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REVIEW ARTICLE

Application of the combinatorial approaches of medicinal and aromatic plants with nanotechnology and its impacts on healthcare

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Abstract

Background Medicinal and aromatic plants are natural raw materials. Since ancient times these herbal materials are being commonly used as herbal drugs, food products, and cosmetics. The phytomolecules isolated from the medicinal and aromatic plants (MAPs) are in high demand specifically in drug industries. However, these phytomolecules have certain limitations of low absorption, high toxicity, and other side effects, bioavailability and efficacy. These limitations may be overcome by using nanotechnological tools. The plant extract or essential oil of MAPs are also useful in the synthesis of nanoparticles. In future this combinatorial application of MAPs and nanotechnology would be advantageous in the healthcare area.

Methods Literature search was performed using databases like Pubmed, Scopus and Google Scholar with the keywords "nanoparticles," "phytomolecules," "medicinal and aromatic plants" and "green synthesis of nanoparticles" in the text.

Result Phytomolecules of medicinal and aromatic plants like curcumin, camptothecin, thymol, and eugenol have certain limitations of bioavailability, efficacy, and solubility. It limits its biological activity and therefore application in the biomedical area. The increment in the biological activity and sustained delivery was observed after the encapsulation of these potent phytomolecules encapsulated in the nanocarriers. Besides, MAPs and/or their molecules/oils mediate the synthesis of metal nanocarriers with less toxicity.

Conclusion This review highlights the impact of the combination of the MAPs with the nanotechnology along with the challenges. It would be an effective technique for the efficient delivery of different phytomolecules and also in the synthesis of novel nano-materials, which escalates the opportunity of exploration of potential molecules of MAPs.

Keywords Medicinal · Aromatic · Plants · Nanoparticles · Biological activity

Introduction

The active constituent, extract, and oils derived from Medicinal and Aromatic Plants (MAPs) play a vital role in herbal remedies to cure and manage various diseases and disorders since antiquity. According to the World Health Organisation (WHO), about 80% of the global population is dependent on traditional plant-based medicines. It is estimated that about 60% medicinal formulations which are available in the market or tested are based on natural products of MAPs. Presently, about 80% of the anticancer, antimicrobial, immunosuppressive and cardiovascular drugs are primarily based on plant sources. Among 177 anticancer drugs, about 70% moieties are based on medicinal plants [1]. Similar to the phytomolecules, aromatic oils/aroma-molecules, have also been used for centuries in healthcare on a global scale. Currently, there are almost 3000 well-known essential oils. Among those, 10% essential oils are known for their commercial importance in various sectors of agronomy, cosmetic, pharmaceutical and perfume industries. Mostly, the chemical constituents present in the aromatic oil are responsible for their biological activity. The major component types are terpenoids, phenylpropanoids, and short-chain aliphatic

Highlights
- Importance of medicinal and aromatic plants along with certain limitations
- The combinatorial approach of nanotechnology with MAPs
- Effectiveness of the approach in phytomolecule delivery and green synthesis of nanoparticles.
- Challenges of the combinatorial approaches

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hydrocarbon derivatives, with characteristics of low molecular weight. There are several approaches to the application of aromatic oils because of its therapeutic effects. In the case of oral administration, the oils are usually diluted in milk or olive oil. Also, for direct application of oils on the skin, the oils are diluted by mixing with other solvents, as pure oil cause skin irritation or darkening of the skin, such as citrus oil are UV sensitive [2]. The external application of pure oil on the injured skin may lead to severe side effects as they are permeation enhancers. [3].

The long-term toxicity, side-effects, low solubility and low stability of the pharmaceutically active compounds of MAPs has become a significant problem which leads to a demand for novel drug delivery system which may reduce or fully overcome the effect associated with the active compounds. In this context, the union of nanotechnology and MAPs could be a useful approach for improving the treatment, diagnosis, monitoring tools in the healthcare system. The technology aims to design and develop new tools and dosage forms in the range of 1 to 100 nm. For this purpose, several nanocarriers have been prepared which include synthetic biodegradable polymers like polysaccharides and lipids. These nanocarriers are useful in the formation of nano dosage forms which enhanced the solubility and bioavailability, reduced toxicity; increase the pharmacological activity, etc.

Every year many nano-drugs enter the clinical investigation and around 56 clinical trials including the term 'nano' were listed as active on ClinicalTrials.gov [4]. Among nano-drugs, two of the top 10 bestselling drugs in the United States in 2013 were polymeric drugs- Copaxone (glatiramer acetate injection, Teva Pharmaceuticals), approved in 1996 for the treatment of relapsing-remitting multiple sclerosis, and Neulasta (Pegfilgrastim, Amgen), recommended in 2002 for chemotherapy-induced neutropenia [5]. Many nano-drugs are being investigated in clinical trials. For example, CRLX101 (drug conjugate formulation of camptothecin and cyclodextran-polyethylene glycol polymer) is investigated alone and also by mixing with different drugs in various phase one and two clinical trials for the treatment of solid tumors, and lung cancers. It was found successful for gastrointestinal cancer and renal cell carcinoma in clinical studies [6].

