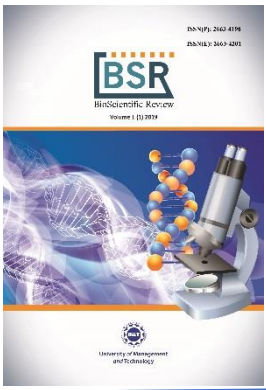

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A Review of the Phyto-pharmacological Significance of the Ajwa Pits (*Phoenix dactylifera* L.)

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Abstract

Phoenix dactylifera L. (Ajwa date) is a natural plant that belongs to the Arecaceae family and is consumed as a fruit. It is cultured all over the world especially in desert areas such as the Arab regions and has nutritional significance and pharmacological value. *Phoenix dactylifera* L. distinguishes itself from other dates because of its richness in dietary fibers, vitamins, minerals and sugars. The current study exhibits that *Phoenix dactylifera* L. contains certain phytochemicals including phenols and flavonoids which act as antimicrobial agents. The distinctive profile of phytochemicals in *Phoenix dactylifera* L. is the reason for its frequent use as a medicinal plant. In vivo and in vitro studies have been performed to understand the complete nature of *Phoenix dactylifera* L. This review article gives an overview of the nutritional significance, pharmacological actions, life stages and phytochemical mechanism of *Phoenix dactylifera* L.

Keywords: Ajwa pits, antimicrobial agent, nutritional significance, *Phoenix dactylifera* L., phytochemicals

1. Introduction

Despite the availability of advance technologies in medical science, patients face the problem of protracted hospitalization. Globally, the reason behind it is the production of drug resistant microbes that make the treatment of the diseases a challenge [1]. Antibiotic resistant bacteria are becoming a grave danger for the public health [2]. Antimicrobial drugs are considered beneficial for humankind. These drugs are synthetic as well as natural products; however, natural products are mostly used due to their valuable pharmacological measures [3]. Conventionally, people use natural products as medicines for the treatment of various diseases. Approximately half of the medicines are derived from natural sources [4]. Moreover, plants containing medicinal properties are found in abundance in Pakistan [5]. Phytochemicals are the key components of the antimicrobial activity of medicinal plants. They are used to develop new drugs and are applied mostly to prevent pathologies [6].

Date palm is among the best natural yeilds. It is also recognized as *Phoenix dactylifera*, which is a commercial crop. It is a vital/crop in the Arabian countries [7]. Around 5000 varieties of dates are cultivated in various countries of the world [8]. Natural products such as dates are not costly and people can use them for the treatment of various disorders, easily [9]. Ajwa is also famous due to its pharmacological actions and nutritional components such as vitamins, sugars, carbohydrates, dietary fibers, minerals, amino acids and lipids [10] It provides

energy to the people and contains a lot of nutrients [11]. The research on *Phoenix dactylifera* L. showed that it increases the components of blood such as the Red Blood Cells (RBCs) [12]. The taxonomical sorting of Ajwa fruit puts it as a member of the Arecaceae family. Its class is Liliopsida and order is Arecales [3]. The fruit of this plant isedible. The phytochemical study of *Phoenix dactylifera* L. shows that it contains saponins, alkaloids, vitamins, flavanoids, tannins and steroids [12]. A recent study on *Phoenix dactylifera* L. demonstrated its antistress properties [13]. Each part of this plant is important for beneficial uses that makes it favorable medicinally and commercially. Some of its uses are shown in Table 1.

Table 1. Uses of Different Parts of *Phoenix dactylifera* L

Parts of *Phoenix dactylifera* L	**Uses**
Pits	To treat neuronal damage. To reduce brain's oxidative stress [18]
Roots	For treatment of toothache [19]
Leaves	Possess antilipaemin and antihyperglyce-mic effects [20]
Fruits	Useful in the treatment of Jaundice [21]

This review focused on the current understanding of the antimicrobial activity of Ajwa pits. It also focuses on the working mechanism of its phytochemicals and its nutritional significance.

