GREEN SYNTHESIS OF PLANT-MEDIATED METAL NANOPARTICLES: THE ROLE OF POLYPHENOLS

LATIF MS, ABBAS S, KORMIN F*, MUSTAFA MK

Department of Technology and Natural Resources, Faculty of Applied Sciences and Technology, Universiti Tun Hussein Onn Malaysia
Kampus Pagoh, KM1, Jalan Panchor, 84000 Muar, Johor, Malaysia. Email: faridahk@uthm.edu.my

ABSTRACT

The use of metal nanoparticles (MNs) in various fields is increasing day-by-day leading to a genuine concern about the issues related to their environmental and biological safety. The major approaches for the synthesis of MNPs include physical and chemical methods which are expensive and hazardous to health in addition to being toxic to the environment. This review highlights the potential of plant extracts to carry out the synthesis of MNPs with a special emphasis on the role of flavonoids in nanosynthesis. This green and clean approach have been actively utilized in recent years as an alternative to conventional hazardous approaches. It has proved as cost-effective, non-toxic, less time and labor consuming, efficient, and eco-friendly method for the synthesis of MNPs with specific biological actions. This review also focuses on the role of polyphenols, including the flavonoids as bioreductants of metal salts for the synthesis of MNPs along with their biomedical applications. Various examples of the MNPs, along with their biological actions, have also been summarized.

Keywords: Green synthesis, Metal nanoparticles, Polyphenols, Flavonoids, Plant extract.

INTRODUCTION

The synthesis of nanoparticles (NPs) can be performed using different methods, including physical, chemical, and biological techniques [1]. The NP synthesis by conventional physical and chemical techniques carries the risk of toxicity and environmental pollution as they release toxic by-products, which are potentially hazardous to the environment [2]. In addition to it, the NPs synthesized by such hazardous methods are unfit for the medical field due to the health-related concerns, particularly in clinical applications [3].

Although the conventional methods are suitable for the synthesis of large quantities of particles, in a lesser period of time, with defined sizes and shapes, these techniques have the drawbacks of being complicated, costly, inefficient, and out fashioned. The recent years have witnessed a growing interest in the nanosynthesis of environment-friendly particles without involving the production of toxic by-products as part of the synthesis process [4-6].

This task is achievable only through adopting environment-friendly synthesis procedures using biotechnology tools of biological nature that is described as safe and environmentally benign for nanosynthesis as an alternative to conventional physical and chemical methods [7,8]. This concept has led to the approach of green technology or green nanobiotechnology. In general, the nanosynthesis procedures involving biological routes such as those which are based on microorganisms (viruses, bacteria, fungi, and algae), plants, plant extracts, or their by-products, for example, proteins, lipids, alkaloids, and flavonoids by applying different biotechnology tools and techniques [9,10]. A graphical summary of plant-based NP synthesis is shown in Fig. 1. The superiority of NPs synthesized by green technology to those produced by conventional methods is quite evident due to several features. For instance, green technology employs the use of cost-effective chemicals, less energy, and produces eco-friendly products, and by-products. The nanobiotechnology is more advantageous over other conventional procedures due to the fact the more components are available by the biological system for the synthesis of NPs [11,12]. By virtue of the rich biodiversity of biological systems, it is now possible to synthesize the bio-nanomaterials which are environment-friendly and have the potential to use in a variety of medical applications. Due to the synthesis of environment-friendly chemical products and by-products, the 12 principles of green chemistry are now considered as a reference guide in related research around the world [13]. Consequently, the green nanobiotechnology has now become a promising alternative route for the synthesis of biocompatible and stable NPs [14,15]. In context to the importance of polyphenols including flavonoids of plant extracts in mediating the synthesis of metal NPs (MNPs), this review attempts to highlight and summarize the role of polyphenols in the synthesis of MNPs as described in recent literature.

Biosynthesis of NPs uses a bottom-up approach in which synthesis is performed by the application of reducing and stabilizing agents [16]. There are three main factors which are described for the biosynthesis of NPs based on a biological system: The choice of solvent medium, the choice of an eco-friendly and environmentally benign reducing agent, and the choice of a nontoxic material as a capping agent to stabilize the synthesized NPs [6].

BIOLIGICAL NANOSYNTHESIS AND ITS APPLICATIONS

In contrast to the physical and chemical methods of nanosynthesis, the biological nanosynthesis relies on the use of microorganisms (bacteria and fungi), enzymes, and plants to produce MNPs [17] (Table 1).

There are numerous examples of a variety of applications of the MNPs in the fields of biomedicine, physicochemistry, agriculture, and environment [9,18], as shown in Fig. 2.

PLANT-BASED NANOMATERIALS

The plant resources based green synthesis of a number of MNPs including copper (Cu), gold (Au), nickel (Ni), platinum (Pt), titanium (Ti), selenium (Se), silver (Ag), and zinc NPs have already been reported [19,20]. The plant-based MNPs have been shown to possess various activities such as antimicrobial, anticancer, anti-diabetic, anti-inflammatory, antioxidant, and immunomodulatory [21-24]. In recent
reviews, the MNPs synthesis using various plant extracts has been reported for cobalt, copper, gold, magnetite, platinum, palladium, and zinc oxide which have been proved as a potent remedy against a variety of infectious diseases along with other acute ailments [19,25]. The role of various phytochemicals such as alkaloids, flavonoids, phenols, sugars, proteins, and terpenoids has been confirmed in most of the previous reports emphasizing their involvement in the bioreduction, capping, and stabilization of metal ions [26,27].

Despite the ease involved in the purification of NPs synthesized using only one single active substance in plant extract, it is important to further study the MNPs with a biomedical perspective for the treatment of particular diseases. At present, limited information is available in the scientific literature regarding the use of a single substance from plant extract for the synthesis of MNPs. Recent reports in literature on this issue show that the flavonoids which have a wide existence in the plant extracts have a major contribution toward the bioreduction, capping, and stabilization of metal ions into NPs formation [28-31].

