- Review paper

A Comprehensive Review on Nanophytomedicines and their Applications

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ABSTRACT: Among natural sources we mainly consider the plant-based phytochemicals. Phytochemicals or the secondary metabolites are the extract obtained from the herbal plants which may serve as a great venture for their utilization as nanomedicine. Drugs or compounds converted to nano range shows unique characteristics which lengthen circulation, ameliorate localization, improve drug efficiency, etc. Nanomedicine is the type of formulation which uses the nanotechnology to deliver the drug in the form of nanoparticles incorporated within the nanocarriers. Nanocarriers intensify solubility and stability of phytochemicals, prolong their half-life in blood and achieve site-targeting delivery. The development of phyto-based nano formulations has been explored to have potential applications in managing life-threatening diseases. The present review highlights the compilation on the potential of phyto nanotherapeutics over the conventional treatments against various serious leading disorders.

Key words: Phytoconstituents, nano formulation, nanoparticles, life-threatening diseases.

INTRODUCTION

From a very long time, we are contingent on the medicines for improvising and extending our lives. Long since from Ayurvedic, Unani, Siddha, Homeopathy to Allopathy, now we are more focused on targeted, long acting and naturopathy like nanomedicines.[1] With modernization in allopathy more or less we reached the heights of success and still uncovering new drug delivery approaches in order to enhance the effectiveness of drug in order to reduce their dose frequency, the resistance developed against antibiotics and to minimize their toxicological profile. Due to the belief of the common people that the drugs obtained from natural origin are more reliable and safer and thus the demand and remarkable growth in phytopharmaceuticals is increased. If we talk about the natural aspect, it indulges plants source (especially the herbs which are showing marvelous therapeutic effectiveness) animal source, minerals, ores. The polyherbals are used as immunostimulant in many aliments. Bestowed strategies reported in ayurvedic medicines are specifically phytochemical extractives, used alone or in combination from historic times.[2-4] Phytochemicals have broad apparent volume of distribution and also lead to accumulation in the organs. Phytochemicals show their therapeutic action by various pathways which includes inhibition of overexpressed proteins, enzymes, amino acids, and hormones.[5,6] However, it is in itself a big challenge to incorporate and administer these phytoconstituents within the body due to their low water solubility, low stability, poor absorption, and rapid metabolism, poor bioavailability which hindered their pharmacological potential and show low therapeutic index.[7-9] These phytoconstituents accelerate generation of protection enzymes.[6] For that the development of novel approach pharmaceutical nanotechnology (inculcate nano sized particles modified into various ways) has created novel formulations to maximize the potential use of phytochemicals. The medicinal compounds in nano range shows unique characteristics such as lengthen circulation, ameliorate localization, upgrade drug efficiency etc. Nanocarriers intensify solubility

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and stability of phytochemicals, prolong their half-life in blood and achieve site-targeting delivery.[10,11] Nanoparticles are a small particle, ranges between 1 to 100 nm in size, comprised of polymers or lipids in which biological or small molecule active pharmaceutical ingredients are encapsulated. These nanoparticles show enhanced properties in relation to their bulk materials which inculcate high surface area to volume ratio, solubility, bioavailability, drug delivery efficiency, systemic adverse side effects and a unique quantum size effect due to special electronic structures.[12] For their use in nanomedicines, a highly regulatory approach is needed. Liposomes are considered the first type of nanocarrier-based treatment approved by the Food and Drug Administration (FDA) in 1970's.[13,14] But, the major challenge with these types of formulations is their stability in different zones. Also, there is no proper standardization or characterisation of physical and chemical analysis which is an obstacle in estimation of their toxicological profile. Furthermore, absence of regulatory procedure for synthesis and characterization limits its clinical utility. So, this article encompasses the development of nanoparticles, nano phyto-formulations and their application in life-threatening diseases. Mostly, phyto-nano formulation is used in multi drug resistant cancer and others also used as cardioprotective, hepatoprotective, antiepileptic, anti-inflammatory and many more.[15-18]

