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Biological Activities of *Ficus carica L.* Fig Leaves and Latex

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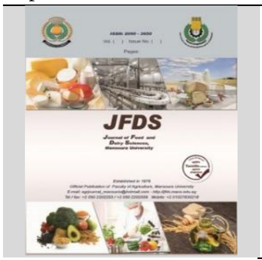

ABSTRACT

Ficus Carica L. fig is a fruit that comes in a variety of forms, including leaves, fruits, seeds, and latex. This article aims to investigate the biological activities of *Ficus Carica L.* figs (leaves and latex), as most of the research focus on the fig's fruits. As well as explore the potential of figs (leaves and latex) for the treatment and prevention of various diseases. Fig leaves and latex have biological activities include antioxidant activity, antidiabetics activity, hepatoprotective activity and anti-cancer activity.

Keywords: Figs; Biological Activities; Fig leaves; Fig latex; antioxidants activity; Anti-cancer activity.

INTRODUCTION

Ficus carica L., a deciduous tree belonging to the Moraceae family often called mulberry family or fig family, is indigenous to southwest Asia and is commonly cultivated in the Mediterranean region. This botanical specimen is among the first trees to have been intentionally grown by humans. The cultivation of fig fruits holds significant global importance as it caters to the demands of both the fresh and dry consumption markets (Çalişkan and Polat, 2011 and Tanwar *et al.,* 2014). According to FAO (2016) the annual production of this substance amounts to approximately one million tons. According to Soni *et al.* (2014), several countries including Turkey, Greece, Egypt, Morocco, Italy, Spain, and Brazil, among others, are prominent producers of figs.

In addition to a wide range of biologically active phytochemical components like anthocyanins, carotenoids, flavonoids, polyphenols, phenolic acids, triterpenoids, glycosides, polysaccharides, reducing compounds, and vitamins C, K, and E, the fig fruit is rich in trace and microelements (Vinson, 1999). Oxidative stress is a state in which the body experiences an imbalance between the production of free radicals and its ability to counteract them. This condition has been implicated in the development of chronic diseases such as heart disease, cancer, and Alzheimer's disease. However, recent studies have shown that phytochemicals with antioxidant activity can protect biological systems against the harmful effects of oxidative stress. Phytochemicals, including phenolics, carotenoids, and curcuminoids possess antioxidant properties that help neutralize free radicals via various mechanisms such as chelating metal ions, reducing metal ions, and scavenging free radicals (Mawa *et al.,*2013).

Figs can be found in many different forms, such as leaves, fruits, seeds, and latex, and their parts are a rich source of phytochemicals and bioactive compounds such as phenolic acids and antioxidants (Rasool *et al.,* 2023). The potential for industrial valorisation of the bioactive components produced from fig leaves is well known. Other secondary metabolites found in fig leaves, such as tannins, flavonoids, and hydrocarbons, also have antioxidant qualities and can be used to treat or prevent a variety of disorders brought on by oxidative stress (Shiraishi *et al.,* 2023).

Latex is a natural adhesive polymer found in various parts of plants, including their vascular system (Santos and Van Ree 2011; Upadhyay 2011). All species of figs have been observed to contain a substance like latex within their vascular systems, which plays a crucial role in safeguarding and repairing the plant against physical attacks. Moreover, fig tree latex has shown potential in medicinal applications, including wart treatment and wound healing (Lansky *et al.,* 2008).

Diverse secondary metabolites of different chemical classes, such as phenols, flavonoids, terpenoids, etc., are responsible for the biological activities demonstrated by *F. Carica* latex. The different metabolites showed diverse biological properties including antibacterial, antifungal, antiviral, anticancer, antiangiogenic, antioxidant, anti-inflammatory, anticoagulant, antihypertensive, and hepatoprotective as well as antiparasitic activities (Hegazy *et al.*,2023).

Therefore, this article aims to investigate the biological activities of *Ficus carica L.* figs, in terms of leaves and latex including the antioxidant activity, antidiabetics activity, hepatoprotective activity and anti-cancer activity. To date, most of the published research has focused on the fig fruits but not their leaves or latex.

2. Fig leaves:

Fig leaves in particular, which are produced as biowaste during fig fruit processing, have the potential to be a useful alternative source of bioactive chemicals for a variety of sectors. Possible uses include substituting organic additives for synthetic ones in the food production industry (Chamorro *et al.,* 2022), improving the physical and sensory qualities of the food products in which they are used.