Plant extracts-mediated synthesis of NPs
To prepare the plant extract, different parts of the plants are used as fresh or dry material such as the fruit, leaf, peel, petal, and shoot. The extraction procedure usually involves soaking the plant material in a green solvent with or without stirring followed by filtration and centrifugation. The filtered extract is rich in the reducing and capping agents required for the bioreduction of metallic ions. The advantage of using dried plant is that it has a long shelf life at room temperature, but it is important to store the fresh plant at −20°C to avoid any deterioration. In addition, the use of dry plant material ensures the elimination of effects of seasonal variations leading to variations in plant constituents [32,33].

Various factors such as temperature, concentrations of the extract, and the metal ions and pH may affect the size and shape of the synthesized NPs [34]. The plant extract based synthesis procedures usually have

Table 1: Methods of nanoparticle synthesis

| Physical | Chemical | Green/biological |
|----------|----------|------------------|
| Mechanical methods | Coprecipitation | Plant extracts-mediated |
| Vapor deposition | Sol-gel | Microbial culture-mediated |
| Sputter deposition | Microemulsions | Agricultural waste-mediated |
| Electric deposition | - | Enzymes-mediated |
| Ion beam method | - | - |
a high rate of reaction, taking several minutes to several hours for completion, depending on the type and amount of the plant extract. Most plants, especially the perennial plants, are almost always naturally available. Usually, the plant extract-based synthesis of metallic NPs is carried out at room temperature, whereas heating of the reaction mixture or culture medium is required for the synthesis of metallic NPs using microorganisms. Due to the ease of handling and flexible reaction conditions, plant extract-mediated synthesis of MNPs is considered as more suitable for large-scale production as compared to microorganisms-based nanosynthesis [5,35,36].

Polyphenols and flavonoids-based MNPs and their biomedical applications

The detail of polyphenols and flavonoids employed in the synthesis of MNPs along with their biomedical efficacy is summarized in Table 2. Recently, it was reported that the major contribution for the synthesis of silver NPs (AgNPs) was of the total flavonoids present in the *Alternanthera tenella* and *Coriandrum sativum* leaf extracts [7]; and shown to be efficacious as antiacne, antidandruff, and anti-breast cancer agent as they were found active against *Propionibacterium acnes*, *Malassezia furfur*, and human breast adenocarcinoma cells, respectively [28,29].

The bioreduction of Ag⁺ to AgNPs was carried out by the water-soluble flavonoids present in *Myrmecodia pendan* extract [37]. It was inferred that the flavonoids of *Dalbergia spinosa* leaf extract may be adsorbed onto the metal ions surface by interacting with carbonyl groups or electrons, thereby exhibiting increased anti-inflammatory, and antibacterial (against *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*) activities [38]. The flavonoids functionalized clove buds extract mediated AuNPs were reported to possess the anticancer activity against various cancer cells [39].

**Mechanisms of flavonoids-mediated NP synthesis**

There are some studies which proposed the plausible mechanism for polyphenols-mediated the synthesis of MNPs, as shown in Table 2. It was proposed that the hydroxyl groups present in the B and C rings of kaempferol participated in the AuNPs synthesis [76,112]. Moreover, the radical scavenging activity of NPs may be attributed to the A ring of kaempferol coating the surface of AuNPs. It was described that the formation of the enol form of luteolin, releasing reactive hydrogen, may be responsible for the reduction of Ag⁺ to Ag⁰ [113].

It was proposed that the dihydromyricetin (DMY)-mediated synthesis of AuNPs occurred through the oxidation of hydroxyl to carbonyl groups. The study reported a shifting in the stretching vibration of the hydroxyl groups of DMY to higher wavenumber after bioreduction of Ag, which indicated the possible participation of hydroxyl in the reaction. In addition, there was a shift in the stretching vibration of carbonyl groups to lower wavenumber due to the oxidation of hydroxyl groups leading to the intramolecular hydrogen bonding [64].

Quercetin was found to chelate at three positions involving the carbonyl and hydroxyl groups at the C3 and C5 positions and the catechol group at the C3′ and C4′ positions. These groups were proposed to chelate different metal ions by the following steps: (1) Adsorption onto the metal surface, (2) budding of NP, (3) aggregation, and (4) bioreduction [59]. The possible mechanism for genistein AuNPs was proposed as follows: (1) Transfer of the electron from genistein into the Au center, (2) reduction of the Au³⁺ to Au⁰ by genistein, and (3) further acted as a stabilizing agent to form a layer of negative ions leading to the formation of the AuNPs [71].

The work of Kasthuri et al. [47] revealed that the reduction of Au³⁺/Ag⁺ ions occurred in a 2-step reaction involving the reduction by hydroxyl groups of the apin followed by the oxidation of hydroxyl groups.
Table 2: Mechanism of synthesis and applications of MNPs

