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A Systematic Review on the Anti-oxidative and Anti-inflammatory Properties of *Ficus carica*

Norfarah, I.R.[1], Adlina, M.[1], and Nadia, M.E.[1*]

[1]*Basic Medical Sciences, Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Menara B, Persiaran MPAJ, Jalan Pandan Utama, Pandan Indah, 55100 Kuala Lumpur, Malaysia*

Oxidative stress (OXS) has been associated with many diseases such as neurodegenerative diseases, cancer, diabetes and osteoporosis as it can alter cellular components in the body. Oxidative stress can be neutralised by anti-oxidative compounds found in many natural products such as berries, turmeric and figs. The objective of this paper is to evaluate the anti-oxidative and anti-inflammatory properties of figs. Fig, or its scientific name *Ficus carica* (*F. carica*), is one of the fruits mentioned in the Quran and is known among the Malays as 'buah tin'. Electronic databases used were Scopus, Ovid, Proquest and Science Direct. The inclusion criteria were studies that utilised the fresh, dried, juice, extract of *F. carica*, written in English, published within 2007 to 2017, studies carried out in tissue culture and animal studies. Anti-oxidative effect, lipid peroxidation inhibition and anti-inflammatory were the key outcomes in this review. A total of 19 studies met all the criteria. The results showed that treatment with *F. carica* increased anti-oxidative enzymes such as catalase, superoxide dismutase, glutathione peroxidase and decreased lipid peroxidation activity. *F. carica* also reported to reduce pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) in acute and chronic inflammation. In conclusion, *F. carica* exhibited anti-oxidative and anti-inflammatory properties.

Keywords: *Ficus carica*, anti-inflammatory, antioxidant, lipid peroxidation

I. INTRODUCTION

Natural products based on plants, herbs, vegetables, and fruits have gained increasing interest among the researchers for medical purposes due to their therapeutic benefits. The natural product is considered as an ideal alternative due to their wide availability, effectiveness, low cost and minimal adverse effects (George, 2011). With the advent of general interest in alternative medicine, natural products such as nuts (Ros, 2010), pomegranate (Lansky and Newman, 2007) and virgin coconut oil (Intahphuak, 2009) can serve as a possible source to offer benefits for the improvement and maintenance of health.

In addition, the natural products are widely known for their therapeutic benefits due to its anti-oxidative effects. The importance of antioxidant on health has been widely discussed. Generally, an antioxidant is a stable molecule that neutralises free radicals and reactive oxygen species (ROS) and inhibits cellular damage (Lü *et al.*, 2010). In normal physiological conditions, our body can fight free radicals and oxidative stress (OXS) due to the protective role of antioxidant system in the body (endogenous). However, weakening of antioxidant defence may

*corresponding author: nadia@usim.edu.my

result in continuous elevation of ROS and thus increases the OXS which causes oxidative damage to biomolecules and cells.

ROS such as hydrogen peroxide (H_2O_2), superoxide anion (O_{2-}), and hydroxyl radical (OH) are products of normal cellular metabolism produced by an aerobic cell during an endogenous metabolic reaction (Birben *et al.*, 2012). However, under a sustained stress, production of ROS may cause significant damage to cell structure and function. It may lead to inflammation and irreversible damage of tissue and subsequently result in the development of various diseases as examples atherosclerosis, rheumatoid arthritis, osteoporosis, diabetes, neurodegenerative disorders, cancer, cardiovascular disease and other inflammatory diseases (Ravipati *et al.*, 2012).

The antioxidant scavenging enzymes such as glutathione peroxidase (GPX), catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR) and also non-enzymatic antioxidants including glutathione (GSH), vitamin C and vitamin D protect the cell against ROS and maintain oxidative equilibrium (Nimse and Pal, 2015). Consumption of antioxidant has been shown to prevent inflammation by enhancing anti-oxidative enzymes and trigger nuclear factor erythroid 2-related factor 2 (Nrf2) to activate endogenous antioxidant.

Ficus carica (*F. carica*) which is commonly known as common fig or "teen" belongs to the family of *Moraceae*. It is grown in certain regions such as tropical, sub-tropical and temperate, for examples in Turkey, Egypt, Morocco, California, and Brazil. Currently, *F. carica* is also actively planted in Southeastern Asia such as Thailand, Indonesia and Malaysia. The other names for *F. carica* are 'Anjir' in India, 'Mo Fa Guo' and 'Wu Hua Guo' in Chinese and 'buah tin' in Malay. This small and deciduous plant is recognised as one of the earliest cultivated trees (Ahmad *et al.*, 2013). The height of fig plant is 10-30 feet. The leaves are large, wavy marginated, palmately veined and usually have five lobes. The branches are muscular and twisting. The colours of the fruit are green, green with brown, brown or purple depending on their varieties.

Ficus carica fruits have a short storage life between seven to ten days but it can become longer within two to four weeks if stored in cooler and carbon dioxide (CO_2)-enriched conditions (Sozzi *et al.*, 2005). Because of their short shelf life, dried figs have gained much interest as it can be stored longer. The fruits as well as leaves, can be consumed fresh, dried, juice, canned, in preserved form, jam, wine, powder and tea (Lianju *et al.*, 2003). Traditionally, fig has been consumed as medicine for fever, asthma, urinary disorders and to melt stones in the urinary tract. Besides, it is also used as pain reliever, expectorant, and supplement for a diabetic. Dried figs are used as a mouthwash to treat a sore throat and mouth ulcer and as an alternative supplement to build up body's resistance against diseases. Meanwhile, the leaves have traditionally been used to cure diabetes and kidney calcification (Joseph and Raj, 2011).

