Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Physicochemistry, Nutritional, and Therapeutic Potential of *Ficus carica* – A Promising Nutraceutical

Muhammad Fattah Fazel[1,2], Izuddin Fahmy Abu[1], Mohamad Haiqal Nizar Mohamad[3], Noor Arniwati Mat Daud[1], Ahmad Najib Hasan[1], Zainie Aboo Bakkar[1], Muhammad Alif Naim Md Khir[4], Norsham Juliana[5], Srijit Das[6], Muhamad Razin Mohd Razali[1], Nurul Hana Zainal Baharin[2], Arashidatul Akmar Ismail[2]

[1]Institute of Medical Science Technology, Universiti Kuala Lumpur, Kuala Lumpur, Malaysia; [2]Faculty of Pharmacy and Biomedical Sciences, MAHSA University, Jenjarom, Selangor, Malaysia; [3]Malaysian Institute of Chemical and Bioengineering Technology, Universiti Kuala Lumpur, Alor Gajah, Malacca, Malaysia; [4]Tropical Infectious Diseases Research and Education Centre (TIDREC), University of Malaya, Kuala Lumpur, Malaysia; [5]Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia; [6]Department of Human and Clinical Anatomy, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman

Correspondence: Izuddin Fahmy Abu, Institute of Medical Science Technology, Universiti Kuala Lumpur, Jalan Sultan Ismail, Kuala Lumpur, 50250, Malaysia, Email izuddin@unikl.edu.my

Abstract: In an era where synthetic supplements have raised concerns regarding their effects on human health, *Ficus carica* has emerged as a natural alternative rich in polyphenolic compounds with potent therapeutic properties. Various studies on *F. carica* focusing on the analysis and validation of its pharmacological and nutritional properties are emerging. This paper summarizes present data and information on the phytochemical, nutritional values, therapeutic potential, as well as the toxicity profile of *F. carica*. An extensive search was conducted from various databases, including PubMed, ScienceDirect, Scopus, and Google Scholar. A total of 126 studies and articles related to *F. carica* that were published between 1999 and 2023 were included in this review. Remarkably, *F. carica* exhibits a diverse array of advantageous effects, including, but not limited to, antioxidant, anti-neurodegenerative, antimicrobial, antiviral, anti-inflammatory, anti-arthritic, antiepileptic, anticonvulsant, anti-hyperlipidemic, anti-angiogenic, antidiabetic, anti-cancer, and antimutagenic properties. Among the highlights include that antioxidants from *F. carica* were demonstrated to inhibit cholinesterase, potentially protecting neurons in Alzheimer's disease and other neurodegenerative conditions. The antimicrobial activities of *F. carica* were attributed to its high flavonoids and terpenoids content, while its virucidal action through the inhibition of DNA and RNA replication was postulated due to its triterpenes content. Inflammatory and arthritic conditions may also benefit from its anti-inflammatory and anti-arthritic properties through the modulation of various signalling proteins. Studies have also shown that *F. carica* extracts were generally safe and exhibit low toxicity profile, although more research in this aspect is required, specifically its effects on the skin. In conclusion, this study highlights the potential of *F. carica* as a valuable natural therapeutic agent and dietary supplement. However, continued exploration on *F. carica*'s safety and efficacy is still required prior to embarking on clinical trials, as its role in personalized nutrition and medication will open a new paradigm to improve health outcomes.

Keywords: antioxidant, dietary supplement, fig, natural compound, phytochemical

Introduction

Since time immemorial, humans have centred their lives on plants in an effort to preserve good health and alleviate ailments and diseases.[1] Currently, synthetic antioxidants are being widely used in food and medication where it can both induce or promote detrimental health effects.[2] Therefore, the use of synthetic antioxidants, especially its concentration, is regulated rigorously during manufacturing processes to ensure the stability and safety of the substances within the allowable limit.[3] For this reason, research on potential natural additives and antioxidants are paramount nowadays. Various fruits and their derivatives are well known for having a high concentration of naturally occurring polyphenolic chemicals.[4] Polyphenols are plant secondary metabolites with antioxidant properties that serve as free radical inhibitors

Received: 28 August 2023
Accepted: 21 March 2024
Published: 30 May 2024

and play essential roles in reducing oxidative stress[4] towards maintaining human health.[5] In line with this, *Ficus carica* L. is a promising lead since it naturally contains polyphenols and other beneficial bioactive compounds.

The fig tree (*F. carica L*) is among the most ancient fruit-bearing trees and valued not only as a source of food, but also for its medicinal properties.[6] *Ficus* is one of the largest angiosperm genera, with over 800 species of trees, shrubs, hemiepiphytes, climbers, and creepers found throughout the tropics and subtropics.[7] *F. carica*, or commonly known as fig, is a deciduous tree in the Moraceae family and is one of the oldest cultivated trees in the world, with both fresh and dry consumption.[8–10] According to a recent market report by Future Market Insights (FMI), the Middle East and Africa regions are the largest markets for fresh *F. carica*, and hold 71.2% of the market share for the year 2022.[11] FMI also reported an increase in the demand for fresh as well as processed *F. carica* products in developed countries owing to the viability of the fresh plant. *F. carica* is valued for its fresh dried fruits because of its abundant source of vitamins, carbohydrates, minerals, sugars, phenolic compounds, organic acids, and fat cholesterol.[2,12,13]

What is most interesting about the *F. carica* plant is that most of its parts, such as fruits, leaves, shoots, roots, latex, and bark as shown in Figure 1, have been widely researched to hold their own values and are used to treat various human diseases.[13,14] *F. carica* latex (F. latex) exhibits antioxidants, milk-clotting,[2] anti-cancer,[15,16] anti-fungal, chitinolytic, cytotoxic, antiviral, antibacterial, and anthelmintic activities.[2,17] Li et al reported that *F. carica* leaves are commonly used in tea as well as traditional medicine.[18] *F. carica* leaves were found to yield beneficial effects in gastrointestinal diseases, respiratory diseases, cardiovascular diseases, diabetes, skin diseases, ulcers, dysentery, hemorrhoids, cough, lung diseases, and dissolution of blood congealed by bruises or falls.[18] The same study also reported that *F. carica* leaves contain a total of 126 chemical constituents and exhibit antioxidant, anti-cancer, antidiabetic, hepatoprotective, antic-holinesterase, anti-*Herpes simplex virus* type 1 (anti-HSV-1), antibacterial, anti-inflammatory, and renoprotective properties.[18] Nevertheless, further research and identification of the constituent functional chemicals are highly essential.

This present review describes *F. carica* as a potential nutraceutical plant that exhibits various pharmacological benefits, and addresses future research directions on the exploration of this medicinal plant.

Materials and Methods

Pertinent articles were gathered from databases including PubMed, ScienceDirect, Scopus, and Google Scholar. Articles related to *F. carica* studies that have been published since 1932 were archived using specific keywords; "*Ficus carica"* OR *"Ficus carica* L*"*. AND "Moraceae*"* OR "Chemistry" OR "In vitro" OR "In vivo" OR "Biological properties" OR "Extracts" OR "Toxicity studies" OR "Phytochemistry" OR "Pharmacodynamics" OR "Pharmacokinetics" OR "Pharmaceuticals" OR "Therapeutics" OR "Nutritional Value".

Studies that were not written in English or had no abstracts were excluded from the initial screening. Articles chosen for this review were filtered after the inclusion and exclusion criteria were met (Figure 2). The review revolved around key findings of *F. carica* studies including its physicochemistry, extraction methods, nutritional values, cosmetic usage, and toxicity profile (Figure 3), and further elaboration on its pharmacological properties (Figure 4) were deeply explored. A total of 126 studies or articles were included in this present review paper.

Extraction of F. carica

In an extraction method described by Mahmoudi et al for phytochemical analysis, 10g of *F. carica* fruit was permeated in 100mL of pure methanol at room temperature for 24h.[12] The mixture of *F. carica* and methanol was filtered and the solvent evaporated using a rotary evaporator at 40°C to obtain the final product.[12] Following the method by Takahashi et al, *F. carica* leaves were freeze-dried and grounded into fine powder, then added with methanol.[19] The mixture was shaken in a rotary shaker at 120rpm for 3h, followed by centrifugation for 10mins at 1700g, and repeatedly until the collected supernatant reached 50mL.[19] The extract was finally filtered using a 0.45μm syringe filter.[19] Meanwhile, Saoudi et al extracted *F. carica* stems by grounding them, then soaked in water, and shaken for 15–20mins (10 g/L, v/w), before filtration using Whatman filter paper.[20]

In a study using *F. carica* seeds, they were grounded into powder form and mixed with petroleum ether for 6h.[21] The product was then subjected to a rotary evaporator to remove the solvent, flushed with nitrogen, and finally stored at −18°C.[21] Harzallah et al used *F. carica* peel and pulp juice extract to assess their phytochemical content.[22] The peel and pulp blend was centrifuged at 3000rpm for 10mins, the supernatant filtered and stored at −20°C for methanolic extraction

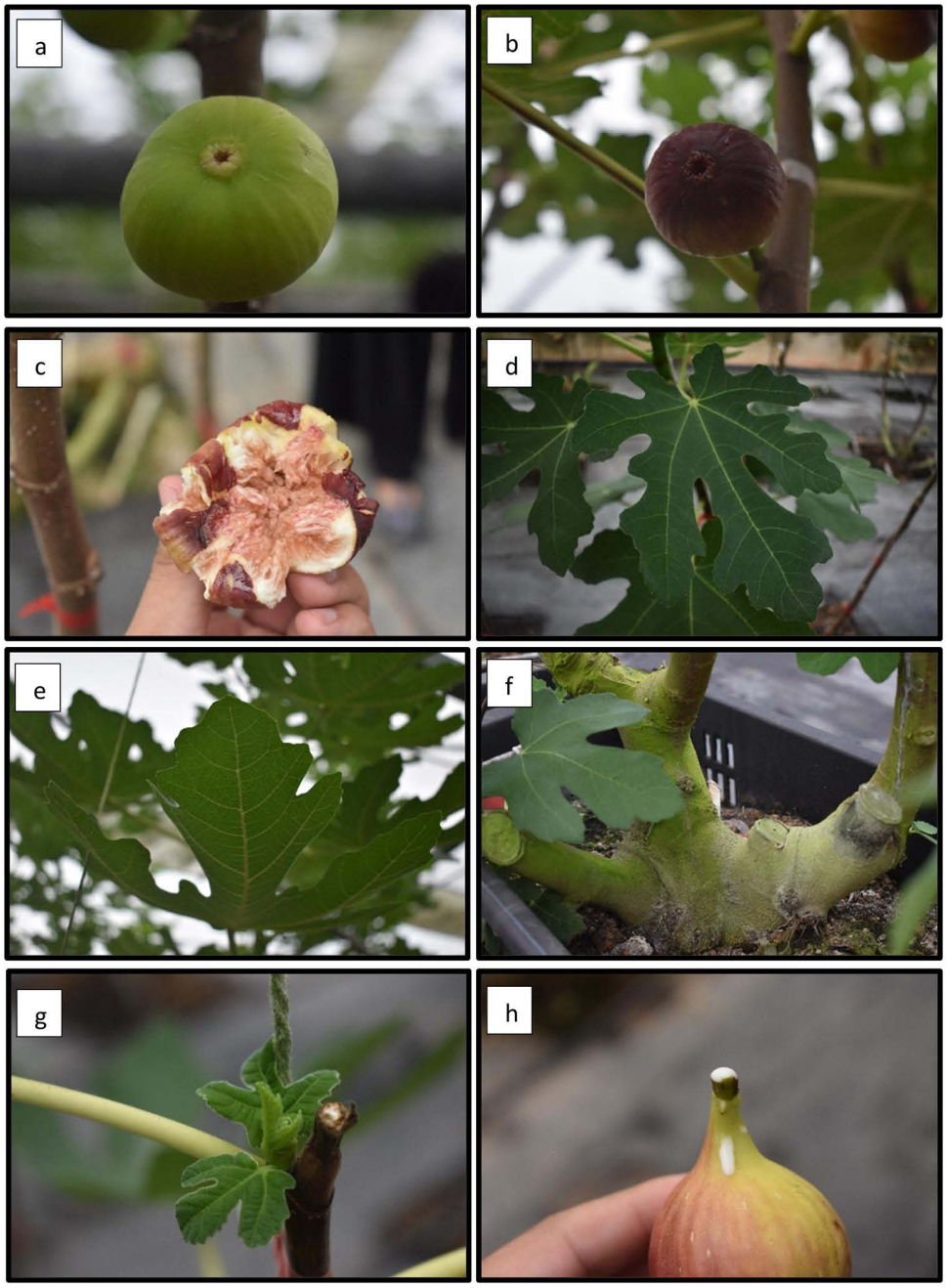

Figure 1 Different part of *F. carica*. (**a**) unripe fruit; (**b**) ripe fruit; (**c**) opened ripe fruit; (**d**) upper side of the leave; (**e**) down side of the leave; (**f**) branches; (**g**) young shoots; (**h**) latex.

process the following day.[22] In another study, dried *F. carica* extract was prepared by dissolving 50g of macerated pulp in 200mL mixture of distilled water, 80% methanol, 70% ethanol, and 50% acetone.[23] The mixture was then agitated at room temperature in the dark for 24h, then concentrated using a rotary evaporator at 40°C.[23] These extraction methods were performed for various purposes such as to determine and calculate the amount or concentration of flavonoids, to identify its active compounds, or to assess its biological properties for potential therapeutic approaches.

