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Review Article

A review of *Ficus* L. genus (Moraceae): a source of bioactive compounds for health and disease. Part 1

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Abstract: The *Ficus* L. genus, belonging to the Moraceae family, includes around 850 species that are widely distributed in tropical and subtropical regions around the world; including the Eastern Mediterranean, Asia, Africa, Australia, and a large territory of America. Among the most important species are *F. deltoidea, F. exasperata, F. sycomorus, F. religiosa, F. microcarpa*, *F. hirta* Vahl, *F. benghalensis, F. racemosa, F. elástica,* and *F. carica*. Different parts of *Ficus* plants (root, stem bark, latex, leaves, pulp and fruits) contain bioactive compounds [flavonoids (flavanols, flavones, flavonols, isoflavones, chalcones, anthocyanins), phenolic acids (hidroxylcinnamic acids, hidroxylbenzoic acids), phytosterols, terpenes (triterpenes, tetraterpenes, diterpenes, sesquiterpenes, monoterpenes), coumarins, hydroxybenzoates, phenylpropanoids, chlorins, pheophytins, megastigmanes, chitinases, organic acids, fatty acids, amino acids, alkaloids, glycosides] which together, are currently useful to more than 30 traditional ethnomedical uses. The present manuscript is the result of scientific search processed with the main electronic databases (PubMEd, SciELO, Latindex, Redalyc, BiologyBrowser, ScienceResearch, ScienceDirect, Academic Journals, Ethnobotany, and Scopus). This first review (Part 1), compiles information from published research (in vitro, in vivo and clinical studies) on its antimicrobial, antifungal, antiviral, anti-helminthic, hypoglycemic, hypolipidemic, hepatoprotective, anti-inflammatory, analgesic, and antipyretic properties; as well as its possible adverse and/or toxicological effects. Given the amount of evidence described in this review it aims to trigger a more detailed scientific research on the important pharmacological properties of all angiosperm plants of the genus *Ficus* L.

Keywords: *Ficus* L., phytochemicals, biological activities, toxicological safety

Introduction

Angiosperm plants of the genus *Ficus* L. belonging to the Moraceae family include more than 850 species of trees, shrubs, hemiepiphytes (a plant that germinates and begins its development on the branches of a tree and later produces its roots to absorb nutrients from the soil), climbers and vines widely distributed in different tropical and subtropical regions of the world. Most of the species tend to grow wild in the eastern Mediterranean, Asia, Africa, Australia, and a large territory of the American continent. Ficus trees are considered ecologically relevant species as they provide food and shelter for many frugivorous animals (both birds and mammals). They are also an important natural resource for humans due to their high economic, nutritional and medicinal values. This is the reason why some species are considered ornamental, sacred, religious plants and have been domesticated (**Table 1**) [1-6]. Among the most important species are *F. deltoidea, F. exasperata, F. sycomorus, F. religiosa, F. microcarpa*, *F. hirta* Vahl, *F. benghalensis, F. racemosa, F. elástica,* and *F. carica*. These last four

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Table 1. Common and traditional uses of the most studied and evaluated Ficus species

Species (Common name)	Uses	Ref
F. deltoidea (Mistletoe fig)	Alimentary (Consumption of fruits) Ornamental Medicinal (Anti-inflammatory, antinociceptive, antibacterial, anticancer, antioxidant, wound healing, antidiabetic, hypoglycemic, hypocholesterolemic, hypolipidemic, aphrodisiac, antiulcerogenic, uterotonic, antirheumatic, action in disorders of the menstrual cycle, decreases cold and headache)	[16]
F. exasperata (Sandpaper tree, forest sandpaper fig, white fig, or sandpaper leaf tree)	Alimentary (Consumption of fruits, fodder for animals) Ornamental Medicinal (Anti-inflammatory, antinociceptive, antipyretic, antimicrobial, antituberculous, antileprous, antidiabetic, hypolipidic, antioxidant, anticancer, anthelmintic, vermifuge, ascaricide, anti-gouty, antihemorrhoids, antiepileptic, antirheumatic, antihypertensive, antiulcer, antihypertensive, diuretic, antidiarrheal, antidysentery, antitussive, anxiety prevention, wound healing, prevention of weakness and malnutrition, action on ophthalmic infections, respiratory tract and venereal diseases, antiarthritic, anxiolytic, uterotonic, effect on kidney disorders)	[17]
F. sycomorus (Sycamore fig or the fig-mulberry)	Alimentary (Consumption of fruits and leaves) Ornamental Medicinal (Anti-inflammatory, antinociceptive, antimicrobial, antifungal, anthelmintic, antiulcer, antiwarts, neuroprotective, antiepileptic, antidiarrheal, prevents respiratory and thoracic diseases, laxative and anticonstipation, antidiabetic, prevents insomnia, healing of wounds and burns, hepatoprotective, effect on infertility and excessive menstrual flow, antihypertensive, antioxidant)	[18-20]
F. religiosa (Sacred fig)	Alimentary (Consumption of fruits) Ornamental and ceremonial plant Medicinal (Anti-inflammatory, antinociceptive, antidiabetic, antidiarrheal, anticancer, antiproliferative, antimutagenic, antiasthmatic, antioxidant, antimicrobial, antiviral, anti-helminthic, hepatoprotective, wound healing, anticoagulant, immunomodulatory, antiepileptic, astringent, laxative, effect on gastric problems, sexual disorders and skin diseases, mosquitocide, stress prevention)	[21-23]
F. microcarpa (Chinese banyan, Malayan banyan, or curtain fig)	Alimentary (Consumption of fruits) Ornamental Medicinal (Antinoceptive, antipyretic, antibacterial, antileper, antiviral, antifungal, antimalarial, antidiabetic, anticancer, antioxidant, antiulcer, antirheumatic, antidiarrhoeal, hepatoprotective, antitussive, prevention of acute enteritis and bronchitis, expectorant, relieves toothache)	[10]
F. benghalensis (Indian banyan or banyan fig)	Alimentary (consumption of fruits) Ornamental Medicinal (Anti-inflammatory, antinociceptive, antimicrobial, antiemetic, antirheumatic, diuretic, antidiabetic, antidiarrheal, antioxidant, anticancer/antitumor, antimutagenic, antiproliferative, hepatoprotective, wound healing, anticoagulant, immunomodulatory, anti-stress potential, mosquitocide, action on respiratory diseases)	[21, 24]
F. racemosa (Cluster fig or red river fig)	Alimentary (Consumption of fruits, fodder for animals) Ceremonial plant Medicinal (Anti-inflammatory, antinociceptive, antipyretic, antimicrobial, antifungal, antifilarial, larvicide, hepatoprotective, antidiarrheal, antidiabetic, antioxidant, antihypertensive, gastroprotective, antihemorrhoids, effect on respiratory and urinary diseases, antitussive, antihyperglycemic, wound healing)	[25, 26]
F. elástica (Rubber tree)	Alimentary (Consumption of fruits) Ornamental (Decorative element for home and office interiors) Medicinal (Anti-inflammatory, antinoceptive, antibacterial, antituberculous, antidiarrheal, antihypertensive, antirheumatic, antidiabetic, anticancer, wound healing, antihemorrhoids, action on skin allergies, improves blood circulation, antiulcer, diuretic, effect on digestive, endocrine and metabolic disorders, anti-dysentery, prevention of anemia, action on reproductive, respiratory, and gastrointestinal disorders, astringent, effect on neurodegenerative disorders and liver problems)	[27]
F. carica (Common fig)	Alimentary (Consumption of fruits) Ornamental Medicinal (Anti-inflammatory, antinociceptive, antipyretic, antimicrobial, antiviral, antifungal, anti-helminthic, antidiabetic, hypoglycemic, hypocholesterolemic, hypolipidimic, antidiarrheal, hepatoprotective, anticancer/antitumor, antimutagenic, antispasmodic, antiplatelet, anticonstipation potential, anticoagulant, antiangiogenic, antioxidant, immunostimulant, haemostatic, erythropoietic stimulant, cardioprotective, antihypertensive, diuretic, anti-warts, action in respiratory and stomach disorders)	[1, 5, 6]

Figure 1. Tree and fruit (immature fig) belonging to the species *F. carica.*

species being the best known and most significant worldwide [5-7]. Specifically, *F. carica* is considered a very popular fruit crop and from a historical point of view, in the first part of the Bible, Genesis, it is mentioned that Adam and Eve, realizing that they were naked, covered themselves with Angiosperm leaves. The oldest evidence of its consumption comes from the Neolithic period (ca. 10,000-8,800 BCE) of southeastern Turkey and it is considered one of the oldest food tree crops domesticated and used by humans [8-10]. Some archaeological evidence suggests that the harvest of its fruit is more than 11,000 years old (before cereal grains) [8-11]. *F. carica*, also known as fig tree or common fig, is a deciduous shrub to 15 to 20 feet, with numerous spreading branches, non-adventitious roots, and bright green, simple, waxy leaves, hairy rough on the upper surface and downy hairy on the bottom. Generally, when the leaves are broken they exude a milky white emulsion with a sticky consistency called latex that contains ficin (protein hydrolytic enzyme). Its fruits (figs) are on the branches organized in pairs or solitary, they are thin-skinned, fleshy, hollow, pear-shaped, with inflorescences inside and can be black (they are the most common), green, purple, and blue. They are consumed by different populations of the world as fresh, dry or dehydrated food, canned, jams, sweets or preserves. Like the fruits, their seeds are edible, of medium size and hollow when not pollinated (**Figure 1**) [1-6]. Ficus plants are native to southwest Asia and the eastern Mediterranean but due to their easy adaptation and dispersion in different types of soil, their domestication process (especially *F. carica*) has increased favoring the constant collection of figs [1-6, 12]. The Food and Agriculture Organization (FAO) of the United Nations (2017) indicated that the main producing countries of this fruit are Turkey, Egypt, Morocco, Algeria, Iran, Syria, Spain, the United States, Brazil, and Tunisia. In the specific case of Mexico, the plant was introduced by the Spanish Franciscan missionaries by placing it in the atriums of the churches. The territorial surface (approximately 1,200 hectares) of *F. carica* cultivation is low (compared to corn and beans) and is located in 10 states [Morelos (58%), Hidalgo (14%), Veracruz (10%), Baja California Sur (6.5%), Mexico City (3.5%), Puebla (2.6%), Durango (2.4%), San Luis Potosí (1.5%), Sonora (1.1%) and Baja California (0.4%)], which together generate an annual production of 6 to 7 thousand tons between the months of August and October [13-15].

Nutritional composition and phytochemistry of the *Ficus* L. genus

Various research has documented the nutritional value of the genus. In general, it is made up of water (80%), starches, sugars (this proportion depends on the maturation time and the most common are glucose, fructose,

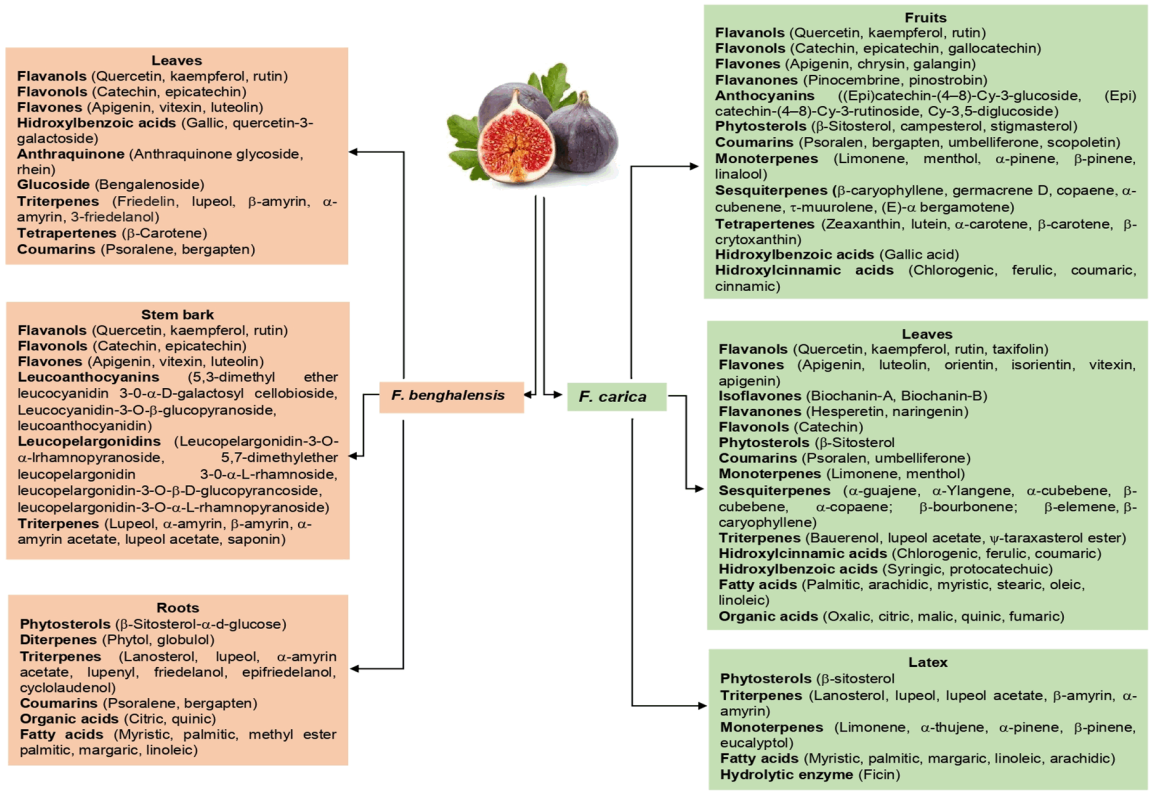

Figure 2. Phytochemical composition in different anatomical parts of *F. benghalensis* and *F. carica* [1-8, 21, 24, 28-30].

sucrose and pectins), amino acids [(especially aspartic acid (Asp) and glutamine Gln)], vitamins (A, C, B1, B2 and B6), organic acids (oxalic, quinic, malic, citric and succinic) minerals [Copper (Cu), Manganese (Mn), Magnesium (Mg), Potassium (K), Calcium (Ca), Sodium (Na), Iron (Fe), Zinc (Zn)] and large amounts of dietary soluble fiber [1-6, 28].

The majority of studies, using different extraction methods, suggest that there are differences in the phytochemical composition of the plant parts (roots, flowers, stems, bark, leaves, seeds, latex, pulp and fruits) between wild and domesticated species; which indisputably modifies its functional and therapeutic properties. These differences can be attributed to environmental conditions (climate, humidity), type of soil of the cultivation sites, harvest time and age of maturity of the bushes [1-6, 28]. **Figures 2** and **3** show the phytochemical composition of the different anatomical parts of four of the common species of *Ficus* L. Likewise, some of the phytochemical compounds identified in the aforementioned species are shown in **Figure 4**.

As mentioned above, the genus *Ficus* L. has the particularity of adapting and growing in different types of soil, which favors its nutritional, medicinal and economic impacts. Although most species have been used as a food source, *F. carica* continues to be the most representative for the biopharmaceutical and nutritional industries; especially for its fruits, which are considered by some authors as nutraceutical agents. That is, a food supplement that is apparently non-toxic and has been scientifically proven to be beneficial for health both in the treatment and in the prevention of some diseases [1, 28]. In this sense, the group and/or combination of bioactive compounds [flavonoids (flavanols, flavones, flavonols, isoflavones, chalcones, anthocyanins), phenolic acids (hydroxylcinnamic acids, hydroxylbenzoic acids), phytosterols, terpenes (triterpenes, tetraterpenes, diterpenes, sesquiterpenes, monoterpenes), coumarins, hydroxybenzoates, phenylpropanoids, chlorins, pheophytins, megastigmanes, chitinases, organic acids, fatty acids, amino acids, alkaloids, glycosides] from different parts of the plant (**Figures 2** and **3**) have

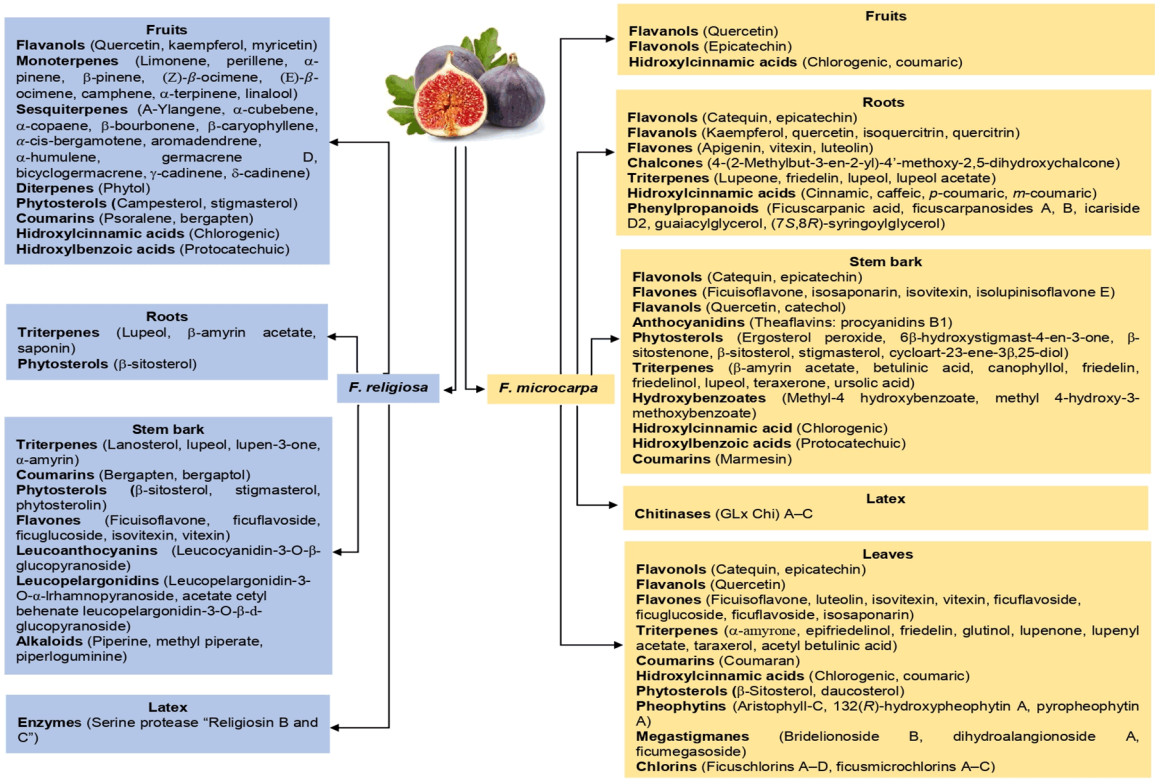

Figure 3. Phytochemical composition in different anatomical parts of *F. religiosa* and *F. microcarpa* [10, 18, 21, 22, 24, 28, 29].

been associated with the control, progression, and prevention of chronic and infectious diseases; mainly its antimicrobial, antifungal, antiviral, anti-helminthic, hypoglycamic, hypolipidemic, hepatoprotective, anti-inflammatory, analgesic, and antipyretic activities. Therefore, when using and combining keywords; as *Ficus* L. genus, *Ficus* plants or species, pharmacological and/or therapeutic properties, phytochemical composition and adverse and/or toxic effects, a scientific search was carried out in the main electronic databases (PubMEd, SciELO, Latindex, Redalyc, BiologyBrowser, ScienceResearch, ScienceDirect, World Wide Science, Web of Science, Academic Journals, Ethnobotany, Scopus and Google Scholar). The present review (Part 1) compiles information from published research (in vitro, in vivo and clinical studies) on these therapeutic and/or pharmacological properties, which will be discussed below. Unlike most scientific articles where the individual characteristics and properties of each species are mainly described; this document brings together the largest number of studies on *Ficus* plants described by different authors.

Biological activities

Antimicrobial effect

A dormant threat when treating bacterial diseases (such as pneumonia, tuberculosis, urinary tract infections, pharyngitis, meningitis) and/or fungal diseases is the resistance that microorganisms develop to avoid being attacked by synthetic anti-infective agents. Thus, natural products are becoming a rich source of these agents that, by working at different target sites, and apparently being safer, can replace synthetic compounds. More than 30,000 compounds with this activity have been extracted from approximately 1,300 plants, including garlic, parsley, oregano, ginger, rosemary, lemongrass, and chili pepper. Among the most relevant anti-infective bioactive compounds are organic acids, thiosulfinates, glucosinolates, saponins, flavonoids and phenols [31].

