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PHYTOCHEMICAL CONSTITUENTS AND BIOLOGICAL EFFECTS OF *FICUS DRUPACEA* THUNB (MORACEAE): A MINI REVIEW

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Abstract

In traditional medicine around the world, some Ficus species have received widespread recognition as treatments for a variety of illnesses. The current review discusses the phytochemical and the biological perspective of *Ficus drupacea* thumb, to bring attention to this species' therapeutic importance. 66 structures were reported as chemical constituents of *Ficus drupacea*, 47 of them were tentatively recognized compounds, and 19 were identified as isolated metabolites. Also, Modern pharmacological investigations revealed that *Ficus drupacea* has a wide range of health benefits, including anti-diabetic, anti-inflammatory, antioxidant, anticancer, antiulcerogenic, wound healing, anti-hyperlipidemic, hepatoprotective, and antibacterial activities. Because of the limited studies on this species, this review draws attention to further biological and phytochemical research on *Ficus drupacea* thunb to discover its medicinal uses.

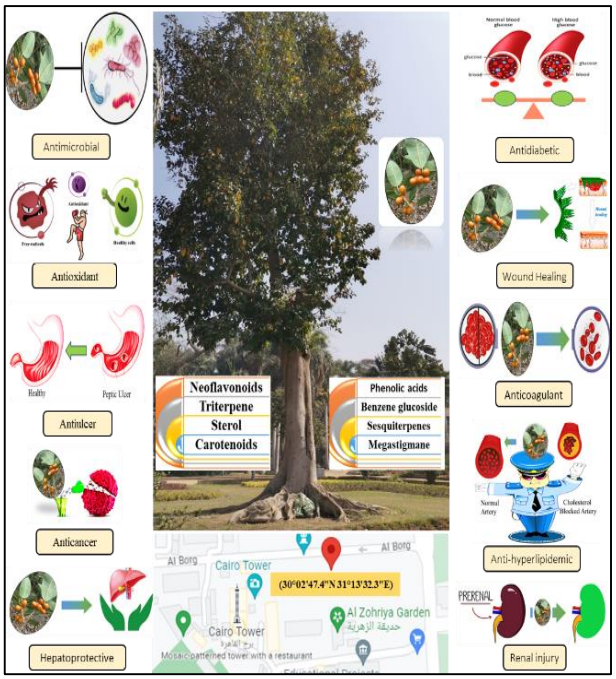
Keywords: *Ficus drupacea* thumb; Taxonomy; Traditional Uses; Phytochemistry; Pharmacological Activity.

1. Introduction

A new and intriguing area of ethnopharmacology has emerged as a result of pharmacological research into the secondary chemicals from edible plants, particularly those that have historically been utilized both for food and medicine. Since ethnobotanical and anthropological field surveyors have well-recorded Ficus species for nutritional applications, ethnopharmacologists rarely discuss them [1].

Ficus is one of the largest angiosperms genera with more than 800 species of trees, shrubs, climbers, and creepers in the tropics and subtropics worldwide [2]. Due to this genus's high economic and nutritional worth and significant contribution to biodiversity in the rainforest's ecosystem, it is an essential genetic resource. In tropical and subtropical regions, they have historically been employed as food and medicine sources, ornamental trees, holy plants, lac hosts, fuel, fodder, and fences [1, 3]. Through pharmacological research, the therapeutic potential of the genus Ficus has been thoroughly examined in recent years. These studies have focused on the plants' anti-oxidant, anti-microbial, anti-cancer, anti-inflammatory, and antidiabetic properties [4-7].

When the genus Ficus is mentioned, attention is always drawn to *F. carica* and *F. sycomorus*, which yield fruits with significant nutritional and medicinal values [1, 8]. Among the genus Ficus, *F. drupacea* thunb has been selected as a subject of interest for the current review, where its phytochemical and biological perspectives were reviewed.



