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The Anti-Cancer Arsenal of the Date Palm (*Phoenix dactylifera* L.): A Review of Bioactive Pathways Across Various Organs

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ABSTRACT

The utilization of natural plant compounds for medicinal applications plays a crucial role in cancer treatment. Cancer arises through various mechanisms, and the date palm (*Phoenix dactylifera*) is notable for its rich array of anticancer compounds found in different organs. This review evaluates the anticancer mechanisms of various organs of the date palm, emphasizing the contribution of their shared and unique compounds. This study, was extracted and reviewed all scientific books and articles related to the anticancer properties of date palm seeds, roots, hearts, leaves, inflorescences (spathe, flowers, and pollen), and fruits from online databases using specialized keywords from 1980 to 2025. The date palm minerals and bioactive compounds may not only aid in cancer prevention but also slow its progression, enhance the efficacy of chemotherapeutic agents, and improve overall treatment outcomes. The bioactive components derived from the date palm exhibit significant abilities to inhibit cancer cell proliferation and induce apoptosis. Although previous research has largely studied the fruit, there is a growing need to study the bioactive compounds of other organs. Findings confirm that underrepresented organs offer potent anticancer bioactivities. Concentrating on optimizing these potent compounds, particularly from less-studied parts, may yield promising results. Future investigations should focus on isolating compounds from various date palm organs, which exhibit varied phytochemical profiles across cultivars. This approach may aid in harnessing the therapeutic potential of the date palm against cancer.

Keywords: Anticancer, Arecaceae, Bioactive components, Minerals

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INTRODUCTION

Cancer is considered one of the most complex and incurable diseases of the past few centuries [1]. Recently, there has been a growing interest in utilizing natural medicinal plants as affordable alternatives for cancer treatment [2]. The date palm (*Phoenix dactylifera* L.) is a tropical plant from the Arecaceae Bercht. & J.Presl family, is commonly found in the countries of the Persian Gulf and tropical regions of the Northern Hemisphere [3]. The date palm exhibits a complex root system characterized by a network of fibrous roots that facilitate nutrient uptake and provide stability in sandy soils. Palms possess long, pinnate, or fan-shaped leaves that emerge from a central crown, playing a crucial role in photosynthesis and transpiration. The date palm seed is a hard, elongated structure encased in a fleshy mesocarp, functioning as a reproductive unit that can germinate under favorable conditions. The date palm produces intricate, branched inflorescences encased in a protective spathe, with pollen grains that are vital for the fertilization of flowers, leading to fruit development. The palm's apical meristem, or heart, is an essential growth point that gives rise to new leaves and plays a critical role in the overall health and vigor of the plant. The date fruit is a single, one-seeded berry, oblong, terete, with a terminal stigma, a fleshy pericarp, and a membranous endocarp present between the seed and the flesh [4, 5]. Iran is the world's fourth-largest producer of dates, and its date production is expected to increase by 20.55% by 2028 [6]. There are around 3000 different date palm cultivars in the world, each with varying contents of salts, flavonoids, phenolic compounds, and fatty acids in their organs [7]. Hypotheses have been proposed about date palm organs' anticancer and antitumor properties [8]. Over the last four decades, there has been extensive research on compounds found in dates. The cancer suppressor pathways reviewed in this article are shown in Figure 1. The present study was conducted to provide a comprehensive review of the anticancer potential of different organs of the date palm, focusing on the shared presence of minerals and bioactive constituents.

MATERIALS AND METHODS

This study systematically collected and reviewed scientific books and research articles addressing the anticancer properties of *P. dactylifera* organs, including seeds, roots, hearts, leaves, inflorescences (spathe, flowers, and pollen), and fruits. Relevant literature was retrieved from major online databases such as NCBI, SpringerLink, PubMed, and Google Scholar, covering the period from 1980 to 2025. The search employed specialized keyword combinations, including anticancer or antioxidant potential/effect + date palm [organ], minerals/bioactive compounds + date palm [organ], and anticancer pathways + bioactive compounds/minerals, to ensure the comprehensive inclusion of studies reporting the biological activities and chemical constituents of different date palm organs. In this article, an attempt has been made to discuss the most striking anticancer compounds in the section related to each organ, and if those compounds exist in other organs, they are listed in tables.

