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Review article

BIOACTIVE COMPOUNDS IN PHYTOMEDICINE: A NEW ERA OF NANOTECHNOLOGICAL INTERVENTIONS FOR ENHANCED PHARMACOLOGICAL EFFICACY

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ABSTRACT
Herbs and spices possess various bioactive compounds, which tend to show vital role in the medicinal plant based phytotherapy for several chronic diseases. These bioactive compounds, known as phytochemicals has become potential therapeutic agents due to the lowest degree of side effects and high safety along with health benefits. Numerous herbs and spices (mustard, turmeric, saffron, kokum, black pepper, nutmeg, cardamom, jeera, coriander, fenugreeink, clove, asafoetida) are known to have various pharmacological activities viz., anti-inflammatory, antioxidant, anti-obesity, antimicrobial, anti-diabetic properties. Conventional plant extract formulations have been transformed into new herbal drug formulation by the use of nanomaterials. Niosomes, metallic and non-metallic nanoparticles (NPs), nanocapsules, nanocrystals, nanoemulsions etc. offer discrete benefits viz., controlled and sustainable release, increase in the stability, solubility, bioavailability of the bioactive compounds. This review provides latest key findings on the role of nanomaterials in therapeutic action of bioactive compounds on various chronic diseases. The plant sources having bioactive components along with therapeutic value and their nanotechnology-based herbal drug delivery formulations have been thoroughly discussed in this review.

1. Introduction

A nutraceutical is categorized as a food extract-based supplement that has been scientifically proven to show numerous health benefits in treating and prevention of various diseases. Categorically they represent various herbal based products, dietary supplements, genetically modified foods possessing bioactive substances, which shows great excel in treatment and prevention of diseases (Ivanišová et al., 2021). Healing herbal tradition is acknowledged since ancient cultures for sustenance and medicine. South Asian countries like, India and China, are enriched with numerous varieties of indigenous plant compounds that are thought to have various medicinal properties. Traditional system of medicines in India such as Siddha and Ayurveda is known for their herbal formulations (Y. S. Jaiswal & Williams, 2017). Herbal extracts from Emblica officinalis (Amla), Peppermint, Saffron, Clove, Ginger, Garlic, Withania somnifera (Ashwagandha), Tulsi, Turmeric, and Holy Basil (Tulsi) are predominantly known for the treatment of immunosuppressive conditions.

Nutraceutical-based formulations (viz., ginseng, Echinacea, green tea, glucosamine, folic acid, and cod liver oil) have evolved from their traditional roots to a versatile configuration with high effectiveness and safety of the products. Nowadays, nutraceuticals have received considerable interest due to their potential nutritional, safety, and enriched therapeutic properties (Priya & Satheeshkumar, 2020). Phytochemicals are the bioactive compounds found in medicinal plants and are known to offer a range of useful properties for treating various diseases. Phytochemicals exhibit a natural defence mechanism against metabolic diseases and cancers. Phytochemicals are categorized as primary (chlorophyll, proteins, sugars, and amino acids) and secondary bioactive constituents (terpenoids, flavonoids, and alkaloids). These compounds have diverse applications in human therapy, agriculture, scientific research, veterinary medicine, and other research fields. The combination of phytochemicals with nanotechnology to enhance health benefits has recently garnered significant attention from researchers.

Advancement in the theranostics of wide range metabolic diseases as well as cancer has been extensively attained by the intervention of nanotechnology by refining the compatibility and bioavailability of natural products. Various nanostructures such as polymeric NPs, lipid-based NPs, and carbon nanotubes can significantly improve the pharmacokinetics, compatibility, bioavailability and stability of many herbal drugs along with reduction in the side effects (Naz et al., 2019). NPs have also gained the keen interest of researchers due to their small size and high surface to volume ratio. It has been established that during bacterial infection, NPs have the ability to efficiently bind and rupture the bacterial cell surface leading to cell death (L. Wang et al., 2017). The NPs are properly capped with natural compounds which inhibit the enzymatic activity that hampers the synthesis of nucleic acids in several microorganisms.

Nanoencapsulation of phytochemicals has been proposed as a promising solution to circumvent such issues by increasing their bioavailability, control stability, solubility, and also provides controlled release of bioactive components. Inorganic nanocarriers, metallic NPs, polymeric NPs have been widely studied and have the capability to encapsulate nutraceuticals. The encapsulating method used to encapsulate natural bioactive components has been proven to be effective to boost up the absorption capacity of phytochemical both *in vitro and in vivo* (Basnet & Skalko-Basnet, 2013).

Multidrug resistance among bacteria has become major crisis in global public health. Bacteria have become resistant to both narrow and broad-spectrum antibiotics. The alternatives for antibiotics can be medicinal plants. These medicinal plants release various phytochemicals, which have been proven to possess antibacterial and anticancer properties. These phytochemicals, in combination with NPs, can be used as an antimicrobial agent. In this review, we have discussed the various phytochemicals present in herbal medicinal plants and evaluated their effectiveness when loaded in NPs, against multidrug-resistant bacteria and in cancer.

2. Herbal medicinal plants with therapeutic effects

The herbal extracts collected from the plants with medicinal properties show a critical role in distinct biological applications and the treatment of chronic and acute health problems such as depression, inflammation, cancer therapy, cardiovascular disease treatment, neural disorder treatment and skin regeneration (Figure 1) (Ismail Iid et al., 2020; Pohl et al., 2016).

Figure 1. Commonly used herbal extracts

The formulation of medicinal herbs can be taken in various forms like, ointment, capsules, essential oils, tablets and syrups. Herbal plants are rich in a variety of compounds, including secondary metabolites like phenols, aromatic substances and tannins. As these naturally derived compounds exhibit various biological activities, they predominate in curing various infections and other illnesses (Kennedy et al., 2016). Currently available plant-derived chemotherapeutic agents have been accepted worldwide for the treatment of cancer and other diseases and these include topotecan, irinotecan vincristine, etoposide, paclitaxel and many more (Dragoi & Alexandru, 2021). Therefore, these herbal plants are important in synthesizing different types of herbal medicine for their antimicrobial and antioxidant potential (Saratale et al., 2018).

2.1. Cinnamon

The Cinnamomum genus is a member of the Lauraceae family and generally contains more than 300 evergreen aromatic trees and shrubs. Cinnamomum-based essential oils are extracted from the bark, leaves, flowers, and fruits of cinnamon and are further incorporated into cosmetics or food items. Moreover, it is traditionally considered a neuroprotective agent and an effective candidate for the treatment of diabetes (Khasnavis & Pahan, 2012). In addition, cinnamon has been valued as a health-promoting agent for diverse conditions such as inflammation, gastrointestinal disorders, and urinary infections, and the antibacterial activity of the ethanolic extract of C. *zeylanicum from barks* against methicillin-resistant *S. aureus* (MRSA) has been demonstrated (Mandal et al., 2011; Saki et al., 2020). The authors concluded that *C. zeylanicum* could act as a valuable support in treating infections and developing antimicrobial agents against MRSA bacteria. The synergistic effects of cinnamon essential oil with antibiotics have been reported by researchers, suggesting significant combinatorial activity against various gram-negative bacteria (Bardají et al., 2016; Saleem et al., 2015). Antibacterial activity of cinnamon essential oil against *E. coli* O157:H7, *Yersinia enterocolitica* O9, *Proteus* spp. and *Klebsiella pneumonia* with very low minimum inhibitory concentration (MIC) values was reported by Al-Mariri and Safi in 2014 (Al-Mariri & Safi, 2014).