Scheme I. Phytochemical constituents and biological effects of *Ficus drupacea*

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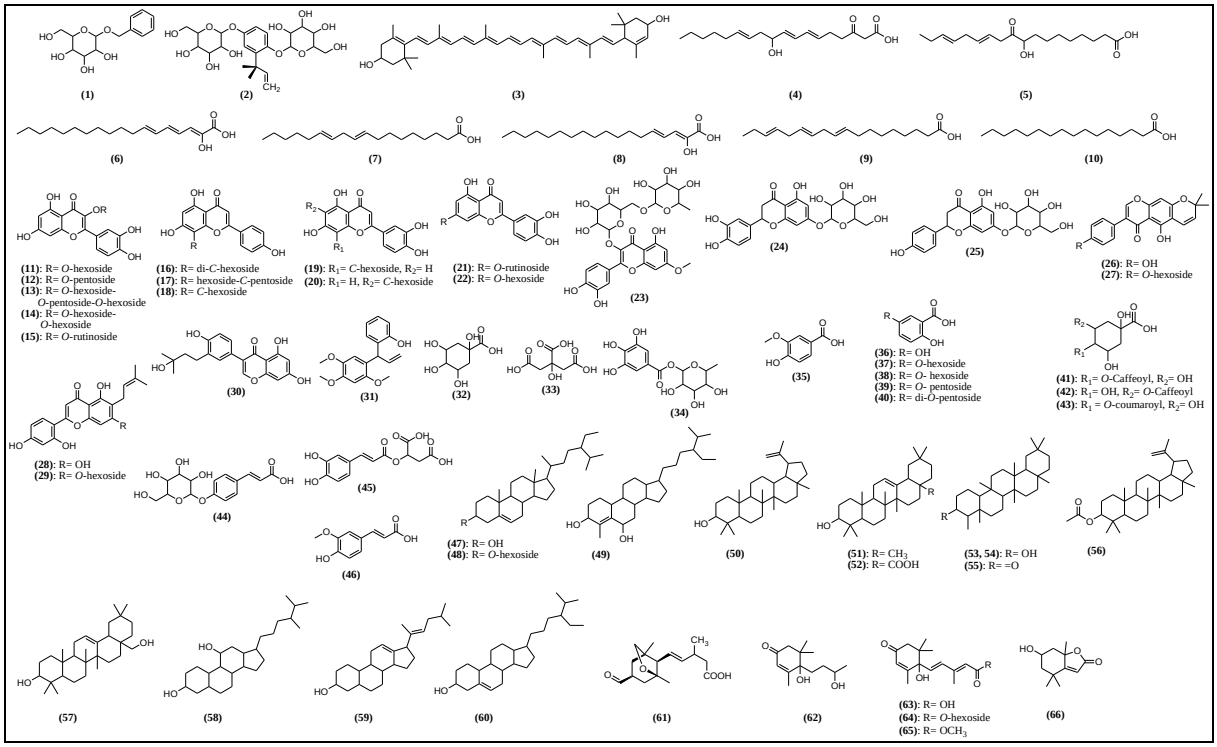

Figure 1. Compounds isolated and identified from *F. drupacea*

2. Search Strategy

Data from various databases such as the Egyptian Knowledge Bank, Scopus, Web of Science, PubMed, Google Scholar, and Elsevier databases were gathered until September 2023. All possible keywords about *Ficus drupacea* thunb (Moraceae), the phytochemical and biological prospective applications, and clinical studies were utilized in the search.

3. Botanical description

3.1. Taxonomic classification

The taxonomic position of *F. drupacea*. (syn. *F. mysorensis*) is as follows [9, 10]:

Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Rosales
Family: Moraceae
Genus: *Ficus*
Species: *F. drupacea* thunb
Syn.: *Ficus drupacea* var. *mysorensis* (B.Heyne ex Roth) M.R.Almeida.
English: brown-woolly fig or Mysore fig

3.2. *Morphological description*

F. drupacea (syn. *F. mysorensis*) is a monoecious evergreen tree that naturally grows from Southeast Asia to Australia. It can reach heights up to 35 m, is hemi-epiphytic or terrestrial, and has glabrous to pale or rusty brown hairy leafy twigs. The leaves are coriaceous, elliptic to oblong or obovate, 10-35 cm long, and 4-16 cm wide. They are spirally arranged or sub- distichous, and have a cord-like or rounded base. The lamina is mostly on the broad veins glabrous to sparsely or thickly brown tomentose or woolly. Figs are sessile and ellipsoid, axillary, in pairs or solitary, 2-3 cm in diameter and up to 4.0–4.5 cm long, glabrous, and golden to orange when mature [11].

3.3. *Geographic distribution*

The plant is distributed in the countries of Asia-Temperate (China), Asia-Tropica (Bangladesh, Bhutan, India, Sri Lanka, and Nepal), India to Southeast Asia, New Guinea, Solomon Islands and Australia (Queensland) [12].

