Int.J.Curr.Microbiol.App.Sci (2023) *12*(02): 148-166

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 Volume 12 Number 2 (2023)
Journal homepage: http://www.ijcmas.com

Review Article https://doi.org/10.20546/ijcmas.2023.1202.015

A Review on Phytosynthesis of Nanoparticles and its Biomedical Applications: An Ecofriendly Approach

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A B S T R A C T

Keywords

Green Synthesis, Nanoparticles, Antioxidant activity, Anticancer activity, Antibiofilm activity

Article Info

Received:
06 January 2023
Accepted:
30 January 2023
Available Online:
10 February 2023

Nanotechnology have remarkable significance in different fields, like pharmaceutical, biomedical, drug delivery, agricultural and energy applications, etc., which deals with the synthesis of different metal/metal oxide nanoparticles. Nanoparticles are solid colloidal in nature with the size ranging from 10 to 1000 nm. Nanoparticles have some excellent characteristics like non-toxicity, biocompatibility, chemical stability, high saturation magnetization and maximum magnetic susceptibility. They are being prepared by silver, gold, nickel, zinc, copper, titanium, magnesium, and alginate etc., by using various bio resources like plant and microorganisms. Nowadays, the biological approaches of green or plant mediated synthesis of nanoparticles expressed safe, cheapest, eco-friendly, more reliable and clean method to propose different biological properties. This review investigates the phytosynthetic mechanisms of nanoparticles and its bio-therapeutic applications such as antimicrobial, antioxidants, anticancer, hyperthermia, bio imaging and biosensors sensing of target molecules and drug delivery etc.

Introduction

Nanotechnology is one of the most promising and powerful branch of science; deals with production and development of different nanomaterials or nanoparticles. It has some altered properties and offered various new profitable products and applications (Ahmad *et al.*, 2020; Jain *et al.*, 2021). Nanoparticles are the vital building elements of the science nanotechnology. They have great attention because of their size and large surface to volume ratio, which lead to both chemical and physical differences in their properties compared to bulk of the same chemical composition (Sanjivkumar *et al.*, 2019). They are being formulated by copper, cobalt, nickel, zinc, titanium, magnesium, gold, alginate and silver. These particles can offer solutions to many technological and environmental challenges in the field of solar energy conversion, wastewater treatment and also influences in optoelectronics, chemical, medical, food, agricultural, electronic and industrial fields (Vanaja *et al.,* 2013; Alabdallah and Hasan, 2021).

Nanotechnology has generated more attention among various scientists, because of its notable outcomes in various fields influencing different methodologies for the synthesis of nanoparticles with different size and shapes (Bahrulolum *et al.,* 2021). The nanoparticles are being synthesized by different methodologies like physical, chemical, and biological. Physical and chemically mediated synthesize of nanoparticles require high pressure, temperature and which also exhibits high cost and toxicity. In order to reduce such difficulties, an alternative way like biological methods has been evolved (Akintelu *et al.,* 2020; Jain *et al.,* 2021). The influences of biological entities in the nanoparticle growth is gaining numerous advantages like synthesis of anisotropic nanoparticles with size and shape control and intensive energy. The biological methods of synthesis of nanoparticles by using enzymes, microorganisms and plants or plant extracts have been recommended as possible eco-friendly alternatives to chemical and physical methods. (Vanaja *et al.,* 2013; Jain *et al.,* 2021) Eco-friendly biosynthesis of nanoparticles using bacteria, fungi, algae and plant materials are of great interest in the current research scenario.

Among them, the rapid production of nanoparticles from plant resources has more advantages over other biological methods, because it is inexpensive and does not need any special conditions (Bahrulolum *et al.,* 2021). Using plants for nanoparticle synthesis can be advantageous over other biological processes such as microbial route, because it eliminates the elaborate process of maintaining cell cultures and can also be suitably scaled up for large-scale synthesis of nanoparticles (Gour and Jain, 2019). The usages of plant resources for production of nanoparticles are known as green synthesis or phytosynthesis (Rico *et al.,* 2013; Dikshit *et al.,* 2021). For the synthesis of metal/metal oxide nanoparticles, plant biodiversity has been broadly considered due to the availability of effective phytochemicals in various plant extracts, particularly in leaves such as ketones, aldehydes, flavones, amides, terpenoids, carboxylic acids, phenols, and ascorbic acids. These components are capable of reducing metal salts into metal nanoparticles (Singh *et al.,* 2018).

The benefit of using plant resources for the production of nanoparticles is that they are easily available, safe to handle, and possess a broad variability of metabolites that may aid in reduction (Alabdallah and Hasan, 2021). The motivation for choosing the plant was its medicinal properties, and capping or reducing agents are available in this plant. The size, shape, stability, and the synthesis of nanoparticles were dependent on the various factors (capping agents, pH, templates and temperature) (Singh *et al.,* 2018; Sanjivkumar *et al.,* 2022). Plant resources like its stem, latex, leaf, seed and roots are being employed for the production of metal-oxide nanoparticles. Phytosynthesis of nanoparticles provides advancement over other physical and chemical methods and are rapidly produced due to the exposure of metal salts to the desirable plant extracts (Sharma *et al.,* 2020; Akintelu *et al.,* 2020; Dikshit *et al.,* 2021). The nature of nanoparticle especially size and shape, are modulated by varying the ratio of pH, temperature and the concentration of both plant extract and metal salts in the reaction medium. From these, this review will be summarized the phytosynthesis of nanoparticles and its biomedical applications.

