



# Nanoformulation Strategies for *Phoenix dactylifera* Bioactives: Phytochemical Profile, Mechanistic Insights, and Translational Challenges

Shrishty Bahuguna<sup>1</sup>, Saumya Das<sup>1</sup>, Priyanka Bansal<sup>1</sup>, Monika<sup>1</sup>, Sachin Kumar Singh<sup>2</sup>

<sup>1</sup>Noida Institute of Engineering and Technology (Pharmacy Institute), 19 Knowledge Park- II, Greater Noida, 201306 Uttar Pradesh, India

<sup>2</sup>School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar-Delhi, G.T. Road, Phagwara, Punjab, 144411, India

Corresponding author: Saumya Das

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## KEYWORDS

Phoenix dactylifera, phytochemical profile, nanoformulation mechanism, nanoformulations, existing nanoformulations, plant-derived products limitations

## ABSTRACT:

Botanical bioactives remain a mainstay in pharmaceutical discovery and development; yet, its translational use in medicine is often hampered due to their low hydrophilicity, chemical liability, accelerated metabolism, and limited system bioavailability. *Phoenix dactylifera* L. (date palm tree) is a dietary as well as medically high-value therapeutic herb known to be high in polyphenols, flavonoids, carotenoids, sterols, dietary fibers, and micronutrients and exhibiting established and documented antioxidant, anti-inflammatory, metabolic, and cytoprotective properties. Regardless of their ideal and spectacular multitargeted biological characterization and activity, their therapeutic and pharmaceutical use particularly concerning their active principles remains limited and hampered due to formulation-based problems. The present review aims to provide a global as well as current synthesis on nanoformulation approaches for herbal phytoconstituents with a special focus on their possible and pertinent use on *P. dactylifera* bioactives. The objective is to examine and critique several nanocarrier systems containing polymeric nanoparticles, lipid nanocarriers (solid Lipid Nanoparticles/Nano-Structured Lipid Carriers and liposomes), nanoemulsions, nanogels, and metallic nanoparticles synthesized through green methods. These nano-systems are evaluated on their possible roles and uses in improving solubility, confining breakdown, facilitating cellular uptake, controlling and regulating sustained and targeted drug delivery.

**Introduction:** *Phoenix dactylifera* or date palm, a herbal plant of *Arecaceae* family has antioxidant, anti-inflammatory, antimicrobial, and neuroprotective activities. Its applications in medicine are limited because of lower solubility, stability, and bioavailability.

**Objective:** To analyse the phytochemical profiling, mechanism of nanoformulation of *Phoenix dactylifera* for enhancement of therapeutic properties.

**Methods:** The comprehensive survey of the literatures was performed in PubMed, Scopus, and Google Scholar in order to obtain results from the period of 2001 to 2025 by using keywords of "*Phoenix dactylifera*," "phytochemical profiling," "mechanism of nanoformulation," and "nanoformulation." Peer-reviewed articles written in English language were considered in order to understand the concept of nanoformulations.

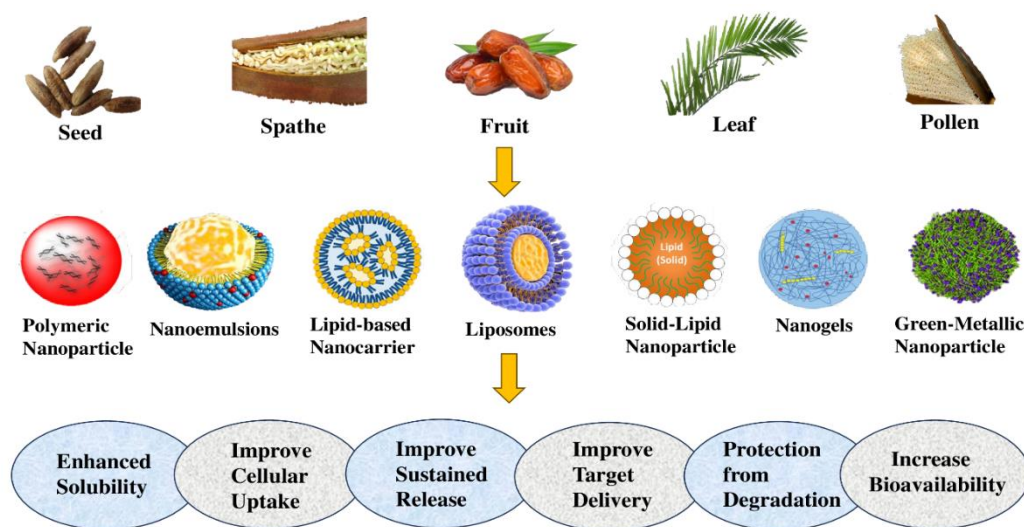
**Results:** The pharmacological potentials of *P. dactylifera* involve several biologically active components like flavonoids, phenolic acids, carotenoids, sterols, triterpenoids, polyphenols, tocopherols, and essential oils. Nano-formulation approaches like polymeric nanoparticles, liposomes, nanoemulsions, nanogels, and green-synthesized metallic nanoparticles have been



effective enough to enhance solubility, permeability, degradation, and controlled release. Nano-formulation approaches could hold potential to overcome the challenges related to bioavailability and in the fields of pharmaceuticals, nutraceuticals, and cosmeceuticals.

Conclusion: Nanotechnology provides promising solutions towards optimizing the medicinal benefits of *Phoenix dactylifera*. Further studies are to be done for establishing clinical efficacy, standardization of formulations, and larger-scale productions for broader therapeutic use.

### Graphical abstract



## [1] INTRODUCTION

A traditional major source for the creation of these plant-based natural products is plant extracts. The plant extracts might be therapeutic medications, which has helped provide evidence that roughly one-half of current approved drugs are made directly and indirectly from plant phytochemicals [1]. Though the potential is vast, many bioactive compounds face substantial limitations such as poor water solubility, instability to chemical conditions, rapid metabolism, and exposition to degradation in the gastrointestinal tract, to name a few, affecting their translational potential in the clinic [2–4]. During the recent years, the area of nanotechnology has played a paradigmatic role in filling the above-mentioned gaps by improving solubility enhancement, molecular stabilization, target-specific delivery, and overall pharmacokinetic properties [5,6]. This growing synergy between traditional herbals and innovative nanocarriers has opened up newer avenues for the development of rationally designed phytopharmaceuticals, which

possess high efficacy and greater therapeutic potential [7,8].

*Phoenix dactylifera* L. (date palm tree), being a medicinal plant, has one of the oldest histories of cultivation, both with regard to nutritional quality and therapeutic properties. It is an essential ingredient of medicine in South Asia, South Africa, and the South-West Asia & Arabian regions [9]. Phytochemical analysis has shown the presence of high levels of phytochemicals such as polyphenols, sterols, flavonoids, carotenoids, and dietary fibers. Phytochemicals in *P. dactylifera* have been shown to have strong therapeutic properties in areas of antioxidant, anti-inflammatory, antidiabetic, hepatoprotective and neuroprotective [10,11]. Among these constituents, key compounds including phenolic acid (gallic, ferulic, and caffeic acid) and flavonoids (quercetin, luteolin, and apigenin), play their vital function through modulation of fundamental mechanism of oxidative stress and inflammatory pathways [12]. Experimental studies show evidence on the ability of *P.*



*dactylifera* extract to reduce lipid peroxidation, enhance antioxidant enzyme activity, and offer neuroprotection as well as protection to liver cell membranes. This evidence makes known its role as a treatment tool in clinical studies on neuroprotection and metabolism [10,13].

