Biomedical Applications of Phytonanotechnology

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Abstract Phytonanotechnology is an emerging area of agricultural biotechnology that should consider different physicochemical and biological processes for the formulation of nanoparticles to load the extracts derived from innumerable plant parts. Methods exploited for the synthesis of the plant-based nanoparticles have some potential advantages like simple and fast techniques, cost-effectiveness, eco-friendly, stable for a prolonged time, convenient, and reproducible. Apart from these advantages, the phytonanoparticles have tremendous applications in operations related to catalysis, optoelectronics, diagnostic agents, in making of biosensing devices, antimicrobials, therapeutics, etc. It also allows the controlled release of fertilizers, pesticides, herbicides and is involved in the targeted delivery of biomolecules such as nucleotides, proteins, and activators. This chapter summarizes the past, present scenarios of phytonanotechnology in medicinal and pharmaceutical applications. The different classes of nanoformulations using plant extracts with their advantages have been emphasized. The commercial applications of phytonanoparticles in different sectors have been discussed. The use of plant-derived nanoformulations as antimicrobial, wound healing, anticancer agents, diagnostic agents, and targeted drug and gene delivery was discussed. Finally, the future scope of phytonanotechnology was covered in this chapter.

Keywords Phytonanoparticles · Biomedicine · Anti-cancer agent · Gene delivery · Drug targeting

1 Introduction

In past decades, herbal active principles and natural remedies are being used to cure diseases. The employed herbal active principles are alkaloidic, phenolic, flavonoidic, and polyphenolic in nature. Vitamin C, citric acid, and other phytonutrients present in plant-derived products work jointly to fight against a specific disease (Mahesh et al.

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M. P. Shah and A. Roy (eds.), *Phytonanotechnology*,
https://doi.org/10.1007/978-981-19-4811-4_4

2021a, b). Herbal therapeutic agents need a scientific approach to modify the active principle to change the delivery pattern that suits sustained and target release. This approach helps to increase patient compliance and avoids frequent dosing. As per the reports published by so many researchers, nanotechnology is the best alternative to overcome the toxicity and bioavailability problems associated with conventional dosage forms (Mitchell et al. 2021). The global market assumes the faster growth of the nanotechnology market from $5.2 billion in 2021 to $23.6 billion by 2026 with a 35.5% of growth rate (Dublin-Business Wire 2021).

Extensive research in the field of phytonanoformulations can improve the volume of innovative products, with lesser side effects than existing synthetic and conventional herbal formulations. Researchers investigated various herbal drug delivery techniques to suit the diversified structures of natural compounds, at the same time without loss of any physicochemical and biological properties. World Health Organization (WHO) has provided the suitable technical aid to expand a methodological analysis of plant-derived drugs for safety and quality aspects.

Among the Indian population, approximately 65% of people show interest to use traditional medicines. People of developed countries also demand herbal drugs as well. There is a steady demand for traditional medicines in developed countries. India is in second place, behind China in the herbal market. The AYUSH system of India presently covers 8000 herbal remedies with a domestic market worth of $5 billion. Annually over half a billion dollars revenue is generated through Ayurveda, Siddha, and Unani. The global market expects a profit of 111 billion dollars through plant-based medicines by 2023. Still, the phyto-pharma sector is in a nascent stage in India and in so many developed countries. The advancements in nanotechnology and advantages of nanoformulations over conventional products may increase the demand for phytopharmaceuticals, thereby offering an excellent opportunity for phytonanoformulations shortly.

The new research approaches in novel drug delivery systems can allow pharmaceutical companies to explore phytonanopharmaceuticals more constructively (Business World 2021).

The combined knowledge of science and technology directs the synthesis of nanoparticles to develop various nanotherapeutics and diagnostic agents in 1–100 nm size range.

Nanoparticles offer the following advantages over conventional formulations (Pandit et al. 2022).

1. Improved solubility thereby enhancing the bioavailability
2. Increased resident time in the body
3. Promotes targeted drug delivery
4. High carrier capacity with high stability
5. Maintenance of balance between efficacy and toxicity of a therapeutic compound.

1.1 Different Approaches to Synthesize Phytonanoparticles

Currently, various approaches are available to incorporate the herbal active principles into nano delivery vesicles to reach the target thereby being involved in the enhancement of therapeutic activity. Figure 1 outlined various approaches in the synthesis of phytonanoformulations (Roy et al. 2022).

Phytonanoparticles have wide applications in various sectors like agriculture, medicine, and industry. Figure 2 briefly depicts the applications of phytonanoparticles in various fields (Ahmed et al. 2021).

The smaller size and greater surface capacity of a drug containing nanoparticles may establish the rise in solubility and facilitate the bioavailability, in addition, overcome the barrier limitations in various routes of administration. Undoubtedly, people who are taking the conventional herbal formulations for various conditions may shift to the biogenic phytonanoformulations because of their added advantages. The advancements in nano-drug formulations and their delivery can occupy a significant market place and motivate various manufacturers involved in herbal formulations in the coming future (Abhijeet et al. 2021). Figure 3 describes the schematic depiction of phytonanoformulation synthesis and its uses.