Phytosynthesis of nanoparticles

Plants have some ability to accumulate certain amounts of heavy metals in their diverse parts and can be utilized to reduce the metals and stabilize the phytosynthesized metallic nanoparticles under *in-vitro* conditions (Begum *et al.,* 2011). Many researchers have performed phytosynthesis of metal or metal oxide nanoparticles by using the reaction mixture supplementary with metal salts and extracts of different plant materials such as leaf, flower, seed, stem and root systems to further explore their different uses (Devi and Singh, 2014). Various plants such as *Citrus limon*, *Coriandrum sativum, Aloe barbadensis, Osimum sanctum*, *Brassica juncea*, *Azadirachta indica*, *Cymbopogon flexuosus* and *Avena sativa* have been utilized for phytosynthesis of different nanoparticles (Singh *et al.,* 2018).

There are different parameters such as phytochemicals (flavonoids, terpenoids, sugars, carboxylic acids, aldehydes, ketones and amides), nature and concentration of metal salts, temperature and pH nature of the plant leaf extract are could able to control the yield and stability of produced nanoparticles (Dwivedi and Gopal, 2010). Subsequently, they can able to reduce the metal atoms in a much shorter time as compared to other bio resources like fungi, algae and bacteria, which offers the higher incubation time (Devi and Singh, 2014). Hence, plant leaf extracts are more promotable source for metal oxide nanoparticle production.

Moreover, the leaf extracts also acted as both stabilizing and reducing agents in the production process. Yadav and Rai (2011) documented the phytosynthesis of silver nanoparticles (AgNPs) from leaf extract of *Holarrhena antidysenterica* through laboratory condition.

They were also denoted that the phytochemical terpenoids are responsible for the reducing agent of silver ions. In an another study, Singh *et al.,* (2011) performed the phytosynthesis of zinc oxide nanoparticles from harnessed latex of *Calotropis procera* and subsequently characterized the nanoparticles by TEM analysis with the average size range of 5 - 40nm. They also observed the latex of *C. procera* plant could able to reduce and stabilize zinc oxide nanoparticles.

Mechanism of nanoparticle biosynthesis

The biosynthesis of nanoparticles from plants and plant mediated extracts has gained more acceptance due to its cost-effective, quick development, single-step production method, non-pathogenicity, and eco-friendly in nature. Phytosynthesis tends to be faster than other microorganisms such as fungi and bacteria. Hence, in phytosynthesis, the usage of plant mediated extract has encouraged in many studies and researched them so far (Akintelu *et al.,* 2020; Jain *et al.,* 2021). Plants or plant mediated (leaves, flowers, seeds, barks, stems, shoots, and their derivatives) extracts for the phytosynthesis of nanoparticles have been used predominantly for the benefits of being readily available and safe to treat, as well as having a wide variety of bioactive agents that can aid in the reduction of metal ions (Li *et al.,* 2007; Kumar *et al.,* 2014). The phytosynthesis of nanoparticles can be attained through three different methods, like (i) intracellular (ii) extracellular and (iii) using distinct phytochemicals obtained from plant resources. The plants have the ability of metal accumulation and successive conversion of these accumulated metals to nanoparticles intra/extracellular (Alabdallah and Hasan, 2021). The occurrence of several plant based biomolecules such as polysaccharides, proteins, amino acids, vitamins, aldehydes, flavones, alkaloids, ketones, phenolics, tannins, saponins and terpenoids plays an important role in the reduction of metals (Fig.1). The bioactive molecules from plant bioresources allow stabilization and reduction of metal atoms, subsequently create highly stable nanoparticles (Kharissova *et al.,* 2013).

The mechanism of biosynthesis of metal nanoparticles from plant mediated extracts was attained through three different stages. (i) The reduction of metal ions (M^+ or M^{2+}) to metal atoms (M^0) and successive nucleation of the reduced metal atoms occurs, (ii) the combination of small adjacent NPs into larger size particles occurs with simultaneous increase in thermodynamic stability, (iii) the termination of the process takes place while giving the final shape to the nanoparticles were stated by Dikshit *et al.,* (2021). The differences in size, shape, and characteristics of phytosynthesized nanoparticles are denoted due to the variation in reducing and stabilizing efficacy of bioactive molecules found in the plant. In general, the phytosynthesis of nanoparticles is achieved through the mixing of plant biomass or plant mediated extract with a metal salt solution at a preferred pH and temperature (Akintelu *et al.,* 2020). Shankar *et al.,* (2003) documented the phytosynthesis of AgNPs from Geranium leaf extract under laboratory condition. They also observed that the incorporation of extract into $AgNO_3$solution, which made rapid degradation of Ag ions has led to the formation of highly stable AgNPs with 40nm in size.

In an another study, the leaf extract of *Capsicum annuum* constitute a number of bioactive molecules (enzymes, polysaccharides, proteins, amino acids, and vitamins) acted as bioreductants for metal ions or as scaffolds to direct the synthesis of silver nanoparticles in solution under *in-vitro* conditions, were observed by Li *et al.,* (2007). Kumar *et al.,* (2014) studied the phytosynthesis of AgNPs from *Boerhaavia diffusa* extract under laboratory condition, in where the plant extract exhibited as both a capping and reducing agent to make stable nanoparticles. Logaranjan *et al.,* (2016) attained different size and shape based controlled AgNPs from *Aloe vera* extract under *in-vitro* conditions with the size range of 68nm.

Similarly, the AgNPs are phytosynthesized using methanol mediated leaf extract of *Leptadenia reticulate* under optimized condition, expressed crystalline, spherical particles with the diameter range of 50 - 70nm (Swamy *et al.,* 2015). Kumar *et al.,* (2017) documented the green synthesis of AuNP's from *Gelidium amansii* under laboratory condition showed the average size range of nanoparticles are 5 to 25nm.