Phytochemistry of F. carica

Phytochemicals are defined as bioactive nutrient plant chemicals that may provide desirable health benefits beyond basic nutrition.[24] It can be classified as primary or secondary constituents depending on their roles in plant metabolism.

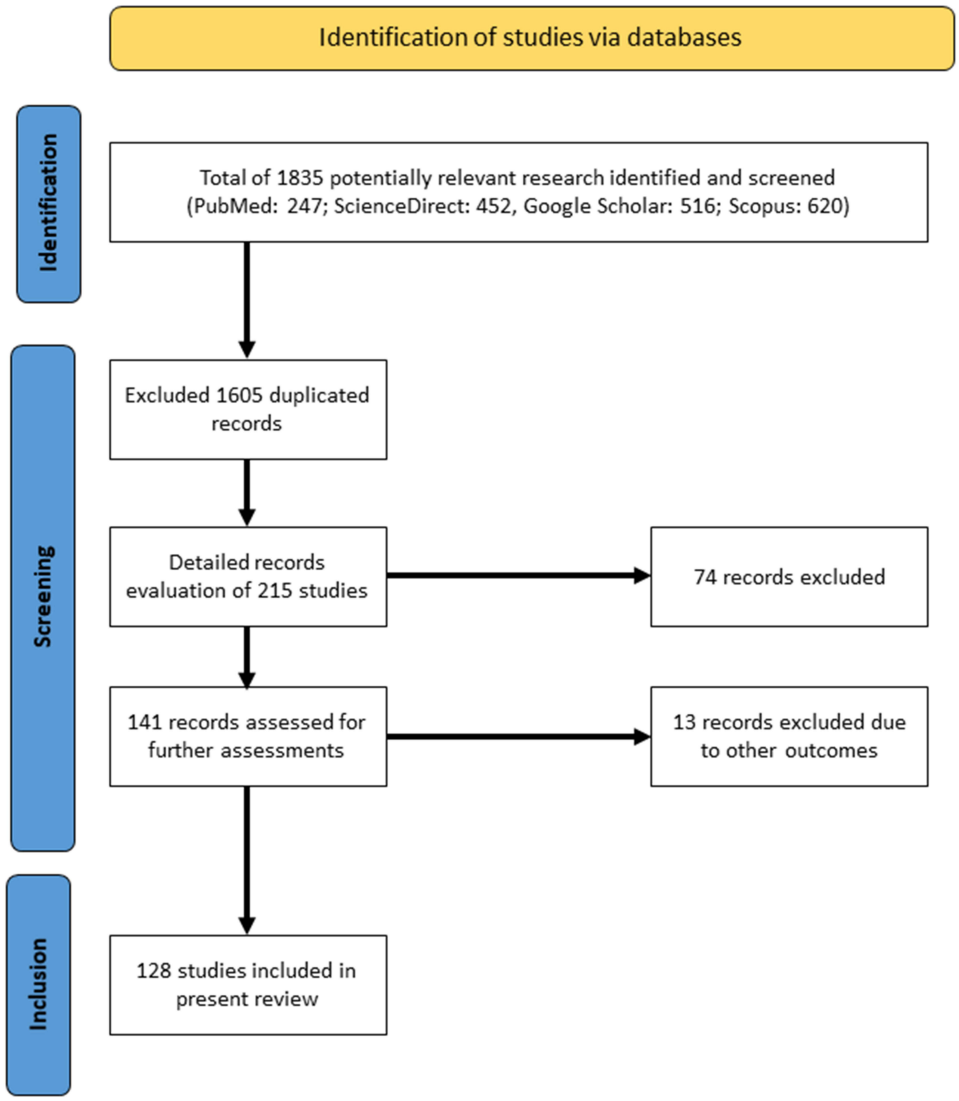

Figure 2 Flow chart of the identification and screening of the studies included in this review.

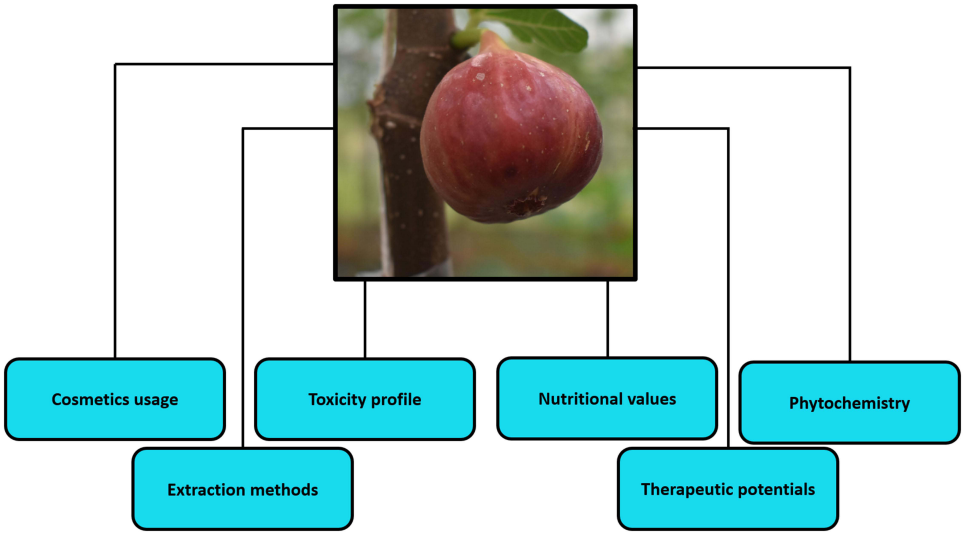

Figure 3 Key properties and findings on *F. carica* included in this review.

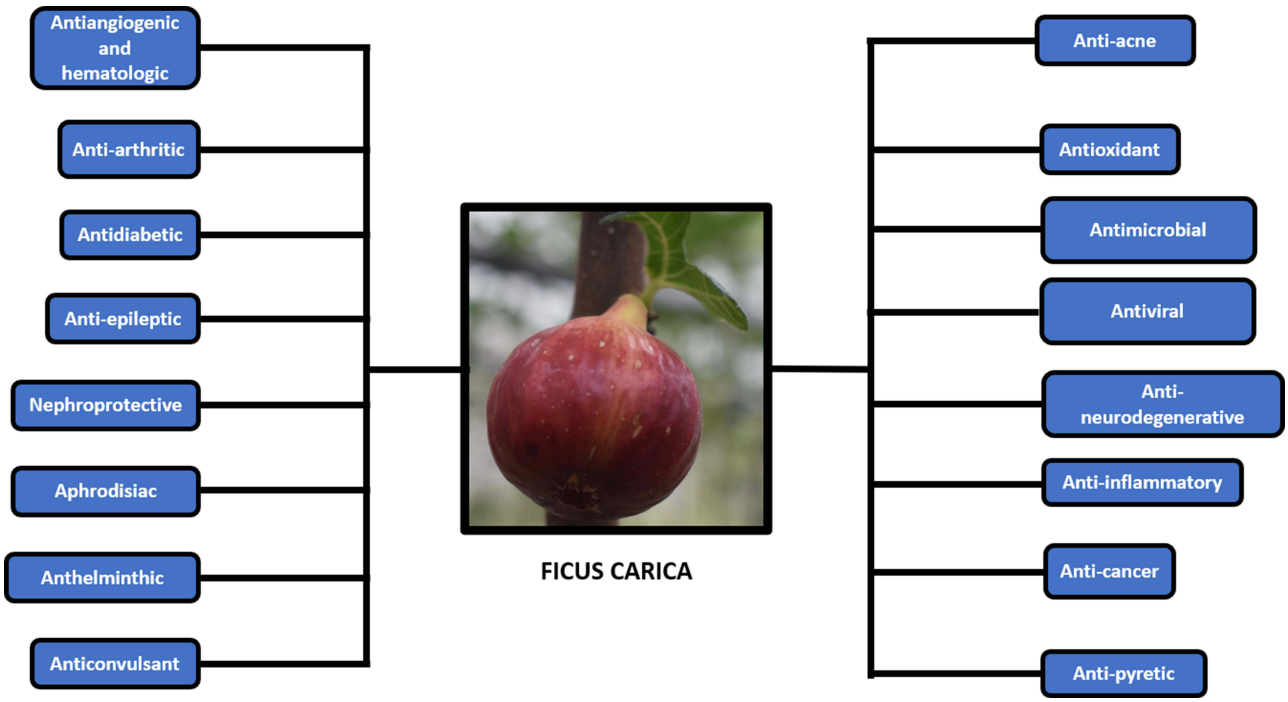

Figure 4 Potential therapeutic and pharmacological properties of *F. carica*.

Secondary metabolites can be further classified based on their chemical structures and functional groups, including polyphenols, terpenoids, alkaloids, phytosterols, and organosulfur compounds as shown in Figure 5.[25]

In contrast to primary metabolites, secondary metabolites have drawn increased attention owing to their remarkable therapeutic properties, such as antioxidant,[26] antimicrobial,[27–29] anti-cancer,[30,31] and hepatoprotective properties.[32,33] Recently, secondary metabolites have been widely used as valuable compounds in the pharmaceutical, cosmetic, fine chemical, and nutraceutical industries, with potential health benefits.[34]

Flavonoids are present in nearly all plant tissues, including *F. carica*.[35] Numerous studies have shown that flavonoids have multiple beneficial attributes, including antioxidant, anti-cancer, antimicrobial, anti-inflammatory, neuroprotective, and anti-fungal activities.[6] Flavonoids typically feature a basic structure consisting of a 15-carbon skeleton with two phenyl rings and a heterocyclic ring.[36] Flavonoids are further divided into subclasses based on their heterocyclic ring oxidation and substitutes.[36] Figure 6 shows the sub-classes of flavonoids which have been found in *F. carica*, which are flavones, anthocyanidins, flavan-3-ols, isoflavones, and flavonols.[36–41] The phytochemical analysis of *F. carica* has led to the isolation of several classes of compounds and metabolites from various parts of the plant, and studied for their biological properties as listed in Table 1.

Nutritional Values of F. carica

F. carica was also found to possess various nutritional values. Table 2 highlights the nutritional composition of *F. carica* (50mg per serving) obtained from the United States Department of Agriculture (USDA) FoodData Central.[51] In the most recent publication, it was reported that *F. carica* fruit is rich in vitamins, nutrients, phytochemicals, and minerals, and low in fat and cholesterol.[6] Among the minerals, calcium (Ca) is the most abundant in fig seeds and leaves, while in fig fruits, potassium (K) is found the most concentrated.[6] Other minerals such as magnesium (Mg), sodium (Na), and phosphorus (P). Zinc (Zn), manganese (Mn), copper (Cu), and iron (Fe) are also present in varying amounts.[6,51]

Therapeutic Potential of F. carica

F. carica has been reported to possess a diverse array of pharmacological properties. Many parts of this plant such as the leaves and roots are used to treat various conditions, such as gastrointestinal (colic, indigestion, loss of appetite, and diarrhea), respiratory (sore throat, cough, and bronchial problems), inflammatory, and cardiovascular disorders, as well as

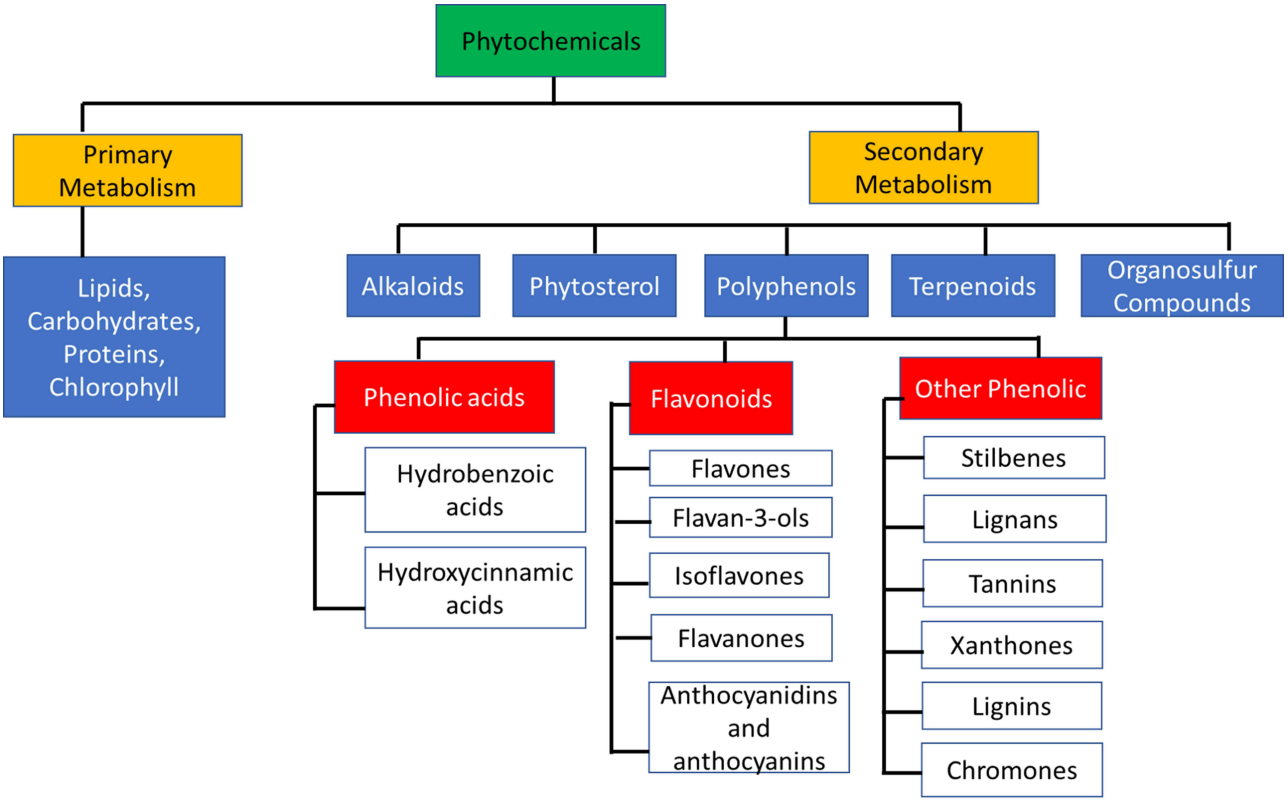

Figure 5 Classification of known phytochemicals of *F. carica*.