Traditional medicine has amassed a substantial body of evidence supporting the viability of fig leaves natural constituents as a source of natural medicine. As previously reported in Ayuso *et al.* (2022), fig leaves contain valuable biomolecules that have antidiabetic, antipyretic, antioxidant, and antihypertensive properties. Fig leaves have the potential to be a distinctive and different source of chemical compounds, particularly plant components including organic

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acids, phenols, flavonoids, coumarins, and volatile components, claim Li *et al.* (2021).

Fig leaves have the potential to be a distinctive and different source of chemical compounds, particularly plant components including organic acids, phenols, flavonoids, coumarins, and volatile components (Li *et al.,* 2021). The dermatological potential of fig leaves in the treatment of psoriasis and vitiligo is also noteworthy, as reported in previous studies (Oliveira *et al.,* 2009; Takahashi *et al.,* 2014; Raskovic *et al.,*2016; Pucci *et al.,*2022).

3. Biological activities of fig leaves

Antioxidant Activity:

Antioxidant activity is a crucial indicator of the biological characteristics of medicinal plants and their ingredients, according to Conforti *et al.* (2012). Phenolic compounds are a type of antioxidant that can scavenge free radicals, suppress enzyme activity, and chelate pro-oxidant metal ions. Free radicals are unstable molecules that can damage cells and tissues. Cells can be shielded from free radical damage with the aid of antioxidants. Heart disease, cancer, and Alzheimer's disease are just a few of the chronic diseases that have been related to free radical damage (Halliwell, Clement, and Long, 2000; Silva *et al.,* 2004). For the antioxidant's activity for fig leaves, it depends on the harvest season, fig leaves antioxidant activity has reportedly been shown to vary. According to research by Marrelli *et al.* (2014), leaves harvested in July exhibited stronger antioxidant activity than leaves gathered in June and September.

The antioxidant activity of fig leaves was shown to be greater than that of fig wood and bark (Singab *et al.,*2010; Conforti *et al.,*2012; Belguith-Hadriche *et al.,*2017). Additionally, only the leaves can scavenge superoxide anion radicals (Oliveira, *et al.,* 2009). Caffeoyl-malic acid and psoralen-glucoside are the two most prevalent hydroxycinnamic acids with oxygen radical adsorption capacity (ORAC) (Dávalos, *et al.,* 2004). Ficus pumila commonly known as the creeping fig, is a species of fig tree that is native to East Asia. The leaves of Ficus pumila contain flavonoid glycosides which exhibit potent antioxidant properties and confer advantageous impacts on human health. The most potent antioxidant compound, rutin, was extracted from the leaves of Ficus pumila through the utilization of a 50% aqueous ethanol solution. F. pumila is utilized as a form of herbal therapy for the management of diabetes and hypertension (Leong *et al.,* 2008).

Antidiabetics Activity

The condition is marked by elevated levels of glucose in the blood and decreased sensitivity to insulin. Its impact is significant, with a widespread increase in its occurrence (Qian *et al.,*2002). The incidence of type 2 diabetes (T2D) is escalating worldwide, and it is anticipated that the global prevalence will reach 552 million by 2030 (Whiting, *et al.,*2011 and Saeedi *et al.,*2019).

Fruits and vegetables are essential constituents of a nutritious diet and are deemed to play a significant role in the prevention of T2D. The consumption of a greater quantity of fruits has been found to be associated with alterations in gut microbiota and metabolic processes, which in turn have been linked to a decreased likelihood of developing T2D. This finding supports the recommendation for increased fruit intake in preventing T2D in the general population (Jiang *etal.,*2020).

The extract obtained from fig leaves exhibits a distinct hypoglycaemic impact. The observed effect cannot be attributed to a gradual rise in insulin secretion, thus suggesting the presence of an unspecified peripheral effect that mimics insulin (Guarrera,2005). Several studies have shown that fig leaves decoction can have a hypoglycaemic effect, meaning that it can help to lower blood sugar levels. For example, a study done by Serraclara *et al.,* (1998) found that fig leaves decoction was able to significantly lower blood sugar levels in type one diabetic patients.

The utilization of fig leaves for diabetes treatment has been documented in traditional medicine (Ercisli *et al.,*2012) The 70% ethanol extract derived from fig leaves was observed to decrease elevated blood glucose levels in diabetic rats to a level that is within the normal range, as reported in a previous study by Carvalho, *et al.,* (2015). According to a study by Perez *et al.,* (2000) the diabetic rat experienced a decrease in plasma glucose levels through an augmented uptake of glucose by skeletal muscle, because of the consumption of the aqueous extract of leaves.

