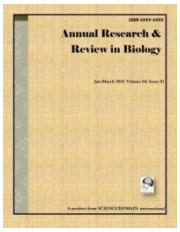

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Phytochemical, Pharmacological and Toxicological Properties of *Ficus deltoidea*: A Review of a Recent Research

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SR and SRD performed the literature review and designed the format of this review article. Authors CK and JKS jointly wrote the first draft of the manuscript. Finally all authors read and approved the final version of manuscript.

Mini Review Article

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ABSTRACT

Ficus deltoidea (Mas Cotek) is one of the commonly used medicinal plants in Malaysia and it belongs to the family of Moraceae. It is a shrub that reaches a height of six feet, used as an ornamental plant in the tropics or in the home and conservatories. This plant is native to Southeast Asia and Philiphines. It has been used to relieve headache, fever, pneumonia, heart problems, migraines, skin diseases, diarrhea, and toothache. It is also used as an aphrodisiac tonic. Decoction of the whole plant has been used as herbal drink by women after birth to strengthen the uterus and vaginal muscles. It also improves blood circulation and regains body strength as well as treats disorders related to menstrual cycle. This plant is basically a Malay traditional medicine which was very popular ever since it has good medicinal properties. Based on ethnobotanical approaches, *F. deltoidea* has been claimed to possess antidiabetic, antiulcerogenic, antioxidant, anti-melanogenic, anti-inflammatory, analgesic, antihypertensive properties. Recently, there were a lot of investigations that was carried out to isolate some of the chemical constituents in *F. deltoidea* to understand how it influences the pharmacological

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properties of the plant. The plant contains flavonoid, tannins, triterpenoids and phenols. It has been investigated that generally *F. deltoidea* is safe and nontoxic. However, there are different studies that are still going on to investigate more about the toxicological effects and drug interactions in the long run of human consumption. Therefore, the objective of the review is to summarise the phytochemical, pharmacological and toxicological properties of this important medicinal plant.

Keywords: Ficus deltoidea; pharmacology; phytochemical; toxicology.

1. INTRODUCTION

Ficus deltoidea can also be known as mistletoe fig or mas cotek. The plant is grown widely in Malaysia. In Indonesia it is called Tabat Barito whereas in Central Africa it is referred to as Kangkaliban. One of the most important conditions of this plant needs to grow on is the soil condition which should have a good drainage system, although it requires minimal amount of water but during the hot and dry season, it requires a lot of water to continue its growth. The genus Ficus is made up of about 1,000 species from pantropical and subtropical origins. *Ficus deltoidea* falls in two categories which is male plant and female plant. The difference between the male and female plant is, the male plant has leaves which is more elongated compared to the female plant that has big and round long leaves. It has been said the female plant is more effective due to its higher anti-oxidant potential in which it helps to scavenge more free radicals [1]. This plant is generally small which approximately 2-3 meters high (Table 1 and Fig. 1).The leaves can come in various shapes such as in lanceolate, spatulate and obovate forms. The stem part of this plant exudes a natural rubber, accounting for one of its names, the "mistletoe rubber tree". This whole plant became more popular ever since it has good medicinal properties [2]. Many said that this plant is good for human reproductive organs, especially for female fertility. This plant is basically a Malay traditional medicine, where the plant's juice is used for the treatment of diabetes, high blood pressure and gout. It is also used for migraines, skin diseases, and diarrhea, pneumonia and heart problems. The herb is often used after childbirth to regain energy, repair blood flows and its associated problems and can be used as herbal juices for health and beauty. It is said to be helpful in detoxifying the body, improving blood circulation and reducing cholesterol and it also cures low libido energy [3]. Researches have been carried out to prove the effectiveness of this plant as a medicinal herb. However, there are studies that are still going on to elucidate the toxicological effects and drug interactions. Hence, it should be used with caution.

Fig. 1. *Ficus deltoidea* (Mas cotek leaves)

Table 1. The classification and description of taxonomy of *Ficus deltoidea*

Kingdom	*Plantae* (Plants)
Subkingdom	Tracheobionta (Vascular plants)
Superdivision	*Spermatophyta* (Seed plants)
Division	Magnoliophuta (Flowering plants)
Class	*Magnoliopsida* (Dicots, dycotyledons)
Subclass	Hamamelidae
Order	*Urticales*
Family	*Moraceae* (Mulberry family)
Genus	*Ficus*(Blume), *Ficus*(Dest), *Ficus*(Miq)
Species	*Ficus deltoida* var *angustifolia* sp.
Latin	*Ficus deltoidea* Jack
Common names	Mas Cotek, serapat, sempit-sempit, agoluran (Sabah), tabatbarito (Indonesia) and mistletoe fig, mistletoe rubber plant.