The following section highlights the biomedical applications of herbal nanoformulations that were fabricated with various phytoactive principles.

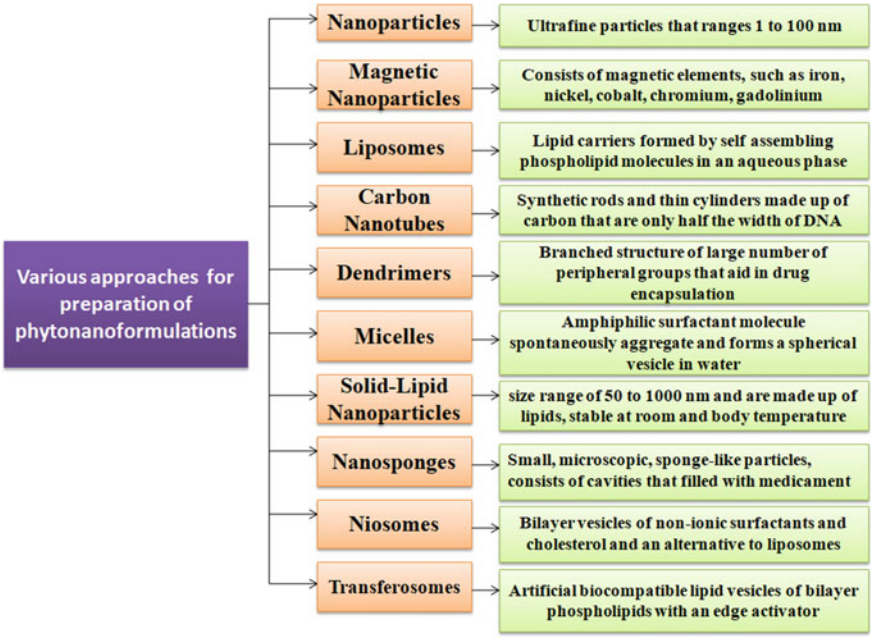

Fig. 1 Various approaches in the synthesis of phytonanoformulations

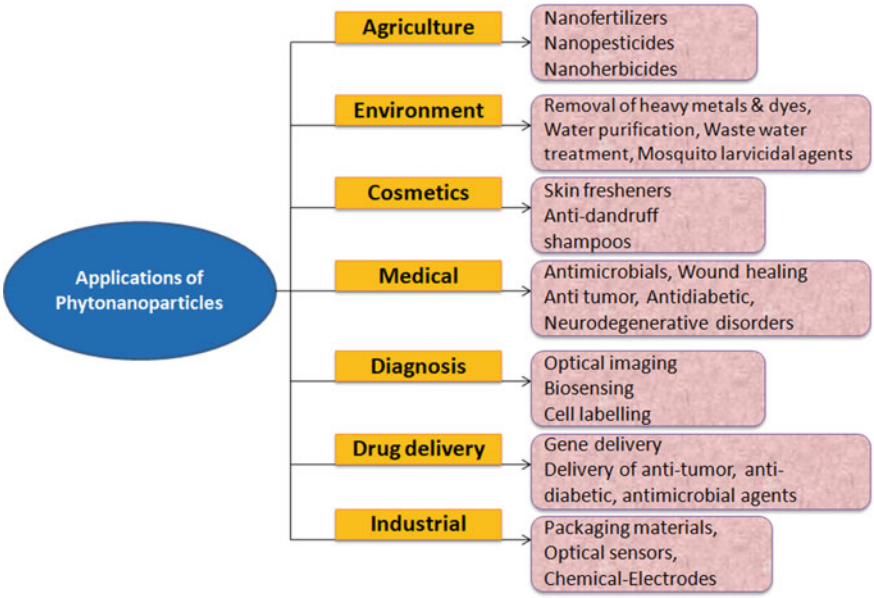

Fig. 2 Thrust areas of phytonanoformulations

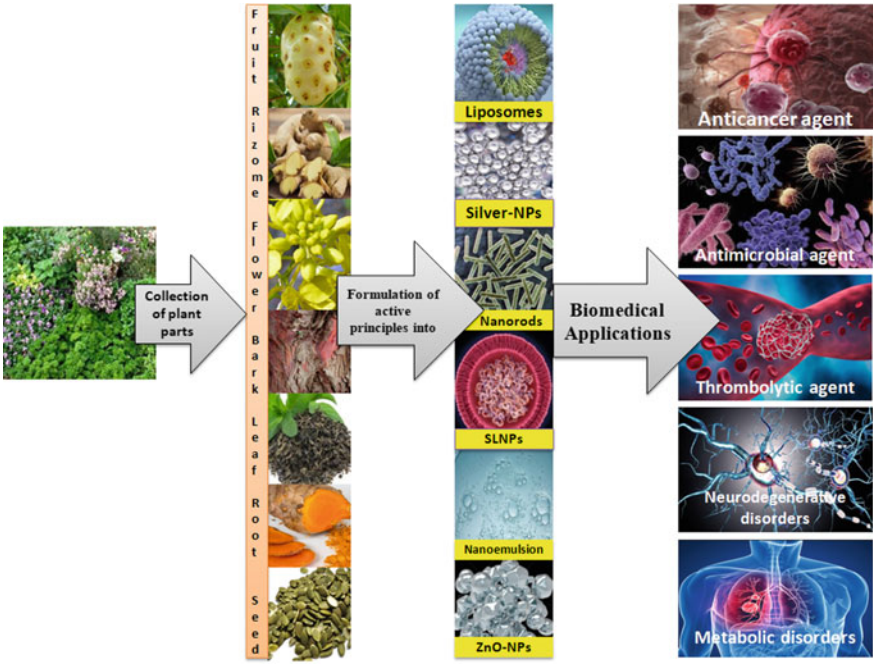

Fig. 3 Schematic depiction of phytonanoformulation synthesis and their potential uses

2 Phytonanoformulations and their Diversified Therapeutic Applications

2.1 As an Anticancer Agent

Targeted drug delivery of nanoformulations overcomes the insolubility and toxicity problems associated with conventional chemotherapeutic agents against cancer. The anticancer activity containing bioactive molecules is isolated from abundant plant parts like fruits, flowers, grains, etc. Plant-derived phyto-medicines are comparatively harmless and well compatible in healthy cells even in high doses than synthetic chemotherapeutic agents. Numerous examples of phytonanoparticles that are currently utilizing for cancer treatment are summarized here.

Extracts of various parts of *Moringa oleifera* reported anti-cancer activity (Charlette et al. 2018). Gold nanoparticles (AuNPs) were synthesized by flower parts of this plant (Anand et al. 2015). Niazimicin is the active principle found in *M. oleifera* that ascribes to anticancer activity. The flowers are fabricated to AuNPs that are cytotoxic to lung cancer cells (A549). The anticancer potentiality also exhibited against MCF7 (Michigan Cancer Foundation-7), HCT116 (human colorectal carcinoma)/Caco2 (human colorectal adenocarcinoma cells), and HepG2 (Human hepatoma cell line) cells with the nanoformulations of leaves and roots of the plant (Abd-Rabou et al. 2017).

