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Biomedical applications of biogenic phytonanoparticles: A review

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Abstract
This review aimed to compile published reports on biogenic phytonanoparticles, their pharmacological activities and put forth the therapeutic potential of metallic nanoparticles. In recent years, the green chemistry synthesis of metallic nanoparticles method has to turn out to be a promising approach in the field of research. A broad review of the literature existing in several documented databases comprising logical script and scientific texts, search engines relevant books, websites, scientific publications, and dissertations were utilized as a source of information that provided an up-to-date review. Herb-mediated synthesis of biogenic metal ion nanoparticles like copper iron (Fe), (Cu), silver (Ag), gold (Au), platinum (Pt), lead (Pb), cadmium (Cd), and additional metal oxides such as zinc oxide (ZnO), titanium oxide (TiO) etc. are found to be more reliable and economic route. The herb-mediated synthesis method ensures a highly controlled approach making them appropriate for the synthesis of a metal nanoparticle. Artificially fabricated phytonanomaterials, naturally occurring or synthesized nanomaterials of natural origin all exhibit their specific, physical, chemical and biological activities. Several pharmacological activities of phytonanoparticles are attributed to the presence of valuable bioactive phytoconstituents, which reduce metal ions for the formation of nanoparticles. Additionally, the plant-mediated biogenic nanoparticles are utilized as prospective therapeutic agents for the treatment of venerable diseases and can be used as antimicrobial, antileishmanial, antifungal, antibacterial, larvicidal, anthelmintic, anticancer, antioxidant and antidiabetic properties. Given these facts, an attempt is made to present an inclusive review enlightening the pharmacological activities of biogenic nanoparticles. Future research can be focused on widespread investigation about the synthesis of novel biogenic phytonanoparticles acquiring safety records its clinical trials, pharmacokinetics, and adding new scopes to the therapeutic utilization of phytonanoparticles.

Keywords: biogenic nanoparticles, green synthesis, phytonanoparticles, bioreduction, nanotechnology

Introduction

Nanotechnology principal emphasizes the design, synthesis, and manipulation of structure and size of the particles with dimensions lesser than 100 nm. Nanotechnology syndicates the physical and chemical properties to generate nanoparticles with a specific function. Nanotechnology is now generating a growing sense of interest in biomedical devices and medicine. Nanoparticles unveil completely novel or enriched properties based on particular characteristics such as size, shape, and orientation [1]. Previous few decades have seen various therapeutics based on phytonanoparticles (PNPs) introduced for treating several diseases and disorders. Developments in nanotechnology and the significance of nanoparticle characteristics (size, shape, and surface properties) for biological interactions at the molecular level have created novel opportunities for the development of NPs for useful therapeutic applications. Nature is providing several means and insight into the synthesis of unconventional nanoparticles. Several works of literature have reported that biological systems can be useful bio laboratory for the fabrication of metal and metal oxide particles at the nanometer scale employing a biomimetic approach. The idea of Nanomedicine appeared as a novel platform for therapeutics as this offers exceptional advantages. Nanomedicine based methodologies address the problems related to conventional dosage forms of drug delivery and enhanced safety. Nano emulsion-based delivery systems have assured to be a worthy solution to improve the biological efficiencies of diverse phytochemicals and their oral bioavailability [2]. Plant-mediated synthesis of nanoparticle has been considered as a green chemistry approach as there is no involvement of lethal solvents and reagents. The approach of this technique is simple, trustworthy, cost-effective, and environment-friendly. Plant systems have established substantial attention as suitable alternatives to physical and chemical techniques for the green synthesis of PNPs. In comparison to green synthesis chemical methods of synthesis employes chemicals as reducing, or capping stabilizing agents, which in turn are non-economic, highly toxic, and non-environment friendly. Plants possess important physical and chemical properties for the green synthesis of nanoparticles as they are nonpathogenic, and phytoconstituents are controlled assembly for nanoparticle synthesis. Therefore, plant-mediated synthesized PNPs possess a characterized nanoparticle that has a novel application. The PNPs sustain a targeted and site-specific activity that increases the efficiency of the drug. This mechanism of PNPs bypasses immune responses and crosses the impermeable membranes thus it can be a useful anticancer agent. Plants have been recognized to show the ability to absorb, hyperaccumulation, and degrade inorganic metallic and metallic oxide ions from their neighbouring environment. In recent times, it has been revealed that phytochemicals can act as effective bio-factory to significantly reduce environmental pollutants in addition to being capable of retrieving metals from industrial waste. A remarkable characteristic of the PNPs it shows absorbance at particular wavelengths due to their shapes and sizes properties. Metal nanoparticles (MNPs) of Ag, Au, Ce, Fe, Se, Si, Ti, and Zn offer a unique opportunity in the area of nanotechnology as a therapeutic agent [3]. The phytochemical reduction of metal ions to base metal is a rapid process, freely accomplished at normal room temperature, and can be effortlessly scaled up. Literature reveals several examples of plant-based synthesis of MNPs utilizing Ag, Au, Ce, Fe, Se, Si, Ti, Zn, and metal oxides such as ZnO, TiO2, CuO, CeO2, Co3O4, Fe3O4, and MgO (Fig.1). Phytoextracts of more than a few plant species have been effectively employed in the preparation of PNPs. Different concentrations of phytoextracts and their combinations act as reducing agents. These reducing agents comprise several water-soluble plant secondary metabolites (e.g., alkaloids, terpenoids, and phenolic compounds) (Fig.2) and coenzymes. Phytoconstituents, therefore, can be used as reducing and stabilizing agents for PNPs synthesis. Plant phenolics possess hydroxyl and ketone groups which are capable of binding or chelating with metals ions. Synthesis of PNPs, has thus emerged as an exciting area of nanotechnology by employing natural products, such as plant extracts, decoction, vitamins, polymers, amino acids, and polysaccharides. Plants used in the synthesis of nanoparticles have drawn more interest of workers because it provides a single step biosynthesis process [4]. The phytochemicals present in the plant source have enormous functionalities, so the metal nanoparticle synthesis using plant extract has emerged [5].