Nanoparticle (NP) may be broadly classified based on their physical properties such as carbon nanotubes, metal NPs, lipid-based NPs, polymeric NPs, semiconductors and ceramic NPs.[14,19] Carbon nanotubes and fullerenes are two major classes of carbon-based NPs. Fullerenes contain nanomaterial made up of globular hollow cage that contains pentagonal and hexagonal carbon units. These are elongated, tubular structure, 1-2 nm in size and shows a structure resemblance to graphite sheet rolling on itself. On the basis of rolled sheet they can be single, double or multiwalled carbon nanotubes.[20,21] Carbon nanotubes are used in many commercial applications such as fillers due to resembling vast physical, chemical and mechanical characteristics. Carbon nanotubes (CNTs) are cylindrical molecules that consist of rolled-up sheets of single-layer carbon atoms (graphene). They can be single-walled (SWCNT) with a diameter of less than 1 nm or multi-walled (MWCNT), consisting of several concentrically interlinked nanotubes, with diameters reaching more than 100 nm. Their length can reach several micrometers or even millimeters.[22] Metallic nanoparticles have unique optoelectrical properties called modifiable localized surface plasmon resonance (LSPR) and based on its configurational and element alterations, it can be used in various applications such as optical sensing, biomedical imaging, photon energy harvesting, photocatalysis and spectroscopy etc.[23,24] Alkali and novel metals show a broad absorption band in the visible zone of electromagnetic solar spectrum. Gold NPs are greatly used for sampling in SEM for enhancing electronic stream, obtaining high resolution images.[25,26] Sources of Au nanoparticles are achieved by employing plants, as they are biological factories via green chemistry-based techniques. Leaf extract of *Eucalyptus macrocarpa* could be used to synthesize gold nanoparticle.[27,28] Titanium dioxide nanoparticle can be efficiently synthesized from *Annona squamosa* pee and *Nyctanthes arbortristis* leaf extracts which lead to formation of round particles, ranged from 100 to 150 nm. Lipid-based nanoparticles are characteristically spherical ranging from 10 to 1000 nm. They possess a solid core made of lipid and matrix contain soluble lipophillic molecule. Organic polymer-based NPs are generally nanospheres and nano capsular shaped. Nanospheres are matrix particle whose overall mass is solid and others are adsorbed at outer boundary of spherical surfaces.[29] These NPs can be synthesized by two step methods based on emulsification, solvent diffusion, emulsification reverse salting out. Semiconductor nanoparticles shows properties of semiconductors between metals and non-metals. They show an explanatory usage in photocatalysis, photo-optics and electronic devices. Also, these can be employed to prevent water splitting due to their suitable bandgap and band edge positions**.** For instance, if quantum dots core

which contains semiconductor materials like cadmium selenium, cadmium tellurium, indium phosphate, indium arsenate, overcoated with a shell, can remarkably increase the optical activity and prevent the leakage of toxic heavy materials.[30] Ceramic inorganic compounds with porous properties used as a vehicle for API and they are capable of transporting molecules.[31] Silica and aluminium are the most commonly used compounds to prepare ceramic nanoparticles such as CeO_2 capped mesoporous silica nanoparticle act as vehicle for drug delivering beta cyclodextrin into lung cancer.[32] The classification of nanoparticles is shown in Figure 1.