Syzygium cumini fruit (Malabar plum) extract was used for formulation of AgNPs and exhibited significant anti-neoplastic and antioxidant potential on Dalton lymphoma cell lines (Mittal et al. 2014).

AgNPs derived from *Origanum vulgare* (Oregano) plant extract have high amounts of monoterpenoid phenols, exhibited increased anti-neoplastic activity on lung carcinoma culture (A549) with increased concentration (Sankar et al. 2013).

Compared to other chemotherapeutic drugs, AgNPs synthesized by green technology using *Morinda citrifolia* (MC) (Noni fruit) exhibited a higher cytotoxic effect against HeLa (cervical carcinoma cells of Henrietta Lacks) cell lines (Suman et al. 2013).

Zinc oxide nanoparticles (ZONPs) of *Salvadora persica* (toothbrush tree) extract were synthesized under optimum conditions (Miri and Sarani 2019).

Apigenin is a familiar class of flavanoid obtained from parsley, chamomile, celery, vine-spinach, artichokes, and oregano. Apigenin exhibits anticancer activity by the following mechanisms such as apoptosis of cells and autophagy, regulating cell cycle, hampering the cell migration, invasion, and initiating the immune responses (Yan et al. 2017). Different nanoformulations of apigenin and its anticancer potential were shown in Table 1.

Resveratrol is a phytoestrogen obtained from grapes, peanuts, cocoa, and berries of *Vaccinium* species. Because of its significant and multi-activity against many cancers, it has drawn so many researcher's attention (Jiang et al. 2017). The nanoformulations developed using resveratrol improved the solubility, bioavailability, and reversed the drug resistance acquired in transformed cell lines (Mondal and Bennett 2016). Some

Table 1 Phytonanoformulation as anticancer agents (Abd-Rabou et al. 2017; Mahesh et al. 2021a, b; Yongvongsoontorn et al. 2019; Wang et al. 2018a, b; Manatunga et al. 2017; Minaei et al. 2016; Zhang et al. 2018; Zhu et al. 2017; Hu et al. 2018; Wang et al. 2015)