| Source                        | MNP (size)       | Mechanism                                                                 | Application                    | Reference |
|-------------------------------|------------------|---------------------------------------------------------------------------|--------------------------------|-----------|
| Abutilon indicum (Polyphenols) | AuNPs (1–20 nm) | Hydroxyl and carbonyl groups of polyphenols mediated bioreduction of Au metal ions | Anticancer                     | [40]      |
| Acacia rigidula (Phenolic compounds) | AgNPs (8–66 nm) | Hydroxyl groups of polyphenols mediated bioreduction of Ag metal ions | Antibacterial                  | [41]      |
| Acalypha indica (Phenolic compounds) | AgNPs (20–30 nm) | Hydroxyl groups of polyphenols mediated bioreduction of Ag metal ions | Antibacterial                  | [42]      |
| Achyranthes aspera (Phenolic compounds) | AgNPs (7–14 nm) | Hydroxyl groups of polyphenols mediated bioreduction of Ag metal ions | Larvicidal against mosquito    | [43]      |
| Allium sativum (Phenolic compounds) | AgNPs (3–6 nm) | Hydroxyl groups of polyphenols mediated bioreduction of Ag metal ions | Antibacterial                  | [44]      |
| Alpinia calcarata (Phenolic compounds) | AgNPs (20–30 nm) | Hydroxyl groups of polyphenols mediated bioreduction of Ag metal ions | Antioxidant                    | [45]      |
| Andean blackberry (Flavonoids) | AgNPs (7–14 nm) | Hydroxyl groups of flavonoids mediated bioreduction of Ag metal ions | Antibacterial                  | [46]      |
| Apiin (Apigenin glycoside) (Phenolic compounds) | AuNPs (21 nm) | Apiin hydroxyl groups-mediated reduction of metal ions and subsequent formation of carbonyl groups that bind to metal ions leading to apiin coated NPs | Anticancer                     | [47]      |
| Azadirachta indica (Phenolic compounds) | AgNPs (34 nm) | Hydroxyl groups of polyphenols mediated reduction of Ag metal ions | -                              | [48]      |
| Baicalein (Phenolic compounds) | AgNPs (26.5 nm) | Hydroxyl groups of baicalein mediated reduction of Ag metal ions - | Antibiofilm activity against P. aeruginosa | [49]      |
| Brassica oleracea (Flavonoids) | AgNPs (24 nm) | Hydroxyl groups of polyols-mediated reduction of Ag metal ions | Cytotoxicity                   | [50]      |
| Butea monosperma (Polyphenols) | AgNPs (12–50 nm) | Hydroxyl groups of polyphenols/protein-mediated reduction of Au metal ions | Anticancer                     | [51]      |
| Cassia fistula (Flavonoids, polyphenols) | ZnNPs (5–15 nm) | Hydroxyl groups mediated reduction of Si metal ions | Dye reduction                  | [52]      |
| Catechin (Phenolic compounds) | c-SiNPs | Hydroxyl groups mediated reduction of Si metal ions | Enhanced antioxidant activity and hippocampal cell survival | [53]      |
| Centella asiatica (Phenolic compounds) | AuNPs (20–140 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Au metal ions | Antiproteasome                 | [54]      |
| Citrus maxima (Flavonoids, phenolic compounds) | AuNPs (15–35 nm) | Hydroxyl and amide groups mediated reduction of Au metal ions | Catalytic dye reduction        | [55]      |
| Citrus sinensis (Flanolic compounds) | AgNPs (10–35 nm) | Hydroxyl groups of polyphenols mediated reduction of Ag metal ions | Anticancer against cancer of the human cervix, human chronic myelogenous leukemia, human colorectal adenocarcinoma, and human renal carcinoma | [56]      |
| Coleus aromaticus (Phenolic compounds) | AgNPs (44 nm) | Hydroxyl groups of polyphenols mediated reduction of Ag metal ions | Antiacne (Propionibacterium acnes), antidiandruff (Malassezia furfur) and anticancer against human breast cancer | [57]      |
| Coriandrum sativum (Flavonoids) | AgNPs (37 nm) | Hydroxyl groups mediated reduction of Ag metal ions | -                              | [58]      |
| Coriandrum sativum (Luteolin) (Flavonoids, phenolic compounds) | AgNPs (13 nm) | Conversion of Ag⁺ to Ag⁰ by the freely released reactive hydrogen from the enol form of luteolin. | Antibacterial against B. subtilis | [59]      |
| Curcuma longa (Phenolic compounds) | AgNPs (58 nm) | Hydroxyl groups of polyphenols mediated reduction of Ag metal ions | -                              | [60]      |

(Contd...)
Hydroxyl/carbonyl groups mediated reduction of Au
Catalytic dye reduction

Antibacterial

AuNPs

AgNPs

AuNPs

AgNPs

AuNPs

AgNPs

AgNPs

AgNPs

AgNPs

AgNPs

Table 2: (Continued)