The rapid advancement in plant-based medications is greatly derived from nanotechnology which directly resolve the critical formulation difficulties, including low aqueous solubility, molecular instability, accelerated metabolism and limited oral bioavailability of bioactive constituents. Nanoscale delivery systems including polymeric nanoparticles, lipid-based nano carriers, liposomes, nanostructured lipid carriers, nanoemulsions and solid lipid nanoparticle are vital for enhancing translational prospects of herbal compounds. The systems offer increased therapeutic effect, protecting Labile bioactive from degradation, controlled drug release and increased bioavailability via improved cellular uptake and specific tissue delivery [7,14,15] Green or biogenic strategies utilizing extracts of plant as reducing and capping agents have simplified the yield of nanoparticles. This approach is advantageous as it possesses valuable biological activities, mainly antimicrobial properties and antioxidant activities [16]. *Phoenix dactylifera* (date palm) has high content of polyphenols, flavonoids as well as polysaccharides which makes them ideal candidates for nano-scale carriers. Recent research indicates that integrating date-palm constituents into nano-system significantly increases their efficacy, exemplified by PEGylation of date-fruit extract successfully displayed improved solubility, amplified cytotoxic effects in cell culture models compare to the unformulated extract[17]. Silver nanoparticles produced using phytochemicals within date-palm extract (fruit, leaf and seed) demonstrate significant antibacterial and antineoplastic properties[18,19]; Zinc oxide (ZnO) nanoparticles that are biosynthesized using date polyphenols demonstrate a higher antimicrobial and antioxidant activity in comparison to the crude date extract[20]. Furthermore, nanolipid carriers and mucoadhesive polysaccharides nanoparticles have been tailored for topical and colonic delivery of date extracts. This illustrates the dual capacity of date-palm constituents as potential therapeutic agent and functional components in nano-formulations[21]. This is further supported by the cumulative evidence that nanoformulation systems do enhance the stability,

bioavailability, and overall bio-efficacy of the components in *P. dactylifera*. Success should be a precursor to their development toward standardized nano-herbal therapeutics

However, while the field recently experiences growing scholarly attention, comprehensive explorations of nanoformulation of *P. dactylifera* bioactive compounds remains scanty. Bibliometric trends, between 2004 and 2023, for "herbal nanoparticles" indicate marked expansion but simultaneously demonstrates the dominance of selective bioactives-especially curcumin-and concentrated research foci, overshadowing the literature on underexplored species, date palm inclusive, with regard to the prevailing imbalances in scholarly attention across the botanical sources [22]. Such observations underscore the large research gap for such studies, thus posing an opportunity for conducting research on formulations at the nano-level for *P. dactylifera*. The use of nanotechnology with a variety of photochemical bases of *P. dactylifera* represents a strategic approach for enhancing the therapeutic efficiency of the compound

The aim of the present review is to offer an exhaustive overview of the current nanoformulation approaches for plant-based bioactive compounds. To this purpose, the present review aims to: (i) offer an in-depth characterization of the phytochemical characterization and therapeutic potential of *P. dactylifera*; (ii) briefly discuss the major approaches for the nanoformulation of bioactive compounds; (iii) discuss the underlying mechanisms that promote the enhanced therapeutic efficacy of plant-based extracts mediated through nanocarrier-based delivery; (iv) examine the current nanoformulation approaches for *P. dactylifera*, or, in the absence of such data, draw inferences based on comparative analyses based on other plant-based bioactive; and (v) critically discuss the major existing issues as well as the future prospects for designing nanosized delivery carriers for the therapeutic constituent of *P. dactylifera*.

## [2] PHYTOCHEMICAL COMPOSITION OF PHOENIX DACTYLIFERA

The fruits of *P. dactylifera* have been known over generations because of their rich phytochemical composition. The nutritional and biochemical



constitution establishes the rich presence of carbohydrates (primarily in the form of simple sugars), dietary fibers, and numerous secondary bioactive constituents. The variation in the quantity and quality of these is largely affected by variables such as differences in the growers, maturity stages, soil quality, and post-production processing. The total carbohydrate content in dates (*P. dactylifera L.*) has been established at 66% of their weight[22–25]. Table 1 summarises the phytochemicals present in *Phoenix dactylifera*.

#### [2.1] Carbohydrates, sugars and dietary fibre in *Phoenix dactylifera* (Date Fruit)

Date palm fruits are valued because of the high energy density content owing to the richness of carbohydrates, which signifies the dual utility of the fruit as both nutritional and functional use in arid and semi-arid regions [26,27]. The carbohydrate composition of *P. dactylifera* fruits is variable according to their growers, stage of ripening, and conditions of post-harvest handling. It is dominated by the presence of soluble carbohydrates such as glucose, fructose, and sucrose, accompanied by adequate amounts of non-digestible polysaccharides and fiber [26–28]. Dry matter analysis studies have shown that the carbohydrates content in date fruits ranges from 40 to 80 percent depending on the farmer and environmental conditions. For example, the soft-textured varieties like Sukkari contain 69.2-84.2%, while varieties such as Khasab recorded lower carbohydrate content, reflecting the interaction of genetic and environmental factors. [28,29]. These variability results highlight the importance of the type of cultivator, environment, ripening stage, and moisture content to ensure proper interpretation of date fruit composition[26,28].

The sugar content of the fruits of *P. dactylifera* is dominated by the genetic factor, as well as the types or stages of ripeness. Glucose, fructose, and sucrose were found to be the major components. Sucrose varied according to the sample analysed [26]. These varieties of date are categorized as “invert-sugar type” such as Barhi Dates and Medjool Dates. These varieties are rich in glucose, fructose, but minimal in sucrose. It makes the date softer in texture along with an intensified sweet sensation[27,30]. In contrast, dried/semi-dried “cane-sugar type” varieties such as Deglet Nour may contain a higher proportion of sucrose to reducing sugars. Varieties

described as “intermediate” both sucrose and reducing sugars are affected by the degree of ripening[31]. Besides the simple sugars, the date fruit further contains dietary fibers and polysaccharides in the form of cellulose, hemicellulose, pectin, and  $\beta$ -glucans [27,32] Date fruit on a dry weight basis contains 6.5% to 11.5% dietary fiber with a predominant component being insoluble and a smaller portion being soluble fiber[28,33]. These non-digestible carbohydrates have beneficial physiological effects such as gastrointestinal functions, blood sugar regulation, and increased satiety. This makes the functional and nutrient values of dates more diversified as compared to their major use as a source of energy[27,28].

Biochemical changes occurring due to sugar composition take place in the ripened date fruits. The initial stages of development (Khalal/Kimri stages) are differentiated as the predominance occurs due to sucrose. Later stages (Rutab and Tamr stages) see the action of the endogenous invertase enzyme that splits the sucrose molecule into glucose and fructose; that is, the increase in the content of the reducing sugar [28,31]. The high glucose and fructose levels in dates make them a quick source of energy. This property underlines their cultural and nutritional use in fasting, supporting endurance exercises, and as a convenient calorie source when food is not available in large quantities in regions[32]. In addition, the diversity of sugar content among date varieties underlines the soft, invert sugar date is more ideal for instant energy needs or as a natural sweetener agent in comparison to the semi-dry and dry date varieties for preservation purposes or development of date-based commercialized products [31,34].

#### [2.2] Minor Macronutrients: Proteins, lipids, oils

In *P. dactylifera* fruits, minor constituents like proteins and lipids, although quantitatively less prominent compared to carbohydrates, have a tremendous role in terms of nutrition. The date fruits, as collected from a survey, have been reported to possess a mean of 2-6 grams of proteins per hundred grams of dry weight[26,35,36]. Despite these values being comparatively low compared to the content of protein-rich crops such as oil seeds and legumes, the presence of a broad spectrum of amino acids including the important ones like lysine, leucine, isoleucine, and arginine increases the nutritional efficiency of cereals as food in



arid regions[26,36]. In a recent review of date palm and food security, the importance of the date palm was reaffirmed in issues pertaining to the concentration of protein levels ranging from 2.3% to 5.6% (dry weight) in amino acids and micronutrients as a minor macronutrient[36]. In 2025, a literature review on the composition and values of date fruit called attention to the fact that lower levels of protein, even 1.7 to 12.5 grams per 100 grams, depending on variety and moisture content, are physiologically meaningful as it acts as a precursor for bioactive peptides [26].

The seed of *P. dactylifera* is consistently richer in protein than the flesh. Reports from Moroccan and Middle Eastern cultivars indicate seed protein levels ranging from 4 to 9% of dry weight[37–39]. In Medjool seed flour, ~7.6% of protein and ~10.2% of lipid has been identified along with considerable fiber and phenolic compounds underscoring its potential as functional food rather than waste material[38]. Investigations of North African and Gulf cultivars stated that seed meals represent protein and dense fiber with functional application in bakery, beverage, and snack products[37,39]. More recently, enzymatic treatments of seed proteins with food-grade proteases have enhanced solubility, emulsification and antioxidant activity, suggesting their use in generating specialized protein formulations and peptide rich extracts[40].

Lipid concentration in date is very low, typically less than 1% of fresh weight due to which it is characterized as fat-poor fruit[26,35,36]. Conversely, the seed represents a promising alternative oil source. Studies conducted since 2018 have reported that date seed oil (DSO) yields in the range of 5 to 13% of seed dry weight which varies according to cultivar type, maturity stage, and extraction methodology[41–43]. According to Nehdi et al. mean oil content of 6 Saudi date cultivars was approximately 7%. The analysis revealed that oleic acid was the major fatty acid (~49%) followed by lauric, stearic, palmitic and linoleic acids[41]. Subsequent studies between multiple cultivars identified that oleic acid is the principal fatty acid, however the relative levels of lauric, palmitic and linoleic acids vary substantially among varieties leading to modulation in saturation and melting behaviours of the oils[42–44].