2. Life Stages of *Phoenix dactylifera* L.

Hebabauk, kimri, khalal, rutab and *tamer* are the five stages of pre-maturation, maturation, and ripening of the date [14]. Differences in color, chemical composition, texture and sweetness were observed in the different stages of ripening [15].

The most important traits of a date are its moisture, color and flavor. *Phoenix dactylifera* L. is rich in carbohydrates and also contains folate, pantothenic (B5), pyridoxine (B6), niacin (B3), riboflavin (B2) and thiamine (B1) [16]. The fruit grows in a hot and dry climateand can tolerate alkaline and salty conditions. From pollination to the harvesting period, the plant requires low humidity and a small amount of rain. However, a basic requirement for the fruit is access to an excessive amount of underground water for its growth. An old Arabic saying describes its position as *'its feet in the water and its head in the fire'* [17].

The five life stages of the date are as follows:

2.1. Hebabauk

This stage appears after the pollination and fertilization process. The fruit has a round shape with a white color. This stage continues for 4-5 weeks. At this stage, the fruit is immature [18]. The color changes are shown in figures 1.

2.2. Kimri

The meaning of this word in Arabic is "unripe". It is the longest stage and lasts for about 9-14 weeks. In this stage, the fruit is green colored, young and elongated [19].

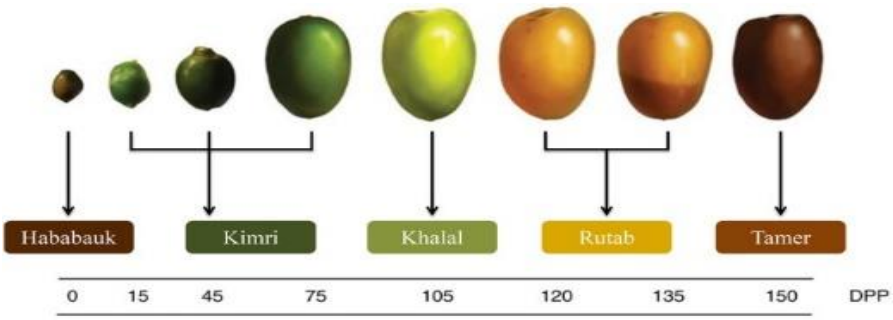

Figure 1. Color changes in the developmental stages of the Ajwa [31]

2.3. Khalal

In this stage, the fruit attains its maximum size and shows a mixture of purple, pink, red and yellow colors owing to the degradation of the chlorophyll. This stage lasts for 3-5 weeks [20].

2.4. Rutab

It lasts for about four weeks. Ash, fat and protein percentages decrease in this phase [16].

2.5. Tamar

It extends up to 2 weeks and it is the last stage in the fruit ripening process. The ratio of water with sugar increases it hinders the fermentation process. The storage stability is remarkable at this stage [21].

3. Nutritional Importance of *Phoenix dactylifera* L. Pits

American Institute for Cancer Research (AICR) and World Cancer Research Fund International (WCRF) suggested that people should regulate their need for nutrition through a routine diet, rather than by taking dietary supplements and medicines [22, 23]. Ajwa date has been found to fulfill the nutritional needs of a population (Table 2) [24]. A research illustrated that its pit contains 80% of the reducing sugars accompanied with many proteins, fats and amino acids [25]. *Phoenix dactylifera* L. is also supplemented with diverse minerals such as potassium, in collaboration with calcium and zinc [26]. The pit of *Phoenix dactylifera* L. contains a small volume of sugar that is approximately 7.2% to 7.6% [27].

Research on *Phoenix dactylifera* L. found that it contains a large amount of essential amino acids such as histidine, proline, leucine, aspartic acid, lysine, glutathione and glycine [28]. Ion exchange chromatography revealed that *Phoenix dactylifera* L. consists of both proteinogenic and non-proteinogenic amino acids including γ-amino-n-butyric acid,1-aminocyclopropane-1-carboxylic acid, (2S,4R)-4-hydroxyproline, β-alanine, traces of 5-hydroxylysine, L-allo-isoleucine and (S)-β-amino isobutyric acid [29]. These non-proteinogenic amino acids combine with the antibodies and activate T-lymphocytes which detoxify the cancerous cells and reduce the rate of creatinine [13]. Dietary fibers also play an important role in the human body. According to the previous research, *Phoenix dactylifera* L. flesh and pits contain both soluble and insoluble dietary fibers [30].