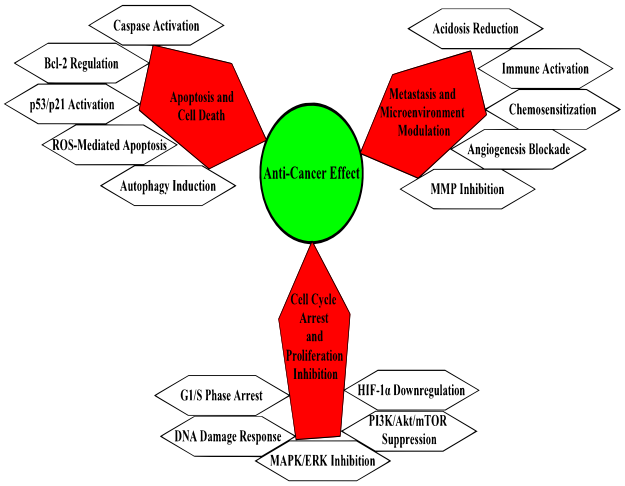

Fig. 1 Pathways of anticancer effects associated with date palm

Ethnobotanical, Nutritional, and Pharmacological Applications of Date Palm Organs

The date palm is repeatedly mentioned in the Holy Qur'an as a plant of blessing and sustenance, and its multiple organs have been integrated for centuries into traditional diets, medicine, and crafts [9]. Ethnobotanical records show that the roots are used in decoctions to relieve toothache, stomach upset, and intestinal disorders, while modern studies have detected phenolic acids and antioxidant compounds in root extracts that explain their antimicrobial and anti-inflammatory actions [10-12]. In comparative analyses, leaves contain higher total phenolic and flavonoid contents than roots, conferring stronger radical-scavenging and anti-inflammatory properties [12]. Traditionally, leaves are boiled for treating hypertension and fever, and the dried fronds are woven into mats, baskets, and handicrafts, illustrating both medicinal and practical utility [11]. The pollen, consumed to improve male infertility and sexual weakness, has shown a significant increase in serum testosterone and a reduction in luteinizing hormone in controlled human trials, confirming its long-standing role in reproductive medicine [13]. The seeds, rich in polyphenols and natural antioxidants, are ground into powders to aid liver disorders and diabetes, while experimental studies highlight their antimicrobial and cytoprotective effects that support nutraceutical development [14]. The heart of the palm, tender and nutrient-dense, is eaten raw in salads and incorporated into functional foods, such as low-fat camel-milk ice cream, where it enhances protein and fiber content and maintains microbial stability [15]. Comparative analyses demonstrated that the male flowers possess greater phenolic and flavonoid concentrations than the spathes, explaining their stronger antioxidant capacity and justifying their use in herbal tonics for fatigue, urinary infections, and general weakness [16]. Collectively, these findings validate the traditional and medicinal importance of each organ, confirming *P. dactylifera* as a culturally, nutritionally, and pharmacologically significant species.

Anticancer Properties of Date Seeds

The compounds in date palm seeds vary depending on the palm cultivar [17]. Date seeds contain varying amounts of carbohydrates, minerals, fats, water, phenolic compounds, flavonoid compounds, and antioxidants. Two of the main phenolic compounds in these seeds are vanillin and catechin [18]. Vanillin is associated with vanilloid receptors and has been found to induce changes in cancer cells. These changes include decreasing the levels of cyclin D1/A2/B, p38, and p65, while also increasing the levels of p53 and p21 [19]. This suggests that vanillin could be effective in treating cancer. Catechin inhibits the growth of cancer cells and can make them undergo apoptosis by increasing the activity of III, VIII, and IX caspases and p38 phosphorylation, and regulating the expression of cyclins A and B1 [20-22]. Flavonoids and Non-flavonoid phenolic compounds of different organs have been reviewed in Table 1 and Table 2, respectively. The Date seed oil contains four major phenolic compounds, including 2-hydroxycinnamic acid, vanillic acid, 4-hydroxybenzoic acid, and 4-hydroxycinnamic acid [23]. 2-Hydroxycinnamic acid can increase the expression of caspase III and annexin V, aiding in destroying the DNA of cancer cells [24]. Vanillic acid has the potential to suppress HIF-1α expression, halting cancer cells in the G1 phase [25, 26]. It may also have anticancer effects in obese cancer patients [27]. 4-Hydroxybenzoic acid inhibits HSP90α by aiding in its acetylation, reducing cancer cell resistance to Adriamycin by inhibiting the histone deacetylase 6 enzyme, thereby decreasing cancer cell survival [28-30]. 4-Hydroxycinnamic acid can also reduce cancer cell proliferation and has potential use as a vector in targeted cancer treatment, while also preventing oxidative stress [31, 32]. Types of tocopherols have been found in date seeds [33]. The most abundant type in these seeds is alpha-tocopherol, which is important in cancer prevention, probably with its antioxidant activity [34]. Oleic acid and Lauric acid are the main fatty acids found in date seed extract (Table 3) [35, 36]. Oleic acid can prevent cancer cell proliferation by stopping the cell cycle in the G1 phase, while lauric acid induces cancer cell apoptosis by increasing reactive oxygen levels [37, 38]. The bioactive compounds in date seed extract can remain active in the digestive system [39, 40]. This extract significantly reduces the proliferation of liver, colorectal, and breast cancer cells through apoptosis mechanisms [41]. Date seeds protect against oxidative stress by reducing enzymes like lactate dehydrogenase and creatine kinase [42]. In general, depending on the palm cultivar, date seeds may have a potential impact on cancer treatment [43, 44].

Table 1 Flavonoids and anti-cancer mechanisms in different organs of the date palm.