Fig 1: Types of Biogenic metallic nanoparticles synthesized from plant extracts

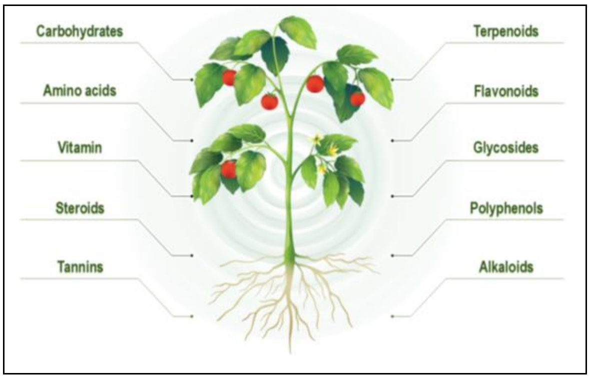

Fig 2: Phytochemicals involved in Green synthesized of Biogenic nanoparticles

Phytoextracts have become a chief focus of researchers due to the following reasons [6]

Fabrication of phytonanoparticles have become an environment-friendly method and avoids the use of harsh, toxic, and expensive chemicals. This method is more stable and its rate of synthesis is more rapid. It is a very economic and valuable alternative for large-scale fabrication. Plant extracts containing phytomolecules can act as both reducing and capping agents in NP synthesis (Fig.3). A broad variety of biomolecules in plant extracts increases the rate of metal ion reduction, the formation of NPs, and their stabilization. In this method, there is no requirement of high temperatures, pressures, and energy levels and does not demand sophisticated laboratory facilities.

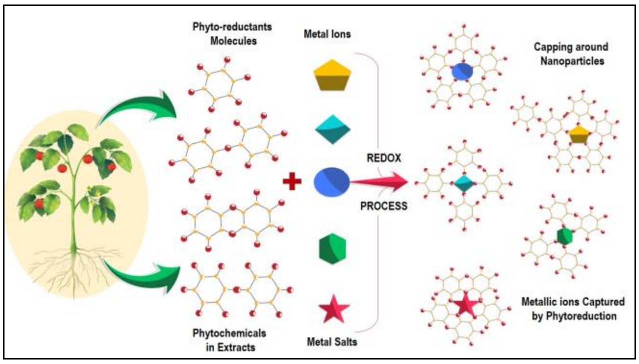

Fig 3: Mechanism involved in synthesized Biogenic nanonanoparticles using plant extracts

Advantages of Phytonanoparticles(PNPs) Formulation [7]

- They lead to a high surface area to volume ratio.
- There is an improvement in solubility and bioavailability.
- Efficient Reticuloendothelial system (RES) uptake noted.
- An enriched penetrability, absorption, and retention effect observed.
- They show enhanced physicochemical stability.
- *In-vivo* they safeguard drugs from degrading before they reach their target site.
- By averting drugs from interacting with normal cells, they evade severe side effects.
- In the body cells or tissues, they control the over-timing and distribution of drugs.
- They upsurge the absorption of drugs into oncogenic cells and tumours.

