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REVIEW ARTICLE

Bioactivity and Pharmacological Potential of Date Palm (*Phoenix dactylifera* L.) Against Pandemic COVID-19: a Comprehensive Review

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Abstract

A novel coronavirus disease (COVID-19) or severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), transmitted from person to person, has quickly emerged as the pandemic responsible for the current global health crisis. This infection has been declared a global pandemic, resulting in a concerning number of deaths as well as complications post-infection, primarily among vulnerable groups particularly older people and those with multiple comorbidities. In this article, we review the most recent research on the role of date palm (*Phoenix dactylifera* L.) fruits (DPFs) to prevent or treat COVID-19 infection. The mechanisms underlying this preventive or therapeutic effect are also discussed in terms of bioactivity potentials in date palm, e.g., antimicrobial, antioxidant, anticancer, anti-diabetic, anti-inflammatory, neuroprotective, and hemolytic potential, as well as prospect against COVID-19 disease and the potential product development. Therefore, it can be concluded that regular consumption of DPFs may be associated with a lower risk of some chronic diseases. Indeed, DPFs have been widely used in folk medicine since ancient times to treat a variety of health conditions, demonstrating the importance of DPFs as a nutraceutical and source of functional nourishment. This comprehensive review aims to summarize the majority of the research on DPFs in terms of nutrient content and biologically active components such as phenolic compounds, with an emphasis on their roles in improving overall health as well as the potential product development to ensure consumers' satisfaction in a current pandemic situation. In conclusion, DPFs can be given to COVID-19 patients as a safe and effective add-on medication or supplement in addition to routine treatments.

Keywords COVID-19 · SARS-CoV-2 · Coronavirus · Date palm · *Phoenix dactylifera* · Bioactivity · Nutraceutical

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Introduction

The date palm (*Phoenix dactylifera* L.) is a perennial tree species that has been cultivated for its delicious edible fruits in arid and semi-arid places around the world for the past six millennials [1, 2]. The monocotyledon *Phoenix dactylifera* belongs to the Arecaceae family and is dioecious [3]. In most Arabic countries, date palm fruit (DPF), which consists of a seed covered by a soft and sweet pericarp, is a staple food. About 5000 date variations are growing in various parts of the world that vary depending on their type and stage of maturity [4, 5]. Khalal (unripe), Rutab (semi-ripe), and Tamar (totally ripe) are the three phases of fruit maturation that are typically consumed [6].

Currently, Egypt is the main producer of DPF, with 1.7 million tonnes produced annually, covering for 17.7% of global dates output and 24.4% of Arab countries [7]. Due to their high glucose (51.2–54.5%), fructose (48.5–52%), maltose (22.5%), and sucrose (22.5%) content, DPFs are high in specific nutrients and provide a worthy source of quick energy (3.1–3.2 percent) [4, 8]. DPFs also include fat (0.1–0.70%), protein (1.8–3.8%), nitrogen (0.25–0.55%), carbs (74.5–82.4%), dietary fiber (6.40–11.50%), minerals (0.10–916 mg/100 g dry weight), and some vitamins (C, B1, B2, B3, and A) [9–12]. As a result, knowledge of date health benefits may stimulate their use as a nutraceutical [13, 14], nutricosmetics [12], and functional food ingredients such as nutritional bars [15] or by-products in the food industry [16]. Date fruits have gained significant importance in human nutrition since then due to their high content of important nutrients [4, 17]. Date production, consumption, and industrialization have all been rapidly increasing around the world [16].

In response to the numerous health benefits of dates, numerous in vitro and animal studies, as well as the identification and quantification of diverse classes of phytochemicals, have been done globally in recent years [5, 12, 18–22]. Researchers discovered that date palms have inherent viral immunity against plant viruses as well as UV radiation resistance [23, 24]. Current research has revealed the possible application of palm leaf extract against COVID-19 [25, 26]. As a result, the goal of this study was to see if DPFs have pharmacological and therapeutics effect on the COVID-19 virus.

SARS-COV-1 and SARS-COV-2: Evolution and Current Mutation

The term “severe acute respiratory syndrome” (SARS) first appeared during the 2003 coronavirus outbreak. SARS coronavirus-1 (SARS-CoV-1) is to blame for the outbreak, which began with a bat bite. In late 2019, a new coronavirus that is similar to SARS-CoV-1 has emerged causing coronavirus disease 19 (COVID-19), also known as SARS-CoV-2. Both viruses belong to a subgroup of *Betacoronavirus* [27]. A study reported that SARS-CoV-2 has a 96% similarity of its genome sequence with coronavirus strain found in horseshoe bat, *Rhinolophus affinis* (RatG13). This strain was found in Yunnan Province, China, in 2013 [28].

Aside from SARS and COVID-19, coronavirus was also responsible for a Middle East respiratory syndrome (MERS) outbreak in 2012 [29]. The coronaviruses that have caused pandemic outbreaks of the diseases are abundantly found in bats and other mammals, therefore causing the uncontrollable zoonotic transmission to human populations. When animals infected with different coronaviruses come into close contact and exchange virus, recombination between distinct strains of the virus can occur, resulting in diversity. When animals infected with different coronaviruses come into close contact and exchange virus, recombination between distinct strains of the virus can occur, resulting in diversity. The genetic evolution of the SARS-CoV-2 variant has led to the current COVID-19 pandemic [27]. COVID-19 virus variant is referring to mutated strains of SARS-CoV-2, which differ from the predominant or original sequence. The mutation happens during the replication process where more variants are produced with the increasing number of the replication process. Depending on the location of the mutation, the virus variants can change the virus properties such as transmissibility and severity.

Earlier, the emergence of dominant D614G variants seems to have a minimal evolution effect as this strain only increases transmissibility, without causing any severity to the disease [30]. SARS-CoV-2 has several variants, which have been classified into three categories: variant of concern (VOC), variant of interest (VOI), and variant of high consequences (VHC) [31, 32]. The nomenclature system by GISAID, Nextstrain, and Pango is currently used for naming and tracing SARS-CoV-2 lineage variation [33]. Based on the definition provided by the World Health Organization (WHO), few types of VOC strains have been identified since the beginning of the COVID-19 pandemic including Alpha (B.1.1.7 lineage), Beta (B.1.351 lineage), Gamma (P.1 lineage), and Delta (B.1.617.2 lineage). These strains were categorized as VOC since they can enhance transmission and virulence, evade detection by host cells, and reduce neutralization antibodies production, hence reducing the effectiveness of treatments or vaccinations. As for VOI, seven variants have been reported, namely Epsilon (B.1.427 and B.1.429 lineages), Zeta (P.2 lineage), Eta (B.1.525 lineage), Theta (P.3 lineage), Iota (B.1.526 lineage), Kappa (B.1.617.1 lineage), and Lambda (C.37 lineage). These strains were reported to reduce treatment and vaccination efficacy, increase the severity of the disease, increase transmissibility, and give changes to receptor binding [31, 34]. There is no SARS-CoV-2 variant that has been classified as VHC at this time.

Since the first time describe in December 2019, multiple new SARS-CoV-2 variants have appeared. Each variant with spike protein mutation such as Alpha, Beta, Gamma, Delta, and Lambda has changed the virus to become more transmissible, easier to evade the immune defenses, and increased hospitalization and death. By reducing the production of neutralization antibodies, the infection of variant strains was also reported to reduce the efficacy of treatment and vaccinations [35]. Therefore, further comprehensive work by the WHO, CDC, and other public health agencies in monitoring the spread of identified variants is critically essential.

