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A Review of the Phytochemical Compounds and Pharmacological Activities from Selected Ficus Plants

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Abstract

The Ficus genus belongs to the Moraceae family were used for medicinal purposes. Distributed in America, Asia, Africa, and Australia, there were sixteen species accepted in Indonesia. They were *Ficus callosa, Ficus melinocarpa, Ficus elastica, Ficus drupaceae, Ficus geocarpa, Ficus Superba, Ficus heteropoda, Ficus fistulosa, Ficus hirta, Ficus ampelas, Ficus adenosperma, Ficus ardisioides, Ficus consociate, Ficus ribes, Ficus lyrata, Ficus virens Aiton*. This article reviewed the scientific work of the Ficus genus. Their traditional usage, phytochemical compounds, and pharmacological activity were summarized. This study aims at providing a collection of publications on selected species of Ficus genus. A critical review of the literature data revealed secondary metabolite like triterpenoid, steroid, saponin, flavonoid, phenolic compound and alkaloid were found in some species of Ficus. Some pure compounds such as quercetin, quercetin 3-O-α-L-arabinopyranoside, epilupeol acetate, oleanolic acid, friedelin, elastiquinone, pinocembrin-7-O-β-D-glucoside, and ficusoside B were isolated. A wide range of pharmacological activities was observed. Antimicrobial, antioxidant, antiviral, antiparasitic, cytotoxic, and antimalarial were found in previous researches. Ficus genus was potential to be developed as a medicinal plant.

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INTRODUCTION

Family Moraceae consists of over 50 genera and nearly 1400 species distributed in the tropical and subtropical region as American, Asia, Afrika, and Australia (Zerega *et al.*, 2005). Ficus is one large family plant comprises of over 800 species (Herre *et al.*, 2008) and one of about 40 genera of mulberry family Moraceae (Hamed, 2011). Twenty-two species were recorded in Indonesian, among which 16 are accepted name and six synonyms, which are all deciduous plants, and most are essentially hemiepiphytic. Ficus plant species can be edible food and traditional medicine to improve the human health of about ten thousand years. Several species used were recorded in Ayurvedic and traditional Chinese medicine (Lansky *et al.*, 2008). People who live at Xishuangbanna in Southwest China consumed Ficus leaves as wild vegetables by the ethnic group. Ficus have many edible species such as *Ficus virens Ait var. sublanceolata* (Miq.) Corner, *Ficus auriculata* Lour., *Ficus vasculosa* Wall ex Miq., *Ficus callosa* Willd, *Ficus virens Ait var. verins*, *Ficus racemosa* L. and *Ficus oligodon* Miq (Shi *et al.*, 2011).

Traditional uses

Several of Ficus plants have been applied in tradi-

Table 1: Traditional uses of Ficus genus in Pakistan

Ficus species	Local name	Plant Part	Traditional uses	
F. elastica	rabber plant	bark, fruits and leaves	Enlargement of liver and spleen, dysentery, diarrhea, diabetes, leprosy, lung complaints, leucorrhoea, heart diseases, cough, asthma, piles, ulcers, gonorrhea, rheumatism and for different skin diseases	(Nisar *et al.*, 2014; Teinkela *et al.*, 2018)
F. lyrata	beeri patta	whole plant	Gastrointestinal problems, anthelmintic, diabetes, anti-tumor activity, asthma, cough, sexual disorders, diarrhea, ear-ache and toothache, migraine, eye troubles, scabies, gonorrhea, bleeding, paralysis, bone fracture, antiseptic and astringent	(Nisar *et al.*, 2014).
F. virens	jangli pipit	leaves, fruit and bark	Diabetes, ulcer, menstrual disorder, leucorrhea	(Khan *et al.*, 2011)

Table 2: IC_{50} from various extracts of Ficus species

Ficus species	Plant Part	Extract	IC_{50}	Ref.
F. carica	Leaves	Water	76.38 mg/ml	(Wahyuni and Hertiani, 2016).
		Methanol	275.23 μg/ml	(Ayoub *et al.*, 2019)
	Fruits	Water	33.38 mg/ml	(Wahyuni and Hertiani, 2016).
F. pareintalis	Leaves	Water	44.01 mg/ml	(Wahyuni and Hertiani, 2016).
	Fruits	Water	35.69 mg/ml	
F. deltoidea	Leaves	Methanol	111.2 μg/ml	(Misbah *et al.*, 2013).
		Ethanol	16.5 μg/ml	(Aslam *et al.*, 2017)
F. maclellandii	Fruits	Ethanol	210.3 μg/ml	(Tamuly *et al.*, 2015)
F. racemosa	Fruits	Ethanol	228.4 μg/ml	