F. carica contains various bioactive compounds such as quercetin, anthocyanin, phenolic acid and alkaloid (Vinson *et al.*, 2005; Solomon *et al.*, 2006; Soni *et al.*, 2014; Wojdyło *et al.*, 2016). Meanwhile, the leaves consist of flavonoids, alkaloids, coumarins, saponins, steroids and tannin (Ali *et al.*, 2012; Mahmoudi *et al.*, 2016). These dietary compounds have

been widely recognised as a potent antioxidant especially phenolic and quercetin. Ouchemoukh *et al.* (2012) reported that there was a positive correlation between phenolic compounds and antioxidant activities. Quercetin also has been reported to be an excellent antioxidant and has a strong ability to scavenge ROS. *F. carica* has been shown to inhibit 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) radical and nitric oxide scavenging capacity (Oliveira *et al.*, 2009). It was also able to reduce ferric activity which is measured via an assay known as ferric reducing ability of plasma (FRAP) (Pande and Akoh, 2010) and inhibit lipid peroxide level (Viuda-Martos *et al.*, 2015). These tests are done via in vitro method that exhibited different mechanisms to evaluate antioxidant capacity of each compound. Antioxidant activity in DPPH test is evaluated by measuring the potential of natural product as antioxidant agent to scavenge free radicals by donating hydrogen atom or an electron to DPPH, resulting in decolourisation of deep violet colour (Kedare and Singh, 2011). Besides, nitric oxide (NO) scavenging capacity evaluates antioxidant activity by assessing the inhibition of NO. The in vitro lipid peroxidation is to measure antioxidant activity by measuring inhibition of phospholipid peroxidation. Meanwhile, in FRAP assay, no radical substance is involved as this assay evaluates the potential of antioxidant compound to reduce ferric ions into ferrous complex (Alam *et al.*, 2013). It is strongly recommended to perform at least two different tests to evaluate an antioxidant activity of natural product or compound as different tests applied different mechanism.

Inflammation is the body's immune system response as protection from tissue injury or external agents including allergens, pathogen, radiation, toxic chemicals, autoimmune and obesity, high-calorie diet, alcohol and tobacco use (Hussain *et al.*, 2016). It is described by increased permeability of postcapillary venule to plasma proteins, fluid and polymorphonuclear leukocytes emigration to injured tissues (Medzhitov, 2008). Consequently, this event may cause tissue damage due to increase of white blood cells (leucocytosis), fibroplasia and overproduction of pro-inflammatory cytokines (Buckley *et al.*, 2001).

Inflammation can be categorised as acute and chronic inflammation. Acute inflammation is a rapid response which involves innate immunity, a non-specific defence mechanism. It is triggered by localise microbial infection or tissue injury which involve delivery of blood components such as plasma and leukocytes to the inflamed tissue. During this event, blood flow and vascular permeability are increased and leukocytes mainly neutrophils and inflammatory mediators such as cytokines are accumulated (Markiewski and Lambris, 2007).

Meanwhile, chronic inflammation occurs in long-term due to unresolved or deregulated inflammation which involves specific humoral and cellular immune response including macrophages, and T-cells recruitment. The host is more prone to get a chronic disease such as cancer (Hussain and Harris, 2007; Lin and Karin, 2007). Recruitment of mast cells, macrophages and leukocytes to the site of injury may result in rapid released of ROS also known as "respiratory burst" due to an increased consumption of oxygen (Coussens and Werb, 2002; Hussain *et al.*, 2003).

Histamine, serotonin, prostaglandins and cy-

tokines such as tumor necrosis factor α (TNF-α), interferon, interleukin 1β (IL-1β) are examples of chemical mediators of inflammation. The expression of nuclear factor nuclear factor kappa B (NF-kB) is activated by TNF-α and IL-1 which will then induce other pro-inflammatory mediators including chemokines, adhesion molecules, intercellular adhesion molecules-1, and E selectin, cyclooxygenase (COX) enzymes-1 (COX-1) and COX-2, inducible nitric oxide synthase and metalloproteases. Overproduction and prolonged release of pro-inflammatory mediators are harmful to the host and it could be more severe if not treated properly (Tak *et al.*, 2001).

To date, synthetic anti-inflammatory agents including aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are widely used due to their effectiveness in reducing inflammation. Aspirin has the ability to block prostaglandins and thromboxanes by inhibiting COX-1 and COX-2 while NSAIDs inhibit COX-2 and prostaglandins (PGE_2). However, these drugs are known to cause drug-related toxicity, especially on long-term use. The adverse effects are such as gastric irritation, gastric erosion, kidney damage and cardiovascular problems (Tak *et al.*, 2001). Therefore, natural products are being explored as source of new anti-inflammatory agents. This is because, plant secondary metabolites such as alkaloids, glycosides, terpenoids, polysaccharides, flavonoids, phenolic compounds, steroid and fatty acids possess a lot of therapeutic advantages including anti-inflammatory and anti-oxidative properties.

Hence, supplementation with natural products rich in antioxidants and anti-inflammatory properties such as *F. carica* may be beneficial in the treatment and prevention against wide range of diseases.

II. METHOD

A. Source and search strategy

The objective of this review is to evaluate the anti-oxidative and anti-inflammatory properties of *F. carica* on animal and tissue culture studies. Searches were conducted using electronic databases such as Scopus, Sciencedirect, Ovid and Proquest. These electronic databases were assessed from 2016 to 2017. Additional studies were also identified by retrieving from the reference list based on title of journal and individual keywords related to *F. carica*, antioxidant (i.e., malondialdehyde, oxidative stress) and inflammation (i.e., cyclooxygenase, interleukin, cytokines and TNF-α).

B. Keyword search

- "Ficus carica" OR figs AND antioxidant AND anti-inflammatory
- "Ficus carica" OR figs AND antioxidant
- "Ficus carica" OR figs AND inflammat* OR anti-inflammatory

C. Selection of research article/Inclusion and exclusion criteria

The results were limited to research articles published from 2007 to June 2017 in English language. Inclusion criteria are as follow:

1. Full-length research article;

2. Studies reported in English;
3. Studies carried out in tissue culture and animal;
4. Studies carried out within 2007 to 2017;
5. Studies that utilised the fresh, dried, juice, extract of *F. carica*; and
6. Studies that determining anti-oxidative effect and anti-inflammatory role of *F. carica*.