2. COMMERCIAL PRODUCTS of *Ficus deltoidea*

Production of Mas Cotek started in 2005. The number of manufacturers increased in the year 2006 and 2007. Most consumers were middle aged. The increased numbers of manufacturers of Mas cotek from year 2004 to 2007 can be seen in the Tables 2 and 3. From a survey conducted in states such as Kedah, Selangor, Melaka, Negeri Sembilan and Johor, it was seen that the most preferred product is tea. Three companies that produce Mas cotek capsules are Delto Medicama Plantation (M) SdnBhd, I and R Herbs Marketing and D'Pilah Herbs. However, Delto Medicama Plantation (M) SdnBhd produced massage oil and coffee powder. There is a large increase of mascotek products variety from the year 2004 to 2007 which is shown in Table 4 [3].

Table 2. Number of manufacturers for Mas cotek from the year 2004 to 2007

Year	No. of manufacturers
2004	1
2005	4
2006	11
2007	11

Table. 3. Number of companies manufacturing Mas Cotek products at various states of Peninsular Malaysia

State	No. of companies
Kedah	1
Pulau Pinang	1
Perak	1
Melaka	2
Negeri Sembilan	2
Johor	2
Selangor	3
Kelantan	3
Total	**15**

Table 4. Availability of list of Mas Cotek products from the year 2004 to 2007

Year	Products
2004	Tea and massage oil
2005	Tea, Pill/Capsule, massage oil
2006	Tea, Coffee, Pill/Capsule, massage oil, extract powder
2007	Tea, Coffee, Pill/Capsule, massage oil, extract powder, Cordial juice

3. PHYTOCHEMICAL STUDIES OF *Ficus deltoidea*

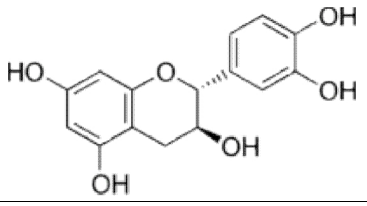
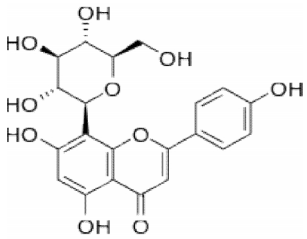
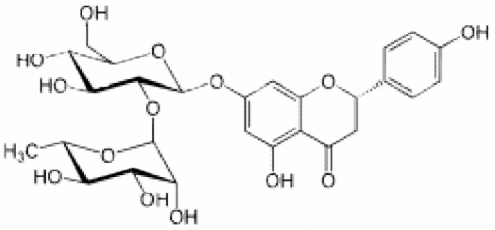
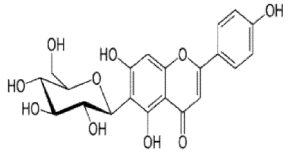
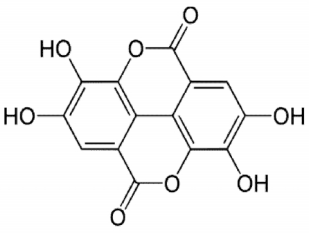
There are few major constituents that are involved in the plant *Ficus deltoidea* which includes flavonoid, tannins, triterpenoids, proanthocyanins, phenols, flavanoids, phenols and tannins are strong natural antioxidants. Antioxidants do not allow oxidation of other molecules easily. This is done via a chemical reaction, whereby the electron is transferred from the substance to an oxidizing agent. This may result in the elimination of free radicals that can damage cells. However, antioxidants like flavonoids, phenolic compounds can prevent this by eliminating the free radical intermediates such as peroxide or hydroperoxide compounds. Antioxidants can treat cardiovascular problems. However, fewisolation of chemical constituents had been done for *Ficus deltoidea*, therefore only three exact compounds was determined and the rest was compounds generally present in *Ficus deltoidea* in three major groups; phenolic compounds, tannins and phenylisopropanoid [4].The first major group is phenolic compounds play a major role in the relationship between plants and their biological activities. Depending on the environmental condition, phenolic compounds can accumulate in different plant tissues and cells during ontogenesis. A study showed that localization of many types of phenolic compounds in cell walls, vacuoles and cell nuclei have anti-inflammatory and anti-septic properties. It decreases the occurrence of lesions [5].