4. Ethnobotanical uses

In traditional medicine, *F. drupacea* leaves were used in the treatment of paragonimiasis, malaria, anasarca, nasosinusitis, and sinusitis [13, 14].

5. Chemical composition

Different phytochemical compounds have been isolated from the leaves and stem bark of *F. drupacea*. A comprehensive review noticed around 19 isolated natural metabolites. Compounds reported comprise one neoflavonoid compound, 12 terpenoid compounds, 3 sterol compounds, and other compounds. In addition, 59 compounds were tentatively identified from leaves using UPLC-PDA-ESI-MS/MS illustrated in Table (1) and Figure (1) [15, 16]. According to a previous study on three different ficus species, *F. drupacea* leaf extract was characterized by the presence of Alpinumisoflavone and its glucoside, and Luteone-*O*-hexoside [15].

6. Biological activities

6.1. Antioxidant activity

The antioxidant properties of both ethanol and hexane extracts of *F. drupacea* leaves were evaluated using 2,2-diphenylpicrylhydrazyl (DPPH) assay showing that hexane extract was the highest one with an inhibition percentage of 85.61%/100 µg DPPH- [20]. In another study, the methanolic extract of *F. drupacea* leaves showed significant scavenging effects on the DPPH radical where the

antioxidant activity of the extract was 95% of the standard [18]. Moreover, phenolic acids rich fraction from extract of *F. drupacea* leaves showed higher DPPH radical scavenging activity with IC_{50} value of 231±0.074 µg/ml [15]. The antioxidant effect may be due to the presence of phenolic compounds which react with a variety of free radicals [17]

6.2. Antiulcerogenic activity

Rats were used to assess the gastroprotective effect of *F. drupacea* water fraction against ethanol-induced ulcers. Increased gastric juice volume, ulcer lesions, and decreased stomach pH were all observed in ulcerogenic rats. On the other hand, pretreatment with extract (100 mg/kg b.wt., p.o.) significantly decreased the lesion index, reduced gastric juice volume by 56.09%, and raised gastric pH value. When administered following ethanol, the same amount of extract significantly sped up the process of healing of the gastric ulcer, reduced gastric juice volume by 75.60%, and raised pH levels. Superoxide dismutase and reduced glutathione levels in gastric homogenate increased, and malondialdehyde levels dropped in both prophylactic and therapeutic treatment groups. Additionally, lactate dehydrogenase and succinate dehydrogenase levels were elevated, whereas acid phosphatase activity was reduced. Additionally, there was a significant rise in the inflammatory markers PGE2 and IL-10. The foregoing findings were confirmed by the histopathology findings. Accordingly, phenolic acids, as well as QA and its derivatives, may be responsible for the gastroprotective and ulcer-healing properties [15].

6.3. Wound healing activity

Drupin, a cysteine protease isolated from the latex of *F. drupacea*, was evaluated for its ability to speed up the healing of wounds. Matrix Metalloprotease (MMP)-9 was downregulated, whereas MMP-8 expression was unaffected, which quicker wound healing. In addition, drupin increased arginase 1 activity at the wound site which speeds up collagen formation. Additionally, drupin promoted the production of arginase 1 in macrophages and acted on the MAP kinase and PI3K/Akt pathways to promote cell proliferation and motility [18].

6.4. ***Anticoagulant activity***

Drupin isolated from latex *F. drupacea* has pro-coagulant properties and shortens the duration that mice tails bleed. By triggering nuclear factor-κB, mitogen-activated protein kinases, and the PI3K/Akt signaling cascade, which in turn phosphorylates cytosolic phospholipase A2 and causes the release of thromboxane A2 from the granules, it stimulates the aggregation of nearby platelets. In addition, the findings demonstrated that PAR1 and PAR4 worked together synergistically to mediate the drupin-induced platelet aggregation [19] (Figure 2).