[2.3] Phenolic Compounds and Flavonoids in *Phoenix dactylifera*

The fruits and seeds of *P. dactylifera* are not only provide good amounts of sugars, fiber and carbohydrate but also harbours diverse phenolic compounds such as phenolic acid, flavonoids and polyphenols. These constituents are recognized for their significant role in antioxidant activity, antimicrobial activity and broader health promoting effects [45]. A comprehensive knowledge about their diversity and variability is necessary for nutritional assessment as well as valorisation of date residues [45,46].

#### [2.3.1] Phenolic Acids and Related Polyphenols

Studies of mature fruits of *P. dactylifera* revealed the high concentration of total phenolic content (TPC) with values ranging into the several hundred mg of GAE per 100 g DW. This indicated the presence of a high number of phenolic acids and polyphenols[45,47]. In addition, the TPC has been shown to be strongly heterogeneous in published values largely owing to differences in cultivars, stages of ripening, specified solvent for extraction as well as methods utilized [45]. Various phenolic acids were found to be present in the fruits of *P. dactylifera* species like gallic, caffeic, p-coumaric, vanillic, chlorogenic syringic, ferulic, and sinapic acids. These acids were analyzed quantitatively in seed extracts or fruit extracts prepared using aqueous or methanolic solvents[48,49]. In a comparative study carried out using 9 varieties, it was found that total phenolic content had a pronounced positive relationship with antioxidant and antibacterial activities, proving the significance of such phenolic acids [50].

By-products like date pits or date seeds have increasingly been recognized as a prospective source of phenolics. In 2020, research was conducted on the TPC content of which exceeded 2000 mg GAE per 100 gm dried weight in certain seed varieties with higher Total Flavonoid Content (TFC) to be used in nutraceutical applications[39]. In addition, the polyphenol composition of date fruits (flesh as well as seeds) has variability according to genotype, origin, stages of ripeness, and subsequent treatments after harvesting, indicating the need for choice of cultivar in research on nutrition studies as well as in its use[47].

#### [2.3.2] Flavonoids & Other Polyphenolic Compounds

Aside from the existence of common phenolic acids, the date fruits and seeds also contain complex flavonoids and



polyphenolic compounds such as flavonols, flavones, and flavan-3-ols [46,50]. High resolution LC-MS/MS analysis of various cultivars revealed the presence of upto 69 separate polyphenolic compounds in the fruit and seed extract, thus exemplifying the complex phytochemicals and antioxidant properties of such plant extracts [47]. In numerous studies, some of these widely detected flavonoids are found to be quercetin, apigenin, luteolin, catechin, epicatechin, and rutin and their glycosides such as naringenin-7-O-glucoside and isorhamnetin glycosides. The coexistence of aglycones and glycosides reveals a variability in polarity and solubility, capable of affecting bioavailability[49].

Analyses of antioxidant evaluation using DPPH, ABTS, FRAP, phosphomolybdenum and chelation-based assay revealed that fruits and seeds exhibit radical scavenging and reducing activities which generally correlates with their total phenolic and flavonoid concentrations[38,46]. Distinct differences among cultivars focused the role of genetic variability and environmental conditions on phytochemical composition and resultant bioactivity[38,50]. Recent investigations reveal additional biological properties of date-fruit and seed extracts, such as anti-bacterial, anti-inflammatory and anti-glycation and even antitumor or cytoprotective activities across in vitro and in vivo models[33,51]. Seed and fruit preparations have exhibited significant bacterial proliferation, such as staphylococcus aureus and bacillus cereus, which is appeared to be linked with their rich polyphenolic levels[50].

#### [2.4] Minor Bioactive Compounds: Carotenoids, Sterols, Triterpenoids and Micronutrients

As the nutritional profile of *P. dactylifera* is mainly characterized by carbohydrates, fibers, phenols and flavonoids, but the fruit and its by-products, like peel and seed contains notable lipophilic micronutrients and minor secondary metabolites that enhance its functional and therapeutic potential. These include carotenoids, tocopherols, phytosterols, triterpenoids, and a spectrum of essential minerals and trace elements[27,52–54]. These constituents provide antioxidant defense, provitamin properties, cholesterol-lowering effects and micronutrients support functions, making them relevant in the use of nanoformulation application for lipophilic date-derived bioactives[55].

Carotenoids represent as a well-defined group of minor constituents of dates. compositional assessment highlight lutein and beta-carotene as the principal carotenoids in date pulp and seed oil with smaller fractions of beta cryptoxanthin and lycopene detected at lower levels across certain varieties [35,56,57]. Investigations using chromatographic profiling demonstrate that across several cultivars and ripening phases demonstrate that carotenoid content are at peak in dates during khalal and subsequently reduces as fruits progress to rutab and tamr which reflects oxidative degradation and structural isomerization during maturation and storage[35,56]. Beyond compositional changes these carotenoids provide provitamin A activity, acts as singlet oxygen scavengers, and stabilize cellular membranes which together support ocular integrity and systemic health outcomes. However, their poor aqueous solubility and sensitivity to degradation under light, heat and oxygen restrict their stability and bioavailability in traditional preparations. Accordingly, encapsulation using lipid-based or polymeric nanocarriers offers a strategy to improve their protection and facilitate efficient delivery[53,56–58].

Beyond carotenoids, date-seed oil contains tocopherols and tocotrienols, particularly  $\alpha$ -tocopherol and  $\gamma$ -tocopherol[53,59,60]. These vitamin E homologues act as lipid-soluble antioxidants, capable of interrupting lipid peroxidation cascades in both cellular membranes and food systems. As a result, date seed oil has been suggested as a suitable carrier for lipophilic molecules to enhance oxidative stability in food applications[42,59,60]. From a nanoformulation point of view, the intrinsic tocopherol in date-derived oils may provide synergistic antioxidant effects by protecting encapsulated carotenoids and phenolic compounds[61–64].

Phytosterols are another notable constitute within the unsaponifiable fraction in date fruit and seed oil. Quantitative analyses have disclosed a total sterol level of 3000-3500 mg/kg of oil, with  $\beta$ -Sitosterol being identified as a major sterol, accompanied by Campesterol and  $\Delta^5$ -Avenasterol. Plant sterols are recognised for their cholesterol-lowering, anti-inflammatory, and exert anticancer effects, which are mediated partly through competitive inhibition with cholesterol during intestinal absorption and modulation of inflammatory signalling



pathways. In nanocarrier systems, the native sterol composition of date seed oil is shown to have a crucial role in membrane formation, interfacial properties, or stability of lipid-based nanocarriers regarding nanoparticle formulations based on compositional information[42,59,60,65].

Besides the minor organic phytoconstituents, the mineral composition of date fruit *P. dactylifera* is very important. There have been reports on the levels of the major mineral constituents, which include potassium (400-700 mg/100 g), alongside considerable quantities of magnesium, calcium, and phosphorus. Lower levels, though still a nutrient, have been found in iron, zinc, copper, manganese, and selenium [29,52,54,66,67].

Potassium is importantly involved in blood pressure regulation and electrolyte homeostasis, while magnesium and calcium play pivotal roles in neuromuscular excitability and bone affairs. Other components like Selenium and Zinc are additionally involved in antioxidant actions and immunomodulation[52,54,66]. Variability in mineral content is mainly dependent on the cultivar and the soil and growing practices [29,66,67]. Recent studies focusing on specific date cultivars such as Sukkari confirms that potassium, magnesium, copper and selenium largely contribute to daily intake, which highlights dates as “mineral-rich” dietary component than other simple saccharide sources[29,60].