Role of cinnamon extracts and its essential oils as a potential candidate against oral cavity infections has been extensively studied. In 2012, Chaudhari et al. showed that cinnamon essential oil was potent against *Streptococcus mutans* and can be a good alternative to various existing antibacterial compounds used in curing oral cavities (Chaudhari et al., 2012). Higher zone of inhibition and sensitivity in the presence of cinnamon extracts was reported in the case of *S. epidermidis* strains. The antibacterial activity of the samples is due to the presence of phenolic compounds such as cinnamaldehyde and eugenol, and it was observed that these cinnamon extracts could be used to develop new formulations for acne treatment (Shu et al., 2024).

2.2. Ginger

Ginger (*Zingiber officinale)* is a type of flowering plant that belongs to *Zingiberaceae* family and is commonly used in cooking to make food healthier and more delicious. It is closely related with turmeric, cardamom, and galangal. The rhizome of the ginger categorised as a spice has known to be the part of traditional medicine since ages. It has been validated that root extracts of ginger are enriched with various volatile oils like sesquiterpenes, zingeberene, curcumene, farnesene, terpineol, terpenes and many more (Rupasinghe & Gunathilake, 2015). Strong antimicrobial, antioxidant, anti-inflammatory and antitumor activity of ginger was reported in the root extract of *Z. officinale* plant (Rahmani et al., 2014). The effectiveness of ginger powder in the treatment of common migraine attacks were observed due to its antiepileptic drug-like properties (Maghbooli et al., 2014). Ginger has been found in numerous trails to help prevent cancer and to treat nausea and vomiting caused by pregnancy and chemotherapy (Ryan et al., 2012). The extract of ginger was shown to enhance immune system responses differently in smokers and non-smokers. Non-smokers exhibited a stronger humoral immunity, indicated by increased levels of immunoglobulin M (IgM), which is crucial for antibody response to infections (Mahassni & Bukhari, 2019). In 2005, Kim et al. demonstrated that [6]-gingerol has anti-angiogenesis properties, making it a potential candidate for the treatment of tumours (Kim et al., 2005). Research indicates that ginger lowers blood pressure by blocking voltage-dependent calcium channels. This mechanism was demonstrated in studies where ginger extract caused a dose-dependent reduction in arterial blood pressure in animal models, such as anesthetized rats, and relaxed vascular contractions induced by agents like phenylephrine and potassium (Hasani et al., 2019).

2.3. Clove

Syzygium aromaticum (clove) is the most widely used herb and possesses anti-inflammatory, antimicrobial, antithrombotic, antioxidant, antimutagenic, and anti-ulcerogenic properties (Ökmen et al., 2018). Eugenol, the main bioactive compound present in clove, can destroy the integrity and reduce the quality of biofilm, disrupt the bacterial membrane, and form vesicles on the surface of the cytoplasmic membrane, which causes cytoplasm leakage (Miladi et al., 2017). The effectiveness of eugenol derivatives for the treatment of flaviviruses like dengue, Zika and yellow fever has been demonstrated and documented by researchers (De Oliveira et al., 2019). Similarly, Eugenol showed the ability to promote lymphocyte growth, which in turn gives anti-HIV-1 effects (Lane et al., 2019). The early stage of HIV-1 infection can be inhibited by significantly reducing the replication of the virus with eugenol.

Clove oil and eugenol cause extensive lesions in the fungal cell membrane, which leads to increased permeability, allowing propidium iodide to penetrate the cells, which indicates compromised membrane integrity. Such disruption is critical for the fungicidal effect observed in various fungal pathogens, including *Candida* and *Aspergillus* species (Rana et al., 2011). The antibacterial activity of clove extract against *gram-positive (Staphylococcus aureus* and *Bacillus subtilis) and gram-negative bacteria* (*E. coli* and *P. aeruginosa)* has been widely studied (Cortés-Rojas et al., 2014; Faujdar et al., 2020; Saikumari et al., 2016). Another natural component present in clove oil is humulene (a sesquiterpene), which contributes to the complex aroma and potential therapeutic properties (Guesmi et al., 2018).

Humulene exhibits anti-inflammatory effects, which are attributed to its ability to inhibit pro-inflammatory cytokines such as TNF-α and IL-1β, which play significant roles in inflammatory processes (Hata Viveiros et al., 2022). The model mice and rats treated orally with caryophyllene and humulene showed anti-inflammatory effects that were comparable to those of dexamethasone treatment. Further, the anticancer effects of humulene at moderate levels have been reported, with its potential to generate reactive oxygen species (ROS) (Hata Viveiros et al., 2022). The clove extract possesses strong antioxidant effects, due to which neutralization of the ROS production and other free radicals in the lipid chain and further oxidation of lipids can be inhibited by clove (Nikousaleh & Prakash, 2016).

2.4. Withania somnifera

A popular ayurvedic herb Ashwagandha is commonly known as “Indian Winter cherry” or “Indian Ginseng”. The term ‘Ashwagandha’ has been assigned as the root of ashwagandha smells like horse (“ashwa”) and also provides the power like a horse when consumed. In addition, somnifera refers to "sleep-inducing" in Latin due to its sedative properties. Some herbalists recommended ashwagandha as Indian ginseng because of their wide used in herbal formulation and in ayurvedic medicine. This herb is commonly known for its wide range of health benefits. Withanolides, steroidal lactones that form the primary bioactive phytoconstituents of Ashwagandha include withaferin-A (WFA) and withanolide-D (WFD) possess several pharmacological activities (Bashir et al., 2023). WFA has been reported to inhibit β-amyloid aggregation and reduce neuroinflammation by modulating pro-inflammatory cytokines (Mikulska et al., 2023; Sharifi-Rad et al., 2021).