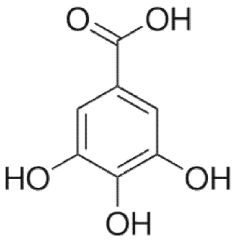
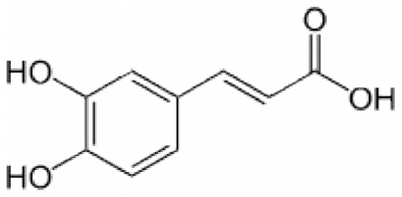
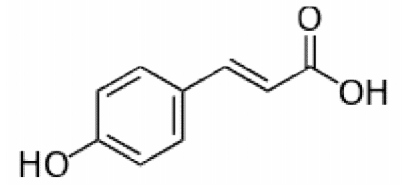
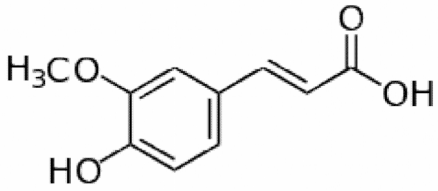
The chemical constituents present under this group are catechins, flavones, naringin, vitexin, isovitexin, anthocyanins and proanthocyanins. Due to the ability of flavanoids to scavenge for the hydroxyl radicals, superoxide anions, and lipid peroxy radicals, it contributes to some vital biological activities such as antibacterial, anti-inflammatory, anti-allergic, antimutagenic, antiviral, antineoplastic, anti-thrombotic and vasodilatory activity. It also helps in providing good blood circulation and liver protection [6] Naringin can reduce cholesterol level by lowering the low density lipoprotein levels which helps to balance the lipid level in plasma. Vitexin and isovitexin are strong anti-oxidants [7]. Proanthocyanins are condensed tannins which are also under the polymeric flavanoids category. It protects circulation from damage-heart, hand, feet and eyes. They are powerful antioxidant. It has the ability to reduce capillary permeability and to increase the level of vitamins C and prevent disruption of collagen.

The second major group is tannins. Tannins are able to prevent lipid oxidization as a reducing agent, free radical scavengers and chelators of pro-oxidant catalytic metals [8]. It is tightened over relaxed tissue, to dry excessive watery secretion that is diarrhea and protects damage tissues like eczema or burnt. The chemical constituents involved are ellagic acid and gallic acid. Gallic acid residues are linked to glucose via glycosidic bonds. It is also an anti-oxidant; therefore it can go against cardiovascular disease, arthritis and aging. Ellagic acid also has antiviral and antibacterial activities. It decreases the total hepatic mucosal cytochromes. It could also prevent cancer by binding to the molecules causing cancer and inactivating them [9].

The third group is phenyl isopropanoids. The chemical constituents involved are caffeic acid, coumaric acid and ferulic acid. Caffeic acid exhibits high levels of antioxidant properties, which prevents oxidation of other molecules that will produce free radicals and damage cells. Supposing if free radicals such as superoxide, nitric oxide and hydroxyl radical are already generated, it can be neutralized by coumaric acid. It treats menopausal syndromes. Ferulic acid helps to protect the skin from ultraviolet light. The chemical structures of the isolated compounds from different parts of *Ficus deltoidea* are shown in Table 5.