Nutraceutical Compounds in Date Palm Fruit

Date palms contain a wide range of nutritious and cosmetic compounds [12]. These bioactive chemicals have been used in a variety of fields, including medicine and industry. The potential of palm dates as an antioxidant, antimutagenic, antimicrobial, anti-inflammatory, antihyperlipidemic, gastroprotective, hepatoprotective, nephroprotective, anticancer, antifibrotic, antiproliferative, and immunostimulant activities has been demonstrated in studies [18, 36–41] (Fig. 1). Furthermore, scientists revealed that various portions of palm dates contain different valuable compounds. The nutraceutical potentials are summarized and explored in Table 1. Nutraceutical compounds such as anthocyanins, phenolics, sterols, carotenoids, and flavonoids have been found to have free radical scavenging action and

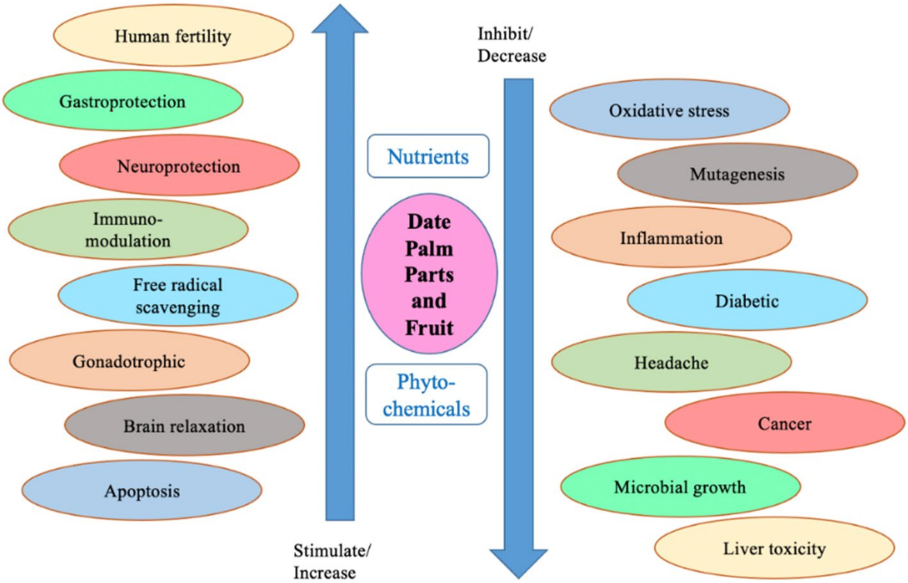

Fig. 1 Pharmacological properties of date fruits and various part of palm date trees

provide protection against oxidative damage in humans [9]. The primary amino acids, phenolic, and flavonoid chemicals present in date palms are depicted in Figs. 2, 3, and 4.

Antimicrobial Activity

SARS-CoV-2, the virus that causes COVID-19 disease, is causing a global epidemic. To date, there is no cure found to treat this disease. Vaccination is presently the most effective way to lower the chance of developing severe COVID-19 disease. Infection with COVID-19 is linked to the development of secondary bacterial and fungal illnesses [57–62]. The likelihood of secondary bacterial infection has been related to a number of factors, including post-tocilizumab IL-6 suppression, poor immunological signaling, and changes in the lung microbiome, which have become a greater predictor of death [59, 63]. Meanwhile, the risk of acquiring fungal infection due to "black fungi/mucormycosis" and invasive aspergillosis by *Aspergillus fumigatus* is attributable to the usage of steroids that is related to the invasive Delta (B.1.617.2 and B.1.617.2.1 or AY.1) strain of SARS-CoV-2 [62].

A study comparing secondary bacterial infections occurring among COVID-19 versus influenza patients in Israel showed that it is more prevalent in COVID patients, and the organisms isolated were *P. aeruginosa* followed by *S. aureus* with the most prevalent infection which is from Gram-negative bacteria in both groups [60]. Another study showed quite a similar picture whereby the source of infections was from respiratory, bloodstream, and urinary with the most organisms isolated which were Gram-negative bacteria (i.e., *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, *E. coli*) followed by Gram-positive bacteria (*Staphylococcus* sp., *E. faecium*), virus, fungi (*Candida albicans*), and others [58].

DPF is well-known for its antimicrobial activities because it possesses antibacterial, antifungal, and antiviral properties. Several parts of the date palm tree can be used for

Table 1 Nutraceuticals properties from different parts of date palm (*P. dactylifera*)

Palm parts of *P. dactylifera*	Nutraceutical properties	References
Date fruits	Antioxidant, anti-tumor, anti-diabetic, antifungal, antiviral, antibacterial, immunomodulatory, antiparasitic, hepatoprotective, anti-inflammatory, and anticoccidial activities; human reproductive system	[5, 12, 18–22, 36, 42–45]
Fruit suspension	Aphrodisiac activity	[46]
Pollen	Aphrodisiac activity, antibacterial and antioxidant, anti-diabetic	[11, 47]
Leaf extract	Antiviral	[25, 48]
Seed/pit/kernels	Anti-inflammatory; immunostimulant; anti-diabetic; antibacterial; antiviral; antixodant; antiatherogenic	[12, 23, 41, 49–56]