The total lipid yield in *Phoenix dactylifera* L. is about 8.9%. The

Table 2. Composition of Ajwa date pits

Varieties	Moisture %	Protein %	Fat %	Ash %	Carbohydrate %	References
Mabseeli	3.1	3.9	5.0	1.0	87.0	42
Um-sellah	4.4	5.4	5.9	1.2	83.1	42
Shahal	5.2	2.3	5.1	0.9	86.5	42
Fard	10.3	5.7	9.9	1.4	72.7	43
Khalas	7.1	6.0	13.2	1.8	71.9	43
Lulu	9.9	5.2	10.5	1.0	73.4	43
Degletnoor	9.4	5.0	9.2	1.0	75.4	44
Allig	8.6	4.7	11.6	1.0	74.1	44
Ruzeiz	5.4	6.4	9.7	1.0	77.5	45
Sifri	4.5	5.9	10.0	1.1	78.5	45
Average	6.8	5.1	9.0	1.1	78.0	46

dominating specie is triacylglycerol that includes 1, 2-dioleoyl-3-inoleoyl-sn-glycerol and dilinoleoyl-1-oleoylsn glycerol. Free fatty acids (3.1%) are present in *Phoenix dactylifera* L. It consists of linoleic acid, oleic acid, palmitic acid, myristic acid and steric acid. Ajwa seed oil can be used in the pharmaceutical industry [31]. Minerals and vitamins are very important for the human body because they help in the maintenance of the biochemical reactions, cellular functions and in the growth of the skeleton. Hence, a certain amount of such minerals is important for the human body to grow properly. It was reported that *Phoenix dactylifera* L. is enriched with minerals and vitamins needed for the human body [28].

Dietary fibers play an important role in the human body. According to the previous research, *Phoenix dactylifera* L. flesh and pits contain both soluble and insoluble dietary fibers [21].There is no need to cook or process the dates since they are readily available for consumption [32].

Another study on Ajwa date pits showed that they contain high concentrations of calcium, magnesium and iron but a low concentration of sodium, which is very beneficial for the people suffering from hypersensitivity [22]. They also contain a good number of vitamins and phenolic compounds which contributes to their antioxidant property [33].

Phoenix dactylifera is an excellent source of antioxidants, mainly carotenoids and phenolics [34]. They are used to heal problems related with the intestine [35] and for the efficient absorption of food. They also help in digestion and improve the metabolism due to the presesnce of digestible fibers in them [36]. *Phoenix dactylifera* pits, dried and grinded with other nutritional components, can be consumed to overcome any nutritional deficiency. They can also be helpful in the production of juice, vinegar, and food flavors. [37]. Carbohydrates are present in *Phoenix dactylifera* upto 60% to 80%. Inverted sugar is also present in the dates that are semi-dried, whereas a high content of sucrose is present in the fully dried dates. [38].

This tree is mentioned as a sacred tree and the bread of the desert [39]. Instead of giving any other sweet dish to children, they should be given this date

because of its nutritional value and long shelf life [40].

4. Biological and Pharmacological Activities

The efficiency of drugs has reduced due to the increased tolerance and resistance of the currently available drugs by the bacteria and viruses. The pharmaceutical industry is therefore working to enhace the trend of obtaining drugs from natural plant sources instead of creating synthetic ones. The natural plant sources are supplemented with phytochemicals [23]. These phytochemicals have found many applications in antibacterial, antiviral and antifungal activities and they are also involved in the prevention of diseases [6].