| Source | MNP (size) | Mechanism | Application | Reference |
|--------|------------|-----------|-------------|-----------|
| Dalbergia spinosa (Flavonoids) | AgNPs (18 nm) | Interaction of carbonyl groups or electrons with the metal surface | Anti-inflammatory activity. | [38] |
| Decalepis hamiltonii (Phenolic compounds) | AgNPs | Hydroxyl groups of flavonoids and phenolic compounds mediated reduction of Ag metal ions | Antibacterial | [62] |
| Delonix regia (Polyphenols) | AuNPs (2-4 nm) | Hydroxyl/carbonyl groups mediated reduction of Au metal ions | - | [64] |
| Dioscorea bulbifera (Phenolic compounds) | AgNPs (6-20 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Synergism with antibacterial agents | [65] |
| Durio zibethinus (Phenolic compounds) | AgNPs (20-72 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Antioxidant | [66] |
| Ecklonia cava (Phenolic compounds) | AgNPs (43 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Antioxidant | [67] |
| Epicatechin and Theaflavin (Flavonoids, phenolic compounds) | AgNPs (31 nm) | Carboxyl groups mediated bioreduction of AgNO3 leading to synthesis and stabilization of AgNPs | Antibacterial against human epidermoid larynx carcinoma cells | [68] |
| Erythrina suberosa (Phenolic compounds) | AgNPs (15-34 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Antimicrobial | [69] |
| Galenia africana (Flavonoids, phenolic compounds) | AuNPs | Hydroxyl/carbonyl groups mediated reduction of Au metal ions | Anticancer | [70] |
| Genistein | AuNPs (64.64 nm) | Reduction of Au3+ to Au0 by the transfer of an electron from genistein leading to the formation of AuNPs by stabilizing them with a layer of negative ions | Antibacterial against human epithelial lung carcinoma and melanoma cells | [71] |
| Gloriosa superba leaf extract | Ag/Au (20 nm) | - | Antibacterial | [72] |
| Glycyrrhiza glabra (Phenolic compounds) | AgNPs (9 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Antimicrobial | [73] |
| Glycyrrhiza uralensis (Phenolic compounds) | AgNPs (8 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag and Au metal ions | Antimicrobial | [74] |
| Hybanthus enneaspermus (Phenolic compounds) | AgNPs (16-26 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Catalytic dye reduction | [75] |
| Hypoxis hemerocallidea (Flavonoids, phenolic compounds) | AuNPs | Hydroxyl/carbonyl groups mediated reduction of Au metal ions | Larvicidal against mosquito | [70] |
| Kaempferol | AuNPs (16.5 nm) | Hydroxyl Groups B and C rings of kaempferol mediated the synthesis of k-AuNPs | Antibacterial against human breast cancer | [76] |
| Lawsonia inermis (Phenolic compounds) | CuNPs | - | - | [77] |
| Lantana camara (Phenolic compounds) | AgNPs (2.3-30 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Antibacterial catalytic dye reduction | [78] |
| Lilium casa blanca (Flavonoids rich extract) | AuNPs (9-13 nm) | Hydroxyl/carbonyl groups mediated reduction of Au metal ions | Catalytic dye reduction | [79] |
| Luma apiculata (Phenolic compounds) | FeONPs (7-13 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Fe metal ions | Photocatalytic dye reduction | [80] |
| Mimusops elengi (Phenolic compounds) | AgNPs (12-30 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Antioxidant | [81] |
| Morinda citrifolia L (Phenolic compounds) | AgNPs (10-60 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Antimicrobial | [82] |
| Myrtus communis (Phenolic compounds) | FeNPs (20-40 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Fe metal ions | Antioxidant | [83] |
| Nigella arvensis (Phenolic compounds) | AgNPs (2-15 nm) | Hydroxyl groups mediated reduction of Ag metal ions | Antimicrobial | [84] |
| Ocimum sanctum (Phenolic compounds) | AgNPs (18 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Antioxidant | [85] |

(Contd...)
### Table 2: (Continued)

| Source | MNP (size) | Mechanism | Application | Reference |
|--------|------------|-----------|-------------|-----------|
| Potentilla fulgens (Flavonoids) | AgNPs (10–15 nm) | Hydroxyl, carbonyl, and amide groups mediated reduction of Ag metal ions | Anticancer against human breast cancer and human glioblastoma cancer cells | [86] |
| Pueraria tuberosa [Flavonoids/phenolic compounds] | AgNPs (1.62 nm) | Hydroxyl groups of flavonoids/phenolic compounds mediated reduction of Ag metal ions | Antioxidant | [88] |
| Pulicaria glutinosa (Phenolic compounds) | AgNPs (40–60 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Anticancer | [89] |
| Panica granatum (Flavonoids, phenolic compounds) | AgNPs (40–70 nm) | Hydroxyl groups of flavonoids/polyphenols mediated reduction of Ag metal ions | Anticancer | [90] |
| Quercetin | Ag-SeNPs (30–35 nm) | Hydroxyl/carbonyl groups mediated reduction of Ag/Se metal ions | Antioxidant, antimicrobial, and anticancer activities | [91] |
| Quercus brantii (Flavonoids/polyphenols) | AgNPs (6 nm) | Hydroxyl groups of flavonoids/polyphenols mediated reduction of Ag metal ions | - | [92] |
| Ranunculus muricatus (Flavonoids) | Au/TiO2 (50–90 nm) | Hydroxyl groups interact with metal ions through a covalent bond | Antibacterial against S. aureus and E. coli | [93] |
| Rosmarinus officinalis (Phenolic compounds) | AgNPs (10–30 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Antimicrobial | [94] |
| Salacia chinensis (Phenolic compounds) | AgNPs (40–80 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Anticancer | [95] |
| Satureja intermedia (Phenolic compounds) | AgNPs (28 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Antioxidant | [96] |
| Sesbania grandiflora (Flavonoids, polyphenols) | AuNPs (7–34 nm) | Hydroxyl/carbonyl groups mediated reduction of Au metal ions | Catalytic dye reduction | [97] |
| Siberian ginseng | AgNPs (126 nm) | Hydroxyl groups of polyphenols mediated reduction of Ag metal ions | Antimicrobial | [98] |
| Sterculia acuminata (Polyphenols) | AuNPs (9–38 nm) | Hydroxyl groups of polyphenols mediated reduction of Au metal ions | Catalytic dye reduction | [99] |
| Swertia monica (Phenolic compounds) | AuNPs (3–25 nm) | Hydroxyl groups of polyphenols mediated reduction of Au metal ions | Antioxidant | [100] |
| Sunflower oil | AgNPs (50 nm) | Hydroxyl groups of polyphenols mediated reduction of Au metal ions | Anticancer | [101] |
| Syzygium cumini (Phenolic compounds) | AgNPs (20–60 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | Antibacterial | [102] |
| Syzygium cumini (Phenolic compounds) | AgNPs (30–92 nm) | Hydroxyl groups of phenolic compounds mediated reduction of Ag metal ions | - | [103] |
| Syzygium samarangense (Polyphenols) | AgNPs (80–120 nm) | Hydroxyl groups of polyphenols mediated reduction of Au metal ions | - | [104] |
| Tamanduia indica (Phenolic compounds) | AuNPs (52 nm) | Hydroxyl/carboxylic groups mediated reduction of Au metal ions | - | [105] |
| Tea extract (Phenolic compounds) | AuNPs (8–24 nm) | Hydroxyl groups of polyphenols mediated reduction of Ag metal ions | Catalytic dye reduction | [106] |
| Tephrosia tinctoria (Flavonoids) | AgNPs (<100 nm) | Hydroxyl/carboxylic groups mediated reduction of Au metal ions | Anti-diabetic | [107] |
| Terminalia arjuna (Polyphenols) | AuNPs (20–50 nm) | Hydroxyl/carboxylic groups mediated reduction of Au metal ions | Enhancement of seed germination activity in G. superba | [108] |
| Terminalia catappa (Phenol) | AuNPs (10–35 nm) | Hydroxyl/carbonyl groups mediated reduction of Au metal ions | - | [109] |
| Walnut green husk (Polyphenols) | AgNPs (31.4 nm) | Hydroxyl groups of polyphenols mediated reduction of Ag metal ions | Antioxidant | [110] |
| Zingiber officinale (Phenolic compounds) | AgNPs (10–20 nm) | Hydroxyl groups of polyphenols mediated reduction of Ag metal ions | Anti-microbial | [111] |
groups to the carbonyl groups. Finally, the binding of carbonyl groups of alpin to the metal ion, thereby coating the NPs surfaces to prevent agglomeration. Most of these cited references from available literature give a clear indication that both the hydroxyl and the carbonyl groups of polyphenols collectively play a key role in the formation of MNPs.