The genus *Ficus* L. is not an exception, since the analysis of its antimicrobial capacity has generated a significant number of investigations in recent decades. Mousa *et al*. (1994)

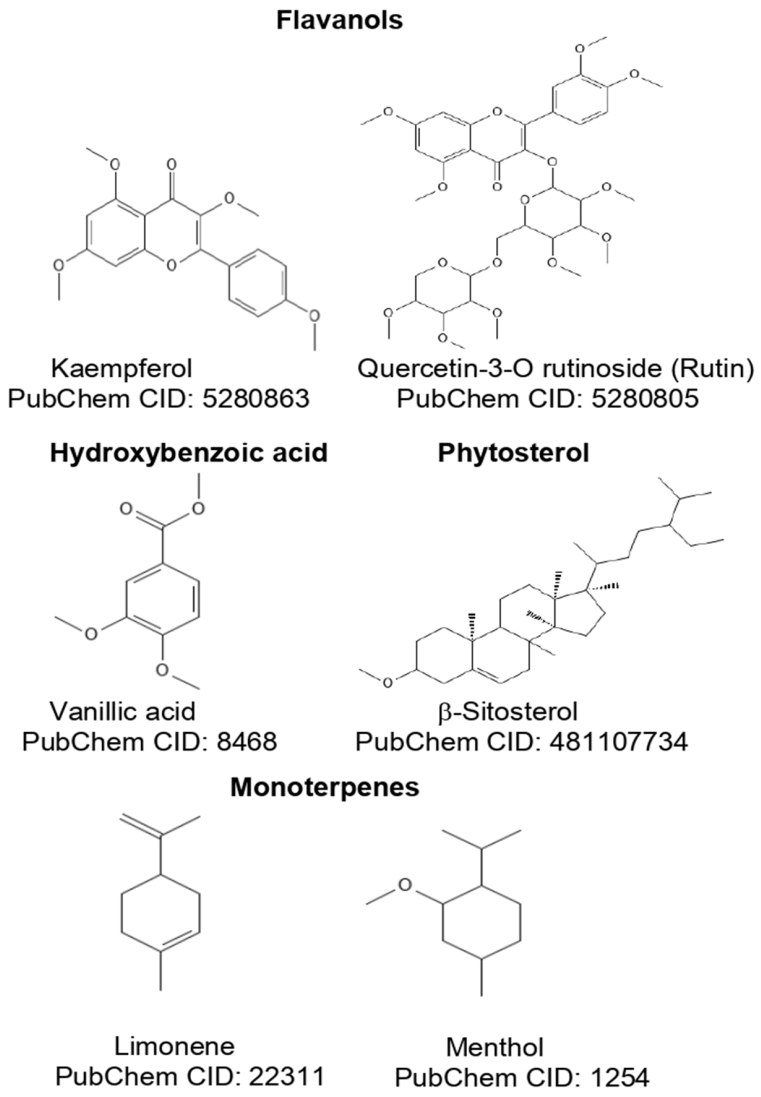

Figure 4. Flavanols, monoterpenes, hydroxybenzoic acid, and phytosterol identified in *Ficus* species.

and Valsaraj *et al*. (1997) initiated this field of study. First, the bioactivity of fruit extracts from four Egyptian species of *Ficus* was evaluated; finding an antimicrobial effect with *F. benghalensis* and *F. religiosa* by inhibiting the growth of *Azobacter chroococcum*, *Bacillus cereus*, *Bacillus megaterium*, *Streptococcus faecalis*, and *Klebsiella pneumonia* [32]. This therapeutic activity of 78 medicinal plants from India was confirmed in the second study, in which aqueous and ethanolic extracts from the leaves of *F. religiosa* developed antibacterial action against *Staphylococcus aureus*, *Escherichia coli, Salmonella paratyphi, Salmonella typhi, Shigella dysenteriae*, *S. typhimurium*, *Pseudomonas aeruginosa*, and *Bacillus subtilis* [33]. Farrukh and Iqbal (2003) confirmed these results by inhibiting the growth of these bacteria with an ethanolic (EtOH) extract from the same *Ficus* species [34]. Considering the therapeutic impact shown by *F. religiosa*, extracts of methanol (MeOH), chloroform (Chl) and water from its leaves were analyzed, confirming that the greatest antibacterial spectrum corresponded to chloroform (Chl) [35]. On the other hand, when analyzing a methanol (MeOH) extract obtained from the bark of *F. microcarpa*, the inhibition of *Bacillus brevis*, *Bacillus cereus*, *Bacillus subtilis*, and *Escherichia coli* was evidenced [36]. Similarly, when using the same type of extract but from *F. carica* leaves, a strong antibacterial activity was shown against *Streptococcus anginosus*, *Streptococcus gordonii*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* (bacteria common in the oral cavity) [37].

To date, different extracts [(aqueous, methanol (MeOH), ethanol (EtOH), hexane (Hx), chloroform (Chl), ethyl acetate (EtOAc), dichloromethane (DCM), petroleum ether and acetone (Ace)] evaluated and obtained from the leaves, fruits, latex, roots, and stem bark of *F. elástica, F. benghalensis, F. racemose, F. religiosa, F. sycomorus*, and *F. carica* (mainly these last two species) have demonstrated their potential to inhibit the growth of Gram-negative bacteria (*Salmonella typhimurium, Salmonella typhi, Escherichia coli, Pseudomonas aeruginosa, Shigella flexneri, Shigella boydii, Vibrio cholerae, Enterobacter cloacae, Enterobacter aerogenes, Enterobacter sakazakii, Klebsiella pneumoniae, Citrobacter freundii, Proteus mirabilis, Proteus vulgaris, Klebsiella oxytoca, Chromobacterium violaceum, Prevotella intermedia, Aggregatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis*) and Gr-

am-positive bacteria (*Staphylococcus aureus, Staphylococcus saprophyticus, Staphylococcus epidermidis, Bacillus subtilis, Bacillus cereus, Bacillus pumilis, Enterococcus faecalis, Mycobacterium tuberculosis, Streptococcus pyogenes, Streptococcus gordonii, Clostridium perfringens, Streptococcus anginosus, Listeria innocua* and *Listeria monocytogenes*) (**Table 2**).

Several authors agree and consider that flavonoids, tannins, terpenoids, sterols, saponins and coumarins are involved in the antimicrobial activity of extracts from the *Ficus* genus. Flavonoids especially, (such as rutin, quercetin and luteolin) have multiple cellular targets where they form complexes with proteins through hydrogen bonds and/or covalent bonds. These complexes induce an antimicrobial action by inactivating microbial adhesins, enzymes and cell envelope transport proteins. In general, flavonoids inhibit nucleic acid synthesis, reduce energy metabolism and alter the function of the cytoplasmic membrane [38-40].

On the other hand, tannins are considered toxic compounds for bacteria, because they bind to their cell walls and prevent their growth (they form hydrogen bonds with proteins and phospholipids in the bacterial membrane, causing damage, leakage of metabolites and reduction of microbial biochemical activity). Terpenoids are also believed to modify the bacterial membrane through the action and alteration of lipophilic compounds. Finally, coumarins (such as psoralen and bergapten) have shown similar mechanisms of action against Gram-positive and Gram-negative bacteria [41, 42].

Antifungal effect

Regarding the antifungal effect, Mavlonov *et al.* (2008) identified a low molecular weight antifungal protein from the latex of *F. carica* [59]. This motivated the group of Lazreg Aref (2010) to evaluate the antifungal activity of different extracts (MeOH, Hx, Chl, and EtOAc) from *F. carica* latex against *Aspergillus fumigates, Trichophyton rubrum, Trichophyton soudanense, Microsporum canis, Scopulariopsis brevicaulis, Candida albicans* and *Cryptococcus neoformans*. Their results showed that the MeOH, Hx, and EtOAc fractions were the most effective in inhibiting *C. albicans* and *M. canis* [43].

In general, relevant antifungal action has been observed against *Candida albicans, Aspergillus fumigatus, Aspergillus niger, Trichophyton rubrum, Trichophyton soudanense, Microsporum canis, Scopulariopsis brevicaulis, Penicillium notatum, Penicillium italicum, Cryptococcus neoformans, Fusarium solani, Saccharomyces cerevisiae, Alternaria alternata, F. chlamydosporum, Rhizoctonia bataticola,* and *Trichoderma viride*. **Table 3** shows the main studies that demonstrate the antifungal effects of the genus *Ficus* L.

As well as the antimicrobial effect, most studies suggest that the antifungal potential can also be attributed to the bioactive compounds found in the different extracts, especially flavonoids, coumarins, hydroxybenzoic acids, terpenoids and sterols (**Figure 4**) [2, 5, 17, 18, 29]. Specifically, flavonoids inhibit fungal growth through several mechanisms including plasma membrane alteration, induction of mitochondrial dysfunction, inhibition of cell wall formation, modification of cell division and blocking of RNA and protein synthesis [60]. Wan *et al*. (2017) isolated and evaluated the antifungal activity of pinocembrin-7-O-β-D-glucoside (a flavonoid present in an EtOH extract of *F. hirta* fruits) against postharvest citrus infections caused by *P. italicum* (blue mold). The results showed a significant decrease in the phytopathogen during spore germination and mycelium growth when they are exposed to the flavonoid. It was concluded that pinocembrin inhibited mycelial growth by interfering with energy homeostasis and cell membrane damage [61].

In the case of coumarins, Aboody *et al*. (2020) studied 40 of these phytochemicals against *C. albicans*, *A. fumigates* and *F. solani*. They found that ostenol and 4-acetatecoumarin showed a very significant antifungal activity [60]. Another study also confirmed that 4-methoxycoumarin showed relevant antifungal activity against *F. solani* [62]. This research suggests that the death of fungal mycelia occurs by affecting the structure and function of peroxisomes and mitochondria and by inhibiting β-oxidation of fatty acids.

When evaluating vanillic acid (hydroxybenzoic acid) on the growth of *Sclerotium rolfsii*, we observed that concentrations of 0.05 and 0.10% significantly inhibited the growth of the

Table 2. Studies testing for antimicrobial effects of the most representative species of the genus *Ficus* L.

Extract or phytochemical/Plant part	Objective and biological effect	Ref
F. carica		
Mixture of aqueous and EtOH (80:20)/fruit peel and pulp	After identifying bioactive compounds and the antibacterial effect of the extract mixture. The results showed that the phenolic and nutritional profiles were higher in the fig skin. However, the extracts of both plant parts showed practically the same potential to reduce the growth of *S. aureus E. coli* and *M. morga*nii (MIC between 2.5 and 5.0 mg/mL)	[4]
MeOH/leaves	The extract showed an MIC of 1600 µg/mL against the H37Rv strain of *M. tuberculosis*	[6]
MeOH/leaves	The extract showed a minimum inhibitory concentration (MIC) between 0.156 and 5 mg/ml against bacteria from the oral cavity (*S. anginosus, S. gordonii, P. intermedia, A. actinomycetemcomitans* and *P. gingivalis*). It is suggested that figs could be used as natural antibacterial agents in oral care products	[37]
EtOH/leaves	The purpose of the study was to determine the MIC and the minimum bactericidal concentration (MBC) of the extract against *E. faecalis* and its cytotoxicity in fibroblastic cells in vitro. The results showed a reduction in bacterial growth at a concentration of 25% of the extract; while the MBC was 50%. Fibroblasts did not show any cytotoxic effect	[38]
Hx/latex	The final result of the study showed a MIC of 19 µg/mL, especially for *S. saprophyticus* and *S. aureus.* Apparently, this antibacterial activity could be attributed to the coumarins present in the chemical composition of the extract	[41]
MeOH, Chl, Hx and EtOAc/latex	The results indicated that EtOAc acted on the proliferation of 5 bacterial species (*E. faecalis, C. freundei, P. aeruginosa, E. coli* and *P. mirabilis*). While MeOH only inhibited *P. mirabilis*	[43]
MeOH/leaves	The microbroth dilution method showed MIC ranges between 31.25 and 250 g/ml against *S. aromaticum, S. aureus, S. epidermidis, S. pyogenes, S. typhi* and *P. aeruginosa*. These results suggest that *F. carica* could provide natural antimicrobial agents to control infections caused by bacteria resistant to conventional antibiotics	[44]
MeOH, EtOH, DCM/Whole plant	Quorum sensing (QS), as the basis of bacterial communication, is a promising approach to reduce the incidence of multidrug resistance. Therefore, the anti-QS properties of some extracts against *C. violaceum* and *P. aeruginosa* were evaluated. After evaluating this activity by violacein production and swarm motility, the conclusion was that the DCM extract showed the most pronounced inhibition for both bacteria	[45]
MeOH/fruits	Initially, the antioxidant and antibacterial activities of MeOH extracts from some edible fruits were evaluated. Subsequently, nanocomposite biofilms based on chitosan and carboxymethylcellulose were characterized, adding the most significant fruit extract. The best antibacterial effects belong to *P. granatum* and *F. carica*; especially against *S. aureus, B. subtilis, B. cereus, L. monocytogenes, S. typhimurium* and *E. coli*. With this result, 1% of the extract of *F. carica* was added to the nanocomposite biofilms and its antimicrobial activity was again evaluated; concluding that both the antioxidant activity and the halos of bacterial inhibition increased	[46, 47]
Aqueous, EtOH, MeOH and Ace/pulp	Using the Folin-Ciocalteu method and HPLC, it was revealed that the extracts contained polyphenols, flavonoids and tannins. On the other hand, the microplate assay and diffusion in agar medium confirmed that EtOH and MeOH extracts were the most effective to inhibit the growth of most of the tested strains (*L. innocua, B. subtilis, C. perfringens, E. faecalis and S. aureus, V. cholerae, P. aeruginosa, E. coli, E. sakazakii, E. cloacae, P. mirabilis, C. freundii, K. oxytoca* and *S. odorifera*)	[48]

Aqueous and MeOH/fruits	After using matrix-assisted laser desorption ionization time in flight mass spectrometry (MALDI-TOF MS), 3 bacteria belonging to the species *E. cloacae* were identified. Subsequently, its control was analyzed using the aforementioned extracts. The MIC and MBC results showed that the extracts significantly inhibited the activity of *E. cloacae*. This seems to provide good guidance for the use of dried figs against infections by this bacterial species	[49]
F. benghalensis		
Flavonoids/stem bark	The evaluation showed that flavonoids significantly inhibited *P. vulgaris, S. aureus* and *P. aeruginosa* (MIC between 25 and 100 mg/ml)	[50]
Flavonoids/stem bark	The relationship between the antibacterial activity of flavonoids (2 polymethoxyflavones and 4 isoflavonoids) and their interaction with the *E. coli* membrane was analyzed. A positive correlation between the antibacterial capacity and the effect of membrane rigidity was evidenced and a quantitative structure-activity relationship (QSAR) study demonstrated that the effect of flavonoids is attributed to a molecular hydrophobicity and charges on C atom at position3 (C3). Probably, the QSAR model can predict the antibacterial activity of other flavonoids	[51]
F. religiose		
EtOH/Whole plant	Phytochemical groups, cytotoxicity (lethality test of brine shrimp) and antibacterial action (agar disk diffusion method) of the extract were determined. The results indicated the presence of alkaloids, glycosides, steroids, gums, reducing sugars, tannins, flavonoids and saponins. Shrimp mortality increased as the extract dose increased, obtaining an LC_{50} of 2.7 µg/ml. Of the 14 pathogenic bacteria evaluated, *E. faecalis* was the most inhibited (MIC: 250-500 µg/ml)	[52]
EtOH/fruits	At the end of the study, the extract showed an MIC of 15 mg/ml for *S. aureus* and *S. epidermidis*. While for *K. pneumoniae* and *P. vulgaris* it was 30 mg/ml	[53]
F. sycomorus		
Aqueous/leaves and latex	Silver nanoparticles (SNPs) obtained from latex and an aqueous extract were tested against Gram positive and negative pathogenic bacteria. The SNPs showed antibacterial activity in all strains tested (*S. typhimurium, S. typhi, S. flexneri, E. faecalis, E. cloacae, E. aerogenes, P. aeruginosa, K. pneumoniae, E. coli*, and *S. aureus*). However, the most significant effectiveness corresponded to the liquid medium (aqueous extract); probably due to the higher silver content and better contact with bacteria	[54]
MeOH and Ace/ leaves (LE) and stem-bark (SBE)	The results showed that the Ace extract was the one with the highest antimicrobial activity against *A. baumannii* and *S. aureus*, recording a MIC of 2.5 mg/ml; for LE and for SBE of 4.9 mg/ml	[55]
EtOH and EtOAc/ fruits	The evidence suggests that both extracts inhibited the growth of *S. aureus, B. cereus, E. coli* and *S. typhimurium* with a MIC between 12.72 and 17.11 mm. In addition, Gas Chromatography coupled to Mass Spectrometry (GC/MS) analysis identified high concentrations of flavonoids, tannins, alkaloids, and steroids; which, together, favor the antimicrobial effectiveness	[56]
F. racemose		
Ether/leaves	The antibacterial potency of the extract against *E. coli, B. pumilis, B. subtilis, P. aeruginosa* and *S. aureus* was determined. The study confirmed an inhibitory activity comparable to that of chloramphenicol. This property could be attributed to the terpenoids present in its chemical composition	[25]
MeOH/leaves (MCELFr) and fruits (MCEFFr)	After identifying the bioactive polyphenols by high performance liquid chromatography with diode array detector (HPLC-DAD) of the extracts. Its antioxidant and antibacterial activity was determined. The HPLC-DAD analysis evidenced the presence of flavonoids and tannins. Both MCELFr and MCEFFr inhibited the growth of *E. coli, S. flexneri, S. boydii,* and *S. epidermidis*. In addition, they showed the ability to eliminate superoxide and hydroxyl radicals	[57]
F. elastica		
MeOH/aerial roots	The phytochemical analysis of the extract showed Linear aliphatic alkanes with n-hexacosane, β-sitosterol, biochanin A, sitosteril 3-O-β-Dglucopyranoside, elasticamide, elastiquinone and ficusoside B. The latter demonstrated significant inhibition against *S. aureus, E. coli, P. vulgaris, P. stuartii,* and *P. aeruginosa*	[58]

Table 3. Studies testing for antifungal effects of the most representative species of the genus *Ficus* L.

Extract or phytochemical/Plant part	Objective and biological effect	Ref
F. hirta Vahl		
EtOH/fruits	Two carboline alkaloids, five sesquiterpenoids/norsesquiterpenoids, three flavonoids, and one phenylpropane-1,2-diol were identified for the first time from this extract by 1D and 2D NMR and HR-ESI-MS analysis. On the other hand, the antifungal assay revealed that the flavonoid (pinocembrin-7-O-β-d-glucoside) showed an inhibition effect against *P. italicum* of 13.70% at 25 μg/mL	[61]
Aqueous/fruits	The Xinyu mandarin is a perishable citrus vulnerable to *P. italicum* infections. To reduce economic losses caused by fungal damage, edible coatings based on *F. hirta* Vahl. fruits extract-incorporated chitosan have been applied. Such coating decreased fungal growth on mandarins stored at 5°C reducing postharvest losses and improving the storage capacity of Xinyu mandarins	[65]
EtOAc and Ace/fruits	Through in vitro tests, the antioxidant and antifungal activity of various solvent extracts of its fruits was evaluated. The EtOAc and Ace extracts showed abundant antioxidant components, emphasizing the flavonoid content; to which an important antifungal activity against *P. italicum* was attributed	[66]
Fruits	As mentioned above, *P. italicum* affects the postharvest of citrus fruits. Therefore, after obtaining a flavonone (pinocembroside) from the fruit of *F. hirta* Vahl., its antifungal activity against this blue mold was evaluated. Mycelial growth in Newhall navel oranges was inhibited by flavonone in a dose-dependent manner (minimum fungicidal concentration (MFC): 800 mg/L). The conclusion is that flavonone could increase the permeability of the membrane, accelerating lipid peroxidation in the fungus	[67]
F. carica		
Latex	Using mass spectroscopy and an amino acid sequencer, a low molecular weight (6481 Da) antifungal protein was isolated. In general, composed of Arginine (Arg), Proline (Pro), Aspartic Acid (Asp), Phenylalanine (Phe), Leucine (Leu) and Glutamine (Glu)	[59]
MeOH, Chl, Hx, and EtOAc/latex	The antifungal potential of the extracts against opportunistic pathogenic yeasts was explored. The Chl and EtOAc fractions showed the highest inhibition (100%) in all fungi. In contrast, the MeOH fraction only inhibited *C. albicans* and *M. canis* (500 μg/ml concentration); unfortunately, it had no effect against *C. neoformans*. Finally, the Hx extract showed low inhibitory capacity	[43]
Latex	Fig latex contains proteases (mainly ficin) and chitinolytic enzymes that protect the plant from pathogens. For this reason, the changes in its composition of proteins, enzymes and antifungal activity during the ripening of the fruit were studied. The latex samples showed a uniform increase in protein concentration and a decrease in ficin content according to the ripening time of the fruit. Another important observation was that the antifungal activity against *S. cerevisiae* was more extensive in Spring	[68]
F. religiose		
EtOH/Whole plant	16 extracts from 22 Indian medicinal plants showed antifungal activity against 5 filamentous fungi (*A. niger, A. alternata, F. chlamydosporum, R. bataticola* and *T. viride*) and one yeast (*C. albicans*); highlighting *F. religiosa* by significantly inhibiting the growth of *C. albicans*	[34]
Aqueous, MeOH and Chl/leaves	The results indicated that all the extracts were active against fungal strains, especially *A. niger* and *P. notatum*	[35]
F. elastica		
MeOH/aerial roots	Initially, a ficusoside B was isolated from the extract with antimicrobial activity against *S. aureus* and *E. coli*. Subsequently, the same methodological process was developed to analyze the antifungal capacity of ficusoside B. It was found that it also inhibits the growth of *C. albicans*	[58]

fungus. Its inhibition is attributable to a morphological distortion of hyphae and sclerotia, and to a reduction in fungal enzymatic activity (catalase, peroxidase, polyphenol oxidase and phenylalanine ammonia-lyase) [63]. Finally, Leite-Andrade *et al*. (2022) demonstrated that D-limonene (natural Monoterpene) showed a relevant antifungal and antivirulent activity against *Candida parapsilosis* by inhibiting the morphogenesis of its yeasts, adhering to the human epithelium and inducing an apoptotic mechanism [64].

