats were injected with carrageenan (which refers to a class of high-molecular-weight sulfated polysaccharides derived from seaweeds and may induce inflammation) into the paw to induce acute inflammation. The rats were then treated orally using different leaves extracts at dosage 300 and 600 mg/kg. This study found that chloroform (CE), ethanol (EE), and petroleum ether (PEE) extracts of *F. carica* leaves action against carrageenan-induced rat paw edema and all extracts exhibit anti-inflammatory greater than compared with the indomethacin drug.(Patil & Patil, 2011) Similar experiments also support the idea of an anti-inflammatory effect in rats. They suggest we can use *F. carica* fruits and leaves as anti-inflammatory drugs.(B. Ali et al., 2012; Bouyahya et al., 2016).

Anti-ulcer:

Ulcerative colitis considers one of the most common GIT diseases. Components of *F. carica* include polysaccharides, carbohydrates, phenolics and flavonoids. *Ficus carica* alleviates ulcerative colitis symptoms with constipation pathophysiology, so the result after consumption of the fruit showed significantly increased gastrointestinal transit ratio and gastric emptying (Rtibi et al., 2018). *F. carica* fruit has prenylated isoflavone derivatives such as ficucaricones that exhibit anti-inflammatory, the prenylated isoflavone derivatives was greater in inhibiting the production of NO with IC50 values between (0.89 ± 0.05) µM to (8.49 ± 0.18) µM compared to hydrocortisone which was utilized as a positive control (Y-P. Liu et al., 2019). *Ficus carica* can be useful in the development of novel anti-inflammatory drugs (Y.-P. Liu et al., 2019).

Antipyretic:

The most common symptom of diseases and a side effect of drugs is fever. Fever can be treated with medications such as nonsteroidal anti-inflammatory medicines such as diclofenac, ibuprofen, or paracetamol, but they come with serious side effects such as peptic ulcers and hepatotoxicity if used regularly. It is thus important to find natural alternatives like *F. carica* to treat fever (Drini, 2017). Research was performed on adult albino rats to test the antipyretic effects of *F. carica*. The antipyretic effect was tested against the normal temperature of rats and against induced yeast pyrexia. The first test was against normal temperature as the rats' temperatures were measured before giving them oral dosages of 300, 200, and 100 mg/kg of the ethanolic extract of *F. carica*. In the first test the body temperature was significantly reduced at dosage of 200 and 300 mg/kg. The second test was against induced yeast pyrexia; *F. carica* extracts were shown to have

substantial antipyretic efficacy against yeast-induced pyrexia, having comparable effects to the common medication paracetamol (Bhangale and Patil, 2015). Other studies testing the leaves of *F. carica* showed similar results to support claims of using leaf extracts as antipyretics (Bouyahya et al., 2016; Patil et al., 2010).

Anti-constipation:

One of the most common gut problems caused by loperamide is constipation. A study was performed on rats to test the effectiveness of *F. carica* in treating constipation induced by loperamide, an opioid derivative and an anti-diarrhea drug. When fig-treated mice were compared to control mice, fecal quantity, weight, and water content increased (Lee et al., 2012). Clinical study observed that *F. carica* fruit supplements improved the symptoms of patients with functional constipation. The study showed that *F. carica* fruit supplements result in increased bowel movement, reduced defecation time, and relieved abdominal pain (Kim et al., 2010). Both the experiments described above suggest the use of the *F. carica* as a therapeutic strategy for treating and preventing chronic constipation.

Dermatological effect:

Research was performed to test the ability of *F. carica* in treating mild to moderate atopic dermatitis in children. Calcium, magnesium, amino acids, zinc, and copper are known to promote wound healing (Veberic et al., 2008). The study participants were infants and children up to the age of 15 diagnosed with mild to moderate atopic dermatitis. The study was randomized and lasted 14 days. There were two groups: one who used topical *F. carica* cream 8%, and another that used a base cream of hydrocortisone 1.0%, or a placebo. For two weeks, a tip-of-finger unit was applied to the skin lesions twice daily. Both the *F. carica* extract and 1.0% hydrocortisone observed to reduce severity of pruritus. Furthermore, children with mild to moderate atopic dermatitis, *F. carica* extract showed significant improvements over hydrocortisone 1.0% (Abbasi et al., 2017).

Another research evaluated the influence of the 4% concentrated cream of the extract of the *F. carica* fruit on skin diseases including sebum production and moisture content, as well as melanin, transepidermal water loss, and erythema and compared it with base cream. The tests showed that the *F. carica* extract cream significantly reduced skin sebum, melanin, and transepidermal water loss while significantly improving skin moisture. The latter could be utilized to treat acne, wrinkles , hyperpigmentation, and freckles (Khan et al., 2014). Studies show that *F. carica* leaves contain furocoumarins (Figure 1), such as psoralen, which causes phototoxicity, and latex also contains enzymes (lipodiastase ,protease, and amylase) have irritant and keratolytic effects and also these enzymes cause severe phototoxicity secondary to the application and it can be used as a tanning agent (McCloud et al., 1992; Micali et al., 1995).

Hemostatic:

The hemostatic system triggers clot formation to stop blood loss (Brown et al., 1993). A study investigated the possible anticoagulant effects of *F. carica* extract. To verify this, *F. carica* extract was tested in vitro in normal plasma utilizing the prothrombin time (PT) as well as quick time (QT) tests by the way of the exogenous coagulation pathway. The findings indicate that this variety's fig polyphenolic extracts exhibit anticoagulant effects, which might be beneficial in treating clots (Belattar & Himour, 2019). Another study investigated the hematological parameters of *F. carica* in rabbits. Hematological indices such as white blood cell (WBC) count, hemoglobin concentration, platelet count, and packed cell volume were studied. One group was given *F. carica* extract, while the control group was given distilled water. Blood was taken from all the rats to test the hematological indices, the rats which were given the extract of *F. carica* compared to the control group and untreated rats showed increased hemoglobin concentrations. There was a substantial rise in WBC counts at doses 20 and 25 mg/kg. Platelet counts also showed a significant increase. These results concluded that *F. carica* extract has a hemostatic effect because of an active compound in this plant, ficin (Figure 4), and it mechanism by activating factor X (G. Richter et al., 2002).