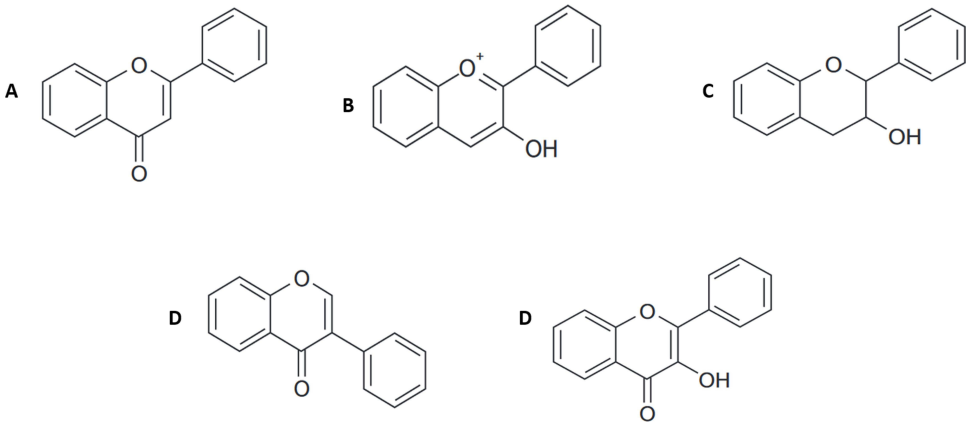

Figure 6 The flavonoids which have been found to be contained in *F. carica*. (**A**) flavones; (**B**) anthocyanidins; (**C**) flavan-3-ols; (**D**) isoflavones; (**E**) flavonols.

antispasmodic.[52] Studies using both in vitro and in vivo models have identified numerous other biological properties such as antioxidant, antimicrobial, anti-neurodegenerative, anti-arthritic, anti-cancer, anti-diabetic and many more.[52–57]

Antioxidant Properties

Benmaghnia et al reported that dried *F. carica* has high antioxidant properties owing to the presence of phenolic compounds, flavonoids, and tannins.[23] As previous studies have suggested that cell death rates can be lowered by the scavenging effects of natural antioxidants,[58,59] various researches have been conducted on numerous natural compounds, particularly those with high phenolic content. Multiple pre-clinical studies have reported that *F. carica* possess good antioxidant properties.[54,57,60] Phenolic compounds are common secondary metabolites that play a role as antioxidative

Table 1 Phytochemical Studies Conducted on F. Carica

Reference	Plant Part	Compound	Class	Biological Properties
Ivanov et al 2018[26]	Leaf	• Palmitic acid, stearic acid, α-linolenic acid, linoleic acid • Acyclic diterpene alcohol phytol • β-sitosterol, stigmasterol, germanicol, lanosterol • α-Amyrin, β-amyrin and lupeol	• Fatty acids • Fatty alcohols • Phytosterol • Triterpene • Alkenes	• Co-emulsifiers • Emollients • Antioxidant • Antimicrobial • Anti-inflammatory
Wojdyło et al 2016[40]	Leaf	• Not evaluated	• Polyphenols • Alkaloids • Flavonoids • Saponins • Cumarins • Anthocyanins • Terpenoids	• Antioxidants
Zhao et al 2021[42]	Leaf	• Quercetin 3-O-hexobioside-7-O-hexoside, • 2-carboxyl-1,4-naphthohydroquinone-4-O-hexoside, • Luteolin 6-C-hexoside, • 8-C-pentoside, • Kaempferol 6-C-hexoside-8-C-hexoside, • Quercetin6-C-hexobioside, • Kaempferol 6-C-hexoside-8-C-hexoside, • Apigenin 2″-O-pentoside, • Apigenin 6-C-hexoside, • Quercetin 3-O-hexoside, • Kaempferol 3-O-hexobioside.	• Polyphenol (flavonoids)	Not evaluated
Liu et al 1029[43]	Fruit	• Ficucaricone	• (Polyphenol) Prenylated isoflavone	• Antiproliferative • Anti-Inflammatory
Jain et al 2013[44]	Root	• 5-(1',1'-dimethylallyl)-8-methyl psoralen, 2'-O-acetyl oxypeucedanin hydrate-3'-methyl ether (furanocou-marins)	• Polyphenols • Triterpenoids • Steroid	Not evaluated
Oliveira et al 2010[45]	Latex	• β-sitosterol, lupeol, lanosterol, lupeol acetate, beta-amyrin, beta sitosterol, alpha-amyrin • Myristic, pentadecanoic, heptadecanoic, cis-10-heptadecenoic, linoleic, arachidic, heneicosanoic, behenic, tricosanoic, and lignoceric acid, Palmitic acid • Glycine, glutamine, Cysteine, tyrosine, tryptophan, phenylalanine	• Phytosterols • Fatty acids • Amino acid	• Anticarcinogenic • Antimicrobial • Neurotransmitters
Oliveira et al 2009[46]	Leaf, pulp, peel	• 3-O- and 5-O-caffeoylquinic acids, • Ferulic acid, • Quercetin-3-O-glucoside, • Quercetin-3-O-rutinoside, • Psoralen, • Bergapten • Organic acids (oxalic, citric, malic, shikimic, and fumaric acids) • Quinic acid	• Phenolic acids	• Antioxidant
Liu et al 2011[47]	Leaf	• Coumarin	• Phenolic acids	• Nematicidal activity
Saeed & Sabir 2002[48]	Leaf	• Bauerenol, • Lupeol acetate, • Methyl maslinate, • Oleanolic acid	• Triterpenoids	• Irritant potential
Raafat & Wurglics 2019[49]	Stem bark	• Oligosaccharide (alpha-d-glucopyranoside)	• Polyphenol (lignin)	• Anticonvulsant
Odo et al 2016[50]	Leaf	• Not evaluated	• Alkaloid • Flavonoid, • Tannins, • Cardiac glycosides, • Steroids, • Saponins	• Hepatoprotective

Table 2 Nutritional Composition of F. Carica Based on 50g per-Serving

Composition	Amount
Water	39.6g
Energy	37Kcal
	155kJ
Protein	0.375g
Total lipid (fat)	0.15g
Fiber	1.45g
Total Sugars	8.15g
Vitamin C (total ascorbic acid)	1mg
Vitamin B-6	0.057mg
Vitamin A	3.5µg
Vitamin E (alpha-tocopherol)	0.055mg
Vitamin K (phylloquinone)	2.35µg
Selenium	0.1µg
Manganese, Mn	0.064mg
Potassium, K	116mg
Calcium, Ca	17.5mg
Magnesium, Mg	8.5mg
Iron, Fe	0.185mg
Phosphorus, P	7mg
Zinc, Zn	0.075mg
Copper, Cu	0.035mg
Sodium, Na	0.5mg
Thiamin	0.03mg
Riboflavin	0.025mg
Niacin	0.2mg
Folate	3µg
Choline	2.35mg
Carotene, beta	42.5µg

Note: Agriculture Research Service, US Department of Agriculture (USDA), FoodData Central.[51]

agent by donating a hydrogen atom or electron to other compounds, thus scavenging free radicals, and quenching singlet oxygen.[61]

In a previous study using high-performance liquid chromatography (HPLC), the phenolic content of F. latex extract was found to be predominantly chlorogenic (59%), followed by rutin (20%), catechin, protocatechuic acid (both 8%),

caffeic acid (3%), vanillic acid, and sinapic acid (both 1%).[54] Calculating the total phenolic content as gallic acid equivalents (GAE) per gram of the dry plant material, and total flavonoid content as catechin equivalent (CE) per gram, the total phenolic and flavonoid content determined in the study were 50.2GAE/g and 12.5CE/g latex, respectively.[54] However, using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay to evaluate antioxidant properties reported slightly lower antioxidant activities of the F. latex extract with 13.6µg/mL compared to *Ficus sycomorus* (7.0µg/mL) and *Euphorbia tirucalli* (6.0µg/mL) methanolic latex extracts.[54] Mahmoudi et al also evaluated the antioxidant properties of *F. carica* leaf extract using DPPH assay from ten varieties of Algerian *F. carica* trees, including Onk Elhamam, Chatwi, Bidha, Bither, and Zarrouk.[60] They found that antioxidant capacity in *F. carica* leaves was significantly correlated with phenolic content (r=0.748).[60] A previous study extracted the phenolic compounds from *F. carica* using the Soxhlet method, followed by analysis using the Folin–Ciocalteu colorimetric method.[62] It was found that the Chatwi extract had the lowest IC_{50} value among all other types of extracts with 659.97±0.92mg/mL indicating the highest free radical scavenging activity.[62]

An in vitro analysis evaluating the antioxidant properties of *F. carica* and *Ginkgo biloba* using DPPH assay revealed that both extracts demonstrated good antioxidant effects as the concentration increased, whereby the IC_{50} value of *F. carica* (203.8µg/mL) was slightly higher compared to *Ginkgo biloba* (183.7µg/mL).[57] However, at the same concentration of 250µg/mL, both extracts showed a similar percentage of antioxidant activities with 71.2% and 72.7% for *F. carica* and *Ginkgo biloba*, respectively.[57] In a study assessing the potential of *F. Carica* leaves, fruits, and pulps, it was revealed that *F. carica* leaves methanolic extract exerted the highest DPPH inhibition effect, indicating high antioxidant potential owing to their high phenolic content.[49]

Anti-Neurodegenerative Properties

Due to the largely irreversible nature of neurodegenerative disorders, it has become a challenge for scientists around the world to find alternatives for treatment of related diseases. Current treatments may also cause adverse effects that can be harmful to patients, especially when neurodegenerative diseases mostly affect older people. Neurodegenerative disorders are often related to oxidative stress as the main contributing factor.[63] Recent researches on *F. carica* exposing its high levels of antioxidants due to its phytochemical composition has paved the way for the studies of its use as treatments for neurodegenerative diseases which is highly associated with oxidative stress. Hence, multiple *F. carica* studies have been conducted to assess its effects as a neuroprotective agent owing to its antioxidative properties.[64,65]

In addition, *F. carica* has been shown to demonstrate cholinesterase inhibitory activity. These inhibitory effects are not only focused on the neuroprotection in Alzheimer's disease, but they extend to the therapy of glaucoma, myasthenia gravis, and treatment of intellectual disabilities such as Down's syndrome due to their cholinergic action.[64] The study revealed that n-hexane and acetone extracts of *F. carica* exerted a notable inhibition activities against acetylcholinesterase (AChE) at 62.9±0.9% and 50.8±2.1%, respectively, and butyrylcholinesterase (BChE) at 76.9±2.2% and 45.6±1.3%, respectively.[64] Previous studies that looked into the effects of *F. carica* on Alzheimer's disease and other conditions related to neurodegenerative disorders are listed in Table 3.

Antiepileptic and Anticonvulsant Properties

Epilepsy is a central nervous system disorder in which brain activities become abnormal.[70] Although studies on the direct activity of *F. carica* extraction in epilepsy cases are still limited, studies are worthwhile because of its properties that can act as a skeletal muscle relaxant and anxiolytic action on the central nervous system.[71] Bhanushali et al suggested that *F. carica* can be a potential alternative for treating anxiety and epilepsy by modulating norepinephrine and 5-hydroxytryptamine in the brain.[72] Essa et al observed that *F. carica* extract significantly reduced neuroinflammation by reducing the activities of inflammatory cytokines interleukin (IL)-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, tumor necrosis factor (TNF)-α, and Eotaxin in APPsw/Tg2576 mice.[73]

A study by Bhanushali et al reported the effect of aerial parts of *F. carica* aqueous acetonic extract on the central nervous system (CNS) in mice.[71] In the study, *F. carica* concentrations of 250mg/kg and 500mg/kg reduced sleep latency and increased ketamine-induced sleeping time, similar to conventional drug, diazepam (0.5mg/kg), indicating its

Table 3 Studies on the Therapeutic Potential of F. Carica for Conditions Related to Neurodegenerative Disorders

Reference	Type of Study	Results
Ergül et al 2019[13]	Methanolic and aqueous extract of *F. carica* leaves	Inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activities which are enzymes related to Alzheimer's disease (AD)
Essa et al 2015[62]	*F. carica* fruit supplementation on transgenic mice of AD model	Reduced levels of Aβ1-40 and Aβ1-42 in both cortex and hippocampus brain region of mice
Oliveira et al 2010[66]	Latex extraction from immature *F. carica* fruit	Latex extract shows improved AChE inhibition compared to leaves, peel and pulp extract
Subash et al 2016[67]	*F. carica* fruit supplementation on transgenic mice of AD model	Improved spatial memory, learning ability and motor coordination, as well as reduced anxiety in the rats
Alharthy & Bawazir 2019[68]	Mixture of *F. carica* and olive oil on scopolamine-induced AD model	Reduced AChE, and improve spatial learning and memory function
Abdillah & Prakoso 2018[69]	*F. carica* ethanolic extract effects on advanced glycation end products (AGEs)	Medium strength in AGEs Inhibition when compared to quercetin

sedative-hypnotic properties.[71] Various tests to evaluate *F. carica's* muscle relaxant and anxiolytic properties such as motor coordination Rotarod test, Elevated-plus maze test, and Staircase test revealed that the effects of both doses of *F. carica* (250mg/kg and 500mg/kg) were similar to that of diazepam (0.5mg/kg).[71] Utilizing mouse seizure models, the same study also demonstrated that *F. carica* extract at both doses suppressed clonic seizures induced by Pentylenetetrazole and tonic seizures induced by maximal electroshock.[71] These findings provided evidences of *F. carica* as antiepileptic, sedative-hypnotic, skeletal muscle relaxant and anxiolytic drug to improve CNS disorders.