Fig. 3 depicts the mechanism of polyphenols-based GNP synthesis. The adjacent hydroxyl groups of polyphenolic compounds from a 5-member chelate ring structure followed by oxidation of the chelated dihydroxy groups to quinones. Due to the high oxidation-reduction potential of Au(III), the quinones subsequently reduce the gold metal ions from Au(III) to Au(0). The synthesis of gold NPs occurs after a collision between the adjacent Au(0) atoms, and the NPs thus formed are stabilized by polyphenolic compounds including the quinones [114].

**CONCLUSION**

The emerging threats related to the toxic and hazardous nature of the conventional methods of NP synthesis have led to the plant extracts-mediated synthesis of MNPs. The green nanosynthesis approach thus adopted is cost and time effective, and environment-friendly with the potential to easily scale up the product. Such a non-toxic approach is especially desirable to synthesize the NPs that must not be toxic if they are destined for the therapeutic applications. The NPs of controlled size and shape can be synthesized using various plant extracts of which the polyphenols, including flavonoids, are considered as the most active bioreductants of metal ions. The MNPs synthesized using natural polyphenols and flavonoids have shown a number of biomedical applications, including their therapeutic activity against various ailments.

**ACKNOWLEDGMENT**

This study was financially supported by the Research Management Centre (RMC), Universiti Tun Hussein Onn Malaysia through TIER-1 Vot No. H256 and Geran Penyelidikan Pascasiswazah (GP3S) Vot No. U49/0.

**AUTHORS’ CONTRIBUTIONS**

All the authors of this review paper have contributed equally in retrieving, collecting, and compiling the data as well as writing and proofreading of the manuscript.

**CONFLICTS OF INTEREST**

The authors declare that there are no conflicts of interest regarding the publication of this review paper.

**REFERENCES**

1. Zhang XF, Liu ZG, Shen W, Gurunathan S. Silver nanoparticles: Synthesis, characterization, properties, applications, and therapeutic approaches. Int J Mol Sci 2016;17:E1534.

2. Bundschuh M, Filser J, Lüderwald S, McKee MS, Metreveli G, Schaumann GE, et al. Nanoparticles in the environment: Where do we come from, where do we go to? Environ Sci Eur 2018;30:6.

3. Latif et al. Asian J Pharm Clin Res, Vol 7, Issue 7, 2019, 75-84

4. Saratale RG, Saratale GD, Shin HS, Jacob JM, Pugazhendhi A, Bhaisare M, et al. New insights on the green synthesis of metallic nanoparticles using plant and waste biomaterials: Current knowledge, their agricultural and environmental applications. Environ Sci Pollut Res Int 2018;25:10164-83.

5. Iravani S. Methods for preparation of metal nanoparticles. In: Thota S, Debbie CC, editors. Metal Nanoparticles: Synthesis and Applications in Pharmaceutical Sciences. USA: Wiley-VCH Verlag; 2018. p. 15-32.

6. Shah M, Fawcett D, Sharma S, Tripathy SK, Poinern GE. Green synthesis of metallic nanoparticles via biological entities. Materials (Basel) 2015;8:7278-308.

7. Sathishkumar P, Gu FL, Zhan Q, Palvannan T, Yussof AR. Flavonoids mediated ‘green’ nanomaterials: A novel nanomedicine system to treat various diseases current trends and future perspective. Mater Lett 2018;210:26-30.

8. Santhoshkumar J, Rajeshkumar S, Kumar SV. Phyto-assisted synthesis, characterization and applications of gold nanoparticles-a review. Biochem Biophys Rep 2017;11:46-57.

9. Singh P, Kim YJ, Zhang D, Yang DC. Biological synthesis of nanoparticles from plants and microorganisms. Trends Biotechnol 2016;34:588-99.

10. Ovais M, Khalil AT, Islam NU, Ahmad I, Ayaz M, Saravanam M, et al. Role of plant phytochemicals and microbial enzymes in biosynthesis of metallic nanoparticles. Appl Microbiol Biotechnol 2018;102:6799-814.

11. Ahmed S, Annu, Ikram S, Yudha SS. Biosynthesis of gold nanoparticles: A green approach. J Photochem Photobiol B 2016;161:141-53.

12. Fakruddin M, Hossain Z, Alfroz H. Prospects and applications of nanobiotechnology: A medical perspective. J Nanobiotechnology 2012;10:31.