6.5. Antimicrobial activity

Using microdilution method *n*-hexane extract of *F. drupacea* stem bark and the isolated compounds 5-*O*-methyllatifolin and epilupeol acetate exhibited the highest antifungal (*Aspergillus flavus*, *Aspergillus versicolor*, *Aspergillus niger*, *Aspergillus ochraceus*, *Candida albicans*, *Penicillium funiculosum and Penicillium ochrochloron*) and antibacterial (*Bacillus cereus*, *Listeria monocytogenes*, *Micrococcus flavus*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*) activities against the screened microorganisms. The most susceptible fungi to the screening compounds were *A. versicolor* and *A. ochraceus*, while *C. albicans* was the most resistant. Except for *S. aureus* and *E. coli*, oleanolic acid, epifriedelanol, and friedelin did not show significant differences in their antibacterial activity. The activity of the isolated compounds (*β*-amyrin, *β*-sitosterol-3-*O*-*β*-D-glucopyranoside, 5-*O*-methyllatifolin, oleanolic acid, epifriedelanol, friedelin, and epilupeol acetate) against fungus and bacteria was significantly greater than that of the crude extract [20]. In another study, the methanolic extract of *F. drupacea* leaves showed weak antimicrobial activity against gram-positive bacteria (*Bacillus subtilis, S. aureus*), gram-negative bacteria (*P. aeruginosa*, *E. coli*) and Fungi (*Aspergillus fumigatus, C. albicans*) using disc diffusion method in comparison to standard drugs [21].

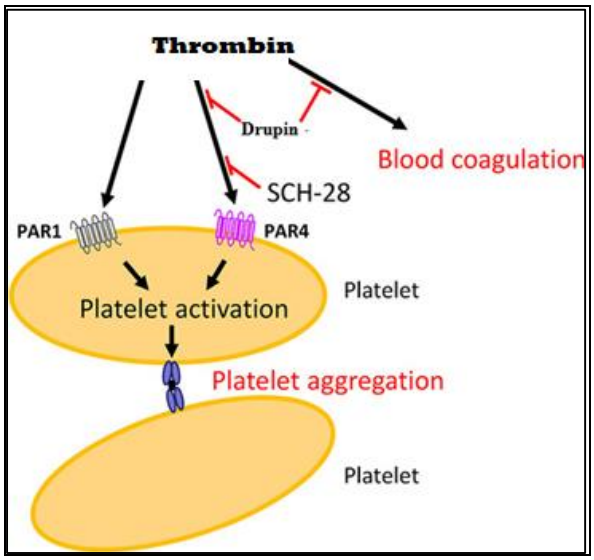

Figure 2. Anticoagulant activity

6.6. Anticancer activity

F. drupacea stem bark *n*-hexane extract and isolated compounds (5-*O*-methyllatifolin, oleanolic acid, epifriedelanol, friedelin, and epilupeol acetate) exhibited dose-dependent cell viability loss on different cell lines (HeLa, MCF-7, Jurkat, HT-29 and T24). In HeLa cells, the IC_{50} values for crude extract and compounds were 60, 29.07, 20.38, 52.16, 20.42, and 15.16 µg/ml, respectively. The IC_{50} values for crude extract and isolated compounds in MCF-7 were 39.16, 25.34, 16.28, 44.84, 22.81, and 20.03 µg/ml, respectively. The antiproliferative actions of oleanolic acid, friedelin, and epilupeol acetate against most cancer cells were the strongest [20]. Another study found that the methanolic extract of *F. drupacea* leaves had weak cytotoxic activity against hepatocellular carcinoma (HEP-G2) cell line with IC_{50} 22.6 µg/ml compared to the standard Doxorubicin (IC_{50} 1.2 µg/ml) and strong cytotoxic activity against human colon carcinoma (HCT-116) cell line, with an IC_{50} value of 1.5 µg/ml compared to standard vinblastine (IC_{50} 2.38 µg/ml) [21] (Figure 3).