Withania somnifera (WS) flowers are small and green, while the ripe fruit is orange-red and has milk-coagulating properties, roots of WS are mainly used for medicinal purposes. The methanol extract of WS roots showed the presence of a novel bioactive compound named withanolide sulfoxide having the activity to suppress human tumor cell proliferation. In addition, complete suppression of TNF-induced NF-κB activation was associated with the presence of S-containing dimeric withanolides. This herb exhibits significant anti-inflammatory effects by inhibiting the production of inflammatory cytokines like TNF-α and IL-6 which makes it beneficial for conditions such as arthritis and autoimmune diseases (Mikulska et al., 2023). The utilisation of phytochemicals derived from the *Withania somnifera* plant in the development of biogenic MNPs with a motive to investigate their anticancer effects was studied (Gupta Soni et al., 2023). The results underlined the potential of *Withania somnifera* as a source of bioactive compounds for cancer therapy and illustrated the efficiency of these NPs against cancer cells. The antioxidant behaviour of Ashwagandha helps protect cells from oxidative damage, contributing to overall health maintenance (Bashir et al., 2023; Munir et al., 2022).

The antibacterial activity of Ashwagandha is primarily linked to its root and leaf extracts, which contain bioactive compounds such as withanolides, alkaloids, and flavonoids. These compounds exhibit varying degrees of effectiveness against both gram-positive and gram-negative bacteria, including *Escherichia coli* and *Staphylococcus aureus* (Ezez et al., 2023; M. Kumari & Gupta, 2015). The study indicated that the aqueous root extract of Ashwagandha showed a minimum inhibitory concentration (MIC) of 1:16 against *E. coli* O78, indicating a strong potential as an antibacterial agent (M. Kumari & Gupta, 2015).

2.5. Peppermint

Mentha piperita L. (peppermint) is a perennial plant belonging to the *Lamiaceae family* that is widely spread throughout the Mediterranean region. Peppermint is known for its aromatic properties and extensive medicinal uses, hence, long been considered an economically important plant. Its leaves and essential oil are rich in bioactive compounds that contribute to its therapeutic properties. The primary active compound in peppermint oil, i.e., menthol, is responsible for its antispasmodic and analgesic properties (Li et al., 2022). It helps relax smooth muscles in the gastrointestinal tract, alleviating symptoms of digestive disorders such as irritable bowel syndrome (IBS) (Hilfiger et al., 2021). Luteolin and kaempferol are the flavonoids present in peppermint, which are known for their anti-inflammatory and antioxidant properties (Zeljković et al., 2021).

The antibacterial effect of peppermint extracts is due to the presence of phenolic compounds, which disrupt the essential activity of bacteria by permeating cell membranes with chelated membrane cations (Alammar et al., 2019). The synergistic effect of the essential oils of cinnamon, lemon grass, peppermint, ginger, clove, and rosemary, along with eight antimicrobial drugs, was determined against the strains of *S. aureus* and *E. coli*. The findings suggest that combining essential oils with conventional antibiotics could be a promising strategy to enhance antibacterial activity (Zago et al., 2009). Some studies suggest that phenolic compounds in peppermint may have anticancer properties by promoting apoptosis in cancer cells, which could be beneficial in cancer prevention strategies (Chakraborty et al., 2022).

2.6. Saffron

Saffron (*Crocus sativus L.)* belongs to the iris family and is considered as red gold due to its beneficial effects in pharmaceutical, food and textile industries (Hadizadeh et al., 2010). Some studies show that phenolics and flavonoids of saffron have high antioxidant capabilities (Mahood et al., 2023). Gallic acid and pyrogallol are two bioactive compounds present in saffron extract, have antioxidant properties, and help in reducing oxidative stress and may have anti-inflammatory and anticancer effects. Another study reported that the petroleum ether extract of saffron stamen inhibited the growth of *Proteus mirabilis*, *Malassezia furfur* and *Trichophyton rubrum* (Mir et al., 2018). Saffron has been shown to alleviate symptoms of mild to moderate depression and anxiety. Studies suggest that its active constituents can provide antidepressant effects comparable to standard medications, but with fewer side effects (Tóth et al., 2019). The anticancer properties of saffron by-products, namely petals and leaves, have been tested by researchers *in vitro* and *in vivo* (Zheng et al., 2016). Also, the bioactive compounds, crocetin and crocin present in saffron have been reported to induce their antioxidant, anti-inflammatory properties, hence, promoting kidney health.

2.7. Aloe vera

Aloe vera is an herb that is used since ancient times due to its great ability in phytotherapy or phytomedicines. It bears high water holding capacity so it is used for the treatment of various skin problems, enhance the restoration of wound and stimulate the cell growth. The slimy material of the Aloe vera leaf, generally called as gel, has been used to treat the digestion related issues, sunburn and skin wounds and it is considered to have more than 75 active agents (Shireen et al., 2015). The active compounds present in aloe vera plant generally includes saponins, aloesin, aloeemodin, aloin, aloeride, methylchromones, flavonoids, sterols, anthraquinones, lignin and salicylic acid and shows great importance in the treatment of numerous diseases (Radha & Laxmipriya, 2015). Further, the aloe vera plant extract has been reported to show great antibacterial, antifungal, anti-inflammatory, antioxidant, antiseptic and antiarthritic properties (Sánchez et al., 2020). The leaf and roots extract of aloe vera showed excellent results against *F. oxysporum* and *A. niger* with great zone of inhibition (Danish et al., 2020).

The anti-cancer properties of polysaccharides isolated from Aloe vera have been investigated in several animal species (Sahu et al., 2013). Also, the glycoproteins present in Aloe vera gel have been reported to have antitumor and antiulcer activity and to increase the proliferation of normal human skin cells (Surjushe et al., 2008). Further, the hepatoprotective activity of aloe vera has been investigated and the phytosterols, named lophenol and cycloartenol, present in the aloe vera, have been shown to induce downregulation of fatty acid synthesis along with upregulation of fatty acid oxidation in the liver, thus reducing intra-abdominal fat and improving hyperlipidemia (Radha & Laxmipriya, 2015; Zagórska-Dziok et al., 2017).

2.8. Garlic

Garlic (*Allium sativum*) is considered as one of the oldest plants used as a spice in food and also used as a medicine due to its numerous benefits to human health and wellbeing (Botas et al., 2019). The major component in garlic that serve as a precursor of the flavor and odor compounds is (+)-S-allyle-L-cysteine sulphoxide (ACSO or alliin) (Rose et al., 2019). Garlic peptides obtained by hydrolysing protein in garlic and other bioactive compounds have been reported to have antihypertensive, antimicrobial, anti-diabetic, anti-obesity, neuroprotective and immunomodulatory activity (Gao et al., 2020; Shang et al., 2019). The organo-sulphur compounds present in garlic are the reason for its antimicrobial properties and thus, garlic is known to have a bactericidal effect (Filocamo et al., 2012; Peinado et al., 2012). Therefore, researchers keep studying the garlic extract and associated compounds for investigating their potential in altering the gut microbiome (Sari et al., 2022). Additionally, garlic has been studied to reduce the risk of cancer, boosting the immune system and protecting against inflammation as well as infectious diseases (Sasi et al., 2021). The ability of garlic extracts to inhibit the growth of some pathogenic microorganisms has been widely studied (Ciric et al., 2020). The impact of garlic and eucalyptus extracts on oral carcinogenic bacteria such as *Streptococcus mutans* and *Lactobacillus acidophilus* was proven to be effective depending upon the concentration of both the extracts. Under the influence of garlic extract, high phenolic content has initiated strong antioxidant activity and scavenging intracellular ROS (Kshirsagar et al., 2018).