Phytochemical	Source	Nanoformulation	Type of cancer cell lines
Niazimicin	*Moringa oleifera*	AuNPs	A549 lung cancer cells MCF7, HCT116/$CaCo_2$ and HepG2cells
γ-sitosterol and Kaempferol 7-Omethylether	*Syzygium cumini*	AgNPs	Dalton lymphoma cell lines
Monoterpenoidic phenols	*Origanum vulgare*	AgNPs	Lung carcinoma
Trisaccharide fatty acid ester (polysaccharides)	*Morinda citrifolia*	AgNPs	HeLa cell lines
Benzyl isothiocyanate	*Salvadora persica*	ZONPs	Oral cancer
Apigenin	*Petroselinum crispum*, *Matricaria recutita*, *Apium graveolens*, *Basella alba*, *Cynara cardunculus*, *Origanum vulgare*	PLGA-NPs (Poly(lactic-co-glycolide acid) Phospholipid phytosome	Mouse skin cancer Liver carcinoma
Resveratrol	*Vitis vinifera*, *Arachis hypogaea*, *Theobroma cacao*, *Vaccinium subg. Oxycoccus*, *Vaccinium sect. Cyanococcus*	Gelatin Liposomes PLGA AgNPs	Lung cancer Glioblastoma Prostate cancer Hepatoma
Curcumin	*Curcuma longa*	Carbon nano-tubes PLGA	Lung glandular cancer Pancreatic tumors
EGCG (epigallocatechin-3-gallate)	*Camellia sinensis*	PLA–PEG-NPs Chitosan NP PEG–EGCG with Sunitinib	22Rv1 prostate carcinoma cell Mel 928 Human melanoma Human renal cell cancer-allografted mice
6-Gingerol	*Zingiber officinale*	Nanosized proliposome Lipid nanocapsules PEGylated nanoniosome Magnetic hydroxyapatite	Liver cancer Liver cancer Breast cancer Breast and liver cancer
6-Gingerol and curcumin	*Zingiber officinale* *Curcuma longa*	Hydroxyapatite bilayered iron oxide NP composite	Breast tumor

(continued)

Table 1 (continued)

Phytochemical	Source	Nanoformulation	Type of cancer cell lines
Quercetin Quercetin–Doxorubicin Quercetin–Vincristine Quercetin–Cisplatin	*Allium cepa*, *Malus domestica*, *Vitis vinifera*	Lecithin Au nanocages Lipid-polymeric Lipid calcium phosphate	Breast cancer Breast cancer Lymphoma Bladder carcinoma
Vincristine sulfate and verapamil hydrochloride	*Catharanthus rosea*	Poly(lactic-coupled-glycolic acid) NPs	Breast tumor
Paclitaxel and etoposide	*Taxus brevifolia*	PLGA-NPs	Bone cancer cell lines

of the resveratrol nanoformulations and their potential uses were described in Table 1.

Curcumin, the bioactive principle isolated from the *Curcuma longa* roots. Curcumin is the familiar traditional herbal component employed in various applications like heart burn, ulcerative colitis, antiseptic, and antimalarial agent (Wilken et al. 2011). A list of the curcumin nanoformulation was shown in Table 1 with their potential uses.

Green tea contains a profuse amount of polyphenolic catechins which shows its impact on cancer cells proliferation, growth, and metastasis. Because of its less stability and low solubility, results in poor bioavailability. Table 1 describes the EGCG nanoformulations with their advantages compared to the conventional formulation.

Ginger is the most common spice used abundantly for the treatment of various ailments. The isolated herbal active principle, 6-Gingerol, was formulated into nano-composites to conquer the obstructions associated with traditional formulation thereby to enhance the medicinal activity. Gingerol nanoformulations were listed with their biological activity in Table 1.

Various fruit and vegetables such as apples, onions, and red grapes contain a profuse amount of quercetin (QUR), which is a pentahydroxyflavone, evidenced to exhibit diversified pharmacological benefits (Kulisic et al. 2012). Verma et al. (2013), delivered formulated core–shell structure of magnetic NPs of QUR through nebulisation and studied the cytotoxic capability of QUR against cancer carcinoma cells. Anticancer activities of quercetin in combination with other chemotherapeutic agents were shown in Table 1.

In addition to the examples covered under Table 1, some other researchers had investigated multiple nanoformulations loaded with phytoactive principles for anticancer activity (Amer et al. 2021).

2.2 As Antimicrobial Agents

Plant and plant derivatives of nanoformulations are extensively used in chronic wound gauzes, tissue grafts, drips, and blood transfusion sacks because of their germicidal activity. The potential antimicrobial activity of various phytonanoformulations has been studied collectively on bacterial pathogens, fungal, and viral microorganisms (Roy and Bharadvaja 2019). Because of the added advantages, all the phytonanoformulations exhibit better antimicrobial activities than the traditional herbal formulations.

The active principles of plant parts can enhance the native germicidal activity of AgNPs (Elani et al. 2018). The AgNPs fabricated with phytochemicals altered permeability property of membrane and lead to destruction of *Candida* sp. and allow the intracellular components to burst out from fungi (Logeswari et al. 2013).

Shyam et al. (2016), studied the formulation of AgNPs using *Saraca indica* leaf extract. This was utilized to determine the antibacterial capability on *Escherichia coli*, *Staphylococcus aureus*, and *Micrococcus luteus*, exhibited potential antibacterial activity with round-shaped AgNPs of herbal extract.

Homogenous root extract of *S. persica* utilized in formulation of AgNPs and was examined its activity on two bacterial pathogens (Arshad et al. 2021).