Antiviral effect

In relation to the antiviral effect; again, natural products are a good alternative for the treatment of viral infections that are responsible for various chronic and acute diseases associated with high rates of morbidity and mortality. A wide variety of bioactive and/or phytochemical compounds (such as coumarins, flavonoids, terpenoids, organosulfur compounds, lignans, polyphenols, saponins, proteins, and peptides) have been found to influence cell functions, membrane permeability, and viral replication [31]. To date, there are few studies on the genus *Ficus* L. where its antiviral potential has been evaluated. The first was developed by Wang *et al*. (2004) to determine the anti-HSV-1 (herpes simplex type 1) effect of the aqueous extract of *F. carica* leaves on human epithelial (Hep-2), baby hamster kidney fibroblasts (BHK21) and primary rat kidney (PRK) cells. Ultimately, they confirmed low cell toxicity and direct virus killing at a maximum tolerated concentration (MTC) of 15 mg/ml [69]. Subsequently, they analyzed the antiviral activity of five extracts (MeOH, Hx, EtOAc, Chl, and Hx/EtOAc) from *F. carica* latex against HSV-1, echovirus type 11 (ECV-11) and adenovirus (ADV). The results showed that the Hx extract and the Hx/EtOAc (V/V) mixture were the best candidates to inhibit viral replication in Vero cells [70]. Finally, considering the above results, *F. carica* latex was added to Madin Darby bovine kidney (MDBK) cell cultures infected with caprine herpesvirus-1 (CpHV-1). The addition of latex showed significant MTC, reducing CpHV-1 infection and suggesting that latex possibly interferes with viral replication [71].

In this sense, several authors [7, 70-73] consider that the combination of caoutchouc, resin, albumin, cerin, malic acid, rennin, proteolytics enzymes (mainly ficin), esterase, lipase, catalase, peroxidase, bioactive compounds of latex, affect viral infection by acting on cellular receptors, and preventing adsorption and/or penetration of the virus into host cells (that is, they can be active on intracellular viral replication). Lazreg-Aref *et al.* (2012) have also suggested that coumarins have an inhibitory effect on DNA gyrase and that it may be related to anti-HIV (human immunodeficiency virus) activity [41].

Recently, Dell'Annunziata *et al*. (2022) investigated on VERO CCL-81 cell lines the antiviral potential of three extracts (MeOH, Hx and EtOAc) from *F. rubiginosa* leaves against Herpes simplex virus-1 (HSV-1), Human coronavirus (HCoV)-229E, and Poliovirus-1 (PV-1). After analyzing different stages of viral infection through viral pretreatment, cotreatment, cell pretreatment, and post-infection assays; their results showed that the extracts exerted their inhibitory early action in the viral infection cycle, mainly during the absorption and/or penetration into the host cell. They were found to be active against HSV-1 and HCoV-229E through direct interaction with viral particles and by blocking the access of the viruses to host cells. This mode of action was similar for both wrapped viruses, but not for naked viruses (such as PV-1), suggesting that MeOH, Hx and EtOAc might act on the outermost viral structure, particularly on the envelope glycoproteins [74].

Anti-helminthic effect

Although antiparasitic drugs (also called anthelmintics) are often effective, there is still a high prevalence of taeniasis (*Taenia saginata, Taenia solium, and Taenia asiatica*), ascariasis (*Ascaris lumbricoides*), and threadworm infection (*Enterobius vermicularis*) in Asia, Africa, and Latin America. Anthelmintic or vermifuge medicinal plants (capacity to kill or expel worms), constitute an alternative to help conventional treatments to avoid discomfort and/or serious damage to the health of the host [75]. Among the most common plants with vermifuge capacity are pumpkin (*Cucurbita pepo*), papaya (*Carica papaya*), epazote (*Dysphania ambrosioides*) and, indisputably, the genus *Ficus*. This field of research began with Nagaty

et al. (1959) using latex extracts of *F. carica* and *C. papaya* to control canine ascariasis [76]. Considering that the latex of the genus *Ficus* has a high content of a proteolytic enzyme (Ficin), the effect of *F. glabrata* against intestinal helminthiasis in three Amazonian villages was analyzed. The results of the clinical trial demonstrated that a dose of 1.0 cm^3 of latex/kg/day for 3 days and repeating this treatment every 3 months reduced the incidence of *Strongyloides stercoralis, Trichuris trichiura, Necator americanus, T. asiatica*, and *A. lumbricoides*; especially against this last helminth where a lethal effect was presented, whose effectiveness was related to the action of ficin [77]. Similar data were also obtained with latex extracted from *F. insipida* and *F. carica* when administered intragastrically (4 mL/kg/day for 3 days) to NIH mice infected with *Syphacia obvelata, Aspiculuris tetraptera*, and *Vampirolepis nana* [78]. On the other hand, Mishra *et al*. (2005) studied the effect of EtOH and aqueous extracts of the fruits of *F. racemosa* on the movements of *Setaria cervi* both of the whole parasite and in preparations of the nervous muscle; as well as in the survival of their microfilariae. Both extracts (concentrations between 50 and 350 μg/mL) inhibited the spontaneous motility of the worm and in the tissue analyzed. In addition, the in vitro assay confirmed an antifilaria effect at a lethal concentration 90 (LC_{90}) between 21 and 42 ng/ml [79]. In order to clarify the mechanism of action and compare the anthelmintic efficacy of cysteine proteinases (CPs) from various fruits, including figs, an in vitro assay was developed using the rodent gastrointestinal nematode *Heligmosomoides polygyrus*. After a 2-h incubation, cysteine proteinases caused damage to the protective cuticle of the worms; especially those belonging to the raw latex extracted from the fig. The data obtained suggested that these plant enzymes (particularly ficin) may be potential candidates for new anthelmintic agents [80]. *F. racemosa* has also shown vermifuge capacity. In a first study it was shown that aqueous extracts (50 mg/mL) significantly inhibited the motility of adult earthworms [81]. While at a dose of 10 mg of its latex per gram of soil, the population of the root-knot nematode *Meloidogyne incognita* was suppressed [82]. Both results suggest that *F. racemosa* could be considered for farmers as a biocontrol agent against infective management of earthworms. Other parasites, such as *Bursaphelenchus xylophilus* (pine wood nematode), *Panagrellus redivivus* (fish microparasite) and *Caenorhabditis elegans* (soil worm) have also been killed (mortality between 73 and 98%) by methanolic extracts from the leaves of *F. carica*; suggesting that this nematicidal effect is attributed to a coumarin called psoralen [83].

Nigerian researchers examined the potential of three ethnoveterinary plants (*Irvingia gabonensis*, *F. exasperata* and *Vernonia amygdalina* Delile) to treat worm infestation in eastern Nigeria. After infecting mice with *Heligmosomoides bakeri* larvae and administering different doses (200, 400, 800 mg/kg) of the leaf extracts, they confirmed that *F. exasperata* was the one that showed the best anthelmintic effect, causing 100% larval mortality [84]. Subsequently, the antischistosomal activity of aqueous extracts of *Calotropis procera* (Cp), *Zingiber officinale* (Zo) and *F. elastica* (Fe) was compared in male mice infected with *Schistosoma mansoni*. After oral administration (500 mg/kg for three consecutive days) with aqueous latex from stem and flower, the researchers evaluated the safety, worm recovery, tissue egg load and oogram pattern. The results of the study were that Cp and Fe reduced the number of S. mansoni and affected the egg load in the tissues and the pattern of oograms; unlike Zo, which slightly decreased 7.0% of the worms. In addition, it was established that the Fe extract was safer; since Cp proved to be toxic even in a small dose (250 mg/kg) [85]. Because the data suggest that ficin and psoralen in latex are the bioactive compounds responsible for exerting its vermifuge capacity; Guo *et al*. (2016) isolated from an EtOH extract of *F. carica* leaves two linear furocoumarins (bergapten and psoralen), which again had a nematicidal effect against *Bursaphelenchus xylophilus* by inhibiting its amylase, cellulase and acetylcholinesterase; confirming that bergapten is also involved in the vermifugal potential [86]. Finally, Wanderley *et al*. (2018) studied the anthelmintic activity of a purified cysteine protease (FbP) from *F. benjamina* latex against *Haemonchus contortus* (a gastrointestinal nematode found in ruminant herds). FbP had an approximate molecular weight of 24 kDa and its proteolytic activity was stable at pH ranges between 6 and 10 where it inhibited both larval development and unsheathing [87].

In general, the anthelmintic potential of the different extracts of *Ficus* plants has been attributed to the synergistic action of their flavonoids, aminoacids, steroids, saponins, coumarins and tannins [88-90]. These phytoconstituents favor an individual or combined effect by killing the parasite (vermicidal and/or nematicidal), or by inducing its paralysis in the gastrointestinal tract of the infected host. As mentioned, furocoumarins (bergapten and psoralen) have demonstrated nematicidal potential by inhibiting enzymatic activities of the parasites [83, 86].

In the case of ficin and CPs, their mechanism of action is similar, since they have a high proteolytic activity (digestion and/or elimination) on the protective cuticles (mainly formed by graticuled collagens linked by disulfide bonds) of nematodes. Therefore, if the cuticle is degraded, it turns the parasite into a weak organism, without motility and sensitive to elimination. Some authors consider ficin and CPs an alternative strategy in the treatment of gastrointestinal nematode infections (both in humans and animals); since the risk of developing resistance is presumably low (in comparison to the use of ivermectin, albendazole, and levamisole). This hypothesis is based on the consideration that nematodes would have to alter the structure or components of their cuticle, and/or encode inhibitors of ficin or CPs to prevent their insertion into the cuticle [78, 80, 87, 91]. On the other hand, Athanasiadou *et al*. (2001) and Ahamat *et al*. (2021) reported and agreed that gallic and gentisic acids present in the chemical composition of tannins extracted from *F. sycomorus* are toxic to *Caenorhabditis elegans* and *Onchocerca ochengi.* Possibly, death is attributed to the binding of tannins to glycoproteins of the cuticle of the parasites in the gastrointestinal tract of the host [89, 92].

Hypoglycemic and hypolipidemic effect

The metabolic syndrome (MetS) is the set of metabolic abnormalities of carbohydrates and lipids that describes insulin resistance and/or type 2 diabetes mellitus (DM2) associated with abdominal obesity (AO) and cardiovascular diseases. These alterations are closely related; when there is a decrease in glucose uptake, stimulated by insulin, and an increase in visceral fat (mainly in the liver, muscles and pancreas) they induce the formation of adipokines that favors proinflammatory and prothrombotic states that contribute to the development of insulin resistance, hyperinsulinemia, endothelial dysfunction, macrovascular (atherosclerosis) and microvascular (retinopathy, nephropathy and neuropathy) complications. In addition, poor clinical control of patients can cause serious problems in the kidneys and heart [31]. It should be remembered that oxidative stress (OXs) is also related to insulin resistance and AO and that a high concentration of reactive oxygen species (ROS) can induce and/or favor the development of MetS [31, 93].

After studying the antimicrobial and antifungal effects, the greatest scientific interest in the genus *Ficus* L. has focused on its ability to treat DM2 and AO. To date, approximately 42 scientific articles have been published since the 1960s; 33 of which belong to in vivo studies (mainly using rodents and rabbits), 5 are in vitro trials and 4 of them are clinical investigations.

Research on hypoglycemic and hypolipidemic activity began with Brahmachari and Augusti (1962) and Ambika and Rao (1967). The first authors found that administering an aqueous extract of *F. religiosa* root bark (2.5 g/kg) to albino rabbits reduced blood glucose levels [94]. Subsequently, a sitosteryl-d-glucoside (phytosterolin) was isolated from the same *Ficus* species, which was also administered to rabbits. Intravenous (i.v.) administration of phytosterolin (7.5 mg/kg) decreased glucose concentration, suggesting that this phytochemical could be responsible for the hypoglycemic effect of the cortex [95].

Later, Spanish scientists carried out six studies that were essential to expand this field of research. Their analysis began with the effect of an aqueous extract of *F. carica* leaves on rats with streptozocin-induced diabetes (STZ). Oral (v.o.) and intraperitoneal (i.p.) administration of the extract prevented loss of body weight in the animals and increased the survival rate that had been affected by elevated plasma insulin levels [96]. In a second study, the decoction of *F. carica* leaves (aqueous extract) and its supplementation at breakfast in patients with insulin-dependent diabetes mellitus (IDDM) were evaluated on preprandial and postprandial glycemia, glycosylated hemoglobin (HbA1c), and total cholesterol (T-Cho). At the end of the month of treatment, all the

parameters had been significantly reduced; in particular, the administration of insulin was reduced and there were no alterations in preprandial glycemia [97]. Using a rat model of hypertriglyceridemia, i.p. administration of the same decoction of leaves was measured. After injection of the extract, plasma triglyceride (TG) levels had significantly decreased [98]. In the fourth study, diabetic rats were changed from regular water consumption to the aqueous extract for three weeks. At the end of the period, the extract reduced plasma glucose in diabetic animals and in non-diabetic rats, insulin levels had also decreased. The combination of both data sets suggested that in addition to hypoglycemic activity, there may be a peripheral insulin-like effect [99]. These results led to the analysis of a Chl extract obtained from the decoction of leaves on the cholesterolemia of diabetic rats. Administration of the organic phase in diabetic animals with STZ improved T-Cho levels and reduced hyperglycemia [100]. Finally, parameters related to the OXs were studied in diabetic rats. Elevated levels of erythrocyte catalase (CAT), saturated fatty acids, and monounsaturated and polyunsaturated fatty acids returned to normal values with the administration of a single dose of a chloroform extract of *F. carica* [101]. Taken together, these results suggest that *F. carica* has hypoglycemic activity, influence on lipid catabolism, and antioxidant potential. In this regard, Deepa *et al*. (2018) reported that crude extracts and active compounds of various species of *Ficus*; especially *F. benghalensis, F. capensis, F. religiosa, F. microcarpa, F. racemosa, F. glumosa, F. deltoidea* and *F. carica* by means of in vitro and in vivo models have demonstrated their antidiabetic properties. In particular, the trials with the use of alloxane (Allox) and STZ showed antidiabetic actions related to the inhibition of glucose absorption and regulation of enzyme activities in the intestinal tract, stimulation of secretion and improvement of insulin sensitivity, increase in hepatic glycogen synthesis and peripheral glucose uptake and favorable stimulation of antioxidant status [102]. Given that the information is very extensive, **Table 4** summarizes and analyzes the most significant documents of the genus *Ficus* L. on DM2 and AO.

Different authors agree that the mechanisms of action involved in the hypoglycemic and hypolipidemic effect of *Ficus* species are diverse (**Figure 5**). In general, these mechanisms are related to: a) inhibition of glucose absorption in the intestinal tract, b) improvement of glucose uptake in skeletal muscle, c) reduction of blood glucose through an antioxidant mechanism, and d) pancreatic and hepatic homeostatic regulation of blood glucose levels. The latter, divided into two forms; either by breaking down glycogen (glycogenesis) or by synthesizing glucose from other metabolites such as amino acids, lactate, pyruvate and glycerol (gluconeogenesis) [102-109]. Bioactive compounds isolated from *Ficus* species with antidiabetic potential are quercetin, psoralen, kaempferol, ficusin, α-amyrin acetate, vitexin, isovitexin and naringenin [102-106].

Hepatoprotective effect

The liver is the key organ responsible for regulating the body's metabolism, secretion, storage, and detoxification. Therefore, if it is affected or damaged (by various toxic components acquired through food and/or medication), its functions will be distorted. Although there are many advances in modern medicine, liver diseases continue to be a constant threat to public health; and unfortunately, there are no completely effective drugs that offer a total protection of the organ or help to regenerate its cells [129]. Therefore, the use of some plants and the consumption of different fruits have played an important role due to their hepatoprotective capacity and their extracts and/or constituents, mainly from the leaves, roots, fruits and latex of different species of *Ficus* L., which have evidenced this property. The studies that promoted the exploration of the investigations were those carried out by Mandal *et al*. (2000) and Mohan *et al*. (2007), who, when evaluating MeOH extracts from *F. hispida* and *F. carica* leaves, found that both plant species decreased the serum levels of transaminases [Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT)], bilirubin and alkaline phosphatase (ALP) in rats with acetaminophen-induced liver injury (APAP) [130] and carbon tetrachloride (CCl_4) [131]. The same type of extract (250 and 500 mg/kg doses), but obtained from the bark of *F. glomerata* also showed a strong antioxidant and hepatoprotective activity against CCl_4. Both the histological study and the significant reversal of biochemical changes in serum, liver and kidney confirmed these

Table 4. Scientific evidence of the most representative species of the genus *Ficus* L. on diabetes and obesity

Type of Study	Extract or phytochemical/ Plant part	Objective and biological effect	Ref
F. carica			
In vivo	Aqueous/leaves	Since excessive lipid storage affects the net yield of poultry meat, it was questioned whether the dietary supplement of the extract could decrease TG and T-Cho content in livers of 8-week-old roosters. It was concluded that the extract drastically decreased the level of TG and the secretion of Cho depending on the concentration of the extract	[110]
In vivo	Flavonoids/fruits (FFc) and leaves (LFc)	This study was developed to identify the flavonoid content in the fruit (FFc) and leaves (LFc) and to investigate its Action on blood sugar level, daily food intake, body weight gain, feed efficiency ratio, serum lipid profile, renal function and liver function in diabetic rats. Phytochemical analysis of FFc and LFc revealed the presence of progalic acid, ferulic acid, coumaric acid, galangin, cinnamic acid, and pinostorbin quercetin. The elevation of sugar in the rats injected with Allox improved when. FFc and LFc were included in their diet. In addition, both hypercholesterolemia and hyperlipidemia, as well as hepatic and renal functions improved remarkably. Presumably, the antioxidant power, the fiber content and the presence of flavonoids in FFc and LFc were the bases for such beneficial reactions	[111]
In vivo	MeOH/Leaves (MELFc)	The objective of the research was to determine the antidiabetic effect of the extract (MELFc) in allox-induced diabetic rats. MELFc administration (200 mg/kg p.o. dose) showed a reduction in blood glucose and TG levels; as well as a significant improvement in body weights	[112]
In vivo	Aqueous/leaves (AELFc)	Joerin *et al.* investigated the preventive potential of the extract (AELFc) on hyperlipidemia in obese male Sprague-Dawley rats induced by a high-fat diet (HFD). The benefit of AELFc was more significant than pioglitazone (positive control), since it significantly improved the lipid profile (T-Cho, TG, and LDL) and decreased interleukin-6 (IL-6) levels and adipogenic risk factors; probably attributed to an improvement in HDL levels	[113]
In vivo	Leaves	The study evaluated the antioxidant, antilipidemic, and antidiabetic effects of ficusin isolated from *F. carica* and its action on GLUT4 translocation and PPARγ expression in HFD-STZ-induced type 2 diabetic rats. Ficusin (20 and 40 mg/kg doses) decreased serum antioxidant enzyme levels (SOD, CAT, and GPx), lipids, plasma insulin, and fasting blood glucose concentrations to nearly normal values. It also improved the PPARγ expression and GLUT4 translocation and activation in adipose tissue; suggesting promising interactions of GLUT4 and PPARγ at their active sites	[106]
In vitro	EtOH/fruits, leaves, and stem bark	The role of some extracts from the aerial parts of *F. carica* in the antioxidant, antidiabetic and antiobesogenic effects was studied. In addition, their content of polyphenols and flavonoids was estimated. The EtOH extract of the fruits was the most significant by inhibiting α-amylase and α-glucosidase (antidiabetic capacity), reducing antilipase activity (antiobesogenic potential) and showing a high antioxidant effect (attributed to a high amount of polyphenols and flavonoids)	[114]
In vivo	EtOAc/leaves	The action of an EtOAc extract on glucose, lipid and carbohydrate metabolism enzyme levels in HFD-STZ-induced type 2 diabetic Wistar rats was determined. After 28 days of administering the extract (250 and 500 mg/kg), they demonstrated a positive action on oral glucose tolerance (OGTT), intraperitoneal insulin tolerance test (ITT), T-Cho, TG, and body weight. Furthermore, the activity of G6Pase, fructose-1,6-bisphosphatase and hexokinase in liver tissue was enhanced. An immunohistochemical study confirmed the protective effect of pancreatic β cells	[115]
In vitro In vivo	Aqueous-EtOH/two cultivars (Whole plant)	Using a Chromatography-Diode Array Detection-Electrospray Ionization-Quadrupole Time-of-Flight-Mass Spectrometry (HPLC-DAD-QTOF-MS) analysis, the phenolic components of an aqueous-EtOH extract were studied. Finding mainly dihydroxybenzoic acid, dipentoside, rutin, psoralen and methoxypsoralen. With this result, we proceeded to determine the hypoglycemic, lipid-lowering and antioxidant activities of both cultivars in diabetic rats induced by allox. The extract improved the lipid profile and the blood glucose level. Likewise, the activity of antioxidant enzymes present in liver and heart tissue, increased	[116]