2.9. Tulsi

Tulsi (*Ocimum sanctum* Linn), also known as holy basil, holds a prominent place in Ayurveda due to its broad spectrum of health benefits. The research evidences confirm that Tulsi helps to alleviate anxiety, improve cognitive function, making it effective for mental health management (Cohen, 2014). The major bioactive components that are mainly observed in tulsi leaf are ursolic acid, eugenol, rosmarinic acid, linalool, carvacrol, β caryophyllene, and oleanolic acid (Bernhardt et al., 2015). The pharmacological properties of Tulsi leave have been investigated through several *in-vitro* and animal studies which include anti-microbial, anti-cancer, anti-diabetic, antioxidant, anti-inflammatory and immunomodulatory behaviour (Lin et al., 2014; Panprommin et al., 2016). Tulsi has been effective in improving the lipid profile and basal metabolic rate. The observations recorded from 24 human studies reported Tulsi as a safe herbal intervention which may help in controlling blood pressure, blood glucose and lipid profiles, and dealing with psychological and immunological stress (Jamshidi & Cohen, 2017).

3. Phytochemicals of Herbal Plants

Phytochemicals are the bioactive compounds present in various plants and are used to cure numerous diseases. Based on their function in plant metabolism, phytochemicals are categorized into two groups, i.e., primary and secondary metabolites (Figure 2). Primary metabolites are essential for plant life, which comprises carbohydrates, amino acids, proteins, lipids, purines, and pyrimidines of nucleic acids, while the secondary metabolites are the remaining plant chemicals developed by the cells through metabolic pathways derived from the primary metabolic pathways (A. Hussein & A. El-Anssary, 2019).

These chemical components have been described as antiviral, antifungal, and antibiotic, which are responsible for protecting plants from pathogens (Table 1). Due to their great biological activities, plant secondary metabolites have been used for centuries in traditional medicine and the medicinal effects of the plants come from these molecules (Jamwal et al., 2018). Moreover, various tissues and organs of medicinal plants could have peculiar medicinal properties at specific developmental phases (Bartwal et al., 2013). Nowadays, they are associated with valuable industries such as pharmaceutics, cosmetics, and fine chemicals. Based on their biosynthetic pathway, secondary metabolites in plants are divided into three main groups, which include (a) nitrogen-containing compounds such as alkaloids, glucosinolates, and cyanogenic glycosides, (b) phenolic compounds such as phenylpropanoids and flavonoids, and (c) terpenes (Jamwal et al., 2018; Jan et al., 2021). Alkaloids are a class of nitrogen-containing compounds produced in plants in response to biotic or abiotic environments, which endows alkaloids to possess remarkable biological activities and structural diversity (Ng et al., 2015). Some of the phytochemicals present in herbal plants have been discussed below:

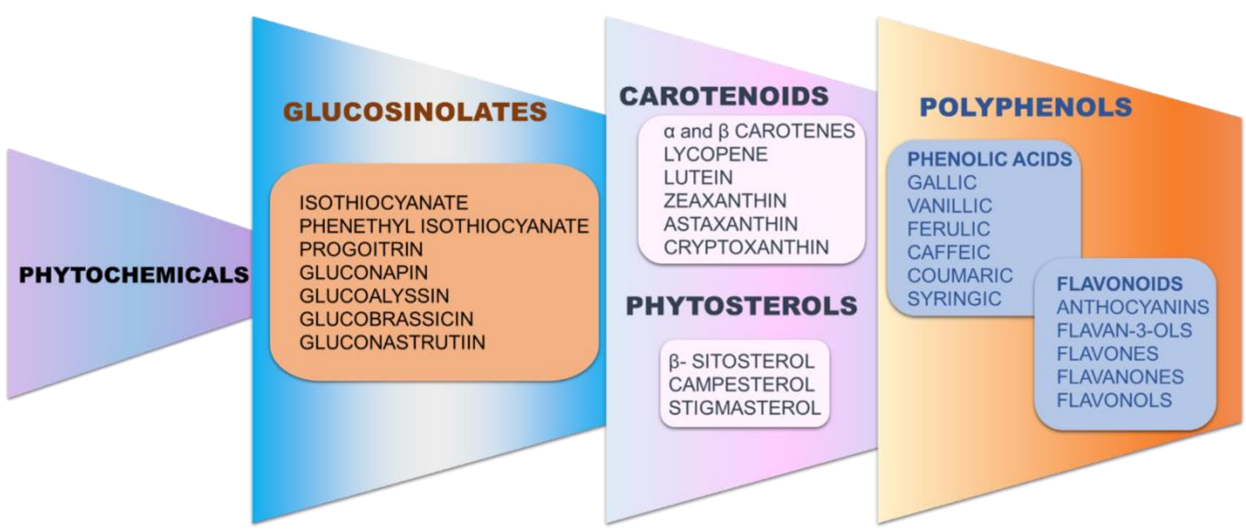

Figure 2. Phytochemical contents in herbal medicinal plants.

Table 1. List of phytochemicals emphasizing on their pharmacological activities.