13. de Marco BA, Rechelo BS, Tótoli EG, Kogawa AC, Salgado HR. Evolution of green chemistry and its multidimensional impacts: A review. Saudi Pharm J 2019;27:1-8.

14. Gilbertson LM, Zimmerman JB, Plata DL., Hutchinson JE, Anasat PT. Designing nanomaterials to maximize performance and minimize undesirable implications guided by the principles of green chemistry. Chem Soc Rev 2015;44:5758-77.

15. Kratošová G, Holišová V, Konvičková Z, Ingle AP, Gaikwad S, Škrlová K, et al. From biotechnology principles to functional and low-cost metal bionanocatalysts. Biotechnol Adv 2019;37:154-76.

16. Kalpana VN, Rajeswari VD. A review on green synthesis, biomedical applications, and toxicity studies of znO NPs. Bioinorg Chem Appl 2018;2018:3569758.

17. Das RK, Pachapaur VL, Lonappan L, Naghdī M, Pulicharla R, Maiti S, et al. Biological synthesis of metallic nanoparticles: Plants, animals and microbial aspects. Nanotechnol Environ Eng 2017;2:18.

18. Khan I, Saeed K, Khan I. Nanoparticles: Properties, applications and toxicities. Arabian J Chem 2017. Doi: 10.1016/j.arabjc.2017.05.011.

19. Kuppusamy P, Yussof MM, Maniam GP, Govindan N. Biosynthesis of metallic nanoparticles using plant derivatives and their new avenues in pharmacological applications-an updated report. Saudi Pharm J 2016;34:473-84.

20. Thakkar KN, Mhatre SS, Parmik RY. Biological synthesis of metallic nanoparticles. Nanomedicine 2010;6:257-62.

21. Reddy NJ, Nagoor Vali D, Rani M, Rani SS. Evaluation of antioxidant, antibacterial and cytotoxic effects of green synthesized silver nanoparticles by *Piper longum* fruit. Mater Sci Eng C Mater Biol Appl 2014;34:115-22.
22. Rehana D, Mahendiran D, Kumar RS, Rahiman AK. In vitro antioxidant and antidiabetic activities of zinc oxide nanoparticles synthesized using different plant extracts. Bioprocess Biosyst Eng 2017;40:433-57.

23. Fahmirsad R, Ajaloueeian F, Ghorbanpour M. Synthesis and therapeutic potential of silver nanomaterials derived from plant extracts. Ecotoxicol Environ Saf 2019;168:260-78.

24. Rao PV, Nallappan D, Madhavi K, Rahiman S, Jun Wei L, Gan SH, et al. Phytochemicals and biogenic metallic nanoparticles as anticancer agents. Oxid Med Cell Longev 2016;2016:368567.

25. Ovais M, Raza A, Naz S, Islam NU, Khalil AT, Ali S, et al. Current state and prospects of the photosynthesized colloidal gold nanoparticles and their applications in cancer theranostics. Appl Microbiol Biotechnol 2017;101:151-65.

26. Jayaprakash N, Vijaya J, Kaviyarasu K, Kombaiha K, Kennedy LJ, Ramalingam RJ, et al. Green synthesis of ag nanoparticles using tamarind fruit extract for the antibacterial studies. J Photochem Photobiol B 2017;169:65-74.

27. Khodadadi B, Bordbar M, Naseollahzadeh M. Green synthesis of pd nanoparticles at apricot kernel shell substrate using Salvia hydrangea extract: Catalytic activity for reduction of organic dyes. J Colloid Interface Sci 2017;490:1-10.

28. Sathishkumar P, Preeti J, Vijayan R, Mohd Yusof AR, Ameen F, Suresh S, et al. Anti-angiogenic, anti-dandruff and anti-breast cancer efficacy of green synthesized silver nanoparticles using Coriandrum sativum leaf extract. J Photochem Photobiol B 2016;163:69-76.

29. Sathishkumar P, Venmila K, Jayakumar R, Yusof AR, Hadaribia T, Thirumurugan T, et al. Phyto-synthesis of silver nanoparticles using Alternanthera tenella leaf extract: An effective inhibitor for the migration of human breast adenocarcinoma (MCF-7) cells. Bioprocess Biosyst Eng 2016;39:651-9.

30. Marslin G, Siram K, Macbqool P, Selvakesavan RK, Kruziska D, Kaelhlick P, et al. Secondary metabolites in the green synthesis of metallic nanoparticles. Materials (Basel) 2018;8:11940.

31. Jain S, Mehta MS. Medicinal plant leaf extract and pure flavonoid mediated green synthesis of silver nanoparticles and their enhanced antibacterial property. Sci Rep 2017;7:15867.

32. Ingle KP, Deshmukh AG, Padole DA, Dudhare MS, Moharil MP, Sathishkumar P, Preethi J, Vijaya JJ, Kaviyarasu K, Kombaiah K, Kennedy LJ, Rao PV, Nallappan D, Madhavi K, Rahman S, Jun Wei L, Gan SH, et al. Functionalization of metallic nanoparticles: A review of literature, factors affecting synthesis, characterization techniques and applications. J Environ Chem Eng 2017;5:4866-81.

33. Kumar V, Yadav SK. Plant-mediated synthesis of silver and gold nanoparticles and their applications. J Chem Biotechnol 2009;84:151-7.

34. Ahmed S, Ahmad M, Swami BL, Ikram S. A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications: A green expertise. J Adv Res 2016;7:17-28.

35. Zouas O, Hamim N, Sampora Y. Bio-synthesis of silver nanoparticles using Myristica esculenta leaf extract: An effective inhibitor for the migration of human breast adenocarcinoma (MCF-7) cells. J Photochem Photobiol B 2016;166:110-2.
Synthesis of silver nanoparticles using Dioscorea bulbifera tuber extract and evaluation of its synergistic potential in combination with antimicrobial agents. Int J Nanomedicine 2012;7:483-96.