Compound	Anticancer mechanism	Found in	References
Catechin	↑ Caspases III/VIII/IX; Regulates cyclins A/B1 → Apoptosis	Fruit, Heart, Leaf, Pollen, Seed	[18, 20-22, 58, 69, 92, 96, 120]
Quercetin	Activates caspase III → Apoptosis/autophagy	Fruit, Heart, Leaf, Pollen	[58, 69, 92, 96, 98, 120, 122, 125]
Luteolin	Induces cell cycle arrest via DNA damage/redox regulation	Fruit, Leaf, Seed	[18, 94, 98, 120, 123, 125]
Apigenin	↓ PI3K, MMP; ↑ Bax, p53, p16	Fruit, Heart, Leaf, Pollen	[58, 69, 94, 96, 98, 120, 124, 125]
Naringenin	↓ ERK1/2/JNK phosphorylation; ↑ Caspase III, p53 → Apoptosis (melanoma)	Fruit, Heart, Pollen	[58, 62, 63, 94, 96, 98, 125]
Isorhamnetin	Inhibits PI3K/AKT signaling → Antitumor effects	Pollen, Seed	[69, 94, 95]
Hesperidin	Activates caspases; Deactivates kinases → Apoptosis	Pollen	[96-98]
Rutin	Induces cell cycle arrest; ↓ DNA damage; ↑ Caspases, p53	Fruit, Heart, Leaf, Pollen	[58, 69, 92, 94, 96, 98, 125, 127]

Symbol Key: ↑ = Increase/Activation; ↓ = Decrease/Inhibition; → = Leads to.

Table 2 Non-flavonoid phenolic compounds and anti-cancer mechanisms in different organs of the date palm.

Compound	Anticancer mechanism	Found in	References
Vanillin	↓ Cyclin D1/A2/B, p38, p65; ↑ p53, p21	Heart, Seed	[18, 58, 69, 92, 96, 120]
2-Hydroxycinnamic acid	↑ Caspase III, Annexin V → DNA damage	Fruit, Pollen, Seed	[23, 24, 96, 120]
4-Hydroxybenzoic acid	Inhibits HSP90α acetylation → ↓ HDAC6 → ↓ Adriamycin resistance	Fruit, Root, Leaf, Seed	[12, 23, 28-30, 69, 120]
4-Hydroxycinnamic acid	↓ Cancer cell proliferation; Prevents oxidative stress	Fruit, Root, Leaf, Pollen, Seed	[12, 23, 31, 32, 69, 96, 120, 125]
Hydroxystilbenes	Inhibits Bcl-2; Activates caspases III/VII; Induces autophagy via Hsp-70 activation	Root	[45, 46]
Chlorogenic acid	↑ SUMO1 → ↓ miR-17; ↑ p21 → ↓ proliferation/invasion/motility	Heart, Pollen	[58, 59, 94, 96]
Syringic acid	Inhibits mTOR/AKT pathway; ↑ ROS → Mitochondrial membrane disruption	Fruit, Root, Leaf, Heart	[12,49, 50, 58, 120]
Ferulic acid	↓ MMP-9 mRNA expression → ↑ chemotherapy efficacy	Fruit, Heart, Root, Leaf, Pollen, Seed	[12, 18, 51, 52, 58, 69, 94, 96, 120, 125]
Methyl gallate	↓ MMP9/MMP2; ↑ TIMP-2 → Inhibits migration/invasion	Heart, Leaf	[58, 69, 70]
Protocatechuic acid	↓ Ras/Akt/NF-κB pathway; Targets RhoB → Inhibits migration	Fruit, Leaf, Pollen	[69, 71, 72, 96, 120, 125]
3,4-Dimethoxy toluene	↑ GABA → Inhibits MMP-2/MMP-9; ↓ Gastric cancer/liver metastasis	Spathe	[72, 76-78, 80]
β-Caryophyllene	Binds CB2 receptor → ↑ Proapoptotic factors	Spathe	[78-80]
Caffeic acid	Triggers intrinsic apoptosis	Fruit, Heart, Pollen, Seed	[18, 23, 58, 92, 93, 96, 120]
Pyrogallol	Reduces tumor size (doxorubicin-like effect)	Pollen	[96, 99]
Ellagic acid	Regulates PI3K/Akt, JNK, mitochondrial, Bcl-2/Bax, TGF-β/Smad3 pathways	Heart, Pollen	[58, 96, 98, 100]
Quinic acid	↓ Cyclin D1 → Inhibits oral cancer proliferation	Fruit	[125, 126]
Vanillic acid	Suppresses HIF-1α → G1 phase arrest	Fruit, Pollen, Seed	[18, 23, 25-27, 92, 96, 120]
Epicatechin	↑ Sensitivity to radiation/chemotherapy	Fruit, Leaf, Pollen, Seed	[69, 92, 96, 120, 127, 128]

Symbol Key: ↑ = Increase/Activation; ↓ = Decrease/Inhibition; → = Leads to.