**Table 1: Summary of phytochemicals present in *Phoenix dactylifera***

PHYTOCHEMICAL CLASS	REPRESENTATIVE COMPOUNDS IN <i>P. dactylifera</i>	FUNCTIONAL ACTIVITIES REPORTED	SUPPORTING REFERENCES
Carbohydrates & Simple Sugars	Glucose, fructose, sucrose; oligosaccharides (raffinose, maltose)	Rapid energy source, glycaemic modulation, osmotic balance, supports endurance and fasting nutrition	[26–34]
Dietary Fiber & Polysaccharides	Cellulose, hemicellulose, pectin, $\beta$ -glucans	Prebiotic effect, gastrointestinal regulation, improved satiety, glycaemic control, lipid-lowering	[27–33]
Proteins & Amino Acids	Essential amino acids: lysine, leucine, isoleucine, arginine	Nutritional enhancement, precursor for bioactive peptides, supports metabolic and enzymatic functions	[26,35–40]
Fatty Acids (Seed Oil)	Oleic acid (major), lauric, palmitic, stearic, linoleic acids	Energy-dense oil, membrane health, antioxidant synergy, supports functional food formulations	[41–44]



Phenolic Acids	Gallic, caffeic, p-coumaric, ferulic, vanillic, syringic, chlorogenic acids	Antioxidant, antimicrobial, cytoprotective activity, anti-inflammatory, anti-glycation	[45–51]
Flavonoids & Polyphenols	Quercetin, rutin, catechin, epicatechin, apigenin, luteolin, naringenin glycosides	Strong antioxidant activity, antibacterial effects, anti-inflammatory, antitumor potential, neuroprotection	[46–51]
Carotenoids	Lutein, $\beta$ -carotene, $\beta$ -cryptoxanthin, lycopene	Provitamin A activity, singlet oxygen scavenging, membrane stabilization, vision protection	[35,56,57]
Tocopherols & Tocotrienols (Vitamin E)	$\alpha$ -tocopherol, $\gamma$ -tocopherol	Lipid-phase antioxidant, prevention of lipid peroxidation, enhances stability of lipophilic molecules	[53,59–64]
Phytosterols	$\beta$ -sitosterol (major), campesterol, $\Delta^5$ -avenasterol	Cholesterol-lowering, anti-inflammatory, supports membrane structure, enhances nanoparticle stability	[42,59,60,65]
Triterpenoids	(e.g., lupeol, ursolic acid reported in seeds by GC–MS screening)	Anti-inflammatory, hepatoprotective, anticancer potential, antioxidant properties	[52–54]
Minerals & Trace Elements	K, Mg, Ca, P, Fe, Zn, Cu, Mn, Se	Electrolyte balance, neuromuscular function, bone health, immune support, antioxidant enzyme cofactor roles	[29,52,54,66,67]

### [3] NANOFORMULATION STRATEGIES FOR PALNT BIOACTIVES

#### [3.1] Polymeric nanoparticles for plant bioactives

Polymeric nanoparticles (PNPs) have emerged as a versatile platform for the delivery of plant bioactives, attributed to their biodegradability, biocompatibility with biological system, particle dimensions and dual encapsulation ability for both hydrophilic and hydrophobic molecules[68,69]. Natural biopolymers including chitosan, alginate, pectin, and cellulose derivatives with synthetic biodegradable carriers like

PLGA and PCL, have been widely utilized to stabilize polyphenols, flavonoids, carotenoids and many bioactives because of their advantageous physiochemical stability and mucoadhesive nature[68,70]. These polymeric formulations enhance interaction of phytoconstituents with biological membranes and safeguard them from early degradation[69]. Polymeric encapsulation provides a strategic means to overcome the inherent drawbacks of plant bioactive including poor solubility in aqueous environment, gastrointestinal instability, rapid metabolic clearance and poor permeability[68,69]. Polymeric nanocarriers protects



these bioactives from oxidative damage, enzymatic breakdown and pH-mediated degradation, thereby enhancing their biological half-life and improving systematic bioavailability[70,71]. In addition, the delivery systems offer control and release of the components that ensure a constant therapeutic concentration and reduce the need for dosing as opposed to conventional dosage forms [70,72].

Recent advancement in polymer-lipid hybrid nanoparticles has emerged as a promising nano-delivery strategy which marks the mechanical durability of polymer with high solubilizing advantages of lipids [70]. Such systems are more effective in encapsulating lipophilic phytochemicals found in *P. dactylifera*, for example, carotenoids, tocopherols, sterols, and terpenoids. PLHNPs have improved encapsulation, stability, and pharmacokinetic profiles [70,72]. In fact, their distinctive bipolar nature also allows for the co-encapsulation of multiple phytoconstituents, thereby fostering synergistic effects and overall therapeutic value in phytochemicals-rich preparations[70,73,74]. Recent research attention has been devoted to the advancement of green-engineered polymeric nanocarriers produced through solvent-free, low-solvent or eco-friendly methods utilizing biodegradable polymers[71]. These methodologies ideally suited for food and herbal therapeutic systems where safety, non-toxicity and strict regulatory compliance are essential requirements[71,72,75]. Furthermore, surface-engineered polymeric nanoparticles targeting ligands including folate, peptides, antibodies and polysaccharides have shown marked efficacy in improving their potential cell-specific delivery to cancerous tissues, inflamed tissues and specific molecular receptors[69,72,76]. Such ligand-conjugated nanocarriers promote higher site-specific decomposition of phytoconstituents and minimizing off-target toxicity[72,76]. In parallel, stimuli-responsive polymeric nanoparticles are capable of releasing phytochemicals under microenvironmental triggers such as pH, enzymatic activity, temperature shifts, or redox changes, thereby recognized as powerful approach for precision delivery in oncology and inflammatory pathologies[76,77].

[3.2] Lipid-based nanocarriers for delivery of plant bioactives

The development of lipid-based nanocarriers is recognized as promising delivery platforms for plant-derived bioactives. Their resemblance to biological membranes, capacity to solubilize hydrophobic compounds, and proven safety across several applications in food, nutraceuticals, and pharmaceuticals[78,79]. Among the various platforms, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes systems represent the substantial evidence offering enhancements in phytochemical stability, improving phytochemical bioavailability and enhancing therapeutic efficacy[79,80]. *P. dactylifera* components, like carotenoids, tocopherols, steroids, or polyphenols, which are lipophilic or sensitive to simulated gastrointestinal environments, require nanoscale lipid carriers for optimized formulation and target delivery. SLNs, NLCs, and liposomes protect these components, like carotenoids and tocopherols, against oxidation, whereas liposomes can increase the permeability level and uptake of phenolic acids and flavonoids. These nanoscale carrier systems have been recognized to enhance the oral bioavailability and efficacy of phytoconstituents in dates[54,81,82].

### [3.2.1] Solid Lipid Nanoparticles [SLNs]

Solid lipid nanoparticles consist of a solid lipid core that is stabilized using surfactants. They hold potential in encapsulating plant-derived compounds such as polyphenols, carotenoids, flavonoids, and terpenoids [83–86]. The crystalline structure of the lipid core provides them with excellent resistance capabilities against oxidative stress, photodegradation, as well as biological degradation, thus making them a suitable carrier for encapsulating *P. dactylifera*-derived unstable bioactive compounds[87–89]. However, rigid structural organization is a disadvantage because it limits drug loading capacity and causes bioactive leakage during drug storage. Despite these limitations, extensive evidence has demonstrated their ability to enhance oral bioavailability and reinforce antioxidant potential of encapsulated phytochemicals.[89,90].

### [3.2.2] Nanostructured Lipid Carriers [NLCs]

Classified as second-generation lipid nanoparticles, the NLCs are prepared by combining solid and liquid lipids to create an imperfect matrix that showcases better drug



loading capacity than SLNs [83,85]. This flexible matrix also exhibits good drug incorporation properties without the leakage of the drug, ensuring the control release [85,86]. Experimental evidence indicates that the absorption and bioavailability of herbal materials increased with the use of NLCs, which are beneficial for the bioactive compounds found within the *P. dactylifera* because of their liability to degradation and poor aqueous solubility [86]. Further evidence indicates that the properties such as antioxidant activities, anti-inflammatory effects, and the healing process are enhanced with the application of plant extracts that are improved by the use of NLCs [85,86].

### [3.2.3] Liposomes

Liposomes are versatile bilayer vesicles composed of phospholipids which possess the ability to entrap hydrophilic compounds within their aqueous interior and lipophilic compounds within their bilayer structure making them promising carriers for natural products [91]. The natural biocompatibility of their bilayer structure and similarity to cellular membranes make them efficient for cellular uptake and penetration of biological barriers [91,92]. Recent advances like ultradeformable liposomes, phytosomes, niosomes, and PEGylated liposomes demonstrate greater stability and also enhance the delivery of phytoconstituents like polyphenols, flavonoids, and carotenoids [92–94]. Liposomal preparations have demonstrated promise for the delivery of an antioxidant enriched natural plant extract, thereby enhancing their cytoprotective activity and therapeutic response in various studies done *in vitro* and *in vivo* [91,93].