66. Amitha V, Kavitha, Shalini S, Chinu SV, Gopinath SC, Anbu P, et al. Phyto-mediated photo catalysed green synthesis of silver nanoparticles using Durio zibethinus seed extract: Antimicrobial and cytotoxic activity and photocatalytic applications. Molecules 2018;23:3317.

67. Venkatesan J, Kim SK, Shim MS. Antimicrobial, antioxidant, and anticancer activities of biosynthesized silver nanoparticles using marine algae Ecklonia cava. Nanomaterials (Basel) 2016;6:235.

68. Satyavani K, Gurudeeban S, Ramanathan T, Balasubramanian T. Biomedical potential of silver nanoparticles synthesized from calli cells of Curcuma colosynthis (L.) schrad. J Nanobiotechnology 2011;9:43.

69. Mohanta YK, Panda SK, Jayabalran B, Sharma N, Bastia AK, Mohanta TK. et al. Antimicrobial, antioxidant and cytotoxic activity of silver nanoparticles synthesized by leaf extract of Erythrina suberosa (Kob). Front Mol Biosci 2017;4:14.

70. Elbagory A, Meyer M, Cupido C, Hussein A. Inhibition of bacteria associated with wound infection by biocompatible green synthesized gold nanoparticles from South African plant extracts. Nanomaterials (Basel) 2017;7.

71. Stolareczky EU, Stolareczky K, Laszez M, Kubiszewski M, Maruszak W, Olejarz W, et al. Synthesis and characterization of genistein conjugated with gold nanoparticles and the study of their cytotoxic properties. Eur J Pharm Sci 2017;96:176-85.

72. Gopinath SC, Sabarvanshi S, Bhakayamaly M, Mohan S, Venkatesh KS, Easakkiran J, et al. Green synthesis of gold, silver and gold/silver bimetallic nanoparticles using the Gloriosa superba leaf extract and their antibacterial and antiinfectious activities. Microb Pathog 2016;101:1-11.

73. Rodriguez-Luis OE, Hernandez-Delgadillo R, Sanchez-Najera RL, Martinez-Castanón GA, Niño-Martinez N, Navarro MC, et al. Green synthesis of silver nanoparticles and their bactericidal and antimycotic activities against oral microbes. J Nanomater 2016;2016:10.

74. Huo Y, Singh P, Kim YJ, Soshnikova V, Kang J, Markus J, et al. Biological synthesis of gold and silver chloride nanoparticles by Glycyrrhiza uralensis at room temperature evaluation of their stability and its larvicidal activity against human pathogens. Colloids Surf B Biointerfaces 2014;130:13-8.

75. Venkatesan J, Kim SK, Shim MS. Antimicrobial, antioxidant and cytotoxic activity and photocatalytic applications of gold nanoparticles using extracts of Syzygium samarangense cencephalum. Spectrochim Acta A Mol Biomol Spectrosc 2014;130:13-8.

76. Raghavan BS, Kondath S, Anantanarayanan R, Rajaram R. Kaempferol mediated synthesis of gold nanoparticles and the study of their antimicrobial and cytotoxic activities. J Phytochem Pharmacol 2016;8:43.

77. Rajavashisth D, Shukla S, Choudhary J, Jeet P, et al. Green synthesis of silver and gold nanoparticles using the aqueous extract of Ocimum sanctum leaves. J Photochem Photobiol B 2015:80:44-92.

78. Du J, Zhou Z, Zhang X, Wu S, Xiong J, Wang W, et al. Biosynthesis of gold nanoparticles by flavonoids from Citrullus colocynthis (L.) schrad. J Nanobiotechnology 2017;15:69.

79. Thaing RG, Reddy YA, Sharmer S, Rajkumar KS, Suneertha Y, Reddy PS, et al. Lantana camara leaf extract mediated synthesis of silver nanoparticles: Antibacterial, green catalyst. J Photochem Photobiol B 2015:80:44-92.

80. Salgado P, Mármol F, Contraseras D, Vidal G. The effect of phenolic compounds on the synthesis of iron nanoparticles (Fe3Oy-NPs) with photocatalytic activity. Appl Nanosci 2019;9:371.

81. Kumar HA, Mandal BK, Kumar KM, Maddinedi SB, Sai Kumar T, et al. Biosynthesis of silver nanoparticles using aqueous leaf extract of Pomegranate (Punica granatum) and their anticancer activity on human cervical cancer cells. Adv Nat Sci Nanosci Nanotechnol 2018;9:25014.

82. Mittal AK, Kumar S, Banerjee UC. Quercetin and gallic acid mediated synthesis of bimetallic (silver and selenium) nanoparticles and their antimicrobial and antiviral potential. J Colloid Interface Sci 2014;431:194-9.

83. KorbeKandi H, Chitsazi MR, Asghari B, Rahim NaJafi R, Badiai A, Irvani S, et al. Green biosynthesis of silver nanoparticles using Quercus brantii (oak) leaves hydroalcoholic extract. Pharm Biol 2015:53:807-12.

84. Tahir K, Ahmad A, Li B, Khan AU, Nazir S, Khan S, et al. Preparation, characterization and an efficient photocatalytic activity of Au/TiO2 nanocomposite prepared by green deposition method. Mater Lett 2016;178:56-9.

85. Ghadgi M, YoussefniaJad M, Safapour M, Khafrizy HZ, Parkaik M. Rosmarinus officinalis leaf extract mediated green synthesis of silver nanoparticles and investigation of its antimicrobial properties. J Carbohydr Polym 2015:86:503-13.