Considering the unique properties of PNPs, some important applications are listed below.

Applications of Phytonanoparticles [8]

- Antimicrobial activity Antiviral activity, Antibacterial activity, Antifungal activity.
- Anticancer activity via, induction of apoptosis, antimetastatic activity, and cytotoxic effect.
- Metallic ion detection.
- Organic synthesis reaction catalysis.
- Potential in Free Radical Scavenging Activity.
- Diagnosis and Imaging Activity of Silver Nanoparticles.
- Wound Healing Activity of Silver Nanoparticles.
- Biogenic Nanoparticles are recently introduced as catalysts for various industrial applications.

Using nanoparticles for medicinal and diagnostic agents with the innovation of drug delivery is imperative and a need of the hour. Formulations containing proteins or nucleic acids require a more inventive type of carrier to increase their efficiency and defend them from undesirable degradation. Here the effectiveness of drug delivery systems of the formulation may be indirectly associated with particle size.

The minor size and big surface capacity of a nanoparticle drug may demonstrate the rise in solubility and hence enhance the bioavailability, supplementary the ability to cross the blood-brain barrier (BBB), pulmonary system and can be absorbed through endothelial cells of the skin. Precisely made biogenic nanoparticles of the natural source are the acquisition of attention since they can be modified for targeted drugs delivery, enhance bioavailability and increase controlled release efficiency of the drug. Besides, the advancement in new drug delivery systems may provide alternate formulation. These new phytonano-formulations may be useful to the patients and can create a good marketplace for motivating the development of even more effective delivery methods [9].

Pharmacological applications of Phytonanoparticles

Herbal medicines are used conventionally for the management of many syndromes and have scientifically proved as therapeutic agents. These findings can be applied to treat various as PNPs have with advantages like nano-sized, fastest release to the target drugs, the bioavailability of the drug, less concentration of less drug substance, the potential crossing of blood-brain barriers. PNPs synthesized by different techniques have been extensively been studied for their *in-vivo* and *in-vitro* applications (Fig.4) [10]. Phytonanoparticles, due to their biocompatibility, has remarkable pharmacological applications in biomedicine (Table1).

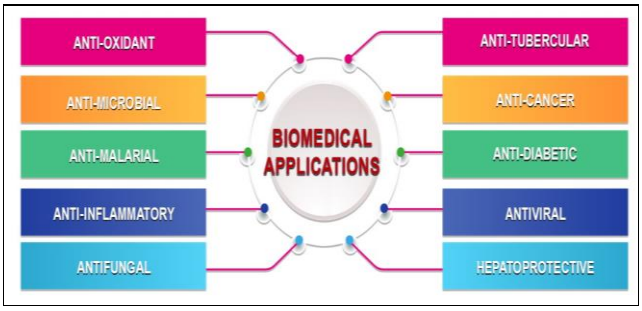

Fig 4: Pharmacological applications of phytonanoparticles

Table 1: Pharmacological applications of biogenic Phytonanoparticles

Plant	Nanoparticle	Pharmacological activity	References
Abelmoschus esculentus	*Au*	Anticancer,	11
Azadirachta indica	*ZnO*	Anti-dengue	12
Aegle marmelos	Ag	Antimicrobial	13
Boswellia ovalifoliolata	ZnO	Antimicrobial	14
Boswellia serrata	Au	Anti-acute myeloid leukaemia	15
Commelina maculata	Ag	Antioxidant	16
Clausena anisata	Ag	Antimicrobial	17
Dimocarpus Longan	Ag	Antibacterial, Anti-cancer	18
Diopyros kaki	Ag,Pd	Antibacterial	19
Euphorbia milii	ZnO	Antinociceptive	20
Foeniculum vulgare	Au	Antibacterial	21
Gardenia jasminoides	Fe	Antibacterial	22
Glycyrrhiza glabra L.	TiO2	Antibacterial	23
Hydrastis canadensis	ZnO	Antioxidant	24
Ipomoea carnea	Zno	Antioxidant	25
Justicia gendarussa L.	TiO2	Photocatalytic	26
Lonicera japonica	ZnO,CuO	Antibacterial	27
Medicago sativa (alfalfa)	FeO	Anti-cancer, Antimicrobial	28
Nyctanthes arbortristis	ZnO	Antifungal	29
Ocimum sanctum L.	Ag	Antidiabetic	30
Olea europea	ZnO	Antioxidant	31
Pelargonium sidoides DC	Ag	Antibacterial	32
Piper nigrum L.	Ag	Anti-Inflammatory	33
Rumex acetosa	Ag, FeO	Antioxidant	34
Salvadora oleoides	ZnO	Antibacterial	35
Syzygium aromaticum	Cu	Cytotoxic	36
Terminalia arjuna	Ag	Antibacterial	37
Trigonella-foenum graecum	Fe	Antibacterial	38
Vitex altissima	Zno	Antioxidant	39
Vitex negundo L.	Ag	Anti-cancer,	40
Withania somnifera	Se	Antimicrobial	41
Zingiber officinale Rosc.	Ni	Anti-cancer, Antibacterial, Antifungal	42