Table 3: Antimicrobial activity of Ficus genus

Ficus species	Plant Part	Extract	Bacterial/Fungi	
F. callosa	Leaves	Methanol	*Escherichia coli, Staphylococcus aureus, Bacillus subtilis*	(Wibowo *et al.*, 2018b)
F. drupacea	Leaves	Methanol	*E. coli, S. aureus, B. subtilis*	
	Stem bark	n-Hexane	*Aspergillus flavus, A. versicolor, A. niger, A. ochraceus, Candida albicans, Penicillium funiculosum, P. ochrochloron*	(Yessoufou *et al.*, 2015)
			B. cereus, Listeria monocytogenes, Micrococcus flavus, S. aureus, E. coli, Salmonella typhimurium, Pseudomonas aeruginosa, Enterobacter cloacae	
F. melinocarpa	Leaves	Methanol	*S. aureus, B. subtilis*	(Wibowo *et al.*, 2018b)
F. geocarpa	Leaves	Methanol	*E. coli, S. aureus, B. subtilis*	
F. consociata	Leaves	Methanol	*E. coli, S.aureus, B. subtilis*	
F. ribes	Leaves	Methanol	*E. coli, S. aureus, B. subtilis*	
F. ardisioides	Leaves	Methanol	*E. coli, S. aureus, B. subtilis*	(Wibowo *et al.*, 2018b)
F. heteropoda	Leaves	Methanol	*S. aureus, B. subtilis*	
F. hirta	Leaves	Methanol	*S. aureus*	
F. elastica	Roots	Methanol	*S. aureus, E. coli, Proteus vulgaris, Providencia stuartii, P. aeruginosa, C. albicans*	(Teinkela *et al.*, 2018)
	Root barks	MeOH/ CHCl3	*Enterococcus faecalis, S. aureus, S. saprophyticus, S. epidermididis, Trichophyton rubrum, C. albican, E. coli, Klebsiella pneumoniae, and S. typhi*	(Mbosso *et al.*, 2012)
F. fistulosa	Leaves	Methanol, Water	*E. coli, E. coli mutants, S. aureus, B. subtilis, K. pneumoniae, P. aeruginosae*	(Raka *et al.*, 2019)
F. hirta	Fruits	Ethanol	*Penicillium italicum*	(Wan *et al.*, 2017)
F. lyrata	Latex	Ethyl acetate	*C. albicans*	(Bidarigh *et al.*, 2011)
	Leaves	Ethanol	*S. aureus, E. coli, K. pneumonia, P. aeruginosa, methicillin-resistant Staphylococcus aureus, S. pneumoniae*	(Tkachenko *et al.*, 2016)
F. carica	Leaves	Ethanol	*E. coli, P. aeruginosa, MRSA, S. aureus*	(Tkachenko *et al.*, 2017)

Table 4: Cytotoxic activity of isolated compound

Compounds	Tumor cell line (IC_{50} μg/ml)				
	HeLa	MCF-7	Jurkat	HT-29	T24
Oleanolic acid	20.38 ± 2.6	16.28 ± 1.3	21.17 ± 2.2	25.58 ± 1.3	27.61 ± 1.3
Friedelin	20.42 ± 2.3	22.81 ± 2.1	29.15 ± 2.3	37.21 ± 3.61	12.81 ± 1.4
Epilupeol acetate	15.16 ± 1.6	20.03 ± 3.2	19.64 ± 2.6	26.21 ± 1.7	58.26 ± 2.3