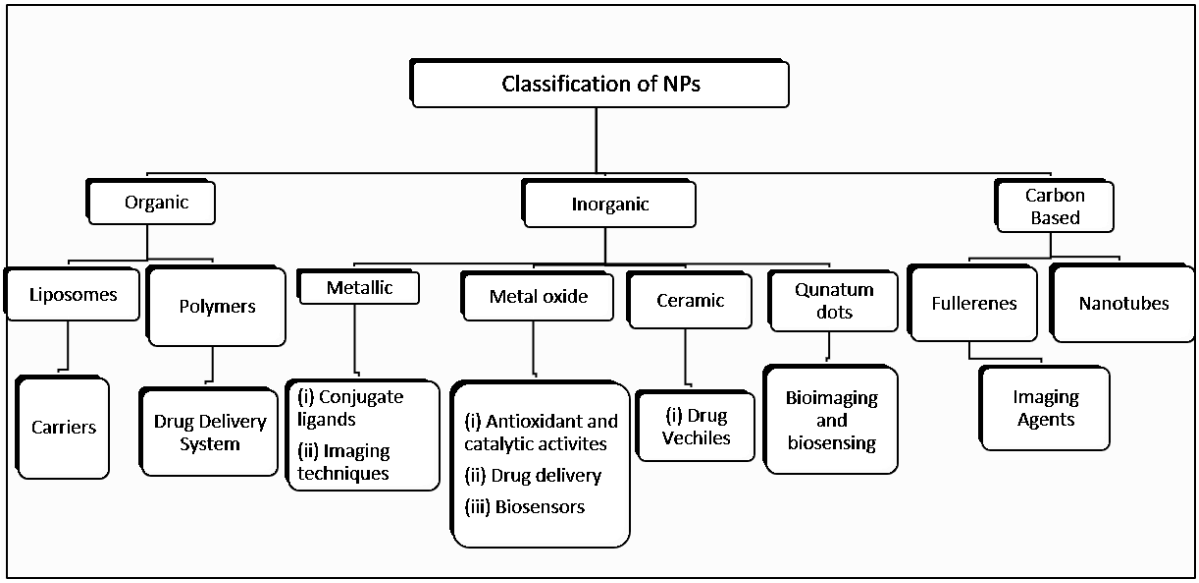

Figure 1. Classification of nanoparticles.

Application of phytochemical nano formulations in cancer treatment. Cancer is one of the leading fatal diseases all over the world and being the cause of so high mortalities. Cancer is a condition in which the cell growth is uncontrolled in the body forming a mass of tissue called as tumor. Cancer develops when the body's normal control mechanism stops working. Some cancers, such as leukaemia, do not form tumors.[33] It is a topic of immense concern as well as a major challenge to eradication worldwide. It is estimated that the global burden of cancer will be nearly double [30 to 40 billion] by the coming 20 years and most suffered will be the middle and lowers class groups of population due to less availability of resources.[34] Also, certain obstacles create a lag in the treatment and the procedure to go through for betterment of affected patient such as lack of reliance, improper use of resource, lack of practices, inadequate evidences and multi-drug resistance. A patient undergoing chemotherapeutic treatments has to face lot sufferings since the surgical procedures specifically radiation therapy harms the healthy cells along with destroying the cancer cells, leading to an add-up to the fatality of this disease.[35]

Implementation of phytochemicals in nano formulations for cancer therapy. Ayurveda since ever relies on the strategies to inculcate the use of phytochemical extractives alone or in combinations in many immunostimulant and other disease ailments.[36] Poly herbals containing natural secondary metabolites are beneficial to the body in regulating the internal processes. Phytochemicals have been proved to be effective in accelerating the production of protective enzymes as well as inhibiting the over-expressed proteins, enzymes, hormones etc and in this way, boosting the immunity, instead of affecting

healthy cells (to certain concentrations). Many plant origin phytochemicals like irinotecan, marijuana, epipodophyllotoxin, and curcumin show anticancer effects.[37] Having high distribution in tissues leads to accumulation in body that could be non-acceptable as well as creates a pathway to resistance to their effective use in cancer ailments.[2,35] To overcome this, nanotechnology-based delivery of phytochemicals is in use as they assure numerous advantages in solubility, dissolution, permeability, bioavailability, site-specific drug delivery, controlled release and many more.[38] Some of the nano-formulation consisting various plant-based phytochemicals along with their actions against cancer type are given in table 1.

Table 1, Various nano formulations with phytoconstituents from plant origin used in different types of cancer treatment.