4.1. Antiviral Activity

A study conducted on the antiviral activity of the acetonic extract of the pits of *Phoenix dactylifera* L. against pseudomonas phage shows that antiviral activity occurred by the binding of pseudomonas phage to date pits MIC of < 10 µg/ml. The D-value for 100µg/ml was found to be 2.36, whereas for 1000µg/ml it was found to be 0.25. The higher D-values depict the ability of date pits to inhibit the pseudomonas phage infectivity. The inhibition of phage can be caused by the interference of date pits with the lytic cycle of the phage. The average value of the concentration exponent was determined to be 0.954. The extract of *Phoenix dactylifera* L. was found to be an inexpensive way to defend patients against viral infections [41].

4.2. Antifungal Activity

In 2012, it was found that methanolic, acetonic and aqueous extracts of the pits of *Phoenix dactylifera* L. retarded the growth of A. alternata, Trichoderma sp., A. flavus, Alternaria spp., F.oxysporum, F. solani and Fusarium sp. The *Phoenix dactylifera* L. pits also demonstrated an inhibitory activity of 38.5% against Fusarium sp. and 40.9% against A. alternata. High antifungal activity was demonstrated by the methanolic pit extracts followed by the methanolic leaves extracts, as well as the acetonic extract of the pits and the acetonic extract of the leaves [42]. In another study, it was found that dichloromethanalic extract of Phoenix *dactylifera* L. also exhibited antifungal activity against *Fusarium oxysporum* [43].

In 2015, Mehrdad Khatami and Shahram Pourseyedi formed the silver nanoparticles of Ajwa pits in an aqueous extract which showed high inhibition against *Klebsiella pneumonia* (PCI 602) and *Acinetobacter baumannii* [43].

4.3. Antibacterial Activity

The acetonic and methanolic extracts of the pits and the leaves of the three cultivars of *Phoenix dactylifera* L. demonstrated antibacterial activity against *B. subtilis, S. aureus, E. coli, P. aeruginosa, S. flexeneri and S. pyogenes*. Whereas, aqueous extracts had little or no effect on the selected bacterial species. Pit extracts of *Phoenix dactylifera* L. for all solvents showed better results than the leaves extracts. Antibacterial activity of the Barhee variety of *Phoenix dactylifera* L. against selected bacteria showed that the doxycycline and the methanolic extracts of the pits were potent against all bacterial species except *E. faecalis.* [16]

The antibacterial activity of the methanolic extract of the pits of the Sukri variety of *Phoenix dactylifera* L. showed the largest inhibition zone of 32mm against *S. pyogenes*, whereas the largest

inhibition zone of 29.3mm was observed for the methanolic extract of the pits of the Rothna variety of *Phoenix dactylifera* L. All three extracts of the leaves and pits of *Phoenix dactylifera* L. were found to be ineffective against E. faecalis, whereas *S. pyogenes* was found to be the most sensitive against all the three extracts. Minimum inhibitory concentration (MIC) towards *S. pyogenes* was reported to be 1.15 mg/ml for the methanolic pits extract, 1.33 mg/ml for the methanolic leaves extract, 1.4 mg/ml for the acetonic pit extract and 1.6 mg/ml for the acetonic leaves extract [16].

It has been demonstrated that the pits of *Phoenix dactylifera* L. serve as effective antibiotics. This is because of the variability in the bacterial resistance as the pits of *Phoenix dactylifera* L. show antibacterial activity against *K. pneumonia* and *E. coli* [44].

4.3.1. Mechanism of action of antimicrobial agents Ajwa shows resistance against different bacterial strains due to changes in the membrane permeability of cells and creates hindrance in the entrance of the enzymes due to changes in chemical constituents [44]. The phenolic compounds in Ajwa are responsible for its antimicrobial activity. These compounds bind with the cell wall and inhibit the growth of the microorganisms. A special class of phenols called polyphenols (such as tannins) play an important role in the precipitation of proteins and the inhibition of enzymes in the microorganisms [45].