Ag and AuNPs synthesized from rhizome extract of *C. longa* exhibited significant activity on commonly occurring contaminants (Sharma et al. 2020). The freely soluble extract of *Angelica pubescens* Maxim was broadly used to make AgNPs to control pathogenic bacteria (Markus et al. 2017).

Leaf extract of *Garcinia mangostana*-based AgNPs were expressed activity on various drug-resistant pathogens. *Artemisia nilagirica* (Asteraceae)-based AgNPs also displayed superior action on numerous organisms. AgNPs of marine seaweed *Sargassum wightii* showed effective antibacterial activity against *S. aureus*, *Klebsiella pneumoniae*, and *Salmonella typhi*. Silver NPs of *Ocimum sanctum* leaf extract, *Origanum vulgare* (Oregano), Coptidis rhizome, *Carissa carandas* (Karonda) berry water extract, and *Salicornia bigelovii* displayed competent antibacterial activity on common microbes that comparable with generic antibiotics.

Plant-based AgNPs also exhibited antifungal activity against various fungal pathogens. The most commonly occurring fungal infections are due to *Candida* species (Wilson 2019). Recent studies showed the inhibition of opportunistic human fungal pathogens with Tulsi (*O. sanctum*)-mediated AgNPs (Rout 2012). Synthesized AgNPs with extracts of *Shoreatum buggaia*, *Boswellia ovalifoliolata*, and *Svensonia hyderobadensis* showed inhibitory activity against different species of *Aspergillus niger*, *Aspergillus flavus*, *Curvularia* sp., *Fusarium* sp., and *Rhizopus* sp. (Savithramma et al. 2011). *Svensonia hyderobadensis* showed higher anti-fungal activity with other nanoformulations compared to synthesized AgNPs.

Plant-based AgNPs were reported to contain bioactive principles isolated from various plants and exhibited antiviral activity against feline coronavirus (FCoV), Influenza virus, HIV, Adenovirus, Herpes simplex virus, Dengue virus, Chikungunya virus (Sharma et al. 2019), and Norovirus. The intrinsic antiviral activity of

Table 2 Phytonanoformulation as antiviral agents

Source	Nanoformulation	Type of virus	References
Phyllanthus niruri, *Andrographis paniculata*, and *Tinospora cordifolia*	AgNPs	Chikungunya virus	Sharma et al. (2019)
Centroceras clavulatum	AgNPs	Dengue fever virus	Murugan et al. (2016)
M. oleifera seed extract	AgNPs	Dengue serotype DEN-2	Sujitha et al. (2015)
Curcuma longa	AgNPs	Respiratory syncytial virus infection	Yang et al. (2016)

AgNPs is demonstrated by different mechanisms by inhibiting viral reproduction or by denaturing viral protein (gp120) that can block the entrance into host cells. A list of the phytonanoformulations with antiviral activity were shown in Table 2.

2.3 As Wound Healing Agents

Wounds are if unprotected, susceptible to microbial attack and pathogenesis. Wound dressings loaded with phytonanoparticles provide certain advantages such as reduction in healing time, inhibiting a variety of bacterial organisms, and exhibiting more antibacterial activity than AgNPs. Wound dressings encapsulated with phytonanoparticles are used in the control of burns, chronic ulcers, and diabetic foot ulcers (Cavanagh et al. 2010). Table 3 described some examples of wound dressings loaded with phytonanoparticles.

Table 3 Phytonanoformulations as wound dressings

Source	Nanoformulation	Material for dressing	Activity against	References
Piper nigrum leaf extract	AgNPs	Electrospun PCL (polycaprolactone) membrane	*S. aureus* and *E. Coli*	Augustine et al. (2016a, b)
Biophytum sensitivum	AgNPs	Nano-micro dual-porous calcium pectinate scaffolds	Human pathogens	Augustine et al. (2016a, b)
Mimosa pudica	AgNPs	PVA membranes	Human pathogens	Sundaramoorthi et al. (2009)

2.4 As Drug and Gene Delivery Agents

The main objective of nanoformulation is the site-specific release of entrapped drug formulations. A green approach to nanoparticle synthesis is finding a way to overcome the toxic effects associated with synthetic nanoparticles. *Trichoderma viride* AuNPs conjugated with vancomycin are very effective in the suppression of vancomycin-tolerating *S. aureus* at minimum concentration (Mohammed Fayaz et al. 2011). Nps of *Butea monosperma* leaf extract was fabricated and conjugated with anticancer drug doxorubicin showed enhanced anticancer activity by inhibiting cell proliferation. Another study showed the effective delivery of doxorubicin by *Peltophorum pterocarpum* mediated green-synthesized AuNPs (Patra et al. 2015).

