PHYTOCHEMICALS AND THERAPEUTIC USE OF DATE PALM (PHOENIX DACTYLIFERA L) – A NARRATIVE REVIEW

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ABSTRACT

This article provides a summary of phytochemical composition, nutritional value and health benefits of Pheonix Dactylifera L, commonly known as dates. Additionally, the article explores the potential of date fruit to be utilized as a food medicine in the treatment of various human diseases. We conducted a comprehensive review of the existing literature on the biological functions of date palm and its potential health benefits, utilizing databases literature search engines including PubMed, Scopus, Science Direct and google scholar. Regular consumption of date palm fruits (DPFs) may lower the risk of developing various chronic diseases due to its antioxidant, antidiabetic, antibacterial, anticancer and anti-mutagenic properties. Additionally, the pollen of date palm trees contains high levels of protein, fat, and carbohydrates, making it an excellent natural supplement with substantial nutritional value and energy-boosting properties. Date palm components have demonstrated potent antioxidant effects and have played a crucial role in both male and female reproductive systems, promoting fertility in both genders. Date palm pollen (DPP) has shown gonadal-stimulating potency in females and can significantly increase testosterone levels in individuals with Oligoasthenozoospermia and follicle-stimulating hormone (FSH) levels in patients with Azoospermia, making it as a potential treatment for reproductive health. According to the literature, date fruit is a highly nutritious fruit compared to other commonly consumed fruits. In conclusion dates have been shown to have a significant impact on various female reproductive parameters such as oogenesis, oocyte development, hormone modulation, and pregnancy strength.

Key Words: Date palm pollen, infertility, Phytochemicals, Phoenyx dactylifera, Azoospermia, Oligoasthenozoospermia

INTRODUCTION

In many societies, infertility is viewed negatively and considered a form of illness when there is a disruption in the reproductive system. World Health Organization (WHO) defines infertility as the inability of a couple to become pregnant after 12 months of sexual activity, without using any contraception (1). Approximately 15% of couples in their reproductive years have been reported to be infertile after one year of consistent unprotected sexual activity, with around 10% of cases with unknown causes, globally. In specific regions of the world such as Sub-Saharan Africa, Central Asia, Eastern and Central Europe, and South Asia, the rates of infertility are higher and can even surpass 30% (2, 3). The ranges of cases have involved regional variations around the world. Infertility involves mental health issues affecting both male and females equally(4). According to re-

search, males account for 40% of infertility cases, women for 40%, and in 20 % of cases both partners show inability to conceive (5). In Pakistan 22% of cases are reported to have infertility, out of which 4% are reportedly have secondary infertility, due to other causes. Women undergo psychological trauma as a result of social norms that associate infertility with failure on a personal, emotional, and social level (6).

GLOBAL BURDEN OF INFERTILITY

Given the rising pattern of infertility around the world, it is becoming a significant global concern in both high and low-income countries. The United States' Centers for Disease Control and Prevention (CDC) asserts that infertility has significant public health implications, extending beyond just a decline in quality of life. This includes negative consequences such as economic burden, social stigma, psychological distress, and marital problems (7). Infertility affects a significant portion of couples of reproductive age worldwide, with estimates ranging from 10-25% (48 to 180 million couples). Furthermore, infertility has shown negative impact on physical as well as mental health. This is also associated with financial difficulties, social stigma, increased risk of domestic violence, and marital instability. Both men and women are equally susceptible to infertility, but it is typically women who experience the social ramifications, particularly in societies where a woman's worth is linked to her ability to conceive and have children (8).