Herbal Medicinal plants	Phytochemicals	Pharmacological Activities	References
Syzygium aromaticum	Phenols	Kidney dysfunction in rats	(Lee et al., 2021)
Z. officinale	Terpineol, Terpenes, Gingerols, Shogaols, Paradole, Gingerone.	Antimicrobial, anti-oxidant, anti-inflammatory and antitumor activity	(Rupasinghe & Gunathilake, 2015)
Ziziphoratenuior	Amine group, Carbonyl group, Hydroxyl groups	Antimicrobial, anti-oxidant, anti-inflammatory and antitumor activity	(Sadeghi & Gholamhoseinpoor, 2015)
S. aromaticum	Eugenol	Antimicrobial, anti-oxidant, anti-inflammatory and antitumor activity, antiviral activity	(Ökmen et al., 2018)
Withania somnifera	Polyphenols. Withaferin, Withanaloids	Antioxidant, antibacterial and anticancer activity	(Munir et al., 2022)
Azadirachta indica	Flavanoids	Antibacterial and anticancer activities	(Guchhait et al., 2022)
Aloe vera	Saponins, Aloin, Flavonoids, Anthraquinones, Amino acids, Lignin and Salicylic acid	Antibacterial, antifungal, anti-inflammatory	(S. Kumar et al., 2015; Radha & Laxmipriya, 2015)
Crocus sativus	Anthocyanin, Glycosides, Flavonoids and Phenolic compounds	Antimicrobial and antioxidant	(Naim et al., 2022)
Mint	Flavonoids (naringenin)	Anticancer	(S. Singh et al., 2023)
Cinchona tree	Alkaloids	Antimalarial	(Ambwani et al., 2018)
Green tea	Polyphenols (catechins)	Anticancer	(Barani et al., 2021)
Sweet wormwood	Terpenoids	Antimalarial	(Prajapati et al., 2022)
Yew tree	Terpenoids (Taxol)	Anticancer	(Iqubal et al., 2020)
Cilembu sweet potatoes	Ascorbic acid, Riboflavin, Phenolic compounds, Proteins	Antibacterial	(Mendoza-Reséndez et al., 2013)
Portulaca	Ascorbic acid, a-tocopherols, omega-3 fatty acids, Apigenin, Gallotannins, Quercetin, and Kaempferol.	Antioxidant, Antibacterial, Antifungal	(S. Jaiswal & Rajwade, 2017)
Tribulus terrestris	Polyphenols Flavonoid, Tannin, and Phenolic acids	Antimicrobial, antihypertensive, anticancer, and analgesic, antiviral and antioxidant	(P. & K. D., 2017)
Thymus vulgaris	Carvacrol, Thymol, and Phenols	Antibacterial, antioxidant, anticancer, and anti-inflammatory, antiviral	(Tzima et al., 2015)
Mentha pulegium	Phenols	Antimicrobial, Antiviral	(Al-Rajhi et al., 2022)
Eucalyptus	Flavonols, Hydroxybenzoic acids, and Hydrolyzable tannins	Antioxidant, antiviral	(Brezáni et al., 2018)

Azadirachta indica	Limonoids, Nimbin, Nimbidin, and Azadirachtin	Antifungal	(Ahmed et al., 2023)

3.1. Polyphenols

Polyphenolic compounds (PC) are among the most abundant secondary metabolites found in nature. Due to the presence of electron-donating phenolic groups in their structures, they act as antioxidants. Numerous studies have been conducted to determine the antioxidant function of polyphenols for the prevention of oxidative stress-related cellular and extracellular damage (Fakhri et al., 2022; Gasmi et al., 2022; Kawabata et al., 2019). Polyphenols provide various functions, which include antioxidant, antimicrobial, anti-inflammatory, anti-angiogenic, and anti-tumour properties (Azeem et al., 2023; Gasmi et al., 2022). Polyphenols are identified for their broad-spectrum applicability in the prevention of dreadful diseases, such as cardiovascular disease, neurodegeneration, and cancer (Obrenovich et al., 2022). Flavonoids are an important bioactive group of polyphenols and have more than 6000 members. Flavonoids are secondary metabolites present in all green plants and play a vital role in protecting the plants against pathogens. Flavonoids possess an expressive antibacterial effect, either alone, or in synergistic combination with other phytochemicals of plants.

Flavonoids have been examined to destructively affect bacteria and/or decrease their virulence by quorum quenching activity and act synergistically with antibiotics, and generate antimicrobial susceptibility of some bacteria by efflux pump inhibition (Górniak et al., 2019). The flavonoids are known to induce the disruption of phospholipid bilayers, thereby inhibiting the respiratory chain and ATP synthesis of the bacterial cell membrane. Yuan et al. distinguish two basic mechanisms of flavonoid interaction with the phospholipid bilayer: (i) polar phospholipid heads interact with hydrophilic flavonoids and (ii) lipophilic flavonoids tend to intervene in the phospholipid bilayer, leading to higher membrane affinity, in turn, a greater activity (Yuan et al., 2021). Moreover, flavonoids can control major activities like: inhibition of peptidoglycan and nucleic acid synthesis, blocking the fatty acid synthesis, resulting in antibacterial (Osonga et al., 2019).

3.2. Alkaloids

Alkaloids are organic compounds, categorized into different types on the basis of their chemical structures, biochemical precursors, and pharmacokinetics. The most commonly used alkaloids are heterocyclic alkaloids (typical alkaloids), which carry nitrogen in their cyclic ring. Cushnie et al. reviewed on several antibacterial results of alkaloids: (i) inhibition of nucleic acid synthesis through action on dihydrofolate reductase or topoisomerases, (ii) inhibition of bacterial cell division protein FtsZ, (iii) inhibition of bacterial enzymes (like, sortase A), which leads to disruption of bacterial homeostasis, (iv) disruption of the outer membrane and the integrity of the cytoplasmic bacterial membrane (Cushnie et al., 2014). Alkaloid hinders the efflux pumps and affects multiple virulence factors. Turker & Usta observed that the aerial part of *Solanum dulcamara* L., rich in alkaloids, was found to have antibacterial activity against *Streptococcus pyogenes*, *Staphylococcus epidermidis* and *S. aureus* (Turker & Usta, 2008).

3.3. Terpenes

This class comprises natural products which have been deduced from five- carbon isoprene units. Utmost of the terpenoids have multi cyclic structures that differ from one another by their functional groups and introductory carbon configurations. Terpenoids are the most abundant group of plant secondary metabolites typically produced in flowers, vegetative tissues, and, root. Organic acids are intermediate or end products in various fundamental pathways in plant metabolism and catabolism (Rivasseau et al., 2006).

3.4. Amino acid

The nonprotein amino acids are structurally similar to protein amino acids and particularly participate in plant defence against stress and act as essential mediators in response to abiotic factors (Rodrigues-Corrêa & Fett-Neto, 2019). Amines are nitrogenous compounds with low molecular weight which are naturally found in plants and are responsible for various biological effects such as acting as crucial precursors of hormones (Ordóñez et al., 2013).

4. Nano-formulation of Herbal plants-based phytochemicals

Nanotechnology has become one of the most advanced domains for the development of innovative therapeutic products for biomedical applications. Researchers have started focussing on the roles of various nanoparticles (NPs) in improving the bioavailability and sustainability of drugs and biomolecules. These nanomaterials have interesting biomedical applications for the delivery of medicinal plant extracts, due to their unique physical and chemical properties (Figure 3). In addition to the above-mentioned properties, nanomaterials are reported to possess extracellular or intracellular antibacterial properties as well. These NPs are distinguished by their unique physical and chemical properties, which are attributed to their quantum size, leading to a variety of intriguing biomedical applications involving different medicinal plants. In light of the ongoing rise in antibiotic resistance, scientists are persistently exploring alternative antibacterial solutions to minimize toxicity and side effects. Recently, NPs have gained traction as promising antibacterial agents. The bactericidal mechanisms of NPs can occur either extracellularly or intracellularly. Plant-derived NPs can attach to bacterial surfaces, inhibiting favorable signal inductions and cellular transport. Conversely, these NPs may penetrate the microbial cytoplasm, trigger the release of nanoparticles and subsequently modify bacterial functions. Utilizing medication delivery systems that are based on NPs is a unique approach that has the potential to improve the bioavailability and effectiveness of herbal extracts. Enhancement of therapeutic advantages and regulated release of the active constituent can be accomplished through the encapsulation of herbal extracts within NPs (Table 2).