Studies with these criteria were included in this systematic review. Exclusion criteria are as follow;

1. Review article, news, letter, editorial, case study and unpublished data such as thesis;
2. Studies that assessed on toxicity effect, antioxidant compound, antioxidant capacity, phytochemical compound and ethnobotanical study;
3. Studies that utilized combination of plants and isolated compound;
4. Studies tested on isolated organ;
5. Duplicate studies; and
6. Irrelevant title.

Studies with these criteria were excluded.

D. Data extraction and management

Papers were thoroughly screened before being chosen in this systematic review. First, any paper which did not meet the inclusion criteria on the title was excluded. Second, abstracts of the papers were screened and again any paper that did not meet the inclusion criteria were excluded and duplicate study was removed. Lastly, the remaining papers were scrutinised and any paper that did not meet inclusion criteria were excluded.

1. The following data were recorded from the papers:
2. Parts of Ficus carica used (fruit/leaves/latex/bark)
3. Types of sample processing (fresh/dried/extract/isolated compound)
4. Types of study (animal study/ tissue culture)
5. Methods of study
6. Results of study
7. Comments of study

III. SEARCH RESULT

As showed in the flow diagram (Figure 1), in the beginning about 10,984 articles were identified using the keywords. After several screening processes based on inclusion and exclusion criteria, only 19 articles were chosen to be reviewed and summarised in Table 1 and Table 2.

A. Study characteristics

All animal and tissue culture studies that were conducted between 2007 to 2017 were chosen. In antioxidant study, all eight studies evaluated the effects of *F. carica* on antioxidative enzymes and lipid peroxide. Mean-

while, in anti-inflammatory study, six studies used rat models and four studies on tissue culture. Anti-inflammatory rat models used were carrageenan-induced paw edema, cotton wool granuloma, air pouch model and formalin-induced paw edema. Other methods used to determine anti-inflammatory activity of *F. carica* were pro-inflammatory cytokines and enzymes analysis.

IV. DISCUSSION

A. Anti-oxidative Effects of *Ficus carica*

Natural products mostly contain variety of bioactive compounds such as alkaloids, terpenes and phenolic compounds which exhibit (Loizzo *et al.*, 2014) antioxidant effects with various other biological activities including anti-microbial and anti-parasitic. *F. carica* contains a lot of bioactive compounds including polyphenols, flavonoids, and anthocyanins which contributed to their high antioxidant properties (Çalişkan and Aytekin Polat, 2011). In vitro antioxidant studies such as DPPH, ABTS and FRAP assay have been widely performed by researchers to study on the antioxidant capacity of *F. carica* (Ammar *et al.*, 2015; Loizzo *et al.*, 2014; Oliveira *et al.*, 2009). Besides that, in vivo antioxidant studies also have been done to provide detailed information on antioxidant effect on the cells itself. This type of study should be performed to reflect antioxidant action which not only involves in scavenging activity against free radicals but also in upregulation of anti-oxidative enzymes, detoxifying enzymes, modulation of redox cell signalling and gene expressions (López-Alarcón and Denicola, 2013). Anti-oxidative effects of *F. carica* have been evaluated by in vivo study in which *F. carica* was administered in animal and after a specified time, blood, serum or tissue were analysed. There are various animal models have been used by researchers including diabetic, hyperlipidemic, hepatotoxicity and hyperglycemic rats to investigate the anti-oxidative effects of *F. carica*.

A study was done by Belguith-Hadriche *et al.* (2016) to determine the anti-oxidative effects of aqueous of *F. carica* on liver, kidney and heart tissues of hyperlipidemic rats. This study was performed by assessing the lipid peroxidation level as an indicator in the presence of reactive oxygen species (ROS) and anti-oxidative enzymes such as glutathione peroxidase (GPX), superoxide dismutase (SOD) and catalase (CAT). These anti-oxidative enzymes play a crucial role in protecting cells by alleviating OXS and tissue damage. High cholesterol diet is known to increase malondialdehyde (MDA) which is the final product of lipid peroxidation and significantly decreased the anti-oxidative enzymes levels. With supplementation of *F. carica* extract, MDA level was significantly reduced and antioxidant enzymes were shown to increase significantly in liver, kidney and heart tissues. The positive effects of *F. carica* supplementation on oxidative status of hyperlipidemic rats are due to its phenolic content. In the same study, the authors detected the major phenolic compounds in figs are quercetin-3-o-rutinoside, apigenin 8-C-glucoside, dihydroxybenzoic acid di-pentoside and cyaniding 3-rutinoside. These phenolic compounds are responsible to exhibit antioxidant effects and reduce OXS which helps in preventing hyperlipidemia.

In a different study, Turan and Celik (2016)