Plant name	Phytochemicals	Formulation	Cancer type	References
Betula alba	Betulinic acid	Polymeric nanoparticles	Triple negative breast and laryngeal cancer	39
Silybum marianum	Silibinin	Nanomicelles	Liver cancer	40
Withania somnifera	Withanolide-A	Gold nanoparticles	Breast cancer	41
Curcuma wenyujin	-	Gold nanoparticles	Breast cancer	42
C. longa	Curcumin	Carbon nanotubes	Lung cancer	43
Onion	Quercetin	Nanomicelles	Prostate cancer	44
Mulberries, Peanuts, Grapes	Resveratrol	Liposomes	Hepatocellular Cancer	45
Albizia lebbeck	-	Gold nanoparticles	Colon cancer	46
C. longa	Curcumin	Dendrimer	Hepatocellular cancer	47
S. marianum	Silibinin	Magnetic nanoparticles	Lung cancer	48
Sasa borealis	Leaf extract	Gold nanoparticles	Anticancer	49
Eurycoma longifolia	Branch extract	Silver nanoparticles	Anticancer	50
Nilgirianthus ciliatus Nees	Ethanolic extract	Gelatin nanoparticles	Antidiabetic	51
Talinum portulacifolium	Ethanolic extract	Silver nanoparticles	Antidiabetic	51
Salvia multiorrhiza	Ethanolic extract	Iron oxide nanoparticles	Cardioprotective	51
Emblica officinalis	Fruit extract	Silver nanoparticles	Hepatoprotective	51
Cassia auriculate	Biocomponent	Gold nanoparticles	Antidiabetic	52
Trigonella foenumgraecum	Aqueous extract	Gold nanoparticles	Hepatoprotective	53
Euphrasia officinalis	Ethanolic extract	Gold nanoparticles	Anti-inflammatory	54
Piper nigrum	Aqueous extract	Silver nanoparticles	Anti-inflammatory	55
Terminalia bellerica	Fruit extract	Silver nanoparticles	Antibacterial	56
Salvia spinosa	Aqueous plant extract	Silver nanoparticles	Antibacterial	57
Curcumin longa	Nisin	Polylactic acid nanoparticles	Cardioprotective	58
Parthenium hysterophorus	Leaf extract	Zinc oxide nanoparticles	Antifungal	59
Withania somnifera	Withanolide-A	Gold nanoparticles	Breast cancer	60
Mulberries, Peanuts, Grapes	Fruit extracts	Liposomes	Heptacellular carcinoma	61

Moreover, phytoconstituents from plants have been used in combination with many approved synthetic chemotherapeutics to synergise the effect on many types of cancers. These phytochemicals play major role in suppressing cancer cells by activating enzymes and signalling pathways such as CDK4, CDK2 kinases, topoisomerase enzymes, cyclooxygenase, cytokines, DNA repair mechanism, inducing antioxidant actions, thereby demonstrating strong anticancer effects.[54,62] Detailed information about these medicinal plants and their specific anti-cancer phyto-constituents in combination with anti-cancer drugs against particular type of cancers is given in table 2.

Table 2. Several reported studies based on phytochemicals in combination with several bio-actives against different types of cancers.

Plant name	Phytochemicals	Chemotherapeutic agent	Cancer type	Reference
Olea europaea L.	Olive	Metformin	Breast cancer	63
Scrophularia nodosa	Diosmin	Dactolisib	Colorectal cancer	64
Ephedra alata Decne	Plant extract	Cisplatin	Breast cancer	65
Mulberries, peanuts, grapes	Resveratrol	Docetaxel	Prostate cancer	66
Allium sativum L.	Allicin	5-Fluorouracil	Lung and colorectal cancer	67
Plumbago zeylanica L.	Plumbagin	Cisplatin	Tongue squamous cell cancer	68
Mulberries, peanuts, grapes	Resveratrol	Temozolomide	Glioblastoma	69
Citrus fruits and tomato (*Lycopersicum esculentum*)	Naringin	5-Fluorouracil	Breast cancer	70
Longan flower extract	-	5-Fluorouracil	Colorectal cancer	71
Parijoto fruit	-	Cisplatin	Cervical cancer	72
Alpinia galangal	Galangin	Cisplatin	Lung cancer	73
Curcumin longa	Curcumin	Irinotecan	Colon cancer	74
Mulberries, Peanuts, Grapes	Resveratrol	Sorafenib/Cisplatin	Breast cancer	75
Nasturtium (Watercress)	Phenylethyl isothiocyanate	Cisplatin	Ovarian and biliary tract cancer	76

The World Health Organization (WHO) gives preferences to eco-friendly, harmless and cost-effective treatment approaches. Besides cancer, other illnesses like diabetes mellitus, obesity and hypertension are also contributing to the mortality rates worldwide. A variety of phytoconstituents are considered as complementary and alternative medicines and play a crucial role in inhibiting these illnesses by different pathways.[77] Many nanoparticles formulation consisting of these bioactive have been explored for activity potential against diabetes, obesity and hypertension. Few researches on plant based bioactive as nano formulation on different animal models for various illness are presented as Table 3.

Table 3. Phytoconstituents based nano formulation and their applications in different diseases.