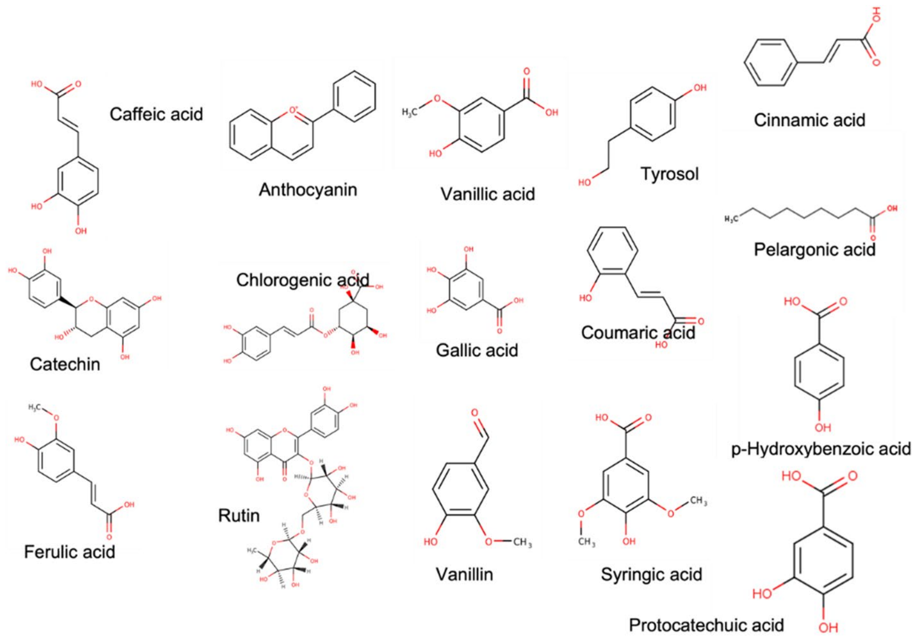

Fig. 2 Phenolic compounds found in date palms

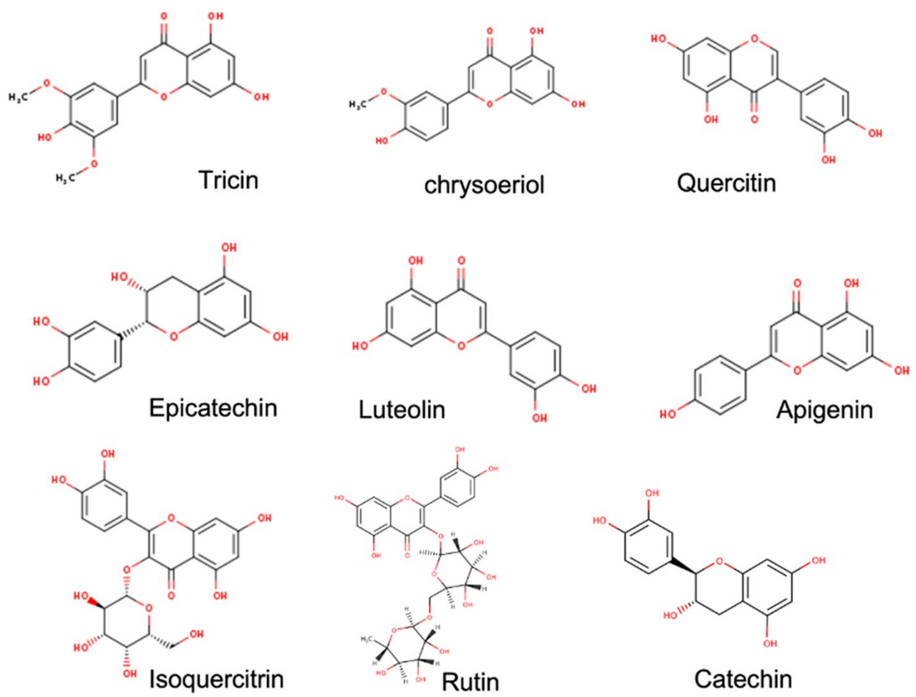

Fig. 3 Flavonoids compounds in date palms

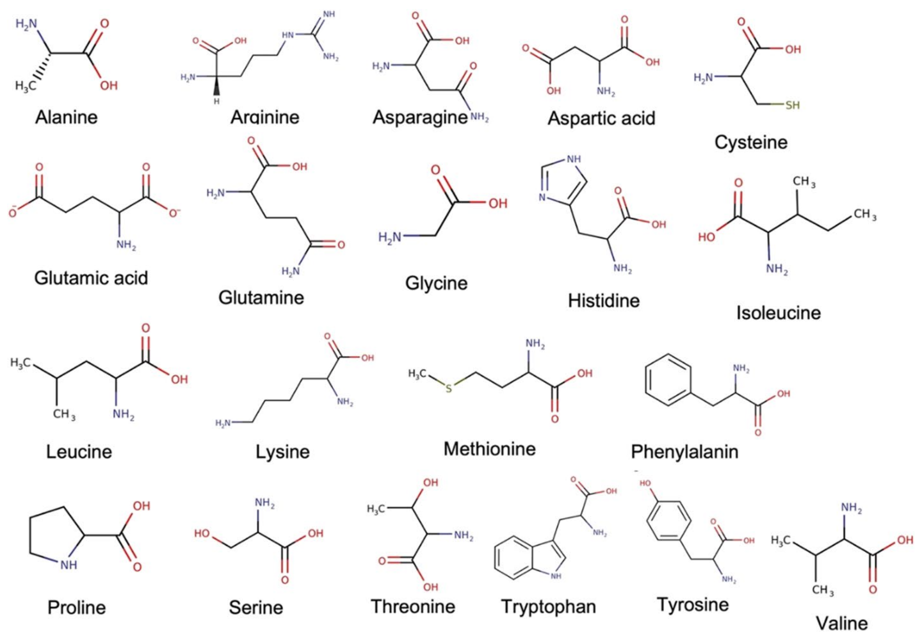

Fig. 4 Amino acids found in date palm fruits

medicinal purposes such as the dried leaves [25, 64], fruit [64–66], pollen [67, 68], seed [64, 68, 69], and tree bark extracts [64]. A date palm fruit consists of several components such as skin (epicarp), pulp (mesocarp), endocarp, and seed (kernel or pit) [15].

There are several compounds from parts of date palm tree that possess antimicrobial properties such as polyphenols and flavonoids. Polyphenols are further classified as benzoic acid derivatives and cinnamic acid derivatives [70]. Examples of benzoic acid derivatives are p-hydroxybenzoic acid, vanillic acid, protocatechuic acid, syringic acid and gallic acid. Examples of cinnamic acid derivatives are p-coumaric acid, o-coumaric acid, ferulic acid, and caffeic acid. Flavonoids are secondary metabolites of polyphenolic plants that are further classified into several subgroups such as flavones, flavanones, flavonols, flavanonol, isoflavones, isoflavonones, flavan-3-ols, and anthocyanidins [70].

It has antibacterial activities against various bacteria such as *Staphylococcus aureus*, *Escherichia coli*, and *P. aeruginosa* [64]; imipenem-resistant bacteria *P. aeruginosa* [71]; Gram-positive bacteria *Bacillus subtilis*, *Bacillus cereus*, and *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella abony* [72]; *Staphylococcus aureus*, *Bacillus cereus*, *Serratia marcescens*, and *Escherichia coli* [73]; *Escherichia coli and Staphylococcus aureus* [74]; and toward various Gram-positive and Gram-negative organisms [75].

Apart from antibacterial activity, date palms that are rich in phenolic contents also possessed antifungal properties. A study showed that the date palm extract has antifungal properties toward several types of *Fusarium oxysporum* species [66, 68, 76]. Besides, date palm pollen showed antifungal properties toward yeast, *Candida albicans*, and also mold, *Aspergillus niger* [67]. The different extracts and various findings are shown in Table 2.

However, there is limited study on the antiviral properties of date palm studied. A study on *Pseudomonas* phage ATCC 14,209-B1 showed that acetone extract of the date palm pits

Table 2 Antimicrobial properties of date palm extracts

Date palm compounds	Extracts	Antimicrobial properties	Findings	References
Flavonoid glycosides	Date palm fruits (full ripe)	Antibacterial	Potent inhibitory activity against imipenem-resistant *P. aeruginosa*	[71]
Acetone, methanol, water extracts contain carbohydrates, alkaloids, steroids, saponins, flavonoids, and tannins	Date palm fruit, leaves, bark, seed	Antibacterial	Acetone fruit extract has the highest antibacterial activity towards *S. aureus* Methanol leaves extract has potent antibacterial activity towards *E.coli* and *P. aeruginosa* Water extract has the least antibacterial activity	[64]
Phenolic acid (gallic acid) in water and ethanol extracts	Date palm fruits	Antibacterial	Water and ethanol extracts have potent antibacterial activity toward *E. coli*, *Salmonella enterica*, *Bacillus subtilis*, and moderate antibacterial activity toward *S. aureus* and *E. faecalis*	[77]
Phenolic, flavonoids	Date palm fruits (6 types of Moroccan dates: *Bouskri*, *Bousrdon*, *Boust-hammi*, *Boufgous*, *Jihl* and *Majhoul*)	Antibacterial	*Bousrdon* and *Jihl* extracts have potent antibacterial activities toward *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella abony*)	[72]

Table 2 (continued)

Date palm compounds	Extracts	Antimicrobial properties	Findings	References
Methanol and acetone extracts of phenolic compounds	Date palm fruits	Antibacterial	Methanol extract of Ajwa exhibits antibacterial activity towards *Staphylococcus aureus*, *Bacillus cereus*, *Serratia marcescens*, and *Escherichia coli* Methanol extract of Mabroom has potent antibacterial activiry toward *S. aureus* in comparison with methanol extract of Ajwa and Mariami Mabroom and Mariami have no antibacterial activity against Gram-negative bacteria Safawi has no antibacterial activity against *S. marcescens*	[73]
Polyphenols	Sterilized date syrup (made from date palm fruits)	Antibacterial	Date syrup and date syrup polyphenols exhibit antibacterial activity toward *E. coli* and *S. aureus*	[74]
Phenolic compounds	Date palm fruits extracts (3 types of dates chose *Allig*, *Bejo*, and *Deglet Nour*)	Antibacterial	All date extracts exhibit antibacterial activity towards Gram-positive bacteria, *S. aureus, Bacillus cereus, Bacillus subtilis, Enterococcus faecalis,* and *Micrococcus luteus*, and three Gram-negative bacteria, *E. coli*, *Klebsiella*, and *Salmonella*	[75]

Table 2 (continued)

Date palm compounds	Extracts	Antimicrobial properties	Findings	References
Fatty acids (palmitic acid and hydnocarpic acid), phytosterol (α-sitosterol)	Date palm pollen	Antibacterial and antifungal	Date pollen extracts have good antibacterial activity toward *Staphylococcus epidermidis*, *Bacillus cereus*, *Micrococcus luteus*, *S. aureus*, *Escherichia coli*, and *Klebsiella* species and antifungal activity toward *Candida albicans* and *Aspergillus niger*	[67]
Fatty acids such as oleic and lauric acids in date palm seed Fatty acids such as palmitic, linoleic, and linolenic acids in date palm pollen	Date palm pollens and seeds from 3 types of dates: *Deglet Nour, Takerbucht*, and *Bent Kbala*	Antibacterial and antifungal (Yeast: *C. albicans* and mold, 5 *Fusarium oxysporum* species; sp. *albedinis*, sp. *Canariensis,* sp. *Lycopersici*, sp. *Phaseoli*, and sp. *Melonis*	*Deglet Nour* extract has potent antibacterial and antifungal activities towards *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *C. albicans* *Takerbucht* extract has moderate antibacterial activity towards all bacteria tested Date palm pollen extracts have important antifungal activity toward all mold tested	[68]
Methanol, ethyl acetate, hexane, and dichloromethanic extracts of polyphenols	Date palm fruits	Antifungal	It exhibits antifungal activity toward *Fusarium oxysporum* sp. *albedinis*	[76]
Phenolic compounds	Date palm leaf extract	Antiviral	Date palm leaf extract is effective in reducing inflammatory marker levels such as CRP, ESR, WBC, and LDH and cause an increment in partial pressure of oxygen (PO^2) in mild to moderate COVID-19 patients	[25]

of ≥ 100 μg mL^{-1} was able to prevent infectivity towards *P. aeruginosa* [23]. In this review, we want to see the antiviral properties of date palm against the SARS-CoV-2 virus as illustrated in the literature.