Table 5. Structures of the isolated compounds from different parts of *Ficus deltoidea*

Name	Structure	Compound ID
Catechin		I
Vitexin		III
Naringin		II
Isovitexin		IV
Ellagic acid		V

Gallic acid		VI
Caffeic acid		VII
p-coumaric acid		VIII
Ferulic acid		IX

4. PHARMACOLOGICAL STUDIES OF *Ficus deltoidea*

4.1 Antidiabetic Activity

Effect on α- glucosidase and postprandial hyperglycemia. This epiphytic plant, from the Moraceae family has been claimed to have antidiabetic property. The plant *Ficus deltoidea* most apparent function is treating diabetes. A research was conducted to evaluate the potential of *Ficus deltoidea* to inhibit the enzyme, α-gucosidase in the small intestine, as this is known to be an antidiabetic mechanism. The results of the in vitro study had shown that hot aqueous, ethanol and methanol extractsof *Ficus deltoidea* inhibit rat intestine α-glucosidase activity significantly, in a concentration dependent manner. The IC_{50}values of these extracts are 4.15, 2.06 and 1.72 mg mLG^{1}, respectively. In an animal study, all extracts, when used at a dose of 1000 mg kgG^{1}b.wt., reduce postprandial hyperglycemia following sucrose administration. This was true in normaland in diabetic rats, as shown by the significant attenuation of the value of $AUC_{Glucose}$ compared to the control group. The methanol extract is the most potent inhibitor of α- glucosidase, followed by the ethanol and hot aqueous extracts. They suggest that theinhibition of α-glucosidase in the small intestine in part mediates the antidiabetic property of *Ficus deltoidea*[10].

However, scientific evidence to confirm its efficacy is still lacking. Secondly, the other study was undertaken to evaluate the effect of ethanol extract of *F. deltoidea* on glucose level in normal rats at different prandial state. The results showed that, all doses of ethanol extract of *F. deltoidea* reduced fasting blood glucose particularly after 6 h of administration. Interestingly, the extract did not produce severe hypoglycemia as shown by its comparable effect with metformin. Likewise, postprandial hyperglycemia was also significantly reduced particularly after 4 and 6 h of administration. Furthermore, extract was used at a dose of 1000 mg/kg b.w., reduced postprandial hyperglycemia similar to metformin. This suggests that postprandial antihyperglycemic mechanism of this extract is mediated through enhancement of glucose uptake into muscle cells and reduction of hepatic gluconeogenesis. Glucose tolerance activity was also significantly improved in the presence of ethanol extract of *F. deltoidea*. From this study, it is suggested that ethanol extract of *F. deltoidea* reduced postprandial hyperglycemia and improves glucose tolerance activity in normal rats [11-12].

The partitioned extracts, sub fractions and pure bioactive constituents were subjected to α-glucosidase inhibition assay. The identified bioactive constituents were administered orally to sucrose loaded normoglycemic mice and induced diabetic rats. The postprandial blood glucose levels were monitored at 30 min interval. Acute toxicity was evaluated in both normoglycemic mice and induced diabetic rats. Bioactivity guided fractionation led to the isolation of both vitexin and isovitexin. Oral administration of 1 mg/kg of either vitexin or isovitexin significantly ($p<0.05$) reduced the postprandial blood glucose level in sucrose loaded normoglycemic mice at 30 min. The percentage of postprandial blood glucose reduction was highest in sucrose loaded induced diabetic rats administered orally with 200 mg/kg of vitexin or 100 mg/kg of isovitexin. Both vitexin and isovitexindid not exert any signs of toxicity at the highest dose of 2 g/kg administered orally to normoglycemic mice and induced diabetic rats [13].

4.2 Mechanism of Anti-diabetic Activity

Ficus deltoidea has been scientifically proven to reduce hyperglycemia at different prandial states. Another study was undertaken to evaluate the mechanisms that underlie antihyperglycemic action of *Ficus deltoidea*. The results had shown that hot aqueous extract of *Ficus deltoidea* stimulated insulin secretion significantly with the highest magnitude of stimulation was 7.31-fold ($P < 0.001$). The insulin secretory actions of the hot aqueous extract involved K+ ATP channel-dependent and K^+-ATP channel- independent pathway. The extract also has the ability to induce the usage of intracellular Ca^{2+} to trigger insulin release. The ethanol and methanol extracts enhanced basal and insulin-mediated glucose uptake into adipocytes cells. The extracts possess either insulin-mimetic or insulin-sensitizing property or combination of both properties during enhancing glucose uptake into such cells. Meanwhile, the hot aqueous and methanol extracts augmented basal and insulin-stimulated adiponectin secretion from adipocytes cells. From this study, it was suggested that *Ficus deltoidea* has the potential to be developed as future oral antidiabetic agent. Also, it was suggested that the antihyperglycemic actions of *F. deltoidea* are mediated through stimulation of insulin secretion from pancreatic β cells, enhancement of glucose uptake by adipocytes cells, and augmentation of adiponectin secretion from adipocytes cells as well [14].