4.4. Antioxidant Activity

Phoenix dactylifera L. fruits are widely used by the people of the Arabian countries. In *Phoenix dactylefera* L. phenolic compounds, carotenoids, vitamins and melatonin show antioxidant effectiveness [46]. Lemine and colleagues in 2014 investigated the antioxidant activity of the methanolic extracts of the fruit of six cultivars of *Phoenix dactylifera* L. from Mauritania. The fruit was collected at two ripening stages, that is, blah (khalal) and tamr. According to the results, the highest antioxidant activity was exhibited by the cultivars of *Phoenix dactylifera* at the blah (khalal) stage with an average of 107.5 µmol TEAC/100g DM. At the tamr ripening stage, the cultivars of *Phoenix dactylifera* L. showed antioxidant activity with an average of 91.2 µmol TEAC/100g DM, ranging between 75.6 and 99.3 µmol TEAC/100g DM. *Phoenix dactylifera* L. from Mauritania could serve as a source of natural antioxidants [47]. Allaith in 2008 investigated sixteen cultivars of *Phoenix dactylifera* L. to check their antioxidant activity at different ripening stages. The highest antioxidant activity was possessed by biser (kimri) with an average FRAP value of 5.71 ± 4.31 mmol/100g FW, whereas the lowest antioxidant activity was possessed by tamr with an average value of 0.941 ± 0.21mmol/100g FW [48].

A study evaluated the hepatic hematological parameters, hormone testosterone, and antioxidant in the testis in male rats. The results showed that the pits highly increased the concentration of hemoglobin and decreased the concentration of proteins. Testosterone level, antioxidant status in the testis and the biochemical values of the serum also improved [49].

4.5. Antidiarheal Activity

Phoenix dactylifera L. was found to be helpful in the treatment of diarrhea. The aqueous extract of the plant, when compared to normal saline, was found to

reduce the mean number of defecation. The activity of *Phoenix dactylifera* L. against diarrhea also depends upon the mode of dose delivery [50].

4.6. Hematopoietic Activity

Phoenix dactylifera L. also possesses hematopoietic activity. The study conducted by Onuh and colleagues on 50 rats showed that methanolic and aqueous extracts of *Phoenix dactylifera* L. increase the count of PCV, hemoglobin, platelets, reticulocytes and RBC and there is a considerable increase as compared to the control group. However, the number of WBC and the amount of bone marrow did not significantly differ from the control group. This shows that *Phoenix dactylifera* L. also shows hematopoietic activity in rats [15].

4.7. Cerebroprotective and Neuro-protective Activity

The extracts of *Phoenix dactylifera* L. were found to be ineffective against *E. faecalis* pits, which showed cerebroprotective activity against rats having cerebral ischemia. The seed extract of the plant reduces the neural damage in rats. The oxidative stress of the brain is also reduced due to the pits' extracts and the antioxidant enzymes are restored [18].

A research conducted by Pujari and colleagues on mice having ischemia induced by bilateral common carotid artery occlusion showed that *Phoenix dactylifera* L. causes neuroprotective activity due to the presence of antioxidant enzymes [51].

4.8. Antihypertensive Activity

According to the study conducted by Tahraoui, *Phoenix dactylifera* L. is used for the treatment of hypertension in east Morocco [52].

4.9. Antidiabetic Activity

A study conducted on *Phoenix dactylifera* L. showed that this plant is also used for the treatment of diabetes and diabetic retinopathy [53]. As *Phoenix dactylifera* L. causes antioxidant activity, it can play a role in antidiabetic activity as well. The plant does this by searching for the free radicals [54].

Phoenix dactylifera L. was found to reduce blood glucose level in diabetic rats. The use of the seeds and fruits of Ajwa also restores the kidney and liver functioning [55].

4.10. Anti-inflammatory Activity

Inflammation is a defense mechanism against allergens, infection, toxic chemicals, and burns. [56]. A study conducted in 2007 demonstrated that the phytochemicals present in *Phoenix dactylifera* L. such as phenolics and flavanoids act as anti-inflammatory agents [57].

5. Phytochemicals in *Phoenix dactylifera* L. Pits

Phytochemicals are bioactive compounds produced by plants. Phytochemicals play an important role in the growth of the plant and provide a defense to the plant against certain microorganisms [58]. The phytochemical analysis of the methanolic extracts of *Phoenix dactylifera* L. pits showed the presence of tannins, alkaloids, flavonoids, phenols and terpenoids. Phytochemicals in the ethanolic extracts of pits were terpenoids, saponins, glycosides and phenols [59]. The petroleum ether extract consists of diterapenes. The ethyl acetate extract consists of alkaloids,

flavonoids, saponins, glycosides, terpenoids, diterapenes, phenols and tannins [60].