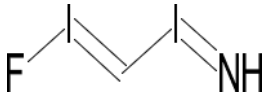

Figure 4 Ficin

Antioxidants:

Several phenolic compounds found in *F. carica* play important physiological roles in plants and have many benefits for human health. They act as antioxidants through different mechanisms such as by acting as hydrogen donators and free radical scavengers. The ferric reducing antioxidant method was used to identify the reducing agents as well as antioxidant activities. Figs contain the greatest amounts of polyphenols, anthocyanidin, and flavonoids, which lead to increased antioxidant activity (Çalişkan & Polat, 2011). The total flavonoids and profile of anthocyanidin were analyzed for the antioxidant effects of figs (Solomon et al., 2006). Different concentrations were used in studies using reverse phase liquid chromatography, and the major aglycone used in studies was cyanidin (Slatnar et al., 2011; Solomon et al., 2006; Veberic et al., 2008). It was discovered the dried *F. carica* fruit is rich in fiber, phenol antioxidants, and minerals (Badgujar, 2011; Badgujar & Mahajan, 2009). Total flavonoids of *F. carica* fruit have scavenging activity against superoxide anion free radicals and hydroxyl, Xiao-ming Yang et al., 2009 research was conducted to investigate the effect of phenols which is enriching lipoproteins in plasma and can preserve them from oxidation. Human plasma can produce antioxidants, and the extraction of water from dried figs inhibits significant growth of certain types of cancer, such as Ehrlich carcinoma and hepatocellular carcinoma in mice, and the effect of polysaccharide that extraxted from *F. carica* fruit shows anticancer effects that modulate the immune function. and the antioxidant properties of *F. carica* fruit water extraction and crude hot-water soluble polysaccharide can be determine by several methods, such as hydroxyl scavenging activity, DPPH radical scavenging assay, as well as superoxide radical scavenging assay (Xiao-ming Yang et al., 2009). As a concentration-dependent mechanism, the total flavonoid extract exhibited a significant scavenging effect for both hydroxyl and superoxide anion free radicals (Chawla et al., 2012). *Ficus carica* extract is very effective against free radicals, and figs prevent oxidative damage specifically in diabetes due to an increase in lipo peroxidation and malondialdehyde in the long term use (Hartley et al., 1997; Nourooz-Zadeh et al., 1997; Perez et al., 1996, 2003; Rice-Evans et al., 1995). Following severe diabetes problems with tissue damage caused by free radical peroxidation of lipids, which promotes membrane dysfunction and tissue damage, *F. carica* can enhance insulin secretion and B-cell function that prevents oxidative stress by antioxidant substances along with catalase glutathione peroxidase and superoxide dismutase. Also inhibiting the oxidative stress has protective effect in rats which were given streptozotocin to induced diabetes (Arunachalam & Parimelazhagan, 2013; Gothai et al., 2016; Mahboob et al., 2005; Ríos et al., 2015). Purnamasari et al., 2019 research showed *Ficus carica* leaves and fruit extracts contain numerous antioxidants, including flavonoid as well as tannin, and hence, have antioxidant activity. The half-maximal inhibitory concentration (IC50) of leveas extract of *F. carica* was 7.9875 mcg/mL, whereas fruit extract of *F. carica* had an IC50 of 13.402 mcg/mL. There was also a reduction in free radicals (Purnamasari et al., 2019).
The results of further research showed the leaves extract of *F. carica* had high antioxidant properties , with 1 mg/ml able to scavenge 75.7% DPPH (Abdel-Rahman et al., 2021). The most common property of figs is that of an antioxidant that can be protect the liver against free radical. The common active compounds are quercetin-3-O-β-D-glucopyranoside (Figure 5), kaempferol-3-O-α-L-rhamnopyranoside, caffeic acid, umbelliferone, and quercetin-3-O-α-L-rhamnopyranoside. their mechanism by raise the glutathione and superoxide dismutase levels in the blood. As a result, 150 mg/kg methanol extract of *F. Carica* in combination with *Morus alba* showed significant antioxidant and hepatoprotective effects. (Singab et al., 2010).

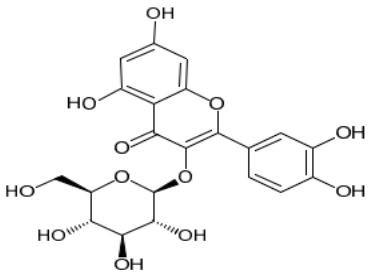

Figure 5 Quercetin-3-O-glucoside

The goal of one study was to identify polyphenols such as anthocyanins (-3-O-rutinoside and -3,5-O-di-glucoside), phenolic acids, flavons and flavan-3-ols, flavonols, triterpenoids such as betulinic acid, and one pelargonidin derivative. Oleanolic acid in the fruit of *F. carica* showed the greatest antioxidant activity (Wojdyło et al., 2016)

Anti-angiogenesis:

Ficus carica has significant antioxidant activity and can prevent inflammation and antiangiogenesis. A leaf extract was administered in a rat air pouch model of inflammation triggered by a carrageenan solution, which enhanced vascular permeability with cellular infiltration, leading to an inflammatory response. Carrageenan was injected into pouches, and

F.carica extract was administered at 5, 25, 50 mg/pouch, which resulted in a significant decrease of production of inflammatory mediators and decreased angiogenesis at all doses; also , *F.carica* extract had similar inhibition to diclofenac as an anti-inflammatory effect that reduced the risk of rheumatoid arthritis and chronic inflammatory disease (Eteraf-Oskouei et al., 2015; Onat et al., 2010). Hamid, 2021 Study showed the leaves extract of *F. carica* in Dimethylsulfoxide 2% as solvent for extraction (DMSO; produce analgesic effects and anti-inflammatory) at a dose of 110 µg decrease the expression of Matrix metallopeptidase 9 (MMP-9; is a zinc-metalloproteinase family enzyme that is involved in the proteolysis for the matrix of extracellular throughout physiological processes such as angiogenesis) and blood vessels total, total macrophage in chicken embryo, and no significant difierance with celecoxib treatment in decreasing the effect of bFGF. (Hamid, 2021).

Anticancer:

Initial research has shown that the cytotoxic effects of the *Ficus* species may be primarily observed in the resin of the latex. It can inhibit the development and growth of mammary, spontaneous, and transplanted cancers (ULLMAN, 1952; ULLMAN et al., 1952). Further studies focused on the effects of *F. carica* leaves and fruit extracts on apoptosis, proliferation, and Huh7it (liver cancer cells) necrosis. were found that the *Ficus carica* leaves able to inhibit 82.78% of liver cancer cell progression, while, fruits were 11.84% at the similar dose of 1000 mcg/mL; with doxorubicin as a positive control, the leaf extract showed higher activity than fruit extract. The cause of these differences may be the contents of compounds in the leaves and the fruit (Purnamasari et al., 2019). Luteolin and apigenin (Figure 1, Figure 6) act on hepatocellular cancer (HepG2) by causing stop in the cycle of the cell in the G1 phase, and this will cause apoptosis of Hep3B liver cancer cells (Yee et al., 2015). Quercetin can increase gene regulatory activity including p53 and p21; it stabilizes p53 and increases the Bax/Bcl-2 ratio, both of which cause apoptosis in HepG2 cells (Tanigawa et al., 2008). Furthermore, quercetin causes a DNA reaction in breast cancer cells (Srivastava et al., 2016), which can act on the S phase of colorectal carcinoma cells and esophageal cancer cells, the G0/G1 phase of leukemia cells, and the G2/M phase of breast cancer cells (J.-A. Choi et al., 2001; T.-J. Lee et al., 2006; M. Richter et al., 1999; Yuan et al., 2012; Q. Zhang et al., 2008).