In vitro	Aqueous, Hx, EtOAc and EtOH/fruit, leaves and stem bark	Different types of extracts were obtained from which their total content of polyphenols and flavonoids was estimated. Subsequently, its antioxidant, antidiabetic and antiobesogenic effects were demonstrated. The use of GC/MS showed that the EtOH extract of the fruits contained the highest amount of polyphenols and flavonoids (highlighting butyl butyrate, 5-hydroxymethyl furfural, 1-butoxy-1-isobutoxy butane, malic acid, tetradecanoic acid, phytol acetate, trans phytol, n-hexadecanoic acid, stearic acid, sitosterol, and 2,4,5-trimethyl-2,4-dihydro-3H-pyrazol-3-one). This set of phytochemicals is possibly responsible for inhibiting α-amylase, α-glucosidase, and antilipase	[117]
In vivo	MeOH/leaves (MELFc) and branches (MEBFc)	Using methanolic extracts, their protective effects were investigated in hyperlipidemic Swiss albino mice induced by Triton WR-1339. Also, their contents of phenols, flavonoids and anthocyanins, and their antioxidant activities were determined by means of DPPH*, (2,2-Diphenyl-1-Picrylhydrazil), ABTS*+ (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) and iron reducing capacity of plasma (FRAP). After 24 hours of administration to MELFc and MEBFc in doses higher than 5,000 mg/kg, no signs of toxicity were evident. Conversely, blood tests indicated a decrease in TG, T-Cho, and LDL levels, while HDL increased. Likewise, the DPPH*, ABTS*+ and FRAP trials demonstrated its high antioxidant potential. The suggestion is that flavonoids and anthocyanins may have a synergistic effect on hyperlipidemia	[103]
Clinical study	Abscisic acid (ABA)/fruits	This investigation examined the protective effect of two fig fruit extracts (FFEs), each administered in two different doses of ABA, on the glycemic index (GI) and insulinemic index (II) of a standard glucose drink ingested by healthy adults. Test beverages contained 200 mg FFE-50× and 1,200 mg FFE-10× and were ingested by subjects with postprandial glucose and insulin assessed at regular intervals for 2 h to determine GI and II responses. After supplementing both doses, the GI and II values were significantly reduced; suggesting that FFEs may be a promising nutritional intervention for the management of insulin homeostasis	[118]
In vivo	MeOH/Whole plant	The protective effect of *F. carica* (CEFc) was evaluated in type 2 diabetic Wistar rats induced by HFD-STZ. CEFc (250 mg/kg/day) controlled DM2 by reducing body weight, serum glucose, T-Cho, TG, LDL, and very-low-density lipoproteins (VLDL); It also increased the beneficial effect of HDL and SOD	[119]
In vivo	MeOH/seeds	The purpose of the study was to compare and investigate whether the extracts of *F. carica* (MESFc) and *Lepidium sativum* (MESLs) showed any protective effect on blood sugar levels in normal and diabetic rats induced with STZ. For five weeks, MESFc and MESLs (100 and 200 mg/kg) were administered v.o., and at the end of this period glucose levels, lipid profile, and liver enzymes remarkably restored. A significant increase in HbA1c levels was also observed. However, the most significant beneficial effect corresponded to MEFcS	[120]
In vitro	Flavonoids/fruit peel	Extracts rich in flavonoids were tested against five enzymes (α-glucosidase, tyrosinase, urease, acetylcholinesterase, and butyrylcholinesterase) and their antioxidant activities were evaluated. The extracts were mainly effective in inhibiting tyrosinase and α-glucosidase. However, all the extracts showed a relevant antioxidant potential. On the other hand, the phytochemical analysis revealed large amounts of flavonoids (mainly flavonols, 81%). Since *F. carica* has shown hypoglycemic action, its flavonoids could be considered multifunctional bioactive ingredients to be used in pharmaceutical formulations	[121]
In vivo	EtOH/leaves	Despite fig leaves have been shown to lower blood glucose levels, their collection and use are not entirely practical or consistent. For this reason, this research determined the antidiabetic efficiency of an extract using dosages formulated in tablets. Three formulations were prepared with doses of 40, 60 and 80 mg of the extract and administered for 14 days to diabetic rats induced with allox. The results proved that all three types of tablets lowered blood glucose levels	[122]
F. racemosa			
In vivo	EtOH/stem bark (EEBFr)	The aim of the study was to investigate the antihyperglycemic and hypolipidemic activity of the extract (EEBFr) in alloxan (Allox)-induced diabetic rats. Oral administration (100-500 mg/kg) of EEBFr reduced glucose, T-Cho, TG, and HDL levels in Allox-treated rats in a dose-dependent manner	[123]
In vivo	Ace/stem bark	After separating a tannin fraction (TF) from the extract, two doses (100 and 200 mg/kg) were orally administered (v.o.) to hypercholesterolemic and diabetic rats to evaluate their effects on lipid and antioxidant profiles. Administration of TF supplementation reversed the STZ-induced increase in blood glucose and decreased the elevated levels of T-Cho, TG, and LDL caused by the high-fat diet. Additionally, the antioxidant status was improved by restoring the activity of SOD, CAT and decreasing GSH-Px	[124]

Clinical study	Aqueous/stem bark	In order to know the hypoglycemic effect of *F. racemosa* in diabetic patients who were taking sulfonylureas, they were suggested to ingest 5 ml (approximately 100 mg) of an extract of its bark twice a week for 15 days. At the end of the period, blood samples where there was a notable decrease in the sugar level an hour and a half after breakfast were analyzed. Normal values of bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein and urea were presented	[125]
In vivo	Flavonoids/stem bark	Using infrared spectroscopy and nuclear magnetic resonance, four flavonoids were isolated and administered once a day for one week to diabetic rats. The results indicated that its flavonoids (100 mg/kg dose) reduced the blood glucose level and the body weight of the animals increased by the STZ. There was a decrease in lipid profile parameters. Besides, oxidative stress biomarkers and liver enzymes were normalized. In addition, coupling studies suggest that the antidiabetic potential of flavonoids is related to PPARγ and GLUT1 receptors	[126]
F. religiosa			
In vivo	Aqueous/stem bark (AEBFr)	Evidence indicate that OXs is related to the pathogenesis of DM2. Therefore, the potential of the extract (AEBFr) to lower fasting blood glucose in diabetic Wistar rats induced by STZ was evaluated. Orally administered doses of AEBFr (100 and 200 mg/kg) modulated and restored antioxidant enzymes [CAT, glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD)] to normal values. In addition, the highest dose significantly lowered blood glucose	[127]
In vivo	Aqueous/stem bark (AEBFr)	Pandit *et al.* investigated the effect of oral administration (25, 50 and 100 mg/kg) of the extract in normal, glucose loaded, hyperglycemic and diabetic rats induced by STZ. The three doses caused a reduction in blood glucose in all the experimental models. In addition, higher doses increased serum insulin, body weight, and liver glycogen content. Such phenomena are comparable to glibenclamide. AEBFr also presented an antilipoperoxidative effect by reducing the levels of TG and T-Cho	[128]

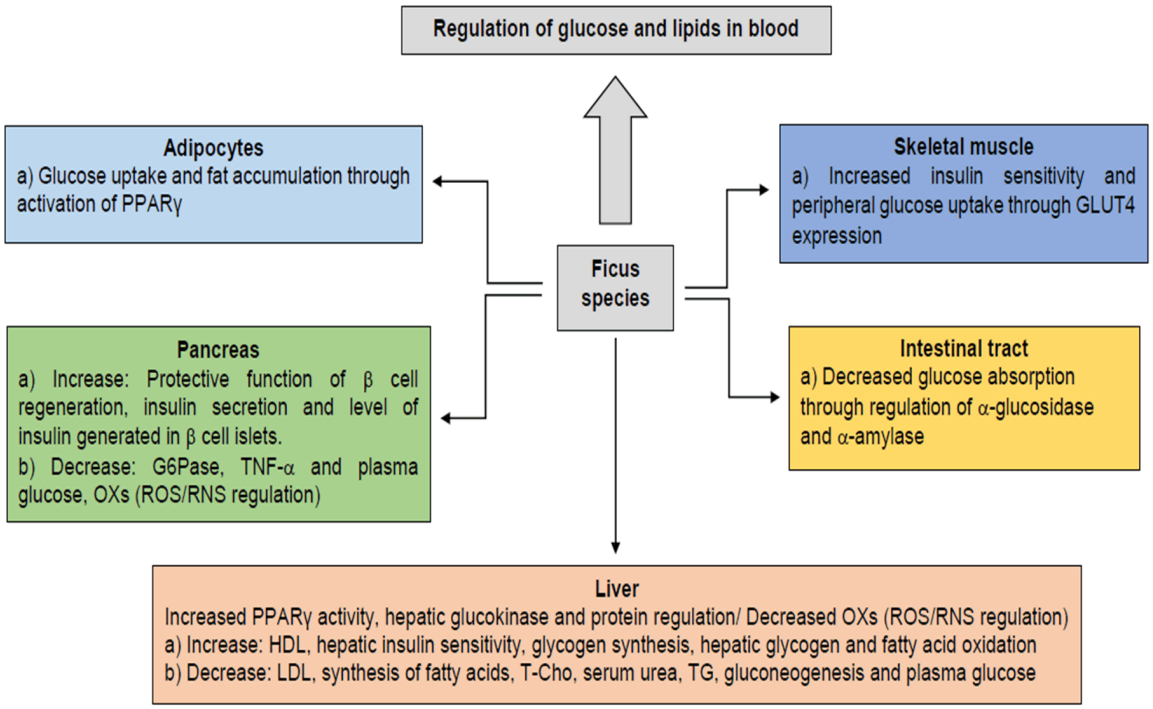

Figure 5. Hypoglycemic and hypolipidemic mechanisms of *Ficus* species. LDL: Low-density lipoproteins; HDL: High-density lipoproteins; PPARγ: Peroxisome proliferator-activated receptor gamma; G6Pase: Glucose-6-phosphatase; GLUT4: Glucose transporter-4; TNF-α: Tumor necrosis factor alpha; RNS: Reactive nitrogen species; TG: Triglycerides.

properties and were comparable to silymarin (well known hepatoprotective agent). Furthermore, acute toxicity tests demonstrated that the extract was safe up to 5,000 mg/kg of body weight [132]. On the other hand, when studying the effect of *F. hirta* aqueous extract (FhAE) on liver injury induced by N,N-Dimethylformamide (DMF) in C57BL/6 and ICR mice, it turned out that after orally administering FhAE (100, 200, 300 g/kg) for 5 days, organ damage was attenuated as ALT, AST, and lactate dehydrogenase (LDH) activities were markedly reduced [133]. Not only the species above mentioned have shown antihepatotoxic activities. **Table 5** presents a summary of the main studies that confirm this beneficial and promising property, mainly attributed to anti-inflammatory and antioxidant mechanisms basically related to its phenolic components, flavonoids, saponins, steroids and glycosides [134-143].

In this regard, Parameswari *et al*. (2013) and Mujeeb *et a*l. (2011) reported the presence of flavonoids and phenolic compounds in *Ficus* plant extracts, which suggests that the hepatoprotective activity of the genus can be attributed to these phytoconstituents. Both groups of researchers agree that the antioxidant effect is the main mechanism of action against liver toxicity [136, 141]. On the other hand, El-Hawary *et al*. (2019) identified four phenolic compounds (gallic, chlorogenic, caffeic acid and rutin) in different *Ficus* extracts (*F. mysorensis Roth ex Roem. & Schult, F. pyriformis Hook. & Arn., F. auriculata Lour., F. trigonata* L.*,* and *F. sprague*ana *Mildbr. & Burret*). Subsequently, in rats with intrahepatic cholestasis induced by 17a-Ethinylestradiol (EE) and treated simultaneously with these extracts, they confirmed an improvement of liver regeneration and suppression of proinflammatory cytokines. Taken together, their results suggested that the extracts present a promising hepatoprotective potential against EE by modulating the signaling pathways of nuclear factor kappa β (NF-κB) and tumor necrosis factor alpha (TNF-α). Furthermore, a molecular coupling revealed that rutin and chlorogenic acid act effectively as Farnesoid X receptor (FXR) agonists [144].

Anti-inflammatory, analgesic and antipyretic activity

Inflammation, pain and fever are the body's biological responses to potential threats such as trauma (blows), infections (caused by pathogens) and/or chronic degenerative diseases (activation of non-infectious endogenous molecules). Inflammation can be classified as acute and chronic. Other symptoms might be flushing or redness (produced by increased blood flow), edema or swelling (accumulation of fluid in the tissue), increased temperature (heat in the affected area) and pain. In general, acute inflammation is a rapid protective action of the immune system where leukocytes and plasma proteins accumulate. In this process, proinflammatory cytokines (including TNF-α, IL-1β, IL-6), mediators such as NO and PGE2 are increased in the body producing ROS. The transcription of the IL-1, IL-6 and TNF-α genes is induced by the nuclear factor kappa β (NF-κβ). Stimulatory agents lead to the expression of NF-κβ and then to the transcription of genes related to proinflammatory proteins. Several regulatory enzymes involving phospholipase A2 (PLA2), cyclooxygenase (COX), and lipoxygenase (LOX) play critical roles in the production of proinflammatory mediators. Therefore, any failure in these stages can lead to prolonged or chronic periods of inflammation. Also, the same inflammatory process stimulates nerve terminals in the area and induces activation of prostaglandins, which is why pain is produced [145, 146]. On the other hand, fever (elevation of body temperature above 37°C) is a characteristic sign of infectious diseases; where apparently, pathogens are responsible of temperature increase. The reality is that endogenous pyrogens favor the elevation of body temperature. The process begins when bacterial lipopolysaccharides (LPS) are detected and an immunological protein binds to form the LPS-LBS complex. This complex binds to the CD14 receptor of macrophages, favoring the synthesis of IL-1, IL-6 and TNF-α; which reach the brain where they bind to microglial cells to activate the arachidonic acid pathway and induce PLA2 and COX that synthesize and release PGE2 (eicosanoid responsible of raising the temperature) [147].

The treatment of inflammatory diseases (acute and chronic) and the control of pain and fever are a great threat to public health. Therefore, the World Health Organization (WHO) considers them as fundamental issues that require great importance. Once again, natural remedies are a good strategy, and in the case of the genus *Ficus* L., a considerable amount of research

Table 5. Main studies examining the hepatoprotective effects of the most representative species of the genus *Ficus* L.

Extract or phytochemical/ Plant part	Objective and biological effect	Ref
F. carica		
Petroleum ether/ leaves	Gond *et al*. administered the extract to rats with liver damage induced by rifampicin. They obtained a significant reversal of the histological changes generated by hepatic toxicity; as well as a reduction of dysregulated serum levels of ALT, AST and bilirubin	[134]
MeOH/leaves (MELFc)	The absence of reliable liver protective drugs in modern medicine motivated scientists to determine the antioxidant and hepatoprotective activity of MELFc. His administration (50 mg/kg) regulated the activity of GSH (Glutathione), SOD and CAT. In addition, it decreased the elevated levels of AST, ALT, ALP, and bilirubin induced by CCl_4. This finding suggests that its phenolic components may be responsible for the protective effect	[135]
EtOH/leaves	Various doses (50, 100, 200, 400 and 800 mg/kg) of the extract were administered to male albino mice (Study A) and rats Wistar (Study B) previously intoxicated with CCl_4. Both studies confirmed that CCl_4 increased the serum levels of ALT, AST, ALP, total bilirubin, total protein (TP), and total albumin (TA), and induced changes in the liver architecture of the animals. These alterations were significantly reversed by the extract in a dose-dependent manner	[136, 137]
Dried fruit (DFFc)	The objective of this study was to investigate the experimental exposure during 50 days of dried fig against liver damage induced by EtOH consumption in rats. At the end of the evaluation period, the results established that DFFc had antioxidant and hepatoprotective potential, since it improves liver histopathology, decreased the elevation of serum enzymes, and restored the MDA content. The bioactive compounds of DFFc are suggested to inhibit the excessive generation of free radicals induced by EtOH	[138]
Aqueous/fruits	The hepatoprotective and antioxidant activity of a mixture of the edible parts of *Cynara cardunculus* (artichoke), *Morus nigra* (blackberry) and *F. carica* was studied and compared in rats and in a culture of HepG2 cells, both experimental designs treated with CCl_4. Beneficial activities were more significant in the in vivo study; since the consumption of the mixture decreased from 47 to 37% to the AST and ALT; and increased from 77 to 101% to GSH. Besides, the phytochemical analysis showed that the fig and the artichoke have a greater amount of phenolic compounds, which probably act synergistically to combat the EOx generated by CCl4	[139]
EtOH/branches	After seven days of joint exposure of Tebuconazole and extract to fruitarian bats, a hepatoprotective effect was confirmed by attenuating oxidative stress markers in the liver and testicles of bats. Among the parameters evaluated, the decrease in lipid peroxidation, SOD, CAT, vascular congestion and inflammatory infiltrates stood out	[140]
F. religiosa		
MeOH/leaves (MELFr)	The hepatoprotective potential of MELFr against damage induced by the mixture of isoniazid-rifampicin and paracetamol (INH+RIF+APAB) was investigated in Wistar rats. Upon concluding the protocol and administering the substances, the animals were sacrificed and blood and liver samples were obtained for biochemical and histological analyses, respectively. The administration of INH+RIF+APAB caused a significant elevation in the levels of liver enzymes and TBARS. This phenomenon was reversed by MELFr. In addition, by increasing the levels of GSH and TP, the improvement of the histological profile was supported and corroborated	[141]

Petroleum ether/latex (PEELFr)	The experimental protocol of the study was established to evaluate the protective effects of PEELFr on cisplatin-induced liver injury in Wistar rats. While cisplatin markedly degenerated liver cells and significantly increased AST, ALT, and ALP; PEELFr administration (300 mg/kg) prevented the inflammatory process, liver necrosis, and reversed the hepatic parameters that were analyzed	[142]
F. microcarpa		
Petroleum ether, EtOH and EtOAc/stem bark	The antioxidant and hepatoprotective activity of the extracts was analyzed against the toxicity induced by CCl_4 and APAP in rats. The EtOAc extract revealed the highest protective activity by reducing the changes induced by toxic agents. Phytochemical studies confirmed the presence of catechin, a phenolic compound, which possibly interferes with the formation of free radicals and may explain its hepatoprotective effects	[143]

has been carried out on its anti-inflammatory, analgesic and antipyretic role, which can favor the prevention of unwanted side affects generated by conventional medications [145].

Finding that oral administration (2 and 10 mg/kg doses) of an aqueous extract of *F. elastica* was effective against inflammation induced by Carrageenin (CA) and pain caused by an experimental arthritis process (both test models carried out in rats) began these fields of study [148]. Subsequently, it was observed that an aqueous extract of the bark of *F. religiosa* had a significant anti-inflammatory effect both in an acute test (CA-induced hind paw edema) and in a chronic model (Cotton pellet implantation) in male albine rats. Additionally, it protected mast cells from degranulation in vitro induced by propranolol and carbachol [149]. Mandal *et al*. (2000) induced rat hind paw edema using various substances (including CA, serotonin, histamine and dextran) and found that an extract of *F. racemosa* (200 and 400 mg/kg) also decreased the inflammatory process in all experimental models [150]. These results motivated another investigation to determine the anti-inflammatory and antinociceptive effect of an aqueous extract (AEFb) and methanolic extract of *F. benghalensis* (MEFb). After oral pretreatment (v.o.) with each extract, it was shown that MEFb had the most relevant potential for both properties; since the edema of the hind paw produced by CA, the granuloma induced by cotton granules, and the contortions induced by acetic acid (AcOH) all decreased. In addition, it prevented increased malondialdehyde (MDA) formation and increased AST, ALT, and ALP enzyme activity in inflammatory conditions. This evidence suggested that the benefits of MEFb could be attributed to its antioxidant and stabilizing effects on the lysosomal membrane [151]. *F. pumila* is another species that has also shown significant therapeutic properties. Histopathologically, it was verified that a methanolic extract (MEFp) decreased the level of swelling of the edematous paws, the levels of inflammatory mediators such as NO, IL-1β, TNF-α and cyclooxygenase-2 (COX-2). In addition to reducing the writhing response in the AcOH test and the licking time in the formalin test. Rutin, luteolin and apigenin were the three bioactive compounds directly related to their antinociceptive and anti-inflammatory activities [152].

Interestingly, Rao *et al*. (2002) and Patil *et al*. (2010) have provided the only evidence on the antipyretic potential of the genus *Ficus* L. In both studies, they induced an increase in rectal temperature by subcutaneous injection of a yeast suspension in albino rats. Pyrexia was decreased; in the first case, by a MeOH extract of *F. racemosa* stem bark (MEFrSB) and in the second study, by an EtOH extract of *F. carica* leaves (EEFcL). The protective effect of the three doses (100, 200 and 300 mg/kg) tested of MEFrSB and EEFcL were better than the standard antipyretic agent APAB; as the benefit extended for 5 hours after treatment of the extracts [153, 154].