Table 3 Common non-phenolic substances and anticancer mechanisms in different organs of date palm.

Substance	Classification	Anticancer mechanism	Found in	References
Alpha-tocopherol	as Vitamin E	Prevents cancer by its antioxidant activity	Seed, Pollen, Fruit	[18, 33, 34, 101, 121]
Lauric acid	Fatty acid	Induces apoptosis by increasing ROS	Seed, Pollen	[18, 23, 33, 35, 38, 98, 101]
Lysine	Amino acid	Reduces metastasis and enhances chemotherapy	Pollen, Fruit	[101, 106-109]
Oleic acid	Fatty acid	Arrests cell cycle in G1 phase	Seed, Pollen	[18, 23, 33, 35-37, 98, 101]
Palmitic acid	Fatty acid	Upregulates caspases and p53, suppresses Bcl-2	Seed, Pollen	[18, 23, 33, 35, 98, 101-103]
Phenylalanine	Amino acid	Serves as a drug carrier and inhibits prostate cancer	Pollen, Fruit	[101, 106, 110, 111]

Anticancer Properties of Date Tree Roots

Date palm roots contain significant amounts of Hydroxystilbenes [45]; Stilbenes can enter cancer cells to undergo apoptosis by inhibiting anti-apoptotic proteins such as Bcl-2 and activating III and VII caspases. They can also force cancer cells to undergo autophagy by activating Hsp-70. They can also initiate antioxidant cascade pathways by activating P13K/Akt [46]. One of the highest elements absorbed by date palm roots is potassium [47]. Elevated levels of potassium have been shown to correlate with reduced cancer risk and the suppression of tumor growth; This is due to the role of potassium in regulating cell growth and proliferation [48]; In Table 4, the minerals of different organs have been reviewed. Syringic acid and ferulic acid are two notable phenolic compounds in date palm roots [12]. Syringic acid may exhibit notable anticancer properties by modulating crucial signaling pathways that affect oncogenic transcription factors and apoptosis-related proteins, leading to the inhibition of proliferation across various cancer types, such as colorectal and breast cancer. This compound can regulate cell cycle progression and promote apoptosis by upregulating pro-apoptotic proteins while downregulating anti-apoptotic factors, potentially enhancing the effects of conventional chemotherapy through synergistic actions targeting pathways related to cancer resistance and progression. Additionally, syringic acid may disrupt mitochondrial membrane potential by increasing the generation of reactive oxygen species (ROS) and can inhibit the mTOR/AKT signaling pathway, thus representing a promising candidate for therapeutic intervention in gastric cancer through its complex anti-cancer mechanisms [49, 50]. Ferulic acid prevents cancer cell proliferation, induces apoptosis by reducing MMP-9 mRNA expression, and enhances the effectiveness of anticancer drugs in chemotherapy [51, 52]. *Geotrichum candidum* and *Penicillium citrinum* are two fungal endophytes found in date palm roots [53]. It has been shown that the extracts of these endophytes have significant antioxidant properties, and it is speculated that unknown metabolites extracted from them can be effective in slowing down the progression of cancer. Although the research about these roots is limited, the fact that silver nanoparticles synthesized from them have shown anti-cancer activity can be promising to focus more on this organ in the future [54].

Table 4 Minerals and a summary of their anti-cancer effects in different organs of the date palm.

Minerals	Anti-cancer effects	Found in	References
Potassium	Cell growth regulator, tumor suppression	Fruit, Root, Leaf, Seed, Heart, Pollen	[23, 35, 47, 48, 55, 65, 96, 106, 113, 121]
Indium	Caspase modulation, angiogenesis inhibition	Heart	[55, 56]
Strontium	ROS generation, apoptosis	Heart	[55, 57]
Zinc	DNA repair, caspase activation	Fruit, Seed, Leaf, Heart, Pollen	[55, 65, 66, 96, 101, 106, 121]
Manganese	Mitochondrial regulation, apoptosis	Fruit, Seed, Leaf, Heart, Pollen	[23, 55, 65, 67, 96, 101, 106, 121]
Selenium	Antioxidant, apoptosis inducer	Fruit, Seed, Leaf, Heart, Pollen	[55, 65, 101, 113, 114, 116]