Not only deliveries of phytomolecules, but MAPs are also useful in the synthesis of various metallic nanoparticles. It is known that metallic nanoparticles possess unique properties, which make them suitable for industrial, agricultural, biomedical and household applications. As a result, the global production of metallic nanoparticles for 2010 was 260,000–309,000 metric tons [7]. In the first three decades of the twenty-first century, several nano-based products are exposed to society. Metallic nanoparticles are synthesized not only by chemical methods, but it can also be produced by using MAPs, which is known as a green method. A literature search using ScienceDirect.com and keywords 'green synthesis of metal nanoparticles' showed 13,457 results while PubMed showed 1761 results as on July 26, 2018. This current review focuses on how does the combination of MAPs with nanotechnology could improve or overcome the issues associated with plant-based herbal medicines. Additionally, it also showed the importance of MAPs in the green synthesis of nanoparticles with specific biological activity, which might be useful in the healthcare area.

Effectiveness and limitations of MAPs in healthcare

The chemical constituents in the plant's extract act as an active ingredient in the medicinal formulation. The active constituents of plant extracts like tannins, flavonoids, alkaloids, phenylpropanoids, and terpenoids are water soluble but shows poor absorption, which then results in decreased bioavailability and efficacy. The efficacy of any medicine is mainly dependent on the delivery of therapeutic active compounds to its site of action. Studies have shown that herbal formulations shows bioactivity under *in-vitro* conditions but fail to reproduce the same effect in *in-vivo*. The most common and well-studied example of plant-based molecules is Curcumin (diferuloylmethane) which is the most studied chemopreventive agent. It is a polyphenol which is assimilated in the rhizome part of *Curcuma longa* [8]. It has also been applied for the treatment of neurodegenerative diseases, diabetes, bronchitis, cardiovascular diseases, rheumatoid arthritis, inflammatory bowel diseases, psoriasis, renal ischemia, scleroderma, acquired immunodeficiency disease, cancer, anti-aging, and scar formation agent [9]. Regardless of showing unique medicinal properties, curcumin has limitations like low solubility, rapid metabolism and poor bioavailability [10].

Another example is *Cannabis sativa* which is generally used for the treatment of malaria, constipation, rheumatic pains and during childbirth. The plant mainly consists of 60 terpenophenolic compounds named as phytocannabinoids [11]. The first reported active component found in *Cannabis sativa* was Δ9 -tetrahydrocannabinol (Δ9 -THC). The cannabinoids have typical symptoms and side effects like nausea, vomiting, loss of appetite and cachexia [12]. Camptothecin, is a potential drug-like molecule, exhibiting antitumor activity against prostate, lung, breast, stomach, bladder and ovarian cancers. It is a pentacyclic alkaloid isolated from Chinese tree *camptotheca acuminate*. However, its efficacy was significantly restricted by its poor solubility, stability, and toxic side effects like, nausea and myelosuppression, which restricts its application in targeted therapies [13].

The aromatic oils are also known for their excellent medicinal properties like antimicrobial, anti-oxidant, but the chemical constituents can readily undergo oxidation reactions which result in allergenic products with decreased biological activity and increased side effect. These problems make these drug a poor candidate for medicinal and therapeutic use [14]. For example, Thymol, which is a natural monoterpenoid phenol derivative and antimicrobial agent isolated from thyme. According to the United States Food and Drug Administration (FDA), thymol is generally recognized as a safe food additive. However, due to its poor water solubility, a strong result in flavoring food led to interaction with the food components like fat and protein, it is difficult to disperse it [15]. It has been reported that the antimicrobial activity of thymol is related to depolarization of the bacterial cytoplasmic membrane and high concentration of thymol was required in altering the structure of the membrane [16]. In aroma molecules, the complexity mainly starts with poor membrane permeability [17].

Similarly, Menthol is a broadly used flavoring agent used in several products like toothpaste, chewing gum, balms, etc. It is monocyclic monoterpene alcohol, naturally isolated from the peppermint oil. Many previous studies showed the antibacterial and antifungal activity of menthol. However, its high volatility, insolubility, instability and high crystallization in aqueous medium becomes a critical problem in its application and shelf life [18]. So, there are still requirements of carrier systems which can be useful in herbal drug delivery system.

Importance of combinatorial approaches of nanotechnology and MAPs

The idea of 'nanotechnology' was first initiated by Richard P. Feynman in 1959, followed by the discovery of carbon nanotubes in 1991. Nanotechnology is an interdisciplinary approach which includes production and implementation of materials, equipment's or systems in the range of nanometer. Nanotechnology is expected to play a critical role in biomedical applications, not only in drug delivery but also in molecular imaging, biomarkers, and biosensors. At present, several biocompatible polymers, liposomes, and micelles are being researched as carriers system for vaccines, drugs, and genes. The application of nanocarriers/nanomaterial is very beneficial in the formulation of herbal drugs or administration of pure phytomolecule or aroma molecule. It does so by acting as a drug delivery carrier to deliver optimum drugs doses to its site of action. There is an increasing hope that nanotechnology, in combination with MAPs , will bring significant advances in the field of biomedical science.