2.5 In Neurodegenerative Disorders

Functional and structural damage of nerves leads to neurodegenerative disorders (NDs). The changes in the nervous system may result in retardation in thinking, motion, perception, and recollection. Alzheimer's disease (AD) and other types of dementia, Parkinson's disease (PD), and PD-related other disorders are most common NDs; multiple sclerosis (MS), Huntington's disease (HD), and Amyotrophic lateral sclerosis (ALS) are the most frequent types. Worldwide, for every four members, one person is going to suffer from NDs (Hodjat et al. 2017). Researchers have been reported the therapeutic benefits of herbal active principles in NDs patients. Phytochemicals such as polyphenols (Davatgaran-Taghipour et al. 2017), alkaloids (Wang et al. 2018a, b), and terpenoids (Khazdair 2015) from a variety of plants were extensively studied and reported. Nanoformulation-based phytochemicals are superior than the conventional dosage forms for curing neurodegenerative disorders-targeting delivery to brain, break down naturally, low toxicity to peripheral organs, modulation of inflammatory events, neuronal tissue restoration, inhibit neural apoptosis or toxicity, and regulate other functions (Seyed et al. 2020). Table 4 describes the phytonanoformulations with their uses in neurodegenerative disorders.

2.6 As an Anti-Diabetic Agent

Phytonanoformulations are studied extensively in the treatment of diabetes mellitus. Nanotechnology-based phytoformulations are recommended for improved therapeutic efficacy against diabetes mellitus (Kesharwani et al. 2018). Nanophytoformulations offer all the advantages of nanoformulations such as delivery of drugs precisely to the target, allowing the various routes of administration, enhanced systemic availability, improved stability of drugs, and reduced risk of toxicity. Table 5 highlighted the plant-based nanoformulations against diabetes. The researchers have

Table 4 Phytonanoformulations in neurodegenerative disorders (Seyed et al. 2020)

Type of nanoformulation	Benefits
Curcumin	
Lactoferrin NPs	Protect SKN-SH neuroblastoma cell line of dopaminergic cells
Lipid-polyethyleneglycolpolylactide nanoparticles	↓ the Aβ (amyloid-beta) aggregation
Plain liposomes and anti-transferrin antibody tagged liposomes	↑ the brain permeation of drug in AD patients
PLGA associated Cur NPs coupled with Tet-1 peptide	AD
Zwitterionic polymer-NPs	Block the fibrillation of Aβ42 fibrils
Solid lipid NPs (SLNPs)	↑ 3-nitro1-propionic acid (3-NP)-enhanced HD in rats
Selenium-conjugated PLGA nanospheres	AD
Drug-loaded lipid-based nanoformulation	PD
Entraped PEG-PLA	Significant increase in memory cue
Cur-loaded lipid core nanocapsules	AD
Quercetin	
Nano lipidic carriers	Elevated drug concentration in plasma and target specific delivery
Nanocrystals	PD
SLNPs	Retention of memory in animal models
Liposomes	Reduced degradation and degradation of cholinergic neurons
Liposome	Dispensing via nasal cavity resulted decreased oxidative damage
PLGA nanocapsule	Higher brain intake and enhanced bioavailability
Resveratrol	
PS80-layered poly(lactide) NPs	↓neuronal damage properties
Lipid-core NPs	Aβ-provoked neuroinflammation was regulated
Mesoporous nano-selenium	Accumulation of Aβ was blocked, decreases oxidative stress, and improves memory
Polymeric micelles	Repression of the Aβ-induced damages via reducing oxidative stress and apoptosis
Nanoemulsion loaded with Vitamin E	Positive effects in PD
SLNPs conjugated with apolipoprotein E	Bioavailability and concentration get enhanced thereby permeation of the drug in the brain improved
Chitosan-over-layered PLGA NPs	Reduced concentration of inflammatory cytokines, enhance the neuroprotective IL-10 concentration

(continued)

Table 4 (continued)

Type of nanoformulation	Benefits
Piperine	
Tween-modified monoolein cubosomes	Higher potency over conventional drugs and ability to re-establish the perception function
Intranasal chitosan NPs	Showed more efficacy in AD model
Gallic Acid	
GA-entrapped chitosan NPs (GANP)	Scopolamine-intensified amnesia in vivo
Ferulic Acid	
SLNPs	Repressed Aβ-promoted cell death, reduced ROS (Reactive oxygen species) production, and inhibit the apoptosis pathway
SLNPs	Induced phosphoinositide 3-kinases (PI3Ks) pathway in ischemic neural injuries mode

investigated the pharmacological effects and enhanced biopharmaceutical properties with various phytoactive principles containing nanoformulations such as rosmarinic acid, berberine, Stevia glycosides, Asiatic acid Glycyrrhizin, α-Eleostearic acid, Scutellarin, Silybum Flavonolignans, Gallic acid, Catechins, Pelargonidin, Thymoquinone, and Ferulic Acid.

2.7 *In the Treatment of Metabolic Disorders*

Metabolic disorder or the syndrome is a group of medical conditions that leads to an unhealthy condition in humans. Metabolic syndromes increase the risk of cardiovascular disorders such as atherosclerosis, obesity, resistance to insulin, hypertension, cerebrovascular accident, and atherogenic dyslipidemia (McCracken et al. 2018).

Several phytopharmaceuticals are fabricated into nanoformulations that induce molecular mechanisms against diverse pharmacological targets. Table 6 described the list of phytoactive principles and nanosizing methods employed with their improved pharmacological activities.