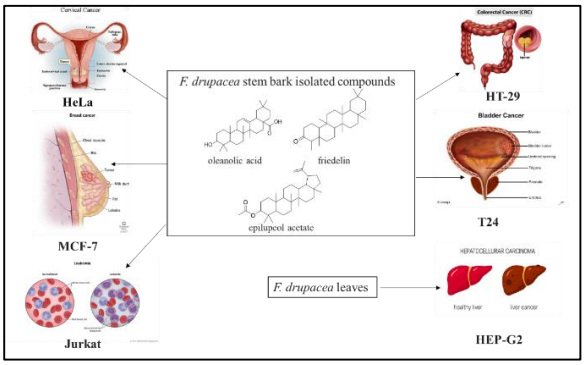

Figure 3. Anticancer activity

6.7. Antidiabetic activity

Diabetes-related high blood sugar can be treated by using *α*-glucosidase Inhibitors. *F. drupacea* leaves extract and isolated compounds 4'-dihydrophaseate sodium, 5-*O*-methyllatifolin, 1,4-di-*O*-*β*-D-glucopyranosyl-2-(1,1-dimethyl propenyl) benzene, benzyl-*O*-*β*-D-glucopyranoside, oleanolic acid, epifriedelanol, friedelin, epilupeol acetate, and xanthophyll were evaluated for their *α*-glucosidase Inhibitory activity. At a concentration of 100 µg/ml, the results showed that the whole extract has a 39% *α*-glucosidase inhibitory action. Oleanolic acid also demonstrated the highest level of activity among the compounds, with an inhibition percentage of 49.9% at a concentration of 100 µM. Oleanolic acid was followed by friedelin and epilupeol acetate, while the rest of the compounds displayed minimal to no activity when compared to acarbose, which was used as a positive control and had an inhibition percentage of 82.5% [13] (Figure 4).

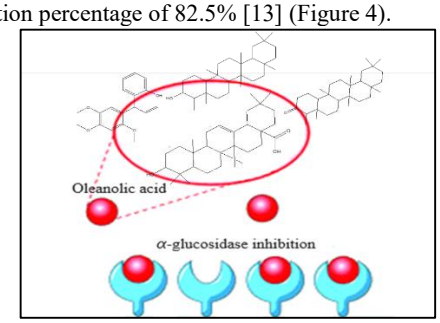

Figure 4. Antidiabetic activity

6.8. Anti-hyperlipidemic activity

Some Ficus species methanolic and hexane extracts were evaluated *in vitro* against hyperlipidemia by evaluating the rate-limiting enzyme of cholesterol biosynthesis; *β*-hydroxy-*β*-methylglutaryl coenzyme A reductase (HMGCoA reductase). The maximum hypolipidaemic activity was demonstrated by the hexane extract of *F. drupacea* (94.38%). To assess it *in vivo*, hypercholesterolemic rats were used to estimate their lipid profile and several antioxidant markers. Based on this finding, *F. drupacea* serves as an anti-atherogenic agent in the current investigation by reducing lipid peroxidation and increasing high-density lipoprotein (HDL) cholesterol [22]. Triterpenes and sterols that were isolated from the hexane extract may be the cause of this activity. These findings align with previous research on the hypolipidemic effects of triterpenes obtained from plants. Rats' atherogenic index and coronary risk index significantly decreased when exposed to triterpene from *Protorhus longifolia* stem bark [23]. In addition, consumption of plant sterol and their esters has also been reported to not only lower intestinal cholesterol absorption but also decrease blood levels of the atherogenic LDL-c [24, 25] (Figure 5).

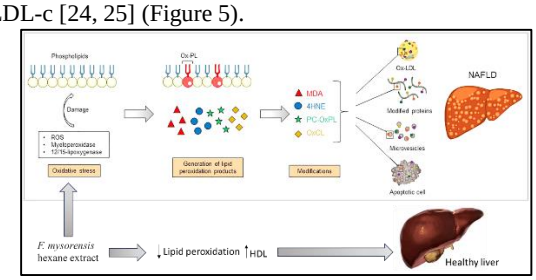

Figure 5. Anti-hyperlipidemic activity

6.9. Activity against renal disorder

F. drupacea leaves succeed in reducing the negative effects of hypercholesterolemia on the renal system by improving kidney function indicators (urea nitrogen, creatinine, serum protein, and albumin), kidney disorder biochemical parameters (NO, Na-KATPase, and phospholipids), blood profile (hemoglobin, RBCs, and WBCs), and kidney histopathology [26].