Anticancer Activity of Phytonanparticles

Sathishkumar *et al*. (2016) reported a synthesis of AgNPs employing a leaf extract of *Alternanthera tenella*. AgNPs showed a noteworthy anticancer activity against human breast adenocarcinoma (MCF-7) cells [43]. Sre *et al*. (2015) evaluated the anticancer efficacy of biogenic AgNPs synthesized from the extract of *Erythrina indica* on MCF-7 (breast cancer) cells and HepG2 (hepatocellular carcinoma) cells, Studies showed a reduction in the viability of proliferative cells upon treatment with increasing concentrations of AgNP [44].

Antidiabetic Activity of Phytonanparticles

Saratale *et al*. (2018) reported an innovative synthesis of AgNPs by utilizing leaf extract of *Punica granatum* and evaluated for antidiabetic activity. AgNPs of Punica granatum exhibited effective antidiabetic potential by showing inhibition of α-amylase and α-glucosidase (IC_{50}; 65.2 and 53.8 µg/mL, correspondingly). The AgNPs displayed a dose-dependent activity counter to human liver cancer cells (HepG2) (IC_{50}; 70 µg/mL) by inhibiting and killing the cancer cells. In addition to anticancer AGNPs were screened for Antioxidant activity using ABTS at (IC_{50}; 52.2 µg/mL) and DPPH (IC_{50}; 67.1µg/mL). Biogenic AgNPs Showed broad-spectrum anticancer and antioxidant activity [45]. Preety *et al*. (2020) reported the synthesis of *cumin* oil mediated AgNPs and evaluated it for its anti-diabetic activity using the α-amylase inhibitory assay. Biogenic cumin oil AgNPs inhibited α-amylase in a dose-dependent manner, which can control postprandial hyperglycemia [46].

Anti-inflammatory Activity of Phytonanparticles

Vijayaraj *et al*. (2016) studied the synthesis of biogenic AgNPs using *Acranythes aspera* seed extracts its anti-inflammatory activity. Ethanolic extract of *A.aspera* and biogenic AgNPs of *A.aspera* were evaluated for anti-inflammatory assay in carrageenan-induced oedema in rats paw with comparison to the indomethacin drug as standard. The orally ingested ethanolic extracts of *A. aspera* (100 and 200 mg/kg) and biogenic AgNPs (100 mg/kg) exhibited noteworthy inhibition. The anti-inflammatory effect induced by standard indomethacin gradually increased and extended a maximum of 44.12% after 3hrs ($p<0.001$). Biogenic AgNPs showed better inhibition of oedema with comparison to the standard drug [47]. Baharara *et al*. (2017) Evaluated antioxidant and anti-inflammatory activity of *Salvia officinalis* extract mediated AgNPs. Biogenic AgNPs were synthesized utilizing *S. officinalis* and their toxicity on MCF-7 cells was tested using an MTT assay. AgNPs displayed decreased cells viability with inhibitory concentration (IC_{50}) of 25 µg/ml and 20 µg/ml after 24 and 48 h, respectively. Anti-inflammatory genes expression was confirmed by MCF-7 cells that were treated with 20 µg/ml AgNPs (concentration below of IC_{50} value according to MTT assay). Semi-quantitative RT-PCR investigation indicated that AgNPs amplified IL-8 and TNF-α genes expression 28% and 42%, correspondingly, but blocked cyclooxygenase-2 gene expression with 20.5% associating to control groups [48].