### [3.3] Nanoemulsions

Nanoemulsions are kinetically stable, isotropic mixtures of oil and water stabilized by surfactants. Droplet diameters range characteristically between 20 and 200 nm. This nanoscale system offers superior physicochemical properties enabling the efficacious delivery of poorly water-soluble plant-derived bioactives with limited membrane permeability [95]. The decrease in droplet dimensions increases interfacial area, enhancing dissolution kinetics and thereby promoting rapid translocation across complex biological barriers like gastrointestinal and skin barriers [96,97]. Nanoemulsion-based formulations offer a significant

advantage to the phytoconstituents of *P. dactylifera*, such as phenolic, flavonoid, and lipophilic constituents, by enhancing their solubility and chemical stability and preventing oxidative damage during fabrication and storage [98]. Their high colloidal stability is further supplemented when gravitational separation and Oswald ripening are hindered, especially in those formulations where long-chain triglyceride oil and non-ionic surfactants are incorporated [99]. Essentially, at a nanoscale dimension, the droplets in nanoemulsions facilitate effective transport across cellular and paracellular passage, while membrane fluidization by surfactants favor better intracellular uptake. This twin effect has been responsible for their better bioavailability and therapeutic response compared to conventional emulsions [100]. Recent scientific research on nanoemulsion formulations using polyphenol and medicinal extracts of *P. dactylifera* show significant enhancement of DPPH and ABTS scavenging activities, improved oxidative shelf life, and promotion of tissue protective activity against chemically induced oxidative stress [101,102]. In addition, orally delivered nanoemulsion formulations exhibit the potency to evade the first-pass effect through improved lymphatic absorption, which has significant benefits for lipophilic compounds like flavonoids and sterols of *P. dactylifera* [103]. Advanced preparation technology like high-pressure homogenization, sonication, and low energy spontaneous emulsification enables exact manipulation of nano-emulsion droplets regarding size, polydispersity values, and thermodynamic stability [104]. The nano-emulsion formulations also demonstrate broad applicability for topical, oral, and drink formulations, which acts positively towards enhanced usage within the field of cosmeceutical and nutraceutical usage of *P. dactylifera* bioactives [105]. It should also be noted that successful nano-emulsion formulation requires efficient optimization strategies and requires perceptual evaluations of surfactants and oil phase use along with stress tests of environmental factors which straightaway impacts both physicochemical properties and therapeutic performance [106]. Nanoemulsions possess collective attributes such as improved solubility, physicochemical stability, enhanced permeability, and site-specific delivery, making them a next-generation system with great potential for harnessing pharmacological benefits of *P. dactylifera* phytoconstituents.



### [3.4] Nanogels

Nanogels are described as hydrophilic cross-linked hydro-gel particles of nanometer size which possess substantial volumes of water absorption capabilities and a physio-chemical characteristic of being under 200nm large and stable as a colloidal solution. These properties make them efficient delivery systems for *P. dactylifera* and other plant-derived bio-actives[107,108]. The three-dimensional structure of nanogels enables them to hold hydrophilic and slightly lipophilic compounds and protect them from unstable phytoconstituents of hydrolysis, oxidation, and enzymatic degradation[107,109]. Relative to traditional polymeric nanoparticles, nanogels demonstrate larger drug loading capacity, adjust swelling dynamics and ease of surface modification which facilitate passive as well as active targeting strategies[107,108]. The combination of high-water content, deformable polymeric networks, and cross-link density in nanogels permit precise control over drug release. Such systems respond to physiological triggers such as pH, redox potential, and enzymatic activity, as well as external stimuli like temperature, light, and magnetic fields. These stimulus-responsive act is advantageous for site-specific release of herbal derived antioxidants and anti-inflammatory phytoconstituents[107,108,110].

Chitosan-derived nanogels are advantageous for natural phytoconstituents due to chitosan's biocompatible, biodegradable and mucoadhesive characteristics. Ionic gelation or polyelectrolyte complexation generates positive nanogels that facilitate electrostatic interaction with anionic mucosal and epithelial surfaces which enhances absorption and residence time[109,111]. Detailed toxicological investigation of chitosan-based nanogels confirm that purified chitosan nanogels are biocompatible, non-cytotoxic and non-inflammatory at relevant concentrations, which supports its utility in intra-articular and other localized delivery applications[109]. In dermatological applications, these nanogels improve penetration through the skin, enable control deposition across layers, limit systemic distribution which is beneficial for chronic inflammatory conditions and for the topical delivery of antioxidant-rich bioactives[110,111]. Recent studies highlight flavonoid based-nanogels as an innovative delivery formulation because flavonoid act as encapsulated bioactive agent as

well as functional or structural components of the gel network. Such multifunctionality approach is relevant for polyphenol-rich botanicals like *P. dactylifera*[112].

### [3.5] Green-synthesized metallic nanoparticles

Green-synthesized metallic nanoparticles (GS-MNPs) represent a sustainable, cost-efficient and biocompatible nanopatform for the delivery of plant-derived bioactives including those derived from *P. dactylifera*. In contrast to convention chemical synthesis which relies on toxic reagents and stabilizing agents, green synthesis focuses on phytochemicals such as phenolics, flavonoids, sugars and amino acid. These biomolecules simultaneously reduce metal ions and capping materials which generate nanoparticles with intrinsic functionalization and exhibit enhanced biological performance[113,114]. These bioactive mediated redox reactions facilitate the generation of metallic nanoparticles such as AgNPs, AuNPs, ZnO-NPs and iron oxide at neutral pH and moderate temperatures. This approach guarantees environmental compatibility and therapeutic relevance[115]. The intrinsic antioxidant, antimicrobial, and anti-inflammatory activities of herbal metabolites remain associated with the nanoparticle surface. This provides synergistic benefits that accelerate oxidative stability, enhances bioavailability, and amplifies therapeutic performance[116].

Particle sizes of GS-MNPs are small, ranging from 10 to 80nm. They possess highly reactive surfaces and a flexible nature, allowing for efficient accumulation in cells, enhanced capacity for radical scavenging, and targeted cell death of diseased cells or tumor models[117]. Nanotechnology presents enormous advantages over phytochemicals in botanicals, as it can protectable compounds from degradation, facilitate controlled release, and promote targeted delivery by conjugation of biomolecules to nanoparticle surfaces[115,118]. More specifically, plant-mediated synthesis of silver and gold nanoparticles has a strong possess free radical scavenging activity and metal-enhanced catalytic activity, rendering these particles promising carriers or adjuvants of the bioflavonoid and polyphenolic compounds that exist in date fruits[116,119]. In addition, the strong UV blocking, wound-healing, and antimicrobial activity of zinc oxide extracted from leaf or fruit materials supports its incorporation in dermatological applications[120,121].



According to latest studies, GS-MNPs have less cytotoxicity than their synthetically produced counterparts because they contain natural capping agents which reduce uncontrolled metal ion release and avoid aggregate formation[113]. By modifying phytochemical content, extraction solvents, or precursor levels, the use of botanical extracts also permits precise manipulation of nanoparticle dimensions, shape, and stability[115]. Green nanotechnology breakthroughs have aided in improving the scalability of GS-MNPs using microwave-assisted methods, ultrasonic reactions, and continuous bioreactors, making them perfect for translational study purposes[118]. In a nutshell, green-synthesized metallic nanoparticles can be considered an eco-friendly and biologically relevant nano-delivery system for *P. dactylifera* biological active compounds with improved efficacy, non-toxicity, and convergence with plant-derived nanomedicine.

#### [4] MECHANISM OF NANOFORMULATIONS

##### [4.1] Enhanced solubility

One of the major ways through which nano-formulations can increase the efficacy of poorly soluble agents is through solubility enhancement. The poor solubility of drugs in water is a critical problem in pharmaceutical research. Nearly 40% of drugs in the market and most of the new chemical entities have poor solubility in water. Nano-formulations can prove to be an advantageous approach in this scenario[122,123].

At the core of this technology is the reduction in size of particles. A consequence of reducing the size of pharmaceutical particles into the nanometre range (<1 $\mu$ m) is a substantial increase in the total surface area in relation to volume. Based on established physicochemical principles, an increased surface area will improve the interaction of pharmaceutical particles with the dissolution system, resulting in an increased dissolution rate and apparent solubility. Such principles have been formulated in the Noyes-Whitney equation, where a direct relationship lies between the dissolution rate and surface area[124]. Another important factor is enhanced wettability. Hydrophobic regions in poorly water-soluble agents do not allow easy interaction with water molecules, thus hampering the dissolution process. Encapsulating or formulating such agents into nanosized systems such as nanoparticles, nanoemulsions, or

nanosuspensions can improve the wettability of these agents, thus helping them disperse evenly in the medium and preventing them from aggregating in a particular area. Surfactants, stabilizers, and polymers in nano-preparations can therefore enhance wettability and prevent particle agglomeration[125,126].