Biomedical efficacy of nanoparticles

There are different types of nanoparticles phytosynthesized by using different types of plant resources, have multiple applications such as antimicrobial, anti-parasitic, antioxidant, anticancer, anti-inflammatory, antidiabetic and anti-biofilm activities etc. (Fig. 2 a & b), They are as follow

Nanoparticle as an antimicrobial agent

Antibacterial activity

Various research has been used to determine antimicrobial functions because of developing microbial resistance towards the most common antibiotics. *In-vitro* antimicrobial activities, the metal oxide nanoparticles efficiently inhibit the growth of various microbial species by means of material used for synthesis of the nanoparticles and their particle size (Dizaj *et al.,* 2014). Over the time, microbial resistance to antimicrobial drugs has become gradually increased and is consequently a significant threat to public health. This problem was overcome by utilizing nanoparticles as antimicrobial agents, could able to denature the outer membrane of the bacteria, creation of pits/gaps in the bacterial cell membrane and the destruction of metabolic processes (Egger *et al.,* 2009). Azam *et al.,* (2012) studied the antimicrobial efficacy of copper (CuO), iron (Fe_2O_3) and zinc (ZnO) oxide nanoparticles against gram-negative (*E. coli* and *P. aeruginosa*) and gram-positive (*S. aureus* and *B. subtilis*) bacteria under laboratory condition. Accordingly, they were observed the ZnO nanoparticles expressed the maximum (23mm) zone of growth inhibition against *E. coli*.

In an another report, a plant leaf extract of *Tridax procumbens* was used for the production of copper oxide (CuONPs) nanoparticles by Gopalkrishnan *et al.,* (2012). In where, the authors denoted that the phytochemicals found in plant extract were responsible for the reduction of metal oxide into CuONPs expressed the highest (100%) percentage of inhibition against *E. coli* at 30µg concentration. Silver nanoparticles (AgNPs) are one of the most important nanoparticles from the plant resources expressed various biomedical properties such as antibacterial, antifungal and antioxidant activities

(Sanjivkumar *et al.,* 2019). Ali *et al.,*(2016) documented the biosynthesis of AgNPs from apple extract exhibited minimum bactericidal concentration (MBC) against the bacteria like *E. coli, S. aureus, P. aeruginosa* under laboratory condition. The results also expressed the concentration of 125*μ*g/mL of AgNPs showed bactericidal effect against *E. coli*. Oda *et al.,* (2019) assessed the phytosynthesis of AgNPs from *Brassica oleracea* and its antibacterial efficiency through agar well diffusion assay. Who also observed the zone of inhibitions 27, 23 and 28mm against *V. cholera, E. coli* and *B. subtilis*.

Similarly, the antibacterial efficacy of AgNPs from different plant resources such as *Latrunculia apurinae, Aegle marmelos, Cucumis prophetarum* and *Wedelia acapulcensis* were documented by different researchers like, Sheryl *et al.,* (2018); Devi *et al.,* (2020); Hemlata *et al.,* (2020) and Garibo *et al.,* (2020).

Khan *et al.,* (2018) investigated the phytosynthesis of gold nanoparticles (AuNPs) from aqueous leaves extract of *Acer pentapomicum* expressed highest activity (81%) against *Klebisiella pneumoniae*. Gupta *et al.,* (2018) documented the phytosynthesis of ZnONPs from leaf extract of *Catharanthus roseus* exhibited the antibacterial activity against the bacterial strains such as *S. aureus* (MTCC9760), *S. pyogenes* (MTCC1926), *B. cereus* (MTCC430), *P. aeruginosa* (MTCC424), *P. mirabilis* (MTCC3310) and *E. coli* (MTCC40) with the inhibition zones of 11.09 - 11.74mm. Sharma *et al.,* (2020) achieved phytosynthesis of MgONPs from *Annona squamosa* seeds showed antibacterial effect against *Pactobacterium carotovorum* with the maximum zone of inhibition was found to be 23.4mm.

Likewise, Demissie *et al.,* (2020) performed phytosynthesis of zinc oxide nanoparticles from an aqueous leaf extract of *Lippia adoensis* through *in-vitro* condition and also evaluated its antibacterial activity against the pathogens such as *S. aureus, K. pneumoniae, E. faecalis,* and *E. coli* by disc diffusion method. Muniyappan *et al.,* (2021) revealed the green synthesis of AuNPs from *Curcuma pseudomontana* and tested its antibacterial efficacy against *P. aeruginosa* (23mm), *S. aureus* (25mm), *B. subtilis* (26mm) and *E. coli* (28mm) through agar well diffusion assay at 100μg/mL concentration. Based on these, the antimicrobial activity of different phytosynthesized nanoparticles from various plant bioresources penetrate the cell membrane of the pathogens and which also influence cell death either through the formation of reactive oxygen species (ROS) or disruption of cell function thereby inhibiting the synthesis of proteins and DNA.