Anticancer Properties of Date Palm Heart

In addition to the valuable minerals, the heart of the date palm also contains Indium and Strontium [55]. Indium (III) complexes can exhibit significant anticancer activity by targeting various signaling pathways involved in cell proliferation and survival. These complexes may induce apoptosis in cancer cells via the regulation of apoptotic markers such as caspases and Bcl-2 family proteins, potentially inhibiting tumor growth. Additionally, indium compounds can affect angiogenesis-related pathways, impairing the formation of new blood vessels supporting tumor growth. Moreover, the ability of Indium complexes to generate reactive oxygen species may synergistically enhance their cytotoxic effects against neoplastic cells [56]. Strontium complexes can exhibit significant anticancer potential by modulation of key cellular pathways. These complexes may increase reactive oxygen species (ROS) levels and decrease mitochondrial membrane potential (MMP), leading to cell cycle arrest and apoptosis in cancer cells, particularly in A375 melanoma cells. Such mechanisms indicate that strontium can enhance the selective cytotoxicity towards malignant cells while potentially preserving normal tissues [57]. The extract of date palm heart may significantly inhibit cell viability in a concentration-dependent manner, which can be attributed to alterations in cancer cell morphology and declining viability rates. The extract's cytotoxic effects align with its phenolic and flavonoid content, which may activate specific apoptotic pathways while inhibiting cancer cell proliferation; Chlorogenic acid and Naringenin are powerful phenolic compounds in this regard [58]. Chlorogenic acid may demonstrate anticancer properties through the modulation of critical signaling pathways that facilitate cancer cell differentiation. It can enhance the expression of SUMO1, leading to the sumoylation of c-Myc and the subsequent downregulation of the miR-17 family while promoting p21 expression. This signaling cascade can diminish cancer cell proliferation, invasion, and motility, ultimately fostering a differentiated state across various cancer cell types [59]. Moreover, in vivo experiments suggest that chlorogenic acid may inhibit tumor growth in hepatoma and glioma models, presenting a promising avenue for cancer therapy by instigating cellular education rather than direct cytotoxic effects. In addition, chlorogenic acid can be converted into dihydrocaffeic acid, which may exert significant anticancer effects through its engagement with vital cancer pathways. Dihydrocaffeic acid can induce selective apoptosis in specific cancer cell lines like MCF-7, PC-3, and HCT-116, thereby leading to decreased cell viability in a concentration-dependent manner. While its precise mechanisms remain unclear, it may act similarly to caffeic acid, influencing apoptosis and cell cycle regulation through key signaling molecules [60, 61]. Naringenin may exert notable anticancer effects by modulating multiple signaling pathways that govern tumor behavior and progression, particularly in melanoma and angiogenesis. It can inhibit cell proliferation and migration in melanoma cells, which may be associated with reduced phosphorylation of key proteins such as ERK1/2 and JNK MAPK, emphasizing its impact on the MAPK pathway. Furthermore, naringenin may induce apoptosis through the upregulation of pro-apoptotic factors like activated caspase III and p53 while lowering anti-apoptotic signals, thereby highlighting its potential role in therapeutic strategies against cancer [62, 63]. The extract of date palm heart may enhance the regulation of specific anti-cancer pathways, particularly through the elevation of antioxidant enzymes and suppression of apoptosis-related markers such as caspase III and cyclooxygenase-2 levels. It is suggested that treatment with this extract might activate programmed cell death protein-1 (PD-1), which can help mitigate oxidative stress and associated cellular damage. Overall, the findings indicate that the heart of palm extract may serve as a valuable supplement for preventing oxidative injury in cancer therapies involving adriamycin [64].

Anticancer Properties of Date Leaves

Zinc and Manganese are among the elements found in date palm leaves [65]; Zinc may play a pivotal role in various anticancer pathways, potentially influencing the regulation of oxidative stress, DNA damage repair, cell cycle progression, and apoptosis. Key proteins involved include p53, caspases, copper/zinc superoxide dismutase, and various DNA repair proteins reliant on zinc for proper function. Zinc deficiency can disrupt these pathways, leading to increased DNA damage and cancer risk, while adequate zinc levels may enhance the structural stability of p53, activate caspases, and promote effective DNA repair mechanisms, contributing to its chemoprotective effects against malignancies such as colorectal, pancreatic, esophageal, and head and neck cancers [66]. Manganese in its divalent form, when complexed with arginine dithiocarbamate, has demonstrated significant anticancer potential by exhibiting cytotoxic effects against the MCF-7 breast cancer cell line. This complex may initiate apoptosis through various mechanisms, including the induction of G0/G1 phase cell cycle arrest, interference with DNA repair, and promotion of proteasomal inhibition. Specifically, the involved proteins and pathways include arginase, glutamine synthetase, Mn-superoxide dismutase, and the complex's interaction with DNA through hydrogen bonding, showcasing its multifaceted role in cancer therapy [67]. Date palm leaves contain important polyphenolic compounds and antioxidants [68]. Methyl gallate and protocatechuic acid are two significant compounds found in date palm leaves [69]. Methyl gallate inhibits cancer cell migration by decreasing MMP9 and MMP2 expression and increasing TIMP-2 expression and invasion without harming normal cells [70]. Protocatechuic acid stops cancer cell migration and induces apoptosis involving the down-regulation of Ras/Akt/NF-κB pathway and MMP-2 production by targeting RhoB activation [71, 72]. Although the bioactive compounds in date palm leaves may vary depending on their cultivar, they still exhibit a positive effect in halting the cancer process [73, 74].