A previous study by Raafat and Wurglics reported that the *F. carica* stem bark ethanolic extract and its most active fraction, the oligosaccharide-rich fraction (OFG) possessed anticonvulsant activity with a good safety margin.[74] In the study, both *F. carica* extract and OFG suppressed convulsion induced by strychnine, and protected the experimental animals from strychnine-lethality.[74,75]

Antimicrobial Properties

Flavonoids, tannins, and terpenoids in *F. carica* leaf extract have been proven to possess antibacterial properties, as reported by Nirwana et al who showed no bacterial growth at 50% *F. carica* extract concentration.[76] Benmaghnia et al also revealed that dried *F. carica* possessed antimicrobial activities against various bacteria such as *Bacillus subtilis, Clostridium perfringens, Vibrio cholera, Escherichia coli*, and *Proteus mirabilis*, demonstrating a large inhibition zone when compared with gentamicin.[23]

Utilizing two antimicrobial assays, a disc diffusion and macrodilution assays, Mahmoudi et al tested ten varieties of *F. carica* leaf extract and reported the effects of its phenolic compounds on both Gram-negative and Gram-positive bacteria.[60] In another study, *Staphylococcus aureus* and *Bacillus cereus,* which are foodborne pathogens, were found to be sensitive to the extracts, and reported moderate anti-fungal activity.[77] In addition, Gram-positive bacteria revealed to be more susceptible to inhibition by *F. carica* leaf extract than Gram-negative with 15.4±0.6mm and 11.3±0.2mm, respectively.[77] Using a macrodilution assay to evaluate the minimal inhibitory concentration (MIC) and minimal lethal concentration (MLC) of the *F. carica* extracts, *B. cereus* was found to be the most susceptible to the extracts with 2.19mg/mL and 4.38mg/mL of extracts concentration for MIC and MLC, respectively.[60] This finding shows that lower concentrations of *F. carica* leaf extract (Dhokkar variety) were able to inhibit and kill the tested bacteria.[60]

Another study by Souhila et al reported the antimicrobial properties of the methanolic extract of dried *F. carica* fruit (Sidi Bendjebbar variety) on one of the urinary tract infectious agents, *Enterobacter cloacae*.[53] Using the paper disk method to measure the zone of inhibition against *E. cloacae*, the methanolic extract of this plant produced 17mm

inhibition zones when compared to ampicillin and aqueous extract, both with 15mm inhibition zones indicating the extract's potential to treat urinary tract infection.[53]

Antiviral Properties

The activity of F. Latex against *Herpes simplex virus* type 2 (HSV-2) was confirmed by significantly decreasing the number of viral copies in the HSV-2 culture medium.[78] Interestingly, F. Latex produced a positive synergistic effect when combined with standard drug, acyclovir, producing a stronger effect on HSV-2 than acyclovir alone.[78] F. latex from the Tunisian Jrani caprifig variety has also been reported to possess antiviral properties, postulated to be attributed to its high level of Triterpenes.[13,27,79] Their mode of action against HSV-1, *Echovirus*-11 (ECV-11), and *Adenovirus* influenza virus (ADV) were discovered to be at all stages of multiplication, hence is a potential application for treatment of those virus infections.[27] *F. carica* and F. Latex have also been reported to reduce viral titers in an in vitro study and were able to interfere with *Caprine Herpesvirus* type 1 (CpHV-1) replication.[13,72,80]

F. carica L and F. Latex have long been documented for their strong therapeutic effects and antiviral properties, and produce no cytotoxicity in Vero cells.[57,81,82] The study by Antonopoulou et al reported that the aqueous extract, hexanic and hexane-ethyl acetate from the latex of *F. carica* have been shown to be effective antivirals against HSV-1, ECV-11, and ADV.[83] It was shown that the viruses were inhibited when the extracts were incubated with infected cells as well as when they were incubated prior to virus contacts with the cells.[83] The study also documented that *F. carica* extracts could inhibit viral DNA for HSV-1 and ADV and RNA replication for ECV-11, as well as demonstrating virucidal action.[83] Mawa et al reported that the water extract of *F. carica* leaves exhibited the ability to directly kill HSV and exert low levels of toxicity.[84] Ali et al reported a total of 21 active compounds in F. Latex, where the compounds lupeol, α-amyrin, and luteolin showed the highest binding affinities and intense interactions with the SARS-CoV-2 vital catalytic residues His 41 and Cys 145.[85] Molecular dynamics simulation revealed that amyrin was the most stable compound with higher binding free energy, suggesting that this compound can compete with the native ligands of the SARS-CoV-2 main protease inhibitor in mediating viral replications and transcriptions.[85]

An in vitro study by Camero et al reported that F. Latex reduced the viral titers produced by CpHV-1-infected Madin-Darby bovine kidney (MDBK) cells by interfering with the replication of CpHV-1.[80] A recent report by Sieniawska et al which compiled a wide range of antiviral properties from different species of *Ficus* as shown in Table 4, reported that F. latex inhibited caprine herpes virus-1 (CpHV-1) replication in MDBK cells, as well as HHV-1, ECV-11 and ADV replication in Vero cells.[86]

Anti-Inflammatory and Anti-Arthritic Properties

The effects of *F. carica* against inflammation-induced injuries have been reported in several studies. Eteraf-Oskouei et al investigated the anti-inflammatory mechanisms of *F. carica* leaf methanolic extract compared with diclofenac and

Table 4 Various Ficus Species and Its Potential Antiviral Properties

Types of Ficus Species	Antiviral Properties
F. carica	The latex inhibited caprine herpes virus-1 (CpHV-1) replication in MDBK cells, as well as HHV-1, ECV-11 and ADV replication in Vero cells.
F. benjamina	Ethanolic extracts from leaves inhibited human herpes virus type 1 (HHV-1, HSV-1) and type 2 (HHV-2, HSV-2), and varicella-zoster virus (HHV-3, VZV), while fruit extracts were active only against HHV-3.
F. septica	Leaf methanol extraction able to impede dengue virus (DENV) replication in various infected cell types.
F. religiosa	The bark extracts showed activity against human rhinovirus (HRV) and human respiratory syncytial virus (RSV) and HHV-2.
F. fistulosa	Ethanol extract from leaves demonstrated anti-HIV activity.
F. sur	The leaves methanolic extract showed noticeable yet limited antiviral activity against HHV-1, diminished cytopathic effect (CPE) development and reduced the virus titer. The stem bark infusion and methanolic extract showed antineoplastic activity against cervical adenocarcinoma and colon cancer cell lines.

Note: Data from Sieniawska et al.[86]

dexamethasone.[87] In the study, the highest dose of *F. carica* leaf methanolic extract (50mg/pouch) led to a significant inhibition of WBC with 76.5% rate.[87] As the dosage of the extract increased, the exudate volume decreased significantly, and these effects were found to be similar when using diclofenac (1.0mg/kg) and dexamethasone (0.4mg/kg).[87] In addition, the highest extract dose of 50mg/pouch resulted in the highest reduction in granulomatous tissue weight when compared to the other doses (5 and 25mg/pouch), and was similar to diclofenac.[87] It was postulated that the mechanism underlying the anti-inflammatory properties of *F. carica* leaf extract was through the downregulation of tumour necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF) and pro-inflammatory prostaglandin E2 (PGE2) which are important cytokine mediators involved in the angiogenesis of inflammation.[87]

A study on paracetamol-induced acute hepatitis found that *F. carica* leaf extract could significantly reduce the levels of aspartate transaminase (SGOT) and alanine transaminase (SGPT) compared to the controls.[55]

A phytochemical analysis of *F. carica* leaves observed a potent anti-arthritic activity based on in vitro inhibition using a protein denaturation method.[52] Notably, it was found that several secondary metabolites, such as steroids, triterpenoids, alkaloids, and flavonoids, were responsible for these properties.[52] An increase concentration of the extract resulted in increased percentage inhibition of protein denaturation suggesting a protective mechanism.[52] Another study by Bahadori et al revealed that lupeol, a dietary triterpene found in *F. carica* also demonstrated anti-arthritic properties, although the mechanism is yet to be fully elucidated.[56]

Anti-Hyperlipidemic Properties

An earlier study on the benefit of *F. carica* as a lipid-lowering agent was performed by Pérez et al in 1999.[88] The study utilized a hypertriglyceridemia rat model by allowing the animal free access to 20% of long-chain triglyceride (LCT) emulsion without supplying other food for 2 hours after a fasting period of 22 hours.[88] Acute intraperitoneal administration of *F. carica* leaf decoction (5000mg/kg) resulted in a significant reduction in plasma triglyceride (TG) levels at 60 and 90min post-treatment.[88] In another study, acute administration of *F. carica* leaf aqueous extract (aqueous fraction that remained in the petroleum ether-treated total extract) at various dosages of 10, 50, and 250g/kg, lowered total cholesterol (TC) levels in the serum and liver of hyperlipidemic-induced rats.[89] Phytochemical screening from the same study showed that the *F. carica* leaf extract had a small amount of alkaloids, moderate level of flavonoids, and a large amount of tannins that may contribute to the acute in vivo anti-hyperlipidemic effects.[89]

Administration of *F. carica* leaves and twigs extracts with the dosage of 150 and 300mg/kg in hyperlipidemia-induced mice with a single intravenous injection of Triton WR 1339 (300mg/kg body weight) resulted in a significant decrease of serum TG, TC, low-density lipoprotein (LDL-C) and very low density lipoprotein (VLDL-C), while the high-density lipoprotein (HDL-C) was increased.[50] The study recorded the LD_{50} value of twigs and leaves extracts of *F. carica* greater than 5000mg/kg, while the phenolic and flavonoid content of *F. carica* leaves and twigs varied from 12.84 to 19.78mg gallic acid equivalents (GAE), and 5.02 to 9.72mg EQ/g dry matter, respectively.[50]

The protective effect of chronic administration of *F. carica* ranging from 3 to 12 weeks against hyperlipidemic and hypercholesterolemic animal models has been previously documented.[90–93] Supplementation of *F. carica* leaf extracts at doses of 50 and 100mg/kg for 6 weeks,[91] and 400mg/kg for 3 weeks[93] in high-fat diet (HFD) rats led to significant reductions in TG, interleukin-6 (IL-6), atherogenic index (AI), coronary risk index (CRI), TC, and LDL-C.

Similarly, there were significant reductions in the plasma levels of TC, TG, LDL-C, and AI after HFD-induced rats were supplemented with 400mg/kg of *F. carica* fruit extracts for 3 weeks[93] and 8 weeks.[90] These findings suggest that the hypolipidemic and hypocholesterolemic effects of the fruit extract may be due to the presence of flavonoids, especially apigenin 8-C-glucoside (vitexin) and quercetin-3-O- rutinoside (rutin).[90] Recently, Perveen et al demonstrated similar findings where supplementation with *F. carica* pulp extracts (1250mg/kg) for 12 weeks in HFD-induced rats resulted in a significant decrease in the plasma levels of TC, TG, LDL-C, HDL/LDL ratio and AI, with elevated HDL-C.[92] Studies on the effects of *F. carica* extracts as therapeutic agents against hyperlipidemia and hypercholesterolemia in rodents are summarized in Table 5.