A randomized double-blinded clinical trial among mild to moderate COVID-19 patients that received standard treatment for COVID-19 plus DPF leaf extract or placebo showed that the palm leaf extract solution was able to improve inflammatory markers such as CRP, ESR, WBC, and LDH as well as the partial pressure of oxygen (PaO^2) [25].

We hypothesize that the in vitro action of DPF extracts could help to reduce mortality in COVID-19 patients with secondary bacterial or fungal infections. However, in terms of direct effects of date palm extracts toward COVID-19 infection itself, it needs further study and research to look for its antiviral properties.

Anticancer and Antioxidant Activities of *Phoenix dactylifera* L.

Generally, the anticancer and antioxidant activities of plant extracts are due to bioactive compounds inside them [78]. Usually, the compound that can contribute to anticancer activities will also exert antioxidant properties. Based on previous studies, many bioactive compounds are present in *Phoenix dactylifera* L. such as phytosterols, flavonoids, alkaloids, protein, carbohydrates, cardiac glycosides, holosides, mucilage, phenolic compounds, tannins, catechin, gallic acid, terpenoids, saponins, coumarins, lignin, oil, fats, and many types of essential minerals [79–81]. Phenolic compounds are among phytochemicals that have been shown to have both anticancer and antioxidant properties. Table 3 and Table 4 showed several findings of *Phoenix dactylifera* L. concerning its anticancer and antioxidant activities.

When normal cells are injured in various ways, mislocalized, or grow improperly, they undergo apoptosis [108]. Apoptosis targeting is an efficient cancer treatment strategy that involves altering the cell's own mechanism of death in order to destroy tumor cells [109]. Free radical causes oxidative stress and antioxidant can help to avoid cellular oxidative stress. Figure 5 shows the mechanism of apoptosis that was found triggered by medicinal plants including *Phoenix dactylifera* L. and Fig. 6 shows how antioxidants can prevent cell damage by free radicals.

Anti-inflammatory Effect

Human-to-human transmission has quickly spread the COVID-19 illness over the world. The virus that causes SARS is SARS-CoV-2, which is more infectious than other coronaviruses [110, 111]. The person who is infected with COVID-19 may manifest a wide range of clinical symptoms such as fever, cough, shortness of breath, and chest infection that can lead to acute respiratory distress syndrome and systematic shock [112] with a mortality rate of 3.6–5.7%. Even more alarming is the fact that long-term immunity has yet to be demonstrated in COVID-19 patients who recover, and there is still a risk of re-infection in healthy people [113]. SARS-CoV-2 pathogenesis has been identified in order to obtain the necessary information to focus specifically on the development of efficient treatments to combat this disease [114].

The inflammatory response that is caused by the SARS-CoV-2 virus appears to be the leading contributing factor to cause higher morbidity and mortality [115] that can

Table 3 Anticancer activities of *Phoenix dactylifera* L

Origin/active compound/extract	Activities	References
Muscat, Oman; ethyl acetate extract	Reduced pancreatic stellate cell activation and fibrotic protein formation	[40]
Ajwa dates, Saudi Arabia; aqueous extract	Reversed the diethylnitrosamine-induced liver cancer; showed anti-inflammatory, hepatoprotective and anticancer properties	[82]
Medina, Saudi Arabia; ethyl acetate extract	Induced apoptosis and cell cycle arrest in prostate cancer cells	[83]
Libya; polysaccharide (glucan)	Anti-tumor effect in allogenic solid Sarcoma-180 ascites in mouse	[84]
Saudi Arabia; whole fruit	Ajwa consumption reduced infection, hospital admission due to neutropenic fever; increased survival rate in nonrandomized control trial of pediatric cancer patient	[85]
Iran; seed ethanolic extract containing 9-octadecenoic acid (Z)-methyl ester and dodecanoic acid methyl ester	Cytotoxic towards breast cancer cells in vitro (MCF-7) and in vivo using DMBA-induced breast cancer in Sprague Dawley rats- it reduces analytes that are related to cancer progression, and increase analytes that associated with cancer healing and health improvement	[86]
Sana'a, Yaman; seed hexane extract containing oleic acid	Antiproliferative against breast cancer cell MCF-7, lung cancer cells A549 and liver cancer cells HepG-2 cells (with IC_{50}: 675.6 µg/mL, 909.1 µg/mL, and 735.2 µg/mL respectively)	[87]
Degache, Tunisia; leaves aqueous-ethanolic extract containing picatechin-3-gallate, isoorientin, and dihexosyl quercetin	Inhibit the growth of human melanoma cells IGR-39 starting from 18 mg/mL	[88]
Jordan; whole fruit	Has protective effect against DMBA-induced breast cancer in Sprague Dawley rats	[89]
UAE; extracts from varieties of organic solvent and water-organic solvent combination	Exerted cytotoxic effect against triple negative breast cancer cells MDA-MB-231	[90]
Jeddah, Saudi Arabia; root aqueous extract	Showed cytotoxicity against breast cancer cells MCF-7 with IC50 29.6 µg/mL, induced apoptosis and cell cycle arrest at S-phase	[91]
Degache, Tunisia; aqueous-ethanolic extract	Cytotoxic against breast cancer cell MDA-MB-231 and MCF-7 with IC_{50} 50 mg/mL and 25 mg/mL respectively	[45]
Medina, Saudi Arabia; aqueous extract	Polylactic-co-glycolic acid (PLGA)-encapsulated 5-Fu combined with Ajwa date Extract showed better anticancer effect compared to PLGA-encapsulated 5-FU alone; in terms of antiproliferative activity and apoptosis induction in breast cancer cells MCF-7	[92]

Table 3 (continued)

Origin/active compound/extract	Activities	References
Medina, Saudi Arabia; aqueous extract	Ajwa date extract normalized circulatory CD161 NK cells and breast tissue TNF-alpha, cell size and proliferation and improve overall survival rates in DMBA-induced breast cancer in Sprague Dawley rats	[93]
Tehran, Iran; *Phoenix dactylifera* pollen grain	Antimutagenicity and anticancer activities were tested using standard reverse mutation assay (Ames Test) with 46% and 49% activities respectively	[94]
Medina, Saudi Arabia; seed aqueous extract	Inhibited melanogenesis in B16F10 cells by downregulating the PKA signaling pathways	[95]
Al-Ain, UAE; aqueous-methanolic extract	Reduced viability in MCF-7, CaCo2 and Hep-G2 cells at 1000 µg/mL	[96]