METHODOLOGY

The purpose of this study was to collect articles published between 2010 and 2022 that explore the relationship between Phoenix dactylifera, (date palm), and male and female infertility, as well as its role in various biological activities. To achieve this goal, several databases such as PubMed, Scopus, Web of Knowledge, Clinical Keys, Embase, Google Scholar Search Engine, Scientific Information Database (SID), and IRCT (Iranian Registry of Clinical Trials) were searched using relevant keywords. A manual search was also conducted in pertinent journal databases to ensure that no relevant articles were missed. Additionally, all references cited in review papers were examined to identify any recent relevant research. By utilizing this comprehensive search strategy, a broad range of articles related to date palm and infertility were collected and analyzed. The findings of this study will contribute to a better understanding of the potential benefits of date palm in the context of reproductive health.

THE PREVALENCE OF INFERTILITY

Infertility rate varies in gender and also across different countries, with data collected from demographic surveys not distinguishing between voluntary and involuntary infertility. In developed countries, the percentage of infertility ranges from approximately 10-18% in men and 5-10% in women, with higher rates in some countries like Finland, Switzerland, Sweden, and Canada. However, differences between countries may be attributable to the varying rates of voluntary infertility. Low-middle-income countries including Pakistan reported to have relatively higher rates of infertility, associated with minimal understanding of the condition, as well as limited access to healthcare system (6). Reported rate of infertility in Pakistan is 22%, with 18% primary infertility and secondary infertility accounting for 4%. The epidemiology of secondary infertility is not well understood (9). There is limited information available regarding the occurrence and potential causes of secondary infertility in Pakistan. However, research indicates that unsafe practices are commonly used by healthcare providers and women during childbirth and the postpartum period, leading to pelvic inflammatory disease (PID), tubal blockages, and ultimately resulting in infertility (10). This raises the rate of infertility among women.

CAUSES OF INFERTILITY

Various factors contribute to infertility and can vary depending on the region of the world. However, common determinants across most areas include lifestyle factors, epidemic infections, sexually transmitted diseases, and nutritional deficiencies (11). Changes in sexual behavior and the elimination of restrictions, as well as lifestyle factors such as smoking and alcohol consumption, can affect sperm quality. Historically, research on infertility has focused on various factors, including issues related to ovulation (accounting for 20% of infertility cases), utero-tubal peritoneal factors (accounting for 30% of cases), sperm migration issues (accounting for 10% of cases), and male factor infertility (accounting for 30% of cases) (12). 15% of male and 10% of female infertile may have genetic abnormalities, such as chromosome aberrations and single gene mutations (13). There are three primary pathological factors that can affect a woman's fertility: endometriosis, congenital or acquired uterine abnormalities, and post-infectious tubal damage. Congenital issues, such as a septate uterus, and acquired conditions like myomas and synechiae can lead to infertility, miscarriage, and other obstetric complications. Additionally, medical conditions such as thyroid disorders and diabetes can also contribute to fertility issues (14). The most common cause of tubal injury is pelvic inflammatory disease (15). Unhealthy lifestyle choices, including poor eating habits, stress, drinking alcohol, smoking, and obesity, can have negative impacts on a person's overall health and reproductive ability. These factors have been found to significantly decrease the likelihood of pregnancy in women. The WHO distinguishes between primary infertility, which refers to a woman's inability to conceive, and secondary infertility, which occurs when a woman has previously had at least one successful pregnancy in her marriage but is unable to conceive again (16). Primary infertility accounts for 57.5% of instances compared to secondary infertility's 42.5% (17).

Figure: 1 Risk factors of infertility.

DATE PALM

Date palm tree, botanically known as Phoenyx dactylifera is a member of the family Arecaceae (palms), subfamily Coryphoideae and order Arecales, monocotyledonous. It is perennial tree (18). The plant is of medium size and can grow either individually or in clusters with multiple branches stemming from a single root system. Its flower is the primary source of economic value. The plant typically reaches a height of 15 to 25 meters, and its leaves are pinnate, measuring around 4 to 6 meters in length and featuring approximately 150 leaflets with spines on the petiole. The leaflets themselves are 2 centimeters wide and 30 centimeters long. The plant's full crown spans can vary from 6 to 10 meters (19). The date palm, one of the oldest fruit crops in the world, is primarily cultivated for its highly nutritious fruits, which serve as a staple food in many countries, particularly in the Gulf region. In Pakistan, the date palm is the third most important fruit crop, following citrus and mango. It

is cultivated on approximately 90,000 acres of land across the country's four provinces, yielding an annual production of roughly 600,000 metric tons (20).