Some nanoformulations may affect the solid-state characteristics of an active pharmaceutical ingredient. For instance, nanosizing can induce amorphization (the transition through a crystalline state to an amorphous state) for a substance. Such amorphous phases have elevated energy and solubility than crystalline phases. Their increased solubility can be achieved by incorporating an additional layer such as a polymer coat on their surface[127]. Colloidal carrier systems such as nanoemulsions and lipid nanoparticles provide yet another pathway for enhancing solubility. Nanoemulsions and lipid nanoparticles can encapsulate lipophilic agents into a core surfactant micelle, thus suspending the agents in an aqueous system without dissolving them in their native solid crystalline state. Nanoemulsions have a higher interfacial surface area, thus providing a good capacity for agents with quicker dissolution time than conventional systems[128]. Overall, an increased solubility based on nano-formulations can be attributed to not only the smaller size but also a higher surface area of the particles, increased wettability and dispersion, amorphous nature/physicochemical conversion of the pharmaceutical, and carrier systems which can aid in interaction with fluid biological systems[129].

##### [4.2] Improved cellular uptake

Enhanced cellular uptake is a primary pathway where nanoformulations lead to an intensified biological activity of plant constituents. This is due to the use of nanocarriers that enhance uptake using physicochemical, and biological approaches to facilitate the cellular uptake of the cargo beyond the cellular membrane compared to phytochemicals. Firstly, size and shape matter significantly as particles with a size range of approximately 20-200 nm preferably use active endocytic pathways such as clathrin- or caveolae-mediated endocytosis for uptake in a wide range of cells. Moreover, smaller particles could preferentially use other uptake methods[130,131]. Second, Surface chemistry and charge impact cellular membrane



interactions and the protein corona that produce in physiological fluids. Positive surfaces improve electrostatic attraction to negatively charged membranes and certain membrane proteins, while hydrophilic polymer coatings (PEG, polysaccharides) can inhibit opsonization (for systemic delivery) or be functionalized for improved receptor-mediated uptake by incorporating target ligands[132,133]. Third, active ligand-mediated targeting enhances the uptake in the desired cell populations. The attachment of an antibody/peptide/aptamer/ligand to the nanoparticle surface takes advantage of the mechanism of receptor-mediated endocytosis; hence, there is an enhanced internalization of these particles by cells expressing the targeted receptors compared to non-targeted particles. The method has found applications in cancer cell targeting, hepatic receptors, and immune cells[131,134]. The fourth component is how mechanical and biophysical properties like stiffness and shape of particles impact endocytosis in terms of membrane wrapping and force of traction. Less stiff particles or particles of particular shapes like rods or disks may have a higher chance of uptake due to favourable kinetics of membrane deformation and wrapping. This aspect of design helps cross the cell barriers that prevent stiff or undesirably shaped particles. Finally, intracellular trafficking post-uptake is also relevant: those delivery systems designed to enhance endosomal escape (pH-sensitive polymers, lipids disrupting membranes) suppress lysosomal degradation, leaving bioactive compounds in cytosols/organelles targeted by bioactive compounds. Taking it all together, improved uptake is a system-level result of dimension, surface properties, ligands, shape, and endosomal escape properties being turned to maximize bioactive delivery of compounds derived from plants[132,134,135].

#### [4.3] Sustained release

The main advantage of nano-formulations over conventional formulations is sustained or controlled release. Conventional plant-based or small molecule formulations give fast dissolution and clearance which results in fluctuation in concentrations of formulations in the blood and lower effectiveness of formulation. The main approach of nano-formulations is based on controlling diffusion, erosion, and degradation rates of formulations to achieve sustained formulation

release[7,136]. One of the main methods used in sustained release is encapsulation based on polymeric or lipid network. Polymeric nanoparticles and nanogels contains bioactive that can be encapsulated in a cross-linked or biodegradable polymeric matrix (like PLGA, chitosan, or alginate). In these methods, the drug is released slowly by a diffusion or by erosion or hydrolysis of the polymers. This leads to the release of the drug over a period of hours or several days[137]. In the case of lipids, there are similar approaches like Solid Lipid Nanoparticles (SLNs) or Nanostructured Lipid Carriers (NLCs), wherein the bioactive is entrapped in a solid or semi-solid core in which the diffusivity is low[138].

Moreover, physicochemical interactions between the carrier and phytochemical influence release properties. Hydrogen bonding, hydrophobic interactions, and ionic interactions between phytochemicals and carriers result in slower burst release and leakages. Changes in the concentration of Lipid, cross-link density, and molecular weight of polymer can make nanoformulations close to zero-order and biphasic release conditions [7,139] Another important area is stimuli-responsive sustained release. Contemporary nanoformulations are being made responsive to physiological stimuli such as pH change, temperature, enzymes, or redox potentials. pH-responsive nano-carriers, for instance, would achieve stability in physiological environments but would release the cargo faster when they come into contact with acidic environments like that in tumors or inflamed tissue. Such nanoformulations not only provide sustained delivery but also coordinate delivery in synchronization with the pathological conditions[5,140]. In addition to these, sustained-release properties enhance resistance to enzymatic breakdown and metabolism of the phytoconstituents. The nanocarriers protect phytoconstituents from extreme physiological conditions in the gastrointestinal and systemic circulations by allowing the phytochemicals to remain at the site of target for longer periods and at high concentrations. This is useful for herbal drugs having short half-lives or greater metabolic liability[138,141].

#### [4.4] Targeted delivery

Targeted delivery is a major mechanistic strategy by which nanoformulation improves their clinical outcome through their preferential delivery to pathological tissues while reducing systemic distribution. The traditional



formulation provides medication in a non-specific manner. This generally results in less availability at the site and unwanted effects. The disadvantages of non-specific targeting may be overcome by nanoformulations by both passive and active methods. It is mostly the passive targeting mechanism, which relies on clinical circumstances, including poor vascular status and lymph circulation malfunction. This allows suitably sized nanoparticles (preferably 50-200 nm) to accumulate at target sites due to the Enhanced Permeability and Retention (EPR) phenomenon[142]. This ensures the retention of the drug within the medical region for a prolonged period of time without changing the chemistry. Conversely, active targeting relies on the surface modification of nanocarriers using ligands including peptides, antibodies, or small molecules that show specific binding to receptors with highly expression levels. The interaction between a ligand and its receptor triggers receptor-dependent endocytosis, promoting enhanced cellular uptake and intracellular delivery of encapsulated phytoconstituents relative to conventional delivery systems[143]. Targeted nanoformulation is designed for organ-targeted delivery, achieving organ-specific delivery, promoting selective accumulation in tissues like the liver, tumors, or brain through the exploitation of endogenous pathways and biological patterns of receptor expression[144]. This is of particular importance in the case of phytochemicals, most of which possess poor permeability across cellular barriers, including the blood-brain barrier. More recently, nanoformulation has been designed to target bioactives at the subcellular level by means of stimulus responsive or signal-guided pathways, improving therapeutic effect and limiting intracellular breakdown[5,145]. Altogether, passive accumulation, ligand-mediated recognition, and crossing of cellular barriers enable nanoformulation to enhance the treatment specificity, effectiveness, and safety of drugs[5,146].

#### [4.5] Protection from degradation

Resistance from degradation is a primary approach by which nanoformulations improve the stability, replicability, and clinical efficacy of biologically active molecules, especially from herbal sources, which are prone to degradation. Many bioactive molecules are more likely than others to undergo degradation from oxidative, hydrolytic, or photo-degradation pathways,

resulting in considerable loss of biologic activity before actual administration of the drug[7,96]. Due to this, encapsulation of these molecules in biodegradable polymeric particles, nanogel, lipids, or nanoemulsions will protect these molecules from exposure to the surrounding environment, such as oxygen, moisture, and ultraviolet light, thereby improving the chemical stability and shelf life of these molecules [96,141]. Moreover, after administration, these molecules get degraded due to increased biologic exposure, as these molecules come in contact with enzymes in the gastrointestinal tract, as well as plasma esterases, and the hepatic metabolism pathway, which, in turn causes a decrease in half-life as well as poor systemic availability [147]. Nanoformulation will prevent this degradation of molecules by entrapping these molecules in a controlled structure, preventing direct exposure of these molecules to enzymes, as a result of which the molecules will get degraded at a slower rate [5,141]. Moreover, nanostructured lipids, such as solid lipid particles, will prevent this degradation through embedding of molecules in lipid particles that do not allow molecules to diffuse easily in the biological environment due to which the molecules limit diffusion and reduce leaking of actives in the gastrointestinal tract as well as in the systemic circulation which results in an extended duration of time [80]. pH-instability of molecules is another factor for degradation. Molecules from plants get degraded in an acidic pH of the stomach as well as in an alkaline pH of the intestine which destroy molecules; however, pH-stability of molecules, which is an attribute of nanoformulation, will protect these molecules from degradation due to pH-instability in the biologic environment as these molecules will get released in an environment that would favor their activity, thus preventing pH-dependent degradation [137]. Rapid opsonization and reticuloendothelial uptake during systemic circulation led to premature clearance and reduced effectiveness, whereas hydrophilic polymer-modified nanocarriers evade immune recognition, prolong circulation, and protect bioactives against intracellular breakdown [5,145]. Moreover, nanoformulation-mediated uptake restricts lysosomal exposure and regulates intracellular trafficking, preserving bioactive integrity [148]. Overall, nanoformulations safeguard against breakdown via environmental protection, isolation from enzymatic attack, stabilization within lipid or polymeric matrices,



pH-dependent regulation, reduce immune recognition, and controlled intracellular trafficking, thereby allowing sensitive phytoconstituents to maintain structural integrity and therapeutic function across systemic delivery.