Anti- Microbial Activity of Phytonanparticles

Kirupagaran R et.al. (2016) studied the green synthesis of selenium nanoparticles using an aqueous extract of *Leucas lavandulifolia* leaf. They reported that synthesized selenium nanoparticles exhibited spherical shape with an average diameter range is 56 nm - 75 nm. Also carried out the antibacterial activity of Green synthesized selenium nanoparticles where the high antibacterial activity of selenium nanoparticles was observed is due to its extremely large surface area, which could provide better contact with microorganisms [49]. Kahsay *et al*. (2019) reported the synthesis of biogenic zinc oxide (ZnO) nanostructures employing water extract of *Dolichos lablab* L leaf. as the reducing and capping agent. The ZnO nanostructures were subjected to antimicrobial activity utilizing the agar well diffusion method against *Bacillus pumilus* and *Sphingomonas paucimobilis* that showed the maximum zones of inhibition of 18 mm and 20 mm, respectively [50].

Antioxidant Activity of Phytonanparticles

Kharat and Mendhulkar (2016) illustrated green synthesis of silver nanoparticle using leaf extract of *Elephantopus scaber L*. Biogenic AgNPs evaluated for antioxidant activity by using DPPH radical scavenging assay. Free radical scavenging was observed with a low concentration of biogenic AgNP at 50 µg/ml was 15 ± 0.04 and this scavenging capacity was improved to 85± 0.08 upon increasing concentration to 250 µg/ml. Though, the scavenging ability was documented for aqueous leaf extract when compared with both concentrations showed an average IC50 value. This study revealed that the biogenic AgNPs possessed a strong antioxidant activity comparable with aqueous plant extract [51]. Keerthiga *et al*. (2016) employed cumin oil in the synthesis of biogenic AgNPs and evaluated the antioxidant activity of the biogenic cumin oil mediated silver nanoparticles. Biogenic AgNPs were assayed using the DPPH method to determine the antioxidant activity. Biogenic Cumin oil mediated AgNPs showed potent antioxidant activity compared to standard [52].

Antiviral Activity of Phytonanparticles

Fatima et.al (2016) attempted to synthesize biogenic AgNPs utilizing bark extract of *Cinnamomum cassia* and evaluated its antiviral activity against pathogenic *avian* influenza virus subtype H7N3. Individually bark extract and AgNPs were assayed against H7N3 influenza *A virus* in Vero cells and the sustainability of cells was evaluated by tetrazolium dye (MTT) assay. Cinnamon AgNPs exhibited higher antiviral action and were established to be active in individually when incubated along with the virus before infection and introduced to cells after infection. The concentrations of extract and biogenic AgNPs tested were up to 500 µg/ml and remained non-toxic to Vero cells. Thus it concluded that biogenic AgNPs can prove to be a hopeful approach against influenza virus infections [53]. Meléndez-Villanueva et.al (2019) reported a green synthesis AuNPs of garlic extract (*Allium sativa*) evaluated it for antiviral activity. Garlic AuNPs showed active inhibition of MeV replication in Vero cells at a 50% concentration (EC50) of 9 µg/mL, and 16 selectivity index (SI) was noted. AuNPs-As probably constrain viral contamination by directly obstructing viral particles, presenting an effective virucidal effect [54].

Conclusions

Herb-mediated green synthesis approach has acquired significant attention due to its biodegradable nature. Furthermore, the herb-mediated synthesis of nanoparticles is reliable, rapid, and simple. Different plant parts such as seeds, roots, stems, leaves, bark, flowers, fruit, and peel are used for the synthesis of nanoparticles. An array of physicochemical parameters controls the size and shape of Phyto-nanoparticles. Plant extracts are involved synergistically in the bioreduction processes of metal salt for the synthesis of nanoparticles. Therefore, further research is a prerequisite to recognizing the precise phytomolecules that mediate the exact mechanism for the synthesis of nanoparticles. Identification of specific plant molecules will help in controlling the shape and size of nanomaterials that provides a wide range of medical, industrial, and agricultural applications. The biogenic method of phytonanoparticle fabrication is of great attention owing to its conceivable applications in the treatment of several diseases. The field is still in its infancy but recent successes in preparation warrant its bright future. The future outcomes of PNPs seem to be very promising in increasing the efficacy of existing treatments and the development of new therapies. A formulation containing Phyto-nanoparticles with low toxicity and potential pharmacological applications devoid of toxicity is the need of the hour. Similarly, if other NPs containing formulations are prepared it will contribute to the design PNPs mediated drug carriers. PNPs can be used for clinical diagnosis and therapies, based on their size, biocompatibility, surface chemistry, relatively good stability, and adjustable toxicity in biological systems. It can be expected that the application of PNPs in pharmacotherapy will greatly improve current methods of drug delivery therapy while reducing toxicity compared to formulations of synthetic drug.

Conflict of interest

The authors declare no conflict of interest.

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