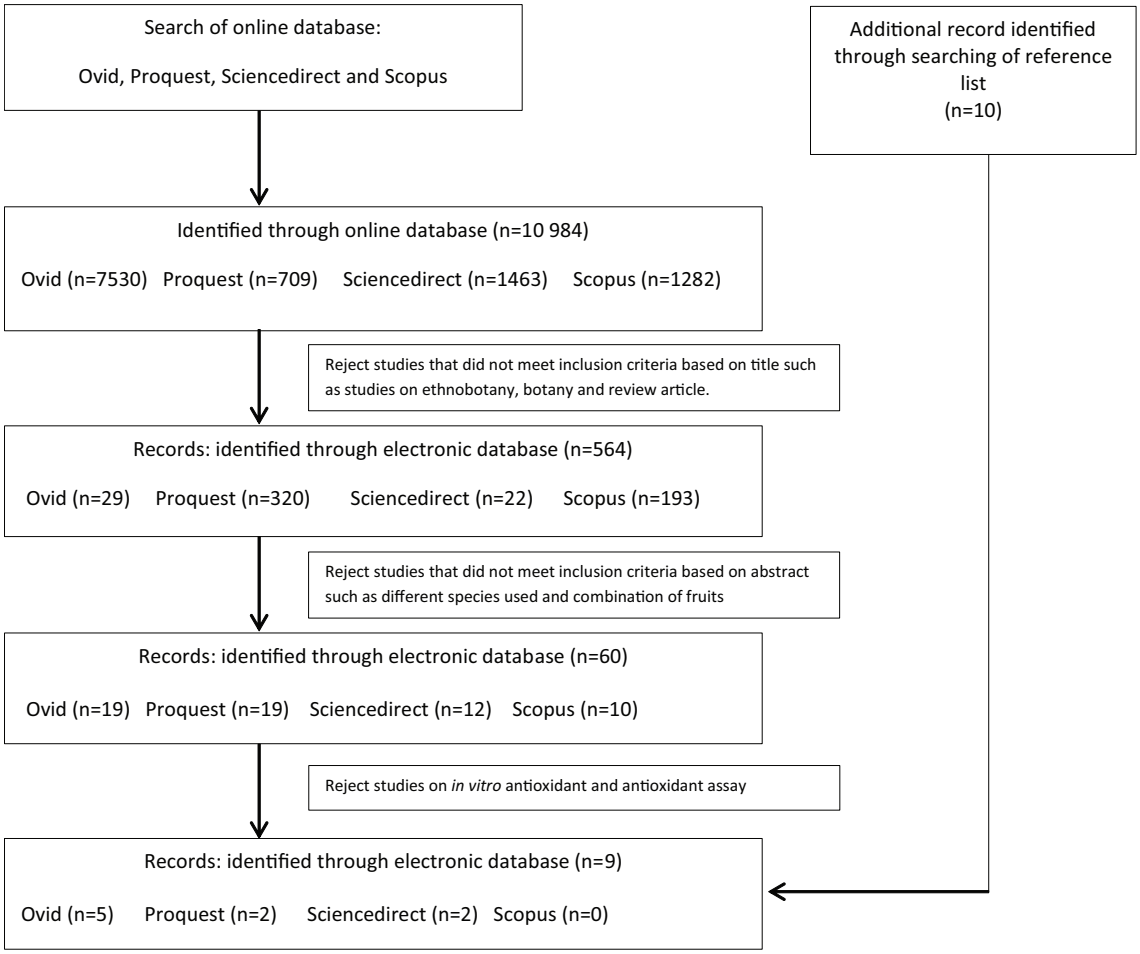

Figure 1. Flow chart of selection process

found that dried *F. carica* supplementation possessed hepatoprotective effect due to its anti-oxidative effect. It was shown that dried figs were able to restore MDA and anti-oxidative enzymes such as superoxide dismutase (SOD), glutathione S-transferase (GST), reduced glutathione (GSH), glutathione reductase (GR) and catalase (CAT) in ethanol-induced OXS and hepatotoxicity in rats. This study has proved that, antioxidant properties in dried *F. carica* are well preserved throughout drying process and this is consistent with previous study by Slatnar *et al.* (2011), which demonstrated that dried figs still contain phenolic compounds after drying process.

Hence, dried figs have additional advantages over fresh *F. carica* due to well preserve antioxidant properties, longer shelf life and easily available throughout years.

Recently, Gholami *et al.* (2017) discovered the protective effect of aqueous extract of *F. carica* fruits and aqueous extract of Cydonia oblonga against doxorubicin (DOX)-induced cardiotoxicity. DOX used in this study is an anti-neoplastic drug and the use of this drug may cause cardiotoxicity (Chatterjee *et al.*, 2010). Cardiotoxicity is mainly caused by OXS and mitochondrial dysfunction as DOX increases

the formation of mitochondrial ROS and alter the mitochondrial function (Štěrba *et al.*, 2013; Mitry and Edwards, 2016). The extract significantly reduced mitochondrial ROS of DOX-treated rats after 30 minutes of incubation. A reduction in GSH level and the increment of MDA levels were prevented by 200μg/mL of aqueous extract of *F. carica* fruit. GSH prevents oxidative damage caused by lipids and free radicals as well as maintaining intracellular and intramitochondrial homeostasis. It also prevented lipid peroxidation which is generated as a product of ROS formation and OXS. Hence, *F. carica* fruit was suggested to play a role in protecting cardiotoxicity caused by DOX by preventing mitochondrial OXS and dysfunction via its anti-oxidative effects. However, the anti-oxidative effect of *F. carica* is slightly lower compared to *Cydonia oblonga*. This study does not include the active components present in aqueous extract of fig which responsible in preventing cardiotoxicity. *F. carica* have been reported to contain saponin, quercetin, flavonoid and anthocyanin (Vallejo *et al.*, 2011; Loizzo *et al.*, 2014). These compounds have been recognised to exert anti-oxidative properties and as well as cardioprotective activity (Gunavathy and Benitasherine, 2016).

Mohan *et al.* (2007) discovered that 500mg/kg methanolic extract of *F. carica* leaves was able to significantly reduce MDA level in liver of CCI_4-induced hepatotoxicity in rats and the result was comparable to one of the known hepatoprotective natural compounds which is silymarin. Silymarin has been proved to prevent hepatic injuries via its antioxidant properties by enhancing the activities of SOD and glutathione-related enzyme systems and inhibit lipid peroxidation in the rats liver (Toklu *et al.*, 2008). In this study, carbon tetrachloride (CCI_4) was induced to evoke hepatic cirrhosis in rats. The authors suggested the hepatoprotective effects offered by *F. carica* leaves are due to its anti-oxidative activities.