Table 4 Antioxidant activities of *Phoenix dactylifera* L

Origin/ active compound/ extract	Activities	References
Saudi Arabia; rutin and quercetin compounds	Reduce the adverse effect doxorubicin (DOX) in nude mice breast cancer, without affecting the therapeutic activities of DOX	[97]
Degache, Tunisia; aqueous-ethanolic extract	Showed an antioxidant activity in DPPH radical scavenging (IC_{50} value: 0.15 ± 0.011 mg)	[45]
Kuwait; aqueous extract of fruit	scavenge 50% of superoxide radicals was equivalent to 0.8 mg/mL; scavenge 50% of hydoxyl radicals at 2.2 mg/mL	[98]
Tehran, Iran; methanol-aqueous extract	2,2′-Azinobis (3-ethylbenzothiazoline-6-sulphonic acid) radical cation (ABTS) assay and the ferric reducing/antioxidant power method (FRAP) assay showed maximum antioxidant capacity: 500.33 µmol (Trolox equivalents/100 g dw) and 387.34 µmol (FRAP/100 g dw)	[99]
Bahrain; fruit homogenized with 0.3 M of acetate buffer	The highest FRAP values are 14.06 mmol ∕ 100 g FW	[100]
Jadavpur, West Bengal; aqueous-methanolic extract containing pyrocatechol and gallic acid	Showed an antioxidant activity in DPPH radical scavenging (IC_{50} value: 160 µg/mL; nitric oxide scavenging activity (IC_{50} 1.4 mg/mL); Hydroxyl radical scavenging activity (IC_{50} 1.05 mg/mL); Superoxide radical scavenging activity (IC_{50} 1.115 mg/mL)	[101]
Ghardaia, Algeria; aqueous-methanolic extract	Showed an antioxidant activity in DPPH radical scavenging activity, with range of EC_{50} 4.55 µg/µg to 12.7 µg/µg (µg samples/µg DPPH)	[102]
Riyadh, Saudi Arabia; aqueous and methanol extract	Among Ajwa, Sukkari and Khalas: Khalas has the best Lipid peroxidase inhibition and radical scavenging activities with EC_{50} range 0.96–1.88 mg/mL and 6.60–9.10 mg/mL respectively	[37]
Medina, Saudi Arabia; seed aqueous extract	DPPH scavenging capacity: $49.97 \pm 2.9\%$, $81.36 \pm 0.56\%$, and $78.53 \pm 3.83\%$ of the control for the extract concentrations of 0.0049, 0.0245, and 0.049 (mg/mL), respectively; $ABTS^{+}$ scavenging capacity: $5.69 \pm 1.36\%$, $18.81 \pm 0.68\%$, and $66.82 \pm 8.51\%$ of the control at concentrations of 0.0098, 0.049, and 0.098 mg/mL, respectively	[95]
Zagora region, Southern Morocco; methanolic extract	Showed an antioxidant activity with IC_{50} values of samples ranged between 0.219 and 2.028 mg/mL for FRAP; 2.411 and 9.738 mg/mL for DPPH	[103]
Al-Ain, UAE; degraded date pits using Solid State Degradation (SSD) using fungus Trichoderma reesei	Scavenging ability on DPPH radicals was 78%; enhanced the Ferric reducing antioxidant power of DP from 24.56 mmol TE/100 g DW to 36.23 mmol TE/100 g DW	[104]

Table 4 (continued)

Origin/ active compound/ extract	Activities	References
Saudi Arabia; seed & leaves; ultrasonicated methanol-acetone–water (7:7:6)	TEAC, DPPH and hydroxyl radicals scavenging activities ranging from 0.0007 to 76.74 mmol TE/ gram sample	[105]
Oasis of Tozeur, South Tunisia; methanolic extract	Showed DPPH radical scavenging activity with $IC5_0$ values of the samples ranged from 0.16 to 0.31 mg/mL; ABTS free radical scavenging activity ranged from 744.25 to 1813.80 µmol TE/100 g; FRAP assay showed reducing power ranged from 624.16 to 1228.53 µmol TE/100 g FW	[106]
Al-Ain, UAE; seed-based product	Study on 16 healthy adults—evaluate antioxidant effect after consuming seed-based product; GSH level increased significantly compared to the baseline, 1 h after ingestion ranged from 36.44 to 57.11%	[56]
Medina, Saudi Arabia; polyphenol extract	Treatment of date plyphenol extract on hypercholesrolemic rats increased the antioxidant enzymes from rat liver: catalase, superoxide dismutase and glutathion peroxidase (using DPPH assay)	[107]

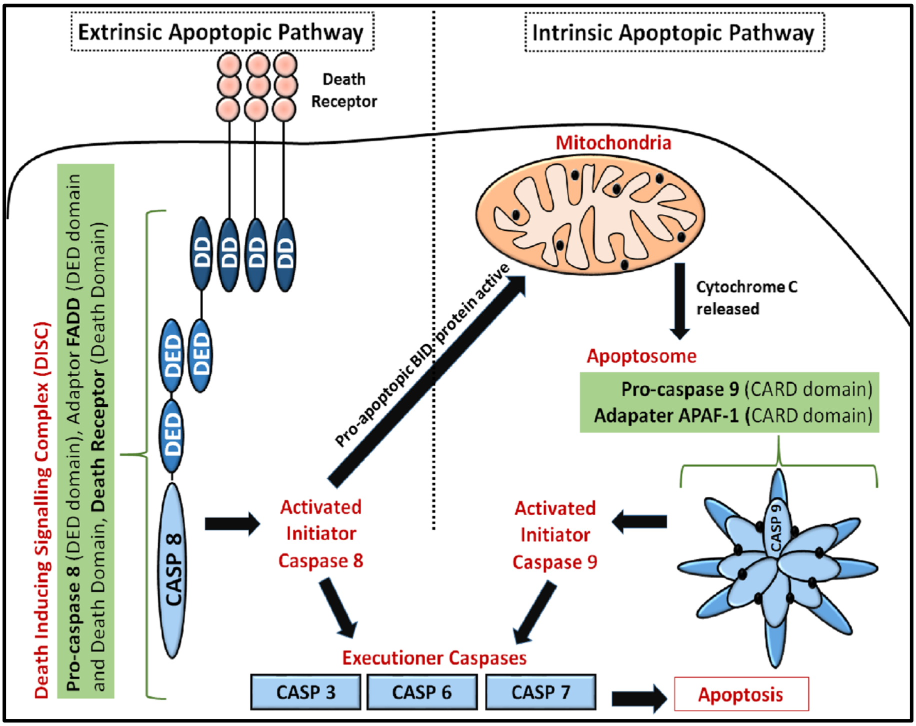

Fig. 5 Mechanism of apoptosis; most of medicinal plants can trigger apoptosis via both intrinsic and extrinsic pathways

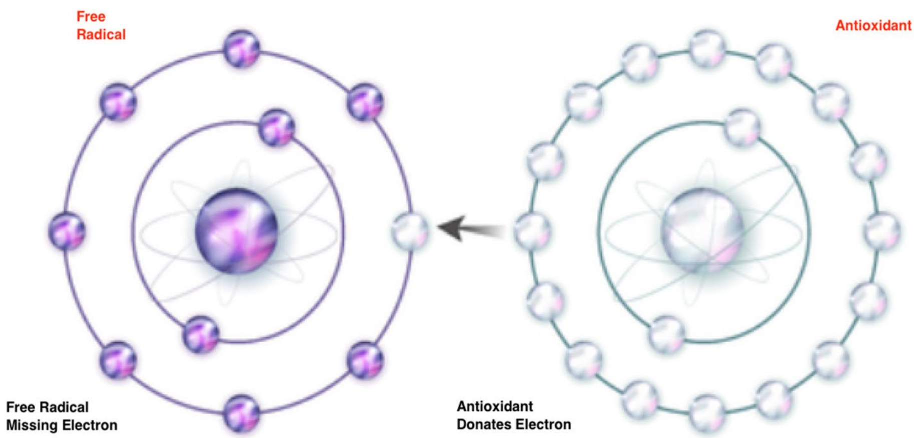

Fig. 6 Antioxidants can eliminate free radicals by donating electron

deteriorate to acute respiratory distress syndrome (ARDS) that requires oxygen supplement or even intubation. In addition, the SARS-CoV-2 virus can trigger a pro-inflammatory response, and immune cells generate cytokines to initiate an immunological response. Thus, the immune cells will be triggered and eventually will cause a "cytokine storm" that produces serious clinical manifestations. To prevent these complications, early pharmacological strategies to reduce inflammation that act as anti-inflammatory should be addressed as well as other specific anti-COVID-19 targets as the monotherapy might not be enough to control its complex effects in the human body.

The most popular pharmaceuticals used to treat inflammation are nonsteroidal anti-inflammatory drugs (NSAIDs), which work by blocking the cyclooxygenase (COX) pathway of arachidonic acid metabolism, which creates prostaglandins [116]. NSAIDs work by inhibiting the regulating enzymes cyclooxygenase/prostaglandin-endoperoxide synthase (PGHS-1 and PGHS-2), which are involved in the manufacture of prostaglandin (PG) that is closely linked to inflammation. On the other hand, natural sources such as *Phoenix dactylifera* (date palm) can act as a potent antioxidant, anti-inflammatory, and antitumoral, thus providing an alternative therapy in various diseases. The anti-inflammatory capability of the aqueous-ethanolic extract was determined by its inhibitory effect on phospholipase A2 activity and carrageenan-induced paw edema in mice (Fig. 7). In in vitro, the extract suppressed phospholipase A2 activity with an IC50 of 130 g/mL, and in vivo studies demonstrated a substantial reduction in paw edema after 1 h when compared to the control group [45, 117].