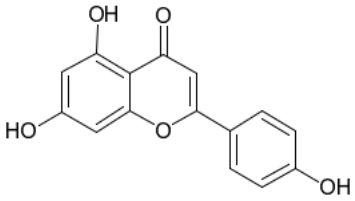

Figure 6 Apigenin

Some compounds have been extracted from *F. carica* latex, such as palmitoyl derivative (6-O-palmitoyl-β-D-glucosyl-β-sitosterol) (6-PGS) (Figure 7) and 6-O-acyl-β-D-glucosyl-β-sitosterols (6-AGS). These bioactive compounds are effective on prostate cancer, Burkitt B cell lymphoma, T-cell leukemia, and mammary cancer. One of most potent synthetic inhibitor for various types of cancers is palmitoyl derivative, which has an antimutagenic effect at doses of 12.5-50 mcg/g. 6-AGS acts through a molecular interaction, which may lead to disastrous changes in the tumor cells membrane permeability and this will lead to death of the cell (Rubnov et al., 2001). Moreover, steroidal saponin fatty acid ester, orsaponin (OSW-1) (Figure 8), is a highly effective

antitumor agent acting on oxysterol binding protein-related protein (ORP) family includes OSBP and ORP4L3 and it mechanism by inactivating OSBP and ORP4L3 also, activating the Golgi stress response, leading to apoptosis (Kimura et al., 2019; Rubnov et al., 2001). OSW-1 acts against ovarian cancer cells; OSBP related protein 4 (ORP4) was compared to the standard drugs, paclitaxel and cisplatin and found it was more selective target (Bensen et al., 2021).

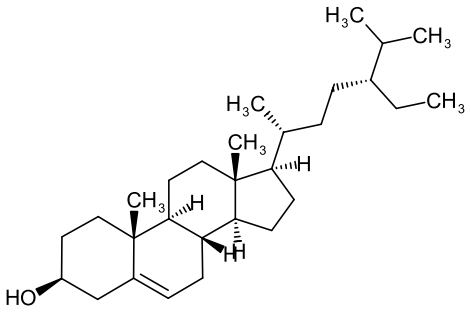

Figure 7 β-Sitosterol

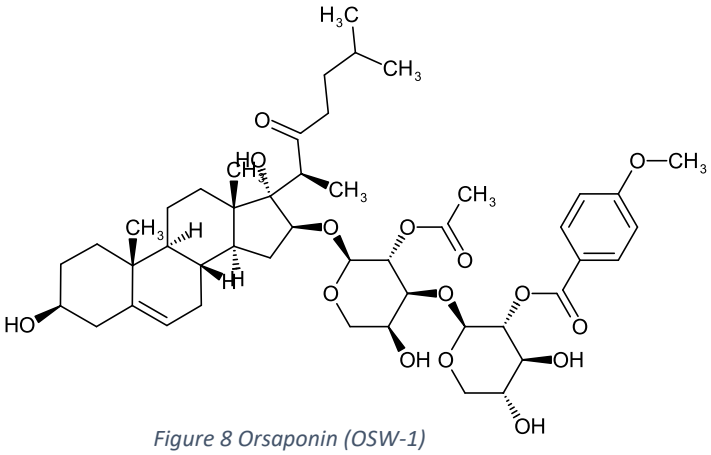

Figure 8 Orsaponin (OSW-1)

Chemotherapy for colorectal cancer causes chemoresistance and toxicity (Van der Jeught et al., 2018), which has led to the development of novel drugs from natural sources that have minor side effects and are effective (Aung et al., 2017). Ethyl acetate extracts of *F. carica* (Latex, bark, roots, leaves, etc) were prepared. Fig latex in a lot of in vitro and in vivo studies shown an antiproliferative activity to reduce HCT-116 (a human colon cancer cell line obtained from an adult male) with doses between 402 to 206 µg/ml, as well as HT-29 (Epithelial morphology human colorectal adenocarcinoma cell line) with doses (503 and 182 µg/ml) in several colorectal cancer cell lines. The leaf extracts seemed to be the most efficient in suppressing HCT-116 growth, at doses of 320 and 177 µg/ml, and HT-29 (260 and 230 µg/ml) colon cancer cells when compared to other extracts of *F. carica* (Soltana et al., 2019). Furthermore, ethyl acetate extracts of *F. carica* increased the level of cleaved PARP expression (Soltana et al., 2019). *F. carica* extracts demonstrated significant antiproliferative and pro-apoptotic activity over both HCT-116 and HT-29 colon cancer cells (Soltana et al., 2019). Other studies have proven that *F. carica* (Moraceae) fruit acts on breast and uterus cancers (Samouh et al., 2019), and that it can act on digestive cancer (Kabbaj et al., 2012). A study proved the anticancer activity of the leaf *F.carica* extract (FCE), showing strong inhibition of colon cancer cells (CaCo-2); FCE in the highest concentration (5000 mcg /ml) was the highest inhibition of human laryngeal carcinoma (Hep-2). In breast cancer (MCF7), lowest concentration of FCE (156 mcg /ml) was the highest cell viability. FCE showed a various viability of the cell at 1250, 625, and 156 mcg /ml in hepatocellular carcinoma (HepG2). Viability of the cell was the highest at the lowest FCE concentration (156 mcg/ml), in contrast to a potent inhibiting percentage (from 80.7-66.9%) on both Hep2 and HepG2 cells, they were also more susceptible to the lowest doses of therapy (156 mcg /ml) than MCF7 and CaCo-2 cells. Each of these results were comparable to a safe dosage of 5-fluorouracil (0.9 mcg /ml) (Abdel-Rahman et al., 2021). Microscopic image analysis after 48 hours of treating cells with 50 mcg/mL of the methanolic extract of *F. carica* and incubation at 37 °C showed no cytotoxic effects. Furthermore, the viability of the cell increased by slightly more than 110%, indicating that the extract promoted growth and cellular division. Moreover, cell viability was greater than 90% at all doses of the methanolic extract, the hexanic and ethyl acetate extracts showed no cytotoxicity, and the 100 mg/mL of chloroformic extract was induced a weak cellular collapse with a cell viability less than 80% (Lazreg Aref et al., 2011). The normal morphology of the epithelial human of the breast cancer cell line (MDA-MB-231) has fibroblast-like form with an elongated (spindle-shaped) cells morphology and the cell line exhibits cell-cell adhesion and cellular congestion. The shape of the cells line which treated with various doses of *F. carica* latex changed, at a concentration of 0.1%, it showed stress and apoptosis, where in the cells lost the fibroblast-like morphology and microvilli shape, and showed cell blebbing, cytoplasmic vacuolation, an uneven and round shape, as well as a reduction 82% in AMP-activated protein kinase alpha (AMPKa), 77% reduction in glycogen synthase kinase-3 alpha/beta (GSK-3a/b), 66% reduction in extracellular signal-regulated kinase expression, and 56% reduction in cAMP-response element binding protein (CREB) and the