4.3 Effect on Hepatic Basal and Insulin-stimulated Glucose Uptake

Another experimental study was designed to evaluate the potential of five extract and three fractions of *Ficus deltoidea* to enhance basal and insulin-stimulated glucose uptake into Chang liver cell line. The results showed that all *Ficus deltoidea* extracts and fractions except petroleum ether extract have the ability to enhance either basal or insulin-stimulated glucose uptake into liver cell line. Ethanol and methanol extracts as well as acidified chloroform and basified chloroform fractions possess insulin-mimetic activity. Of all extracts and fractions, ethanol extract possess the highest insulin-mimetic activity. Methanol extract and n-butanol fraction possess insulin-sensitizing activity, with the highest activity shown by methanol extract. There is no synergistic effect between *Ficus deltoidea* extracts or fractions with 100 nM insulin. The extracts also possess either insulin-mimeticactivity or insulin-sensitizing activity or combination of both activities. Therefore, it was suggested that the blood glucose lowering effect of *Ficus deltoidea* in rats was mediatedpartly, by the augmentation of glucose uptake into liver cells [15].

4.4 Hypoglycemic Activity

A clinical study was carried out to study the effect of the *Ficus deltoidea* (Mas Cotek) leaves on fasting blood sugar, renal and lipid profile of Type II diabetic patients. This study was carried out at Polyclinic Balok, located in Kuantan, Pahang, Malaysia. In conclusion, the effects on fasting blood sugar, HbA1C, renal and lipid profiles were not significant. The patients in the intervention group felt energetic and fresh compared to the control [16]. Further experimental study was undertaken to evaluate the potential of ethanol extract of *Ficus deltoidea* to reduce hyperglycaemia in streptozotocin induced diabetic rats at different prandial state. It was suggested that ethanol extract of *Ficus deltoidea* at particular doses, possess fasting and postprandial hypoglycemic activity as well as glucose tolerance activityin streptozotocin-induced diabetic rats [17]. Various leaf extracts of *F. deltoidea* was studied for the hypoglycemic and toxicity profiles in rodent models. Extracts of dried powderedleaves were obtained using methanol solution, n-hexane, chloroform, and n-butanol. The methanol extract possessed mixed antidiabetic actions and exhibited a low level of oral toxicity [18].

4.5 Antioxidant Activity

Free radicals are highly reactive and unstable compounds produced in the body during normal metabolic functions or introduced from the external environment such as pollution and cigarette smoke. Studies show that diets high in antioxidants or antioxidant supplements reduce s the risk of cancer cardiovascular and other major diseases. An Investigation was carried out to prove that the extract of *Ficus deltoidea* has a good antioxidant activity. The antioxidant activity was determined using ferric thiocyanate (FTC) and thiobarbituric acid (TBA) methods while the radical scavenging activity was measured by 1, 1-diphenyl-2-picrylydrazyl (DPPH) method. Folin-Ciocalteu reagent was used to estimate the total phenolic content. The hexane extract showed higher TPC value (259.2 mg/gGAE) followed by methanol extract (245.2 mg/g GAE) and chloroform extract (159.2 mg/g GAE). In the DPPH test, the extracts of methanol and chloroform showed more than 50% free radical scavenging activity at 250 µg/mL and 125 µg/mL concentration respectively. All extracts showed strong antioxidant activity in the TBA and FTC tests, with percent inhibition range from 90.70% to 97.78% respectively. In conclusion, the hexane extract from the fruits of *F. deltoidea* displayed highest antioxidant activity followed by

methanol extract and chloroform extract. This study demonstrates that the fruits of *F. deltoidea* are a good source of antioxidant [19].