2.8 *As Thrombolytic Agents*

To overcome the limitations associated with currently available thrombolytic agents, researchers have investigated various plant-derived products for thrombolytic activity (Ali et al. 2021). Akinola et al. (2020) reported the phytosynthesized TiO2 NPs of

Table 5 Phytonanoformulations as anti-diabetic agents (Dewanjee et al. 2020)

Type of nanoformulation	Benefits
Curcumin	
NPs	Fall in fasting blood glucose and improved production of insulin hormone and insulin receptor (IR) mRNAs get expressed in diabetic rats
ZnO–NPs	Decreased blood glucose levels, improved insulin serum concentration, and GLUT2 and glucokinase genes expression in pancreas
PLGA-NPs	Plasma levels of CUR were improved and increased biological half-life
PLGA-PVA-NPs	Delayed cataract formation in diabetic rats
Polylactic acid (PLA) and polyethylene glycol (PEG) conjugated polymeric NPs	Effective in rendering hyperglycaemia, hypoinsulinemia, and diabetes-induced hepatotoxicity
Resveratrol	
Nanocochleates	Effective in the regulation of insulin-resistant diabetes
Casein NPs	pH tolerance, rapid permeation, and support sustained drug release
SLNPs	Increased therapeutic efficacy
PLGA NPs	Improved drug entrapment efficiency and increased dissolution thereby enhance the plasma level of drug concentration
Naringenin	
Nanoemulsion using PVP	Increased solubility results enhanced gastrointestinal absorption, dissolution, and oral bioavailability
Soluthin-maltodextrin nanocarrier	Enhanced oral bioavailability (116 fold) and reduced toxicity
Liposomal nanoformulation	Increased solubility and oral bioavailability
Chitosan core-shell loaded NPs	Enhanced drug loading capacity (> 90%)
Quercetin	
PLGA-NPs	Increased the oral bioavailability of QUR (> five-fold)
Nanorods	Inhibition of hyperglycaemia condition, regulates glucose-metabolizing enzymes, and oxidative stress
PEG-block nanocarrier	Regulation of diabetes and associated nephropathy via enhancing the serum content of QUR in rats

(continued)

Table 5 (continued)

Type of nanoformulation	Benefits
QUR-succinylated chitosan-alginate core-shell-corona structured NPs	Increased oral hypoglycemic effect of QUR in diabetes-induced rats this effect was contrast to native oral QUR
Soluplus micelles	Increased drug plasma level (> 16%) of QUR and sustain the drug release for prolonged time
Apigenin	
Microwave-synthesized -pluronic F127 NPs	Enhanced dissolution rate and oral absorption
Nanomixed micelles system consisting Soluplus and pluronic F127 polymers	Prolonged release pattern, and improved absorption through GIT
Carbon nano powder-based solid dispersion	Improved stability and bioavailability
Nanoliposomes	Repress apoptosis of myocardial cells in diabetic cardiomyopathy rats
Myricitrin	
SLNPs	Recompensate hyperglycaemia, counteract the insulin activity, ruination of glucose uptake by myotubes
Baicalin	
Nanoliposome	Improved pharmacokinetic parameters
Pluronic P123 and sodium taurocholate conjugated Nanomicelles	Improved absorption and resident time in blood
Nanostructured lipid carriers	Change in release pattern of baicalin and elevated anti-diabetic activity
Luteolin	
SLNPs	Enhance solubility, biological half-life, and bioavailability
Mangiferin	
Nanomicelles fabricated with self-assembled phospholipids	Enhanced biopharmaceutical attributes
Nanomixed micelles	Intestinal penetration and enhanced oral bioavailability
β-lactoglobulin NPs	Improved specificity toward target, counteract pepsin activity, safeguarding the probiotic strains in the gut region
Gymnemic Acid	
Nanocrystals	Increased oral bioavailability
Nanocrystals-loaded tablets	Anti-hyperglycemic activity
Reduced gold nanoparticles	Glucose uptake capacity of 3T3-L1 adipocytes was enhanced via the insulin-dependent/independent pathway

(continued)

Table 5 (continued)

Type of nanoformulation	Benefits
Chitosan NPs	Sustain the release pattern of gymnemic acid for 1 day
Emodin	
Nanoemulsion	Enhanced plasma levels of emodin, increased excretion time interval