CHEMICAL COMPONENTS OF DATE PALM

Dates contain varying amounts of phytochemicals, including minerals, flavonoids, phenolics, carotenoids, and vitamins, making them a valuable source of bioactive and functional compounds with potential medicinal benefits. These compounds provide the body with essential energy and may also act as effective therapeutic agents against a range of diseases (21). Depending on size and species, date palm fruit has 20–70 calories and is abundant in carbohydrates (70%) with sugars making up the majority of those calories (88% in certain types) (19). Date fruits are a significant source of vitamins and mineral salts. Among the ten minerals found in dates, the most abundant are selenium, copper, potassium, and magnesium. A 100-gram serving of dates can supply 15% of daily requirements of these minerals. Dates have been reported to be a source of both vitamins B-complex and vitamin C which are essential vitamins for human body for different functions. Additionally, they are rich in dietary fiber, providing approximately 8.0 grams of fiber per 100 grams of dates. The majority of this fiber is insoluble (22).

Dates also contain tocopherols, carotenoids, and polyphenols, including flavonoids and tannins, which possess various biological properties, such as antibacterial and antioxidant activities. Phenolic compounds found in dates have been shown to reduce oxidative stress associated with chronic diseases, including heart disease, neurodegenerative disorders, cancers, and diabetes.

Date palm pits are a rich source of non-reducing sugar, with a composition of 3.82% glucose and 1.68% of fructose. In general, 100g of dates provide 5.1g of proteins, 9.0g of fat, and 73.1g of fiber. The fat content of fresh dates is 0.14 g per 100 g, while dried dates contain 0.38 g/100 g. Additionally, date palm pits are rich in phenolic compounds, with a content of 3942 mg/100g (23). The values of these nutrients may vary according to the differences in cultivation, evaporation conditions, and assessment test methods applied (24).

The carotenoid content of dates is reported to 913 g/100 g and 973 g/100 g in fresh and dry dates respectively. The total carotenoid content varies in yellow and red varieties of dates. While phenol contents differ between fresh (i.e. 193.7 mg/100 g) and dried dates (i.e. 239.5 mg/100 g). Different types of dried dates may have varying in amounts of phenolic compounds (25).

Table 2 The nutritional composition of different parts of date palm.

Date Palm Parts	Nutritional Composition	References
Date leaves	On a dry weight basis, the nutritional composition of this substance includes crude protein (4.8%), crude fiber (31.9%), and ash (12.9%), with an average calcium content of about 7 g/kg and phosphorus content of about 1 g/kg.	(26)
Date seed	The moisture, protein, fat, ash, and dietary fiber content of this substance ranges from 3.1-7.1%, 2.3-6.4%, 5.0-13.2%, 0.9-1.8%, and 22.5-80.2%, respectively. It also contains phenolics (3102-443(mg gallic acid equivalents/100 g), antioxidants, and dietary fiber (78-80 g/100 g).	(27)
Palm pollen grains	The substance has a moisture content of 28.80%, ash content of 4.57%, crude fiber content of 1.37%, crude fat content of 20.74%, protein content of 31.11%, and carbohydrate content of 13.41%.	(27)

The extensive use of the date palm in botany and medicine highlights its significance in promoting human health. Clinical studies have demonstrated various benefits associated with the date palm (28). The leaves, fruits, pits, and pollen of the plant have been used to prevent and treat diverse medical conditions (29). These components serve as the primary source of easily accessible bioactive compounds that are responsible for their biological activities. Historically, the date palm has been employed in addressing issues with the reproductive and endocrine systems. Figure 2 illustrates the impact of the date palm and its constituents on male and female reproductive systems. The potent antioxidant properties of date fruits are vital in enhancing fertility in both men and women (30).