4.6 Anti-inflammatory Activity

F. deltoidea leaves have been used traditionally by the Malays to treat wounds and rheumatism. A study was carried out to investigate the standardized extracts of these various types of *F. deltoidea.* The objective was to prove that this plant has the potential for anti-inflammatory properties. Three *In vitro* assays were used; lipoxygenase, hyaluronidase and 12-O-tetradecanoylphorbol-13 acetate (TPA-induced oedema) to carry out the study. High performance liquid chromatography (HPLC) was used to standardize methanol and aqueous extracts with the aid of vitexin and isovitexin that was taken from the methanol extract of the plant. Vitexin (8-C-glucosyl apigenin) and isovitexin (6-C-glucosyl apigenin) are pharmacologically active markers. This is due to their pharmacological activities which are anti-hypertensive, anti-inflammatory, antispasmodic, antimicrobial and antioxidant. After the validation of the method, it was carried out to standardize the extracts of the plant. The results were compared with the reference compound apigenin, nordihydroguaiaretic acid and indomethacin. The results proved that the leaves of *F. deltoidea* exhibit anti-inflammatory properties on lipoxygenase, hyaluronidase and TPA-induced oedema. The excessive amount of anti-inflammatory of methanol extracts was in TPA-induced oedema [20]. The aqueous extract of *F. deltoidea* leaf was evaluated for anti-inflammatory activity using acute and chronic models of inflammation. *F. deltoidea*, in the doses of 30, 100, and 300 mg/kg, was administered intraperitoneally in rats (n = 6) before the animals were subjected to the carrageenan-induced paw edema test, cotton pellet-induced granuloma test, and formalin test. In conclusion, the leaf of *F. deltoidea* possesses anti-inflammatory activity against acute and chronic inflammatory responses and against pain-associated inflammatory response. These findings justify the traditional uses of *F. deltoidea* leaves for treatment of inflammatory-mediated ailments [20].

4.7 Anti-nociceptive Activity

Pain is a sensorial modality which in many cases represents the only symptom for the diagnosis of several diseases. It often has a protective function [21]. Despite the progress that has occurred in recent years in the development of pain therapy, there is still a need for effective and potent analgesics, especially for the treatment of chronic pain. Plant-derived substances have, and will certainly continue to have, a relevant place in the process of extract discovery, particularly in the development of new analgesics [22]. Antinoci*ceptive is to decrease the sensitivity in painful conditions. The leaves of F. deltoidea,* the aqueous extract was taken to evaluate the antinociceptive activity in three types of nociception, which was acetic acid-induced abdominal writhing, formalin and hot plate test. Observations were made when *F. deltoidea* aqueous extract was consumed at 3 different doses which are 1, 50 and 100 mg/kg. It was given 30 minutes before pain stimulation so that the antinoceptive effect would be dependent on the doses. This involved the central and peripherally mediated activities. Furthermore, it was seen that the antinociceptive effect of the extract in the formalin and hot plate test was reversed by the non-selective opioid receptor antagonist naloxone. Therefore it is precisely the fact that, endogenous opioid system has a role in the analgesic mechanism of action. However the results obtained was sufficient enough to prove that the extract of *F.deltoidea* has a good pharmacological activity which exhibits the antinociceptive activity which helps in treating painful conditions [23].

4.8 Wound Healing Activity

Cutaneous injury is characterised by fibroplasia, angiogenesis and re-epithelisation and involves the migration and proliferation of cells such as fibroblasts, endothelial cells and epithelial cells, deposition of connective tissue and contraction of the wound [24]. Efforts are being made all over the world to discover agents that can promote healing and thereby reduce the cost of hospitalisation and save the patient from amputation or other severe complications. Recently, the traditional use of plants for wound healing has received attention by the scientific community [25]. The aqueous extract of *F. deltoidea* whole plant was investigated to evaluate the rate of wound healing enclosure and the histology of healed wounds in rats. Five groups of adult male Sprague Dawley rats were experimentally wounded in the posterior neck area. Grossly, wounds treated with placebo containing 5%, 10% *F. deltoidea* extract or Intrasite gel significantly accelerated the rate of wound healing compared to wounds treated with sterile deionized water or dressed with blank placebo. Histological analyses of healed wounds were consistent with the results of gross evaluations. Healed wounds dressed with placebo containing 5%, 10% *F. deltoidea* extracts or Intrasite gel showed significantly lesser scar width at the wound enclosure and more fibroblast proliferation, collagen fibers accompanied with angiogenesis in the granulation tissue than blank placebo-treated wounds. Additionally, no macrophages were seen in the extract-treated wounds compared to the wounds dressed with sterile demonized water or blank placebo. These results strongly document the beneficial and significant effects of *F. deltoidea* extract to accelerate the rate of wound healing enclosure in the experimentally-induced wounds in rats. The study was revealed that wounds dressed with *F. deltoidea* extracts, as topical application of wounds significantly accelerate the rate of wound healing process [26].