The MAPs contain several drugs like molecules which shows biological activity but consists of various limitations. The nanotechnological strategies attempted to remove the various limitations and helpful in enhancing the properties and behavior of a drug like a molecule in the biological environment. In nano-formulation research, nano-sized drug delivery system can help in improveing the solubility, bioavailability, stability, toxicity, pharmacological activity, and tissue macrophages distribution, sustained delivery, increase target specificity, etc. The incorporation of nanocarriers and medicinal drugs can efficiently combat many diseases like diabetes, tuberculosis, cancer and many others [19]. The nano-carrier based drug delivery tool not only enhances drugs effectiveness but also helps in reducing toxicity and side effects, which makes this approach attractive. Not only drug delivery but these plants also have a significant role in the production of nanoparticles which are non-toxic. In this review, the impact of a combination approach of MAPs with nanotechnology along with their impacts are discussed.

Combinatorial approach of nanotechnology with phytomolecules of MAPs

An enhancement in the bioavailability of berberine was observed when encapsulated in chitosan nanoparticles without affecting the structure and function of berberine. Additionally, it also enhanced cytotoxic behavior against the cancer cells by directly targeting its nuclei without affecting the normal cells. *In-vivo* studies demonstrated an enhancement in the bioavailability when administered orally, and encapsulation of berberine reduced the dosages up to three times. Several plant-based drugs have been used for cervical cancer [20]. Cisplatin loaded folic acid-conjugated gelatin nanoparticles have shown cellular uptake of 81% in comparison to cisplatin and cisplatin-gelatin nanoparticles, which shows 51% cellular uptake [21]. Based on the nanostructured herbal formulations, several examples are presented in Table 1. Paclitaxel was encapsulated in stearyl amine-based positively charged multi-layered liposomes. Then, the nanoformulation was coated with 'anionic polyacrylic acid' and further by 'cationic chitosan.' The chitosan-polyacrylic acid-paclitaxel liposomes showed sustained release and increased cytotoxicity in HeLa cell lines as compared to paclitaxel liposomal formulation [48]. Similarly, lipid-based nanomaterial encapsulated green tea, and ginseng extracts were prepared in different formulations for enhancing the intake of active ingredients. Liposomes based nanoparticle using *Artemisia arborescens L.* are used for the entry of active constituents through the cytoplasmic boundary [49].

The enhanced antimicrobial activity against *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* was observed in methanolic extract of *Ocimum sanctum L.* encapsulated nanoparticles [50]. Honokiol, also known as 3′,5-di(2-propenyl)-1,1′-biphenyl-2,4′-diol is an active component of *Magnolia officinalis*. It has multiple pharmacological properties but due to certain

Table 1 Nanostructured herbal formulations from medicinal plants and their activity

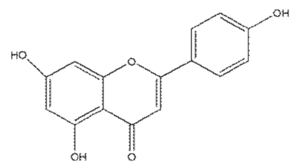
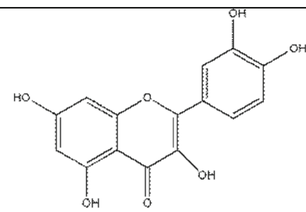
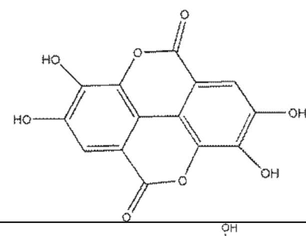
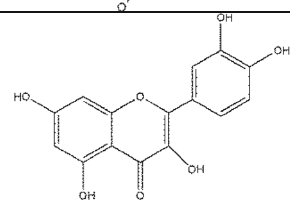
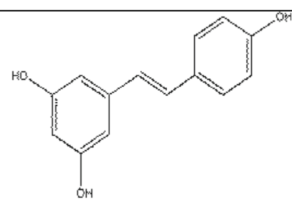
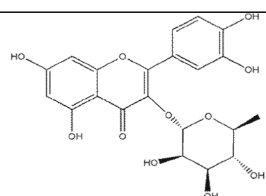
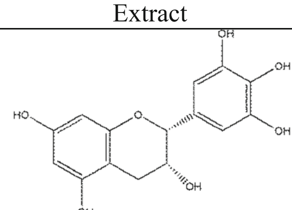
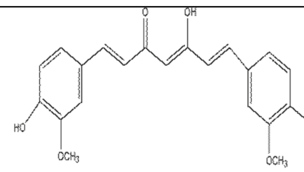
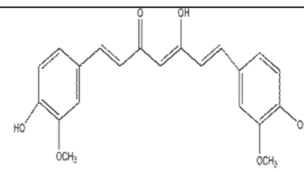
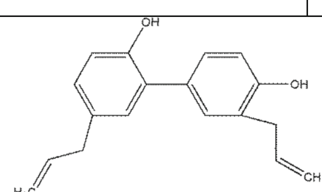
Plant	Extract/ Molecule	Chemical structure/Extract	Nanoparticles used	Reported activity	References
Fruits and vegetables	Apigenin		Poly(lactic-*co*-glycolic acid)	Skin cancer	[22]
Fruits and vegetables	Quercetin		Poly-D,L-lactide	Antioxidant	[23]
Fruits and vegetables	Ellagic acid		Poly(lactic-*co*-glycolic acid)	Antioxidant	[24]
Fruits and vegetables	Quercetin		Liposomes	Antioxidant, Anticancer, Hepato-protector	[25]
Grapes, blueberries, raspberries, mulberries	Resveratrol		Liposomes	Antioxidant	[26]
Albiziachinensis	Quercitrin		Poly(lactic acid)	Antioxidant and anti-inflammatory	[27]
Camellia sinensis	Tea extract	Extract	Polycaprolactone-alginate	Antioxidant	[28]
Camellia sinensis	Tea polyphenols	Extract	Chitosan	Antitumor	[29]
Camellia sinensis	Epigallocatechingallate		Poly(lactic acid) + Poly (ethylene glycol)	Anti-proliferative	[30]