Table 5 Effects of F. Carica Extracts on Hyperlipidemia and Hypercholesterolemia in Rodents

Study	Sample	Intervention Group	Duration	Outcome of FC Supplementation
Pérez et al 1999[78]	20 female Wistar rats (200–230g)	Grp 1 – LCT (purified soya oil (100g), purified egg phospholipids (6g), anhydrous glycerol (11g) Grp 2 – LCT + FC leaf decoction 5000mg/kg	24h fast, 2h LCT emulsion 20% ad libitum, Blood samples collected at 0, 60, 90mins and 24h post IP injection of FC	↓ TG at 60mins and 90mins post-treatment with FC
Rassouli et al 2010[79]	55 male Wistar rats (200–250g)	Grp 1 – Normal diet Grp 2 – HFD (cholesterol (1%), cholic acid (0.1%) and olive oil (2.5%)) Grp 3 – HFD + FC leaf methanol extract 2.5mg/kg Grp 4 – HFD + FC leaf methanol extract 5mg/kg Grp 5 – HFD + FC leaf methanol extract 10mg/kg Grp 6 – HFD + FC leaf aqueous extract A 10mg/kg Grp 7 – HFD + FC leaf aqueous extract A 50mg/kg Grp 8 – HFD + FC leaf aqueous extract A 250mg/kg Grp 9 – HFD + FC leaf aqueous extract B 10mg/kg Grp 10 – HFD + FC leaf aqueous extract B 50mg/kg Grp 11 – HFD + FC leaf aqueous extract B 250mg/kg	HFD – 12 days Extract IP – 14h	Extract A at dosage 10, 50 and 250mg/kg:↓ TC in serum Extract A at dosage 50 and 250mg/kg:↓ TC in liver
Boukhalfa et al 2018[80]	30 male Swiss albino mice (±26g)	Grp 1 – Normal diet Grp 2 – HL induced by Triton WR-1339 Grp 3 – HL + FC leaf extract 150mg/kg Grp 4 – HL + FC leaf extract 300mg/kg Grp 5 – HL + FC twig extract 150mg/kg Grp 6 – HL + FC twig extract 300mg/kg	24h	FC leaf and twig extracts: ↓ TG, TC, LDL-C, VLDL-C; ↑ HDL-C
Belguith-Hadriche et al 2016[72]	30 male Wistar rats (203±5g)	Grp 1 – Normal diet Grp 2 – HFD (normal diet supplemented with 1% cholesterol, 4% fat and 0.1% cholic acid) Grp 3 – HFD + FC fruit extract 400mg/kg	8 weeks	↑ HDL-C↓ TC, TG, LDL-C, AI
Joerin et al 2014[81]	50 male *Sprague-Dawley* rats (180–200g)	Grp 1 – Normal diet Grp 2 – HFD (TD 06414 Teklad Research Rodent Diet) Grp 3 – HFD + pioglitazone 30mg/kg Grp 4 – HFD + FC leaf extract 50mg/kg Grp 5 – HFD + FC leaf extract 100mg/kg	6 weeks	↑ HDL-C; ↓ TG, IL-6, AI, CRI; ↔ TC, LDL-C, adiponectin, leptin, glucose, insulin
Perveen et al 2021[82]	40 male *Sprague-Dawley* rats (130–170g)	Grp 1 – Normal diet Grp 2 – HFD (1g sodium cholate, 1.5g cholesterol and 8mL of coconut oil per 100g standard rat chow diet) Grp 3 – HFD + atorvastatin 30mg/kg Grp 4 – HFD + FC pulp extract 1250mg/kg	12 weeks	↑ HDL-C; ↓ TC, TG, LDL-C, HDL/LDL ratio, AI
Sukowati et al 2019[83]	32 male *Sprague-Dawley* rats (170–190g)	Grp 1 – Normal diet Grp 2 – HFD (normal diet supplemented with 30% fat, 55% carbohydrate, 12% protein, 2% cholesterol, 0.1% cholic acid) Grp 3 – HFD + FC fruit extract 400mg/kg Grp 4 – HFD + FC leaf extract 400mg/kg	10 weeks HFD – 7 weeks FC extract – 3 weeks	↓ TC, LDL-C

Abbreviations: Grp, group; IP, intraperitoneal; FC, *F. carica*; LCT, long-chain triglyceride; HFD, high-fat diet; HL, hyperlipidemia; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein; VLDL-C, very low-density lipoprotein; HDL-C, high-density lipoprotein; AI, atherogenic index; IL-6, interleukin-6; CRI, coronary risk index; ↑, increase; ↓, decrease.

Anti-Angiogenic Properties

Angiogenesis, the formation of new blood vessels from pre-existing vessels is involved in various processes, including embryonic vascular development, wound healing, tumour growth, and diabetic microvascularization.[94] Anti-angiogenic effects of *F. carica* has been suggested to be beneficial in the prevention of angiogenesis-related disorders, especially cancer.[95,96] In an in vitro anti-angiogenic study using a three-dimensional collagen matrix of human umbilical vein endothelial cell (HUVECs) capillary tube formation, different concentrations of F. latex extracts ranging from 50 to 200µg/mL were used.[96] The results showed that the extracts were able to inhibit angiogenesis in HUVECs tube formation model at the concentration of 100–200µg/mL.[96] A study by Ghambarali et al using the same model revealed that angiogenesis was significantly inhibited by *F. carica* leaf ethanolic extract at concentrations from 5 to 25µg/mL in

a concentration-dependent manner, with the ability to significantly decrease the mRNA expression of VEGF-A and integrin β3.[95]

In an in vitro study using the chorioallantoic membrane (CAM) of embryonated chicken eggs, administration of *F. carica* leaf aqueous extract at doses of 75, 90, and 110μg resulted in a significant inhibitions of blood vessels formation as well as marked reduction of VEGF expression in the vascular endothelial cells of the CAM.[97] The study reported that the optimal dose of *F. carica* leaf aqueous extract to inhibit angiogenesis by 65.5% and reduce VEGF expression by 45% was 90μg.[97]

In an in vivo study using a rat air pouch model of inflammation, Eteraf-Oskouei et al investigated the effects of *F. carica* leaf methanolic extract administered intraperitoneally on VEGF and angiogenesis of granulation tissue by measuring the hemoglobin content.[87] The findings demonstrated a significant decrease in hemoglobin and VEGF levels at *F. carica* concentrations of 5, 25, and 50mg/pouch, in a concentration-dependent manner.[87] The reduction in angiogenesis and VEGF by 50mg/pouch of *F. carica* leaf methanolic extract was similar to that of diclofenac sodium used as the positive control in the study.[87]

Hematologic Parameters

The benefit of *F. carica* extract as a blood-building agent has been shown in several animal studies.[98–100] An earlier study by Nebedum et al showed that supplementation with 200mg/kg ethanolic extract of *F. carica* leaves for 14 days in healthy albino rats of both sexes significantly increased the hemoglobin concentration, packed cell volume (PCV), and red blood cell (RBC) count.[99] The study also reported a significant decrease in the total white blood cell (WBC) count and percentage of neutrophils compared to those in the control group.[99] Similar findings were observed in a study that used a longer duration of 4 weeks to administer *F. carica* leaf aqueous extracts (100, 200, and 400mg/kg), where the effects were found to be concentration- and time-dependent.[100]

Furthermore, it was also demonstrated that *F. carica* fruit aqueous extract may provide a protective effect against irradiation-induced free radical injury in different hematological parameters.[98] Prior supplementation of *F. carica* fruit aqueous extract (1mL/day) at a ratio of 1:3 w:v for 3 weeks before a single dose of 8Gy whole-body gamma irradiation resulted in a significant increase of WBC, platelet, lymphocyte, and neutrophil counts along with no significant changes in RBC indices.[98] The presence of flavonoids, tannins, cardiac glycosides, steroids, and saponins, with flavonoid and tannins in high and moderate abundance were postulated to contribute to the effects of *F. carica* as a blood-building agent.[99,100]

Antidiabetic and Hypoglycemic Properties

A study revealed that the use of *F. carica* in every day diet is beneficial for lowering sugar levels and can potentially be used as antidiabetic therapy.[40] Although the use of conventional drugs to treat diabetes is well defined and elaborated, the potential of remedies from various plants as complementary medicine have been widely been explored. For instance, the use of *F. carica* leaf ethanolic extract has been shown to reduce glucose levels in diabetic rats.[101] Another study reported that *F. Carica* extract administered to laboratory animals lowered body weight, serum glucose, cholesterol, TG, LDL-C and VLDL-C, as well as increase the protective effect of HDL-C dose independently.[102] A study also demonstrated that *F. carica* leaves have the ability to reduce glucose levels by increasing the serum levels of insulin, as well as tissue sensitivity to insulin, thus simultaneously facilitate carbohydrate metabolism.[49] Fig leaves, peel and pulp can be utilized as effective remedy to control abnormal carbohydrate metabolism associated with diabetes and hyperglycemia.[49]

Anti-Cancer and Cytotoxic Properties

Flavonoids from *F. carica* have been studied to exert anti-cancer activities in multiple ways, such as by promoting apoptosis, trigger the production of protective conjugate enzymes, suppress angiogenesis, release hydrogen atoms and electrons, prevent lipid peroxidation, and inhibit DNA oxidation.[15,103,104] According to Ghandehari et al, F. latex can reduce the number of mitotic abilities and the extent of apoptosis in breast cancer cells without affecting hematological or histological functions.[105] A study by Purnamasari et al, which evaluated the effects of *F. carica* leaf and fruit extracts treatment on Huh7it liver cancer cell line, reported that the percentage of apoptotic and necrotic cells increased with increasing concentrations of the extracts.[104] The highlight of the study is summarized in Table 6.

Table 6 Percentage of Huh7it Cells That Undergo Apoptosis and Necrosis in Response to Different Concentrations of F. Carica Treatments

Group	Total Apoptosis (%)		Total Necrosis (%)	
	Leaves	Fruits	Leaves	Fruits
Normal control	0.14	0.23	1.87	3.02
Positive control	65.30	65.68	34.39	34.10
400 µg/mL extracts	1.36	0.50	9.94	2.05
600 µg/mL extracts	2.96	0.18	33.06	2.05
800 µg/mL extracts	4.73	0.23	39.37	1.85
1000 µg/mL extracts	5.37	0.44	47.66	2.26

Note: Adapted from Purnamasari R, Winarni D, Permanasari AA, et al. Anticancer Activity of methanol extract of ficus carica leaves and fruits against proliferation, apoptosis, and necrosis in Huh7it cells. *Cancer Inform*. 2019;18:1176935119842576. Creative Commons.[104]

In another study, Ghanbari et al revealed that F. latex can reduce the proliferation of cervical cancer cells via the overexpression of tumour suppressor proteins p53 and pRb, which was likely a result of the low production of human papillomavirus (HPV) oncoproteins E6 and E7.[15] Increased p53 gene activity, which in turn stimulates p21 transcription factors, can cause cyclin-dependent kinase 2 (CDK2) to interact with cyclin E and halt the cell cycle.[104] CDK2 is a serine/threonine protein kinase that plays an important role in the G1/S phase, the initiation of DNA synthesis, and the regulation of the S phase.[106] In addition, studies have shown that flavonoids present in *F. carica*, such as quercetin, can interrupt cell cycle phases such as the G0/G1 phase, S phase, and G2/M phase in different cancer types.[107–109]

A study on molecular docking by Gurung et al demonstrated that the ß-bourbonene compound identified in *F. carica* can act as an anti-cancer candidate molecule against specific macromolecular receptors, namely three targets: topoisomerase-I, topoisomerase-II, and VEGFR-2.[110] Different concentrations of ß-bourbonene inhibited the growth of PC-3M prostate cancer cell line in a dose-dependent manner.[110] In addition, stem bark infusion and methanolic extract of *F. carica* showed antineoplastic activity against cervical adenocarcinoma and colon cancer cell lines.[86]

AlGhalban et al demonstrated that varying concentrations of F. latex were toxic to MDA-MB-231 breast cancer cell line, with anti-proliferative and anti-metastatic activities, as well as substantial effects on cell shape.[16] A study by Jeivad et al examined the cytotoxicity effects of F. latex in HepG2 liver cancer cell and NIH fibroblast cell lines, and found that *F. carica* was 3.4 times more cytotoxic to the HepG2 cells compared to NIH cell lines, with IC_{50} values of 0.219 and 0.748mg/mL, respectively.[111] Another study by Jasmine et al revealed a substantial variation in cell viability (%) of MCF-7 breast cancer cell line based on the concentration of *F. carica* fruit extracts used.[112] The cell viabilities decreased as the *F. carica* extracts concentration increased as summarized in Table 7.[112]

Antimutagenic Properties

A study by Agabeĭli and Kasimova demonstrated that *F. Carica* extract reduced the level of mutagenicity in rat marrow cells induced by sodium fluoride (NaF).[113] Lightburn and Thomas showed that *F. carica* leaf extract suppressed spontaneous DNA damage and enhanced DNA repair in diethylstilbestrol (DES)-Induced DNA strand breaks in MCF10A breast cells, suggesting that it has anti-carcinogenic and anti-cancer effects in the early stages of breast cancer.[114] Cytogenetic studies performed by Fahmy et al evaluating the genetic endpoints such as micronuclei in polychromatic erythrocytes and chromosomal aberrations in the bone marrow, as well as expression of liver genes, namely, TNF-α, iNOS and NF-kB, all yielded favourable findings by *F. carica* in alleviating cisplatin-mediated mutagenic changes.[115]

Table 7 The Cell Viability of MCF-7 Cells Exposed with Different Concentrations of F. Carica Fruit Extracts and Different Time Exposure

F. carica Fruit Extract Concentration (µg/mL)	MCF-7 Cell Viability (%)		
	24H	48H	72H
1000	14.28	11.11	9.52
500	23.80	19.04	17.46
250	34.92	28.57	28.57
125	42.85	38.09	36.50
62.5	50.79	46.03	44.44
31.2	58.73	49.20	52.38
15.6	69.84	60.31	63.49
7.8	84.12	73.01	68.25
Control	100	100	100

Note: Adapted from Jasmine R, Manikandan K, Karthikeyan K. Evaluating the antioxidant and anticancer property of Ficus carica fruits. *Afr J Biotechnol*. 2015;14:634–641. Creative Commons.[112]