tional medicine for many countries. Thailand people used fresh young leaves of leab (*F. Superba)* and phak huead Daeng (*F. virens)* as a vegetable as a curry or used in a salad (Chantarasuwan and Welzen, 2012). The Ayurveda book recorded that traditional people use bark, latex, leaves and fruit of F. virens Aiton for vertigo, blood diseases, diabetes, rheumatism and antioxidant (Rajani *et al.*, 2008). People in Vanuatu used latex from leaves of *F. adenosperma* for menorrhagia; this plant is added to the coconut water (Bourdy and Walter, 1992). Different from people in Papua New Guinea, used for sores and scabies, but fresh roots of *F. adenosperma* is chewed to treat malaria (Mahyar *et al.*, 1991). In Vietnam, leaves of *F. drupaceae* is taken to treat malaria, paragonimiasis, nasosinusitis, sinusitis, and anasarca (Phan *et al.*, 2013). Still, the leaves, roots and bark from *F. microcarpa* were applied to reduce fever and anti-inflammatory. The usage of Ficus species in Pakistan for traditional medicine can be seen in Table 1.

Many kinds of Ficus have been used in Indonesian culture like leaves of uyah-uyah (*F. quercifolia*) to treat skin disease in Balinese people. Gayo ethnic used leaves of leng (*F. deltoidea*) for aphrodisiac like Sundanese people. Another kind of Ficus, fruits of amis Mata (*Ficus Montana*) is used by Sundanese ethnic to treat urinary stones. *Ficus fistulosa* leaves also are used to treat wounds by sharp objects and for anthelmintic in Sumba people. The bark of *Ficus septic* is used for sprue, but the leaves can use for mothers who have just given birth.

Phytochemical compound

Phytochemical screening found that many secondary metabolites such as flavonoid and phenolic compound, p-coumaric acid, caffeic acid, kaemferol, quercetin and leucoanthocyanins frequently occurred in leaves. Triterpenoid (Chiang *et al.*, 2001, 2005), steroid, flavonoid (Van Kiem *et al.*, 2011), lignin (Li and Kuo, 2000), saponin, and alkaloid were known from some species of Ficus (Berg *et al.*, 2006). The structure of some phytochemical compound is shown in Figure 1.

Flavonoid was discovered in all Ficus genus, and several isolates were found from methanol extract of *F. callosa* leaves as megastigmane glycoside, ficalloside (Van *et al.*, 2011). Quercetin, quercetin-3-O-α-D-arabinopyranoside, quercetin-3-O-β-D- galactopyranoside, kaempferol-3-O-α-D-arabinopyranoside, kaempferol-3-O-β-D-galactopyranoside, and vogelin J. were obtained from methanol extract of *F. virens Aiton* (Orabi and Orabi, 2016). Other biochemical compounds from stem bark extracts of *F. drupaceae* included β-amyrin, β -sitosterol-3-O- β-D-glucopyranoside, 5-O-methyllatifolin, oleanolic acid, epifriedelanol, friedelin and epilupeol acetate were isolated and identified (Yessoufou *et al.*, 2015).

Chemical investigation of the ethyl acetate extract of *F. consociata* leaves led to the isolation and structural elucidation of seven compounds. They were luteolin, cirsiliol, isoquercetin, quercetin 3-O-α-L-arabinopyranoside, nikotoflorin, hesperidin, and (2E,4E,1'S,2'R,4'S,6'R)- dihydrophaseic acid (Dat *et al.*, 2019). Ursolic acid and oleanolic acid were isolated from the dichloromethane extract *F. ampelas.* Butyrospermol cinnamate and isolation of lutein from leaves of *F. ampelas* were also exposed (Ragasa *et al.*, 2014).

Methanol extract roots of *Ficus elastic* contained steroidal glucosides called as sitosteryl 3-O-β-D-glucopyranoside, elasticamide, and the highest antimicrobial are elastiquinone, ficusoside B (Teinkela *et al.*, 2018), ficusamide, and elasticoside (Mbosso *et al.*, 2012). Pinocembrin-7-O-β-D-glucoside, in the ethanol extract of *F. hirta* fruits, had antifungal activity (Wan *et al.*, 2017).