To date, 50 investigations have been carried out, of which 32 correspond to in vivo tests. **Table 6** shows the most representative results of the analyzes of different extracts (aqueous, MeOH, EtOH, Chl, petroleum ether), oils, and some chemical mixtures (hydroethanolic, methanol/methylene chloride) from their stem bark, leaves, roots, fruits, branches, and seeds from different *Ficus* species (*F. iteophylla, F. exaspe-*

Table 6. Scientific evidence of the anti-inflammatory, analgesic and antipyretic effects of the most representative species of the genus *Ficus* L.

Extract or phytochemical/ Plant part	Objective and biological effect	Ref
F. carica		
Hydroalcoholic (50% EtOH/50% distilled water)/leaves	The aim of the study was to validate the anti-inflammatory and antioxidant activities of a hydroalcoholic extract. TBARS assay and superoxide scavenging activity confirmed its antioxidant capacity. Subsequently, the CA test demonstrated the anti-inflammatory effect of the extract. The anti-inflammatory activity of the extract could be attributed to its antioxidant potential, generated by the steroids and flavonoids present in its chemical composition	[155]
EtOH/branches (EEBFc)	In this research, an extract of branches and their fractions of water, butanol (BuOH), EtOAc, Hx were prepared to examine their ability to eliminate ROS and inhibit inflammatory reactions. The data showed that the EtOAc fraction contained the highest amount of phenolic compounds and showed the highest ROS removal activity. Particularly, EEBFc and its Hx and EtOAc fractions reduced NO production and TNF-α level in RAW264.7 cells	[156]
MeOH/leaves (MELFc)	After inducing an inflammatory process in rats by injection of CA, the antiangiogenic effect of MELFc was verified. Angiogenesis of granulation tissues was determined by measuring the hemoglobin content. The DPPH* assay showed a significant antioxidant activity related to its total phenolic content. MELFc inhibited leukocyte accumulation, exudate volume, as well as TNF-α and PGE2 production. Possibly, its antiangiogenic effects are related to its antioxidant and inflammatory potential	[157]
Aqueous/leaves (AELFc)	Vascular endothelial growth factor (VEGF), TNF-α, IL-1a and 5 alpha-reductase type II (SRD5A2) gene expression levels were tested in AELFc-treated human keratinocyte (HaCaT) cells. The cells treated with AELFc regulated the gene expression of all the markers evaluated. These results partially explain the antioxidant and anti-inflammatory effects of *F. carica*; which can again be attributed to its polyphenols	[158]
Fruits	Four new prenylated isoflavone derivatives [ficucaricones A-D (1-4), along with 12 known analogues (5-16)] were identified and isolated from the fruits of *F. carica.* Prenylated isoflavone derivatives (1-16) showed remarkable inhibitory effects (comparable to hydrocortisone) against NO production. In addition, all 16 compounds also exhibited antiproliferative activities in various human cancer cell lines	[159]
Aqueous and EtOH/ leaves	The scant information on the impact of the extraction methods and the types of solvents on the profile of antioxidant and anti-inflammatory compounds in the genus *Ficus* L., motivated Alcantara *et al*. to perform an ultrasound-assisted extraction (UAE) and the phenolic analysis of *F. carica* leaves. The results showed that UAE in comparison to conventional extraction had an impact on obtaining total phenols. The antioxidant capacity of the aqueous extract was three times higher than the extract obtained with ethanol for conventional extraction and four times higher with UAE. While the EtOH extract presented a greater anti-inflammatory activity	[160]
Oil/seed (OSFc)	In this study, acute mesenteric ischemia was induced to albino Wistar rats and were administered 3 and 6 ml/kg/day of OSFc. Subsequently, they underwent an ischemia and reperfusion procedure. Both doses of OSFc reduced levels of TNF-α, IL-1β, and the enzymatic activity of SOD and CAT. Oral administration of OSFc reverses ischemia-reperfusion injury in this experimental model, probably due to its antioxidant and anti-inflammatory compounds	[161]
	Rezagholizadeh *et al.* performed a systematic review using search sites such as Scopus, PubMed, Science Direct, and Google Scholar with the purpose of discussing and analyzing the anti-inflammatory effects of *F. carica* emphasizing its impact on key proinflammatory cytokines, including IL-1, IL-6 and TNF-α. The analysis gave as results that its polyphenols and flavonoids are mainly responsible for exerting anti-inflammatory effects by inhibiting or decreasing proinflammatory cytokines	[145]
Morin	Generally, neuropathic pain is triggered through inflammation when vincristine (antineoplastic agent) is used. With that purpose, it was investigated if the morin alleviate this adverse reaction in vivo. Morin was administered via oral and pain behaviors were determined by measuring threshold (PWT) and latency (PWL) of paw withdrawal. Sciatic nerve function deficits were assessed by sciatic functional index and sciatic nerve conduction velocity. Histological abnormalities of their axons were determined and inflammatory mediators were detected by western blotting in dorsal root ganglia. The reduction of PWT and PWL and the increase in body weight of the animals was attenuated by the morin treatment. Histological alterations, neuronal hyperexcitability and increased expression of IL-6 and NF-κB were also abolished	[162]

F. carica and F. benghalensis		
Petroleum ether, Chl, and EtOH/stem bark	Initially, the anti-inflammatory activity of three extracts of *F. benghalensis* from plants with different ages of maturity was compared. Subsequently, they explored the same property of these extracts but obtained from *F. carica*. Both studies confirmed that all the extracts administered orally (600 mg/kg/day) reduced the acute and chronic inflammatory process. However, the best effect (76%) corresponded to the EtOH extracts from young plants of both species. After concluding a phytochemical analysis, the idea that flavonoids, sterols, triterpene compounds, tannins and saponins were possibly responsible for the anti-inflammatory potential, was supported	[163, 164]
F. benghalensis		
Aqueous/roots	An experiment was developed with Swiss albino mice to determine the nociceptive potential of two doses (100 and 200 mg/kg) of an extract. Results were comparable to the indomethacin positive control; confirming that only the highest dose presented analgesic effects both in the hot plate and tail flick test (central action) and in the writhing model (peripheral pain)	[165]
Aqueous/stem bark (AESBFb)	The purpose of the investigation was to study the antinociceptive effect of three doses (100, 200 and 400 mg/kg) of AESBFb using the formalin-induced pain and rapid movement tests. In the tail flick test, all three tested doses increased the time elapsed for the animals to move the tail away from the source of the thermal stimulus. While in the formalin test, only the highest doses significantly reduced the duration of the lick response	[166]
F. religiosa		
MeOH/leaves (MELFr)	Excessive production of inflammatory mediators by activated microglia is known to be related to neurodegeneration in human diseases. Therefore, the effect of MELFr on theproduction of NO and proinflammatory cytokines (TNF-α, IL-1β, and IL-6) induced by LPS in mouse microglial BV-2 cells was demonstrated. MELFr inhibited the production of inflammatory mediators and the expression of mRNA and iNOS in a dose-dependent manner. The molecular mechanism of attenuation is presumed to be related to low activity of the c-Jun N-terminal kinase (JNK) and the p38 mitogen-activated protein kinase (MAPK) pathway, which suppresses NF-κβ activation	[167]
EtOH/leaves (EELFr)	The study focuses on the evaluation of the anti-inflammatory (CA-induced paw edema), antioxidant (DPPH* assay), and healing (incision/excision and histopathology) activity of EELFr. The extract evidenced prominent anti-inflammatory and antioxidant activity. Beneficial effects, probably related to its glycosides and tannins	[168]
Aqueous/stem bark (AESBFr)	Neonatal diabetic rats were orally treated with AESBFr for 4 weeks to investigate its anti-inflammatory capacity. During the period, fasting glycemia, postprandial glycemia and serum TNF-α were quantified. The administration of 200 mg/kg AESBFr decreased all the evaluation parameters. This fact supports the idea that the antidiabetic and anti-inflammatory activity of the extract can modulate the cytokine TNF-α	[169]
MeOH/stem bark (MESBFr)	The extract was evaluated for its anti-inflammatory activity in Wistar albino rats and its analgesic effects in Swiss albino mice. The CA trial demonstrated that three doses of MESBFr had a comparable reduction to indomethacin in the inflammatory process. An inhibition of AcOH-induced writhing was also observed in mice. The analgesic effect was comparable to that caused by aspirin, which is the standard drug	[170]
F. religiosa and F. iteophylla		
Petroleum ether-EtOH/ leaves EtOH/leaves (EELFi)	Using known experimental models (AcOH-induced writhing, rapid tail flick, hot plate test, CA-generated paw edema, and granuloma formation), two investigations were carried out to assess the antinociceptive and anti-inflammatory potentials of two species of *Ficus*. The first focused on the analysis of five fractions (FRI, FRII, FRIII, FRIV and FRV) obtained from a first extract of *F. religiosa*; while the second study analyzed an extract from *F. iteophylla* (EELFi). The set of results showed: a) orally administered FRI and FRIII (40 mg/kg) were the most effective in reducing pain and inflammation, b) the intraperitoneal LD50 of EELFi was found to be above 3,800 ml/kg; therefore, doses of 100, 200 and 400 mg/kg were tested by the same route, c) the same beneficial effects were evidenced in the experimental models and d) both therapeutic activities were related to bioactive compounds (mainly, flavonoids, steroids, tannins and saponins) present in the chemical composition of the fractions and EELFi	[171, 172]
F. deltoidea		
Aqueous/leaves	By means of acute and chronic inflammatory models (CA test, granuloma test induced by cotton pellets and formalin test), the anti-inflammatory activity of an extract intraperitoneally administered to rats was verified. The results showed that a protective activity was exerted in all tests. The conclusion was, therefore, that the leaves of *F. deltoidea* have a beneficial action against acute and chronic inflammatory responses	[173]

EtOH/leaves	Human coronary artery endothelial cells (HCAEC) were incubated with different concentrations of EtOH extracts obtained from 4 varieties of *F. deltoidea* [var. trengganuensis (EELFdT), var. kunstleri (EELFdK), var. deltoidea (EELFdD) and var. intermedia (EELFdI)], together with LPS to determine its action on the expression of proteins and genes of the vascular cell adhesion molecule-1 (VCAM-1), intercellular cell adhesion molecule-1 (ICAM-1), Endothelial leukocyte adhesion molecule-1 (selectin E), IL-6, iNOS, and NF-κB (assessed by ELISA and QuantiGene plex). The adhesion of monocytes to HCAEC and the formation of ROS were also detected. EELFdK showed the highest biomarker inhibition in relation to endothelial activation and inflammation and was the most potent (25%) in decreasing ROS production. It also presented a high reduction in binding to monocytes (17%). In conclusion, this *Ficus* species has significant antiatherogenic effects, possibly mediated through the NF-κB and iNOS pathways	[174]
Aqueous/leaves (AELFd)	An extract of *F. deltoidea* was obtained to determine its possible antinociceptive activity in three models of nociception (acetic acid-induced abdominal writhing, formalin and hot plate test). The results showed that i.p. administration of three doses of AELFd (1, 50, and 100 mg/kg), 30 min before pain induction, produced a dose-dependent analgesic effect in all the models used; which suggest both central and peripheral actions	[175]
Aqueous/leaves (AELFd)	Zolkiffly *et al*. determined the inhibitory properties of AELFd on the proinflammatory mediators involved in LPS-induced microglial cells and quantified isovitexin and vitexin in the extract by HPLC. AELFd did not show cytotoxicity at the concentrations tested (0.1, 1.0, 10, and 100 μg/mL). On the contrary, it showed neuroprotective effects by attenuating the levels of proinflammatory factors (ROS, NO, TNF-α, IL-1β and IL-6 levels) in microglial cells. Possibly, this beneficial property acts on the NF-κB signaling pathway	[176]
F. exasperata		
EtOH/stem bark (EESBFe)	Since the increase in ROS is implicated in inflammatory diseases of the joints, the protective potential of EESBFe was investigated in the Freund's adjuvant-induced arthritis model in rats and the antioxidant effect in vitro. Oral administration of EESBFe (30-300 mg/kg) showed a significant anti-inflammatory effect by reducing arthritic edema in the ipsilateral paw. It also reduced DPPH* and prevented lipid peroxidation in rat brain homogenates. Both activities possibly related to the phenols in the extract	[177]
Methylene chloride/MeOH/leaves (MMELFe) and Aqueous/leaves (AELFe)	The authors conducted two studies. The first one evaluated the topical and systemic anti-inflammatory activities of MMELFe in rodents. The second was on the effects of AELFe on the expression of IL-1β, TNF-α and iNOS induced by LPS in a culture of murine bone marrow-derived macrophages. (BMDM). MMELFe (200 and 400 mg/kg) treatment in rats led to an inhibition of agar and formaldehyde-induced acute and chronic inflammation of their hind paws, respectively. In addition, topical application (5 μg/ear) in mice also decreased (approximately 21%) the edema generated by xylene. The in vitro study revealed that concentrations between 5 and 100 μg AELFe/ml significantly reduced inflammatory mediators. In conclusion, the flavonoids, alkaloids and terpenoids, predominant in each extract, may be the basis of the benefits associated with the popular use of the plant	[178]
F. hirta Vahl		
Phenylpropanoids and phenolic/roots	After the chemical structures of 4 new phenylpropanoids and 10 phenolic compounds were elucidated by spectroscopic analysis. Their anti-inflammatory activities were evaluated. The results indicated that most of the purified compounds showed inhibitory effects on NO production induced by LPS in RAW264.7 macrophages	[179]
EtOH/roots	Seven new undescribed phenolic glycosides (1-7), together with 20 analogues, were isolated from the roots of *F. hirta*. Their structures were determined by comprehensive spectroscopic methods (UV, IR, and NMR). While the antineuroinflammatories of all the compounds were examined by Western blot. The results indicated that compounds 1 and 11 reduced the occurrence of neuroinflammation in BV2 microglia cells, as they regulated the NF-κB, MAPK, and JNK signaling pathways. In addition, compound 11 inhibited p65 NF-κB phosphorylation. Therefore, 1 and 11 could show anti-neuroinflammatory activities	[180]
F. racemose		
EtOH/leaves (EELFr)	A bioassay-guided fractionation of EELFr identified a new compound called racemosic acid "(rel)-4,6-dihydroxy-5-[3-methyl-(E)-propenoic acid-3-yl]-7-beta-glucopyranosyl-[2alpha,3beta-dihydrobenzofuran]-(3,2:b)-[4alpha,5beta-dihydroxy-6alpha-hydroxymethyltetrahydropyran]". Racemosic acid demonstrated strong antioxidant activity to eliminate ABTS*+ free radical cations and a strong inhibitory activity against COX-1 and 5-LOX in vitro	[181]

EtOH/stem bark (EESBFr) and fruits (EEFFr)	Two extracts of *F. racemosa* (EESBFr and EEFFr) were tested for their possible analysis of antinociceptive activity in the acetic acid-induced writhing method in mice. Both extracts demonstrated analgesic activity in experimental animals. However, the most powerful effect corresponded to EEFFr	[182]

rata, F. hirta Vahl*, F. racemosa, F. benghalensis, F. deltoidea, F. religiosa*, and *F. carica*). Again, the last 3 species are the most studied. In summary, the results agree that the three activities (anti-inflammatory, analgesic and antipyretic) present a mechanism of action related to the ability to decrease ROS (antioxidant potential), which could be attributed to phytochemicals (phenolic compounds, polyphenols, flavonoids, terpenoids, alkaloids, steroids, tannins and saponins) predominant in the chemical composition of each extract. Likewise, the evidence suggests that these three pharmacological virtues inhibit and/or regulate signaling pathways such as inducible nitric oxide synthase (iNOS), c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), LOX and COX (1 and 2); which reduce the production of inflammatory mediators (NO, TNF-α, PGE2, NF-κβ, IL-1β and IL-6, IL-8) [145, 155-182].

Toxic evidence of the genus *Ficus* L.

Despite the fact that herbal medicines are considered relatively safe by the public and some health professionals because they are "natural"; little scientific data exists to support this assumption. According to the U.S. Food and Drug and Administration (FDA), it is essential to evaluate any new molecule to determine its possible therapeutic activity and potential for toxicity using animal models. In particular, plants may contain metabolites with synergistic or antagonistic action, or in other cases, induce severe poisoning, hypersensitivity reactions and/or anaphylactic shocks. Therefore, it is crucial to evaluate the adverse and toxic effects of plant extracts and isolated bioactive compounds that are intended to be used for human therapy [21]. Unquestionably, the evidence shown in this review demonstrates the therapeutic properties of the plants of the genus *Ficus* L.; however, they are not exempt from possible adverse and toxic effects. Most of the evidence indicates that its toxicity is related to the number and concentration of toxic chemical compounds (ficin, phytosterolin, furocoumarins and psoralens). The amount of toxic bioactive compounds is not similar in all plants and depends on the plant part, origin of the plant, environmental conditions and the type of soil where it grows. Furthermore, all edible parts of the genus *Ficus* L., like other plants, during cultivation, pre-harvest, post-harvest, processing and subsequent storage are prone to biological, chemical and physical contamination; critical contaminants such as mycotoxins (aflatoxins, ochratoxins, fumonisins), pesticides (Chlorpyrifos, malathion, profenofos, aldrin, dieldrin, chlordane, endosulfan, lindane), heavy metals (Cd, Cr, Pb, As, Hg) and fumigants (Ethylene oxide, phosphine, methylbromide, sulphur, polycyclic aromatic hydrocarbons) which may also have adverse effects on the consumer. Today, the main challenge in the international import/export of medicinal plants (including *Ficus* and/or its products) is the lack of strict regulations, standard limits, evaluative measures and/or monitoring systems. For this reason, good agricultural practices and certified organic products established by each government must be adopted to increase high-quality products, as well as quality assurance systems to provide the safety demanded by consumers [24]. **Table 7** shows the main adverse effects of some species of *Ficus* L. Unfortunately, although *Ficus* plants are considered reliable and safe; even more so when the studies (mainly carried out with aqueous extracts, EtOH, and MeOH of the stem bark, fruits, roots, and leaves from species such as *F. amplissima, F. arnottiana, F. asperifolia, F. benghalensis, F. benjamina, F. carica, F. cunia, F. dalhousiae, F. exasperata, F. iteophylla, F. macrophylla, F. platyphylla, F. pumila, F. racemosa, F. religiosa*, and *F. sycomorus*) suggest lethal doses 50 (LDs_{50}) above 2,000, 3,000, 4,000, 5,000, 6,000, 10,000 and up to 20,000 mg/kg, in oral and intraperitoneal administrations of one, two, three and for 14 days, some authors have identified and reported certain side effects, such as skin irritation and/or allergies (pigmentation on the arms and face), respiratory disease (rhinitis, asthma), abdominal pain, catharsis (evacuation of liquid stools), fluid balance disorders, muscle weak-

Table 7. Possible reactions and/or adverse effects of different species of *Ficus* L.