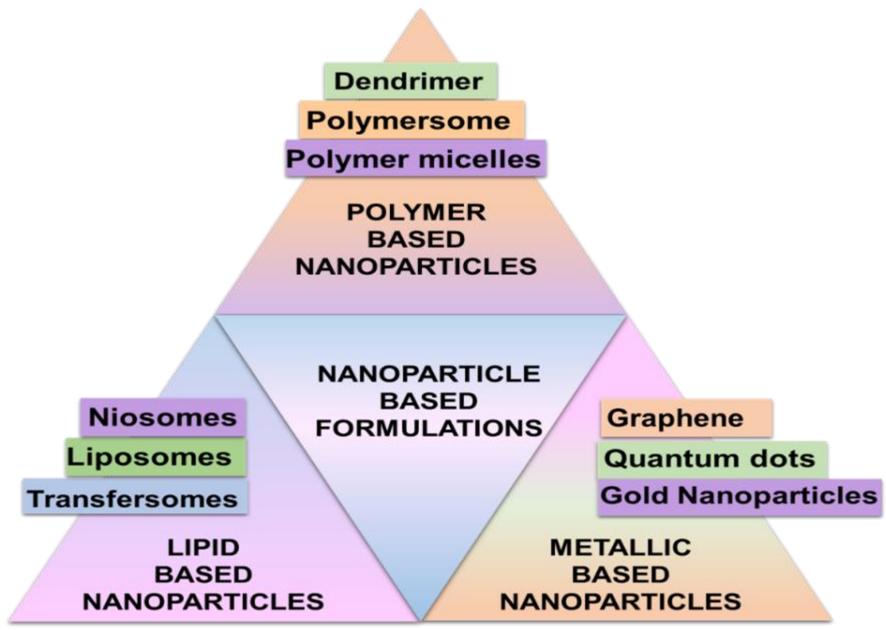

Figure 3. Polymeric Nano-particles (PNPs), Nano-capsules and Nano-spheres

Table 2. Nanoformulations for herbal extracts

Medicinal plant	Nanoformulation	Treatment of diseases	References
Ocimum sanctum	Encapsulated in NLCs, NEs, liposomes, and niosomes	Showed inhibitory features against hyaluronic acid and collagen fiber degradation inhibition.	(Chaiyana et al., 2019, 2020)
Curcuma longa L.	lipid-based NPs	Used for the treatment of various dermatological disorders	(Paul et al., 2022)
Citrus fruits, onions, apples, parsley, sage, tea, and berries	Encapsulated quercetin in zein nanoparticles (NPQ)	Improved memory and cognitive ability in rats	(Moreno et al., 2017)
Solanum tuberosum L. (Solanaceae)	S.tuberosum Lectin NPs	Improved drug delivery Elevated memory and motor function	(C. Zhang et al., 2014)
Oxaliscorniculata L. (Oxalidaceae)	Aqueous extract of O. corniculata and its biofabricated silver nanoparticles (AgNPs)	Antibacterial activity against urinary tract infection (UTI) microorganisms	(Das et al., 2018)
Azadirachta indica	phospholipid-based nanoformulation containing neem oil	Protected skin cell from oxidative stress	(Manca et al., 2021)
Camellia japonica	copper-based NPs	inhibited the growth of the uropathogens *Klebsiella pneumoniae* and *Pse udomonas aeruginosa*	(Rajivgandhi et al., 2019)
Cissus vitiginea	Copper nanoparticles (Cu-NPs)	showed efficacy against several UTI pathogens such as *E. coli*, *Enterococcus* sp., and *Klelbsiella* sp.	(Wu et al., 2020)
Moringa oleifera	titanium dioxide and copper oxide	*Wound healing*	(De Almeida Borges et al., 2016)
Cassia roxburghii	AgNPs	*Wound healing*	(Balashanmugam & Kalaichelvan, 2015)
Azadirachta indica	Ag-embedded mesoporous silica nanoparticles ($mSiO_2$-AgNPs)	*Effective against Candida albicans*	(Qasim et al., 2015)
Silybum marianum	Nanomicelles	Liver cancer	(Ghalehkhondabi et al., 2021)

Withaniasomnifera	Polymeric NPs	Anticancer activity	(Mughees & Wajid, 2020)
Bauhinia tomentosa Linn	Silver NPs	showed significant fluorescence and antibacterial activity	(Mukundan et al., 2015)
Pistacia integerrima	Gold NPs	significant antifungal and antinociceptive activity	(Islam et al., 2019)
Aegle marmelos Correa	nickel NPs	excellent antinflammatory agents and drug carriers	(Angajala et al., 2014)
Syzygiumcumini seed	polymeric NPs	Diabetes mellitus	(Bitencourt et al., 2016)
Eysenhardtiaplatycarpa	nanoemulsion and poly lactic-coglycolic acid (PLGA) NPs	best properties for the treatment of anti-inflammatory disorders	(Domínguez-Villegas et al., 2014)
Tecomella undulate	Polycaprolactone (PCL)/polyvinylpyrrolidone (PVP) nanofiber	treatment of wound healing or dermal bacterial infections	(Suganya et al., 2011)
Jatropha pelargoniifolia	JP-loaded chitosan NPs	Showed Antioxidant, antibacterial and anticancer activity	(Alqahtani et al., 2021)
Panax notoginseng	PNS loaded in conventional PLGA NPs and PNS loaded in liposomes	Acute myocardial ischemia injury in rats.	(J. Zhang et al., 2012)
Phyllanthus amarus	emulsifying the extract with sodium alginate (Nanoencapsulation)	Showed Anticancer activity	(Deepa et al., 2012)