Antifungal activity

Nanoparticles also have antifungal property against various fungal pathogens and are reported by various researchers. Narendhran and Sivaraj (2016) reported the synthesis of ZnONPs from aqueous leaf extract of *Lantana aculeate* Linn. and they also evaluated its antifungal activity through agar-well diffusion assay against *Aspergillus niger* (MTCC10180) and *Fusarium oxysporum* (MTCC3930) with the zone of growth inhibition of 21 and 19mm respectively at 100μgml^{-1} concentration. In an another study, the highest growth reduction was recorded against *F. oxysporium* (43%) and *A. niger* (41.6%) using AuNP's of *Acer pentapomicum* at 100μg/mL concentration by Khan *et al.,* (2018). Alothman and Abeer (2019) documented the production of AgNPs by using different variety of fruit peel such as fruits banana, pear, orange, mandarins and kiwi and studied the antifungal efficacy against *A. niger, A. flavus and F. solani* through *in-vitro* condition. Ahmad *et al.,* (2020) determined the antifungal efficacy of phytosynthesized zinc oxide nanoparticles from *Eucalyptus globules* showed the highest growth inhibition against *Alternaria mali* (76.7%), *Diplodia seriata* (65.4%) and *Botryosphae riadothidea* (55.2%) at the concentration of 100 ppm respectively. This study indicates that the biosynthesized nanoparticles from the plant bioresources exhibited antifungal properties. Moreover, the phytosynthesized nano-antifungal agents are highly safe against various fungal pathogens through disrupting the fungal cell integrity.

Anti-parasitic property

Marimuthu *et al.,* (2011) assessed the anti-parasitic efficacies of phytosynthesized AgNP's of *Mimosa pudica* leaf extract against *Culex quinquefasciatus, Anopheles subpictus* and *Rhipicephalus micropls* larvae under laboratory condition. They also observed highest mortality rate against *A. subpictus*with the LC_{50} value of 13.90mg/L. In an another report, Ponarulselvam *et al.,* (2012) performed anti-parasitic activity of green synthesis of AgNPs of *Catharanthus roseus* against malarial parasite *Plasmodium falciparum*. The nanoparticles expressed the highest percentage of activity 75.0% at 100µg/mL concentration. Mouchet *et al.,* (2008) recorded the toxicology effect with the highest (85%) mortality rate was observed at 500mg/L concentration of double-walled carbon nanotube against the larvae of *Xenopus laevis* under laboratory condition. Similarly, Marimuthu *et al.,* (2011) portrayed the toxicology effect of green synthesized AgNPs (25mg/L) of *Mimosa pudica* expressed 100 and 89% of mortality rate against both *A subpictus* and *R. microplus* respectively with the LC_{50} value of 13.90 and 8.98mg/L respectively. Rajakumar *et al.,* (2015) reported the biosynthesized titanium dioxide nanoparticles (25mg/L) from *Mangifera indica* exhibited the highest (100%) mortality rate against the blood feeding parasites like *A. subpictus* and *C quinquefasciatus* respectively with the LC_{50} value of 7.72 and 8.10mg/L. Likewise, the TiO_2NPs from an aqueous leaves extract of *Catharanthus roseus* showed highest activity (98%) against the adults of *Hippobosca maculata* and *B. ovis* with 7.09 and 6.56mg/L LD_{50} values (Velayutham *et al.,* 2012). The larvicidal activity of phytosynthesized ZnONPs (250 ppm) of *Ficus religiosa* displayed the highest activity (100%) against *A. stephensi* at the incubation time of 24h with the LC_{50} value of 75 ppm were documented by Soni and Dhiman (2020). The different phytosynthesized nanoparticles from various plant origin expressed as effective anti-parasitic activity.

Antiviral property

Haggag *et al.,* (2019) studied antiviral activity of phytosynthesized AgNPs (260.3µg/mL) of *Lampranthus coccineus* by using HAV-10, HSV-1, and CoxB4 viruses through MTT assay. In an another report, Mehmood *et al.,* (2019) documented the antiviral activity of AgNPs from *Syzygium aromaticum* through Spot assay test. In spot assay the antiviral activity was found with lower dilution. Abdelkhalek and Al-Askar (2020) portrayed the antiviral property of green synthesized ZnONPs from aqueous leaf extract of *Mentha spicata* using tobacco mosaic virus through half-leaf method. They also reported that the foliar application of phytosynthesized ZnONPs (100µg/mL) efficiently decreased the severity of disease, promotion of plant growth and reduced the viral accumulation levels in the treated tomato plant. The different phytosynthesized nanoparticles have some antiviral property. Meanwhile, the efficacy of the nano-based antiviral drug should be improved but it becomes more expensive.

Nanoparticles as an antioxidant agent

The nanoparticles from the natural bioresources can able to reduce the toxicity effect of free oxygen radicles in order to act as antioxidant. The antioxidant property of phyto-synthesized AgNPs of *C. reticulata var*. Ponkan peels expressed the highest activity with the IC_{50} value of $0.6 mgml^{-1}$ through 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay under laboratory condition was performed by Ghasemi *et al.,* (2009). Kanipandian *et al.,* (2014) attained the antioxidant activity of green synthesized AgNPs (50 - 1000µg/mL) of *Cleistanthus collinus* through total reducing power, DPPH and H_2O_2 scavenging activity with the highest percentage of inhibition of 84.64, 69 and 84% respectively under *in-vitro* condition. Bhakya (2015) studied the effect of antioxidant activity of green synthesized AgNPs of *Helicteres isora* leaf extract by DPPH assay.

They noted the scavenging activity of DPPH of AgNPs was found to be 90% at 100µg/ml concentration. The antioxidant efficacy of NPs from different plant bioresources are represented in Table 1.