Abbreviations: Anti-HSV-1, anti-*Herpes simplex virus* type 1; *F. carica, Ficus carica*; F. Latex, *F. carica* latex; *F. carica* L, *F. carica* Linn; FD, *Ficus dubia*; AChE, acetylcholinesterase; BChE, butyrylcholinesterase; FSLE, *Ficus sycomorus*; ETLE, *Euphorbia tirucalli*; BHT, butylhydroxytoluene; DPPH, 1.1-diphenyl-2-picrylhydrazyl; MIC, minimal inhibitory concentration; MLC, minimal lethal concentration; HSV-2, *Herpes simplex virus* type 2; ECV-11, *Echovirus*-11; ADV, *Adenovirus* influenza virus; CpHV-1, *Caprine Herpesvirus* type 1; MDBK, Madin-Darby bovine kidney; CPE, cytopathic effect; WBC, white blood cells; TNF-α, necrosis factor-alpha; VEGF, vascular endothelial growth factor; PGE2, proinflammatory prostaglandin E2; SGOT, aspartate transaminase; SGPT, alanine transaminase; CNS, central nervous system; OFG, oligosaccharide-rich fraction; ICV, intracerebroventricular-administration; LCT, long-chain triglyceride; TG, triglyceride; TC, total cholesterol; GAE, gallic acid equivalents; LDL-C, low density lipoprotein; HDL-C, high density lipoprotein; HFD, high fat diet; vitexin, apigenin 8-C-glucoside; rutin, quercetin-3-O- rutinoside; HUVECs, human umbilical vein endothelial cells; VEGF-A, vascular endothelial growth factor A; CAM, chorioallantoic membrane; PCV, packed cell volume; RBC, red blood cell; WBC, white blood cell; HPV, human papilloma virus; CDK2, cyclin-dependent kinase 2; PC-3M, prostate cancer cells; MCF-7, breast cancer cells; MNNG, N-methyl-N'-nitro-N-nitrozoguanidin; DES, Diethylstilbestrol; FcHEx, the *Ficus carica* cell suspension culture extract; IL-1α, interleukin 1-alpha; SRD5A2, 5 alpha-reductase type II; 8-MOP, 8-methoxypsoralen. HHV-1, human herpes virus type 1; HSV-1, human herpes virus type 1; HHV-1, human herpes virus type 2; HSV-2, human herpes virus type 2; HHV-3, varicella-zoster virus; VZV, varicella-zoster virus; HRV, human rhinovirus, RSV, human respiratory syncytial virus.

Cosmetic Applications of F. carica

Apart from its biological properties, *F. carica* has also been studied for potential cosmetic applications. A study by Khan et al claimed that *F. carica*-enriched plant extracts could be used to stimulate and enhance the rate of collagen biosynthesis and recover the hydration level of the dermis.[105] This phenomenon was postulated due to *F. carica's* high level of antioxidant properties such as vitamin C, anthocyanins, carotenoids and phenolic compounds.[116]

An in vitro psychological stress study in the skin keratinocytes revealed that *F. carica* cell suspension culture extract (FcHEx) decreased the levels of epinephrine, IL-6, lipid peroxide, and protein carbonylation, activated ceramide synthesis and ameliorated lipid barrier performance.[117] In the same study, an in vivo analysis demonstrated that the extract of the *F. carica* cell suspension cultures reduced transepidermal water loss, sebum production, desquamation, and

prevention of facial skin turning to pale colour from acute stress.[117] Findings of the study suggests the potential of *F. carica* to fight against the signs of psychological stress in the skin.

A previous study identified several phenolic compounds in the leaf extract of *F. carica* including fumaric acid, ferulic acid, p-coumaric acid, and malic acid which contributes to the cosmetic effects of the plant.[118] For instance, fumaric acid is a common compound used to treat psoriasis,[97] whereas ferulic acid has been shown to protect the skin against damage caused by ultraviolet (UV) irradiation.[119] Malic acid and p-coumaric acids have been shown to possess anti-hyperpigmentation effects, while polyphenols predominantly found *F. carica* are important in cosmetic product development.[120]

An in vitro study by Turkoglu et al demonstrated that the *F. carica* extract significantly downregulated VEGF, TNF-α, interleukin 1-alpha (IL-1α) and 5 alpha-reductase type II (SRD5A2) in human keratinocyte cells compared to the control, suggesting its possible molecular mechanism.[118] VEGF is mainly involved in altered angiogenesis, which is related to many pathological conditions, such as tumour growth, metastasis, atherosclerosis, psoriasis, and other skin diseases.[118] Therefore, the inhibition of angiogenesis through VEGF downregulation can stunt skin cancer cells. This phenomenon could occur indirectly by blocking the supply of nutrients and oxygen to the cells.[97] The TNF-α is synthesized in epidermal keratinocytes and plays a key role in the pathogenesis of hair follicle disease, alopecia areata.[121] Reports have also shown that TNF-α, IL-1α and 5 alpha-reductase type II SRD5A2 were involved in the pathogenesis of acne.[118] Hence, the use of *F. carica* leaf extract to downregulate these genes provide the cosmetic benefits related to skin care.

Toxicity of F. carica

Owing to their natural origin, phytochemicals from medicinal plants are generally considered safe for consumption. A study revealed that varying quantities of *F. Carica* extracts offered no threats to normal, healthy fibroblast cells, demonstrating the general quality of the extracts.[76] Nevertheless, several natural compounds found in commonly consumed plants can be toxic at high doses or in long-term consumption. As for *F. carica*, the studies on its toxicity are still limited. Among the various parts of the *F. carica* plant, dermal exposure to milky sap (latex) exuding from the cut branches, leaves, and skin of the fruits, may be of health concerns.[122] The sap constituents which are composed of various proteolytic enzymes (ficin, triterpenoids, protease, lipodiastase, and amylase) and furocoumarins possess irritant and pruritic properties that are thought to induce various clinical skin syndromes.[122] Many cases of inflammatory skin reactions (phytophotodermatitis) have been reported as a result of external contact with F. latex, primarily leaf and shoot latex.[122] Pain, itching, redness, swelling, and occasionally blister development are the most common symptoms of F. latex-induced phytophotodermatitis.[123] Two natural furocoumarin compounds [5-methoxypsoralen and 8-methoxypsoralen (8-MOP)] in *F. carica* were reported to be responsible for the development of phytophotodermatitis, where furocoumarin binds to DNA upon contact, inducing DNA crosslinking, which prevents cell division, DNA repair, and DNA synthesis, ultimately leading to cell death.[124] This phenomenon occurs mostly in the epidermal DNA, resulting in vesicle production and blistering.[124]

In a reproductive toxicity study, Makoolati et al demonstrated that *F. Carica* had no harmful effects on spermatogonial stem cells and enhanced their viability and proliferation.[125]

Future Direction

In recent years, numerous studies on *F. carica* have focused on its nutraceutical and pharmacological potential. A vast array of pre-clinical studies, in vitro and in vivo experiments have been conducted. However, clinical trials and human studies involving *F. carica* supplementation or intervention are still lacking; hence, more well-designed, randomized control trials are crucial to gather sufficient data and valid evidence for its efficacy and safety in human. This will further validate the nutraceutical potential of *F. carica*, in particular on cancer, neurodegenerative diseases, inflammation, and oxidative stress-related conditions.

It would also be beneficial to explore the molecular mechanisms underlying the therapeutic effects of *F. carica*. Advance genetics, molecular docking, and metabolomic studies should be in the pipeline for future research in personalizing *F. carica* as a therapy or nutritional supplementation with a proper dosage recommendation. This includes

the study of *F. carica* on the gut microbiota and the synergistic combinations of *F. carica* with other supplements or medication to achieve the best outcome while minimizing potential side effects or adverse reactions.

Studies on the compound or drug formulation and delivery to enhance the bioavailability of *F. carica's* bioactive compounds involving nanotechnology, novel extraction techniques, and recent technology in the farming and cultivation practices of *F. carica* should also be considered to improve its efficacy and optimize its potential benefits. Transdisciplinary exploration, and collaboration between researchers, clinicians, and industry partners will be crucial in advancing the potential use of *F. carica* as a promising nutraceutical.

Conclusion

F. carica is considered a potential medicinal plant as it contains numerous beneficial polyphenols and bioactive compounds. Polyphenols serve as free radical inhibitors and play essential roles in reducing oxidative stress, which is involved in various pathological conditions. Multiple parts of *F. carica* have been widely studied and found to possess pharmacological properties for the treatment of various human diseases. Through this present comprehensive review into its bioactive compounds and biological effects, we have gained valuable insights into the various ways *F. carica* can positively affect human health.

As most previous studies on *F. carica* have been limited to in vitro and pre-clinical trials, more clinical and human studies are required before *F. carica* can be fully integrated into clinical practice and personalized nutrition. In depth mechanistic studies, exploration of novel delivery methods, drug synergy, and clinical trials will contribute to a more comprehensive understanding of *F. carica*'s pharmacological effects and its nutraceutical potential for human health.

Acknowledgments

The authors thank Universiti Kuala Lumpur and MAHSA University for providing the facilities and resources necessary to complete this study.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Petrovska BB. Historical review of medicinal plants' usage. *Pharmacogn Rev*. 2012;6(11):1. doi:10.4103/0973-7847.95849
2. Shahinuzzaman M, Yaakob Z, Anuar FH, et al. In vitro antioxidant activity of Ficus carica L. latex from 18 different cultivars. *Sci Rep*. 2020;10:1–14. doi:10.1038/s41598-020-67765-1
3. Costa JLG, Pedreira RS, Gomes ACP, Restan AZ, Vasconcellos RS, Loureiro BA. Concentration of synthetic antioxidants and peroxide value of commercial dry pet foods. *Anim Feed Sci Technol*. 2022;294:115499. doi:10.1016/j.anifeedsci.2022.115499
4. Dhalaria R, Verma R, Kumar D, et al. Bioactive compounds of edible fruits with their anti-aging properties: a comprehensive review to prolong human life. *Antioxidants*. 2020;9:1123. doi:10.3390/antiox9111123
5. Rudrapal M, Khairnar SJ, Khan J, et al. Dietary polyphenols and their role in oxidative stress-induced human diseases: insights into protective effects, antioxidant potentials and mechanism(s) of action. *Front Pharmacol*. 2022;13:1–15. doi:10.3389/fphar.2022.806470
6. Ramadan MF. *Fig (Ficus Carica): Production, Processing, and Properties*. Ramadan MF, ed.. The Springer-Nature;2023. doi:10.1007/978-3-031-16493-4
7. Zhang ZR, Yang X, Li WY, Peng YQ, Gao J. Comparative chloroplast genome analysis of Ficus (Moraceae): insight into adaptive evolution and mutational hotspot regions. *Front Plant Sci*. 2022;13:1–17. doi:10.3389/fpls.2022.965335
8. Sandhu AK, Islam M, Edirisinghe I, Burton-Freeman B. Phytochemical composition and health benefits of figs (fresh and dried): a review of literature from 2000 to 2022. *Nutrients*. 2023;15(11):2623. doi:10.3390/nu15112623
9. Isa MM, Jaafar MN, Kasim KF, Mutalib MFA. Cultivation of Fig (Ficus carica L.) as an alternative high value crop in Malaysia: a brief review. *IOP Conf Ser Mater Sci Eng*. 2020;864:012134. doi:10.1088/1757-899X/864/1/012134
10. Shahrajabian MH, Sun W, Cheng Q. A review of chemical constituents, traditional and modern pharmacology of fig (Ficus carica L.), a super fruit with medical astonishing characteristics. *Pol J Agron*. 2021;44:22–29. doi:10.26114/pja.iung.452.2021.452.04
11. Fresh Figs Market by Nature, Variety, Sales Channel & Region for 2022 – 2032 | global Sales Analysis and Opportunity - 2032 | FMI Available from: futuremarketinsights.com. Accessed February 10, 2024.
12. Mahmoudi S, Khali M, Benkhaled A, et al. Fresh figs (Ficus carica L.): pomological characteristics, nutritional value, and phytochemical properties. *Eur J Hortic Sci*. 2018;83:104–113. doi:10.17660/eJHS.2018/83.2.6
13. Salma S, Shamsi Y, Ansari S, et al. Ficus Carica L.: a panacea of nutritional and medicinal benefits. *Cell Med*. 2020;10:1. doi:10.5667/tang.2020.0001
14. Ergül M, Ergül M, Eruygur N, et al. In vitro evaluation of the chemical composition and various biological activities of Ficus carica leaf extracts. *Turk J Pharm Sci*. 2019;16:401. doi:10.4274/tjps.galenos.2018.70037