In another study done by Singab *et al.* (2010), they reported that even at low dose of 50mg/kg of methanolic extract of *F. carica* leaves significantly increased GSH, SOD and CAT and decreased MDA level as compared with rats induced with CCI_4. The result also showed comparable result with silymarin. Interestingly, the anti-oxidative effects of *F. carica* leaves were better than its fruits. The authors also added that, methanolic extract of *F. carica* leaves contain umbelliferone, caffeic acid, quercetin-3-O-β-D-glucopyranoside, quercetin-3-O-α-L-rhamnopyranoside and kaempferol-3-O-α-L-rhamnopyranoside. These compounds have been reported to exert hepato-protective effect via its anti-oxidative effects and free radical scavenging activities which help in suppressing the production lipid peroxidation-induced hepatic damage (Yang *et al.*, 2013; Wang *et al.*, 2015; Subramaniam and Ellis, 2016; and Miltonprabu *et al.*, 2017). Besides, an ethanolic extract of leaves also showed the same finding with significant increment in GSH level and the activity of both extracts was comparable to silymarin (Mujeeb *et al.*, 2011). Hence, based on these previous studies, *F. carica* leaves have been discovered to possess hepatoprotective activity by improving the anti-oxidative enzymes and decreasing MDA level which consequently prevents formation of free radicals and tissue damage and contribute to the equilibrium of good anti-oxidative defence system.

F. carica stems have been shown to exert anti-oxidative effects. Saoudi and El Feki (2012) reported that supplementation with aqueous extract of *F. carica* stems significantly restored SOD, CAT and GPX level. The extract also significantly reduced MDA level in methanol-induced oxidative hepatic injury in rats. Later, Ahmad *et al.* (2013) reported that diabetic rats treated with the stem extract were shown to have increased GSH level and reduced elevation of MDA significantly. Diabetes has been shown to induce OXS and leads to cellular damage and development of diabetic complication such as diabetic cardiomyopathy and microvascular disease (Fiorentino *et al.*, 2013; Asmat, Abad and Ismail, 2016). According to Ahmad *et al.* (2012), the compounds present in *F. carica* stem are β-amyrin acetate and β-sitosterol acetate and these compounds been reported to have anti-oxidative and anti-diabetic activities (Gupta *et al.*, 2011; Santos *et al.*, 2012; Sunil *et al.*, 2014). Hence, the discovery on natural products with both antioxidant and anti-diabetic properties may be beneficial in treating diabetes

Based on these previous studies, we have observed that, alcoholic as well as aqueous extraction were usually used to investigate the antioxidant activity of extract. This is supported by Mopuri *et al.* (2018), which revealed that ethanolic and aqueous extract of *F. carica* exhibited high antioxidant activity compared to hexane and ethyl acetate extract. This is because, antioxidant compounds are extracted effectively using high polar of solvent. Overall, it can be concluded that treatment with *F. carica* fruits, leaves and stems reduced OXS by increasing anti-oxidative enzymes which include GSH, SOD, GPX, CAT and reducing lipid peroxidation level.

B. Anti-inflammatory Role of *Ficus carica*

Inflammation process is a normal biological response initiated to protect cells against infection and further damages. However, unresolved inflammation may lead to development of cancer, obesity, degenerative diseases (i.e, atherosclerosis, Alzheimer's disease) and metabolic syndromes (Nathan, 2008). Therefore, targeting the inflammatory response such as cytokines, free radicals, prostaglandins and growth factors can help in preventing development of chronic diseases. *F. carica* has been used traditionally to treat inflammation and this claim has been proven by scientific studies (Lansky *et al.*, 2008).

Acute and chronic inflammation: Various studies have done to evaluate anti-inflammatory properties of *F. carica* either in animal study or in vitro study. There were five animal studies conducted to screen for anti-inflammatory effects of *F. carica* extracts using carrageenan-induced paw edema to reflect acute inflammation, cotton pellet-induced granuloma to reflect chronic inflammation and carrageenan-induced air-pouch model. There were four studies on anti-inflammatory activity of *F. carica* leaves and only one study on anti-inflammatory activity of *F. carica* fruit.

In 2010, Patil and Patil evaluated the effect of ethanolic, chloroform and petroleum ether extract of young and matured leaves of *F. carica* against acute inflammation using carrageenan-induced paw edema and chronic inflammation using cotton pellet-induced gran-

uloma. Both methods were used to evaluate anti-inflammatory activity of the plant extract. In acute inflammation study, carrageenan is injected into the rat paw to induce local inflammatory reaction then developing an edema. Carrageenan-induced paw edema comprised two phases. The first phase occurs after one hour of carrageenan injection in which serotonin, histamine and kinins are released due to trauma. The second phase occurs after three hours of injection which involved the released of prostaglandins, cyclooxygenases, lipoxygenase products and bradykinins (Vinegar *et al.*, 1969). The anti-inflammatory effect of extracts and standard drug which is indomethacin were expressed in the percentage of edema inhibition in rat paw. In this study, they discovered that ethanolic extract of young leaves at the dose of 600mg/kg resulted significant inhibition in carrageenan-induced paw edema and cotton pellet granuloma and the findings are comparable to indomethacin. Hence, it was shown that ethanolic extract of young leaves was the most effective in inhibiting inflammation. They proposed that this extract inhibit acute inflammation by inhibiting mediators release after inducing with carrageenan and inhibit chronic inflammation via inhibition of the monocytes infiltration, fibroblast proliferation, angiogenesis and exudation (Meshram *et al.*, 2016).

A study done by Ali *et al.* (2012) worked on lower doses which were 100mg/kg and 200mg/kg of hydroalcoholic (50% ethanol + 50% distilled water) extracts of leaves using carrageenan-induced paw edema method. Both doses were found to significantly inhibit edema expressed in percentage of edema inhibition in rats and these results were comparable to the standard drug indomethacin. The authors assumed that, probably steroids and flavonoid contents in leaves might be responsible for the anti-inflammatory properties of *F. carica*. Then, Singh *et al.* (2012) performed on higher doses which were 250mg/kg, 500mg/kg and 750mg/kg of hydroalcoholic extract using cotton pellet-induced granuloma pouch model. Wet granuloma indicates the volume of transudate adsorbed while dry granuloma is referring to the weight of granulomatous tissues formed. They reported that all doses showed significant inhibition in wet granuloma tissue while only 500mg/kg and 700mg/kg extracts showed significant reduction in dry granuloma. Based on these findings, probably anti-inflammatory effects of *F. carica* fruit was through inhibition of vascular permeability since white blood cells count was also reported to be reduced.