6.10. Hepatoprotective activity

In an intrahepatic cholestasis rat model caused by 17-Ethinylestradiol (EE), the ethanol extract of the leaves of five distinct Ficus species was examined for its hepatoprotective ability. *F. drupacea* was one of the species investigated. The liver index of the group that had been pretreated with *F. drupacea* was 4.98 ± 0.17, represented in mean ± SE. Additionally, only a minimal protective effect was seen in the *F. drupacea* pretreatment group, as seen by the remarkably decreased blood levels of ALT, AST, ALP, GGT, and total bilirubin (by 19.7%, 11.7%, 12.2%, 10.8%, and 24.7%, respectively), as well as the significantly increased levels of total protein (9.68%). According to biochemical changes, it was observed that the protective activity of *F. drupacea* was the lowest with a percentage value of 14.2% for 5′-nucleotidase, 25.9% for total bile acids, 12.1% for total cholesterol and 9.79% for phospholipids. Additionally, compared to the EE group but not better than other Ficus species, *F. drupacea* demonstrated an increase in the Na^+/K^+ -ATPase enzyme activity of 29.7% and a decrease in the hepatic levels of TNF-α, NF-κB, HGF, and OH-1. Additionally, compared to the EE group, *F. drupacea* considerably improved the hepatic antioxidant enzyme activities (SOD, CAT, and GST), along with a marked drop in MDA and NO. However, it was not better compared to other Ficus species [27].

7. Toxicological effects

Acute toxicity of *F. drupacea* leaf extract was studied on 40 male rats at different plant concentrations (50, 100, and 200 mg/kg b. wt) For 15 days. No dead rats were observed during this time, indicative of the safety of the extract [15].

8. Quality control/quality assurance

F. drupacea leaves extract was standardized using key markers quinic acid and chlorogenic acid to contain 21.12±2.19 mg/g of quinic acid and 6.30±3.09 mg/g of chlorogenic acid [15].

Table 1
The identified compounds from *F. drupacea*

Compound	Organ	Reference
Benzyl alcohol glucoside		
Benzyl-*O*-*β*-D-glucopyranoside **(1)** #	Leaves	[21, 28]
Benzenediol glucoside		
1,4-Di-*O*-*β*-D-glucopyranosyl-2-(1,1-dimethylpropenyl)-benzene **(2)** #	Leaves	[28]
Carotenoids		
Xanthophyll **(3)** #	Leaves	[28]
Fatty acid		
Hydroxy-oxo-octadecatrienoic acid **(4)** *	Leaves	[16]
Hydroxy-oxo-octadecadienoic acid **(5)** *	Leaves	[16]
Hydroxyoctadecatrienoic acid **(6)** *	Leaves	[16]
Octadecadienoic acid **(7)** *	Leaves	[16]
Hydroxyoctadecadienoic acid **(8)** *	Leaves	[16]
Linolenic acid **(9)** *	Leaves	[16]
Palmitic acid **(10)** *	Leaves	[16]
Flavonoids		
Flavanol-*O*-glycosides		
Quercetin-*O*-hexoside **(11)** *	Leaves	[16]
Quercetin-*O*-pentoside **(12)** *	Leaves	[16]
Quercetin-*O*-hexoside-*ml* pentoside-*O*-hexoside **(13)** *	Leaves	[16]
Quercetin-*O*-hexoside-*O*-hexoside **(14)** *	Leaves	[16]
Quercetin-*O*-rutinoside (rutin) **(15)** *	Leaves	[16]
Flavone-*C*-glycosides		
Apigenin-di-*C*-hexoside **(16)** *	Leaves	[16]
Apigenin-*C*-hexoside-*C*-pentoside (Schaftoside) **(17)** *	Leaves	[16]
Apigenin-*C*-hexoside (vitexin) **(18)** *	Leaves	[16]
Luteolin-*C*-hexoside (orientin) **(19)** *	Leaves	[16]
Luteolin-*C*-hexoside (Isoorientin) **(20)** *	Leaves	[16]
Flavone-*O*-glycosides		
Luteolin-*O*-rutinoside (scolymoside) **(21)** *	Leaves	[16]
Luteolin-*O*-hexoside **(22)** *	Leaves	[16]
Rhamnetin-*O*-rutinoside **(23)** *	Leaves	[16]
Flavanone-*C*-glycosides		
Tetrahydroxyflavanone -*C*-hexoside (Eriodictyol hexoside) **(24)** *	Leaves	[16]
Flavanone-*O*-glycosides		
Naringenin-*O*-hexoside **(25)** *	Leaves	[16]
Prenylated isoflavone		
Alpinum isoflavone **(26)** *	Leaves	[16]
Alpinumisoflavone-*O*-hexoside **(27)** *	Leaves	[16]
Luteone(6-prenylated isoflavone) **(28)** *	Leaves	[16]
Luteone-*O*-hexoside **(29)** *	Leaves	[16]
Isoflavone		
Isowighteonehydrate **(30)** *	Leaves	[16]
Neoflavonoids		
5-*O*-methyllatifolin **(31)** #	Stem bark, leaves	[20, 28]
Organic acids		
Quinic acid **(32)** *	Leaves	[16]
Citric acid **(33)** *	Leaves	[16]
Phenolic acids		
Galloyl-*O*-deoxyhexoside **(34)** *	Leaves	[16]
Vanillic acid-*O*-hexoside **(35)** *	Leaves	[16]
Dihydroxybenzoic acid **(36)** *	Leaves	[16]
Dihydroxybenzoic acid-*O*- hexoside **(37)** *	Leaves	[16]
Dihydroxybenzoic acid-*O*- pentoside **(38)** *	Leaves	[16]
Dihydroxybenzoic acid di-*O*-pentoside **(39)** *	Leaves	[16]
Chlorogenic acid **(40)** *	Leaves	[16]
Cryptochlorgenic acid **(41)** *	Leaves	[16]
Di-*O*-caffeoylquinic acid **(42)** *	Leaves	[16]
O-coumaroylquinic acid **(43)** *	Leaves	[16]
Coumaric acid-*O*-hexoside **(44)** *	Leaves	[16]
Caffeoylmalic acid **(45)** *	Leaves	[16]
Ferulic acid **(46)** *	Leaves	[16]