Figure: 2 Effects of date palm on male and female reproductive system.

Organisms typically do not require bioactive chemicals for their daily activities as they are naturally generated as secondary metabolites that modulate metabolic processes (31). Date palm fruits contain two types of bioactive molecules: nutritive and non-nutritive bioactive chemicals (32-34). Date Palm fruits contain quickly absorbed carbohydrates such as glucose and fructose, which have no adverse effects on triglycerides and blood sugar levels when consumed by healthy individuals (35). Dates also contain Non Starch Polysaccharides (NSPs) that provide approximately one-fourth of the daily NSP requirement in nine dates per day (36, 37). NSPs play a crucial role in improving gastrointestinal function and regulating digestion, making dates palm fruits a natural laxative that promotes regular bowel movements (32, 38, 39).

BIOLOGICAL POTENTIAL OF DATEPLAM

Date palm fruit is well known for its beneficial nutritional properties for human consumption and health. Cultivars with a variety of bioactive ingredients may significantly reduce the risk of oxidation of vital biological macromolecules (40). Phenolic chemicals have been associated with a variety of biological processes. Thus, research on humans has clearly shown that polyphenols have medicinal potential. The latter has an antimicrobial and antioxidant effect and prevents lipid peroxidation, anti-carcinogenic and platelet aggregation (41).

Antibacterial and Antifungal activity of date palm

Many plants commonly found in our diets have shown potential to prevent and/or treat various infectious diseases and various health conditions. In vitro study by Al-Alawi and colleagues have demonstrated that date palm fruits have antibacterial, antifungal, antioxidant, and anti-mitotic activities (42).

Various components of Phoenix dactylifera, including dried leaves, fruits, seeds, and tree bark, were extracted using water, methanol, and acetone, and their antibacterial efficacy against Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, and Pseudomonas aeruginosa was evaluated. All

parts of the tree showed some degree of antimicrobial activity, however, the fruit extract showed the highest antibiotic potential as compared to the other parts of the tree (43). Some of organic extracts and phenolic substances of date seeds and pollen, are identified in tissue of date seeds, have shown considerable antibacterial properties against both gram positive and gram negative bacteria (44).
Date extract is effective against Candidiasis infections, which is caused by Candida albicans, a significant and well-known Candida yeast species that results in fungal infections in the gynecological and digestive mucosa. The research has shown that the flavonoids in date extracts have an antifungal impact on Candida albicans in vitro, leading to its deformation, weakness, and partial cell collapse (45).

Antioxidant activity of date palm

Date palm fruits are reported to have the highest levels of antioxidants, as compared to strawberries, kiwis, guava, white pomegranates, and purple mulberries (46). Though, the antioxidant capacity of date palm fruits is influenced by a number of factors such as the variety of dates, ripeness, and processing (47, 48). Kriaa et al. examined the phenolic content and antioxidant capacity of three different date palm leaf varieties and found that all extracts exhibited antioxidant and radical-scavenging activity, albeit to varying degrees (49). Chaira et al. attributed the high antiradical activity of the Tunisian Korkobbi variety to its high flavonoid content (50). Moreover, the overall antioxidant activity of dates was observed to decrease after sun drying and storing, which may be due to oxidation or the breakdown of the antioxidants such as tannins become insoluble after drying (51).

Anti-cancer and Anti-mitotic activity of Date palm

Due to their high reactivity, free radicals contribute to the activation of cancer-causing substances by harming live tissue through cellular oxidation processes (33). Furthermore, it has been found that the anticancer effects of date palm fruits components are correlated with the presence of β–glucans (52). Date palm fruits components also have anti-mutagenic qualities because they inhibit mutagenicity. The presence of bioactive chemicals, including anthocyanin, phenolic acids, selenium, and the beta-carotene present in date palm fruits is what constitutes this type of activity (53).