Hepatoprotective Activity:

The extracts and constituents derived from fig leaves have demonstrated the potential to ameliorate liver injury, as evidenced by previous studies (Gond and Khadabadi, 2008; Singab *et al.,*2010; Aghel, *et al.,*2011; Kelany and Abdallah, 2016 and Subramaniam and Ellis, 2016). The findings of an *in vivo* study on hepatoprotective effects indicate that the ethanol extract of leaves has the potential to mitigate fibrosis and inflammation in mice with liver injury induced by carbon tetrachloride ($CCl4$) (Aghel, *et al.,*2011).

A methanolic extract of the fig leaves was found to have a normalizing effect in a rat model of $CCl4$-induced liver injury on the dysregulated serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, total protein, plasma urea, and creatinine (Singab *et al.,* 2010). In a rat study, it was discovered that a petroleum ether extract from fig leaves had a normalizing impact on blood levels of the enzymes glutamic oxalate transaminase, glutamic pyruvate transaminase, and bilirubin that were dysregulated as a result of liver damage brought on by rifampicin. This was reported by Gond, and Khadabadi, (2008).

In a study by Kelany and Abdallah (2016), it was discovered that -caryophyllene normalized the dysregulated levels of serum alanine transaminase, aspartate transaminase, and total malondialdehyde in rats with liver injury brought on by ketoprofen. In rats with liver damage brought on by N-nitrosodiethylamine, it has been shown that umbelliferon has the power to recover total glutathione and alanine transaminase levels as well as lessen hepatic lipid peroxidation.

Anticholinesterase and anti-HSV-1 activities.

In accordance with *in vitro* studies, the extracts of fig leaves obtained through n-hexane and acetone have demonstrated a noteworthy inhibition against acetyl cholinesterase, Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) have been reported in Orhan, Üstün and Şener, (2011). The inhibitory activities on acetylcholinesterase and butyrylcholinesterase for n-hexane and acetone extracts were reported to be $62.9 \pm 0.9\%$ and $76.9 \pm 2.2\%$, and $50.8 \pm 2.1\%$ and $45.6 \pm 1.3\%$, respectively. Furthermore, Guo *et al.,* (2016) found that bergapten and psoralen in fig leaves have been observed to exhibit inhibitory effects on the activity of AChE, with respective IC50 values of 493.11 and 564.59 µg/ml. Alzheimer's disease is a type of neurodegenerative disorder that is marked by a gradual deterioration in cognitive functioning. This deterioration is often accompanied by atypical levels of AChE and BChE within the brain, as has been noted in various studies by Baranowska-W´ojcik *et al.,* (2020) and Haake *et al.,* (2020).

Cholinesterase (ChE) inhibitors have been recognized as significant agents in the management of Alzheimer's disease (Kabir *et al.,* 2019); Haake *et al.,* 2020). According to the study of Wang et al. (2004), an extract derived from fig leaves showed a direct antiviral effect on HSV-1, leading to its elimination. The therapeutic index values of 30.0 were obtained from testing the anti-HSV-1 activity of fig leaves water extract on Hep-2, BHK21 and PRK cells. The infection caused by HSV-1 is believed to contribute to the onset of Alzheimer's disease. The fig leaves exhibit dual properties of anti-HSV-1 and anticholinesterase activity, indicating significant promise for therapeutic application in the management of Alzheimer's disease (Agostini *et al.,* 2014; Piacentini *et al.,* 2014; Agostini *et al.,* 2018).

Anti-cancer Activity

The historical application of fig leaves in the management of diverse malignancies can be traced to the ancient and medieval eras (Zhang *et al.,* 2018). Numerous studies have demonstrated the anti-cancer properties of leaf extracts and their constituents on various types of cancer, including liver, cervical, breast, prostate, and colon cancer (Zhang *et al.,* 2018; Lightbourn and Thomas, 2019; Tulasi *et al.,* 2019). Results of in vitro studies indicate that the fig leaves possess great potential in hindering the proliferation of liver and cervical cancer cells (Tulasi *et al.,* 2019).

Moreover, the anticancer activity of fig leaves has been observed to be more potent than that of fruits (Purnamasari *et al.,* 2019). According to a study, the viability and migration of breast cancer cells were observed to decrease upon exposure to the aqueous extract of fig leaves (Zhang *et al.,* 2018). The results indicate that fig leaves can downregulate the expression of cell cycle-related genes (CDK1, CDK5, CDK9, CDK10) and genes that facilitate migration (MPP2). Conversely, fig leaves may upregulate the expression of genes that promote apoptosis (BAX, TP53, TP21) and genes that suppress migration (TIMP1 and TIMP2) Zhang *et al.,* (2018) and Li *et al.,* (2021) highlighting its therapeutic potential. According to a Li *et al.,* (2021) study, Rutin has been found to impede the proliferation of prostate cancer cells. The antiproliferative effect of β-caryophyllene on colorectal cancer cells has been demonstrated in previous studies (Dahham *et al.,* 2015). Similarly, the growth inhibition of colon cancer cells has been observed with the use of δ-elemene (XIE *et al.,* 2009).