Product analyzed	Assay/via/evaluated species	Reaction and/or adverse effect	Evaluated dose and/or concentration	Ref
F. amplissima				
Bark	Oral/rat toxicity	No effect observed	LD_{50} of 2,000 mg/kg	[184]
F. arnottiana				
Bark Extract	Acute Oral toxicity/Rat	No effect observed	LD_{50} of 3,000 mg/kg	[17]
F. asperifolia				
Aqueous extract	Acute oral toxicity/rat	No effect observed	LD_{50} of 4,000 mg/kg	[185]
F. benghalensis				
Aqueous and EtOH extracts	Oral/rat toxicity	No effect observed	LD_{50} of 2,000 and 5,000 mg/kg	[18]
Erial roots	Oral/rat toxicity	No effect observed	LD_{50} of 300 mg/kg	[186]
F. benjamina				
Leaf EtOH extract	Liver function/rat	No effect observed	LD_{50} of 800 mg/kg	[187]
Latex	Human activity/IgE assay	Oral and/or respiratory allergies (rhinitis, asthma)		[188, 189]
Fresh fruits	Consumption and human activity/IgE assay	Occupational allergy. Skin sensitization in plant keepers		[190, 191]
F. carica				
Aqueous leaf extracts	Oral/rat toxicity	Behavioral changes but no mortality	LD_{50} of 5,000, 5,500, 5,700 and 6,000 mg/kg	[192]
EtOH fruit extract (fig syrup)	Electronic Medicines (EMC)/Human Compendium	Allergy, abdominal pain and evacuation of liquid stools (after an individual overdose) Disorders in fluid balance, albuminuria, hematuria and discoloration of urine (after chronic use)		[193]
Fresh fruits, fruit juice, contact with leaves	Human consumption	Pigmentation in the arms when rubbing the juice of the fruit with exposure to the sun Pigmentation of the face after eating fresh figs (phototoxic reaction), Vesicular dermatitis		[194, 195]
Fresh fruits	Human consumption/IgE assay	Food allergy (rhinitis)		[196, 197]
Aqueous leaf extract	Acute oral toxicity/mice	Mortality	3,000, 4,000 and 8,000 mg/kg after a 12-hour fast	[198]
leaf extract	Brine shrimp bioassay	Mortality	LC_{50} of 0.158 mg/ml	[199]
MeOH extracts from latex	Toxicity in human melanocyte cell line HFB4	No effect observed	LC_{50} of 100 µg/ml	[200]
Silver nanoparticles using dried fruit extract	Oral administration/rats	No effect observed		[201]

F. cunia				
Extract of leaves	Brine Shrimp Bioassay	Mortality	LC_{50} of 55.48 µg/mL	[202]
F. dalhousiae				
Root EtOH Extract	Oral/mice toxicity	Mortality	LD_{50} of 2,000 mg/kg	[203]
F. deltoidea				
Leaf EtOH Extract	Oral/rat toxicity	No effect observed	LD_{50} of 6,400 mg/kg	[204]
F. exasperate				
Aqueous leaf extract	Oral and intraperitoneal toxicity/mouse and rat	No effect observed for 24 hours Daily doses for 14 days, increase in body temperature and decrease in red blood cell count and hemoglobin	LD_{50} of 2,500, 5,000, 10,000 and 20,000 mg/kg administered 24 hours and 14 days	[205]
F. iteophylla				
Leaf EtOH Extract	Intraperitoneal/mouse toxicity	No effect observed	LD_{50} of 3,807 mg/kg	[172]
F. macrophylla and F. pumila				
Fresh fruits	Food/Human Production	Skin irritation		[206]
F. platyphylla				
MeOH extract of stem bark	Intraperitoneal toxicity/mouse	No effect observed	LD_{50} of 5,000 mg/kg	[207]
F. racemose				
MeOH extract of stem bark	Oral/rat toxicity	No effect observed	LD_{50} of 2,000 mg/kg	[208]
F. religiosa				
Aqueous extract of bark/ powdered bark	Oral toxicity/rats	Catharsis/high dose allergy		[209]
Aqueous extract of bark	Oral toxicity/rats	No effect observed	LD_{50} of 2,000 mg/kg	[128]
Leaf EtOH Extract	Oral toxicity/rats	No effect observed	LD_{50} of 4,000 mg/kg	[210]
F. sycomorus				
EtOAc extract of the fruits	Oral toxicity/rats	No effect observed	LD_{50} of 26.80 mg/ml	[211]
MeOH extracts from latex	Toxicity in HFB4 cell line of human melanocytes	No effect observed	LC_{50} of 100 µg/ml	[200]

Median lethal dose (LD_{50}); Median lethal concentration (LC_{50}).

ness, albuminuria, hematuria and discoloration of the urine [2, 5, 21, 183]. Despite these side effects, *Ficus* plants (especially their fruits) continue to be traditional foods of frequent consumption with high agrotechnological potential, maintining that its safety is favored by presenting very high LDs_{50}. Curiously, to date there is no established dose and/or concentration for its consumption and there are different intervals that depend on the route of administration, and the species (humans/animals) in which they are used, along with the approach to use it either in food (fresh, juice or extract) or for experimental evaluation.

Perspectives

(1) The scientific evidence shown in this manuscript confirms the relevance of the genus *Ficus* L., in some pharmacological and/or therapeutic activities. However, they are not the only ones; since some authors have recorded more than 40 traditional ethnomedical uses of its plants; among which are the management of neuropsychiatric disorders (antiparkinsonian, anticonvulsant, anti-anxiety, cognitive enhancer, anti-amnestic activity), gastric problems (antidiarrheal, antiulcerative, antiflatulent/carminative, indigestion, loss of appetite, gut motility, laxative, anti-constipation, antispasmodic), skin diseases (wound healing, antiwarts), cardiovascular disorders (cardioprotective, antihypertensive, endotheilin receptor antagonistic), blood disorders (antiplatelet, anticoagulant, management and/or prevention of anemia), respiratory problems (antiasthmatic, antitussive, expectorant), urinary diseases (diuretic, reduction of kidney stones), parasympathetic modulation, esterogenic, antistress, sexual disorders, menstrual pain, antimigraine, immunomodulatory, oxidative stress related disorders (antioxidant), as well as cytotoxic, an apoptosis inducer, with antiproliferative, antiangiogenic, antimutagenic, anticancer/antitumor effects [1-3, 5, 6, 174, 175, 182]. Due to difficulties of analyzing them all in a single manuscript, the rest of the ethnopharmacological virtues of the genus (specifically, neuropsychiatric disorders, gastric problems, skin diseases, blood disor-ders, respiratory problems, antihypertensive and immunomodulatory actions, diuretic effect, antioxidant potential and genoprotective capacity) will be addressed in a second part of this review.

(2) The data shown in this manuscript on the extracts (aqueous, MeOH, EtOH, Hx, Chl, DCM, Ace, BuOH, EtOAc and petroleum ether), oils and latex of leaves, roots, fruits, stem bark, branches and seeds of the different species of *Ficus* L., confirm their relevant therapeutic effects. However, even though the experiments validated its medicinal uses; unfortunately, most of them come from uncharacterized crude extracts. This makes it difficult to point specifically to the bioactive metabolite. Therefore, it would be essential and necessary to perform a phytochemical standardization and bioactivity-guided identification of the metabolites contained in each type of extract. In some cases, through bioassay-guided fractionation, the phytochemicals responsible for the beneficial effect were identified; such is the case of the proteolytic enzyme ficin and the linear furocoumarins bergapten and psoralen, to which anthelmintic, anti-filarial, vermifuge activity and interference with latex viral replication are attributed. Phytosterolin (sitosteryl-d-glucoside) is considered to be responsible for the hypoglycemic effect of the root bark of *F. religiosa*. Identification and analysis of seven galactolipids from a MeOH extract of *F. microcarpa* leaves demonstrated their ability to inhibit TNF-α-induced IL-8 expression in vitro. Chromatography and experimental rodent models with croton oil-induced ear edema and CA testing, confirmed that coumarins (7-methoxycoumarin, 7-hydroxy-6-methoxycoumarin and methoxy-3,4-dihydrocoumarin), steroids (β-sitosterol and β-sitosterol 3-O-β-glucopyranoside), a flavonoid (trans-4-methoxy-2-β-D-glucopyranosyloxycinnamic acid), and quercetin reduced inflammatory processes. Similar results were found with kaempferol, psoralen, and carpachromene (obtained from the dried roots of *F. formosana*) when placed in a culture of LPS-stimulated RAW264.7 cells. Finally, using another in vitro assay, the inhibitory activity of racemosic acid (extracted from an EtOH extract of *F. racemosa*) against COX-1 and 5-LOX was demonstrated. Therefore, it is clear that it would be convenient to increase the individual studies of each phytochemical, to determine its protective action, since each individual substrate can activate different biochemical reactions and provide important health benefits. In addition, it would be relevant to extend the research to other species to analyze and confirm their pharmacological capacities. In this

sense, it is worth mentioning that the modern pharmaceutical industry is paying more attention to medicinal plants as scientists rediscover that plant life is an almost infinite resource for medicine development. As the case of *F. carica* that has been included in occidental Pharmacopoeias (i.e. Spanish Pharmacopoeia, British Pharmacopoeia) and in therapeutic guides of herbal medicines, as important as the PDR for Herbal Medicines [212-215].

(3) As previously mentioned, the *Ficus* species is used as a nutritional source for humans and its different plant parts (roots, stem, bark, leaves, fruits, pulp, seeds) are medicinally important due to their bioactive phytochemical compounds; most of which have strong antioxidant potential in terms of metal chelation, metal reduction, lipid reduction and ROS removal; capabilities that are useful for reducing oxidative stress in biological systems. Despite the fact that the antioxidant effect of the genus *Ficus* L. has not been explored in detail, a large number of the studies analyzed in this manuscript support this property. Regarding this, some authors consider that the leaves contain more than 120 phytoconstituents, of which polyphenolic compounds predominate; other researchers suggest that phenolic acids and flavonoids are more relevant in fresh and dried figs; however, in both cases their levels (hence their antioxidant capacity) are strongly influenced by factors such as color, part of the fruit, ripeness, and the drying process. In general, dark-colored varieties contain a greater amount of phenolic compounds than light-colored ones. The skin of the fruit contributes more to the amount of phenolic compounds compared to the pulp of the fruit. The stage of maturation affects the concentrations of phenolic compounds in figs, the maximum have been found in ripe fruits. The difference between drying in the air and in the sun also affects the total content of bioactive compounds. For this reason, future research should provide such information and focus on improving the sensitivity and efficiency of the evaluation methods in both fresh products as in by-products since this could offer financial benefits to farmers and solve environmental problems about the sustainable management of these materials. In addition, it would increase the consumption of leaves and fruits (fresh or dried) since the significant content of their phytoconstituents favors them to have a high antioxidant power, perhaps greater than red wine and tea [7, 25, 26, 30, 212].

(4) This review leaves no doubt that the genus *Ficus* L. contains very versatile plants, which may motivate research groups to increase scientific evidence for their therapeutic use. Even more so when observing that most of the results on its biological activities derive mainly from in vitro tests and animal evaluations. That is, few clinical studies have been developed. This fact is striking, considering that many varieties of its plants (domesticated or wild) have been consumed since ancient times and currently continue being essential food for the human population (especially the fruits).

(5) Finally, to establish solid scientific evidence of the genus *Ficus* L., additional analyzes must be carried out; especially with very little evaluated species, to explore their pharmacological properties, identify the pharmacokinetics and/or pharmacodynamics, synergistic/additive/antagonist interactions between the active components, their doses and administration intervals; as well as its possible toxic effects in the short and long term. In addition, the individual identification of the bioactive compounds extracted from its plants could be used in the preparation of pharmaceutical, cosmetological and nutraceutical products for the promotion of human health.

Conclusions

(a) At the end of the scientific search, it was confirmed that there are more than 2,000 documents (scientific articles, reviews, clinical trials and book chapters) that generally describe the individual characteristics and properties of each species. Therefore, an advantage of the present review is the compilation of a significant number of studies on *Ficus* L. described by different authors.

(b) The scientific evidence shown in this manuscript confirms the relevance of the genus *Ficus* L., in 12 pharmacological and/or therapeutic activities (Antimicrobial, antifungal, antiviral, anti-helminthic, anti-filaria, vermicide, hypoglycemic, hypolipidemic, hepatoprotective, anti-inflammatory, analgesic and antipyretic).

(c) In general, most of the results confirm that the different extracts, the oils and latex from

the leaves, roots, fruits, bark stem, branches, and seeds of the different species of *Ficus* L., present therapeutic relevant effects, whose mechanisms of action are related to the inhibition of glucose absorption and regulation of enzymatic activities in the intestinal tract, stimulation of insulin secretion and improvement of insulin sensitivity, increase in hepatic glycogen synthesis and peripheral glucose absorption, influence on lipid catabolism, favorable stimulation of antioxidant status, and activation of various anti-inflammatory mechanisms where signaling pathways such as iNOS, JNK, MAPK, LOX and COX (1 and 2) are apparently inhibited and/or regulated.

(d) It was confirmed that these beneficial properties are possibly attributed to a synergistic and/or combined effect between the different bioactive compounds (phenolic acids, sterols, flavonoids, coumarins, anthocyanins, terpenoids, glycosides, carotenoids, alkaloids, tannins, saponins, proteins, vitamins, organic acids, and soluble fiber).

(e) The most authors consider that the genus *Ficus* L. is safe (even in doses higher than 6,000 mg/kg, in oral and intraperitoneal administrations).

(f) The genus *Ficus* L. is considered to have mild/moderate toxicity due to presenting some adverse effects (mainly, skin irritation, allergies, phototoxicity from topical application, rhinitis, asthma, abdominal pain, and muscle weakness).

(g) Only about 30 angiosperm plants among the more than 850 species of the genus Ficus L have been evaluated; the most studied are *F. benghalensis, F. hirta* Vahl, *F. elástica, F. racemosa, F. religiosa,* and *F. carica*. Unquestionably, *F. carica* continues being the one with the greatest research impact in terms of phytochemicals and biological properties. As a final conclusion, there is still a long way to go in scientific research to understand in more detail the important beneficial properties of genus *Ficus* L.

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Disclosure of conflict of interest

None.

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References

[1] Hajam TA and H S. Phytochemistry, biological activities, industrial and traditional uses of fig (Ficus carica): a review. Chem Biol Interact 2022; 368: 110237.

[2] Li Z, Yang Y, Liu M, Zhang C, Shao J, Hou X, Tian J and Cui Q. A comprehensive review on phytochemistry, bioactivities, toxicity studies, and clinical studies on Ficus carica Linn. Leaves. Biomed Pharmacother 2021; 137: 111393.

[3] Gafoor H, Bhattacharjee A, Hegde K and Shabaraya AR. Ficus carica: a brief review. Int J Pharm Sci Rev Res 2019; 59: 40-43.

[4] Palmeira L, Pereira C, Dias MI, Abreu RMV, Corrêa RCG, Pires TCSP, Alves MJ, Barros L and Ferreira ICFR. Nutritional, chemical and bioactive profiles of different parts of a portuguese common fig (Ficus carica L.) variety. Food Res Int 2019; 126: 108572.

[5] Badgujar SB, Patel VV, Bandivdekar AH and Mahajan RT. Traditional uses, phytochemistry and pharmacology of Ficus carica: a review. Pharm Biol 2014; 52: 1487-503.

[6] Mawa S, Husain K and Jantan I. Ficus carica L. (Moraceae): phytochemistry, traditional uses and biological activities. Evid Based Complement Alternat Med 2013; 2013: 974256.

[7] Ahmad S, Bhatti FR, Khaliq FH, Irshad S and Madn A. A review on the prosperous phytochemical and pharmacological effects of Ficus carica. Int J Bioassays 2013; 2: 843-849.

[8] Shi Y, Mon AM, Fu Y, Zhang Y, Wang C, Yang X and Wang Y. The genus Ficus (Moraceae) used in diet: its plant diversity, distribution, traditional uses and ethnopharmacological importance. J Ethnopharmacol 2018; 226: 185-196.

[9] Fuller DQ and Stevens CJ. Between domestication and civilization: the role of agriculture and arboriculture in the emergence of the first urban societies. Veg Hist Archaeobot 2019; 28: 263-282.
[10] Chiang-Chan EW, Tangah J, Inoue T, Kainuma M, Baba K, Oshiro N, Kezuka M and Kimura N. Botany, uses, chemistry and pharmacology of Ficus microcarpa: a short review. Sys Rev Pharm 2017; 8: 103-111.
[11] Kislev ME, Hartmann A and Bar-Yosef O. Early domesticated fig in the jordan valley. Science 2006; 312: 1372-4.
[12] Rodríguez-Solana R and Romano A. In: Kahramanoglu I, Kafkas NE, Küden A, Cömlekcioğlu S, editors. Chemical and Biological Characteristics of Ficus carica L. Fruits, Leaves, and Derivatives (Wine, Spirit, and Liqueur). Modern fruit industry. Croatia: InTech; 2020. pp. 1-18.
[13] Castañeda-Barrera JO. Thesis. Impact of the organization of fig (Ficus carica L.) producers in the highlands of Morelos. Autonomous University of the State of Morelos. 2021.
[14] Ibarra-Manríquez G, Cornejo-Tenorio G, González-Castañeda N, Piedra-Malagón EM and Luna A. The genus Ficus L. (Moraceae) in Mexico. Bot Sci 2012; 90: 389-452.
[15] González-Castañeda N, Cornejo-Tenorio G and Ibarra-Manríquez G. Ficus (Moreceae) in the balsas basin biogeographic province, Mexico. Bol Soc Bot Méx 2010; 87: 105-124.
[16] Bunawan H, Amin NM, Bunawan SN, Baharum SN and Mohd Noor N. Ficus deltoidea jack: a review on its phytochemical and pharmacological importance. Evid Based Complement Alternat Med 2014; 2014: 902734.
[17] Ahmed F, Ahmed KKM, Abedin MZ and Karim AA. Traditional uses and pharmacological potential of Ficus exasperata Vahl. Sys Rev Pharm 2012; 3: 15-23.
[18] Singh D, Singh B and Goel RK. Traditional uses, phytochemistry and pharmacology of Ficus religiosa: a review. J Ethnopharmacol 2011; 134: 565-83.
[19] Erhirhie EO, Ilodigwe EE and Ihekwereme CP. Ficus sycomorus L (Moraceae): a review on its phytopharmacology and toxicity profile. Discov Phytomedicine 2018; 5: 64-71.
[20] Hossain MA. A review on Ficus sycomorus: a potential indigenous medicinal plant in Oman. J King Saud Univ Sci 2018; 31: 961-965.
[21] Murugesu S, Selamat J and Perumal V. Phytochemistry, pharmacological properties, and recent applications of Ficus benghalensis and Ficus religiosa. Plants (Basel) 2021; 10: 2749.
[22] Chandrasekar SB, Bhanumathy M, Pawar AT and Somasundaram T. Phytopharmacology of Ficus religiosa. Pharmacogn Rev 2010; 4: 195-199.
[23] Deshmukh T, Yadav B, Badole S, Bodhankar S and Dhaneshwar S. Antihyperglycaemic activity of alcoholic extract of Ficus religiosa leaves in alloxan induced diabetic mice. J Herb Med Toxicol 2007; 1: 80-86.
[24] Salehi B, Prakash Mishra A, Nigam M, Karazhan N, Shukla I, Kiełtyka-Dadasiewicz A, Sawicka B, Głowacka A, Abu-Darwish MS, Hussein Tarawneh A, Gadetskaya AV, Cabral C, Salgueiro L, Victoriano M, Martorell M, Docea AO, Abdolshahi A, Calina D and Sharifi-Rad J. Ficus plants: state of the art from a phytochemical, pharmacological, and toxicological perspective. Phytother Res 2021; 35: 1187-1217.
[25] Dubey PK, Yaduwanshi P and Gouttam V. Ficus racemosa Lin-Gooler a review. World J Pharm Res 2018; 7: 325-341.
[26] Ahmed F and Urooj A. Traditional uses, medicinal properties, and phytopharmacology of Ficus racemosa: a review. Pharm Biol 2010; 48: 672-681.
[27] Arsyad AS, Nurrochmad A and Fakhrudin N. Phytochemistry, traditional uses, and pharmacological activities of Ficus elastica Roxb. ex Hornem: a review. J Herbmed Pharmacol 2023; 12: 41-53.
[28] Nawaz H, Waheed R and Nawaz M. In: Kahramanoglu I, Kafkas NE, Küden A, Cömlekcioğlu S, editors. Phytochemical Composition, Antioxidant Potential, and Medicinal Significance of Ficus. Modern fruit industry. Rijeka, Croatia: InTech; 2020. pp. 1-20.
[29] Cruz JMDA, Corrêa RF, Lamarão CV, Kinupp VF, Sanches EA, Campelo PH and Bezerra JA. Ficus spp. fruits: bioactive compounds and chemical, biological and pharmacological properties. Food Res Int 2022; 152: 110928.
[30] Arvaniti OS, Samaras Y, Gatidou G, Thomaidis NS and Stasinakis AS. Review on fresh and dried figs: chemical analysis and occurrence of phytochemical compounds, antioxidant capacity and health effects. Food Res Int 2019; 119: 244-267.
[31] Madrigal-Santillán E, Portillo-Reyes J, Madrigal-Bujaidar E, Sánchez-Gutiérrez M, Mercado-Gonzalez PE, Izquierdo-Vega JA, Vargas-Mendoza N, Álvarez-González I, Fregoso-Aguilar T, Delgado-Olivares L, Morales-González Á, Anguiano-Robledo L and Morales-González JA. Opuntia spp. in human health: a comprehensive summary on its pharmacological, therapeutic and preventive properties. Part 1. Horticulturae 2022; 8: 88.
[32] Mousa O, Vuorela P, Kiviranta J, Wahab SA, Hiltunen R and Vuorela H. Bioactivity of certain Egyptian Ficus species. J Ethnopharmacol 1994; 41: 71-6.