15. Ghanbari A, Le Gresley A, Naughton D, et al. Biological activities of Ficus carica latex for potential therapeutics in Human Papillomavirus (HPV) related cervical cancers. *Sci Rep*. 2019;9:1013. doi:10.1038/s41598-018-37665-6
16. AlGhalban FM, Khan AA, Khattak M. Comparative anticancer activities of Ficus carica and Ficus salicifolia latex in MDA-MB-231 cells. *Saudi J Biol Sci*. 2021;28:3225–3234. doi:10.1016/j.sjbs.2021.02.061
17. Pouryousef A, Eslami E, Shahriarirad S, et al. Effects of topical gel formulation of Ficus carica latex on cutaneous leishmaniasis induced by Leishmania major in BALB/c mice. *BMC Res Notes*. 2021;14:199. doi:10.1186/s13104-021-05614-8
18. Li Z, Yang Y, Liu M, et al. A comprehensive review on phytochemistry, bioactivities, toxicity studies, and clinical studies on Ficus carica Linn. leaves. *Biomed Pharmacother*. 2021;137:111393. doi:10.1016/j.biopha.2021.111393
19. Takahashi T, Okiura A, Saito K, et al. Identification of phenylpropanoids in fig (Ficus carica L.) leaves. *J Agric Food Chem*. 2014;62:10076–10083. doi:10.1021/jf5025938
20. Saoudi M, El Feki A. Protective role of Ficus carica stem extract against hepatic oxidative damage induced by methanol in male Wistar rats. *eCAM*. 2012. doi:10.1155/2012/150458
21. Duman E, Şimşek M, Özcan MM. Monitoring of composition and antimicrobial activity of fig (Ficus carica L.) fruit and seed oil. *J Agric Processes Techol*. 2018;24:75–80.
22. Harzallah A, Amira M, Amri Z, et al. Phytochemical content and antioxidant activity of different fruit parts juices of three figs (Ficus carica L.) varieties grown in Tunisia. *Ind Crops Prod*. 2016;83:255–267. doi:10.1016/j.indcrop.2015.12.043
23. Benmaghnia S, Meddah B, Tir-Touil A, et al. Phytochemical analysis, antioxidant and antimicrobial activities of three samples of dried figs (ficus carica l.) from the region of mascara. *J Microbiol Biotechnol Food Sci*. 2019;9:208–215. doi:10.15414/jmbfs.2019.9.2.208-215
24. Liu L, Cheng Y, Zhang H. Phytochemical Analysis of Anti-Atherogenic Constituents of Xue-Fu-Zhu-Yu-Tang Using HPLC-DAD-ESI-MS. *Chem Pharm Bull*. 2004;52:1295–1301. doi:10.1248/cpb.52.1295
25. Güneş Bayir A, Aksoy AN, Koçyiğit A. The importance of polyphenols as functional food in health. *Bezmialem Sci*. 2019;7:157–163. doi:10.14235/bas.galenos.2018.2486
26. Ivanov I, Dincheva I, Badjakov I, et al. GC-MS analysis of unpolar fraction from Ficus carica L.(fig) leaves. *Int Food Res J*. 2018;25:282–286.
27. Aref HL, Aouni M, Chaumon JP, et al. Identification of a potent antiviral terpenes and coumarins from Tunisian caprifig latex, Jrani variety. *ISJ*. 2021;15:1–7.
28. Chawla A, Kaur R, Kumar A. Ficus carica Linn.: a review on its pharmacognostic, phytochemical and pharmacological aspects. *Int J Pharm Phytopharmacological Res*. 2012;1:215–232.
29. Al-Yousuf HHH. Antibacterial activity of Ficus carica L. extract against six bacterial strains. *IJDDR*. 2012;4:307–310.
30. Hashemi SA, Abediankenari S, Ghasemi M, et al. The effect of fig tree latex (Ficus carica) on stomach cancer line. *Iran Red Crescent Med J*. 2011;13:272–275.
31. Khodarahmi GA, Ghasemi N, Hassanzadeh F, et al. Cytotoxic effects of different extracts and latex of Ficus carica L. on HeLa cell line. *Iran J Pharm Res*. 2011;10:273–277.
32. Gond NY, Khadabadi SS. Hepatoprotective activity of Ficus carica leaf extract on rifampicin induced hepatic damage in rats. *Indian J Pharm Sci*. 2008;70:64–366. doi:10.4103/0250-474X.43003
33. Aghel N, Kalantari H, Rezazadeh S. Hepatoprotective effect of Ficus carica leaf extract on mice intoxicated with carbon tetrachloride. *Iran J Pharm Res*. 2011;10:63–68.
34. Yang L, Wen KS, Ruan X, et al. Response of plant secondary metabolites to environmental factors. *Molecules*. 2018;23:762. doi:10.3390/molecules23040762
35. Ayoub L, Hassan F, Hamid S, et al. Phytochemical screening, antioxidant activity and inhibitory potential of Ficus carica and Olea europaea leaves. *Bioinformation*. 2019;15:226–232. doi:10.6026/97320630015226
36. Lee H, Selvaraj B, Yoo KY, et al. Flavonoids as anti-inflammatory and neuroprotective agents. *Int J Oral Biol*. 2020;45:33–41. doi:10.11620/ijob.2020.45.2.33
37. Al-Halbosiy MMF, Hasan ZYM, Mohammad FI, et al. Biological Activities of Iraqi Fig (Ficuscarica) CrudeEthanolic and Total Flavonoids Extracts. *Iraqi J Sci*. 2020;61:1612–1621. doi:10.24996/ijs.2020.61.7.9
38. Khoo HE, Azlan A, Tang ST, et al. Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. *Food Nutr Res*. 2017;61:1361779. doi:10.1080/16546628.2017.1361779
39. Lama K, Harlev G, Shafran H, et al. Anthocyanin accumulation is initiated by abscisic acid to enhance fruit color during fig (Ficus carica L.) ripening. *J Plant Physiol*. 2020;251:153192. doi:10.1016/j.jplph.2020.153192
40. Wojdyło A, Nowicka P, Carbonell-Barrachina ÁA, et al. Phenolic compounds, antioxidant and antidiabetic activity of different cultivars of Ficus carica L. fruits. *J Funct Foods*. 2016;25:421–432. doi:10.1016/j.jff.2016.06.015
41. Mohammad A, Razaly NI, Rani MDM, et al. A micro-computed tomography (micro-CT) analysis of postmenopausal osteoporotic rat models supplemented with Ficus carica. *J Appl Pharm Sci*. 2018;8:39–45. doi:10.7324/japs.2018.8606
42. Zhao C, Li S, Li C, et al. Flavonoids from Fig (Ficus carica Linn.) leaves: the development of a new extraction method and identification by UPLC-QTOF-MS/MS. *Appl Sci*. 2021;11:7718. doi:10.3390/app11167718
43. Liu YP, Guo JM, Yan G, et al. Anti-inflammatory and antiproliferative prenylated isoflavone derivatives from the fruits of Ficus carica. *J Agric Food Chem*. 2019;67:4817–4823. doi:10.1021/acs.jafc.9b00865
44. Jain R, Jain SC, Bhagchandani T, et al. New furanocoumarins and other chemical constituents from Ficus carica root heartwood. *Z Naturforsch C J Biosci*. 2013;68:3–7. doi:10.1515/znc-2013-1-201
45. Oliveira AP, Silva LR, Andrade PB, et al. Further insight into the latex metabolite profile of Ficus carica. *J Agric Food Chem*. 2010;58:10855–10863. doi:10.1021/jf1031185
46. Oliveira AP, Valentão P, Pereira JA, et al. Ficus carica L.: metabolic and biological screening. *Food Chem Toxicol*. 2009;47:2841–2846. doi:10.1016/j.fct.2009.09.004
47. Liu F, Yang Z, Zheng X, et al. Nematicidal coumarin from Ficus carica L. *J Asia Pac Entomol*. 2011;14:79–81. doi:10.1016/j.aspen.2010.10.006
48. Saeed MA, Sabir AW. Irritant potential of triterpenoids from Ficus carica leaves. *Fitoterapia*. 2002;73:417–420. doi:10.1016/s0367-326x(02)00127-2

49. Iffat A, Syeda HN, Najeeb UR, et al. Comparative antioxidative and antidiabetic activities of ficus carica pulp, peel and leaf and their correlation with phytochemical contents. *Pharm Res*. 2020;4:000197.
50. Boukhalfa F, Kadri N, Bouchemel S, et al. Antioxidant activity and hypolipidemic effect of Ficus carica leaf and twig extracts in Triton WR-1339-induced hyperlipidemic mice. *Med J Nutr Metab*. 2018;11:37–50. doi:10.3233/mnm-17180
51. Agriculture Research Service, US Department of Agriculture. FoodData Central: figs, raw; 2019. Available from: https://fdc.nal.usda.gov/fdc-app.html#/food-details/173021/nutrients. Accessed February 11, 2024.
52. Rajesh B, Ramasubbualakshmi A, Gopalasatheeskumar K, et al. Phytochemical analysis and anti-arthritic activity of ficus carica leaves. *AJRC*. 2020;13:151. doi:10.5958/0974-4150.2020.00030.9
53. Souhila B, Asma B, Boumediene M, et al. Antimicrobial activity of dried fig (Ficus carica L.) extracts from the region of Mascara (Western Algeria) on Enterobacter cloacae identified by MALDI-TOF/MS. *Eur J Biol Res*. 2021;11:234–241.
54. Abdel-Aty AM, Hamed MB, Salama WH. Ficus carica, Ficus sycomorus and Euphorbia tirucalli latex extracts: phytochemical screening, antioxidant and cytotoxic properties. *Biocatal Agric Biotechnol*. 2019;20:101199. doi:10.1016/j.bcab.2019.101199
55. Oktaviani D, Sudharmono U. The effectiveness of boiled figs leaf (Ficus carica L) and rosy periwinkle (Catharantus roseus) on SGOT and SGPT levels of male Wistar strain rats with hepatitis model. *Abst Proceed Int Schol Confer*. 2019;7:850–859. doi:10.35974/isc.v7i1.2190
56. Bahadori S, Salamzadeh J, Kamalinejad M, et al. Study of the effect of an oral formulation of fig and olive on rheumatoid arthritis (RA) remission indicators: a randomized clinical trial. *Iran J Pharm Res*. 2016;15:537–545.
57. Ali H, Monga J, Gupta L, et al. Antioxidant potential of Ficus carica by the DPPH free radical method: in vitro analysis. *Orient J Chem*. 2009;25:257–260.
58. Amessis-Ouchemoukh N, Ouchemoukh S, Meziant N, et al. Bioactive metabolites involved in the antioxidant, anticancer and anticalpain activities of Ficus carica L. Ceratonia siliqua L. and Quercus ilex L. extracts. *Ind Crops Prod*. 2017;95:6–17. doi:10.1016/j.indcrop.2016.10.007
59. Marrelli M, Menichini F, Statti GA, et al. Changes in the phenolic and lipophilic composition, in the enzyme inhibition and antiproliferative activity of Ficus carica L. cultivar Dottato fruits during maturation. *Food Chem Toxicol*. 2012;50:726–733. doi:10.1016/j.fct.2011.12.025
60. Mahmoudi S, Khali M, Benkhaled A, et al. Phenolic and flavonoid contents, antioxidant and antimicrobial activities of leaf extracts from ten Algerian Ficus carica L. varieties. *Asian Pac J Trop Biomed*. 2016;6:239–245. doi:10.1016/j.apjtb.2015.12.010
61. Kamiloglu S, Capanoglu E. Polyphenol content in figs (Ficus carica L.): effect of sun-drying. *Int J Food Prop*. 2015;18:521–535. doi:10.1080/10942912.2013.833522
62. Rivero-cruz JF, Granados-pineda J, Pedraza-chaverri J, et al. Phytochemical constituents, antioxidant, cytotoxic, and antimicrobial activities of the ethanolic extract of Mexican brown propolis. *Antioxidants*. 2020;9:1–11. doi:10.3390/antiox9010070
63. Emerit J, Edeas M, Bricaire F. Neurodegenerative diseases and oxidative stress. *Biomed Pharmacother*. 2004;58:39–46. doi:10.1016/j.biopha.2003.11.004
64. Orhan IE, Üstün O, Şener B. Estimation of cholinesterase inhibitory and antioxidant effects of the leaf extracts of Anatolian Ficus carica var. domestica and their total phenol and flavonoid contents. *Nat Prod Commun*. 2011;6:375–378. doi:10.1177/1934578x1100600315
65. Loizzo MR, Bonesi M, Pugliese A, et al. Chemical composition and bioactivity of dried fruits and honey of ficus carica cultivars dottato, San Francesco and citrullara. *J Sci Food Agric*. 2014;94:2179–2186. doi:10.1002/jsfa.6533
66. Oliveira AP, Silva LR, Ferreres F, et al. Chemical assessment and in vitro antioxidant capacity of Ficus carica latex. *J Agric Food Chem*. 2010;58:3393–3398. doi:10.1021/jf9039759
67. Subash S, Essa MM, Braidy N, et al. Consumption of fig fruits grown in Oman can improve memory, anxiety, and learning skills in a transgenic mice model of Alzheimer's disease. *Nutr Neurosci*. 2016;19:475–483. doi:10.1179/1476830514y.0000000131
68. Alharthy NA, Bawazir AE. Effects of the mixture dried figs (Ficus Carica) and olive oil on amnesia model of alzheimer's induced by scopolamine in male albino rats. *Pharmacophore*. 2019;10:62–71.
69. Abdillah S, Prakoso AW. Antioxidant and anti-AGEs (Advanced glycation end-product) activities of ethanolic extract of Ficus carica Linn from Indonesia. *J Pharmacogn Phytochem*. 2018;7:598–601.
70. Sharma M, Patel S, Acharya UR. Automated detection of abnormal EEG signals using localized wavelet filter banks. *Pattern Recognit Lett*. 2020;133:188–194. doi:10.1016/j.patrec.2020.03.009
71. Bhanushali MM, Makhija DT, Joshi YM. Central nervous system activity of an aqueous acetonic extract of Ficus carica L. in mice. *J Ayurveda Integr Med*. 2014;5:89. doi:10.4103/0975-9476.131734
72. Yahiaoui S, Kati DE, Ali LM, et al. Assessment of antioxidant, antiproliferative, anti-inflammatory, and enzyme inhibition activities and UPLC-MS phenolic determination of Ficus carica latex. *Ind Crops Prod*. 2022;178:114629. doi:10.1016/j.indcrop.2022.114629
73. Essa MM, Subash S, Akbar M, et al. Long-term dietary supplementation of pomegranates, figs and dates alleviate neuroinflammation in a transgenic mouse model of Alzheimer's disease. *PLoS One*. 2015;10:e0120964. doi:10.1371/journal.pone.0120964
74. Raafat K, Wurglics M. Phytochemical analysis of Ficus carica L. active compounds possessing anticonvulsant activity. *J Tradit Complement Med*. 2018;9:263–270. doi:10.1016/j.jtcme.2018.01.007
75. Talcott PA. Strychnine. *Small Animal Toxicol*. 2013;1:827–831.
76. Nirwana I, Rianti D, Soekartono RH, et al. Antibacterial activity of fig leaf (Ficus carica Linn.) extract against Enterococcus faecalis and its cytotoxicity effects on fibroblast cells. *Vet World*. 2018;11:342–347. doi:10.14202/vetworld.2018.342-347
77. Walker-York-Moore L, Moore SC, Fox EM. Characterization of enterotoxigenic bacillus cereus sensu lato and Staphylococcus aureus isolates and associated enterotoxin production dynamics in milk or meat-based broth. *Toxins*. 2017;9:1–15. doi:10.3390/toxins9070225
78. Ay E, Duran N Investigation of the antiviral activity of Ficus carica L. latex against HSV-2. International Conference on Advanced Materials and Systems (ICAMS). 2018:33–37. doi:10.24264/icams-2018.i.3
79. Lazreg Aref H, Gaaliche B, Fekih A, et al. In vitro cytotoxic and antiviral activities of Ficus carica latex extracts. *Nat Prod Res*. 2011;25:310–319. doi:10.1080/14786419.2010.528758
80. Camero M, Marinaro M, Lovero A. In vitro antiviral activity of Ficus carica latex against caprine herpesvirus-1. *Nat Prod Res*. 2014;28:2031–2035. doi:10.1080/14786419.2014.918120
81. Ben-Shabat S, Yarmolinsky L, Porat D, et al. Antiviral effect of phytochemicals from medicinal plants: applications and drug. *Drug Deliv Transl Res*. 2020;10:354–367. doi:10.1007/s13346-019-00691-6