Antidiabetic Significance of Date Palm.

Although date palm fruits are rich in monosaccharides (i.e. glucose and fructose), therefore ideally diabetic patients should limit or avoid their consumption. Although there is no strong evidence available showing link of poor glycemic control of development of diabetes (36). The role of date palm fruits components in diabetes management is still uncertain. Nonetheless, a study on alternative sweeteners reported that granulated date sugar has potential antidiabetic properties, making it a natural replacement sweetener for diabetic patients (54). This antidiabetic action may be due to the presence of phenolic compounds that inhibit α-glucosidase and α-amylase activity, which suppresses carbohydrate digestion and reduces the amount of glucose absorbed from the small intestine.

ROLE OF DATE PALM IN FERTILITY

Date palm pollen, which has a high amount of protein, fat, and carbohydrates, stimulates the male reproductive cells. The amino acids glycine glutamine, leucine, tyrosine, phenylalanine, aspartic acid, threonine, arginine, histidine, lysine, proline, methionine, isoleucine, serine, valine, and alanine are the main components of date pollen. Moreover, pollen is an abundant supply of vital vitamins, including vitamin A, vitamins C, E and vitamin B (thiamine, riboflavin, biotin, and folic acid). As a result, pollen should be emphasized as an appropriate natural supplement that provides energy and has significant nutritional value (55). Traditionally, it was thought to be an fertility enhancer in

males thus considered as natural male fertility supplement (30). The presence of estrogens hormone may be the cause of date palm pollen aphrodisiac effects. Date palm pollen has shown gonadal stimulating potency and reproductive promotion actions in women, demonstrating that its pharmacological effects are not just limited to males. Date palm pollen may also significantly increase testosterone levels in individuals with Oligoasthenozoospermia and follicle-stimulating hormone (FSH) levels in patients with azoospermia, as well as be used to treat sexual weakness and incapacity in the Arab world (56). Additionally, date seeds may increase testosterone levels, blood biochemical parameters, and testis antioxidant status (57). Many studies have been conducted to demonstrate the impact of date palm components on variables related to male fertility (58). The reports have shown that date seeds improve testosterone level, and also antioxidant status in testis thus improving male reproductive capacity (59) (Table 2).

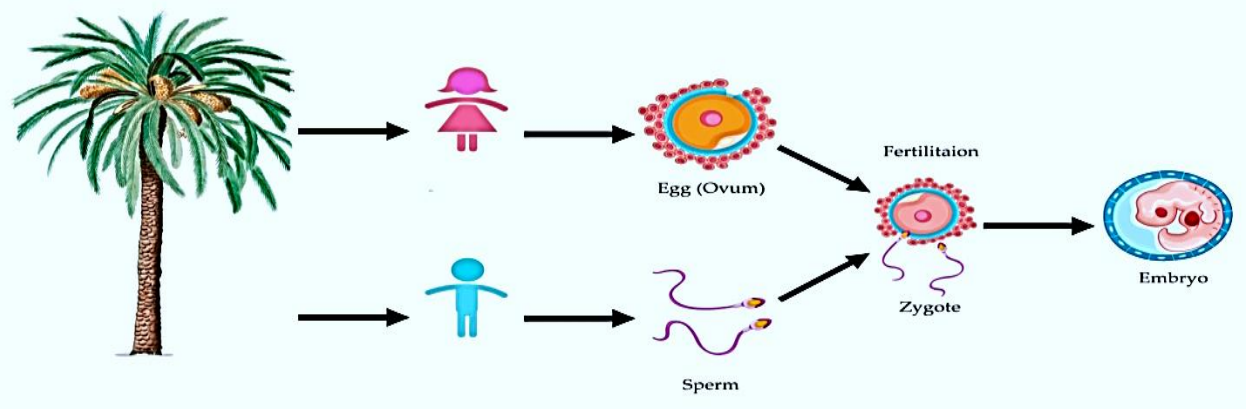

Figure: 3 A diagrams showing how the date palm affects sexual reproduction.