Sterols		
β-sitosterol **(47)** #	Stem bark	[20]
β-sitosterol-3-*O*-*β*-D-glucopyranoside **(48)** #	Leaves	[21, 22]
(24 R)-ethylcholest-4-ene-3 *β*, 6 *β* -diol **(49)** #	Leaves	[22]
Terpenoids		
Triterpenes		
Lupeol **(50)** #	Leaves	[21, 29, 30]
β-amyrin **(51)** #	Leaves, Stem bark	[20, 22]
Oleanolic acid **(52)** #	Stem bark, leaves	[20, 28]
Epifriedelinol **(53)** #	Stem bark, leaves	[20, 28]
β-friedelinol **(54)** #	leaves	[20, 21, 28]
Friedelin **(55)** #	Stem bark, leaves	[20, 28]
Epilupeol acetate **(56)** #	Stem bark, Leaves	[21]
Erythrodiol **(57)** #	Leaves	[21]
4,14,24-trimethyl-cholestane-3,11- *β* -β-diol **(58)** #	Leaves	[22]
Dammara-12, 20(22) Z-dien-3-ol **(59)** #	Leaves	[22]
3*β*, 27-dihydroxyolea-12-ene **(60)** #	Leaves	[22]
Sesquiterpenes		
Phaseic acid **(61)** #	Leaves	[28]
Dihydrovomifoliol **(62)** *	Leaves	[16]
Abscisic acid **(63)** *	Leaves	[16]
Abscisic acid-*O*-hexoside **(64)** *	Leaves	[16]
Abscisic acid methyl ester **(65)** *		
Monoterpene lactone	Leaves	[16]
Loliolide **(66)** *	Leaves	[16]

Isolated components from different organs, * Identified components using LCMS tool

9. Conclusion and future perspectives

The genus *Ficus* has great potential for phytochemical data and biological data. This review provides an updated report regarding the botanical, traditional uses, phytochemistry, analytical methodologies, and pharmacological and toxicological aspects of *F. drupacea.* it has been reported to have beneficial pharmaceutical uses as an antidiabetic, anti-inflammatory, antioxidant, anticancer, antiulcerogenic, wound healing, anti-hyperlipidemic, hepatoprotective, and antibacterial agent.

The majority of the pharmacological studies on *F. drupacea* have used uncharacterized crude extracts. As a result, reproducing the findings of these investigations and identifying the bioactive molecule is difficult. As a result, there is a need for phytochemical standardization and bioactivity-guided identification of bioactive metabolites. A phytochemical study on *F. drupacea* resulted in the isolation of a few types of plant metabolites. However, the documented pharmacological properties of *F. drupacea* indicate that there is still a huge potential for its phytochemical investigation. Moreover, the traditional uses of this Ficus species is not yet confirmed pharmacologically.

Research under investigation revealed promising biological activities of *F. drupacea* that should be investigated further for use as an alternative therapy in the future. Therefore, future studies in the aforementioned areas will give convincing evidence for the clinical application of *F. drupacea* in modern medicine.

10. Conflicts of interest

There are no conflicts of interest.

11. Formatting of funding sources

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