4.1. Polymeric nanoparticles

Polymeric NPs have high drug loading capacities to preserve and hold up the drug against degradation. Therefore, there are more chances of drug penetration and cure the effective part. Due to unique properties like structure and features, they can conquer macrophages and supply the drug delivery to the CNS. Nanospheres are the thick polymeric forms that are synthesized via micro-emulsion polymerization, while nano-capsules are discovered from thin polymeric wall covered with an oil-filled cavity (Ganesan et al., 2015). *Jatropha pelargoniifolia* (JP) is a medicinal plant rich in phenolics and flavonoids bioactive compounds and plays a vital role to oxidative defence mechanisms in human cells. Due to its broad therapeutic activity, JP is utilised in traditional medicines (Zhu et al., 2017). However, JP has limitations, including poor solubility, bioavailability, and stability, and is sensitive to gastric acid pH so it cannot be administered in conventional dosage forms (Alqahtani et al., 2021; Teng et al., 2012). To overcome these limitations by using nanotechnology JP-loaded chitosan NPs (JP-CSNPs) were prepared for their antioxidant activity with antibacterial and anticancer capability (Alqahtani et al., 2021). The results showed that the antioxidant activity of JP-CSNP was greater than that of the pure extract, along with its higher antimicrobial activity against gram-positive bacteria compared to the empty NPs. Gudise et al. synthesized a mixed micelle nano-formulation (MM) delivery system with the active ingredients of *Argyreia pierreana* ethanol extract (APEECE) and *Matelea denticulata* ethanol extract (MDECE), which possess dual pharmacological effects *i.e.,* antidiabetic and antihyperlipidemic in type 2 DM rats and found that MM can increase its solubility in water, improved stability and pharmacokinetic properties, and can make the drug circulation time longer when compared to conventional micelles (made from single copolymers (Gudise et al., 2021; Manjappa et al., 2019). The use of polymeric NPs containing *Withania somnifera* as a potential treatment for breast cancer was investigated by (Nisar et al., 2022). *Withania somnifera* exhibited cytotoxic effects on breast cancer cells, pointing to the plant's possible utility in the treatment of the disease. The fact that *Withania somnifera* was identified as a promising candidate in the study demonstrates how beneficial herbal-based treatments may be in the fight against cancer. Mughees & Wajid, (2020) encapsulated herbal extract within a polymer matrix and observed that encapsulation ensures controlled release, contributing to the sustained and targeted delivery of phytochemicals present in the herbal extract (Mughees & Wajid, 2020). The utilization of polymeric NPs facilitates a controlled release of phytochemicals from herbal extracts. This mechanism enhances the stability and bioavailability of these compounds, potentially improving their therapeutic impact.

4.2. Lipid-based nanoparticles

Phytosomes are an innovative lipid-based delivery system and exhibit liposomes-related structure. It can be used for the entrapment of various types of polyphenolic-based phytoconstituents to enhance their absorption when distributed (D. Kumar et al., 2020). The phytosomes were first discovered by Indena company (Milan, Italy) in the late 1980s and was aimed to excel the bioavailability of drugs by complexing them to phospholipids. The composition of phytosomes includes standardized polyphenolic plant extract which comprises into phospholipids, mainly phosphatidylcholine (PC) (Lu et al., 2019). Phytochemicals exhibit water-soluble polyphenolic rings (i.e., flavonoids and terpenoids) which have high affinity to chemically bind to the hydrophilic moiety of phospholipids (i.e., choline) to synthesise the body of phytosomes, while the phosphatidyl lipophilic moiety of the phospholipids synthesize a tail to comprise the water-soluble choline-bound phytoconstituents.

Sinigrin is a glucosinolate found in the *Brassicaceae* family (Jie et al., 2014). A phytosome delivery system was fabricated for the delivery of sinigrin by Mazumder *et al.,* 2016. The synthesized formulation was found to enhance bioavailability and to conquer the problem of the solubility of sinigrin. The wound-healing activity of sinigrin was compared with the activity of the phytosome–sinigrin complex. Sinigrin-phytosome showed expressive wound-healing results when compared to pure sinigrin. After 42 h, the phytosome–sinigrin complex showed 100% wounds healing activity, whereas pure sinigrin showed 71% wound closure only (Mazumder et al., 2016). This signifies that sinigrin-phytosome enhances wound-healing activity.

Apigenin is a hydrophobic flavonoid compound that displays various biological activities, such as antioxidant, antimicrobial, anti-inflammatory, antiviral, and antidiabetic (Shibata et al., 2014). However, apigenin has limitations, namely, poor water solubility, fast metabolism, and low oral bioavailability, thus limiting its clinical application. In order to reduce these limitations of apigenin, Telange et al., (2017) conducted a study where apigenin was loaded into a phytosome delivery system and showed positive results (Telange et al., 2017).

In order to determine the antioxidant and anticancer activity of taxifolin, a taxifolin ethyl acetate fraction derived from *Cedrus deodara* bark extract was loaded into a phytosome delivery system (S. Kumar et al., 2021). Phytosomes can expand the lipophilicity of the active compound so that they increase the absorption of the active substance and enhance its ability to cross biological membranes (Shah et al., 2024).

Gingerol is a polyphenol belong to *Zingiber officinale family,* which is known to have numerous biological activities, one of which can protect cells against oxidative stress. A gingerol formulation was loaded into a phytosome delivery system, which was then complexed with chitosan to overcome the problem of respiratory tract infections (R. P. Singh et al., 2018). However, these gingerols exhibit low bioavailability and water solubility profiles (Rahmani et al., 2014; R. P. Singh et al., 2017).

4.3. Metallic Nanoparticles

Metallic nanoparticles (MNPs) have gained a keen scientific interest and are now heavily applied in biomedical sciences and engineering. Nowadays, synthesis of MNPs is considered as a progressive area for attracting scientific research with significant importance on imaging and drug delivery in the field of nanobiotechnology (Qadri et al., 2019). MNPs have optical properties such as surface plasmon resonance (SPR) with the ability to control optical field which makes them potential candidates for biomedical applications. The smaller size of MNPs makes them easy to infiltrate through the biological or physiological membrane that is usually impermeable to other macromolecules. MNPs-based drug delivery approach for co-delivering of curcumin and temozolomide has been conducted and found to have greater anti-cancerous activity.

Metallic inorganic NPs, such as silver, gold, copper and iron, have also been used as a nanocarrier for phytocompounds. Ginseng herbal extract, when formulated as silver NPs (AgNPs), exhibits stronger anticancer activity against A549 cells at a minimal dose (P. Singh et al., 2017). AgNPs synthesized from *Azadirachta indica* kernel aqueous extract have shown a significant anti-inflammatory effect *in vitro* and also considered as one of the most useful therapeutic herbs due to its numerous biological activities (Lan Chi et al., 2022). AgNPs synthesized from another traditional plant named *Cotyledon orbiculate* extract tend to show immunomodulatory effects in the THP-1 macrophage by reducing pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β synthesized AgNPs using an aqueous leaf extract of *Bauhinia tomentosa Linn* for determining it's *in-vitro* anticancer activity (Mukundan et al., 2015; Tyavambiza et al., 2021). Fluorescent AgNPs were synthesized using *Artemisia annua* leaf extract and these AgNPs were biocompatible, which was proved by checking the cytotoxicity against human erythrocytes and displayed significant fluorescence and antibacterial activity (Khatoon et al., 2015). Another study determined the stability, antioxidant, DNA cleavage, and antibacterial activities of plant-derived AgNPs and their superiority as compared to their chemically synthesized NPs (Mousavi-Khattat et al., 2018). It was found that the green synthesized NPs from *Datura stramonium* leaf extract showed more desirable qualities such as a narrower size and spherical shape, high antioxidant, great antibacterial and DNA cleavage action than the synthetic NPs.