4. Fig latex.

Large levels of isoforms of ficin, a cysteine protease that is harmful to Lepidoptera caterpillars (Konno *et al.,* 2004) and fungi (Karnchanatat *et al.,* 2011; López-Garca *et al.,* 2012), are present in *Ficus carica* L. latex. Furthermore, the latex contains isoforms of a trypsin inhibitor that is harmful to fungus and insects (Terras *et al.,* 1993; Huynh *et al.,* 1992). The ratio of ficin to trypsin inhibitor exhibited dissimilarities among the latices derived from the unripe fruit and the young petioles. This observation implies that although these parts are in their nascent stage and lack lignification, their latices have implemented distinct defence mechanisms. species of rubber trees, researchers can gain insights into the molecular mechanisms underlying rubber biosynthesis and identify potential targets for genetic engineering (Kitajima *et al.,* 2018).

5. Biological activities of fig latex

Antioxidant Activity:

Fig latex is a natural product that has been shown to have antioxidant properties. Compounds called antioxidants can shield cells from the harm done by free radicals. Free radicals are insecure molecules that have the potential to harm cells and have a role in the emergence of illnesses like cancer, heart disease, and diabetes. Several studies have shown that fig latex has antioxidant activity. For example, a study by Abdel-Aty *et al.* (2019) found that latex from fig fruits collected in Egypt was effective in removing free radicals from DPPH and ABTS. The study also found that the latex had a total antioxidant activity of 39 µg GAE/ml. Another study, conducted by Oliveira *et al.* (2010), found that the latex from immature green fig fruits had antioxidant activity against DPPH, superoxide radical, and nitric oxide. The study found that the latex had a nitric oxide scavenging capacity of 1768 µg/mL.

In a third investigation, Aziz (2012) discovered that fig latex polyphenols and flavonoids exhibit antioxidant activity. The hepatocytes of adult Wistar albino rats were used in this investigation, and it was discovered that polyphenols and flavonoids dramatically reduced the activities of glutathione reductase and superoxide dismutase. These research' findings imply that fig latex possesses antioxidant capabilities that could help shield cells from oxidative cell damage caused by free radicals. These results, as well as the possible health advantages of fig latex, require more investigation. Fig latex has been shown to have other possible health benefits apart from its antioxidant properties. For example, fig latex has been shown to have antidiabetic, anti-inflammatory, and antimicrobial properties. Further research is needed to confirm these findings and to determine the potential therapeutic uses of fig latex.

Hepatoprotective Activity

The latex extract obtained from the neck of fig fruit prior to ripening in Erbil city, located in the northern region of Iraq, exhibited a reduction in lead-induced hepatotoxicity in rats. This effect was attributed to one or more of the proposed mechanisms of action, which included the reduction of oxidative stress, elevation of oxidant enzyme levels, and chelation of lead ions. Furthermore, the study involved the assessment of oxidative stress through the administration of lead acetate in rats using induction techniques. According to Azizs (2012) findings, the fig latex exhibited significant efficacy in mitigating lead-induced hepatotoxicity, which can be attributed to its substantial quantities of total phenols and flavonoids.

Anticancer Activity

Previous research has documented the inhibitory impact of fig latex on the proliferation of cells originating from distinct oesophageal and stomach cancers. Fig latex may slow tumor growth while having no adverse effects on haematological or histological variables, according to the body of available evidence (Ghandehari and Fatemi, 2018; AlGhalban *et al.,* 2021). Fig latex exhibits diverse molecular mechanisms of action, such as antiproliferative and anti-metastatic effects, as well as notable impacts on cellular morphology (AlGhalban *et al.,* 2021).

Additionally, it protects against the damaging effects of oxidative stress brought on by free radicals generated by immune system cells (Ghandehari and Fatemi, 2018). Antioxidant substances like flavonoids and polyphenols, as well as phytochemicals like 6-O-acyl-D-glucosyl-sitosterol and its palmitoyl derivatives, caused the predicted actions. According to studies by Mavlonov et al. (2008), Hashemi et al. (2011), and Raskovic *et al.* (2016), the significant antiproliferative properties of fig latex, which have been linked to its potential as an anticancer agent, can be primarily attributed to the abundant accumulation of proteolytic enzymes.