Anticancer Properties of Date Palm Inflorescences

The spathes

One of the main compounds of date spathe is 3,4-dimethoxy toluene [75]; This aromatic compound can increase the level of γ-amino butyric acid [76]; It can retard the proliferation rates and enhance apoptosis of leukemia cells, inhibit MMP-2 and MMP-9 activity and expression, decrease the number of gastric cancers of the glandular stomach and intrahepatic liver metastasis, and inhibit human liver cancer cell migration and invasion [77]. β-Caryophyllene oxide (in all) and β-Caryophyllene (in most) are common compounds in the spathe of different date cultivars [78]; β-Caryophyllene acts as a phytocannabinoid with a significant affinity for cannabinoid receptor type II but shows no binding to cannabinoid receptor type I, indicating that its mechanism of action may not involve the endocannabinoid system. β-Caryophyllene oxide can alter critical pathways involved in cancer development while decreasing pro-cancer gene expression and enhancing proapoptotic levels, suggesting that β-Caryophyllene

may serve as a potential natural analgesic and anticancer agent, especially valuable in improving the efficacy of traditional chemotherapy in cancer patients dealing with chronic pain [79]. Linalool, Carvacrol, and Spathulenol are three significant terpenoid compounds found in date palm spathe (Tarooneh), representing the alcohol, phenol, and alcohol sub-classes, respectively [80]. Linalool exhibits significant anticancer activity through numerous specific pathways that may open avenues for therapeutic applications. This monoterpene can induce apoptosis in various cancer cells by activating intrinsic apoptotic pathways, evidenced by increased expression of pro-apoptotic factors and decreased levels of anti-apoptotic proteins. Linalool may also impact cell cycle regulation, resulting in arrest at critical phases, ultimately inhibiting proliferation in multiple cancer types. Furthermore, its potential as a chemosensitizing agent suggests that linalool can enhance the efficacy of existing chemotherapy treatments, offering a promising approach to improving cancer therapy outcomes [81-83]. Carvacrol may exert its anticancer effects by modulating key signaling pathways and protein expressions involved in tumor progression. It can downregulate matrix metalloproteinase-2 and -9, pivotal in cancer cell invasion and metastasis. Furthermore, carvacrol induces apoptosis through increased pro-apoptotic protein expression, while decreasing levels of anti-apoptotic proteins such as Bcl-2, thereby disrupting the balance of cell survival. Additionally, it may inhibit the phosphoinositide 3-kinase/protein kinase B pathway, and extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase signaling, alongside promoting the phosphorylation of c-Jun N-terminal kinase and p38 MAPK, which collectively influence cancer cell fate and growth [84]. Spathulenol may exert a significant impact on cancer and tumor pathways, particularly in melanoma. It can modulate the MAPK/ERK pathway, potentially leading to decreased cell proliferation and enhanced apoptosis in SK-MEL-28 cells through mechanisms that may involve alterations in key protein expression. Furthermore, spathulenol may disrupt the BRAF signaling pathway, thus potentially reducing cell viability and contributing to the overall inhibition of tumor growth. By promoting intrinsic apoptotic mechanisms, it can enhance the expression of pro-apoptotic proteins, reinforcing its role as a promising candidate in melanoma treatment [85, 86].

The Flowers

Extracts (especially alkaline extract) obtained from the powder of date male flowers show antioxidant properties; Xylose is a monosaccharide that is significantly found in these extracts [87]; Xylitol and xylulose are derivatives of xylose [88]. Xylitol may selectively trigger cancer cell death by activating specific anti-cancer pathways, potentially inducing apoptosis through the upregulation of CHAC1, which can lead to oxidative stress and promote cell death. This action might involve the induction of endoplasmic reticulum stress, facilitated by ATF4, providing a selective mechanism that spares normal cells while affecting cancerous ones. Furthermore, xylitol may enhance chemotherapeutic efficacy by sensitizing cancer cells to agents like 5-fluorouracil, thereby proposing a supportive role in cancer therapies [89]. Similarly, xylulose is suggested to possess anti-cancer properties, particularly against colorectal cancer, as it may induce apoptosis by upregulating pro-apoptotic proteins while downregulating anti-apoptotic factors like BCL-2, with a mechanism that can attenuate the MAPK signaling pathway and reduce the phosphorylation of JNK, ERK, and P38, positioning it as a promising agent for targeting tumor growth [90]. The extract from male date palm flowers exhibited significant antioxidant properties as evidenced by its effectiveness in various assays, including the scavenging of DPPH radicals, enhancement of ferric reducing power, chelation of ferrous ions, and inhibition of β-carotene bleaching, indicating its potential utility in cancer prevention and treatment strategies [91].