[33] Valsaraj R, Pushpangadan P, Smitt UW, Adsersen A and Nyman U. Antimicrobial screening of selected medicinal plants from India. J Ethnopharmacol 1997; 58: 75-83.
[34] Farrukh A and Iqbal A. Broad-spectrum antibacterial and antifungal properties of certain traditionally used Indian medicinal plant. World J Microbiol Biotechnol 2003; 19: 653-7.
[35] Hemaiswarya S, Poonkothai M, Raja R and Anbazhagan C. Comparative study on the antimicrobial activities of three Indian medicinal plants. Egypt J Biol 2009; 11: 52-4.
[36] Ao C, Li A, Elzaawely AA, Xuan TD and Tawata S. Evaluation of antioxidant and antibacterial activities of Ficus microcarpa L. fil. extract. Food Control 2008; 19: 940-948.
[37] Jeong M, Kim H and Cha J. Antimicrobial activity of methanol extract from Ficus carica leaves against oral bacteria. J Bacteriol Virol 2009; 39: 97-102.
[38] Nirwana I, Rianti D, Soekartono RH, Listyorini RD and Basuki DP. 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.
[39] Cushnie TP and Lamb AJ. Antimicrobial activity of flavonoids. Int J Antimicrob Agents 2005; 26: 343-356.
[40] Mailoa MN, Mahendradatta M, Laga A and Djide N. Antimicrobial activities of tannins extract from guava leaves (Psidium guajava L) on pathogens microbial. Int J Sci Technol Res 2014; 3: 236-239.
[41] Lazreg-Aref H, Mars M, Fekih A, Aouni M and Said K. Chemical composition and antibacterial activity of a hexane extract of Tunisian caprifig latex from the unripe fruit of Ficus carica. Pharm Biol 2012; 50: 407-12.
[42] Bisignano G, Sanogo R, Marino A, Aquino R, D'Angelo V, Germanò MP, De Pasquale R and Pizza C. Antimicrobial activity of Mitracarpus scaber extract and isolated constituents. Lett Appl Microbiol 2000; 30: 105-108.
[43] Aref HL, Salah KB, Chaumont JP, Fekih A, Aouni M and Said K. In vitro antimicrobial activity of four Ficus carica latex fractions against resistant human pathogens (antimicrobial activity of Ficus carica latex). Pak J Pharm Sci 2010; 23: 53-8.
[44] Ali NH, Faizi S and Kazmi SU. Antibacterial activity in spices and local medicinal plants against clinical isolates of Karachi, Pakistan. Pharm Biol 2011; 49: 833-839.
[45] Sun S, Li H, Zhou W, Liu A and Zhu H. Bacterial quorum sensing inhibition activity of the traditional Chinese Herbs, Ficus carica L. and Perilla frutescens. Chemotherapy 2014; 60: 379-83.
[46] Shahbazi Y. Antibacterial and antioxidant properties of methanolic extracts of apple (Malus pumila), grape (Vitis vinifera), pomegranate (Punica granatum L.) and common fig (Ficus carica L.) fruits. Pharm Sci 2017; 24: 308-315.
[47] Shahbazi Y. Characterization of nanocomposite films based on chitosan and carboxymethylcellulose containing Ziziphora clinopodioides essential oil and methanolic Ficus carica extract. J Food Process Preserv 2018; 42: e13444.
[48] Benmaghnia S, Meddah B, Tir-Touil A and Gabaldon-Hernández JA. 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.
[49] Benmaghnia S, Asma B, Boumediene M and Aicha TT. 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.
[50] Manimozhi DM, Sankaranarayanan S and Sampathkumar G. Evaluating the antibacterial activity of flavonoids extracted from Ficus benghalensis. Int J Pharma Bio Sci 2012; 3: 7-18.
[51] Wu T, He M, Zang X, Zhou Y, Qiu T, Pan S and Xu X. A structure-activity relationship study of flavonoids as inhibitors of E. coli by membrane interaction effect. Biochim Biophys Acta 2013; 1828: 2751-2756.
[52] Rahman M, Khatun A, Khan S, Hossain F and Khan A. Phytochemical, cytotoxic and antibacterial activity of two medicinal plants of Bangladesh. Pharmacology 2014; 1: 3-10.
[53] Kaur R, Goyal AK, Kaushik D and Sharma RK. In vitro studies on antibiotic activity of Ficus religiosa fruits extract against human pathogenic Bacteria. J Chem Pharm Res 2014; 6: 80-84.
[54] Salema WM, Haridyb M, Sayeda WF and Hassanc NH. Antibacterial activity of silvernanoparticles synthesized from latex and leaf extract of Ficus sycomorus. Ind Crops Prod 2014; 62: 228-234.
[55] Saleh B, Hammoud R and Al-mariri A. Antimicrobial activity of Ficus sycomorus L. (Moraceae) leaf and stem-bark extracts against multidrug resistant human pathogens. Herba Pol 2015; 61: 39-49.
[56] El-Beltagi HS, Mohamed HI, Abdelazeem AS, Youssef R and Safwat G. GC-MS analysis, antioxidant, antimicrobial and anticancer activities of extracts from Ficus sycomorus fruits and leaves. Not Bot Horti Agrobo 2019; 47: 493-505.
[57] Sumi SA, Siraj MA, Hossain A, Mia MS, Afrin S and Rahman MM. Investigation of the key

pharmacological activities of Ficus racemosa and analysis of its major bioactive polyphenols by HPLC-DAD. Evid Based Complement Alternat Med 2016; 2016: 3874516.
[58] Mbosso THE, Noundou XS, Fannang S, Meyer F, Vardamides JC, Mpondo E, Mpondo RWM, Krause AGB and Azebaze JCA. In vitro antimicrobial activity of the methanol extract and compounds from the wood of Ficus elastica Roxb. ex Hornem. aerial roots. S Afr J Bot 2017; 111: 302-306.
[59] Mavlonov GT, Ubaidullaeva KA, Rakhmanov MI, Abdurakhmonov IY and Abdukarimov A. Chitin-binding antifungal protein from Ficus carica latex. Chem Nat Compd 2008; 44: 216-219.
[60] Aboody MSA and Mickymaray S. Anti-fungal efficacy and mechanisms of flavonoids. Antibiotics (Basel) 2020; 9: 45.
[61] Wan C, Chen C, Li M, Yang Y, Chen M and Chen J. Chemical constituents and antifungal activity of Ficus hirta Vahl. Fruits. Plants (Basel) 2017; 6: 44.
[62] He YH, Shang XF, Li HX, Li AP, Tang C, Zhang BQ, Zhang ZJ, Wang R, Ma Y, Du SS, Hu YM, Wu TL, Zhao WB, Yang CJ and Liu YQ. Antifungal activity and action mechanism study of coumarins from Cnidium monnieri Fruit and structurally related compounds. Chem Biodivers 2021; 18: e2100633.
[63] Yousaf M, Shoaib A, Fatima Q, Bukhari S, Ali N and Fatima U. In vitro antifungal potential of vanillic acid against sclerotium rolfsii. J Biores Manag 2023; 10: 01-08.
[64] Leite-Andrade MC, de Araújo Neto LN, Buonafina-Paz MDS, de Assis Graciano Dos Santos F, da Silva Alves AI, de Castro MCAB, Mori E, de Lacerda BCGV, Araújo IM, Coutinho HDM, Kowalska G, Kowalski R, Baj T and Neves RP. Antifungal effect and inhibition of the virulence mechanism of D-limonene against candida parapsilosis. Molecules 2022; 27: 8884.
[65] Chen C, Nie Z, Wan C and Chen J. Preservation of Xinyu Tangerines with an edible coating using Ficus hirta Vahl. fruits extract-incorporated chitosan. Biomolecules 2019; 9: 46.
[66] Chen C, Peng X, Chen J and Wan C. Antioxidant, antifungal activities of ethnobotanical Ficus Hirta Vahl. and analysis of main constituents by HPLC-MS. Biomedicines 2020; 8: 15.
[67] Chen C, Wan C, Peng X and Chen J. A flavonone pinocembroside inhibits Penicillium italicum growth and blue mold development in 'Newhall' navel oranges by targeting membrane damage mechanism. Pestic Biochem Physiol 2020; 165: 104505.
[68] Raskovic B, Lazic J and Polovic N. Characterisation of general proteolytic, milk clotting and antifungal activity of Ficus carica latex during fruit ripening. J Sci Food Agric 2016; 96: 576-82.
[69] Wang G, Wang H, Song Y, Jia C, Wang Z and Xu H. Studies on anti-HSV effect of Ficus carica leaves. Zhong Yao Cai 2004; 27: 754-6.
[70] Lazreg Aref H, Gaaliche B, Fekih A, Mars M, Aouni M, Pierre Chaumon J and Said K. In vitro cytotoxic and antiviral activities of Ficus carica latex extracts. Nat Prod Res 2011; 25: 310-9.
[71] Camero M, Marinaro M, Lovero A, Elia G, Losurdo M, Buonavoglia C and Tempesta M. In vitro antiviral activity of Ficus carica latex against caprine herpesvirus-1. Nat Prod Res 2014; 28: 2031-5.
[72] Field HJ. Herpes simplex virus antiviral drug resistance-current tends and future prospects. J Clin Virol 2001; 21: 261-269.
[73] Lansky EP, Paavilainen HM, Pawlus AD and Newman RA. Ficus spp. (fig): ethnobotany and potential as anticancer and anti-inflammatory agents. J Ethnopharmacol 2008; 119: 195-213.
[74] Dell'Annunziata F, Sellitto C, Franci G, Marcotullio MC, Piovan A, Della Marca R, Folliero V, Galdiero M, Filippelli A, Conti V and Delfino DV. Antiviral activity of Ficus rubiginosa leaf extracts against HSV-1, HCoV-229E and PV-1. Viruses 2022; 14: 2257.
[75] Werner-Apt B. Frequently parasite infections and their management. Rev Med Clin Condes 2014; 25: 485-528.
[76] Nagaty HF, Rifaat MA and Morsy TA. Trials of the effect on dog Ascaris in vivo produced by the latex of Ficus carica and Papaya carica growing in Cairo gardens. Ann Trop Med Parasitol 1959; 53: 215-9.
[77] Hansson A, Veliz G, Naquira C, Amren M, Arroyo M and Arevalo G. Preclinical and clinical studies with latex from Ficus glabrata HBK, a traditional intestinal anthelminthic in the Amazonian area. J Ethnopharmacol 1986; 7: 105-38.
[78] de Amorin A, Borba HR, Carauta JP, Lopes D and Kaplan MA. Anthelmintic activity of the latex of Ficus species. J Ethnopharmacol 1999; 64: 255-8.
[79] Mishra V, Khan NU and Singhal KC. Potential antifilarial activity of fruit extracts of Ficus racemosa Linn. against Setaria cervi in vitro. Indian J Exp Biol 2005; 43: 346-50.
[80] Stepek G, Buttle DJ, Duce IR, Lowe A and Behnke JM. Assessment of the anthelmintic effect of natural plant cysteine proteinases against the gastrointestinal nematode, Heligmosomoides polygyrus, in vitro. Parasitology 2005; 130: 203-11.
[81] Chandrashekhar CH, Latha KP, Vagdevi HM and Vaidya VP. Anthelmintic activity of the crude extracts of Ficus racemosa. Int J Green Pharm 2008; 2: 100-103.

[82] Badgujar SB and Mahajan RT. Evaluation of nematicidal properties of some laticiferous plants. Green Farming 2009; 2: 680-4.
[83] Liu F, Yang Z, Zheng X, Luo S, Zhang K and Li G. Nematicidal coumarin from F. carica L. J Asia Pac Entomol 2011; 14: 79-81.
[84] Nweze NE, Ogidi A and Ngongeh LA. Anthelmintic potential of three plants used in Nigerian ethnoveterinary medicine. Pharm Biol 2013; 51: 311-5.
[85] Seif el-Din SH, El-Lakkany NM, Mohamed MA, Hamed MM, Sterner O and Botros SS. Potential effect of the medicinal plants Calotropis procera, Ficus elastica and Zingiber officinale against Schistosoma mansoni in mice. Pharm Biol 2014; 52: 144-50.
[86] Guo Q, Du G, He H, Xu H, Guo D and Li R. Two nematicidal furocoumarins from Ficus carica L. leaves and their physiological effects on pine wood nematode (bursaphelenchus xylophilus). Nat Prod Res 2016; 30: 1969-73.
[87] Wanderley LF, Soares AMDS, Silva CRE, Figueiredo IM, Ferreira ATDS, Perales J, Mota HRO, Oliveira JTA and Costa Junior LM. A cysteine protease from the latex of Ficus benjamina has in vitro anthelmintic activity against Haemonchus contortus. Rev Bras Parasitol Vet 2018; 27: 473-480.
[88] Aswar M, Aswar U, Watkar B, Vyas M, Wagh A and Gujar KN. Anthelmintic activity of Ficus benghalensis. Int J Green Pharm 2008; 2008: 170-172.
[89] Ahamat A, Dikti Vildina J, Liebau E and Ndjonka D. Phytochemical composition and anthelmintic activities of Ficus sycomorus L. (Moraceae) on the bovine parasite onchocerca ochengi and drug resistant strains of the free-living nematode caenorhabditis elegans. Int J Herb Med 2021; 9: 100-110.
[90] Pahari N, Majumdar S, Karati D and Mazumder R. Exploring the pharmacognostic properties and pharmacological activities of phytocompounds present in Ficus racemosa linn.: a concise review. Modern Chinese Medicine Pharmacol Res 2022; 4: 100137.
[91] Stepek G, Behnke JM, Buttle DJ and Duce IR. Natural plant cysteine proteinases as anthelmintics? Trends Parasitol 2004; 20: 322-7.
[92] Athanasiadou S, Kyriazakis I, Jackson F and Coop RL. Direct anthelmintic effects of condensed tannins towards different gastrointestinal nematodes of sheep: in vitro and in vivo studies. Vet Parasitol 2001; 99: 205-219.
[93] Holvoet P. Relations between metabolic syndrome, oxidative stress and inflammation and cardiovascular disease. Verh K Acad Geneeskd Belg 2008; 70: 193-219.
[94] Brahmachari HD and Augusti KT. Orally effective hypoglycemic agents from plants. J Pharm Pharmacol 1962; 14: 254-255.
[95] Ambika SH and Rao MRR. Studies on a phytosteroin from the bark of Ficus religiosa. Indian J Pharm 1967; 29: 91-94.
[96] Perez S, Dominguez E, Ramiro J and Torres DA. A study on the glycaemic balance in streptozotocin-diabetic rats treated with an aqueous extract of Ficus Carica (fig tree) leaves. Phytother Res 1996; 10: 82-83.
[97] Serraclara A, Hawkins F, Pérez C, Domínguez E, Campillo JE and Torres MD. Hypoglycemic action of an oral fig-leaf decoction in type-I diabetic patients. Diabetes Res Clin Pract 1998; 39: 19-22.
[98] Pérez C, Canal JR, Campillo JE, Romero A and Torres MD. Hypotriglyceridaemic activity of Ficus carica leaves in experimental hypertriglyceridaemic rats. Phytother Res 1999; 13: 188-191.
[99] Pérez C, Domínguez E, Canal JR, Campillo JE and Torres MD. Hypoglycaemic activity of an aqueous extract from Ficus carica (fig tree) leaves in streptozotocin diabetic rats. Pharm Biol 2000; 38: 181-186.
[100] Canal JR, Torres MD, Romero A and Perez C. A chloroform extract obtained from a decoction of Ficus carica leaves improves the cholesterolaemic status of rats with streptozotocin-induced diabetes. Acta Physiol Hung 2000; 87: 71-76.
[101] Perez C, Canal JR and Torres MD. Experimental diabetes treated with Ficus carica extract: effect on oxidative stress parameters. Acta Diabetol 2003; 40: 3-8.
[102] Deepa P, Sowndhararajan K, Kim S and Park SJ. A role of Ficus species in the management of diabetes mellitus: a review. J Ethnopharmacol 2018; 215: 210-232.
[103] Boukhalfa F, Kadri N, Bouchemel S, Ait Cheikh S, Chebout I, Madani K and Chibane M. Antioxidant activity and hypolipidemic effect of Ficus carica leaf and twig extracts in Triton WR-1339-induced hyperlipidemic mice. Med J Nutrition Metab 2018; 11: 37-50.
[104] Zhang YJ, Gan RY, Li S, Zhou Y, Li AN, Xu DP and Li HB. Antioxidant phytochemicals for the prevention and treatment of chronic diseases. Molecules 2015; 20: 21138-21156.
[105] Mahmoudi S, Khali M, Benkhaled A, Benamirouche K and Baiti I. 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: 82-83.
[106] Irudayaraj SS, Stalin A, Sunil C, Duraipandiyan V, Al-Dhabi NA and Ignacimuthu S. Antioxidant, antilipidemic and antidiabetic effects of ficusin with their effects on GLUT4 translocation and PPARγ expression in type 2 diabetic rats. Chem Biol Interact 2016; 256: 85-93.

[107] Stephen Irudayaraj S, Christudas S, Antony S, Duraipandiyan V, Naif Abdullah AD and Ignacimuthu S. Protective effects of Ficus carica leaves on glucose and lipids levels, carbohydrate metabolism enzymes and beta-cells in type 2 diabetic rats. Pharm Biol 2017; 55: 1074-1081.
[108] Farsi E, Ahmad M, Hor SY, Khadeer Ahamed MB, Yam MF, Asmawi MZ and Khoo BY. Correction to: standardized extract of Ficus deltoidea stimulates insulin secretion and blocks hepatic glucose production by regulating the expression of glucose-metabolic genes in streptozotocin-induced diabetic rats. BMC Complement Altern Med 2018; 18: 262.
[109] Lin L and Zhang Y. Chemical constituents and antidiabetic activity of dichloromethane extract from Ficus carica Leaves. Diabetes Metab Syndr Obes 2023; 16: 979-991.
[110] Asadi F, Pourkabir M, Maclaren R and Shahriari A. Alterations to lipid parameters in response to fig tree (Ficus carica) leaf extract in chicken liver slices. Turk J Vet Anim Sci 2006; 30: 315-318.
[111] El-Shobaki FA, El-Bahay AM, Esmail RSA, El-Megeid AAA and Esmail NS. Effect of figs fruit (Ficus carica L.) and its leaves on hyperglycemia in alloxan diabetic rats. World J Dairy Food Sci 2010; 5: 47-57.
[112] Stalin C, Dineshkumar P and Nithiyananthan K. Evaluation of antidiabetic activity of methanolic leaf extract of Ficus carica in alloxan-induced diabetic rats. Asian J Pharm Clin Res 2012; 5: 85-87.
[113] Joerin L, Kauschka M, Bonnländer B, Pischel I, Benedek B and Butterweck V. 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: 261-7.
[114] Mopuri R and Islam MS. Antidiabetic and antiobesity activity of Ficus carica: in vitro experimental studies. Diabetes Metab 2016; 42: 300.
[115] Stephen Irudayaraj S, Christudas S, Antony S, Duraipandiyan V, Naif Abdullah AD and Ignacimuthu S. Protective effects of Ficus carica leaves on glucose and lipids levels, carbohydrate metabolism enzymes and β-cells in type 2 diabetic rats. Pharm Biol 2017; 55: 1074-1081.
[116] Belguith-Hadriche O, Ammar S, Contreras MDM, Fetoui H, Segura-Carretero A, El Feki A and Bouaziz M. HPLC-DAD-QTOF-MS profiling of phenolics from leaf extracts of two Tunisian fig cultivars: potential as a functional food. Biomed Pharmacother 2017; 89: 185-193.
[117] Mopuri R, Ganjayi M, Meriga B, Koorbanally NA and Islam MS. The effects of Ficus carica on the activity of enzymes related to metabolic syndrome. J Food Drug Anal 2018; 26: 201-210.
[118] Atkinson FS, Villar A, Mulà A, Zangara A, Risco E, Smidt CR, Hontecillas R, Leber A and Bassaganya-Riera J. Abscisic acid standardized fig (Ficus carica) extracts ameliorate postprandial glycemic and insulinemic responses in healthy adults. Nutrients 2019; 11: 1757.
[119] Arafa EA, Hassan W, Murtaza G and Buabeid MA. Ficus carica and Sizigium cumini regulate glucose and lipid parameters in high-fat diet and streptozocin-induced rats. J Diabetes Res 2020; 2020: 6745873.
[120] Ramadan S, Hegab AM, Al-Awthan YS, Al-Duais MA, Tayel AA and Al-Saman MA. Comparison of the efficiency of lepidium sativum, Ficus carica, and punica granatum methanolic extracts in relieving hyperglycemia and hyperlipidemia of streptozotocin-induced diabetic rats. J Diabetes Res 2021; 2021: 6018835.
[121] Meziant L, Bachir-bey M, Bensouici C, Saci F, Boutiche M and Louaileche H. Assessment of inhibitory properties of flavonoid-rich fig (Ficus carica L.) peel extracts against tyrosinase, α-glucosidase, urease and cholinesterases enzymes, and relationship with antioxidant activity. Eur J Integr Med 2021; 43: 101272.
[122] Kurniawan MF and Yusuf FA. The possible antidiabetic effect of Ficus carica L. Tablet on lloxan-induced diabetes model in rats. Maced J Med Sci 2021; 9: 727-734.
[123] Sophia D and Manoharan S. Hypolipidemic activities of Ficus racemosa Linn. bark in alloxan induced diabetic rats. Afr J Tradit Complement Altern Med 2007; 4: 279-288.
[124] Velayutham R, Sankaradoss N and Ahamed KF. Protective effect of tannins from Ficus racemosa in hypercholesterolemia and diabetes induced vascular tissue damage in rats. Asian Pac J Trop Med 2012; 5: 367-73.
[125] Gul-e-Rana, Karim S, Khurhsid R, Saeed-ul-Hassan S, Tariq I, Sultana M, Rashid AJ, Shah SH and Murtaza G. Hypoglycemic activity of Ficus racemosa bark in combination with oral hypoglycemic drug in diabetic human. Acta Pol Pharm 2013; 70: 1045-1049.
[126] Keshari AK, Kumar G, Kushwaha PS, Bhardwaj M, Kumar P, Rawat A, Kumar D, Prakash A, Ghosh B and Saha S. Isolated flavonoids from Ficus racemosa stem bark possess antidiabetic, hypolipidemic and protective effects in albino Wistar rats. J Ethnopharmacol 2016; 181: 252-62.
[127] Kirana H, Agrawal SS and Srinivasan BP. Aqueous extract of Ficus religiosa linn. reduces oxidative stress in experimentally induced type 2 diabetic rats. Indian J Exp Biol 2009; 47: 822-6.