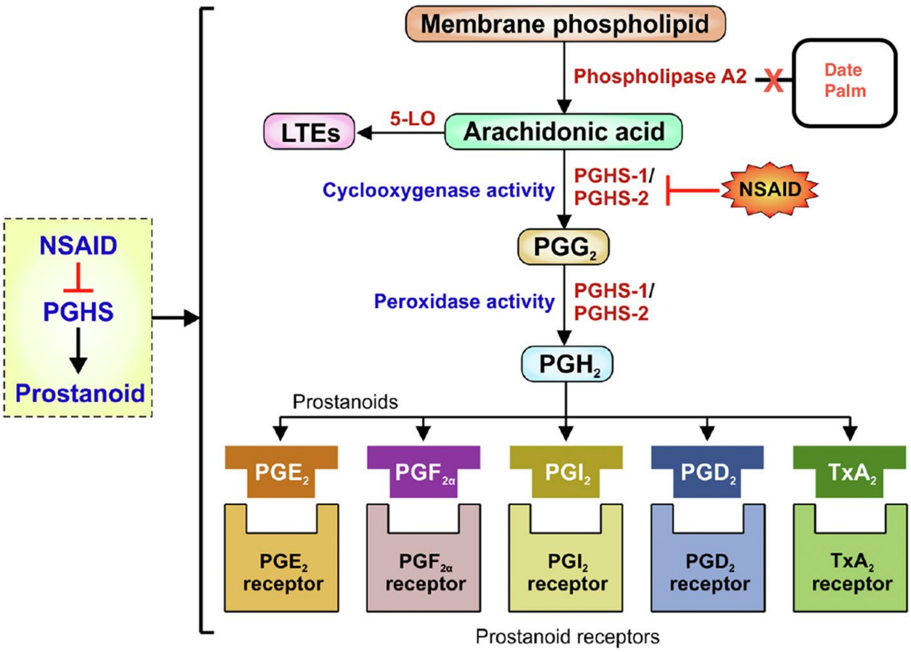

Fig. 7 NSAID-PGHS-prostanoid axis. PGHS-1/2 isoenzyme mediated prostanoid biosynthesis from arachidonic acid. Arachidonic acid is produced from phospholipids of the plasma membrane under the action of phospholipase A2. Date palm can inhibit the phospholipase A activity. In addition to prostaglandin (PG) and thromboxane (Tx) formation by PGHS isoforms in a cell and tissue-specific manner, leukotrienes (LTEs) are other immune mediators which are produced by the enzyme 5-lipoxygenase (5-LO). Each prostanoid interacts with its specific receptor as indicated in the figure (modified from Bindu et al. 2020 [115])

Anti-diabetic

Diabetes mellitus is a complicated chronic condition defined by glucose dysregulation caused by insulin deficiency or ineffectiveness [118]. Diabetes affects about 450 million people globally. It is always accompanied by various comorbidities or complications, such as hypertension, hyperlipidemia, and ischemic heart disease [119]. RNA virus infection is the cause of COVID-19 illness [120]. Because it spread so rapidly, the disease has now been declared a global pandemic. COVID-19 infected around 200 million people worldwide with mortality which was around 2 million people [118]. Preventing and controlling this pandemic can currently be accomplished with a vaccine campaign.

Some research suggests that people with diabetes mellitus have a higher chance of having a COVID-19 infection [121]. Diabetes is likely to have weakened the person's immune system due to their high blood sugar levels which will be more susceptible to infections including COVID-19. Besides those at the highest risk for getting COVID-19, research shows that people with diabetes are more likely than others to suffer serious COVID-19 symptoms. Diabetes mellitus patients infected by COVID-19 tend to have poor control of sugar levels. The mechanism of poor sugar control in COVID-19 patients is linked to a high level of free radical presence causing disrupted insulin production, leading to poor sugar control. Hyperglycemia can later cause more inflammatory responses that can lead to multiple complications. As a result, the purpose of this review is to look at the anti-diabetic properties of palm dates and their potential application for diabetes mellitus patients with COVID-19.

DPFs are high in flavonoids and phenolics, which can help natural antioxidants like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) perform better and reduce free radical oxidation products [122] that help to minimize oxidative stress and thus cell damage, particularly in pancreatic cells. DPF seed extract has also been shown to increase endogenous insulin secretion in streptozotocin-induced type 1 diabetic mice (STZ). When diabetic mice were given dates instead of insulin alone, C-peptide levels increased significantly, indicating increased endogenous insulin secretion. The number of B cells can be increased by flavonoids and a possible mechanism would be to stimulate insulin secretion [123].

An in vitro study found that palm date seed extract (5 mg/mL) inhibits glucosidase enzymes. In comparison to methanol or ethanol, the water extract in dates has the strongest anti-diabetic effect by inhibiting the glucosidase enzyme. Water extracts also inhibit the activity of the amylase enzyme when compared to other solvents [124]. The hydrolysis of starch, disaccharides, and long-chain carbohydrates into glucose is carried out by both enzymes. Inhibiting the activities of -amylase and -glucosidase enzymes is one strategy for regulating postprandial hyperglycemia in diabetes by slowing carbohydrate hydrolysis.

DPFs contain dietary fiber, phenolic compounds, and antioxidants. The seed extracts have previously been shown to inhibit amylase and pancreatic lipase activity [125]. Both enzymes can be inhibited to prevent starch and fat absorption. Blood sugar levels fall when the absorption process is slowed, and diabetes can be avoided.

Several studies have been conducted over the last two decades to investigate the relationship between palm dates and the diabetes mellitus population. In one randomized controlled trial, T2DM patients were given date vinegar (20 mL) along with their regular diet for 7 weeks. Date vinegar significantly reduced the HB1ac level and fasting blood sugar in this group. The main component of date vinegar is acetic acid. It may delay the digestion of starch molecules by inhibiting disaccharide activity and reducing glucose uptake via muscle performance [126].

Bam Mazafati dates and raisins were given to T2DM patients ($n = 15$) as a snack in a crossover clinical experiment. Due to the high polyphenol content in dates, blood glucose levels did not significantly rise after 2 h of eating (2 h after breakfast and 2 h after the date snack). As a result, when compared to sugar-based snacks, DPFs can be a nutrient-rich, healthy snack for diabetic patients [127, 128].

Polyphenols and phenolics are active substances in DPFs that serve as anti-diabetics by blocking the -amylase, pancreatic glucosidase, and lipase enzymes and fighting free radical oxidation. Consumption of palm dates can help to improve and maintain normal blood sugar. However, more research is needed to determine the impact of palm dates on sugar control in diabetic patients with COVID-19.

Date Palm for Natural Radioprotection Agent in Radiotherapy

Radiotherapy treatment used high-energy ionizing radiation of gamma ray, X-ray, and electron beam for invasive cancer treatment [129]. However, high ionizing radiation will cause cytotoxic and genotoxic stress effects on human cells due to continuous oxidative damage induced by free radicals of reactive oxygen species (ROS) [130]. ROS will cause DNA lesion that originated from water radiolysis in cells during and after irradiation [131]. The interactions will produce free radicals known as hydroxyl (OH^-) and hydrogen (H^+) ions as well as superoxide molecules such as hydrogen peroxide (H_2O_2) which have a high potential to break DNA double bonds [132].

Clinically, free radicals will give advantages to kill cancer cells for large tumor contours, but adversely for small volume tumors. This is due to the high accumulation of free radicals that tend to cause continuous oxidative stress and might affect healthy tissues [133]. Theoretically, DNA lesion of health issues might be self-repaired, but mostly depends on the level of the immunity system [134]. For COVID-19 patients with low-level immunity conditions [135] and that need to undergo scheduled radiotherapy, miss repairing or unrepair DNA breakage of health tissues would be critical and promote malignant tumors [136, 137]. Furthermore, the post-infection immunity system for COVID-19 patients is still uncertain and not fully understood [138, 139].

As a result, natural radioprotective medications must be developed to protect health tissues from predicted damage caused by free radicals, which are the primary source of ionizing radiation-induced cellular damage [140]. Radioprotectors are predicted to include antioxidants and free radical scavengers. Naturally, palm date is recognized as an ideal radioprotective agent [141] due to its high antioxidant of bioactive compounds [142] and capability against radiation-induced damage of ROS at the cellular level [143]. Some clinical and animal studies have been done to determine radioprotection properties of palm date in radiotherapy as summarized in Table 5:

From previous studies, extract from various palm date species has a high potential to be promoted as natural radioprotective drugs in radiotherapy. The findings might be beneficial for COVID-19 patients undergoing radiotherapy where no negative side effects have been reported.