Table 1 (continued)

China green tea	Green tea polyphenols extract	Extract	Sodium-caseinate or calcium-caseinate	Antioxidant	[31]
Cinnamomumcasia	Cinnmomum	Extract	Chitosan	Antihypercholesterol	[32]
Cinnamon spice	Cinnamon bark extract	Extract	Poly (lactic-*co*-glycolic acid)	Antimicrobial	[33]
Clerodendruminfortunatum L.	Extract of root	Extract	Polymeric nanoparticles	treating hypercholesterolemia	[34]
Coriandrum sativum	Plant extract	Extract	Polyvinyl alcohol	Antioxidant	[35]
Curcuma longa	Curcumin		Methoxy-poly(ethylene glycol)-poly(D,L-lactide)	Anticancer	[36]
Curcuma longa	Curcumin		Liposomes	Antioxidant, Anti-inflammatory	[37]
Elettariacardamomum	Plant extract	Extract	Polyvinyl alcohol	Antioxidant	[35]
Elsholtziasplendens	Extract	Extract	Chitosan	Antioxidant	[38]
Gelsemiumsempervirens	Ethanolic extract	Extract	Poly(lactic-*co*-glycolic acid)	Anticancer	[39]
Guabiroba	Extract of guabiroba fruit	Extract	Poly(lactic-*co*-glycolic acid)	Antioxidant and antimicrobial	[40]
Magnolia officinalis	Honokiol		Poly(3-caprolactone)-poly(ethylene glycol)-poly(3-caprolactone) copolymer	Anti-proliferative	[41]
Myrtuscommunis	Myrtle	Extract	Liposomes	Antioxidant, Antimicrobial	[42]
Oleaeuropaea	Olive leaves extract	Extract	Poly(lactic acid)	Antioxidant	[43]
Passiflaraserratodigitata L.	Hydroalcoholic Extract	Extract	Poly(epsilon-caprolactone)	Antiulcerogenic	[44]
Scutellariabaicalensis	Ethanolic extract	Extract	Lecithin	Anti-inflammatory	[45]
Silybummarianum	Plant extract	Extract	Polyvinyl alcohol	Antioxidant	[35]
Syzygiumjambolanum	Ethanolic extract of the seeds	Extract	Poly(lactic-*co*-glycolic acid)	Antidiabetic	[46]
Thymus sp.	Thyme extract	Extract	Liposomes	Antioxidant, Antimicrobial	[47]

limitations like high hydrophobicity prevents its vascular administration. However, honokiol encapsulated polymeric nanoparticles increased the possibility of vascular administration and showed better results compared to free honokiol [51]. Like honokiol, quercetin is one of the many flavonoids consisting various pharmacological activities. Quercetin loaded nanoparticles were prepared using polyvinyl alcohol and eudragit®E, to estimate the antioxidant of pure quercetin and quercetin loaded nanoparticles. The system was found to be more effective relative to di (phenyl)-(2,4,6-trinitrophenyl) iminoazanium scavenging, superoxide anion scavenging, anti-superoxide formation, and anti-lipid peroxidation activities, as compared to pure quercetin with encapsulation efficiency higher than 99% [52]. The camptothecin is a potent anticancer molecule but due to low solubility, unstable lactone ring, it was unsuitable for clinical purposes. When camptothecin was loaded in hydrophobically modified glycol chitosan nanoparticle, it showed loading efficiency greater than 80%. It helps in protecting the lactone ring from physiological conditions. It was also demonstrated to have strong antitumoral activity along with higher penetration in tumors, as proved by the near-infrared study [53]. Similarly, when curcumin was loaded in poly(lactic-co-glycolic acid) nanoparticle, it showed 90.88% ± 0.14% encapsulation efficiency with biological activity against prostate cancer [54].

Das et al. (2012) demonstrated that the root extract of *Phytolacca decandra* in the free form and poly(lactic-co-glycolic acid) loaded form in the animal model. It was found that nanoparticles increased the drug's bioavailability and showed better chemopreventive action against lung cancer in both *in vivo* and *in vitro* experiments [55]. Celastrol nanoparticles composed of poly (ethylene glycol)-block poly (ε-caprolactone) nano polymeric micelles and helps in improving hydrophilicity [56]. It was reported that *Panax notoginsenoside*, when encapsulated in core-shell hybrid liposomal vesicles helps in enhancing its bioavailability [57]. When ginkgolides A, B, C and bilobalide from *Ginkgo biloba* extract, was loaded in monomethoxy (polyethylene glycol)-poly (lactide-co-glycolide)-monomethoxy (polyethyleneglycol) by co-encapsulation method, it showed sustained and synchronized release in both *in vitro* and *in vivo* [58].