Likewise, Rehana *et al.,* (2017) studied the antioxidant efficacy of CuONPs from *Murraya koenigii, Hibiscus rosasinensis, Azadirachta indica, Tamarindus indica* and *Moringa oleifera* leaves through ABTS assay. Satpathy *et al.,* (2018) illustrated the *in-vitro* total antioxidant activity of biosynthesized silver nanoparticles (AgNPs) from aqueous extract of *Pueraria tuberosa* with the percentage inhibition of 84% at 450µg/ml concentration. In an another study, Safawo (2018) assessed that the antioxidant activity of green synthesized ZnONPs (100 - 800µg/mL) from the tuber extract of *Coccinia abyssinica* by DPPH assay showed the maximum (85%) percentage of inhibition with the IC_{50} value 127.74µg/ml. Sanaeimehr (2018) investigated the antioxidant property of green-synthesized ZnONPs from *Sargassum muticum* by ABTS assay displayed the maximum radical scavenging activity of 89% at 2800µg/ml concentration with EC50 600µg/ml. Sharmila (2018) studied the antioxidant efficacy of green synthesis of ZnONPs from leaf extract of *Tecoma castanifolia*by DPPH radical scavenging activity. They also noted that the increase in concentration (100µg/mL) of ZnONPs increases the radical scavenging activity of 67 %. Rajeshkumar *et al.,* (2019) performed the antioxidant potential of green synthesized copper nanoparticles (CuNPs) from *Cissus arnotiana* by DPPH assay with the highest (84%) percentage of inhibition was observed at 40µg/ml concentration of nanoparticles. Keshari *et al.,* (2018) described the production of AgNPs using leaf extract of *Cestrum nocturnum* and its antioxidant activity through DPPH method with the percentage of inhibition of 29.55% respectively compared with 24.28% of vitamin C as standard. Donga (2020) achieved antioxidant efficacy of AuNPs from the seed extract of *Mangifera indica* through *in-vitro* condition by DPPH and superoxide radical scavenging assay exhibited maximum percentage of inhibitions of 96 and 78%with the respective IC_{50} values are 256 and 62mg/ml. This review article clearly indicates the biosynthesized nanoparticles from the plant origin could be used to develop an alternative antioxidant agent and it may find more applications in biomedical as well as pharmaceutical industries.

Nanoparticles as an anticancer agent

Now-a-days nanomaterials or nanoparticles are being used to treat cancer diseases and they can able to adversely affect cancer cell division. Various researchers have been reported the influences of nanoparticles in cancer cell line research (Table 2). Sukirtha *et al.,* (2012) documented *in-vitro* anticancer activity of green synthesized AgNPs from *Melia azedarach* using HeLa cell lines with lethal dose (LD_{50}) value was found to be 300 g/mL of AgNPs. Similarly, Jeyaraj *et al.,* (2012) examined the anticancer effects of green synthesized AgNPs of leaf extract of *Sesbania grandiflora* through MTT assay by using A549 and HBL-100 cell lines. Who also observed the growth inhibitory concentration (IC_{50}) of phytosynthesized AgNPs expressed as 30 and 60µg/mL respectively against the both cell lines. Geetha *et al.,* (2013) analyzed the cytotoxic effect of gold nanoparticles extracted from *Couroupita guianensis* using HL60 cell line through MTT assay expressed the highest inhibition percentage with 5.14µM of CC_{50} value. Emima Jeronsia *et al.,* (2016) documented the *in-vitro* cytotoxicity effect of CuONPs against MCF7 using MTT assay showed the decrease in proliferation rate with an increase in the concentration of CuONPs with the inhibitory concentration (IC50) of 62.5µg/ml. In an another report, Rehana *et al.,* (2017) evaluated the *in-vitro* anticancer efficacy of phytosynthesized CuONPs from *Azadirachta indica* using A549 cell line by MTT assay. They also denoted the maximum percentage (94%) of cell inhibition with 20.15mg/ml IC_{50} value. Gnanavel *et al.,* (2017) examined *in-vitro* anticancer activity of CuONPs of *Ormocarpum cochinchinense* using HCT-116 cell lines through MTT assay showed with highest percentage (87%) of inhibition with 40µg/ml of IC50 value.

Table.1 Biomedical efficacy of different nanoparticles synthesized from various plant bioresources

Plant Name	Produced Nanoparticles	Applications	References
Prunus serrulata	Ag & Au	Anti-inflammatory	Priyanka *et al.*, (2018)
Abies spectabilis	CuO	Anti-inflammatory, antibiofilm activity	Liu *et al.*, (2020)
Cissus vitiginea		Antioxidant activity (DPPH assay)	Wu *et al.*, (2020)
Brassia actinophylla		Anticanceractivity (HT-29 cell line-- MTT assay)	Subashini *et al.*, (2019)
Juglans regia		Antioxidant activity (DPPH assay)	Asemani and Anarjan (2019)
Parkia speciosa	Ag	Antioxidant activity(DPPH)	Ravichandran *et al.*, (2019)
Phoenix dactylifera		Anticancer activity (MCF7 cell lines)	Oves *et al.*, (2018)
Achillea millefolium		Antioxidant activity (DPPH)	Yousaf *et al.*, (2020)
Alternaria tenuissima	ZnO	Antioxidant (DPPH) Anticancer (Hfb-4, HEp-2, MCF-7 cell lines) activity	Abdelhakim *et al.*, (2020)
Ulva lactuc		Photocatalytic, antibiofilm and insecticidal activity	Ishwarya *et al.*, (2018)
Andrographis paniculata		Antioxidant (DPPH, nitric oxide scavenging) activity	Rajakumar *et al.*, (2018)
Lotus leguminosae.	Au	Antioxidant (DPPH) and anticancer (MCF-7) activity	Oueslati *et al.*, (2018)
Sargassum muticum		Antioxidant (Reducing power and DPPH assay)	González-Ballesteros *et al.*, (2020)
Curcuma pseudomontana		Antioxidant & anti- inflammatory activity	Muniyappan *et al.*, (2021)
Vitex negundo		Anti-inflammatory (COX-2, lipoxygenase & xanthine oxidase inhibitory) activity	Sunayana *et al.*, (2020)
Annona muricata		Anticancer activity (Hep2 cell lines	Priya *et al.*, (2020)