Table 6 Phytonanoformulations in the treatment of metabolic disorders

Type of nanoformulation	Benefits	References
Curcumin		
PBLG-PEG-PBLG	↑CaSR (calcium-sensing receptor protein), ↑CSE (Cystathionine-γ-lyase), ↑CaM (complementary and alternative medicine) to suppress diabetic cardiomyopathy	Tong et al. (2018)
SNEDDS	↓TNF-α ↓IL-6 in diabetic neuropathy	Joshi et al. (2013)
PLGA-PVA NPs	↓VEGF (vascular endothelial growth factor) ↑cellular uptake, bioavailability to treat diabetic cataract	Grama et al. (2013)
Pluronic nanomicelles	↑Pdx-1 and NKx6.1 in STZ (streptozotocin)-induced diabetes	El-Far et al. (2017)
PLGA-based NPs with Q10	↓CRP (C-reactive protein), IL-6, total cholesterol, ↓plasma triglycerides ↑HDL in diabetes complications	Devadasu et al. (2011)
Nanoemulsion	Inhibition of HMGR (HMG-CoA reductase) along with ACE to control hypertension and hypercholesterolemia	Rachmawati et al. (2016)
Capsicum oleoresin		
Nanoemulsion	↓Adipogenic gene expression ↑PPAR-α (peroxisome proliferator-stimulated receptor), UCP2 (uncoupling protein) and CPT-1α (Carnitine palmitoyltransferase 1) in treating obesity	Kim et al. (2014)

(continued)

Table 6 (continued)

Type of nanoformulation	Benefits	References
Alginate double layer nanoemulsion	↓mRNA expression for PPAR-γ ↓fatty acid binding protein adipocyte protein-2 hormone-sensitive lipase ↑carnitine ↑palmitoyl transferase-1α ↑HSL(hormone-sensitive lipase) and CPT-1α genes ↓PPAR-γ and aP2 to reduce obesity	Lee et al. (2017)
Berberine		
Solid lipid nanoparticles (SLNs)	↓Body mass, ↓fasting blood glucose, HOMA-IR (homeostasis model assessment of insulin resistance) Increased impairment in glucose tolerance	Xue et al. (2013)
PLGA-PEG-PLGA block copolymers	Regulation of PCSK-9 (proprotein convertase subtilisin/kexin type 9) mRNA expression in high LDL cholesterol	Ochin and Garelnabi (2018)
Naringenin		
Alginate-coated chitosan core-shell	No toxicity, better therapeutic effect in diabetes	Shi et al. (2016)
Quercetin		
PLGA NPs	↑CAT (catalase) and SOD (superoxide dismutases) levels ↓drug doses in diabetes	Chitkara et al. (2012)
Emodin		
Transferosome	Upregulation of ATGL (adipose triglyceride lipase) protein expression, suppression of GOS2 protein expression, body weight, and adipocyte size in obesity	Lu et al. (2014)
Gymnemic acid		
Nanosuspension	↓Blood glucose levels in diabetes	Ravichandran (2014)

(continued)

Table 6 (continued)

Type of nanoformulation	Benefits	References
Baicalin		
Nanostructured lipid carriers	↓FBG, HbA1c (Hemoglobin A1c), and TG levels in diabetes	Shi et al. (2016)
Resveratrol		
Nanoliposomes	↑ROS-inactivating enzymes including GSH-Px and SOD in diabetes	Yucel et al. (2018)
Nanocapsule	Blood pressure regulation	Shahraki et al. (2017)
Silybin		
PLGA polymers	↑antioxidant characteristics, rejuvenating activity on β cells' membrane permeability	Das et al. (2014)
Myricitrin		
SLNs	Improvement of SOD level, ↑muscle and myotube glycogen content, regulation of Glut4 gene in skeletal muscle and C2C12 cells, Bcl-2 gene expression, Bax to Bcl-2 ratio of myotubes	Ahangarpour et al. (2018)

distinct *Cola nitida* plant parts and investigated for thrombolytic activity. Phytosynthesized AgNPs incorporated with leaf and seed extracts of *Synsepalum dulcificum* were reported for thrombolytic activity (Lateef et al. 2016).

3 Conclusions and Future Prospective

Synthesis of nanoformulations using phytoactive principles is an efficient and ecofriendly method to deliver the therapeutic agent to a specific target. Products extracted from plants have numerous bioactive principles of both reducing and stability properties to with stand the reaction conditions while synthesizing phytonanoformulations. The derived phytonanoformulations offer advantages like improved solubility, thereby enhancing the bioavailability, maintenance of parity between efficacy and toxicity of a therapeutic compound. The synthesized nanoformulations find agricultural, environmental, cosmetic, medical, diagnostic, drug delivery, and industrial applications. The tremendous growth of nanotechnology supports the fabrication of bioactive principles of plant into phytonanoformulations. Because of less toxicity, the natural plant formulations are might be good competitors to the synthetic nanoformulations in the coming future. It is necessary to describe

the biomolecular interaction of NPs and the regulation of gene expression. Further investigation is needed for the molecular and submolecular level functions of nanophytoformulations.

Acknowledgements I express my heartfelt thanks to Dr. L.Rathaiah the Chairman of Vignan Group of Institutions for providing the necessary facilities to complete this book chapter. My sincere thanks to Dr. Y. Srinivasa Rao, Principal of VIPT, his support and encouragement are indispensable.

Sincere thanks to my colleagues of Vignan Institute of Pharmaceutical Technology (VIPT), Duvvada, Visakhapatnam, for their valuable suggestions.

My acknowledgement would be incomplete without thanking the biggest source of my strength, my family.

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