AgNPs synthesized using *Nepeta defersiana* plant extract showed anticancer activities against human cervical cancer cells, inducing concentration-dependent cytotoxicity as well as decreased glutathione levels (Al-Sheddi et al., 2018). Plant-derived AgNPs using leaf extract of

Cynara scolymus were used in photodynamic therapy which showed anticancer activity via mitochondrial apoptosis in MCF7 cells (Erdogan et al., 2019). Further, AgNPs synthesized using a bioactive fraction of *Pinus roxburghii* have been reported to possess cytotoxic activity against lungs and prostate cancer cells (R. Kumari et al., 2020).

Gold NPs (AuNPs) were developed by using a gall extract of *Pistacia integerrima* and they showed to have the potential for various biomedical and pharmaceutical applications particularly with significant antifungal and antinociceptive activity (Islam et al., 2019). Wang et al. conducted a study on the medicinal plant known as *Rosa Rogusa*-mediated AuNP and showed that it exhibits significant anti-inflammatory effects in keratinocytes (R. Wang et al., 2022). AuNPs loaded with *Hibiscus Syriacus L* extract have been shown to induce autophagy for LPS-induced macrophage's inflammation (Xu et al., 2021). Further, *S. japonica* mediated AuNPs of 20–30 nm size and spherical shape successfully showed its anti-inflammatory activity by decreasing the release of pro-inflammatory cytokines and suppressing the expression of the genes iNOS, COX-2 and TNF-a (Kwak et al., 2022).

Phyto-fabrication of nickel NPs (NiNPs) from *Aegle marmelos Correa* (AMC) aqueous leaf extract (Angajala et al., 2014) and zinc NPs (ZnNPs) from *Anoecsstochilus elatus* leaf extracts (Vijayakumar et al., 2022) was assessed and found that these NPs can be used as excellent anti-inflammatory agents and drug carriers. Further, the anti-cancerous effect of *Ficus religiosa* extract loaded copper NPs (CuNPs) (Sankar et al., 2014) and anti-inflammatory efficacy of *Myrtus Communis* leaves extract loaded CuNPs (Al-Jubouri et al., 2022) was reported by researchers.

Buarki et al. reported the antibacterial potency of iron NPs prepared from the flower extract of *Hibiscus rosasinensis* and $FeCl_3 6H_2O$ solution in the ratio of 1:1 against numerous bacteria *viz.,* which includes *S. aureus, Klebsiella pneumonia, S. typhi*, and *P. aeruginosa* (Buarki et al., 2022). The Iron-NPs work together with the plant extract to promote the generation of free radicals that disrupt the membrane permeability of microorganisms. Alam et al. determined that the iron NPs from *Crocus sativus* showed antifungal activities against wilt-causing fungi (*Verticillium dahlia*) in many crops (Alam et al., 2019). Furthermore, other plant extracts have been investigated for synthesizing plant-derived NPs with antifungal activities, such as *Passiflora foetida* fruits and *Dimocarpus longan* fruit extract against *Fusarium sp., C. albicans, C. neoformans,* and *A. niger*and found effective (Elangovan et al., 2022; Sathiya & Geetha, 2023).

5. Future directions and opportunities

Nanotechnology is revolutionizing the field of phytomedicine by enhancing the efficacy, bioavailability, and stability of herbal medicines. The integration of nanotechnology into herbal formulations presents numerous opportunities and challenges that are shaping future research and applications. Nanotechnology improves the solubility and absorption of poorly soluble phytochemicals, thereby increasing their bioavailability. This is crucial for maximizing therapeutic effects while minimizing side effects associated with higher doses (Anand et al., 2023).

As a novel approach to drug delivery, researchers are examining nanoencapsulation methods for plant extracts to enhance the bioavailability and therapeutic efficacy of phytochemicals. The development of novel drug delivery systems (NDDS) such as liposomes, niosomes, and polymeric NPs allows for sustained release and targeted delivery of phytoconstituents. This can lead to improved patient compliance by reducing the frequency of administration (Dewi et al., 2022). Being vesicles made of lipids, liposomes provide a one-of-a-kind setting for the encapsulation of herbal substances. The liposomal encapsulation technique, which allows for individualized drug delivery, has many advantages, including increased medication solubility and prolonged release of phytochemicals.

Polymeric NPs have shown promise for sustained release of herbal extracts, allowing for regulated and prolonged phytochemical delivery. This controlled release system enhances the accessibility and stability of bioactive components, thereby maximizing their therapeutic value. This approach carries substantial implications, especially in scenarios where the continuous and precise administration of medicinal extracts is vital. Biogenic metallic NPs represent an innovative methodology for the transportation of herbal extracts. The synthesis of metal NPs with phytochemicals as reducing agents enables the development of a dependable platform for the distribution of pharmaceuticals derived from plants. The potential of this approach to enhance the therapeutic efficacy and cellular uptake of herbal extracts is underscored by the improved anticancer properties.

Eco-friendly methods for synthesizing NPs using plant extracts are gaining traction. This approach not only aligns with sustainable practices but also enhances the therapeutic potential of herbal medicines through synergistic effects. Increased focus on clinical research to validate the efficacy of nano-formulations is essential. This includes exploring their pharmacokinetics and pharmacodynamics to establish safety and efficacy profiles (Anand et al., 2023).

The interaction between NPs and plant cellular structures may induce phytotoxicity, which needs careful evaluation during formulation development (Gupta et al., 2024). Establishing clear regulatory frameworks for the approval of nanotechnology-based herbal products is critical to ensure safety and efficacy while fostering innovation in this field (Gupta et al., 2024). The future of nanotechnology in phytomedicine holds significant promise for enhancing the therapeutic potential of herbal medicines. By addressing current challenges and leveraging innovative approaches, researchers can unlock new possibilities for effective treatments that integrate traditional knowledge with modern science. Continued exploration in this field will likely lead to breakthroughs that improve health outcomes globally.

6. Conclusion

Medicinal plants are considered as a major source of herbal extract and are categorised under the conventional drug parameters for the treatment of various types of disorders, including microbial illness, infection and cancer. The active compounds isolated from medicinal plants may not specifically function as drugs but may provide alternatives to cure various diseases. As research progresses, new technologies aid in the improvement of the various antimicrobial or anticancer activities of drugs. Nanotechnology is a field related to NPs, which have prominent potential than normal-sized compounds. Herbal extract encapsulated NPs show various biological activities. By enabling controlled and sustained release of bioactive components, nanotechnology improves pharmacological outcomes and opens new pathways for the treatment of chronic diseases such as diabetes, obesity, cancer, and inflammation-related disorders. The synergistic potential of phytochemicals and nanomaterials paves the way for safer, more effective, and patient-friendly herbal therapeutics. Further, research should focus on optimizing these nano-formulations for large-scale production, regulatory approval, and clinical applications. The continued exploration of nanotechnology in phytomedicine is required to bridge the gap between traditional herbal remedies and modern pharmacology, marking a new era of innovation and therapeutic excellence.

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