Table 5 Clinical and animal studies have been done to determine radioprotection properties of palm date in radiotherapy

Types of palm date	Type of treatment	Absorbed dose	Type of studies	Main findings	Researcher
Ajwa syrup (*Phoenix dactilyfera*)	Gamma ray irradiation	6 Gy	Animal study: Rat liver	↓ DNA strand breakage ↓ percentage of DNA–protein crosslinks (DPCs)	[144]
Date palm pollen (*Phoenix dactylifera L, Palmae*)	Chemotherapy and Gamma ray irradiation	50 Gy to 72 Gy *Cisplatin 100 mg/m^2 every 3 weeks for 3 cycles	Clinical study: Head and neck cancer	↓ mucosal injury ↓ DNA damage	[145]
Siwa extract	Gamma ray irradiation	6 Gy	Animal study: Rat heart	↓acute cardiac damage in male albino rats	[146]
Khalas, Abu Maan, Ajwa, Fard, Mabroom and Lulu extracts	Gamma ray irradiation	6 Gy	Animal study: Mice blood and liver	↑ liver histopathological ↑ pro-inflammatory cascade ↓ hepatotoxicity, oxidative stress, inflammation, and DNA damage	[147]
Siwa extract	Gamma ray irradiation	6 Gy	Animal study: Mice blood and liver	↑ liver histopathological ↑ pro-inflammatory cascade ↓ hepatotoxicity, oxidative stress, inflammation, and DNA damage	[148]
Iranian Kabkab extract	Gamma ray irradiation	7.5 Gy	Animal study: Mice survivability	83% survive with extract injection 41% survive without extract injection	[149]

*Chemotherapy

Neuroprotection and Palm Dates

Progressive malfunction and loss of neuronal structure and function lead to neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis. Potential mechanisms that involve in the pathogenesis and progression of neurodegeneration include oxidative stress, neuroinflammation, apoptosis, mitochondrial dysfunction, loss of growth factors, proteasomal dysfunction, autophagic/lysosomal dysfunction, excitotoxicity, and protein aggregation [150]. Many natural products/antioxidants have been investigated for their neuroprotection potentials against neurodegeneration and targeting the key potential mechanism such as oxidative stress and neuroinflammation. Simultaneously targeting the multiple pathogenic mechanisms may be the strategy to strengthen the neuroprotection effect [150, 151].

Several experimental studies evaluated the neuroprotective potential of palm dates (*Phoenix dactylifera*). Recently, Imad Uddin et al. (2020) published a review on the protective role of date palm (*Phoenix dactylifera* L.) on central nervous system disorders. Different models [pentylenetetrazole, picrotoxin, nicotine and maximal electroshock induced epileptic models [152], Cerebral ischemic model [153–157]; Lead acetate induced neuronal damage [158–160], Artesunate induced cerebellar damage [161], APPsw/Tg2576 Transgenic mice [162, 163], Scopolamine & Streptozotocin-induced memory loss [164], Pentobarbitone induced sleeping time, locomotor activity assessment model [165], Beta-amyloid induced hippocampal damage been used to induce neuronal damage and possible protective effect and mechanism of action of date palm (aqueous/methanolic/ethanolic) extracts been studied and suggested the presence of flavonoids, tannins and other polyphenols constituents in palm date is responsible for its neuroprotective and cerebral anti-ischemic actions [166].

Although the above pre-clinical studies show the neuroprotective effect of date palm, clinical studies are needed to confirm their neuroprotective effect.

Antihemolytic Activity of Date Palm

Antihemolytic activity of a natural product/compound is an important assessment tool to investigate the protective effect against the free radical damage of erythrocyte membrane as well as to assess the mechanical stability of erythrocyte membrane. Since erythrocyte membranes are enriched with polyunsaturated lipids as well as hemoglobin redox reactions linked with oxygen transport, it easily gets oxidized by free radicals generated, resulting in oxidative stress [167]. DPF (*Phoenix dactylifera*) is a natural medicinal food exhibiting good antihemolytic activity and is reported by different studies as given in Table 6.

It has been suggested that the involvement of flavonoids, as well as other polyphenolic contents in date palm, is responsible for their antihemolytic activity and the erythrocyte membrane stability [72, 170].

Potential New Product Development of Date Palm Against the COVID-19 Pandemic

Domestic and international large found in the previous literature fruits are aimed to increase revenue to meet global demand. Increased export commitment has resulted from increased export opportunities and low-risk perceptions [171]. Previous date palm research

Table 6 Antihemolytic property in date palm fruits

Dates variety	Method of hemolysis	Results	Reference
Six Moroccan dates fruit extract such as *Bouskri*, *Bousrdon*, *Bousthammi*, *Boufgous*, *Jihl*, and *Majhoul*	Peroxyl radical initiator, AAPH	*Among the tested date varieties, Jihl* exhibited higher antihemolytic activity with a half time of hemolysis (210.99 min) more than the control (Trolox) with a half time of hemolysis (175.84 min), and the Bouskri variety showed the lowest activity (half time of hemolysis, 158.70 min) A non-significant hemolysis when erythrocytes treated only with date fruit extract indicates these extracts are nontoxic and harmless to the cells	[72]
Ajwa and Khalas ethanolic extracts	Phosphate buffer saline (PBS) and Triton-X-100 as negative and positive controls	Khalas extract exhibit lower red blood cell (RBC) lysis than Ajwah. But both extracts showed less than 3.5% of RBC lysis at the concentrations tested than the positive control Triton-X-100 which showed 90.05% RBC lysis	[168]
Date palm extract (DPE) of Khalas cultivar nanoemulsion (NE) formulations	One mL of each NE formulation incubated at 37°C with 1 mL of erythrocyte suspension for 30 min. Phosphate buffer saline (PBS) and Triton-X-100 as negative and positive controls	All DPE-NE formulations showed percentage of hemolyis in the range of 2.4–6.2% which indicates the nontoxic nature of the formulation to the cells	[169]

indicates that the "Go Niche" strategy can be used to make palm dates a competitive solution [172]. Mahmoudi et al. recommend that processed date palms be positioned within the organic culture segment [173].

The obvious benefits of date palms include being a source of energy for consumers as it contains a high level of natural sugar. The medicinal and nutritional benefits of the date palm also indicate that it is the right product to be invested in and marketed against the pandemic COVID-19 situation. As investigated and proved by the experts [172], inherent medicinal, nutritional, and health advantages of date palm products that have been identified are numerous.

DPFs and seeds can also be used at various stages of development, including stage 1, minimally processed foods; stage 2, processed culinary ingredients; and stage 3, ready-to-consume processed foods and beverages. According to Ghnimi and Umer [174], there are many published patent applications on DPF. These patents cover innovative functional substances, techniques, and formulations including date pulp, seeds, and/or bioactive compounds that have medicinal or nutritional properties. The majority of these patents deal with ethanol production, fruit wine, fiber concentrates, coffee-like beverages, and nutritional and/or medicinal tablets [174].

Consumers, markets, and rivals must all be understood in order to design goods that deliver higher value to customers [175]. In other words, finding and expanding new goods requires a systematic, customer-driven new product development (NPD) approach [176]. In order to further analyze the possibilities of new product development of palm dates against the pandemic COVID-19, designers need to adopt the appropriate discerning mindset [177] to ensure that their process of applying the principle steps in the NPD process results in desirable design outcomes. Typically, a corporation develops hundreds, if not thousands, of ideas during the idea creation stage by sketching individually and in groups [178–180] and continuing prototyping and production ideas in order to come up with a small number of viable options in the end (Fig. 8). Evidence found in the previous literature proved that palm dates have a big potential in producing a quality product that not only as a typical fruit for daily life but as a potential remedy for COVID-19 disease.

Prospects of Date Palm Against COVID-19

COVID-19 was first known and reported in the last quarter of 2019 and was reported to have spread across the globe. With the potential spread and severity of the disease, the World Health Organization announced COVID-19 as a pandemic [181]. There were several reasons that claimed that different types of animals are the causative agents for the disease [182]. Several types of treatments were also tried as there was no medication at the beginning. Medicinal plants or herbal medicine is one of the most important

Fig. 8 The step of production development

areas of research in treating the disease. The researchers and scientists tried to formulate various kinds of herbal and traditional formulations to get rid of the complications of the disease. Several studies reported on medicinal plants and their efficacy on COVID-19. Different types of medicinal plants and traditional medicine have been tried as a preliminary treatment in different countries including China and India [183]. Several types of medications have been directed for the medication of COVID-19 infection and numerous other treatment methods are on the way. However, there is no systematic and effective medicine that has been recommended for the therapy of this newly emerged very complicated viral disease.