In addition, Apocynin, a bioactive organic phytochemical, which is known as a specific NADPH oxidase inhibitor, with potent antioxidant and anti-inflammatory activities. The bioactivity of apocynin was revealed in various diseases like cancer, atherosclerosis, asthma, vascular and neurodegenerative diseases, collagen-induced arthritis and inflammatory bowel disease pharmacotherapy [59]. However, due to its rapid elimination and poor bioavailability properties, it has becomes a challenge for pharmaceutical scientists. The encapsulation of the apocynin in the chitosan-based solid lipid nanoparticle showed potential in enhancing the oral and intravenous bioavailability in rats [60]. These examples help in better understanding of the combinatorial approach of MAPs and nanotechnology.

Combinatorial approach of nanotechnology with aromatic molecules

The nano-encapsulation of the aromatic molecules in modified nanocarriers improves their solubility, stability, and efficacy by maintaining therapeutic drug to their specific target of action [19]. They also possess desirable properties like the controlled and sustained release of the drug molecule, deep penetration through tissue due to nanometer size, helps in protecting its therapeutics potential at both extracellular and intracellular levels [2]. The nanoparticles prepared using polysaccharides are considered to be promising carriers of a hydrophilic drug-like molecule, due to their unique properties. The releasing of essential oil takes place through different processes like dissolution, desorption, diffusion through the matrix; of the surface-bound/adsorbed functional ingredient, matrix erosion including enzyme degradation, and a combination of these processes [61]. Different examples of aromatic component encapsulated nanoparticles are listed in Table 2.

An aromatic molecule, eugenol is one of the main components from the diverse group of essential oil. However, due to its instability, high volatility, sensitivity from oxygen, light, heat, and storage problems, it cannot be used in therapeutic applications. When eugenol was loaded with chitosan nanoparticle, it was found thermally stable, with the average size less than 100 nm [92]. The in vitro release study of solid lipid nanoparticles containing essential oil of *Zataria multiflora* showed 93.2% release of the essential oil after 24 h. Carvacrol, thymol, p-cymene, and c-terpinene were examined as the major components and prepared by using essential oil from *Origanum dictamnus* L. These molecules were entrapped in phosphatidyl choline-based liposomes, led to improvement in its antioxidant activity. Along with this, its antimicrobial activity was investigated against different Gram-positive and Gram-negative bacteria, fungi, and food-borne pathogens showing increment in antimicrobial activities [78].

The insecticidal activity against *Tribolium castaneum* was observed using polyethylene glycol nanoparticle encapsulated garlic essential oil, which helps control the store-product pest [93]. The antimicrobial activity against *E. coli* and *Salmonella* and DPPH radical scavenging activity has been reported using thymol loaded zein coated sodium casinate nanoparticle [94]. The polyvinyl alcohol/cinnamon essential oil/β-cyclodextrin antimicrobial nanofibrous film was developed, which can enhance the

Table 2 Nanostructured herbal formulations from aromatic plants and their activity