82. Üstün E, Önbaş SC, Çelik SK, et al. Green synthesis of iron oxide nanoparticles by using Ficus carica leaf extract and its antioxidant activity. *Biointerface Res Appl Chem*. 2022;12:2108–2116. doi:10.33263/briac122.21082116
83. Antonopoulou I, Sapountzaki E, Rova U, et al. Ferulic acid from plant biomass: a phytochemical with promising antiviral properties. *Front Nutr*. 2022;8:777576. doi:10.3389/fnut.2021.777576
84. Mawa S, Husain K, Jantan I, Ficus Carica L. (Moraceae): phytochemistry, traditional uses and biological activities. *Evid Based Complement Alternat Med*. 2013;2013:974256. doi:10.1155/2013/974256
85. Ali MC, Nur AJ, Khatun MS, et al. Identification of potential SARS-CoV-2 main protease inhibitors from Ficus Carica Latex: an in-silico approach. *J Adv Biotechnol Exp Ther*. 2020;3:57–67. doi:10.5455/jabet.2020.d157
86. Sieniawska E, Świątek Ł, Sinan KI, et al. Phytochemical insights into ficus sur extracts and their biological activity. *Molecules*. 2022;27:1863. doi:10.3390/molecules27061863
87. Eteraf-Oskouei T, Allahyari S, Akbarzadeh-Atashkhosrow A, et al. Methanolic extract of ficus carica Linn. leaves exerts antiangiogenesis effects based on the rat air pouch model of inflammation. *Evid Based Complement Alternat Med*. 2015;1:1–9. doi:10.1155/2015/760405
88. Pérez C, Canal JR, Campillo JE, et al. Hypotriglyceridaemic activity of Ficus carica leaves in experimental hypertriglyceridaemic rats. *Phytother Res*. 1999;13:188–191.
89. Rassouli A, Ardestani F, Asadi F, et al. Effects of Fig tree (Ficus carica) leaf extracts on serum and liver cholesterol levels in hyperlipidemic rats. *Int J Vet Res*. 2010;4:77–80.
90. Belguith-Hadriche O, Ammar S, Contreras MDM, et al. Antihyperlipidemic and antioxidant activities of edible tunisian Ficus Carica L. fruits in high fat diet-induced hyperlipidemic rats. *Plant Foods Hum Nutr*. 2016;71:183–189. doi:10.1007/s11130-016-0541-x
91. Joerin L, Kauschka M, Bonnländer B, et al. Ficus carica leaf extract modulates the lipid profile of rats fed with a high-fat diet through an increase of HDL-C. *Phytother Res*. 2014;28:261–267. doi:10.1002/ptr.4994
92. Perveen F, Khan FA, Irum Z, et al. Anti dyslipidemic effect of Ficus Carica Fruit (Fig) on lipid profile of diet induced hyperlipidemic rats. *Pak J Med Health Sci*. 2021;15:1709–1712. doi:10.53350/pjmhs211571709
93. Sukowati YK, Johan A, Murwani R. Ethanol extracts of ficus carica fruit and leaf normalize high serum lipid profile, TNF-α, and mda due to high fat diet in Sprague Dawley rat. *Curr Res Nutr Food Sci*. 2019;7:772–782. doi:10.12944/crnfsj.7.3.16
94. Warmke N, Platt F, Bruns AF, et al. Pericyte insulin receptors modulate retinal vascular remodeling and endothelial angiopoietin signaling. *Endocrinology*. 2021;162(11):bqab182. doi:10.1210/endocr/bqab182
95. Ghambarali Z, Bidmeshkipouri A, Akrami H, et al. Ethanolic extract of ficus carica leave suppresses angiogenesis by regulating VEGF-A and Integrin β3 mRNA expression in human umbilical vein endothelial cells. *Indian J Physiol Pharmacol*. 2014;58:407–415.
96. Mostafaie A, Mansouri K, Norooznezhad AH, et al. Anti-angiogenic activity of ficus carica latex extract on human umbilical vein endothelial cells ali. *Cell J*. 2010;12:525–528.
97. Hamid IS, Aksono EB, Sukmanadi M, et al. Antiangiogenesis activity test of tin leaf (Ficus carica L.) on the number of blood vessels and VEGF expression of chorioallantoic membrane of embryonated chicken eggs. *Eur J Oncol Pharm*. 2019;1:1–5. doi:10.1097/op9.0000000000000007
98. Fouad D, Al-Obaidi E, Badr A, et al. Modulatory effect of Ficus carica on oxidative stress and hematological changes induced by gamma-radiation in male albino rats. *Biologia*. 2020;75:1313–1324. doi:10.2478/s11756-019-00375-z
99. Nebedum JO, Udeafor PC, Okeke CU. Comparative effects of ethanolic extracts of Ficus carica and Mucuna pruriens leaves on haematological parameters in albino rats. *Biokemistri*. 2010;22:77–84.
100. Odo GE, Agwu JE, Newze N, et al. Toxicity and effects of fig (Ficus carica) leaf aqueous extract on haematology and some biochemical indices of Wistar albino rats (Rattus norvegicus). *J Med Plant Res*. 2016;10:298–305. doi:10.5897/jmpr2015.5580
101. Khan KY, Khan MA, Ahmad M, et al. Ethno-medicinal Species of genus Ficus L. Used to treat diabetes in Pakistan. *J Appl Pharm Sci*. 2011;1:209–211.
102. Arafa ES, Hassan W, Murtaza G, et al. Ficus carica and Syzygium cumini regulate glucose and lipid parameters in high-fat diet and streptozocin-induced rats. *J Diabetes Res*. 2020;28:6745873. doi:10.1155/2020/6745873
103. Chahar MK, Sharma N, Dobhal MP, et al. Flavonoids: a versatile source of anticancer drugs. *Pharmacogn Rev*. 2011;5:1–12. doi:10.4103/0973-7847.79093
104. Purnamasari R, Winarni D, Permanasari AA, et al. Anticancer Activity of methanol extract of ficus carica leaves and fruits against proliferation, apoptosis, and necrosis in Huh7it cells. *Cancer Inform*. 2019;18:1176935119842576. doi:10.1177/1176935119842576
105. Ghandehari F, Fatemi M. The effect of Ficus carica latex on 7, 12-dimethylbenz (a) anthracene-induced breast cancer in rats. *Avicenna J Phytomed*. 2018;8(4):286–295.
106. Peng C, Zeng W, Su J, et al. Cyclin-dependent kinase 2 (CDK2) is a key mediator for EGF-induced cell transformation mediated through the ELK4/c-Fos signaling pathway. *Oncogene*. 2016;35:1170–1179. doi:10.1038/onc.2015.175
107. Li JP, Yang YX, Liu QL, et al. The investigational Aurora kinase A inhibitor alisertib (MLN8237) induces cell cycle G2/M arrest, apoptosis, and autophagy via p38 MAPK and Akt/mTOR signaling pathways in human breast cancer cells. *Drug Des Devel Ther*. 2015;9:1627–1652. doi:10.2147/dddt.s75378
108. Yuan Z, Long C, Junming T, et al. Quercetin-induced apoptosis of HL-60 cells by reducing PI3K/Akt. *Mol Biol Rep*. 2012;39:7785–7793. doi:10.1007/s11033-012-1621-0
109. Zhang Q, Zhao XH, Wang ZJ. Flavones and flavonols exert cytotoxic effects on a human oesophageal adenocarcinoma cell line (OE33) by causing G2/M arrest and inducing apoptosis. *Food Chem Toxicol*. 2008;46:2042–2053. doi:10.1016/j.fct.2008.01.049
110. Gurung AB, Ali MA, Lee J, et al. Molecular docking and dynamics simulation study of bioactive compounds from Ficus carica L. with important anticancer drug targets. *PLoS One*. 2021:16:e0254035. doi:10.1371/journal.pone.0254035
111. Jeivad F, Yassa N, Ostad SN, et al. Ficus Carica L. Latex: possible chemo-preventive, apoptotic activity and safety assessment. *Iran J Pharm Res*. 2020;19:231.
112. Jasmine R, Manikandan K, Karthikeyan K. Evaluating the antioxidant and anticancer property of Ficus carica fruits. *Afr J Biotechnol*. 2015;14:634–641. doi:10.5897/ajb2014.13742
113. Agabeĭli RA, Kasimova TE. Antimutagenic activity of Armoracia rusticana, Zea mays and Ficus carica plant extracts and their mixture. *Tsitol Genet*. 2005;39:75–79.

114. Lightbourn AV, Thomas RD. Crude Edible Fig (Ficus carica) Leaf Extract Prevents Diethylstilbestrol (DES)-Induced DNA Strand Breaks in Single-Cell Gel Electrophoresis (SCGE)/Comet Assay: literature Review and Pilot Study. *J Bioequivalence Bioavailab*. 2019;11(2):19–28.
115. Fahmy MA, Hassan EE, Ibrahim NE, et al. Protective Role of ficus carica extract against hepato-testicular side effects and genotoxicity induced by cisplatin. *Pharmacogn J*. 2020;12:645–656. doi:10.5530/pj.2020.12.96
116. Khan H, Akhtar N, Ali A. Effects of cream containing ficus carica L. fruit extract on skin parameters: in vivo evaluation. *Indian J Pharm Sci*. 2014;76:560–564.
117. Dini I, Falang D, Di Lorenzo R, et al. An extract from ficus carica cell cultures works as an anti-stress ingredient for the skin. *Antioxidants*. 2021;10:1–21. doi:10.3390/antiox10040515
118. Turkoglu M, Pekmezci E, Kilic S, et al. Effect of Ficus carica leaf extract on the gene expression of selected factors in HaCaT cells. *J Cosmet Dermatol*. 2017;16:e54–e58. doi:10.1111/jocd.12344
119. Damiani G, Cazzaniga S, Naldi L. Use of fumaric acid derivatives in Italian reference centers for psoriasis. *Ital J Dermatol Venerol*. 2021;156:36–41. doi:10.23736/s2784-8671.18.06032-7
120. Song K, An SM, Kim M, et al. Comparison of the antimelanogenic effects of p-coumaric acid and its methyl ester and their skin permeabilities. *J Dermatol Sci*. 2011;63:17–22. doi:10.1016/j.jdermsci.2011.03.012
121. Gregoriou S, Papafragkaki D, Kontochristopoulos G, et al. Cytokines and other mediators in alopecia areata. *Mediators Inflamm*. 2010;1:928030. doi:10.1155/2010/928030
122. Son JH, Jin H, You HS, et al. Five cases of phytophotodermatitis caused by fig leaves and relevant literature review. *Ann Dermatol*. 2017;29:86–90. doi:10.5021/ad.2017.29.1.86
123. Imen MS, Ahmadabadi A, Tavousi SH, et al. The curious cases of burn by fig tree leaves. *Indian J Dermatol*. 2019;64:71–73.
124. Bowers AG. Phytophotodermatitis. *Am J Contact Dermat*. 1999;10:89–93.
125. Makoolati Z, Bahrami H, Zamanzadeh Z, et al. Efficacy of Ficus carica leaf extract on morphological and molecular behavior of mice germ stem cells. *Anim Reprod*. 2022;19:e20220036. doi:10.1590/1984-3143-ar2022-0036