result was comparable to untreated cells with cells treated by *F. carica* leaf latex (AlGhalban et al., 2021). Moreover, a sphere shape was dominant at the concentration of latex extract at 0.25%, and there was a slight shrinkage of spindle-shaped MDA-MB-231 cells; at higher concentrations of 0.5% and 1%, the latex extract showed more toxicity for MDA-MB-231 cells; thus, at concentrations of 0.25% and 0.1%, a reduction in cell proliferation was observed, and cell viability was significantly reduced (p value < 0.05); compared to untreated (control) group, the viability of the cell was time- and dose-dependent (AlGhalban et al., 2021). Also, the wound size has shrunk by 446 %, 301 %, as well as 188 % at concentrations of 0.05 %, 0.025 %, and 0.01 % compared to untreated (control) group (AlGhalban et al., 2021). In addition, treated cells showed higher light intensity of the fluorescein isothiocyanate (FITCI) stain and increased cytotoxicity compared to untreated control cells (AlGhalban et al., 2021). Other studies indicate that *F. carica* has anticancer compounds that could significantly improve tumor cell response to chemotherapeutic medicines such as 5-methoxypsoralen (bergapten). The effects of bergapten have now been demonstrated against multiple types of tumors, including ovarian, prostate, lung and breast cancer. Furthermore, the mode of action of bergapten may involve in stopping the cell cycle via inhibiting the phosphoinositide-3 kinase/protein kinase B (PKB), also abbreviated as the Akt (PI3K/AKT) survival pathway, also it was interfering with glycolysis in ZR75 and MCF7 cells and this will cause droping in the glycolytic enzyme 6-phos-phofructo-1-kinase (PFK1) activity this will happens after treated with bergapten at dosages of 20 and 50 μM, and lactate formation was greatly reduced, inhibited the biosynthesis of glucose-6-phosphate dehydrogenase (G6PDH) as well as Glycogen synthase kinase-3 (GSK3) phosphorylation, indicating a blockade of a key regulator of glycogen synthase activity, also , it can alters the use of glucose, and promotes lipid-lowering effect by controlling the metabolic flux pathways and lower triglyceride level relative to untreated cells, also, enhancing lipase activity, and triggered metabolic reprogramming, which all lead to the death of breast cancer cells. In addition, was inducing apoptosis through p53 gene enhancement expression through involvement of the nuclear transcription factor Y (NF-Y) transcriptional factor and activate the p38 Mitogen-activated protein kinase (MAPK). Psoralen can influence various aspects of cell activity by different mechanism including cell apoptosis, inhibiting specific metabolizing enzymes, and proliferation, also it has ability to influencing estrogen receptor stability, as well as cancer therapy resistance of Adriamycin (ADR; adriacin doxorubicin) to breast cancer cell (MCF-7/ADR) (Ikegami et al., 2013; M L Panno et al., 2012; Maria Luisa Panno et al., 2010; Maria Luisa Panno & Giordano, 2014; Santoro et al., 2016; Wang et al., 2016). Psoralen inhibits estrogen synthetase and growth factor signaling in breast cancer by suppressing aromatase, metalloproteinases (MMPs), and cytochrome P450 (CYP) and shows antiproliferative effects in breast cancer via (1) two major mitogenic hormones: insulin-like growth factor I (IGF-I) and estrogen, and (2) the activation of the PI3 kinase/Akt survival pathway(pathway that promotes metabolism, motility, cell growth, proliferation, apoptosis, and survival)(Huang & Hung, 2009; Porta et al., 2014), (3) Lowers the p-Akt survival signal (AKT overexpression has been seen in several malignancies, such as pancreatic, and ovarian, lung tumors, and has been related to enhanced cancer cell survival and proliferation) (Song et al., 2019), (4) raises the level of SMAD4 gene and Poly-Ubiquitin complexed to the estrogen receptor (the SMAD4 protein which can act as both a suppressor for tumor cells and a transcription factor, and the Ubiquitin regulates protein breakdown at the cellular level and have a critical role in progression of the cell cycle, which contributes in treating various myeloma, a kind of blood cancer, by regulating the G1 and S phases in normal and cancer cells)(Emanuele, 2019; medlineplus.gov, n.d.), as well as (5) activates the Erb2 receptor tyrosine kinase (ErbB2 persistently stimulates the Akt/NF-B anti-apoptotic signaling cascade, conferring TNF resistance to tumor cells and lowering host defenses against neoplasia), As a result, the ErbB2 receptor is an attractive target for new cancer treatments.(Maria Luisa Panno & Giordano, 2014; Xia et al., 2014; Yu & Hung, 2000) 5-methoxypsoralen (5-MOP) has at least three time- and dose-dependent mechanisms of action: it kills cells directly and causes arrest of the cells in the G2/M phase of the cell cycle which causes apoptosis. Its indices apoptosis via an additional pathway of cell-cycle arrest. In addition, 5-MOP suppression of cyclin B1 have an essential role in arrest of mitotic, this will provide another approach and cause arrest in the M phase and the overall effect will lead to apoptosis, and does not affect non-malignant breast epithelial cells (MCF10A) on a normal breast epithelial cell line (Maria Luisa Panno & Giordano, 2014; Wang et al., 2016). The cytotoxicity of the *F. carica* leaf, latex and fruit was examined by Khodarahmi et al. (2011). The findings revealed the leaf, latex, and fruit extracts of *F. carica* might diminish viability of the human immortal cervical cancer cell line

(HeLa) at doses as low as 2 mcg/mL in a dose-dependent approach. The IC50 of the latex was approximately 17 mcg/mL (Khodarahmi et al., 2011).

This research aimed to assess the efficacy, safety, and usability of rutin (Figure 1). This may be extracted from *F. carica* and used as a chemotherapeutic drug to treat human kidney cancer at 50 µM, also , to assess functionality of ionic liquids (ILs) in delivering this poorly soluble drug (rutin that extracted from *F. carica)* in a biocompatible manner (Caparica et al., 2020). Research on the latex of *F. carica* was done in two cultivars: cv. Aydin Black (AB-FL) and cv. Sari Lop (SL-FL), both of which showed dose- and time-dependent toxicity on colon (HT-29) cancer cell lines and human prostate (PC3) and cell death was significant increased with $p < 0.05$ at the low dose 10 µg/mL. and observed the PC3 was least sensitive than HT-29, when compared SL-FL administration was substantially less toxic to the cells than AB-FL administration. Furthermore, the IC50 values of AB-FL are substantially lower than those of SL-FL. However, SL-FL at 40 mcg/mL the apoptosis of HT-29 cells was increase by 2 times compared to untreated group. AB-FL, on the other hand, increased apoptosis by 10 times. Furthermore, they were 100 times more effective on tumor cell viability than Iranian *F. carica* latex (Boyacıoğlu et al., 2021). In the study of Y.-P. Liu et al., 2019 the phytochemical was performed on the fruits of *F. carica* and 16 prenylated isoflavone derivatives was identified including 4 new prenylated isoflavone derivatives, ficucaricones along with 12 known analogues and it has a antiproliferative activities, as well as antiproliferative activity against 5 human cancer cell lines: leukemic cells, hepatocellular cancer, lung carcinoma, breast cancer, and colorectal cancer. In vitro, cisplatin was used as a positive control, and overall IC50 values from 0.18 ± 0.03 to 18.76 ± 0.09 µM which might greatly benefit in the creation of novel antitumor agents (Y.-P. Liu et al., 2019)