Plant	Aroma constituents	Nanoparticles	Reported activity	References
Anise myrtle, Mentha spicata	Anethole, Carvone	Poly(lactic-*co*-glycolic acid)	Antimicrobial	[62]
Artemisia arborescens	Essential oil	Liposome	Antiviral	[49]
Cinnamomum verum	Cinnamon oil	Polylactide	Antibacterial	[63]
Cinnamomum verum	trans-cinnamaldehyde, eugenol, cinnamon bark, and clove bud extract	Beta-cyclodextrin complex	Antimicrobial	[64]
Cinnamomum verum	Essential oil	Polylactide + Bimaetallic Ag-Cu nanoparticle	Antibacterial	[65]
Citrus aurantifolia	Lime oil	Chitosan	Antibacterial	[66]
Citrus aurantium	Essential oil	Chitosan	Antioxidant	[67]
Cuminum cyminum	Essential oil	Chitosan	Antioxidant	[68]
Curcuma longa	Turmeric oil	Chitosan and alginate	Antiproliferative	[69]
Cymbopogon citrates	Lemongrass oil	Chitosan and alginate	Antiproliferative	[69]
Cymbopogon citrates	Citral	Nanoemulsion	Antimicrobial	[70]
Eucalyptus staigeriana	Eucalyptus oil	Cashew gum	Antimicrobial	[71]
Eucalyptus staigeriana	Essential oil	Lipid nanoparticle	Antimicrobial	[72]
Eugenia caryophyllata	Essential oil	Solid lipid nanoparticles	Antimicrobial	[73]
Melaleuca alternifolia	Tea Tree Oil	Nanoemulsions	Antifungal	[74]
Melaleuca alternifolia	Tea tree oil	Liposome	Antimicrobial	[75]
Mentha piperita oil	Peppermint oil	Chitosan-cinnamic acid nanogels	Antimicrobial	[76]
Ocimum species	Eugenol	Nanoemulsion	Antimicrobial	[77]
Origanum dictamnus L.	Carvacrol, Thymol	Phosphatidyl choline-based liposomes	Antimicrobial	[78]
Origanum dictamnus L.	Thymol	Liposome	Antimicrobial	[79]
Origanum dictamnus L.	Carvacrol	Liposome	Antimicrobial	[79]
Origanum dictamnus L.	Carvacrol	Chitosan	Antimicrobial	[80]
Origanum dictamnus L.	Thymol	Methyl and Ethylcellulose	Antimicrobial	[81]
Origanum dictamnus L.	Carvacrol, thymol, p-cymene, and c-terpinene	Phosphatidyl choline based liposomes	Antimicrobial	[78]
Pogostemon cablin	Wild patchouli oil	Nanoemulsion	Antibacterial and anti-candida	[82]
Punica granatum	Pomegranate oil	Hydrogel containing silibinin	Anti-inflammatory	[83]
Salvia multicaulis	Essential oil	Nanoemulsion	Antimicrobial & antioxidant	[84]
Saturejamontana	Savory oil	Chitosan	Antimicrobial & antioxidant	[85]
Syzygium aromaticum	Clove oil	Polylactide	Antibacterial	[63]
Syzygium aromaticum	Clove oil	Nanoemulsion	Antibacterial	[86]
Syzygium aromaticum	trans-cinnamaldehyde, eugenol, cinnamon bark, and clove bud extract	Beta-cyclodextrin complex	Antimicrobial	[64]
Thymus daenensis	Essential oil	Nanoemulsion	Antibacterial	[87]
Thymus vulgaris	Thyme oil	Chitosan-benzoic acid nanogel	Antifungal, antiviral and antibacterial	[88]
Thymus vulgaris	Thyme oil	Phospholipon G90, cholesterol and calcium.	Antioxidant	[89]
Zanthoxylum tingoassuiba	Essential oil	Liposome	Antimicrobial	[90]
Zataria multiflora	Essential oil	Chitosan	Antifungal	[91]

shelf life of strawberry, demonstrating its application in food packaging [95]. The peppermint essential oil encapsulated in the bio-nanocomposite film was prepared by filling a pectin matrix with modified halloysite nanotubes, exhibiting antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* [96]. It was reported that the inhibitory activity of thyme essential oil loaded chitosan nanoparticle was higher against *Staphylococcus aureus,* and thyme essential oil loaded chitosan nanocapsules show inhibitory activity against *Bacillus cereus* [66]. It was

Table 3 Summary of the green synthesis of nanoparticles using medicinal and aromatic plants

Plant	Reducing agent	Material precursor	Nano-particle	Application	References
Phaseolus vulgaris	Black bean extract	Copper sulphate	Copper oxide	Anticancer	[100]
Acalypha indica	Leaf extract	Chloroauric acid, silver nitrate	Gold, Silver	Antibacterial	[101]
Allium sativum	Garlic extract	Silver nitrate	Silver	Antibacterial	[102]
Aloysia triphylla	Aqueous extract	Silver nitrate	Silver	Antifungal	[103]
Alternanthe rasessilis	Whole plant	Silver nitrate	Silver	Antioxidant, antimicrobial	[104]
Anisochilus carnosus	Leaf extract	Zinc nitrate	Zinc oxide	Antibacterial and photocatalytic	[105]
Artocarpus heterophyllus	Seed extract	Silver nitrate	Silver	Antibacterial	[106]
Azadirachta indica	Leaf extract	Zinc acetate dihydrate	Zinc oxide	Antibacterial activity, photocatalytic applications	[107]
Caesalpinia coriaria	Leaf extract	Silver nitrate	Silver	Antibacterial	[108]
Calotropis gigantea	leaf extract	Silver nitrate	Silver	Antibacterial	[109]
Calotropis gigantea	flowers extract	Titanium dioxide hydrate	Titanium oxide	Antiparasitic	[110]
Cassia auriculata	propanoic acid 2-(3-acetoxy-4,4,14-trimethylandrost-8-en-17-yl)	Chloroauric acid	Gold	Antidiabetic	[111]
Cassia fistula	plant extract	Zinc nitrate hexahydrate	Zinc oxide	photodegradative, antioxidant and antibacterial	[112]
Cassia tora	leaf extract	Silver nitrate	Silver	Antibacterial	[113]
Catharanthus roseus	leaf extract	Silver nitrate	Silver	Antiplasmodial	[114]
Cauler papeltata, Hypnea valencia, S. myriocystum	leaf extract	Zinc nitrate	Zinc oxide	Antimicrobial	[115]
Chelidonium majus L.	Plant extract	Silver nitrate	Silver	Antioxidant, antimicrobial	[116]
Cinnamomum zeylanicum	leaf extract	Chloroauric acid	Gold	Antibacterial and antifungal	[117]
Citrullus colocynthis	Calli	Silver nitrate	Silver	Antioxidant, anticancer	[118]
Cocous nucifera	methanol and ethyl acetate extracts of the inflorescence	Silver nitrate	Silver	Antibacterial	[119]
Coptidis rhizome	plant extract	Zinc nitrate	Zinc oxide	Antibacterial, antioxidant, and cytotoxic	[120]
Dendropanaxmorbifera	leaf extract	Silver nitrate	Silver Gold	Anticancer	[121]
Dysosma pleiantha	aqueous rhizome extract	Chloroauric acid	Gold	Anti-metastatic	[122]
Gloriosa superba L.	leaf extract	Cerium(III) chloride	Cerium oxide	Antibacterial	[123]
Hibiscus subdariffa	flower extract	Copper nitrate	Copper	Antibacterial	[124]
Hibiscus subdariffa	leaf extract	Zinc acetate	Zinc oxide	Anti-bacterial activity, anti-diabetic	[125]
Laurelia sempervirens	aqueous extract	Silver nitrate	Silver	Antifungal	[103]
Lemon (Citrus sp.)	fruit extract	Copper chloride	Copper	Antibacterial	[126]
Magnolia kobus	leaf extract	Copper sulfatepentahydratesulfate	Copper	Antibacterial	[127]
Mentha piperita	plant extract	Chloroauric acid	Gold	Antibacterial	[128]
Mimusop selengi, Linn.	leaf extract	Silver nitrate	Silver	Antibacterial	[129]
Musa paradisiaca	peel extract	Chloroauric acid	Gold	Antimicrobial	[130]
Musa paradisiaca	Peel extract	Chloroauric acid	Gold	Anticancer	[131]
Nerium oleander	leaf extract	Copper sulphate	Copper	Antibacterial	[132]
Nyctanthes arbortristis	ethanolic flower extract	Silver nitrate	Silver	Antibacterial and cytotoxic	[133]
Ocimum sanctum	leaf extract	Silver nitrate	Silver	Antibacterial	[134]
Parthenium hysterophorus	leaf extract	Zinc nitrate	Zinc	Antifungal	[135]
Phyllanthus Embilica	fruit extract	Copper sulphate	Copper	Antibacterial	[136]
Pleurotus florida	edible mushroom	Chloroauric acid	Gold	Anticancer	[137]