4.9 Anti-ulcer Activity

Herbal medicine has attracted so much interest in this area especially with herbs from the tropics. Ulcers are produced when any factor causes an imbalance between the protective factors (mucus and bicarbonate) and aggressive factors (acid and pepsin) in the stomach [27]. Many tropical herbs have been scientifically reported to possess potent antiulcer activity [28]. Ethanol was used since it is the most prominent chemical compound to stimulate the gastric ulcers rapidly. They stimulate necrotic lesions in gastric mucosa and it decreases the levels of bicarbonates and excretion of mucus which is involved in the formation of gastric ulcers [27]. The ulcer healing activity of whole-plant extract of *F. deltoidea* was studied in gastric ulcer induced by ethanol in rats. Pre-treatment with *F. deltoidea* whole plant extract or omeprazole resulted in significantly less gastric mucosal lesions produced by ulcerogens. The gastric protection was more prominent in 500 mg kg^{-1} *F. deltoidea* extract than 250 mg kg^{-1}. Histological studies confirmed the results wherein compared to the pre-treated and thus cytoprotected groups of rats, the negative control rats showed very severe and deep gastric mucosal necrotic damage, along with edema and leucocytes infiltration of the submucosal layer. The finding suggested that *F. deltoidea* extract promotes ulcer protection as ascertained by the comparative significant decreases in ulcer areas and inhibition of submucosal edema. However, there was still drastic mucosal injuries seen that leaded to edema and leucocytes infiltration of the sub mucosal area when distilled water was used. *F. deltoidea* extract had significantly reduced ulcer area against absolute ethanol-lesion induction and this mechanism probably be due to stimulation of gastric mucous secretion and inhibition of edema and leucocytes infiltration in submucosal gastric tissue [29].

4.10 Anti-hypertensive Activity

Several classes of pharmacological agents have been used in the treatment of hypertension. Hypertension is one of the leading causes of disability, mortality, and morbidity among the population. It is the most common chronic illness among the world faces [30-31]. Hypertension is the most common cardiovascular diseases and constituents a major factor for several cardiovascular complications. The study was performed to characterise the effect of *F. deltoidea* extracts on the serum protein profile of rats, mice and selected cell lines. This would facilitate the identification of serum proteins whose expression dynamics are altered and once these proteins are identified, a possible mechanism by which this plant extract exerts its effects may be postulated. A 2D gel electrophoresis (2DE) analysis showed a number of expressed protein spots. 12 protein spots were determined with the aid of Matrix Assissted Laser Desorbtion/Ionization - Time of Flight analysis (MALDITOF/ TOF). Two main types of protein were responsible in producing effective results of anti-hypertensive which are Apolipoprotein H precursors and alpha-1 macroglobulin precursor. Furthermore, the fruit extract of *F. deltoidea* had excellent inhibitory effects towards ACE activity with the IC_{50} values 47.0 as well as with the leaf extract of *F. deltoidea* with IC_{50} value 43.9µg/ml. While this research was being investigated, a few other results were explored co-incidentally. One of it was, the plant can be used as an anti-cancer agent since it did not affect the normal cells. Besides that, it was also known that the plant extract helped in uterine muscle contraction even with the existence of muscle contraction antagonist which is atropine and indomethacine. Based on results obtained; this study showed that *F. deltoidea* extracts exhibited potential antihypertensive properties. 2DE analysis demonstrated that treatment of the extracts exhibited several differentially expressed protein spots. 12 protein spots were identified using MALDITOF/ TOF and among which are Apo H precursor and alpha-1 macroglobulin precursor. Both proteins has the relationship to the control of hypertension, however, the actual mechanism affected by the extracts remain unclear and require further study. This study also acknowledged the positive effects of this plant in treating diabetes and promoting uterine contraction [32].