Ficus carica polyphenols such as rutin and quercetin, as well as morin, gallic acid, and tannic acid have been shown to be helpful in preventing the growth of lymph node carcinoma in prostate cells at different concentrations and with the same P values < 0.05 (Romero et al., 2002). Furthermore, it was induced apoptosis with different P values (Romero et al., 2002). *Ficus Carica* is used as neoadjuvant anticarcinogenic agent with for Rhabdomyosarcoma (RMS), a form of sarcoma composed of cells that typically grow into skeletal (voluntary) muscles. The findings reveal a potential link in which a low dosage combination of therapeutic approaches throughout the existence of *Ficus Carica* (FC) significantly improves the therapeutic response of chemotherapy for rhabdomyosarcoma (RD) as compared to a single-agent therapeutic approach. The recommended combination of FC with low dose chemo (dacarbazine and doxorubicin-HCl) and Photodynamic therapy (PDT) may give superior therapeutic results in RD treatments and may achieve the best result for RD metastases.(Aziz et al., 2021) The cytotoxic impact of the *F. carica latex Sari Lop* (SL-FL) and *Aydin Black* (AB-FL) trees on two prostate (PC3) and colon (HT-29) cancer cell lines. However, the peroxidase like activity (Enzymes that catalyze the peroxidation of various compounds) of the two *F. carica* latexes differed from ficin peroxidase like activity, suggesting a variation in antiproliferative properties. This suggests that other constituents of the *F. carica* latex could be involved for the cytotoxic and apoptotic properties.(Boyacıoğlu et al., 2021)

Antimutagenic:

The extracts of *F. carica* were found to reduce mutations triggered by N-methyl-N'-nitro-N-nitroso-guanidine in cells of broad bean (*Vicia faba*), mutations induced by the natural compound chlorophyll in the small flowering plant *Arabidopsis thaliana*, and mutations induced by sodium fluoride (NaF) in rat marrow cells. It was proven to be extremely capable of reducing the genotoxicity of environmental mutagens (Agabeĭli & Kasimova, 2005).

Antihelmintic:

Ficus carica leaf extracts using ether, chloroform, methanol, and aqueous exhibited substantial anthelmintic activity at 20 mg/ml, and a comparison was made with the standard drug mebendazole at 20 mg/ml. The aqueous extracts showed paralysis at 2.59 min and death at 6.36 min, and methanolic extract showed paralysis at 3.25 min and death at 8.01 min compared to mebendazole, which showed paralysis at 2.31 min

and death at 6.10 min. A study was conducted on earthworms, which have a mucilaginous layer composed of complex polysaccharides. If there is any damage to these layers, the movement of the worm is paralyzed, and this may lead to the death of the worm. The extract contains flavonoids like rutin, phenolic acids, and phytosterols like taraxasterol, which may be responsible for this action. In addition, aqueous and methanolic extracts showed good anthelmintic activity as compared to other extracts (Malaria and Schools, 2010).

Ficus latex species *F. benghalensis, F. carica* and *F. religiosa* have antihelmintic activities. A study was performed to compare their potentency. Among all aqueous extracts, *F. benghalensis* fruits are the most effective. Furthermore, aqueous extracts of the fruits of both *F. religiosa* as well as *F. carica* were compared, and the extract of *F. carica* was shown to be less effective (Sawarkar et al., 2011). Additional research was made on the *F. carica* latex to assess the antihelmintic activity, so it was found to display a high rate of toxicity in mice. The antihelmintic activity was also low, and this indicated that it has a low therapeutic index; the authors recommend against the use of the latex of *F. carica* as a treatment (de Amorin et al., 1999).

Immunomodulatory:

According to one study, a polysaccharide obtained from *F. carica* fruit have ability to control gene expression and stimulate the immune response, and it capable to take out the superoxide anions and hydroxyl radicals. Furthermore, it has been discovered to up-regulate the production of tumor necrosis factor alpha (TNFα) genes and interleukin 1 beta (IL-1β) and down-regulate gene expression of the 70 kD heat shock proteins (HSP70s) (Xia Yang et al., 2015). Dendritic cells (DCs) serve as mediators between the innate (immediate) and adaptive (long-term) immune systems. Moreover, the research revealed that polysaccharides derived from fruit of *F. carica* is capable of stimulating and maturing DCs via dectin-1, it is recognition receptor which is found mostly on dendritic cells (DCs). It is also able to stimulate the secretion of some inflammatory factors such as interferon gamma (IFN-γ), interleukin-23 (IL-23), as well as interleukin-6 (IL-6), interleukin-12 (IL-12), and tumor necrosis factor alpha (TNFα) by DCs. Furthermore, it could promote the overall intensity of immune stimulus of DCs, resulting in T cell activation and proliferation and enhancing the response. It has also been found to be a potential immune stimulant as well as a candidate to be drug with low toxicity (Tian et al., 2014).

Infertility:

One study found that the extract that came from the leaf of the extract of *F. carica* increased sperm counts and mice treated with the extract had improved non-progressive sperm motility and gonadotropic indices in their testes (Naghdi et al., 2016). Furthermore, ethanolic extract exhibited aphrodisiac action in a dose-dependent manner (Palaniyappan et al., 2013).

Analgesic properties:

According to one research, ethanolic extract of the stem bark or root of *F. carica* exhibits pain relief efficacy that is superior to the conventional NSAID indomethacin (Modi, Kawadkar, & Sheikh, 2012). One study found the alcoholic and aqueous extract of leaves of *F. carica* to be dose-dependent for both chronic and acute pain (Abdulmalik et al., 2011). Another study found that the *F. carica* hydroalcoholic extract which was extracted from the leaves was effective against chronic pain and acute pain (Mirghazanfari et al., 2019). Additional research revealed that an aqueous boiling a *F. carica* alcoholic extract from the fruit was non-lethal and non-toxic, with no anti-nociceptive or anti-inflammatory effects in rat paw whose pain was stimulated by formalin. A petroleum ether extract, on the other hand, is poisonous and lethal, and it has a dose-dependent delayed anti-nociceptive activity as well as a dose-dependent anti-inflammatory effect (Mirghazanfari et al., 2019).

Hypolipidemic:

Ficus carica leaf extract is hypolipidemic and has a preventive effect at 50 to 100 mg/kg administered for 6 weeks, and in a study on hyperlipidaemia in diet with high-fat to induce obesity in male rats. The results

showed significant reduction of interleukin-6 and triglycerides, with higher levels of HDL cholesterol ($p < 0.05$). When compared to pioglitazone, the effect of *F. carica* on lipid profiles was better and more significant, and increase the HDL levels and decreasing the atherogenic index (TG/ HDL-C) also, due to it the ability to increase the HDL-C levels it will decrease the adipogenic risk factors in HFD rats (Joerin et al., 2014).