Air pouch model was used by Eteraf *et al.* (2015) to assess anti-inflammatory activity (acute inflammation) of 5, 25, and 50mg/pouch methanolic extract of leaves. This rat model was used to study localise inflammation without causing any systemic inflammation. Air pouch was created by injecting sterile air subcutaneously. After several days, sterile air was reinjected to preserve the integrity of the air pouch without causing any injury in tissue. Then, inflammation was induced by injecting sterile carrageenan solution directly into the air pouch (Whiteley and Dalrymple, 1998). Results showed that all doses were able to reduce granulomatous tissue weight. Only 50mg/pouch showed comparative result with diclofenac but the extracts showed poor activity when compared to another positive control, dexamethasone. All doses significantly inhibited leukocyte

migration and significantly decreased the exudate volume compared to the control.

All in all, these positive changes in animal studies have proven that the treatment with *F. carica* was able to suppress inflammatory response. Previous studies have found that alcoholic extract of *F. carica* leaves contains rutin, kaempferol, psoralen, bergapten, benzaldehyde and ferulic acid (Li *et al.*, 2011; Kazemipoor, Lorestani and Ansari, 2012; and Trifunschi and Ardelean, 2013). All of these compounds were found to have anti-inflammatory effects (Guardia *et al.*, 2001). However, further studies are needed to elucidate the mechanism in detail.

Cytokines level: There were six studies which revealed the mechanism of anti-inflammatory offered by *F. carica*. Only Park *et al.* (2013) examined the anti-inflammatory effects of *F. carica* branches extract by assessing the inhibition of nitric oxide (NO) production and TNF-α. NO is a key player of immune system. Excess production of NO indicates presence of inflammation in the body. Their study reported that 50μg/mL of ethyl acetate and ethanolic extract showed the highest reduction in NO while ethyl acetate, hexanic and ethanolic extract showed the highest reduction in TNF-α. The authors suggested that the anti-inflammatory properties of *F. carica* probably due to steroids. However, no studies have found the presence of steroid in the *F. carica* branch. Previous study found that, Ahmad *et al.* (2013) reported that the stem contains β amyrin acetate which may be responsible for its the anti-inflammatory properties as this compound has been found by researchers to exhibit anti-inflammatory activity by inhibiting leukocytes migration, inhibit inflammatory response in 12-O-tetradecanoylphorbol-13-acetate-induced inflammation (Akihisa *et al.*, 2010; and Okoye *et al.*, 2014).

Pro-inflammatory cytokines were measured by Essa *et al.* (2015) to determine the effects of *F. carica* fruit in the brain of transgenic mouse model of Alzheimer's disease. They found that, fresh figs were effective in decreasing pro-inflammatory cytokines such as TNF-α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10 levels and Eotaxin, a chemokine which able to alter neurogenesis significantly compared to untreated mice. Based on these observations, fresh figs have a potential to be used as therapeutic agent against neurodegenerative diseases associated with inflammation. Furthermore, Amessis *et al.* (2017) reported that 250μg/ml of ethanolic extract of *F. carica* was the best concentration to suppress activity of xanthine oxidase and ROS. Xanthine oxidase is an enzyme that responsible in generating ROS. According to Mopuri *et al.* (2018), ethanolic extract of *F. carica* contains high polyphenols and flavonoids compared to other types of extraction such as hexane, ethyl acetate and aqueous extract.

The anti-inflammatory activities of *F. carica* fruits are probably attributed to its phenolic, flavonoid, anthocyanin and quercetin. Each of these compounds have been extensively studied to exert variety anti-inflammatory responses by inhibiting nitric oxide, lipoxygenase enzymes, COX enzymes, NF- κB, IL-1α, IL-1β, 1L-6, TNF-α and PGE_2 (Kim *et al.*, 2004; García-Mediavilla *et al.*, 2007; Boots *et al.*, 2011; Miguel, 2011; Ambriz-Perez *et al.*, 2016; and Li *et al.*, 2016).

Study by Joerin *et al.* (2014) found that supplementation with aqueous extract of leaves

at the dose of 50mg/kg and 100mg/kg significantly reduced IL-6 level in the plasma of rats supplemented with high-fat diet (HFD). IL-6 has been shown to be associated with obesity (Stylianos Kapiotis *et al.*, 2013). Stelzer *et al.* (2012) found that overweight and obese participants had significantly increased IL-6 level compared with normal weight participants while participants with high in high density lipoprotein level had low plasma levels of pro-inflammatory IL-6. Later, Turkoglu *et al.* (2017) added that the aqueous extract significantly downregulated vascular endothelial growth factor (VEGF) which is an angiogenic factor and downregulated TNF-α and IL-1α levels compared to the untreated cells. TNF-α is a cytokine involved in various inflammatory diseases such as rheumatoid arthritis, multiple sclerosis and psoriasis while IL-1α causing inflammation in acne (Yang *et al.*, 2014), androgenetic alopecia and alopecia areata pathogenesis (Gregoriou *et al.*, 2010). Hence, by downregulating the expression of TNF-α will help in the treatment and prevention in various inflammatory-related conditions. In another study, 5mg/pouch, 25mg/pouch and 50mg/pouch of methanolic extract of *F. carica* leaves were reported to reduce the production of PGE_2 and TNF-α level respectively compared to the control group (Eteraf-Oskouei *et al.*, 2015). They inferred that, the anti-inflammatory activity of the extract is due to high antioxidant capacity as reflected by the total phenolic content and DPPH inhibition.