Phytochemical	Nano formulation	Disorder	Cellular/animal model	Reference
Curcumin	PBLG-PEG-PBLG	Diabetic, cardiomyopathy	Diabetic rats & H9C2 cells	78,79
	Curcumin nano particles (gelatin microspheres/ hydrogels)	Diabetic wound	STZ-induced diabetic rats	
	SMEDDS	Diabetic neuropathy	STZ-induced diabetic rats	
	Curcumin nanoemulsion	Hypertension & hypercholesterolemia	*In vitro* study	
Capsicum oleoresin	Nanoemulsion	Obesity	High fat (HF) diet induced obesity in rats	80
	Alginate double-layer nanoemulsion	Obesity	HF diet induced obesity in rats and 3T3-LI cell line	
Berberine	Solid lipid nanoparticle (SLNs)	Diabetes	Db/db. diabetic mice	81
Quercetin	Nano particles	Diabetic nephropathy	Diabetic rats	82
Resveratrol	Nanoliposomes	Diabetes mellitus	STZ-induced diabetic cells	83
	Nano capsules	BP regulation	HF diet induced diabetic mice	

Recent advancements in phytochemical nano formulations. The growing cases and high cost of treatment, high toxicity of anti-cancer drugs raised a major challenge to the scientific community to develop an alternative, biocompatible and cost-effective treatment approach in a greener way. Also, recently reported literature revealed high biodegradability and biocompatibility have increased the activity potential of these phyto-constituents against many types of cancer. For instance, Khan et al.[84] and Gaur et al.[85] synthesized flaxseed gold nanoparticles as potent anticancer agents for breast cancer cells using green synthesis method. The flaxseed extract acts as a reducing and capping agent for preparation of Fs-AuNPs. These nanoparticles had shown great non-cytotoxicity, antioxidant, and anti-coagulation properties. Fs-AuNPs also explored as potent anticancer agent. NPs showed significant inhibition activity toward breast adenocarcinoma, hepatocellular carcinoma, and it's followed by colon carcinoma cell lines.[84,85] Swain et al.[86] carried green synthesis of gold NPs using root and leaf extracts of *Vetiveria zizanioides* and *Cannabis sativa* and reported its antifungal activities. AuNPs were capable of showing high antifungal efficacy and have a great potential for anti-fungal therapy.[86] Medina-Cruz D et al.[87] explored *aloe vera* mediated nanostructure with highly potent antibacterial agent and moderate anticancer effects. Tellurium (Te) nanostructures in aqueous media has been developed using *aloe vera* extract as a unique reducing and capping agent and evaluated. The system significantly inhibited bacterial growth after 24 h for both methicillin - resistant *Staphylococcus aureus* & multidrug-resistant *E. coli* at a relative low concentration (5ug/ml). No cytotoxicity towards human dermal fibroblasts were observed after the three days of treatment. *Aloe vera* based TeNPs also showed anticancer properties up to 72h in a range of concentration between 5-100ug/ml.[87] Medina Cruz D et al.[88] synthesized citric juice-mediated synthesis of tellurium nanoparticles with antimicrobial and anticancer properties. Orange, lemon and lime extracts were used as reducing capping agents for the green synthesis of TeNPs, using a microwave-assisted reaction. Moreover, the Te nanostructures showed no significant cytotoxic effects towards human dermal fibroblast at concentration up to 50ug/ml.[88] On similar notes various literatures have been recently introduced to highlight the potential of herbals in nanotechnology for treating serious conditions such as curcumin nano formulations for colorectal cancer[89], silver nanoparticles in combination with naphthoquinones against infections associated with *Staphylococcus aureus*[90], *aloe vera* plant extract based sliver nanocarriers against bacterial infections[91], starch-mediated synthesis of mono & bimetallic silver/gold NPs as antimicrobial & anticancer agents[92], ursolic acid nanoparticles against breast cancer [93], chitosan based nano formulated with (-)-eoigallocatechin-3-gallate for psoriasis.[94]

CONCLUSION

This review paper provides information on phyto-nanomedicines along with their bioactive compounds. The developmental approach of pharmaceutical nanotechnology has enlightened the ways to cure the disease with enhanced efficiency. Cancer, being one of the most fatal diseases, with several MDR cases, is now being cured with the help of immense technology that provides proper drug delivery, its transportation in body, its monitoring and calculating the values to get an idea about dosage regimen. Not only the formulation, but the constituents are playing tremendous roles in treating the ailments either alone or in combination with other chemotherapeutic agents. All this proves to be a great milestone in the treatment of cancer in the most unique ways. However, this phyto nanocarrier must be further investigated clinically to establish the commercial prospects for humans.

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