Antidiabetic:

Streptozotocin (STZ), an alkylating antineoplastic agent, is toxic to insulin-producing beta cells in mice, Streptozotocin compared to 1 g/kg of *F. carica* leaves ethyl acetate extract twice daily for six weeks, which inhibits hepatic gluconeogenesis through the reduction of G6Pase (glucose-6-phosphatase) and PEPCK (phosphoenolpyruvate carboxykinase) on HepG2 hepatocytes and diabetic mice. The extract also stimulates AMPK (AMP-activated protein kinase) and decreases the production of HNF4α (hepatic nuclear factor 4α), FOXO1 (Forkhead transcription factor O1), and PGC-1α (peroxisome proliferator activated receptor-γ coactivator-1α). This study found that *F. carica* leaf extract (FCL) inhibits hepatic gluconeogenesis by activating AMPK and decreasing the activity of gluconeogenic enzymes. Moreover, FCL extract treatment was given to diabetic mellitus rats (C57BL/6 J) at a dose of 1 g/kg tow times daily, substantially lowered fasting blood glucose levels at four and six weeks with $p < 0.05$. Furthermore, HbA1C levels in the FCL subgroup were significantly lower than in the diabetes mellitus subgroup with $p < 0.05$. FCL extract considerably lowered not only blood glucose levels but also TG levels with $p < 0.05$ in the previous trial, whereas there were no substantial differences in cholesterol levels between the FCL, DM, and control groups (Y. Zhang et al., 2019). In insulin-dependent diabetes mellitus (IDDM) patients, the effect of an *F. carica* leaf decoction as a supplement with breakfast was studied. The average insulin dose in the entire group was reduced by 12%. Consuming *F. carica* combined with a diet may help manage postprandial glycemia in people with IDDM (Serraclara et al., 1998). As a result, the efficacy of F. carica leaf aqueous extract on hypotriglyceridaemia, hypoglycemia, and hypocholesterolaemia was investigated during a trial on diabetes management through IDDM patients, The *F.carica* leaf extract was given as a morning supplementary, with usual diets and twice-daily insulin injections to help the patients manage sugar levels. Supplementation with a decoction of *F. carica* leaves decreased postprandial glycemia considerably more than unsweetened commercial tea (Serraclara et al., 1998). Organic phase treatment of rats with streptozocin-induced hyperglycemia results in a lowering in total levels in comparison to the control sample, and together they cause a decrease in hyperglycaemia (Perez et al., 2003). Diabetic rats were administered *F. carica* at 250 mg/kg as well as 500 mg/kg, while diabetic rats were given 0.6 mg/kg glibenclamide one time a day via intragastric tube for 28 days and assessed using the oral glucose tolerance test. *F. carica* increased glucose uptake in diabetic rats peripheral tissues in a dose-dependent approach, and exogenous insulin injection improved insulin sensitivity , and improve insulin sensitivity and stabilization of plasma insulin levels in diabetic rats were investigated. (El Hilaly & Lyoussi, 2002; Liou et al., 2002). According to an *in vitro* study, *F. carica* had various effects including antioxidant, antidiabetic, and antriobesogenic effects. Because the active constituents include polyphenols and flavonoids, according to the findings of this study, the ethanolic extract of *F. carica* exhibits significant anti-diabetic and anti-obesogenic properties. (Mopuri et al., 2018). *F. carica* L. fruits have shown high antidiabetic potential *in vitro* via suppressing carbohydrate-digesting enzymes including α-amylase as well as α-glucosidase. It can considerably minimize the postprandial rise in blood sugar levels and thus be an important step in the treatment of blood sugar levels in borderline patients or even type 2 diabetics (Wojdyło et al., 2016).

Anticonvulsant:

Strychnine is a crystalline alkaloid pesticide that is highly toxic, bitter, and colorless. Both *F. carica* and oligosaccharides were identified as potential anticonvulsants against strychnine-induced convulsion-action via high doses of ICV-injection. *F. carica* methanol extract at 200 mg/kg and oligosaccharides at 50 mg/kg completely protected experimental mice against strychnine-lethality. According to research, the anticonvulsant mode of action of *F. carica*/oligosaccharide proving was done via glycine receptor potentiation so these evidence supports the anticonvulsant effectiveness of F. carica and oligosaccharides, and thus, the

oligosaccharides may have impacts on the development of novel therapies with good safety profiles for specific convulsive disorders (Raafat & Wurglics, 2019).

Antinematicidal:

Bursaphelenchus xylophilus is responsible for pine wilt disease, which has become severe worldwide (Guo et al., 2016). The active compound of *F. carica* consists of two major constituents, bergapten and psoralen, and the mechanism inhibits the activities of cellulase, amylase, and acetylcholinesterase from pine wood nematode. *Ficus carica* (bergapten and psoralen) ethanol extract (1 mg/ml) had significant nematicidal activity against pinewood nematode (Guo et al., 2016).

Endophyte:

Aspergillus neoniger is an endophytes extract from *F. carica* that provides a significant natural compounds with biological activity that might be exploited to create anticancer medicines (Aly et al., 2008). Moreover, bioactive fungal metabolites two natural elements asperazine and asperazine A (Figure 9, Figure 10) were isolated to establish that asperazine had more potent cytotoxic and anticancer effects against blood cancer and HeLa cells (human immortal cervical cancer cell line), human umbilical vein endothelial cells (HUVEC), as well as human immortalized myelogenous leukemia cells (K-562) cells than its homologue asperazine A (Abdou, Alqahtani, et al., 2021). the C-N bond demonstrates the significance that biological action of the diketopiperazine dimer linked by two subunits (Abdou, Alqahtani, et al., 2021). The extract of a strain grown in a malt potato glucose medium demonstrated potent cytotoxic effects against HeLa (CC50 = 6.2 µg/mL) Furthermore , antineoplastic activities against HUVEC and human immortalized myelogenous leukemia cell lines at concentrations required to achieve 50% inhibition of cell proliferation of GI50 = 5.9 and 4.8 µg mL^{-1} (Abdou, Alqahtani, et al., 2021). The findings of the spectroscopic analysis revealed that asperazine exhibited moderate anticancer properties with 50% cytotoxic concentration (CC50) = 18.4 µg mL^{-1} against human immortal cervical cancer cell line and moderate anticancer properties with GI50 = 24.8 to 31.5 (µg/mL) against both human umbilical vein endothelial cells and human immortalized myelogenous leukemia cell lines. However, asperazine A exhibited low cytotoxicity against human immortal cervical cancer cell line at CC50 = 34.6 (µg/mL) and low cytostatic activity against human immortalized myelogenous leukemia cell lines and human umbilical vein endothelial cells at GI50 = 40.7 to 50.2 g mL-1, Both substances are antimicrobially inactive.