Primary agents responsible for impeding tumour growth in fig latex are the phenolic compounds. Among these compounds, protocatechuic acid, which is obtained from the fig latex, plays a significant role in inducing cell death and restraining invasion in the affected cell lines. The fig latex is known to contain a set of proteases, including ficin, caseinolytic, and gelatinolytic enzymes, which have been observed to trigger apoptosis in cancer cells while having no adverse impacts on healthy cells (Ghandehari and Fatemi, 2018; AlGhalban *et al.,* 2021).

Latex of fig has been found to possess the ability to impede the growth of cancerous cell lines through various mechanisms, as reported by Hashemi, *et al.* (2011). Notably, this effect was observed without any accompanying cytotoxicity towards normal human cells. Ghandehari and Fatemi (2018) have reported on the antiproliferative effects of fig latex, specifically its ability to induce apoptosis through modulation of the cell cycle.

This is achieved by increasing the population of cells in the G0/G1 phase while decreasing the population in the S and G2/M phases. According to Wang *et al.* (2008) and Shin *et al.* (2017), another possible mechanism for these effects could be connected to the inhibition of DNA synthesis, the beginning of apoptosis, the arrest of the cell cycle in cancerous cells, and activation of both the extrinsic death receptor and the intrinsic mitochondrial-dependent apoptosis signalling pathway. The study conducted by Ghandehari and Fatemi (2018) validated antiangiogenic and anti-inflammatory properties of the treatment with fig latex. This was evidenced by a marked reduction in the levels of tumour necrosis factor-alpha, prostaglandin E2, and vascular endothelial growth factor.

According to Tezcan *et al.* (2015), the expression of lethal-7d (let-7d) is induced by Fig latex, which in turn prevents invasion. Additionally, it was found that the use of fig latex had an inhibitory effect on the proliferation of endothelial cells that were cultured in a three-dimensional medium with collagen matrix.

Furthermore, the production of capillary tubules from these cells was suppressed without causing any damage to them, as reported by Ghandehari and Fatemi (2018). This study findings indicate that fig latex exhibits promising preventive properties against cancer-induced anaemia, which is a prevalent adverse effect of neoplastic diseases.

This effect is attributed to the inhibition of erythropoietin secretion. According to Ghandehari and Fatemi (2018) findings, the fig latex exhibited anti-inflammatory properties that effectively hindered the deterioration of erythropoietin-secreting tissues, thereby preventing a decline in red blood cell count and blood cell indices.

The administration's use of fig latex prevented malignant tumors from proliferating too much while also preventing any negative impacts on hematologic parameters and the production of tissue inflammation. This outcome can be related to the natural product's inborn characteristics, specifically its antioxidant, anti-inflammatory, and pro-apoptotic activities.

CONCLUSION

The bioactive components found in fig leaves and latex are widely recognized to have a therapeutic property, including antioxidant, anti-inflammatory, antiviral, antibacterial, anti-cancer, and anti-parasitic effects.These properties are likely due to the presence of various phytochemicals in fig leaves and latex, including Mangifera, a phenolic compound with potent antioxidant, anti-diabetic, antimicrobial, and anti-cancer properties. In order to make it easier to prepare food products with health-promoting qualities, the bioactive compounds derived from them have the potential to be used as food additives.

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الخصائص البيولوجية للأوراق والمستحلب الحليبي للتين

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الملخص

التين (*Ficus Carica L.*) هو فاكهة تأتي في أشكال مختلفة، بما في ذلك الأوراق، والفواكه، والبذور، والمستحلب الحليبي. يهدف هذا المقال إلى التحقيق في الخصائص البيولوجية للتين (الأوراق والمستحلب الحليبي) حيث إن معظم الأبحاث تركز على ثمار التين. كما يهدف إلى استكشاف إمكانية استخدام الأوراق والمستحلب الحليبي للتين في علاج ومنع العديد من الأمراض. حيث تمتلك أوراق التين والمستحلب الحليبي خصائص بيولوجية تشمل أنشطة مضادة للأكسدة، أنشطة مضادة لمرض السكري، نشاطاً وقائياً للكبد، ونشاطاً مضاداً للسرطان.

الكلمات الدالة: التين، الخصائص البيولوجية، أوراق التين، المستحلب الحليبي للتين، أنشطة مضادة للأكسدة، ونشاطاً مضاداً للسرطان.