Earlier report has shown effect of DPP to increase concentrations of estradiol and testosterone resulting in an increased epididymis-body weight ratio (71). In another study, infertile patients were given capsules containing 500mg of dried date palm pollen twice daily for three months, which resulted in a significant increase in their sperm counts. This can be attributed to the presence of a gonadotropic active chemical in the DPP. The pollen also contains steroid precursors that may increase the synthesis of testosterone, thereby explaining the rise in testosterone levels (72). In addition, there is also evidence available which has suggested effects of DPP on sexual interactive parameters of male adult rats. The pollen was influencing weight of testicles and also testosterone production thus increasing serum testosterone levels. Additionally, Mehraban et al. conducted a study to determine how DPP extracts affect male rat reproductive parameters. DPP was administered in dosages of 120 and 240 mg/kg, and their results showed that DPP enhances fertility factors. (73). This suggests that DPP has potential to improve male fertility and sexual activities. However, most of the literature reported on animal models in particular rats and mice, limited literature available on human subjects.

CONCLUSIONS

Dates are a rich source of various nutrients, including phytochemicals, saponins, tannins, carotenoids, minerals, and vitamins, which have numerous biological functions in the body. Date palm fruits (DPFs) are found to have the highest antioxidant activity compared to other fruits, making them a potential dietary intervention for individuals with metabolic syndrome and related diseases such as diabetes, CHD, and stroke. Date palm has also been shown to have a positive impact on fertility by increasing testosterone and FSH levels in oligoasthenozoospermia patients and regulating

female reproductive parameters, such as oogenesis and pregnancy. Although most studies have been conducted on rats and mice, more research is required to establish the efficacy of date palm products in treating infertility in humans. This review highlights the phytochemical and pharmacological properties of DPF and its potential use in treating fertility disorders.

Table 2. The bioactive components of date palm and their mechanism.

Date and Date Parts	Active Components	Mechanism	References
Date fruit	Simple sugar	Source of energy for mother's during labor.	(60)
Date fruit	Glucose	Provide energy, strengthens uterine muscles, and nutritional supplement for cervical dilutions	(61)
Date fruit	Calcium	Helps in smooth muscle contraction of the uterus during labor	
Date fruit	Tannin	Helps in smooth muscle contractions of cervix. Tannin and Linoleic acid help in control of bleeding	(62)
Date fruit	Folic acid	Essential for cell division and genetic structure maintenance	(63)
Date fruit	Sugar, Vitamin B1, and Iron	Control uterus movements	(64)
Date fruit	Tannin and Linoleic acid	Control bleeding	(59)
Date fruit	Potuchin hormone	Help to reduce postpartum bleeding	(64)
Date Palm Pollens	Estrogen compounds	Animal model studies suggest effect of estrogen on mice reproductive system	(59)
Date Palm Pollens	Estrogenic compound: estradiol, estriol, and estrone	Gonadotrophic activity in male rats affecting reproductive system	(65)
Date Palm Pollens	Carbohydrates, Saponins and gallic tannins,	Improved male reproductive parameters in mouse models	(66)
Date Palm Pollens	Saponins	Stimulate testosterone production from testes	(67)
Date Palm Pollens	Estradiol components	Helps in spermatogenesis and male reproductive tissue regeneration	(68)
Date Palm Pollen grains	Phytochemicals: alkaloids, saponins, and flavonoids	Improve sexual behaviors in male rat by enhancing androgenic activity.	(69)
Date Palm Pollen grains extracts	Estrogenic materials	Improve male infertility by stimulating gonads	(70)

Conflict of Interest

Authors declare that there is no conflict of interest.

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