Pharmacological activities

Pharmacological activities of some Ficus species were shown in the explanation below:

Antioxidant Activity

Ethanol extract of young leaves of *F. virens Aiton* and *Ficus callosa* had antioxidant activity with DPPH and ABTS assays, which IC_{50} of DPPH *F. virens* Aiton was 0.34 mg/ml, and IC_{50} of ABTS 0.23 mg/ml. It was different with *F. callosa*, IC_{50} of DPPH 0.95 mg/ml, and ABTS 0.35 mg/ml. *F. virens Aiton* had higher

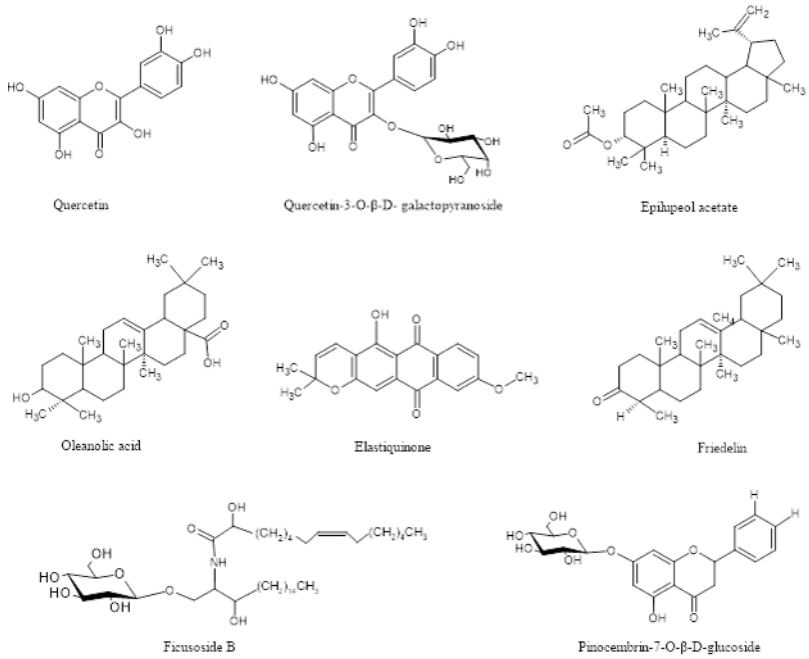

Figure 1: Structure of chemical compounds isolated from Ficus genus

flavonoid and phenolic compounds, which correlated with its antioxidant activity (Shi *et al.*, 2011).

Quercetin from methanol leaves extract of *F. virens Aiton* was the most active DPPH radical scavenging activity with IC_{50} 14 $\pm$ 1.12 μg/ml (Orabi and Orabi, 2016). (Hilfi, 2019), reported that ethanol extract of *F. elastic* gave antioxidant activity with EC_{50} DPPH 6.4166 mg/ml and 0.0768 mg/ml with ABTS. Ficuselastic acid and (1'S,6'R)-8-O-β-D- glucopyranosyl abscisate sodium showed antioxidant activity (Kiem *et al.*, 2012). The methanol extract of leaves of *Ficus fistulosa* presented IC_{50} DPPH 16.66 μg/ml (Raka *et al.*, 2019).

Some Ficus from other country had antioxidant compounds, such as C-glycosylflavone from ethanolic leaves extract of *F. microcarpa* (Van Kiem *et al.*, 2011), and aqueous roots extracts of *F. beecheyana* (Yen *et al.*, 2018). Philippines peoples used antioxidants from the ethanol extract of leaves and fruits of *F. nota* (Santiago *et al.*, 2017). *F. sur* is a traditional medicine from Togo, had antioxidant activity for the whole plant, the highest activity was given by ethanolic bark extract (56.50 $\pm$ 0.29 μg QE/mg), and the ripe fruit had lowest activity (7.3 $\pm$ 0.30 μg QE/mg) (Saloufou *et al.*, 2018). The old leaves of *F. deltoidea* had more potent antioxidant activity than the fresh leaves (Manurung *et al.*, 2017). The value of IC_{50} from other extracts of Ficus species are reported in Table 2.

Antiparasitic Activity

Methanol roots extract of *Ficus elastica* exhibited antiparasitic activity against *Trypanosoma brucei*, with IC_{50} 0.9 μg/mL (Teinkela *et al.*, 2018). The antischistosomal activity was shown by ether latex extract of *F. elastica* (after washing off toxic rubber materials) (el Din *et al.*, 2014).