5.1. Flavonoids

Phoenix dactylifera L. contains higher amounts of flavonoids including luteolin, rutin, quercetin, isoquercetin and apigenin. Flavonoids are essential phenolic compounds structurally derived from flavones. Flavonoids possess antimicrobial, antioxidant, anti-allergic, and anti-inflammatory activities [61]. |They also have a significant role in terminating carcinogens and mutagens by inducing phase II enzymes [62]. They possess anti-microbial properties by complexing the soluble and extracellular proteins and also by complexing the cell wall of the microorganisms [63]. Flavonoids function to enhance cardiac activity, reduce cholesterol levels and decrease anginas. They are also used to treat hypertension and cardiac insufficiency by blocking the kappa-B (necrosis factor) activation [64]. The flavonoids that do not possess the -OH group are more effective against microorganisms than those having the -OH group [65, 66]. Quercetin acts as a chain disintegrating antioxidant and helps in reducing the oxidative stress by inhibiting the oxidation of lipoproteins through metal ions [67]. Rutin is involved in the preservation of food. The previous studies showed that the antifungal activity of rutin can be increased by the introduction of a substitute group that can modify the physiochemical properties [68]. Luteolin was found to prevent angiogenesis. It induces apoptosis and inhibits tumour growth [69]. Apigenin is involved in the prevention of HIV – 1 activation [70].

5.2. Alkaloids

An alkaloid is a physiologically active compound derived from plants. Pteropopine and isopteropidine are alkaloids that demonstrate antimicrobial activity and promote WBCs to discard cell debris [71]. Some alkaloids such as piperine, berberine and harmane intercalate the cell wall and DNA [72]. Serotonin, acetylcholine and dopamine stimulate neurotransmitters and affect CNS at synapses. Alkaloids serve to treat neuralgia, motion sickness, hypertension, and rheumatism and also act as narcotics [73]. They also demonstrate analgesic properties and attenuate pain in the case of septic wounds, abdominal pains and headaches [69]. Alkaloids are useful in treating the Hodgkin's disease and in leukaemia chemotherapy [70]. Protein microtubules involved in the formation of mitotic spindle during cell division are terminated and depolymerized by alkaloids, thus they prevent tumor cells from dividing and hence are involved in the reduction of cancer [74].

5.3. Tannins

Tannins are plant phenolics that have therapeutic properties. They work as antioxidants by reducing the oxidative stress and also prevent degenerative diseases. Through apoptosis they are involved in tumor growth inhibition [75]. Tannins demonstrate antimicrobial activity by deactivating microbial adhesion. These nucleophilic proteins build complexes with cell membrane / wall adhesion proteins through covalent or hydrogen bonds [69]. Tannins are involved in the inactivation of transport proteins and microbial enzymes by reacting with R-SH (sulfhydryl group) proteins [72]. They are involved in microbial growth through the accumulation of metal ions that act as the co-factors of enzymes [69]. Tannins also possess anti-septic, anti-diarrhoeal, anti-fungal and anti-irritant properties and are

used in the healing of wounds and for the improvement of vascular health [76].

5.4. Saponins

Saponins are phytochemicals that have soap-like properties. They are steroids which demonstrate anti-viral, anti-bacterial and anti-fungal activities as well as hypoglycemic and hypo-cholesterolaemic effects [77]. The hypoglycemic effect is due to the inhibition of glucose' transport across the small intestine's brush like border cells and also due to the activation of pancreatic β cells [78]. Micells formed by saponins are involved in lowering the blood cholesterol level. They act as a reserve in elevating the production of antibodies and in activating cell mediated immune response [79]. Saponins were found to be effective in reducing cancer and are important for both hormone and non-hormone dependent cancer [80]. Radix notoginseng is a saponin that reduces the oxygen consumption by heart muscles, elevates coronary artery blood flow and avoids platelet increase [81].