Fig.1 Mechanism of biosynthesis of nanoparticle from plant bioresources

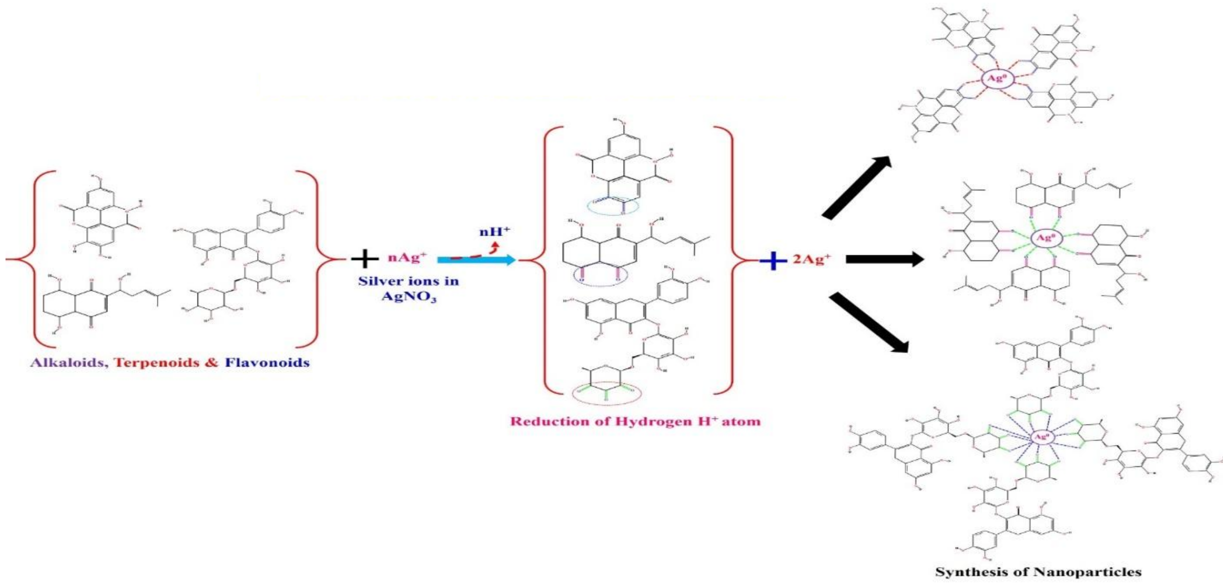


Fig.2a Schematic diagram of phytosynthesis of different nanoparticles and its biomedical applications

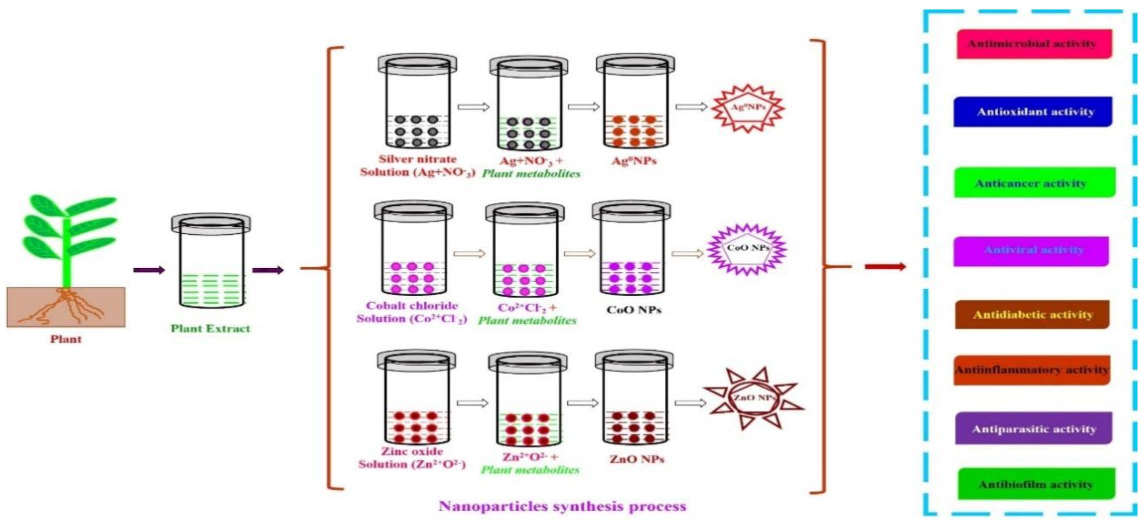
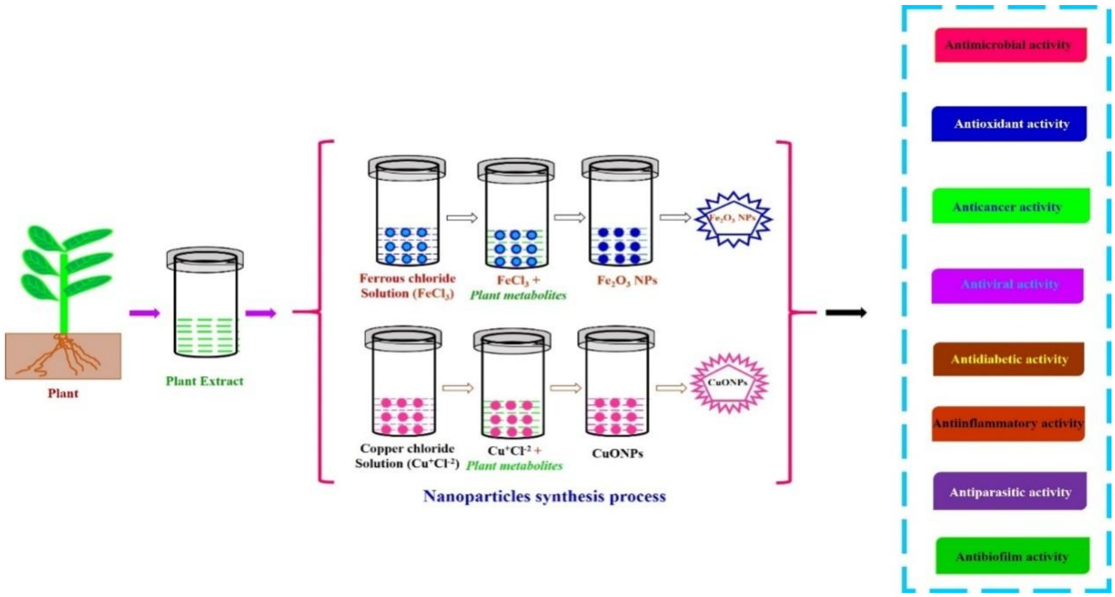