The medicinal plants which belong to different types of families including Zingiberene and Cupressaceae were used to check the efficacy of the plants for COVID-19 [184]. Curcuma longa is one of the important plants been used along with several other plants including *Zingiber officinale*, *Allium cepa*, *Eucalyptus alba*, *Rosmarinus officinalis*, *Ocimum sanctum*, cinnamon, and date palms. The main reason to use these medicinal plants is mainly due to their efficacy in treating viral diseases with potential phytochemicals and secondary metabolites [185]. These plants not only possess single biological activity, but numerous other potential beneficial activities were reported including anti-inflammatory, anticancer, and antibiotic. The secondary metabolites present in these plants play a major role in ameliorating the severity of the disease. Essential oils are also useful in the treatment of bacterial and viral infections [186, 187]. Essential oils are being used as antiviral agents against numerous types of pathogenic viruses. A recently reported study clearly showed hypothetically that the phytochemical components of essential oils have the potential to target the protein in COVID-19.

Phoenix dactylifera is a plant of the DPF family [188]. The family Arecaceae has approximately 200 genera and about 2,500 species. This is one of the most recognized and oldest perennial fruit trees for ages. Flavonoids of this family were reported for potential biological activities including antibacterial, antioxidant, anti-inflammatory, anticancer, anti-allergic, and antiviral, through in vitro and in vivo studies. The plant has been reported on several in vitro and in vivo studies that tested on toxicity in the COVID-19 patients. A very recent study by Ghasem Takdehghan et al. reported that several biochemical parameters amelioration evidenced when compared to the placebo group. The study parameters were on testing the CRP levels, white blood cells, erythrocyte sedimentation rate, lactate dehydrogenase, and the pressure of oxygen (PO2). The study was conducted with 136 patients who were mildly and moderately affected with COVID-19 and the patients have received regular medication along with the date palm leaf extraction solution five times a day. The extraction of 5 mL was diluted in 30 mL water and all the procedures were done under the physician's monitoring. The study reported the decrease of C-reactive proteins (CRP), erythrocyte sedimentation rate, and lactate dehydrogenase in the treated group. The PO2 levels and white blood cells were also significantly increased with the date palm interventions [25]. Another study from Sabah et al. (2007) reported that the date palm extracts are potential against different types of viral cells including human immunodeficiency syndrome (HIV). *Phoenix dactylifera* extracts were significant in inhibiting the contagion of lytic Pseudomonas phage ATCC 14,209-B1 to *P. aeruginosa* due to its interactive mechanism of action through phage binding to the host bacterium [23]. In the same study, it was reported that the extracts of date palm showed highly significant action

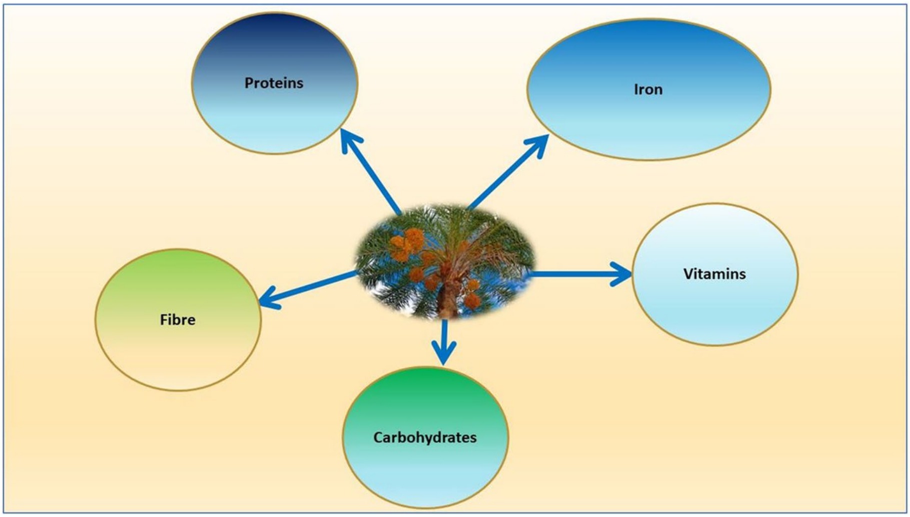

Fig. 9 Different types of biological components available in date palms

in inhibiting the infectivity and blocking the bacterial lysis and this may be a potential for antiviral activities.

Different types of biological components are shown in Fig. 9. Several biological potentials of date palms are shown in Fig. 10.

In this scenario, the palm plantations available in Malaysia may also possess the above-mentioned biological activities including antiviral activities. There is a need for the hour to explore the native Malaysian palm leaves and fruits and their components for antiviral activities including COVID-19 and its complications. More research is needed in the exploration of mechanistic activities of flavonoids and secondary metabolites of date palms against various types of diseases including viral diseases and their complications. The date palm and its products need to be explored much with intense biological activities, especially with various kinds of virus diseases and bacterial diseases with emphasized biochemical and molecular mechanistic pathways.

Conclusion

This current review demonstrated the various bioactivities of DPF contents where they serve an important function as a promising alternative supplement in protecting the human body from COVID-19 disease. All of these nutritional and functional benefits of DPFs imply that DPF constituents could be used in nutraceutical and therapeutic applications. Further research on the functional applications of DPFs is required before they can be used as a part of essential medical treatment particularly in managing COVID-19 patients.

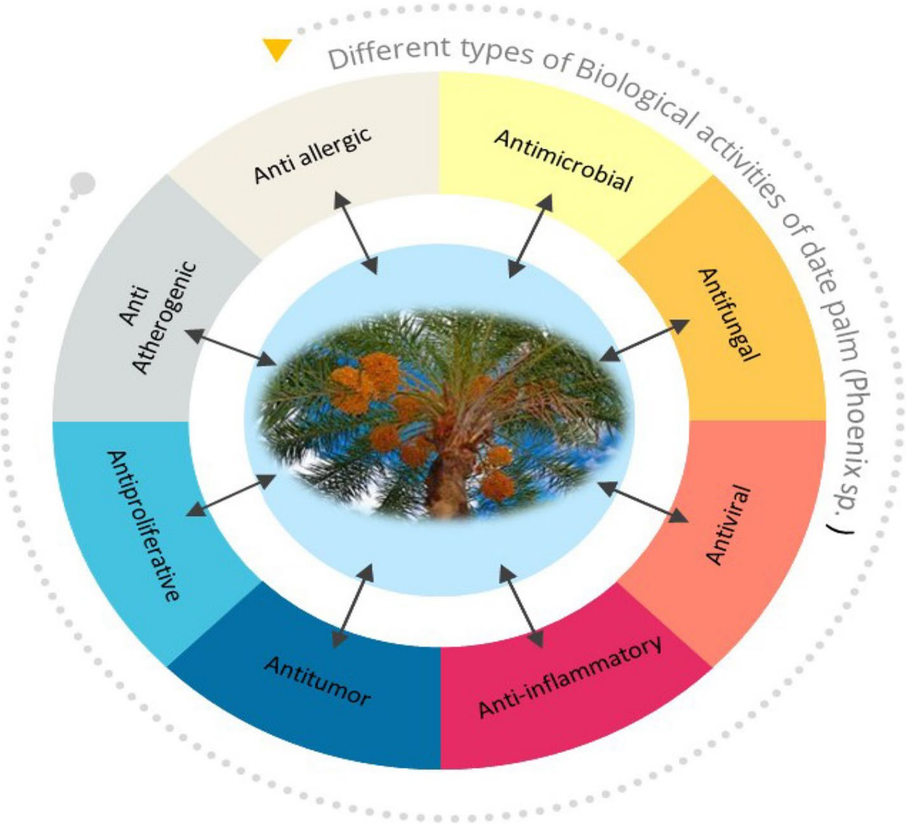

Fig. 10 Different types of biological properties of date palms

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Declarations

Ethics Approval Not applicable.

Informed Consent Not applicable.

Conflict of Interest The authors declare no competing interests.

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