Rashid *et al.* (2017) reported that the leaves extract contains carbohydrates, alkaloids, flavonoids, glycosides, proteins, saponins and terpenoids. Meanwhile, using HPLC analysis, compounds such as rutin, chlorogenic acid, psoralen and bergapten, caffeoylmalic acid were found in the *F. carica* leaves (Takahashi *et al.*, 2014). Flavanoids, saponin, rutin, chlorogenic acid, psoralen, bergapten have been recognised to possess anti-inflammatory properties (Selloum *et al.*, 2003; Bose *et al.*, 2011; Lee, Ku and Bae, 2012; and Hwang *et al.*, 2014). Psoralen which is the predominant compound present in *F. carica* leaves has been widely used as a treatment for psoriasis. Psoriasis is a complex disease which is also related to cytokine disturbance such as IL-8, IL-17, IL-22, IL-23, vascular endothelial growth factor and TNF-α (Coimbra *et al.*, 2010). Therefore, this compound may be beneficial in treating inflammation-related diseases.

V. STRENGTH AND LIMITATION OF THIS REVIEW

Although there are good evidences of anti-oxidative and anti-inflammatory effects of *F. carica*, the results are not sufficient to confirm the mechanisms involved and to make a definitive conclusion. Identification and isolation of active compounds from *F. carica* can be determined to understand the mechanisms.

VI. CONCLUSION

This review concludes that *F. carica* exhibited anti-oxidative and anti-inflammatory effects. These properties are due to of bioactive compounds contain in *F. carica* such as alkaloid, flavonoid, quercetin and anthocyanin (Solomon *et al.*, 2006; Ali *et al.*, 2012; and Soni *et al.*, 2014). *F. carica* has a potential to be used as an alternative agent for the treatment and preven-

tion of diseases associated with oxidative stress and inflammation. Further studies and clinical trials are warranted to provide a more detail and conclusive mechanisms of *F. carica*.

VII. CONFLICT OF INTEREST

The authors declare that they have no competing interests.

VIII. ACKNOWLEDGEMENT

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Table 1. Summary of anti-oxidative effects of *Ficus carica*

PART	SAMPLE PREPARATION	STUDY	METHOD	RESULT	COMMENT	REFERENCES
Fruit	Aqueous extract of F. carica 100 µg/ml and 200 µg/ml	Doxorubicin (DOX)-induced cardiotoxicity Sample: Heart mitochondria	Mitochondrial ROS formation, GSH level and lipid peroxidation	F. carica at both doses significantly prevented ROS formation in isolated heart after 30 min of incubation and reduced MDA concentrations following 60 min of incubation. F. carica at the dose of 200 µg/ml extract significantly increased GSH content compared with DOX group after 60 min of incubation.	F. carica has protective effect against DOX-induced cardiotoxicity.	Gholami et al., 2017
Fruit	Aqueous-ethanolic extract of F. carica 400 mg/kg	High fat diet-induced hyperlipidemic rats Sample: Liver, kidney, heart tissue	TBARS, CAT, SOD and GPX activities	F. carica significantly reduced TBARS and significantly increased in CAT, SOD and GPX activities.	F. carica contains flavonoids and polyphenols which contributed to anti-oxidative effects in HFD-fed rats and exhibited hypocholesterolemic effect.	Belguith-Hadriche et al., 2016
Leaves	Ethanolic extract of F. carica 50, 100 and 200 mg/kg	Carbon tetrachloride-induced hepatotoxicity Sample: Liver	GSH and TBARS	F. carica at the dose of 50, 100 and 200 mg/kg significantly increased the level of GSH and significantly decreased in the level of TBARS compared with the CCl_4 treated control group. Effect of F. carica was comparable with the standard drug silymarin.	F. carica prevented tissue damage and formation of free radicals.	Mujeeb et al., 2011
Leaves and fruit	Methanol extracts of F. carica 150 mg/kg	Carbon tetrachloride (CCl_4)-induced hepatotoxicity Sample: Whole blood to analyse GSH and SOD levels while serum for CAT and MDA levels	GSH, SOD, CAT and MDA *silymarin=standard hepatoprotective compound (50 mg/kg)	F. carica significantly increased GSH, SOD, and CAT activity while significantly reduced MDA.	F. carica exhibited hepatoprotective effect against CCl_4-induced liver damage probably due to the presence of coumarin, caffeic acid and flavonoid. FC leaves showed better result than FC fruits.	Singab et al., 2010
Stem bark	Methanolic extract of F. carica 500 mg/kg	Streptozotocin- induced hyperglycemia Sample: Serum	GSH and TBARS	F. carica significantly increased tissue glutathione and significantly reduced TBARS level in diabetic rats.	Stem bark of F. carica exhibited anti-diabetic activity.	Ahmad et al., 2013
Stems	Aqueous extract of F. carica	Methanol-induced hepatic oxidative damage Sample: Liver	SOD, CAT and GSH and MDA	F. carica significantly restored SOD, CAT and GSH and decreased MDA level.	F. carica inhibited hepatic oxidative damage induced by methanol.	Saoudi & El Feki, 2012
Fruit	Dried F. carica 10%	Ethanol-induced oxidative stress and hepatotoxicity Sample: Brain, kidney, spleen, heart and liver	MDA, GSH, GST, GPX, GR, SOD and CAT	F. carica restored the ethanol-induced MDA and anti-oxidative enzymes such as GSH, GST, GPX, GR, SOD and CAT towards to control.	F. carica prevented hepatotoxicity by reducing oxidative stress.	Turan & Celik. 2016
Leaves	Methanolic extract of F. carica 500 mg/kg	Carbon tetrachloride (CCl_4)-induced hepatotoxicity Sample: Liver	MDA	F. carica significantly reduced MDA level and the result was comparable to standard silymarin activity.	F. carica exhibited protective effect against liver damage induced by carbon tetrachloride.	Mohan et al., 2007
Fruit	Acetone extract of F. carica 4% figs dietary supplemented	Transgenic Mouse Model of Alzheimer's disease Sample: Hippocampus and the cerebral cortex	MDA, protein carbonyl, SOD, CAT, GPX, GR and GSH	F. carica reduced lipid peroxidation and protein carbonyl in Alzheimer's disease mice. F. carica increased antioxidant enzymes include SOD, CAT, GPX, GR and GSH in cortex and hippocampus compare to control.	F. carica has protective effect against Alzheimer's disease.	Subash et al,. 2014