Fig.2b Schematic diagram of phytosynthesis of different nanoparticles and its biomedical applications



Sharmila *et al.,* (2018) portrayed cytotoxic efficacy of green synthesized ZnONP's from the leaf extract of *Tecoma castanifolia* by MTT assay using laboratory condition. They noticed the cytotoxic effects of ZnONPs on A549 cell line expressed the highest percentage (86%) of cell inhibition with IC_{50} value of 65µg/ml. Sunderam *et al.,* (2018) observed the anticancer activity of AuNPs of *Anacardium occidentale* through MTT assays using PBMC and MCF-7 cell lines with the inhibition percentage of 80.3 and 71.5% with the IC_{50} values of 600µg/ml respectively for both cell lines. The maximum inhibition percentage (86%) with 44.91µg/ml of IC_{50} value against MCF7 cell line were attained by using phytosynthesized NiONPs of *Andrographis paniculata* through MTT assay (Karthik *et al.,* 2018). Venugopal *et al.,* (2017) postulated the cytotoxicity efficacy of silver nanoparticle (10 – 100µg/ml) of *Syzygium aromaticum* using MCF-7 and A549 cell lines by MTT assay. They also displayed inhibitory concentrations (IC_{50} value) of phytosynthesized AgNPs was found to be 60 and 50µg/ml respectively against MCF7 and A549 cell lines. Rameshthangam and Chitra (2018) investigated the anticancer activity of phytosynthesized nickel nanoparticles from *Ocimum sanctum* by MTT assay using MCF-7 cell line expressed the percentage of cell viability was gradually decreased (88%, 72%, 50%, 42%, 33% and 12%) while increasing the concentration of nanoparticles (1.56, 3.12, 6.25, 12.5, 25 and 50µg/ml) along with the IC_{50} value of 6.25µg/ml. Awad *et al.,* (2019) achieved the maximum inhibition percentage (84, 87 and 92%) with the IC_{50} values 45.5, 37.2 and 40.6µg/ml were respectively obtained against MCF-7, HCT-116 and HCepG-2 cell lines using AuNPs of *Olea europaea* under *in-vitro* conditions. The cytotoxic effect of green synthesized ZnONPs of *D. tortuousa* expressed the maximum percentage of inhibition 84 and 87% with the IC_{50} values of 193.12 and 136.12µg/ml respectively against Caco-2 and A549 cancer cell lines were achieved by Selim *et al.,* (2020). These review article clearly indicates that the phytosynthesized nanoparticles are highly safe and their application can be extended as efficient anticancer agents for pharmaceutical applications.

Nanoparticles as an anti-inflammatory agent

Govindappa *et al.,* (2018) studied the *in-vitro* anti-inflammatory property of green synthesized AgNPs from leaves extract of *Calophyllum tomentosum* through albumin denaturation method. Singh *et al.,*

(2018) demonstrated *in-vitro* anti-inflammatory efficacy of biosynthesized AgNPs and AuNPs from fruit extract of *Prunus serrulata* expressed the inhibitory percentages of 84 and 79% at 500µg/ml of concentration respectively. In an another study, Mohammad *et al.,* (2019) evaluated the anti-angiogenesis, anti-inflammatory and cytotoxicity properties of green synthesized ZnONP's under laboratory condition. They also investigated the inflammatory genes (IL-1B and IL-10) through real-time quantitative polymerase chain reaction technique. Alkhalaf *et al.,* (2020) achieved the anti-inflammatory activity of AgNPs of *Nigella sativa* through egg albumin denaturation process, which expressed the maximum inhibition percentage of 79% at 400µg/ml of concentration. Similarly, Sharifi-Rad, *et al.,* (2020) reported the *in-vitro* anti-inflammatory activity of AgNPs from root extract of *Astragalus tribuloides* with the maximum percentage of inhibition (82%) was observed at 500µg/ml of concentration. Sharifi-Rad *et al.,* (2020) attained the anti-inflammatory effect of phytosynthesized AgNPs from the root extract of *Astragalus tribuloides* showed the maximum percentage of inhibition (82%) at 450µg/ml concentration. Likewise, green synthesized AuNPs from *Curcuma pseudomontana* showed the maximum inhibition efficiency of 94% was attained by Muniyappan *et al.,* (2021). However, this study expressed that the phytosynthesized nanoparticles showed as efficient anti-inflammatory property.