## [5] Existing Nanoformulations of *Phoenix dactylifera*

### [5.1] Directly Reported Nanoformulations of *Phoenix dactylifera*

In contrast to numerous plant-based medicines, research work primarily related to *Phoenix dactylifera* nanoformulation applications is considerably insufficient; but soon enough, some research has started to find its applications in the field of nanoparticle synthesis and nanomedicine. Most of the research performed until now is related to green synthesized metallic nanostructures, specifically silver nanostructures (AgNPs), using *P. dactylifera* fruit, seed, leaf, or pollen extracts acting as reducing and stabilizing agents. The idea is based on using *Phoenix dactylifera* phytochemicals, mainly its phenolic, flavonoid, sugar, and organic acid content, to promote nanoparticle formation with a biological activity for the nanostructures[20,149,150].

AgNPs have been prepared successfully utilizing the aqueous fruit or seed extract of *P. dactylifera* with an average molecule size within the range of 10-50 nm. These biosynthesized AgNPs have shown improved antioxidant properties with significant enhancement of antimicrobial as well as anticancer properties relative to the unrefined fruit or seed extracts[113,149]. These biosynthesized AgNPs have also shown wide range of antimicrobial properties towards Gram-negative and Gram-positive bacterial cells due to the combined effect of silver ions and phytochemical compounds on the bacterial cell surface[113].

Beside from antimicrobial properties, other studies on anticancer as well as cytotoxic activities of nanostructures formed by *P. dactylifera* have also emerged. In vitro research on human cancer cells revealed that AgNPs synthesized using *P. dactylifera* elicited cytotoxic, oxidative, and apoptotic changes, yet they appeared relatively non-toxic to normal cells compared to others[117,151,152].

Few researches have focused on gold nanoparticles (AuNPs) prepared through *P. dactylifera* extracts,

demonstrating stable nanoscale systems with good antioxidant properties and biocompatibility[153,154]. Even though there is no substantial data on their therapeutic applications, these systems prove that *P. dactylifera* green synthesis can be successfully adopted in nanocarriers. Notably, polymeric, lipid-based nanoemulsion which incorporate *P. dactylifera* extracts are very limited, and thus represented an important research gap[21,155]. As can be inferred, most current research is still limited and restricted to proof-of-concept nanoparticle preparation and biological evaluation in vitro. Nevertheless, the current present data has indicated that the phytoconstituents isolated from *P. dactylifera* possess potential in acting as dual agents that are both biological and as nanoparticle-constituents, validating the translational applicability and the need for optimized carriers[21,153–155]

### [5.2] Comparative nanoformulations of analogous plant systems

As limited data on nanoformulation systems on *Phoenix dactylifera* is present, comparative knowledge of nanoformulated phytoconstituent-rich plant system is vital for understanding molecular as well as translation-level aspects of date-palm phytochemical potential when loaded into innovative nanocarriers[7,141]. Many medicinal herbs like *Curcuma longa* (turmeric), *Camellia sinensis* (green tea), *Vitis vinifera* (grape), *Ginkgo biloba*, *Nigella sativa*, and *Zingiber officinale* (ginger) contain primary phytochemicals common to *P. dactylifera* such as polyphenols, flavonoids, sugars, sterols, and organic acids [7,156]. The similarity among their biochemical constituents renders these plants useful for comparative analyses on nano-encapsulation characteristics, stability improvement, cellular uptake, and bioavailability regulation pertaining to date-palm phytochemicals[7,141,156].

The polymeric nanoparticles have greatly explored for plant bioactive molecules, especially polyphenolics and flavonoids from *Curcuma longa* (curcumin), *Camellia sinensis* (epigallocatechin gallate), *Vitis vinifera* (resveratrol), and *Ginkgo biloba* (ginkgolides) [117,137,139]. The biodegradable polymeric materials for encapsulation like PLGA, chitosan, and alginate has been remarkably assisting in improving physical and chemical properties, protecting sensitive phytochemical molecules from breakdown by enzymes and oxidation



processes [137,139]. The polymeric formulations also offer enhanced cellular uptake and intracellular retention which contributing to increased antioxidant property and anticancer activity over free phytochemical molecules[117,157]. As *P. dactylifera* fruits and seeds contain high amounts of polyphenolics, it is safe to anticipate similar stabilization and controlled release upon nanoencapsulation of *P. dactylifera* extracts[7,117].

Lipid-based nanocarrier technique has also been widely proven for phytoconstituents that are poorly soluble in aqueous solvents. *Ginkgo biloba*, *Vitis vinifera*, and *Nigella sativa* extracts that are highly concentrated in flavonoids/terpenoids were finally encapsulated into SLNs/NLCs, which reduces their gastrointestinal degradation, first-pass effect, and drug-loading capacity[138,158]. This lipid-based carrier supports lymphatic uptake and improves systemic circulation of hydrophobic compounds of plants and enhancing their oral bioavailability[158]. This applicability has a direct relevance to date palm-based flavonoids/sterol-like compounds those who faces problems during solubilization and metabolization similarly like traditional formulations[138,156].

Nanoemulsions of *Nigella sativa*, *Zingiber officinale*, *Camellia sinensis*, and *Curcuma longa* plant extracts led to better dispersibility, improved gastrointestinal absorption, and elevates antioxidant and antimicrobial activities relative to conventional emulsions or plant extracts[96,159]. Besides enabling the enhancement of the bioactivity of the phytoconstituents, nanoemulsions can ensure ease of formulation, physical stability, and large-scale production, thus being a suitable choice for

the translational research of phytochemically rich plant extracts like *P. dactylifera*[159].

Aside from their use in efficacy enhancement, nanoformulation comparison studies of analogous systems in plants have highlighted translational values of nanoformulations in relation to obstacles in formula translation, including formula consistency, reproducibility in batch production and suitable processing for scale-up manufacture[5,141]. It is worth noting that nanoformulations of polymeric nanoparticles, lipid delivery systems, and nanoemulsions used in the delivery of bioactive molecules of plants showed biocompatibility and Generally Recognized as Safe (GRAS) excipient materials which have been considered suitable for translation and development [96,137,158]. Notably, these comparative learnings in nanoformulation overcomes the translation barriers which suggests suitable nanocarrier system for *P. dactylifera* phytoconstituents[141,160]. Cumulatively, the comparative evidence available in the existing literature on the nano-formulated plant systems of *Curcuma longa*, *Camellia sinensis*, *Vitis vinifera*, *Ginkgo biloba*, *Nigella sativa*, and *Zingiber officinale* lends very strong support to the concept of the feasibility and merits of formulating phytoconstituents of *Phoenix dactylifera* into polymer-nanoparticles, lipid-carriers, and nanoemulsions[7,117,138,141,161]. The relative comparison between different plants emphasizes on the strong potential yet poorly studied *P.dactylifera* for futuristic nanoformulation approaches. Table 2 summarizes the nanoformulation strategies in analogous plant systems.