The Pollen

Date palm pollen contains bioactive compounds such as caffeic acid, triggering cancer cell apoptosis [92, 93]. Isorhamnetin in this pollen induces antitumor effects through the PI3K/AKT signaling cascade [94, 95]. Hesperidin, a flavonoid in this pollen, can activate caspases and deactivate kinases, compelling cancer cells to undergo apoptosis [96, 97]. Pyrogallol and ellagic acid, both found in date palm pollen, have shown significant promise in cancer treatment. Pyrogallol can reduce tumor size and has a similar effect to the drug doxorubicin on cancer cells, while ellagic acid can inhibit the proliferation and metastasis of tumor cells by regulating PI3K/Akt signaling pathway, JNK (cJun) signaling pathway, mitochondrial pathway, Bcl-2/Bax signaling pathway, TGF-β/Smad3 signaling pathway [98-100]. Date palm pollen contains a complex of fatty acids, with Palmitic acid being the main component [101]. Palmitic acid has been found to increase the expression of caspases and p53 while decreasing the expression of Bcl-2 [102]. As a result, this fatty acid may help prevent the occurrence and spread of cancer cell metastasis [103]. In general, the extract of date palm pollen can reduce the damage caused by radiation therapy and chemotherapy and also play a role in the cancer treatment process [104, 105].

Anticancer Properties of Date Fruits

Date fruit is rich in Lysine and Phenylalanine, essential amino acids [106]. Lysine reduces prostate cancer cell metastasis by reducing acidosis in and around the tumor, enhances Doxorubicin's effect on breast cancer cells, and can increase hydrogen peroxide levels to halt tumor growth [107-109]. Phenylalanine is used as a drug carrier in targeted cancer treatment [110]. A dipeptide derived from this amino acid has been found to inhibit the growth and metastasis of prostate cancer cells by regulating the expression of ANFSF9 and DUSP1 genes [111]. B vitamins are effective anticancer compounds by preventing the disproportionate increase in DNA methylation and breaks in important genes such as P53 and Apc [112]. However, this amount in date fruit varies during ripening and between different cultivars [113]. Selenium is one of the important minerals that have different amounts in different varieties of dates. The significant selenium in date fruits is involved in antioxidation, regulation of the cell cycle, and apoptosis [114, 115]. In the progression of cancer, there is typically a decrease in the levels of superoxide dismutase, glutathione reductase, glutathione peroxidase, and catalase, while the levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase tend to increase. It has been observed that the aqueous extract of date fruit can reverse both of these processes [116]. Beta D-glucan found in date fruit can be introduced as an antitumor by amplifying phagocytic killing of iC3b-opsonized tumor cells [117, 118]. The bioactive compounds in this fruit aid in the treatment of cancer by inhibiting cancer-causing enzymes like cytochrome p450 and by boosting the activity of anticancer enzymes such as phase II enzymes [119]. Date fruits contain various compounds, including flavonoids, phenols, and carotenoids [120]. Three important flavonoids are Quercetin, Luteolin, and Apigenin [121]. Quercetin activates caspase III, promoting apoptosis and autophagy of cancer cells [122]. Luteolin induces cell cycle arrest

and apoptosis in cancer cell lines by involving DNA damage, regulation of redox, and protein kinases in inhibiting cancer cell proliferation [123]. Apigenin functions by regulating processes associated with cancer suppression, such as the decrease of P13K and MMP and the increase of Bax, p53, and p16 [124]. Date fruits contain quinic acid, rutin, and epicatechin, which are potent anticancer phenolic compounds [125]. Quinic acid reduces the expression of cyclin D1, inhibiting oral cancer cell proliferation [126]. Rutin induces cell cycle arrest in cancer cells by creating changes such as reducing DNA damage and proliferation and increasing caspases and p53; in contrast, epicatechin increases cancer cell sensitivity to radiation and chemotherapy [127, 128]. So far, date fruit extract has been proven to have anticancer properties in multiple independent studies [129-131].

DISCUSSION

Many of the bioactive and anticancer compounds are similar across different organs of the date palm; each organ can also contain unique compounds. The maturation process of the date fruit is characterized by a reduction in its carotenoid levels, resulting in the mature fruit containing significantly lower concentrations than its seeds. In contrast, compounds such as 2-hydroxycinnamic acid, 4-hydroxycinnamic acid, quercetin, and luteolin are found in greater quantities in the seeds compared to the fruits. Ferulic acid is present in higher concentrations in pollen than in seeds, and seeds contain more ferulic acid than fruits. Catechin levels are more pronounced in the leaves than in the fruits, while the fruits exhibit higher catechin content than the seeds. The concentration of apigenin is greater in pollen than in the fruit, and the fruit also contains more caffeic acid than the seeds [132]. This widespread distribution of bioactives across the entire tree suggests that, similar to the fruit, other organs hold significant potential for valorization in the nutraceutical and pharmaceutical industries [133]. The promising anticancer activities of root endophytes further underscore the potential hidden within the underutilized parts of the date palm [53]. Many in vivo studies have been conducted on the effect of extracts taken from different organs of the palm in line with their inhibitory role on cancer-causing agents [134-137].This indicates that lesser-studied organs are not merely alternative sources but can offer unique therapeutic profiles.