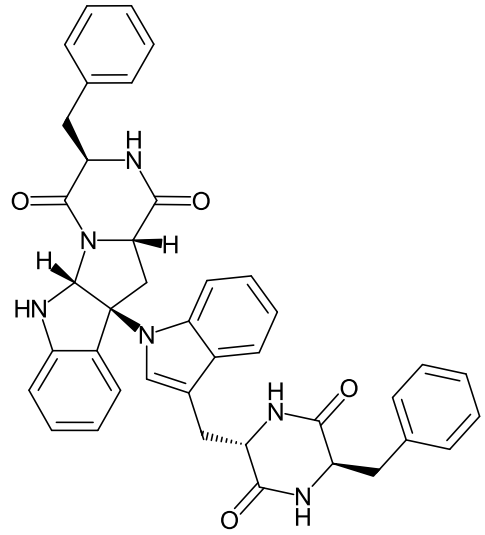

Figure 9 Asperazine A

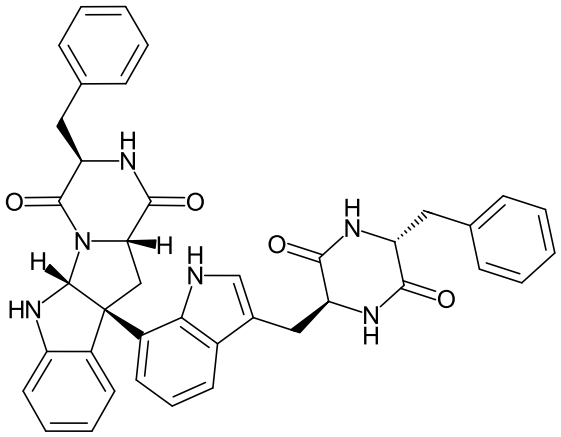

Figure 10 Asperazine

The two cytotoxic compounds isolated from *Aspergillus neoniger*

Other research demonstrated endophytic fungus from *F. carica*: the four compounds helvolic acid (), cyclo(-Phe-Ser), fumitremorgin B, and fumitremorgin C and these compound significantly inhibit growth of *Alternaria brassicae* fungi and *Botrytis cinerea, Fusarium oxysporum f. sp. Niveum* (Feng & Ma, 2010). In addition, endophytic *Aspergillus sp.* derived from *F. carica* and extracted with ethyl acetate exhibited potent antibacterial activity towards *Pseudomonas aeruginosa* (Prabavathy & Nachiyar, 2011). The existence of phenol and amine groups seems responsible for *F. carica* endophytes' antibacterial activity; endophyte natural products with high potency could be used to create new antibiotics.

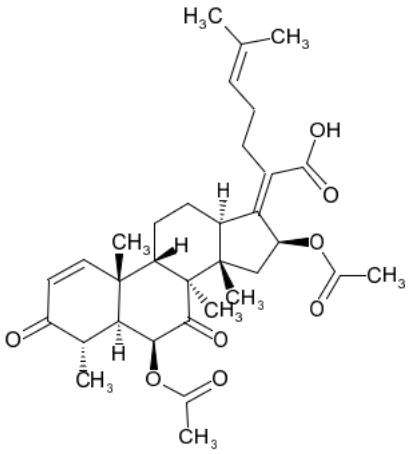

Figure 11 Helvolic acid

Another research found that endophytes extracted from *F. carica* were *Alternaria alternata, Aspergillus neoniger, Chaetomium globosum, Penicillium oxalicum,* and *Fusarium proliferatum*. They all have anticancer and cytotoxic activity against HUVEC as well as human immortalized myelogenous leukemia cells that associated with GI50 ranging from 13.75 to 4.75 (µg mL-1) , and cytotoxicity against the HeLa with 50% cytotoxic concentrations (CC50) that range from 8.25 to 18.75 µg/mL. Both endophytic extracts *A. neoniger* as well as *C. globosum* were the most cytotoxic, associated with CC50 of 9.21(µg mL-1) to 8.25 (µg mL-1) (Abdou, Mojally, et al., 2021). The overall cytostatic potency of *A. neoniger* extract was the strongest against both K-562 and HUVEC cell lines with the GI50 ranges from 7.75 (µg mL-1) to 4.75 (µg mL-1) (Abdou, Mojally, et al., 2021).

Compound 1, a cyclic pentapeptide termed disulfide cyclo-(Leu-Val-Ile-Cys-Cys), was extracted from the culture broth of the endophytic strain FR02 fungus and classified as *Aspergillus tamarii* in *F. carica* root. Compound 1 is named malformin E; 13 additional cyclic peptides ertr identified. In vitro, malformin E exhibited strong antibacterial and cytotoxic action. The results of the antimicrobial property tests indicated that compound 1 had significant antimicrobial activity that MIC values of 0.45, 0.91 , 1.82, and 0.91 µM; it inhibited the growth of *P. aeruginosa, E. coli , S. aureus B. subtilis*. Similarly, it had potent effects against *Fusarium solani*, *P. chrysogenum,* and *Candida albicans* that MIC values of 7.24, 3.62 and 7.24 µM, respectively. With IC50 of 2.42 and 0.65 µM, compound 1 was extremely toxic to human cancer cell strains breast cancer cells (MCF-7) and lung cancer cells (A549) . Furthermore , it exhibited some activities on HepG2 (liver cancer cells) that associated with an IC50 of 36.02 µM, that comparison with adriamycin besides 5-fluorouracil (Ma et al., 2016). It has the potential to become an acceptable for novel chemotherapeutic and antimicrobial medicines in the medical and agricultural industries.

Anti-Stress:

The *F. carica* cell suspension culture extract (FcHEx) acts as an anti-stress agent, decreasing the undesirable effects of stress hormone effect on the skin, including skin blanching, skin barrier modification, and inflammation (Dini et al., 2021). *In vitro* (on keratinocyte cells) and in vivo tests were conducted to show how well it handled stress-hormone-induced skin deterioration (Dini et al., 2021). Both studies revealed that *F. carica* cell culture extracts decreased skin deterioration induced via psychological stress (Dini et al., 2021). FcHEx reduced the production of interleukin 6 (38% and 36% at the concentrations of 0.002% and 0.006%), epinephrine (43% and 24% at the concentrations of 0.002% and 0.006%), protein carbonylation (50%), and

lipid peroxide (25%). FcHEx also increased ceramide production (by 150%) and improved lipid barrier function (Dini et al., 2021). Finally, it is proposed that it can be utilized as an agent to counteract skin indications of psychological stress (Dini et al., 2021).

Antirheumatic:

Angiogenesis is now acknowledged as a critical process in the development and maintenance of the pannus in rheumatoid arthritis (RA), also leading to leucocyte recruitment and synovial inflammation (Clavel et al., 2006). Targeting the central role of proangiogenic cytokine vascular endothelial growth factor (VEGF) in the angiogenesis process, VEGF is a signaling protein that stimulates the formation of new blood vessels. It may also contribute to edema and thus joint swelling in RA, as well as aggravate collagen-induced arthritis (CIA), and it could be a promising novel treatment for RA (Clavel et al., 2006; Paleolog, 2002). The use of a soluble VEGF receptor to inhibit VEGF activity in murine CIA was observed to decrease the severity of the diseases, joint destruction, and paw swelling (Paleolog, 2002). In addition, *F. carica* extract downregulated prostaglandin E2 (PGE2), VEGF levels, and tumor necrosis factor α (TNFα) in the inflammatory exudates, as well as arachidonic acid by inhibiting cyclooxygenase-2 (COX-2) (Eteraf-Oskouei et al., 2015). *F. carica* exert antirheumatic effects (Eteraf-Oskouei et al., 2015).

Anticholinesterase:

A study show that *F. carica* n-hexane and acetone extracts inhibit acetylcholinesterase (AChE) at 62.9 ± 0.9% and 50.8 ± 2.1%, as well as butyrylcholinesterase (BChE) at 76.9 ± 2.2% and 45.6 ± 1.3%, but they had weak antioxidant activity; the methanolic extract was completely inactive against AChE and BChE (Orhan et al., 2011). Bergapten and psoralen have also been shown to suppress AChE activity in leaves with IC50 564.59 and 493.11 mcg/mL (Guo et al., 2016). In patients with Alzheimer's disease levels AChE and BChE in the brain are abnormal, so cholinesterase (ChE) inhibitors play significant role in treatment (Colović et al., 2013; De Boer et al., 2021; Haake et al., 2020; Kabir et al., 2019; Marucci et al., 2021).