**Table 2: Summary of Nanoformulation Strategies in Analogous Plant Systems**

Plant / Extract	Major Bioactive(s)	Nanoformulation Type	Particle Size (nm)	Key Outcome	Reference
<i>Curcuma longa</i> (Turmeric)	Curcumin (polyphenol)	PLGA polymeric nanoparticles	100–250	Improved chemical stability, sustained release, enhanced anticancer and antioxidant activity compared with free curcumin	[117,137]



<i>Camellia sinensis</i> (Green tea)	EGCG, catechins	Chitosan / PLGA nanoparticles	80–200	Enhanced cellular uptake, protection from degradation, improved bioavailability	[137,139]
<i>Vitis vinifera</i> (Grape)	Resveratrol, flavonoids	Polymeric nanoparticles	90–220	Improved solubility, prolonged circulation, enhanced antioxidant and anti-inflammatory effects	[117,139]
Ginkgo biloba	Flavonoids, terpenoids	Solid lipid nanoparticles (SLNs)	120–300	Improved gastrointestinal stability and oral bioavailability	[138,158]
<i>Nigella sativa</i> (Black seed)	Thymoquinone	Nanostructured lipid carriers (NLCs)	100–250	Enhanced encapsulation efficiency, improved bioavailability, lowers toxicity	[138,158]
<i>Zingiber officinale</i> (Ginger)	Gingerols, shogaols	Nanoemulsions	50–200	Improved dispersibility, enhanced antioxidant and antimicrobial activity	[96,159]
<i>Camellia sinensis</i> (Green tea)	Polyphenols	Nanoemulsions	60–180	Rapid absorption, improved stability, enhanced antioxidant efficacy	[96,159]

## [6] Challenges and limitations

As the research interest is growing in the field of nano-delivery of phytoconstituents, the utilization of Phoenix dactylifera bioactive within concrete nanoformulation strategy is currently impeded by a number of interlinked challenges on both the scientific as well as translational fronts[77,162]. The first major challenge can be discrepancy between the currently extensive phytochemical profiling of date palms and the limited formulation-scoping research which integrates the standardization of extracts and the rational design of nanocarriers, ultimately impeding the advancement for the description of bioactivities towards delivery-focused therapy approaches. [163,164] Such limitations are further aggravated by the high heterogeneity and phytochemical variability associated with date palm extracts due to difference in cultivars, climatic factors, ripening time, and post-harvest processing. All these factors show significant effect on nanoparticle formation, encapsulation efficiency, surface chemistry, and release profiles when complicated plant extracts are loaded into nanocarriers[116,165,166]. Additionally, the multicomponent nature of date palm extracts aggravates

formulation complexity, considering that co-existing phytochemicals could act as modifiers of interfacial characteristics, destabilize nanostructures, or influence colloidal stability for longer timescales, events known for their significantly important role within the performance of nanoformulation but currently still sub-optimized within scientific research endeavors for plant-based nanomedicine[165,167]. From a science perspective, the translational efficiency for Phoenix dactylifera nanoformulation preparations is further obstructed by the lack of comprehensive research related to systematic, pharmacokinetic and biodistribution studies in in-vivo condition, considering that the mere establishment of enhanced antioxidant and cytotoxic activities within in-vitro assessments does not necessarily correlate within superior pharmacokinetics and therapeutic efficacy following systemic delivery routes[168–170]. Regulatory aspects associated with safety guidelines makes one more complex level to this panorama, since herbal nanoformulation remains at a current obstacle for which conventional herbal medicine regulatory approaches along with synthetic nanomedicine guidelines applied partially, leading to



unsettled problems for nanoparticle accumulation, immunogenic responses, excipient compatibility, and quality-by-design approaches[171,172]. Problems associated with manufacturing of nanoformulation are next poorly explored area. Many methods are currently utilized at lab-levels but challenging to scale within proper industrial settings for avoiding any impairment related to particle homogeneity, particle stability, and cost-effectiveness, especially for approaches focusing on the application of agricultural byproducts for date palm like seeds and pulp[173–177]. Collectively, although nano-formulation holds immense potential in the enhancement of the Phoenix dactylifera bioactive chemicals, the above methodological, biological, and production-based challenges and complexities emphasize the importance and requirements of standardized characterization, experimental design-based formulation, in-depth in vivo validation, and production and regulation-friendly approaches in the development towards the use of date palms in industrially applicable nanomedicine[77,164,171,175,177,178].

## [7] Future perspectives

Future research should focus on nanoformulations of Phoenix dactylifera moving from exploratory to formulation-driven approaches that encompass standardization of plant bioactives, nanocarrier formulation, and validation. One of the most crucial aspects is the standardization of the preparation of plant extracts and incorporating high-performance analytical profiling to reduce variation among batches and standardize nanoformulation results. Standardization will play a pivotal role in designing nanocarriers such as polymeric nanoparticles, lipid nanocarriers, and nano-emulsions/hybrid carriers on the basis of the physicochemical properties of bioactive compounds from date palm plant instead of trial-and-error methodology. Another area that could be important to investigate needs to be related to biological validation. In vivo pharmacokinetic and distribution and also effectiveness studies should be performed to compare meaningfully the in vitro and in vivo data to establish the therapeutic value of date palm nano-formulations. Priority could be accorded to oral delivery systems because of their therapeutic and dietary applications, and chronic toxicity and immunology, respectively, as a

result of their therapeutic effectiveness over extended periods. From a translational perspective, there is an imminent need to focus on the scalability and sustainability of the manufacture of date palm-based nanoformulations and to harness the power of valorizing date palm by-products like seeds and pulp. Microfluidics and continuous manufacturing may hold some promise to make the translational success of these nanomedical formulations from the laboratory to actual reality. Additionally, greater alignment with the ever-changing guidelines related to herbal nanomedicines will be critical and hence should be taken into consideration right from the commencement of formulation. From the formulation perspective, the future focus should be on optimizing the carrier and structure–function relationships, such as the assessment of encapsulation efficacy, release profiles, and the compatibility between multicomponent botanical matrices and nanocarrier materials. More advanced formulation techniques, such as design-of-experiments, quality-by-design, and modeling, can greatly improve the robustness and scalability of the formulation and shorten the time to development. On the other hand, the selection of biocompatible, food-grade, and biodegradable materials as excipients can greatly facilitate the approval and safe use of the formulation. All together, these future research directions place Phoenix dactylifera as a potential next-generation plant-based nanomedicine, offered that an interdisciplinary approach is used to combine phytochemistry, nanotechnology, and biology.

## [8] Conclusion

Phoenix dactylifera is a phytochemical-rich medicinal plant with established antioxidant, anti-inflammatory, metabolic, and neuroprotective activities, though the practical applications of its bioactive compounds are limited by its low aqueous solubility, instability, speedy metabolism, and limited bioavailability. The current review clearly states that the application of nano-formulation technology is a sensible and efficient solution to mitigate the characteristic limitations and, hence, improve the therapeutic potential and applications of its phytochemicals. Many nanocarrier systems, from polymeric nanoparticles to lipid-based delivery systems, nanoemulsions, nanogels, through to green-synthesized metal nanocarriers, have demonstrated potential in enhancing solubility, protecting labile compounds from



degradation, enhancing sustained release, and improving cellular uptake. These effects can be attributed to the nanoscale, enabling potent size effects, surface modifications, and other interactions between the nanocarrier and the phytochemistry, rendering advanced pharmacokinetics compared to standard formulations for better pharmacodynamics. Evidence from nano-formulated plants with high levels of phytochemistry has therefore substantiated the viability of using similar approaches in *P. dactylifera*. However, the existing research in the nano-formulation of date palm is limited and mostly exploratory, and it is essential that these challenges are met. The role of nanotechnology is, therefore, a groundbreaking approach that can revolutionize the development of a historical medicinal plant, *Phoenix dactylifera*, into nano-herbal drugs.

#### Author's contribution

Shrishty was responsible for conducting the literature search and prepare draft of the manuscript. Saumya Das contributed to the conceptualization of the study and provided critical revisions to refine the manuscript. Priyanka Bansal thoroughly reviewed the manuscript and granted the final approval for submission.

#### List of abbreviations

ABTS	–	2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
AgNPs	–	Silver nanoparticles
AuNPs	–	Gold nanoparticles
BBB	–	Blood–brain barrier
DSO	–	Date seed oil
DPPH	–	2,2-Diphenyl-1-picrylhydrazyl
EPR	–	Enhanced permeability and retention
EGCG	–	Epigallocatechin gallate
FRAP	–	Ferric reducing antioxidant power
GAE	–	Gallic acid equivalents
GC–MS	–	Gas chromatography–mass spectrometry
GI	–	Gastrointestinal
GRAS	–	Generally Recognized as Safe
GS-MNPs	–	Green-synthesized metallic nanoparticles
LC–MS/MS	–	Liquid chromatography–tandem mass spectrometry
NLCs	–	Nanostructured lipid carriers
PLGA	–	Poly(lactic-co-glycolic acid)
PLHNPs	–	Polymer–lipid hybrid nanoparticles
PNPs	–	Polymeric nanoparticles

ROS	–	Reactive oxygen species
SLNs	–	Solid lipid nanoparticles
TFC	–	Total flavonoid content
TPC	–	Total phenolic content
ZnO-NPs	–	Zinc oxide nanoparticles

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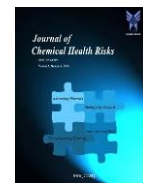
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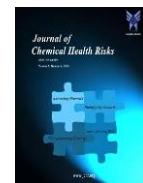
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