5.5. Terpenoids

Terpenoids are isoprene derivatives. They are synthesized from isopentenyl pyrophosphate and dimethylallyl pyrophosphate by enzyme terpene synthase [82]. They possess anti-protozoan, anti-bacterial, anti-viral, anti-fungal and anti-allergic properties [69]. Terpenoids serve as inhibitors in medicines. They inhibit the NF-kB system in the cytoplasm. NF-kB is a sensor that reacts to external and internal signals including hypoxia, genotoxic stress and immune system disturbances. Aucubin (a monoterpenoid) and linalool have anti-tumor characteristics and play a vital role in providing the protection against hepatotoxicity. They also inhibit the metastasis and the proliferation of the mammalian and pancreatic tumors [83]. Terpenoids work by disrupting the hascell membrane. They cross the cell wall / membrane and penetrate into the cell where they interact with the intracellular targets of the cell necessary for any anti-bacterial activity [70].

5.6. Phenolic Acids

Caffeic acid, m-coumeric acid, p-coumeric acid, chlorogenic acid, gallic acid, syringic acid and ferulic acid were found to be the essential phenols in the pits of *Phoenix dactylifera* L. [84]. Phenolic acids have anti-cancer characteristics. Syringic acid works by inhibiting proteasome (an enzyme complex that degrades proteins taking part in the cell development). It thus retards the proliferation of the cancer cells [85]. Ferulic acid is useful in the treatment of cancer, diabetes, cardiovascular, neurodegenerative and inflammatory diseases. Phenolic acids protect against PUFA and the toxicity induced by alcohol. They also help to overcome the harmful effects of alcohol and PUFA. Phenolic acids are involved in enhancing the defense system by overcoming the damage generated by nicotine consumption and they also defend the cell against oxidative damage [86].

5.7. Glycosides

Glycosides obtained from *Phoenix dactylifera* L. pits demonstrate pharmacological activities. They are used to treat heart failure by inhibiting Na+/ K+ ATPase pump, causing a decrease in intracellular K+ and an increase in intracellular Ca2+ and Na+. This strengthens the heart muscles against heart failure [86]. Digitalis supresses the growth of the androgen independent and androgen dependent

prostate cancer by elevating the level of Ca2+ in cells and by initiating apoptosis [87]. Glycosides are effective against fibrillation and are therefore used as diuretics and emetics [70].

6. Therapeutic Options

Phoenix dactylifera L. date pits have medicinal importance due to which they are extensively consumed all over the world.

The use of the pits of *Phoenix dactylifera* L. causes a decrease in the side effects of methylprednisolon. The administration of Ajwa pits during treatment with methylprednisolon causes an increase in noradrenalin, GABA and dopamine. The pits also increase the testosterone serum level and thus are involved in the treatment of male infertility as well as in reducing the side effects of methylprednisolone [88].

6.1. Cancer

Zang and co-workers investigated the effectiveness of *Phoenix dactylifera* L. syrup and found it very effective against several diseases, especially cancer. They reported that polyphenolic compounds present in the date syrup minimize angiogenic responses, such as tube formation. They also demonstrated the role of VEGF (vascular endothelial growth factor receptor) and prostaglandin enzyme cyclooxygenase (COX-2) in angiogenic responses which play an important role in causing cancer. They reported that date syrup reduces inflammation and also suppresses angiogenesis at many stages. This is due to the fact the polyphenolic compounds of the date syrup reduce the expression of VEGF and COX-2 prompted by tumor nacrosis factor-alpha at protein and gene level [89].

Yasin and co-workers studied the therapeutic effects of Ajwa. They explained that it has the ability to inhibit cell damage and helps in the treatment of cancer [90].