Larvicidal activity

Ficus carica possesses a lethal concentration that kills 50% (LC50; 10.2 μg/ml) and a lethal concentration that kills 90% (LC90; 42.3 mcg/ml) of early fourth-stage larvae of *Aedes aegypti L.* Furocoumarins, 8-methoxypsoralen, and 5-methoxypsoralen were extracted from the *F. carica* milky sap, and the LC50 values of 8-methoxypsoralen as well as 5-methoxypsoralen were 56.3 and 9.4 mcg/ml, respectively. these result indicate that the main constituent of *F. caica* milky sap extract playing a substantial role in the toxic effects , and the result show the *F. caica* exhibits bioactivity against mosquito larvae (Chung et al., 2011).

Clinical studies:

Atopic dermatitis:

A randomized, placebo-controlled research showed that a novel therapy compared to hydrocortisone 1.0 % ($p < 0.05$) and was showed had considerably greater efficacy in terms of decreasing the scoring of atopic dermatitis (SCORAD), scale, itch, as well as intensity ratings. Children were divided randomly to be given either *F. carica* topical cream 8% (Melfi cream), or, placebo (base cream) or 1.0 % hydrocortisone. The placebo had no effect on the symptoms. When compared to hydrocortisone 1.0 %, *F. carica* fruit extract had considerably superior safety, effectiveness, acceptability, and symptom alleviation (Abbasi et al., 2017). Clinical research has demonstrated that this extract can be utilized in pediatric patients with mild to moderate atopic dermatitis instead of a low-potency corticosteroid.

Antidiabetic:

In randomized clinical trial, double-blind crossover research was done on 10 healthy people ingested 4 test drinks which had a fig fruit extracts (FFEs), and their postprandial glucose and insulin were measured at regular intervals over 2 hours to evaluate glycemic index (GI) and insulinemic index (II) responses. The drinks which was tested containing 200 mg (FFE-50×) and 1200 mg (FFE-10×) significantly substantially lowered GI values by -25% with $p = 0.001$ and -24% with $p= 0.002$ (Atkinson et al., 2019). When compared to the reference beverage, 2 lower dosages of FFE also lowered GI levels by approximately 14%. In fact, adding FFE to the glucose solution drastically lowered the value of II at all doses. the result showed the extracts of abscisic acid standardized Fig (*Ficus carica*) can be used as dietary supplement to activate lanthionine synthetase C-like 2 enzymes (LANCL2) which reduce inflammation, also, used as dietary intervention to maintain the homeostasis between the insulin and acute postprandial glucose in a high-GI glucose drink or meals , this study suggest the abscisic acid standardized Fig (*Ficus carica*) extracts can be a potential innovative supplementary therapy that aids in the control of hyperglycemic indications in chronic metabolic diseases such as prediabetes, diabetes, and obese (Atkinson et al., 2019).

According to the findings of a study, *F. carica* has short-term hypoglycemic action persisting in IDDM patients. As a result of adding *F. carica* to the diet, 15.5 % of the full daily dose of insulin decreased was observed , which is significantly lower when supplemented with *F. carica* as evidenced by the following mean capillary glycaemia values 293.7 ± 45.0 mg/dl and 156.6 ± 75.9 mg/dl wtih (p <0.001) (Serraclara et al., 1998).

Hemorrhoidal:

When fig leaf fumigation is combined with acupuncture, the clinical efficacy is high and safe in comparison with the use of fig leaf fumigation alone, and it is beneficial for relieving clinical symptoms such as itching, prolapse, blood in the stool, and hemorrhoidal discomfort (Haiyan et al., 2013). A substantial difference was observed between the two groups: overall treated group was superior to the untreated group, with higher total effective rate ($p < 0.05$); in the untreated group it was 88.64%, while in the treatment group, it was 97.78 %. Clinical symptoms improved in both groups after treatment. The treated group improved statistically more than the untreated group with $p < 0.05$ (Haiyan et al., 2013).

Constipation:

One well-known digestive disorder is irritable bowel syndrome and constipation (Pourmasoumi et al., 2019). The bioactive compounds in figs are dietary fiber, carbohydrates, lipids and proteins, and figs acts as an osmotic laxative that elevates viscosity and increases stool defecation (Pourmasoumi et al., 2019). After consumption of 90 g of figs leads to significant improvement of inflammatory bowel disease and also enhances quality of life compared to the control group (Pourmasoumi et al., 2019).

Baek et al. (2016) aimed to use *F. carica* paste to treat functional constipation. Patients were given *F. carica* paste orally for eight weeks, and the efficacy and safety of the *F. carica* paste was measured. The patients who took the *F. carica* paste showed significant improvement in colon transit time and abdominal pain, blood parameters were normal, and no organ toxicity was observed. These results suggest the benefits of using *F. carica* paste with patients suffering from constipation.

Antiviral:

Human papillomaviruses (HPVs) are epitheliotropic, small, double-stranded DNA viruses that causes many diseases (McMurray et al., 2001). clinical study found the latex of *F. carica* was less effective in treating warts compared to cryotherapy. In addition, latex provides various benefits, including a short period of therapy; no reported adverse effects; simplicity of application; patient adherence**;** and recurrence rate of HPVs were low. As a result, the mechanism of antiwart activity remains unknown, but it may be due to the proteolytic activity

of the ficin compound excreted from the leaves and fruits of the fig tree (Bohlooli et al., 2007; Hemmatzadeh et al., 2003).

Papillomaviruses cause benign epithelial tumors in humans, and bovine papillomavirus (BPV) causes mucosal epithelial papillomas in cows (Bloch et al., 1994). A clinical investigation discovered that treating cattle with fig tree latex reduced the number of warts significantly. In addition, there were no changes in the treatment of papillomatosis when compared to salicylic acid, but a local inflammatory reaction appeared in the group that used salicylic acid (Hemmatzadeh et al., 2003).

Conclusion.

In conclusion, in vitro and in vivo studies of 129 active phytoconstituent extracts from *F. carica* root, stem, leaf, latex, and fruit as well as endophytic microorganisms, revealed more than 40 medicinal effects in various disorders such as digestive tract (constipation, dyspepsia, poor appetite, and diarrhea), respiratory (throat irritation, cough, and bronchospasm issues), and cardiac diseases. Comprehensive laboratory and clinical findings have revealed the potential benefits of *F. carica* leaves for a variety of diseases, including diabetes and a protective effect against the toxicity of chemotherapy agents such as doxorubicin on cardiomyocytes and other toxicity. Furthermore, *F. carica* leaves have high antioxidant activity, which can remove free radical damage to all cells in the body, whether in the central nervous system or other organs, which lead to depression, bipolar disorder, and Alzheimer's disease, among other things. Although scientific studies on *F. carica* have been conducted to investigate the chemistry, bioactivity, and molecular mechanisms as an anti-inflammatory effect that can be beneficial in common inflammatory diseases such as rheumatoid arthritis, *F. carica* leaf and fruit extracts for their comparative anti-cancer potential on prostate, breast, lung, and colon. So, in addition to its high nutritional value, which aids in providing the entire body with essential vitamins and minerals, *F. carica* has the prospect to be used as a medicinal product for many disorders. These studies would provide solid scientific evidence to support the use of *F. carica* leaves and their further development for clinical use.

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