Antimalarial Activity

The methanol extract of *F. elastica* roots demonstrated plasmocidal activity (IC_{50} 9.5 μg/ml) against *Plasmodium falciparum* strain 3D7 (Teinkela *et al.*, 2018).

Antimicrobial Activity

The antimicrobial activity of Ficus species has been evaluated by the agar diffusion method. It can be proposed that flavonoids, triterpenoid, and steroid had antimicrobial activities (Wibowo *et al.*, 2018a). Ficus species showed antimicrobial activity against at least one bacteria, which can be seen in Table 3.

Antiviral Activity

Antiviral activity *in vitro* of flavonoids, which was found from *F. virens Aiton* on Coxsackie B4 (CVB4), and hepatitis A virus (HAV) were also carried out. Antiviral activities were also given by quercetin and quercetin-3-O-β-D- galactopyranoside isolated from *F. virens Aiton.* It was tested by 3-(4,5- dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide (MTT) assay. Quercetin gave the highest inhibitory activity (20.3%) on CVB4; meanwhile, quercetin-3-O-β-D- galactopyranoside presented the highest inhibitory activity (12.3%) on HAV (Orabi and Orabi, 2016).

F. fistulosa leaves extract showed antiviral activity (IC_{50} 15.0 μg/ml) against HCV J6/JFH1-P47 strain

and HCV J6/JFH1-P1 strain with IC_{50} 5.7 μg/ml. The chloroform fraction had an anti-HCV activity with IC_{50} 5.67 $\pm$ 1.54 μg/ml, while butanol fraction gave lower activity (IC_{50} 74.10 $\pm$ 18.24 μg/ml) (Hafid *et al.*, 2016). Methanol leaves extract of *F. septica* had antiviral activity against Dengue virus (DENV-1 and DENV-2) with IC_{50} 13.3$\pm$2.6 μg/ml and 10.6$\pm$1.1 μg/ml (Huang *et al.*, 2017).

Cytotoxic Activity

Flavonoid compounds are the secondary metabolites responsible for pharmacological activity in Ficus species. The flavonoid from *F. virens Aiton* showed low cytotoxic activity in Vero cells by the MTT method (Orabi and Orabi, 2016). The ethanol leaves extract of *F. fistulosa* had cytotoxicity concentration (CC_{50}) >200 μg/ml, which was not toxic, while butanol and chloroform fractions gave CC_{50} >100 μg/ml (Hafid *et al.*, 2016). The methanol extract of *F. septica* root inhibited nasopharyngeal carcinoma (HONE-1) and gastric adenocarcinoma (NUGC) cell (Damu *et al.*, 2009) while the ethanolic extract of roots from *F. beecheyana* inhibited HL-60 cell (Yen *et al.*, 2018).

Ficusamide is an isolated compound from *F. elastica* that had medium cytotoxic activity on A-549 lung cancer (Mbosso *et al.*, 2012). Other compounds from *F. elastica* showed weak cytotoxic activity (IC_{50} values 20 μg/ml) on HeLa cell (Teinkela *et al.*, 2018). Meanwhile, compounds from *F. drupacea* stem barks demonstrated the highest antiproliferative activities against most cancer cells, are reported in Table 4 (Yessoufou *et al.*, 2015).

Other Pharmacological Activities

Methanol fruit extract of *Ficus carica* with a concentration of 924 μmol/l reduced 54% the formation of uric acid in mice, which injected with potassium oxonate (Mohamed and Al-Okbi, 2008). *F. carica* leaves showed oedema inhibitory activity (anti-inflammatory) in rats induced by carrageenan as much as 48.8% (Ali *et al.*, 2012). Previous research demonstrated that ethanolic fruit extract of *F. carica* could inhibit α-glucosidase, α-amylase, and pancreatic lipase (Mopuri and Islam, 2016).

CONCLUSIONS

We summarized the traditional usage, phytochemical compounds, and pharmacological activity of selected Ficus plants. Based on the literature review was reported that most of the species were used as a traditional medicine in Asian countries such as Indonesia, Papua New Guinea, Vietnam, Pakistan, Thailand, and Vanuatu. Some species of the Ficus genus need further research on pharmacological activities, based on mechanisms and chemical contents.

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Conflict Of Interest

The authors declare that they have no conflict of interest for this study.

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