Nanoparticles as an antidiabetic agent

Diabetes mellitus is a chronic metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. This problem was overcome by influencing various nanoparticles and these are analyzed by various researchers. Daisy and Saipriya (2012) studied the anti-diabetic property of gold nanoparticles by using mice under laboratory condition. Further, they also confirmed the nanoparticle as a promising agent in the treatment of hyperglycemia respectively compared with streptozotocin-induced mice. Bala *et al.,* (2015) studied the anti-diabetic activity of green synthesized ZnONPs from *Hibiscus subdariffa* exhibited better activity than streptozotocin (STZ) induced diabetic mice. Who also observed the function of Th1, Th2 cells and expressions of insulin receptors, subsequently, the other genes of pancreas associated with diabetes.

In an another study, the antidiabetic ability of biosynthesized AgNPs of *Lonicera japonica* showed highly effective inhibition (79 and 84%) against carbohydrate digestive enzymes like α-glucosidase and α-amylase with 37.86 and 54.56µg/ml IC_{50} values respectively were observed by Balan *et al.,* (2016). Bagyalakshmi and Haritha (2017) studied the green synthesis and characterization of AgNPs using *Pterocarpus marsupium* and assessed its *in-vitro* antidiabetic activity through α- amylase inhibition assay. Rijuta *et al.,* (2018) described the antidiabetic activity of phytosynthesized AgNP's by using *Punica granatum* showed effective inhibition (80 and 86%) against α-amylase and α-glucosidase with the IC_{50} values of 65.2 and 53.8µg/ml, respectively. The *in-vitro* antidiabetic activities of green synthesized silver nanoparticles from *Allium cepa* showed higher level of α-amylase (69%) and α-glucosidase (79%) inhibitory activities (Jini and Sharmila, 2020).

Nanoparticles as an antibiofilm agent

Nanoparticles can also able to detach and inhibition of the biofilm forming bacteria from the substratum. The phytosynthesized AgNPs of *Psidium guajava*was effectively inhibit the growth of biofilm forming bacteria such as *S. aureus* (67%), *E. coli* (80%) and *C. albicans* (79%) under laboratory condition through crystal violet assay by Shabhika *et al.,* (2014). In an another report, Ali *et al.,* (2015) reported anti-biofilm activity of green synthesized AgNPs from the leaves extract of *Eucalyptus globulus* expressed the highest percentage of growth inhibition (84%) was observed against *P. aeruginosa* and 83% of inhibition against *S. aureus*. Gopinath *et al.,* (2016) performed the anti-biofilm activity of green synthesized Ag, Au and Ag/Au bimetallic nanoparticles from the leaf extract of *Gloriosa superba* through laboratory condition. They also stated the obtained NPs exhibited maximum anti-biofilm activity against various gram-positive and gram-negative bacteria. Erci and Torlak (2019) reported the anti-biofilm efficacy of phytosynthesized AgNPs from aqueous leaf extract of *Thymus serpyllum* showed the highest percentage of inhibition (73%) against *S. aureus* at 100µg/mL concentration. Bharathi *et al.,* (2018) documented the anti-biofilm activity of green synthesized silver nanoparticles from fruit extract of *Cordia dichotoma* showed the maximum percentage (90%) of growth inhibition of biofilm forming bacteria like *S. aureus* and *E. coli* respectively. Mohanta *et al.,* (2020) documented the anti-biofilm efficiency of phytosynthesized silver nanoparticles of *Semecarpus anacardium* showed highest activity against various biofilm forming bacteria *P. aeruginosa* (15mm), *E. coli* (20mm), and *S. aureus* (18mm). The different phytosynthesized nanoparticles from various plant origin exhibited as efficient anti-biofilm activity.

Pros and cons of nanotechnology

A wide range of plant bioresources are used in the production of nanoparticles that have remarkable therapeutic effects in the bio-therapeutic field, as a consequence of their ability to synthesize nanoparticles. A major impact that nanotechnology have on medicine in many decades to come will be the development of nanotechnology. There is a major point that needs to be addressed for further technological advancement in the field of nanomaterials. This point has been addressed in the research currently being carried out. The development of commercially viable nanoparticles requires the solution of a number of challenges. In order to produce bioresource nanoparticles in a cost-effective manner, using reproducible, biocompatible, and stable processes, it is now necessary to use cost-effective methods.

From this review, it could be concluded that the phytosynthesis of nanomaterials has been a vast effective and permissible research field over the past decade. The synthesis if nanoparticles from the plant resources are eco-friendly, no-toxicity, inexpensive and does not need any special conditions compared to the other biological agents like bacteria, fungi, and algae etc. Using plant resources for nanoparticle biosynthesis can be have numerous advantageous over other biological processes, because it eliminates the elaborate process of maintaining cell cultures and can also be suitably scaled up for large-scale production of nanoparticles. This review article represents the phytosynthesized nanoparticles are highly emphasised and extensively used in biomedical field as an antibacterial, antifungal, anti-parasitic, antiviral agent and also have antioxidant, anticancer, anti-inflammatory, antidiabetic activities than the other mediated nanoparticles production. Accordingly, the phytosynthesized nanoparticles are more acceptable as a biomedical agent.

Acknowledgement

The authors are gratefully acknowledged the Management and the Principal of K.R. College for their moral support. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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How to cite this article:

Muthusamy Sanjivkumar, Kasilingam Nagajothi, Tamilselvan Silambarasan, Sylvester Sayen Merlin Sophia and Alagarsamy Parameswari. 2023. A Review on Phytosynthesis of Nanoparticles and its Biomedical Applications: An Ecofriendly Approach. *Int.J.Curr.Microbiol.App.Sci.* 12(02): 148-166.
doi: https://doi.org/10.20546/ijcmas.2023.1202.015