Table 2. Summary of anti-inflammatory effects of *Ficus carica*

PART	SAMPLE PREPARATION	STUDY	METHOD	RESULT	COMMENT	REFERENCES
Leaves	50% ethanol with 50% distilled water extract of F. carica 100 and 200 mg /kg	Carrageenan-induced paw oedema Sample: Paw volume	Anti-inflammatory study	Both doses of F. carica showed 48.88% and 56.66% inhibition of oedema in rats and the findings were comparable to standard drug indomethacin (67.22%).	Hydroalcoholic extract of F. carica exhibited antioxidant properties and anti-inflammatory activity probably due to the presence of steroids and flavonoids.	Ali et al., 2012
Fruit	Fresh F. carica	Transgenic mouse model of Alzheimer's disease Sample: Brain and plasma	Cytokine analyses: IL-2, IL-3, IL-4, IL-5, IL-9, IL-10 and Eotaxin Amyloid beta (Aβ) Assessment of IL-1β, TNF-α and IL-6 (proinflammatory cytokines)	F. carica significantly decreased IL-2, IL-3, IL-4, IL-5, IL-9, IL-10 and Eotaxin APPsw/Tg2576 mice transgenic group. F. carica suppressed Aβ peptides including Aβ1-40 and Aβ1-42. F. carica significantly reduced IL-1β, TNF-α and IL-6 level.	F. carica has therapeutic potential against neurodegenerative diseases probably due to phenolic compound present in F. carica fruits.	Essa et al., 2015
Fruit	Ethanolic extract of F. carica	Cell culture -Cell Human glioblastoma (U87) cells	Anti-inflammatory activity: xanthine oxidase inhibition assay and ROS	F. carica inhibited the activity of the enzyme xanthine oxidase and production of ROS.	F. carica had the lowest ROS inhibition compared to Ceratonia siliqua and Quercus ilex	Amessis-Ouchemoukh et al., 2017
Branches	Ethanol, ethyl acetate, hexane, butanol and water extract of F. carica	Cell culture - RAW264.7 cells murine macrophages	Inhibition of NO and TNF-α	Ethyl acetate and ethanolic extract of F. carica branches at the dose of 50 µg/mL reduced NO production by 85% and 98%. Ethyl acetate, hexanic, ethanolic extract of F. carica branches at the dose of 50 µg/mL reduced TNF-α production by about 70%.	F. carica branches possessed anti-inflammatory activities by inhibiting NO and TNF-α activities.	Park et al.. 2013
Leaves	Methanolic extract (100%) of F. carica 5, 25, and 50mg/pouch	Air pouch model of inflammation Sample: Exudate (total leukocytes), granulation tissue and pouch fluid (TNFα and PGE_2)	Total number of leukocytes, exudate volume, tissue weight and determination of TNFα and PGE_2	F. carica leaves significantly inhibited leukocyte migration, significantly decreased the volumes of exudate, reduced granulomatous tissue weight and reduced TNFα and PGE_2 level.	Methanolic extract of F. carica exhibited anti-angiogenesis and anti-inflammatory activities.	Eteraf-Oskouei et al.. 2015
Dried fruit	Ethanolic extract (80%) extract of F. carica 250, 500 and 750 mg/kg	Cotton pellet-induced granuloma pouch model as model of chronic inflammation Sample: Granuloma tissue	Cotton wool granuloma technique	F. carica significantly reduced weight of cotton pellets.	Ethanolic extract of F. carica exhibited anti-inflammatory activity.	Singh et al., 2012
Leaves	Aqueous extract	Cell culture human keratinocyte cells (HaCaT)	gene expression RT-qPCR tested	F. carica leaves significantly downregulated VEGF (angiogenic factor), TNF-a and IL-1a compared to the untreated cells.	Aqueous extract of F. carica leaves exhibited anti-inflammatory effects.	Turkoglu et al., 2017
Leaves	Aqueous extract of F. carica 50 and 100 mg/kg	Model: High fat diet (HFD) rat Sample: blood	IL-6 plasma levels	F. carica leaves significantly lowered IL-6 levels.	Aqueous extract of F. carica leaves have protective effect against metabolic syndrome related disease using HFD rat model.	Joerin et al., 2014
Leaves	Ethanol, chloroform and petroleum ether extract of F. carica 300 and 600 mg/kg/day	Carrageenan-induced paw oedema method (acute inflammatory study) and cotton pellet granuloma method (chronic inflammatory study) Sample: Paw volume and weight of cotton-pellet	Acute and chronic inflammatory study	Ethanolic and chloroform extract of F. carica (mature and young leaves) showed inhibitory effect while petroleum ether extract did not exhibit significant inhibition. Only ethanolic extract of F. carica (mature and young leaves) showed significant inhibition. Activity of young leaves extract significantly higher than mature leaves.	F. carica exhibited anti-inflammatory effect against acute and chronic inflammation and the findings are comparative to standard drug Indomethacin.	Patil & Patil, 2010
Dried fruit	Methanolic, n-hexane, chloroform, ethyl acetate and n-butanol soluble fraction of F. carica	In vitro	Lipoxygenase inhibition assay	Ethyl acetate, methanolic extract and n-hexane extract of F. carica significantly inhibited Lipoxygenase.	F. carica inhibited lipoxygenase enzyme	Ahmad et al., 2016