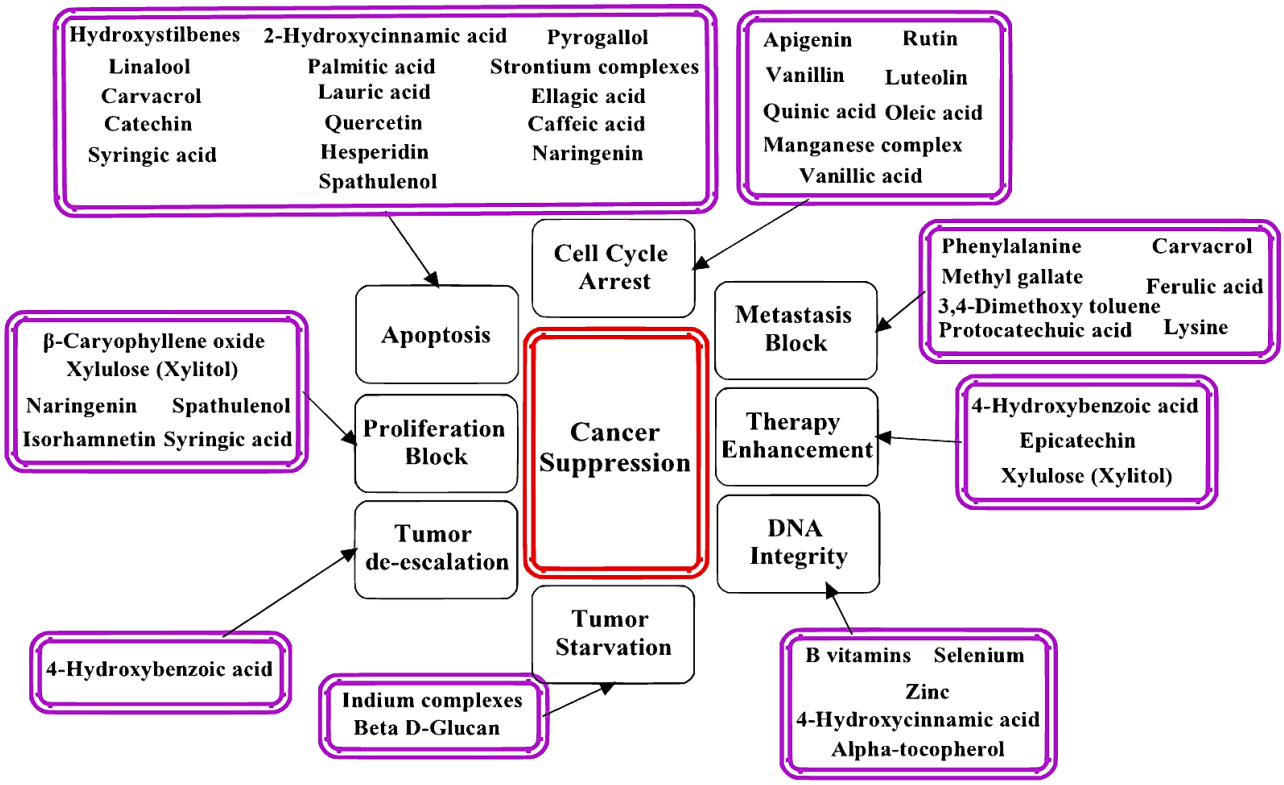

Fig. 2 Pathways of cancer-suppressive action of bioactive compounds of different organs of date palm.

CONCLUSION

It is difficult to compare the amount of bioactive compounds of all the organs in this tree because current studies are more focused on their differences in different cultivars rather than in different organs of the same cultivar. Review suggests that date palms have a high potential in cancer treatment, and their products could be beneficial as a primary or additional treatment. The collective evidence positions the date palm as a comprehensive source of diverse anticancer agents. In Figure 2, the effect of bioactive compounds of different organs of the date palm is reviewed. However, further research is needed to fully understand the role of all effective substances in date palm organs; A direct comparative analysis of bioactive compounds across all organs from a single cultivar is critically needed. In Figure 3, the potential of six different organs is reviewed. Future research should focus on isolating new compounds from less-studied date palm organs and evaluating their synergistic effects with conventional chemotherapeutic agents. Utilizing these underutilized organs could pave the way for innovative and accessible cancer treatments.

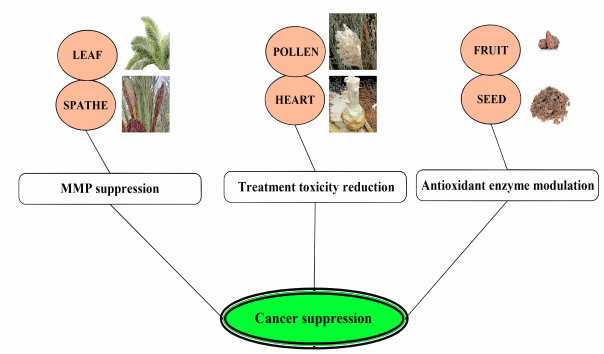

Fig. 3 Potential of six different organs of the date palm in suppressing cancer.

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