demonstrated that when frankincense and myrrh essential oil was loaded in solid lipid nanoparticles using high-pressure homogenization method, enhance its bioavailability and improves hydrophilicity [97]. The combinatorial approach proves to be effective for the delivery of essential molecules.

Combinatorial approach of nanotechnology with MAPs in the synthesis of nanoparticles

Biological synthesis or green synthesis of nanoparticles is an eco-friendly method. There are various biologically active components found in the plants which possess reducing capability in producing metallic nanoparticles with effective therapeutic potential. Plant extracts and essential oils are considered as the best-reducing agents to overcome the problem of toxicity during chemical synthesis. The plant-based molecules like flavonoids, alkaloids, polyphenols, vitamins, tannins, plant pigments polysaccharides, and aroma molecules are responsible for many reduction reactions of metal salts to metal nanoparticles [98]. The application of nanoparticles isolated by employing green synthesis method has played a significant role as antimicrobial agents or potential drug carrier in the treatment of cancer [99]. Several examples of synthesis of nanoparticles using plant MAPs as reducing agents along with their biological activities are listed in Table 3. Gold nanoparticles isolated using flowers of *Couroupita guianensis* tree showed anticancer activity [138]. The highly stabilized gold and silver nanoparticles were synthesized using glucoxylans which were isolated from seeds of *Mimosa pudica* [139]. Silver nanoparticles were developed using *Taraxacum officinale* leaf extract and also showed significant antioxidant and anticancer activity [140]. The silver nanoparticles produced using stem bark extract of *Helicteres isora*, showed antioxidant effects determined using DPPH, hydrogen peroxide and nitric oxide radical scavenging and a reducing power assays. It also exhibits antibacterial effect against test strains, showing significant inhibition. Along with antioxidant and antibacterial, it showed antiproliferative activity which was demonstrated using oral carcinoma (KB) cells with MTT assay [141].

The rod-shaped copper oxide nanoparticle was synthesized using *Carica papaya leaf* extract [142]. The copper nanoparticle synthesized using the aqueous extract of the latex of *Calotropis procera L.* showed long-term stability along with excellent cell viability at 120 μM concentrations [143]. Similar to copper oxide nanoparticles, zinc oxide nanoparticles were also prepared by using flower extract of *Nyctanthes arbortristis,* and exhibit significant antifungal potential [144]. The gold nanoparticles were synthesized by using aromatic plant extract like *Ocimum*, and *Eucalyptus* in size range of 3–16 nm [145]. Silver nanoparticles were prepared by using a solution of *Pimpinella anisum* seeds and showed effective antibacterial potential against *S. pyogenes, A. baumannii, K. pneumoniae, S. typhi, and P. aeruginosa* [146]. The aromatic plants are found to be useful in the production of nanoparticles. For example, gold nanoparticles synthesized using the essential oil of *Mentha piperita* showed high activity against *Aspergillus flavus* [147]. Fluorescent-based peppermint oil nanoparticles exhibited high antibacterial activity and fluorescence in *E. coli* testing and proves to be bifunctional agents as antibacterial and bioimaging applications [148].