[128] Pandit R, Phadke A and Jagtap A. Antidiabetic effect of Ficus religiosa extract in streptozotocin-induced diabetic rats. J Ethnopharmacol 2010; 128: 462-6.
[129] Madrigal-Santillán E, Madrigal-Bujaidar E, Álvarez-González I, Sumaya-Martínez MT, Gutiérrez-Salinas J, Bautista M, Morales-González A, García-Luna y González-Rubio M, Aguilar-Faisal JL and Morales-González JA. Review of natural products with hepatoprotective effects. World J Gastroenterol 2014; 20: 14787-804.
[130] Mandal SC, Saraswathi B, Kumar CK, Mohana Lakshmi S and Maiti BC. Protective effect of leaf extract of Ficus hispida Linn. against paracetamol-induced hepatotoxicity in rats. Phytother Res 2000; 14: 457-9.
[131] Mohan GK, Pallavi E, Ravi KB, Ramesh M and Venkatesh S. Hepatoprotective activity of Ficus Carica Linn. leaf extract against carbon tetrachloride-induced hepatotoxicity in rats. Daru 2007; 15: 162-166.
[132] Channabasavaraj KP, Badami S and Bhojraj S. Hepatoprotective and antioxidant activity of methanol extract of Ficus glomerata. J Nat Med 2008; 62: 379-83.
[133] Lv YJ, Jia FL, Ruan M and Zhang BX. The hepatoprotective effect of aqueous extracts from Ficus hirta on N, N-dimethylformamide induced acute liver injury in mice. Zhong Yao Cai 2008; 31: 1364-8.
[134] Gond NY and Khadabadi SS. Hepatoprotective activity of Ficus carica leaf extract on rifampicin-induced hepatic damage in rats. Indian J Pharm Sci 2008; 70: 364-6.
[135] Singab AN, Ayoub NA, Ali EN and Mostafa NM. Antioxidant and hepatoprotective activities of Egyptian moraceous plants against carbon tetrachloride-induced oxidative stress and liver damage in rats. Pharm Biol 2010; 48: 1255-64.
[136] Mujeeb M, Alam Khan S, Aeri V and Ali B. Hepatoprotective activity of the ethanolic extract of Ficus carica Linn. leaves in carbon tetrachloride-induced hepatotoxicityin rats. Iran J Pharm Res 2011; 10: 301-6.
[137] Aghel N, Kalantari H and Rezazadeh S. Hepatoprotective effect of Ficus carica leaf extract on mice intoxicated with carbon tetrachloride. Iran J Pharm Res 2011; 10: 63-8.
[138] Turan A and Celik I. Antioxidant and hepatoprotective properties of dried fig against oxidative stress and hepatotoxicity in rats. Int J Biol Macromol 2016; 91: 554-9.
[139] Youssef FS, Labib RM, Eldahshan OA and Singab ANB. Synergistic hepatoprotective and antioxidant effect of artichoke, fig, blackberry herbal mixture on HepG2 cells and their metabolic profiling using NMR coupled with chemometrics. Chem Biodivers 2017; 14.
[140] Freitas RMP, Linhares BS, Oliveira JM, Leite JPV, da Matta SLP, Gonçalves RV and Freitas MB. Tebuconazole-induced toxicity and the protective effect of Ficus carica extract in Neotropical fruit-eating bats. Chemosphere 2021; 275: 129985.
[141] Parameswari SA, Chetty CM and Chandrasekhar KB. Hepatoprotective activity of Ficus religiosa leaves against isoniazid+rifampicin and paracetamol induced hepatotoxicity. Pharmacognosy Res 2013; 5: 271-6.
[142] Yadav YC. Hepatoprotective effect of Ficus religiosa latex on cisplatin induced liver injury in Wistar rats. Braz J Pharm 2015; 25: 278-283.
[143] Kalaskar MG and Surana SJ. Free radical scavenging and hepatoprotective potential of Ficus microcarpa L. fil. bark extracts. J Nat Med 2011; 65: 633-40.
[144] El-Hawary SS, Ali ZY and Younis IY. Hepatoprotective potential of standardized Ficus species in intrahepatic cholestasis rat model: involvement of nuclear factor-κB, and Farnesoid X receptor signaling pathways. J Ethnopharmacol 2019; 231: 262-274.
[145] Rezagholizadeh L, Aghamohammadian M, Oloumi M, Banaei S, Mazani M and Ojarudi M. Inhibitory effects of Ficus carica and olea europaea on pro-inflammatory cytokines: a review. Iran J Basic Med Sci 2022; 25: 268-275.
[146] Crespo-Pardo L and Taboada-Iglesias Y. Inflammatory mediators: its connection with chronic pain and associated problems: review. Rev Soc Esp Dolor 2021; 28: 37-46.
[147] Ramón-Romero F and Farías JM. Fever. Rev Fac Med Mex 2014; 57: 20-33.
[148] Sackeyfio AC and Lugeleka OM. The anti-inflammatory effect of a crude aqueous extract of the root bark of Ficus elastica in the rat. Arch Int Pharmacodyn Ther 1986; 281: 169-76.
[149] Viswanathan S, Thirugnanasambantham P, Reddy MK, Narasimhan S and Subramaniam GA. Anti-inflammatory and mast cell protective effect of ficus religiosa. Anc Sci Life 1990; 10: 122-5.
[150] Mandal SC, Maity TK, Das J, Saba BP and Pal M. Anti-inflammatory evaluation of Ficus racemosa Linn. leaf extract. J Ethnopharmacol 2000; 72: 87-92.
[151] Thakare VN, Suralkar AA, Deshpande AD and Naik SR. Stem bark extraction of Ficus bengalensis Linn for anti-inflammatory and analgesic activity in animal models. Indian J Exp Biol 2010; 48: 39-45.
[152] Liao CR, Kao CP, Peng WH, Chang YS, Lai SC and Ho YL. Analgesic and anti-inflammatory activities of methanol extract of Ficus pumila L. in mice. Evid Based Complement Alternat Med 2012; 2012: 340141.

[153] Rao RB, Anupama K, Swaroop KR, Murugesan T, Pal M and Mandal SC. Evaluation of anti-pyretic potential of Ficus racemosa bark. Phytomedicine 2002; 9: 731-3.
[154] Patil VV, Bhangale SC and Patil VR. Evaluation of anti-pyretic potential of Ficus carica leaves. Int J Pharm Sci Rev Res 2010; 2: 48-50.
[155] Ali B, Mujeeb M, Aeri V, Mir SR, Faiyazuddin M and Shakeel F. Anti-inflammatory and antioxidant activity of Ficus carica Linn. leaves. Nat Prod Res 2012; 26: 460-5.
[156] Park S, Han J, Im K, Whang WK and Min H. Antioxidative and anti-inflammatory activities of an ethanol extract from fig (Ficus carica) branches. Food Sci Biotechnol 2013; 22: 1071-1075.
[157] Eteraf-Oskouei T, Allahyari S, Akbarzadeh-Atashkhosrow A, Delazar A, Pashaii M, Gan SH and Najafi M. 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; 2015: 760405.
[158] Turkoglu M, Pekmezci E, Kilic S, Dundar C and Sevinc H. Effect of Ficus carica leaf extract on the gene expression of selected factors in HaCaT cells. J Cosmet Dermatol 2017; 16: e54-e58.
[159] Liu YP, Guo JM, Yan G, Zhang MM, Zhang WH, Qiang L and Fu YH. Anti-inflammatory and antiproliferative prenylated isoflavone derivatives from the fruits of Ficus carica. J Agric Food Chem 2019; 67: 4817-4823.
[160] Alcántara C, Žugčić T, Abdelkebir R, García-Pérez JV, Jambrak AR, Lorenzo JM, Collado MC, Granato D and Barba FJ. Effects of ultrasound-assisted extraction and solvent on the phenolic profile, bacterial growth, and anti-inflammatory/antioxidant activities of mediterranean olive and fig leaves extracts. Molecules 2020; 25: 1718.
[161] Orak C, Şirinyıldız F, Gökmen Yılmaz E, Cesur G and Ek RO. Protective effects of Ficus carica seed oil on ischemia and reperfusion injury in a rat model of acute mesenteric ischemia. Ulus Travma Acil Cerrahi Derg 2021; 27: 402-409.
[162] Jiang K, Shi J and Shi J. Morin alleviates vincristine-induced neuropathic pain via nerve protective effect and inhibition of NF-κB pathway in rats. Cell Mol Neurobiol 2019; 39: 799-808.
[163] Patil VV and Patil VR. A comparative evaluation of anti-inflammatory activity of the bark of ficus bengalensis in plants of different age. J Basic Clin Pharm 2010; 1: 107-13.
[164] Patil VV and Patil VR. Evaluation of anti-inflammatory activity of Ficus carica linn leaves. Indian J Nat Prod Res 2011; 2: 151-155.
[165] Panday DR and Rauniar GP. Effect of root-extracts of Ficus benghalensis (Banyan) in pain in animal models. J Neurosci Rural Pract 2016; 7: 210-5.
[166] Rajdev K, Jain S, C H M and Bhattacharaya SK. Antinociceptive effect of Ficus bengalensis bark extract in experimental models of pain. Cureus 2018; 10: e2259.
[167] Jung HW, Son HY, Minh CV, Kim YH and Park YK. Methanol extract of Ficus leaf inhibits the production of nitric oxide and proinflammatory cytokines in LPS-stimulated microglia via the MAPK pathway. Phytother Res 2008; 22: 1064-9.
[168] Charde RM, Dhongade HJ, Charde MS and Kasture AV. Evaluation of antioxidant, wound healing and anti-inflammatory activity of ethanolic extract of leaves of Ficus religiosa. Int J Pharm Sci Res 2010; 1: 73-82.
[169] Kirana H, Jali MV and Srinivasan BP. The study of aqueous extract of Ficus religiosa Linn. on cytokine TNF-α in type 2 diabetic rats. Pharmacognosy Res 2011; 3: 30-4.
[170] Sreelekshmi R, Latha P, Arafat M, Sukumaran S, Shine VJ, Anuja GI and Rajasekharan S. Anti-inflammatory, analgesic and anti-lipid peroxidation studies on stem bark of Ficus religiosa Linn. Indian J Nat Prod Res 2007; 6: 377-381.
[171] Gulecha V, Sivakumar T, Upaganlawar A, Mahajan M and Upasani C. Screening of Ficus religiosa leaves fractions for analgesic and anti-inflammatory activities. Indian J Pharmacol 2011; 43: 662-6.
[172] Abdulmalik IA, Sule MI, Musa AM, Yaro AH, Abdullahi MI, Abdulkadir MF and Yusuf H. Evaluation of analgesic and anti-inflammatory effects of ethanol extract of Ficus iteophylla leaves in rodents. Afr J Tradit Complement Altern Med 2011; 8: 462-6.
[173] Zakaria ZA, Hussain MK, Mohamad AS, Abdullah FC and Sulaiman MR. Anti-inflammatory activity of the aqueous extract of ficus deltoidea. Biol Res Nurs 2012; 14: 90-7.
[174] Mohd Ariff A, Abu Bakar NA, Abd Muid S, Omar E, Ismail NH, Ali AM, Mohd Kasim NA and Mohd Nawawi H. Ficus deltoidea suppresses endothelial activation, inflammation, monocytes adhesion and oxidative stress via NF-κB and eNOS pathways in stimulated human coronary artery endothelial cells. BMC Complement Med Ther 2020; 20: 56.
[175] Sulaiman MR, Hussain MK, Zakaria ZA, Somchit MN, Moin S, Mohamad AS and Israf DA. Evaluation of the antinociceptive activity of Ficus deltoidea aqueous extract. Fitoterapia 2008; 79: 557-61.
[176] Zolkiffly SZI, Stanslas J, Abdul Hamid H and Mehat MZ. Ficus deltoidea: potential inhibitor of pro-inflammatory mediators in lipopolysac-

charide-induced activation of microglial cells. J Ethnopharmacol 2021; 279: 114309.
[177] Abotsi WM, Woode E, Ainooson GK, Amo-Barimah AK and Boakye-Gyasi E. Antiarthritic and antioxidant effects of the leaf extract of Ficus exasperata P. beauv. (Moraceae). Pharmacognosy Res 2010; 2: 89-97.
[178] Nworu CS, Nwuke HC, Akah PA, Okoye FB and Esimone CO. Extracts of Ficus exasperata leaf inhibit topical and systemic inflammation in rodents and suppress LPS-induced expression of mediators of inflammation in macrophages. J Immunotoxicol 2013; 10: 302-10.
[179] Cheng J, Yi X, Chen H, Wang Y and He X. Anti-inflammatory phenylpropanoids and phenolics from Ficus hirta Vahl. Fitoterapia 2017; 121: 229-234.
[180] Ye X, Tian W, Wang G, Zhang X, Zhou M, Zeng D, Liu X, Yao X, Zhang Y and Chen H. Phenolic glycosides from the roots of Ficus hirta Vahl. and their antineuroinflammatory activities. J Agric Food Chem 2020; 68: 4196-4204.
[181] Li RW, Leach DN, Myers SP, Lin GD, Leach GJ and Waterman PG. A new anti-inflammatory glucoside from Ficus racemosa L. Planta Med 2004; 70: 421-6.
[182] Ferdous M, Rouf R, Shilpi AJ and Uddin SJ. Antinociceptive activity of the ethanolic extract of Ficus racemosa Lin. (Moraceae). Orient Pharm Exp Med 2008; 8: 93-96.
[183] Imran M, Rasool N, Rizwan K, Zubair M, Riaz M, Zia-Ul-Haq M, Rana UA, Nafady A and Jaafar HZ. Chemical composition and biological studies of Ficus benjamina. Chem Cent J 2014; 8: 12.
[184] Arunachalam K and Parimelazhagan T. Antidiabetic activity of Ficus amplissima Smith. bark extract in streptozotocin induced diabetic rats. J Ethnopharmacol 2013; 147: 302-310.
[185] Kalaskar MG and Surana SJ. Pharmacognostic and phytochemical studies on Ficus Microcarpa L. fil. Anc Sci Life 2012; 32: 107-111.
[186] Mazumder PM, Farswan M, Parcha V and Singh V. Hypoglycemic and antioxidant activity of an isolated compound from Ficus arnottiana bark. Pharmacol 2008; 3: 509-519.
[187] Ojo OA, Ojo AB, Ajiboye B, Fadaka A, Imiere OD, Adeyonu O and Olayide I. Protective influence of Ficus asperifolia Miq leaf extract on carbon tetrachloride (CCl4)-induced testicular toxicity in rat's testes. J Appl Pharm Sci 2016; 6: 37-41.
[188] Patel M, Patel P and Patel M. Aqueous extract of Ficus bengalensis Linn. Bark for inflammatory bowel disease. J Young Pharm 2010; 2: 130-6.
[189] Singh RK, Mehta S, Jaiswal D, Rai PK and Watal G. Antidiabetic effect of Ficus bengalensis aerial roots in experimental animals. J Ethnopharmacol 2009; 123: 110-4.
[190] Hasti S, Mora E, Utami R and Yulis LU. Subchronic toxicity of Ficus benjamina L. leaves ethanol extract on the liver function of white mice. Procedia Chem 2014; 13: 204-208.
[191] Díez-Gómez ML, Quirce S, Aragoneses E and Cuevas M. Asthma caused by Ficus benjamina latex: evidence of cross-reactivity with fig fruit and papain. Ann Allergy Asthma Immunol 1998; 80: 24-30.
[192] Chełmińska M. Latex allergy-part I. Pneumonol Alergol Pol 2004; 72: 143-9.
[193] Bircher AJ, Langauer S, Levy F and Wahl R. The allergen of Ficus benjamina in house dust. Clin Exp Allergy 1995; 25: 228-33.
[194] Antico A, Zoccatelli G, Marcotulli C and Curioni A. Oral allergy syndrome to fig. Int Arch Allergy Immunol 2003; 131: 138-42.
[195] Odo GE, Agwu JE, Newze N, Nwadinigwa A, Onyeke CC, Nzekwe U, Ajuziogu GC, Osayi EI and Ikegbunam C. 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.
[196] Coloma PM, Avillach P, Salvo F, Schuemie MJ, Ferrajolo C, Pariente A, Fourrier-Réglat A, Molokhia M, Patadia V, van der Lei J, Sturkenboom M and Trifirò G. Reference standard for evaluation of methods for drug safety signal detection using electronic healthcare record databases. Drug Saf 2013; 36: 13-23.
[197] Ippen H. Phototoxic reaction to figs. Hautarzt 1982; 33: 337-9.
[198] Polat M, Oztas P, Dikilitas MC and Alli N. Phytophotodermatitis due to Ficus carica. Dermatol Online J 2008; 14: 9.
[199] Caiaffa MF, Cataldo VM, Tursi A and Macchia L. Fig and mulberry cross-allergy. Ann Allergy Asthma Immunol 2003; 91: 493-5.
[200] Urbani S, Aruanno A and Nucera E. Adverse reaction to Ficus carica: reported case of a possible cross-reactivity with Der p1. Clin Mol Allergy 2020; 18: 9.
[201] Awobajo FO, Omorodion-Osagie E, Olatunji-Bello II, Adegoke OA and Adeleke TI. Acute oral toxicity test and phytochemistry of some West African medicinal plants. Nig Q J Hosp Med 2009; 19: 53-8.
[202] Hasanat A, Kabir MSH, Ansari MA, Chowdhury TA, Hossain MM, Islam MN, Ahmed S, Chy MNU, Adnan M and Kamal ATMM. Ficus cunia Buch.-Ham. ex Roxb. (leaves): an experimental evaluation of the cytotoxicity, thrombolytic, analgesic and neuropharmacological activities of its methanol extract. J Basic Clin Physiol Pharmacol 2019; 30.

[203] Allahyari S, Delazar A and Najafi M. Evaluation of general toxicity, anti-oxidant activity and effects of ficus carica leaves extract on ischemia/reperfusion injuries in isolated heart of rat. Adv Pharm Bull 2014; 4 Suppl 2: 577-82.
[204] Abdel-Atya AM, Hameda MB, Salamaa WH, Alib MM, Fahmya AS and Mohameda SA. Ficus carica, Ficus sycomorus and euphorbia tirucalli latex extracts: phytochemical screening, antioxidant and cytotoxic properties. Biocatal Agric Biotechnol 2019; 20: 101199.
[205] Jacob SJP, Prasad VLS, Sivasankar S and Muralidharan P. Biosynthesis of silver nanoparticles using dried fruit extract of Ficus carica - Screening for its anticancer activity and toxicity in animal models. Food Chem Toxicol 2017; 109: 951-956.
[206] Ghori SS, Khan M, Qureshi MS and Ghori SK. Analgesic and antipyretic effects of Ficus dalhouseae Miq. leaf ethanolic extract. Res J Pharm Technol 2014; 7: 1014-1019.
[207] Ilyanie Y, Wong TW and Choo CY. Evaluation of hypoglycemic activity and toxicity profiles of the leaves of Ficus deltoidea in rodents. J Complement Integr Med 2011; 8.
[208] Bafor EE and Igbinuwen O. Acute toxicity studies of the leaf extract of Ficus exasperata on haematological parameters, body weight and body temperature. J Ethnopharmacol 2009; 123: 302-7.
[209] Dhyani PP and Khali MP. Fruit yield and economics of jelly and jam production from fruits of some promising Ficus (fig) tree crops. Ecol Food Nutr 1993; 30: 169-178.
[210] Chindo BA, Ya'U J, Danjuma NM, Okhale SE, Gamaniel KS and Becker A. Behavioral and anticonvulsant effects of the standardized extract of Ficus platyphylla stem bark. J Ethnopharmacol 2014; 154: 351-60.
[211] Heroor SS, Beknal A and Mahurkar N. Ficus bark extract enhances the antihyperglycemic activity of glibenclamide in rats: a herb-drug interaction study. Int J Med Res Rev 2014; 2: 395-402.
[212] Barolo MI, Ruiz Mostacero N and López SN. Ficus carica L. (Moraceae): an ancient source of food and health. Food Chem 2014; 164: 119-27.
[213] Cavero RY, Akerreta S and Calvo MI. Medicinal plants used for dermatological affections in Navarra and their pharmacological validation. J Ethnopharmacol 2013; 149: 533-542.
[214] Rojas P, Jung-Cook H, Ruiz-Sánchez E, Rojas-Tomé IS, Rojas C, López-Ramírez AM and Reséndiz-Albor AA. Historical aspects of herbal use and comparison of current regulations of herbal products between Mexico, Canada and the United States of America. Int J Environ Res Public Health 2022; 19: 15690.
[215] British Pharmacopoeia, 2023. Accessed 13. 10.2023. https://www.pharmacopoeia.com/.