4.11 Anti-melanogenic Efficacy

The skin pigmentation processes involve de novo synthesis of melanin in melanocytes and transfer of the synthesised melanin packed in melanosome to neighboring keratinocytes, which eventually turns the skin color into dark [33-34]. Extensive efforts have been made tosearch for novel depigmenting agents with little success. A recent study was carried out to determine the efficacy of *F. deltoidea* for its anti-melanogenic effects. This was accomplished by analyzing the extract with cultured B16F1 melanoma cells. Moreover, it has been said that the extract of *F. deltoidea* with its various doses manage to restrain the melanocyte stimulating hormone (α-MSH)-induced melanin synthesis. The *F. deltoidea* extract decreased mushroom tyrosinase activity and intracellular tyrosinase activity of B16F1. Besides that, the extract of *F.deltoidea* has the ability to lower down the expression of microphthalmia-associated transcription factor (MITF). The application of *F. deltoidea* extract can also be used for down-regulation of the expression of genes involved in the melanogenesis pathways. It was also proved that *F. deltoidea* extract had the ability to serve its purpose as a depigmenting agent for cosmetics. MITF expression was decreased by *F. deltoidea* more than a-MSH none treat control at concentrations 0.05 and 0.1%. It was concluded that, *F. deltoidea* has strong possibilities being whitening cosmetic materials by down-regulation of cellular melanogenic components like tyrosinase, MITF and direct catalytic processas well [35].

4.12 Antimicrobial Activity

Methanol, chloroform, and aqueous extracts of *F. deltoidea* was investigated for the *in vitro* antimicrobial activity at10mg/ml, 20mg/ml and 50 mg/ml, respectively using the discdiffusion method against 2 Gram positive {*Staphylococcus aureus* (IMR S-277), *Bacillus subtilis*(IMR K-1)},2 Gram negative {*Escherichia coli*(IMR E-940), *Pseudomonas aeroginosa*(IMR P-84)} and 1 fungal strain, *Candida albicans* (IMR C-44). The methanol extract significantly inhibited the growth of *S. aureus* forming a wide inhibition zone (15.67 ±0.58 mm) and lowest minimum inhibitory concentration (MIC) value (3.125 mg/ml).Antimicrobial activity of *F. deltoidea In vitro* further justifies its utility in folkleric medicines for the treatment of infections of microbial origin [36].

5. TOXICOLOGY STUDIES OF *Ficus deltoidea*

Numerous researches have been done on the plant which is *Ficus deltoidea* and its extracts. However, not much has been reported about the toxicity of this plant. According to a few studies that were done to determine the sub-chronic toxicity, F. deltoidea did not have an effect on the bone marrow, liver and renal functions [37]. Based on the haematological and biochemical results, *F. deltoidea* aqueous extract did not influence any changes in the blood. The extract was given to two groups of rats at 100 and 300mg/kg/body weight everyday respectively. The toxicity study was conducted using rat for 90 days. The results showed there were no significant changes of the blood parameters in all treated groups compared to the control. It was concluded that they showed no adverse effects so it might be harmless to administer to humans [38]. In another study which was conducted to evaluate the morphology and amount of mouse oocytes which was dependent on the concentration, it was known to us that, as the concentration of *F. deltoidea* increases, it decreased the quantity of mouse oocytes without affecting its morphology [39]. Methanol extract of *F. deltoidea* fruit and leaves were tested for their cytotoxicity on human leukemic (HL60) cell lines and also its effect on reproductivesystem of male rats was also studied. Among the extracts tested, leaves extract showed potent cytotoxic activity than fruit extract. There was a significant effect on testis and epididymis weight, sperm count, sperm viability and the number of normal sperm morphology. However, the mechanism of action of *F. deltoidea* extracts still remains unclear and an intensive research should be needed in the future [38]. Lastly, further studies need to be performed to determine the optimum and appropriate concentration of doses for human consumption. The studies involved should be related to mutagenicity, teratogenicity and carcinogenicity of this plant extract and the possible drug interactions with this herb for those who are under other medication.

6. CONCLUSION

The scientific literature reviewed that *F. deltoidea* is an important medicinal plant with diverse therapeutic potential. This review also highlights the development of this plant into a widely used neutraceutical. Products derived from *F. deltoidea* are now distributed increasingly all over the Malaysia. This has given rise to a concomitant increase in research on the phytochemical constituents and biological activity and toxicity of *Ficus deltoidea.* The detailed phytochemical and pharmacological studies are required to identify the novel lead compounds. In addition, clinical studies are also required to investigate if the observed pharmacological activities are of clinical relevance. These studies may provide a meaningful

way for validating the traditional knowledge of this important medicinal plant for the welfare of the mankind.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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