The silver nanoparticles isolated using leaf extract of *Erythrina suberosa* showed excellent anticancer activity against A-431 osteosarcoma cell line along with antimicrobial and wound healing activity [149]. The free radical scavenging and antimicrobial activity of silver nanoparticles isolated using *Carica papaya* peel extract were reported [150]. The antibacterial activity was reported from silver nanoparticles isolated using seed extract of *Pongamia pinnata* [151].

New approaches and challenges

The incorporation of the nanotechnology and MAPs could be a successful approach in healthcare. The nanoparticles help in the increment of biological activity, overcoming the issues associated with plant-based medicines and also in the formation of novel materials. There are several MAPs which are useful in the synthesis of nanoparticles along with potential biological activities. With the advancement, there are several challenges remain for applying them in clinically feasible therapies. The trials of novel nanoparticles interaction with the biological system and transforming them to therapies depicted current limitations. Some other challenges related to nanoparticles include examining their potential of targeting, fulfilling international standards of toxicity and biocompatibility. Many reports suggest the formation of reactive oxygen species from different metal nanoparticles like zinc oxide, and titanium oxide [152]. Gold can be used as potential carriers for the drug delivery, imaging molecules, and formation of novel cancer therapy formulations [153]. However, the presence of residues from stabilizer CTAB resulted in cytotoxicity. However, toxicity can be reduced by using a green synthesis method or by coating with the prominent polymers.

The toxicity can be affected by the interaction between nanomaterial and *in vivo* system. Recently, studies were conducted for assessing the nanoparticle toxicity. It was found that when 15–20 nm nanosilver given to rat for 28 days, it gets accumulated in all organs with the highest concentration in the liver and spleen [154]. The cytotoxic effect of 20 nm nanosilver was observed using human liver HepG2 and colon Caco2 cells as in vitro models. They found concentration-dependent cytotoxic effects in both HepG2 and colon Caco2 cells, along with mitochondrial injury and loss of double-stranded DNA in both cells. No cellular oxidative stress was found in dichlorofluorescein assay implying that cellular oxidative stress does not show significant role in the cytotoxicity profile of the nanosilver in both cells [155]. The silver nanoparticles synthesized using aloe vera extract were non-toxic to human peripheral blood mononuclear cells, which demonstrates the application for biomedical applications [156].

The toxicity assessment is the primary concern where different cells and organs are treated with different doses of chemicals, and their response was taken at different time points. These experiments are essential in determining the exact amount of the drug-like molecules, i.e., lethal dose (LD_{50}) and inhibition concentration (IC_{50}). In traditional cytotoxic assays, the main concern is upon the chemicals that exhibit the cellular toxicity, whereas, in the case of the nanoparticle, the main focus is on the sizes and their shapes. This is resulting in the agglomeration of the nanoparticles at the target site, which leads to the misstatement of the toxicity data [157]. Some reports showed the problem of DNA damage in the cells due to exposure of nanomaterials, which causes cancer and developmental toxicity. Some other reasons behind toxicity are the surface functionalization of the nanoparticles and the presence of the gaps in the cells allowing the transmission of molecules into the cells. So, alternative methods should be opted to overcome the issue. Green synthesis is one such method which is helpful in the production of safe and effective nanoparticles along with beneficial effects of cost and non-toxic behavior [158].

Future possibilities

Nanoparticles improve pharmacokinetics profile and help in the appropriate diffusion of the drug in the body system. The production of nanoparticles using green methods holds endless opportunities in the field of drug delivery. It also serves as the best tool for limiting the dosage while increasing bioavailability, bioactivities, and cost-effectiveness. Therefore, nanomaterials require effective analysis for detection of long-term toxicity. It is necessary for the drug-loaded nanomaterials as well as nanomaterials to go through the mechanism involved in the injured cells/tissue before using in therapies. Presently, there are various nanoparticles used for the delivery of plant-based molecules. As these experimental assays are time-consuming and require huge resources, scientists have developed computational analysis for, eg. Quantitative Structure-Activity Relationship (QSAR). These models are developed by taking parameters like biochemical chemical or structural descriptors from the published literature, which help in determine the cytotoxicity of nanoparticles. A conceptual understanding is required to develop safe nanoparticles.

For future possibilities, the scientific background for the reactivity of nanoparticles should be a major concern. The interaction between the nanoparticles and the biological system should be under check. Proper clinical trials should be followed before a final decision. There is a need for further extensive research in the field of nano therapy and efforts are on worldwide to exploit the technology for the better healthcare of humanity. If the plant extract, molecules, or oils replace the chemicals/solvents, it may also reduce the chances of toxicity. The combinatorial approach could be a successful technique which will provide opportunities in the diverse application in the area of healthcare.

Conclusion

Overall, MAPs are a beneficial source of natural agents with excellent biological activities. Current pieces of evidence showed combinational approaches of MAPs with the nanotechnology could better support its application in the area of healthcare. However, future mechanistic studies, toxicity assessment, and well-prepared clinical trials are necessary to estimate the safety and efficacy of the obtained products.

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Compliance with ethical standards

Conflict of interest The author(s) confirm that this article content has no conflict of interest.

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