86. Mittal AK, Tripathy D, Choudhary A, Ali PK, Chatterjee A, Singh IP, et al. Bio-synthesis of silver nanoparticles using Potentilla fulgens wall. Ex hook. And its therapeutic evaluation in antinfective and antimicrobial agent. Mater Sci Eng C Mater Biop Appl 2015;53:120-7.

87. Vinodhini A, Govindaraju K, Singaravelu G, Sadiq AM, Kumar VG. Cardioprotective potential of biobased gold nanoparticles. Colloids Surf B Biointerfaces 2014;117:480-6.

88. Sarkar S, Kotteeswaran V. Green synthesis of silver nanoparticles from aqueous leaf extract of Pomegranate (Punica granatum) and their anticancer activity on human cervical cancer cells. Adv Nat Sci Nanosci Nanotechnol 2018;9:25014.

89. Mittal AK, Kumar S, Banerjee UC. Quercetin and gallic acid mediated synthesis of bimetallic (silver and selenium) nanoparticles and their antimicrobial and antiviral potential. J Colloid Interface Sci 2014;431:194-9.

90. Jadhav K, Deore S, Dhamemcha D, Rajeshwari HR, Jagwani S, Jalalpur S, et al. Phytosynthesis of silver nanoparticles: Characterization, biocompatibility studies, and anticancer activity. ACS Biomater Sci Eng 2018;4:892-9.

91. Konar A, Shajideh H, Prabhakaran D, Sheng I, et al. Green synthesis of silver nanoparticles with photocatalytic activity in the reduction of nitro compounds. J Mol Liq 2015;211:868-75.

92. Das J, Velusamy P. Catalytic reduction of methylene blue using biogenic gold nanoparticles from Seshonia grandiflora L. J Taiwan Inst Chem Eng 2016;45:880-5.

93. Abbal R, Madhialagan R, Markus J, Kim YJ, Wang C, Singh P, et al. Green synthesis of multifunctional silver and gold nanoparticles from the oriental herbal adaptogen: Siberian ginseng. Int J Nanomedicine 2016;11:3131-43.

94. Roygredy N, Ahmad A, Mandak BK. Gold nanoparticles-synthesis by Sterculia accuminata extract and its catalytic efficiency in alleviating different organic dyes. J Mol Liq 2015;211:868-75.

95. Rajathi FA, Arunagam R, Saravanar S, Annatharaman P. Phytotrfabrication of gold nanoparticles assisted by leaves of Suaeda monoca and its free radical scavenging property. J Photochem Photobiol B 2014;135:75-80.

96. Thakore S, Rathore PS, Jodeve RN, Thounaojam M, Devkar RV. Sunflower oil mediated biomimetic synthesis and cytotoxicity of monodisperse hexagonal silver nanoparticles. Mater Sci Eng C Mater Biop Appl 2014;44:289-15.

97. Prasad R, Swamy SV. Antibacterial activity of silver nanoparticles synthesized by bark extract of Syzygium cumini. J Nanopart Res 2013;2013:431218.

98. Kumar V, Yadav SC, Yadav SK. Syzygium cumini leaf and seed extract mediated biosynthesis of silver nanoparticles and their characterization. J Chem Technol Biotechnol 2010;85:1301-9.

99. Thomann N, Shalini JV. Bio-prospecting the in vitro antioxidant and anti-cancer activities of silver nanoparticles synthesized from the leaves of Syzygium samarangense cencephalum. Int J Pharm Pharm Sci 2015;7:268-74.

100. Correa SN, Naranjo AM, Herrera AP. Biosynthesis and characterization of gold nanoparticles using extracts of Tamarindus indica L leaves. J Phys Conf Ser 2016;687:12082.

101. Alegra EC, Ribeiro AP, Mendes M, Ferraria AM, do Rego AM, Pombiro AJ, et al. Effect of phenolic compounds on the synthesis of gold nanoparticles and its catalytic activity in the reduction of nitro
107. Rajaram K, Aiswarya DC, Sureshkumar P. Green synthesis of silver nanoparticle using Tephrosia tinctoria and its anti-diabetic activity. Mater Lett 2015;138:251-4.

108. Gopinath K, Gowri S, Karthika V, Arumugam A. Green synthesis of gold nanoparticles from fruit extract of Terminalia arjuna, for the enhanced seed germination activity of Gloriosa superba. J Nanostruct Chem 2014;4:115.

109. Ankannwar B. Biosynthesis of gold nanoparticles (green-gold) using leaf extract of Terminalia catappa. E J Chem 2010;7:1334-9.

110. Khorrami S, Zarrabi A, Khaleghi M, Danaei M, Mozafari MR. Selective cytotoxicity of green synthesized silver nanoparticles against the MCF-7 tumor cell line and their enhanced antioxidant and antimicrobial properties. Int J Nanomedicine 2018;13:8013-24.

111. Velmurugan P, Anbalagan K, Manosathyadevan M, Lee KJ, Cho M, Lee SM, et al. Green synthesis of silver and gold nanoparticles using Zingiber officinale root extract and antibacterial activity of silver nanoparticles against food pathogens. Bioprocess Biosyst Eng 2014;37:1935-43.

112. Halder A, Das S, Bera T, Mukherjee A. Rapid synthesis for monodispersed gold nanoparticles in kaempferol and anti-leishmanial efficacy against wild and drug resistant strains. RSC Adv 2017;7:14159-67.

113. Nazeruddin GM, Prasad NR, Prasad SR, Shaikh YI, Waghmare SR, Adhyapak P. Coriandrum sativum seed extract assisted in situ green synthesis of silver nanoparticle and its anti-microbial activity. Ind Crops Prod 2014;60:212-6.

114. Dash SS, Bag BG. Synthesis of gold nanoparticles using renewable Punica granatum juice and study of its catalytic activity. Appl Nanosci 2014;4:55-9.