F. Khan and co-workers investigated the effectiveness of Ajwa date (*Phoenix dactylifera L*) extract on the breast adenocarcinoma cells (MCF7) and found it to be very effective. They reported that the methanolic extract of Ajwa date induces the activation of both instrinsic and extrinsic pathways of human breast adenocarcinoma MCF7 cells which inhibit the cells by arresting cell cycle and apoptosis. They observed mild effects of methanolic extract on MCF7 cells. If the methanolic extract of Ajwa date is purified and the individual components of the methanolic extract are evaluated to find their anti-cancer properties, it would be a huge achievement in the clinical field [91].

6.2. Hyperlipidemia

Hyperlipidemia or obesity is a condition in which the accumulation of surplus body fat causes adverse health effects. Obesity is a known contributor of many other diseases including myocardial infarction, Type 2 diabetes, and hypertension. The phytochemical analysis of *Phoenix dactylifera* L. by Vembu and colleagues in 2012 showed the involvement of fixed oils and sterols in lowering the lipid concentration of the body. Sterols in *Phoenix dactylifera* L. decrease the cholesterol absorption of the body and increase the excretion of steroids, thus lower the lipid content of the body. Flavonoids in *Phoenix dactylifer* L. may also elevate LCAT activity which incorporates free cholesterol in high-density lipids and thus increases its concentration. High-density lipids are then transferred back into low density lipids and very low-

density lipids. Eventually, they are reabsorbed by the liver cells. An elevated concentration of the high-density lipids is affiliated with a decrease in the coronary artery disease [92].

6.3. Diabetes mellitus

A large number of people around the globe suffer from diabetes mellitus which increases the death rate. In diabetes, the blood glucose level increases and the pancreas do not produce enough insulin to control /it. In *Phoenix dactylifera* L., flavanoids, saponins, steroids and phenols are responsible for antidiabetic activity. Phenolic compounds reduce the efficacy of α-glucosidase enzymes that reduce glucose absorption in the small intestine and kidneys. Antioxidant agents in this plant remove free radicals that also decrease the blood glucose level [93].

6.4. Treatment of Hematotoxicity

The concentration of hematocrits (WBC, RBC, hemoglobin, monocytes and lymphocytes) is reduced due to the ingestion of lead, whereas the neutrophil count is increased. A study was conducted in which 20 out of 40 rats were induced by lead acetate. The treatment of the rats with *Phoenix dactylifera* L. showed that it reversed all the adverse effects caused by lead ingestion. The study clearly demonstrated that *Phoenix dactylifera* L. is good for the health of blood and can be used in the treatment of hematotoxicity induced by lead [94].

6.5. Nephrotoxicity

Nephrotoxicity occurs commonly due to the side effects of antibiotics. Antibiotics generate mycotoxins such as ochratoxin which affect the kidneys, leading to kidney failure [95].

Qarawi observed that gentamicin nephrotoxicity is a source of the high content of urea and plasma creatinine in the body. So, to inhibit its effect they used the extract of Ajwa which showed a significant role in reducing gentamycin nephrotoxicity [96].

6.6. Gastroprotective Activity

In a study conducted in 2005, Qarawi found that the ethanolic and aqueous extracts of the pits and fruits of *Phoenix dactylifera* L. are used for the treatment of ulcers induced by ethanol in rats. The extracts of the pits and fruits of the Ajwa plant normalize the levels of gastrin and histamine raised due to the ulcers [97].

In another study, Qarawi found that the ingestion of ethanolic and aqueous extracts of the pits and fruits of *Phoenix dactylifera* L. increases the process of gastric emptying [98].

7. Conclusion

This review article discussed the nutritional significance of *Phoenix dactylifera* L. and the utilization of the Ajwa in the Arab countries due to its richness in vitamins, minerals, dietary fibers and sugars. The phytochemical analysis of the Ajwa showed the presence of phenols, carotenoids, sterols, and flavonoids which act as antimicrobial agents. Due to its nutritional and pharmacological significance, it is consumed all over the world and is used in the treatment of many diseases. The absolute properties of the individual components of *Phoenix dactylifera* L. are still unknown against certain diseases. Therefore, further research is required on this plant. As antimicrobial resistance is increasing day by day, there is a need to redeem synthetic drugs prepared from *Phoenix dactylifera* L.

Conflict of Interest: There is no conflict of interest.

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