

Prospective Application of Nanoparticles Green Synthesized Using Medicinal Plant Extracts as Novel Nanomedicines

Rajendran K Selvakesavan 
Gregory Franklin 

Institute of Plant Genetics of the Polish
Academy of Sciences, Poznan, Poland

Abstract: The use of medicinal plants in green synthesis of metal nanoparticles is increasing day by day. A simple search for the keywords “green synthesis” and “nanoparticles” yields more than 33,000 articles in Scopus. As of August 10, 2021, more than 4000 articles have been published in 2021 alone. Besides demonstrating the ease and environmental-friendly route of synthesizing nanomaterials, many studies report the superior pharmacological properties of green synthesized nanoparticles compared to those synthesized by other methods. This is probably due to the fact that bioactive molecules are entrapped on the surface of these nanoparticles. On the other hand, recent studies have confirmed the nano-dimension and biocompatibility of metal ash (*Bhasma*) preparations, which are commonly macerated with biological products and administered for the treatment of various diseases in Indian medicine since ancient times. This perspective article argues for the prospective medical application of green nanoparticles in the light of *Bhasma*.

Keywords: green synthesis, nanoparticle, *Bhasma*, medicinal plants, phytonanomedicine

Introduction

Miniaturization is the central dogma of nanoscience, and the materials that are nanoscale in at least one dimension are nanomaterials.¹ Surface area, size-to-charge ratio, reactivity, activation by visible light, thermal stability, conductivity, pH, magnetic behavior, charge storage, etc. are greatly enhanced at the nanoscale of materials.² These physicochemical properties make nanomaterials more useful than their bulk forms in many fields such as industry, agriculture, engineering and medicine.^{3,4}

Nanoparticles open up new possibilities in modern medicine with many research advances.^{5–7} In particular, their nano size helps the particles to easily reach the human cell, which promotes their application in disease detection to drug delivery.^{3,8,9} Organic nanoparticles synthesized from proteins, nucleic acids, lipids, carbohydrates and polymers are non-toxic and biocompatible.¹⁰ Although inorganic nanoparticles such as silver (Ag), gold (Au), copper (Cu), zinc oxide (ZnO), etc. are also used in medicine, their stability and biocompatibility need to be improved by coating or encapsulating them with some organic materials.^{10,11} Ferumoxytol is an example of iron (Fe) metal nanoparticles used in the treatment of anemia.^{12,13} The optical property of Au nanoparticles has been used in diagnostics. For example, the color change of Au nanoparticles due to aggregation by alkaline phosphatase has

Correspondence: Gregory Franklin
Institute of Plant Genetics of the Polish
Academy of Sciences, 34 Strzeszynska
street, Poznan, 60-479, Poland
Tel +48 61 655 0266
Email fgre@igr.poznan.pl

been used in the development of a colorimetric method to detect the concentration of ochratoxin A,¹⁴ indicating the expansion of the alkaline phosphatase-related disease detection technique. Organo-metallic nanoparticles are known for controlled and targeted delivery of drugs for the treatment of a number of diseases including cancer.^{15–17}

The use of nanomaterials in medicine dates back to ancient times. Ayurveda, a traditional system of medicine practiced in the Indian subcontinent since the 7th century uses metal ash (*Bhasma*) to treat various diseases.¹⁸ *Bhasma* are metallic/mineral preparations treated with herbal juices or decoctions and exposed to a certain amount of heat, as in the *puta* system of Ayurveda. *Bhasmas* are widely recommended in India for the treatment of many disease conditions.¹⁹ *Bhasma* preparation is a top-down approach often begins with the burning of metals, ores, minerals, etc. at very high temperature and repeated titration with plant extract or other organic materials for purification.²⁰ Wet grinding of purified metal ash with plant extracts or powders in *Bhasma* preparation could create microscopic thermal cavities that allow secondary plant metabolites to be activated and act as chelating agents. Since *Bhasma* processing requires repeated cycles of high temperatures, eg, 600 °C in the final stages of preparation,¹⁹ secondary metabolites bound to the metal ash could be lost as a result of maceration. However, in Ayurvedic treatment practice, *Bhasma* is administered either alone or in combination with medicinal plant extracts or powders as required.²¹ Recent studies have shown that many of the *Bhasma* preparations are submicron nanoparticles and organometallic in nature.^{22,23} The biocompatibility of *Bhasma* has been demonstrated in recent studies.^{24,25} The metals showed toxic effects when present in macro size and showed medicinally beneficial effects when present in micro or nano size.²⁶ The need for repeated washing, drying and *puta* steps makes the process of *Bhasma* preparation time consuming.^{19,22,25}

Recent advances in green chemistry have developed simple, rapid and inexpensive methods for the synthesis of nanoparticles, popularly known as green synthesis.⁴ Green synthesis of nanoparticles can be performed both in vivo and in vitro using biomolecules (nucleic acids and proteins),^{27,28} microorganisms^{7,29} and plant extracts.^{30–32} In particular, extracts of various medicinal plants have been widely used for the reduction of metal ions to nanoparticles because of their phytochemical richness.^{33,34} The resulting nanoparticles are often found to be biocompatible and more bioactive than their counterparts synthesized by other methods and the plant extracts used in the

synthesis.^{35,36} These enhanced bioactivities and biocompatibilities can be attributed to the complexation of phytochemicals/secondary metabolites with the nanoparticles.⁴

The potential anticancer, antidiabetic, and antimicrobial applications of green nanoparticles have been discussed in some review articles.^{37–40} To the best of our knowledge, a perspective on the application of nanoparticles synthesized with medicinal plant extracts is not available in the light of *Bhasma*. By discussing the parallels between *Bhasma* and green nanoparticles, we argue for the application of the latter in medicine. A schematic representation of the *Bhasma* preparation and green synthesis of nanoparticles and how these processes lead to the formation of organometallic nanocomplexes is shown in Figure 1.

Use of Plant Products and Metals in *Bhasma*

Bhasma preparation is basically done in three steps, namely, 1) *shodhana* (purification/detoxification), 2) *bhavana* (purging) and 3) *marana* (burning).²⁰ The impure metal is purified or detoxified with the help of plant and animal products in the first step *shodhana*. *Bhavana* is a process of wet grinding in which the purified metal is mixed with a certain liquid medium and ground well. Finally, the ground metal products are dried and packed in a mud pot and burnt several times at high temperature, producing fine ash of the particular metal.²⁰ It is believed that the above process of purification, levigation and combustion in the presence of plant and animal products removes impurities and detoxifies the metallic preparations, reduces the size to nano level and increases their effectiveness.^{25,41,42} The particle size of *Bhasma* was probably stabilized by the calcium present in the plants used, despite repeated burning at high temperatures.⁴³ According to the traditional Ayurvedic system of medicine, these *Bhasma* impart biocompatibility and increased bioavailability to organic molecules from plant extracts.^{19,21}

The physico-chemical properties of *Bhasma* have been characterized by several conventional tests suggested in Ayurvedic textbooks. The physical properties observed are *verna* (color), *nishchandratvam* (lustreless), *varitara* (lightness) and *rekhapurnatvam* (fineness). The chemical properties tested include *apunarbhavata* (inability to recover the original metallic form) and *niruttha* (inability to recover the metallic form).¹⁹ Recently, many studies reported the properties of *Bhasma* using advanced scientific methods. Transmission electron

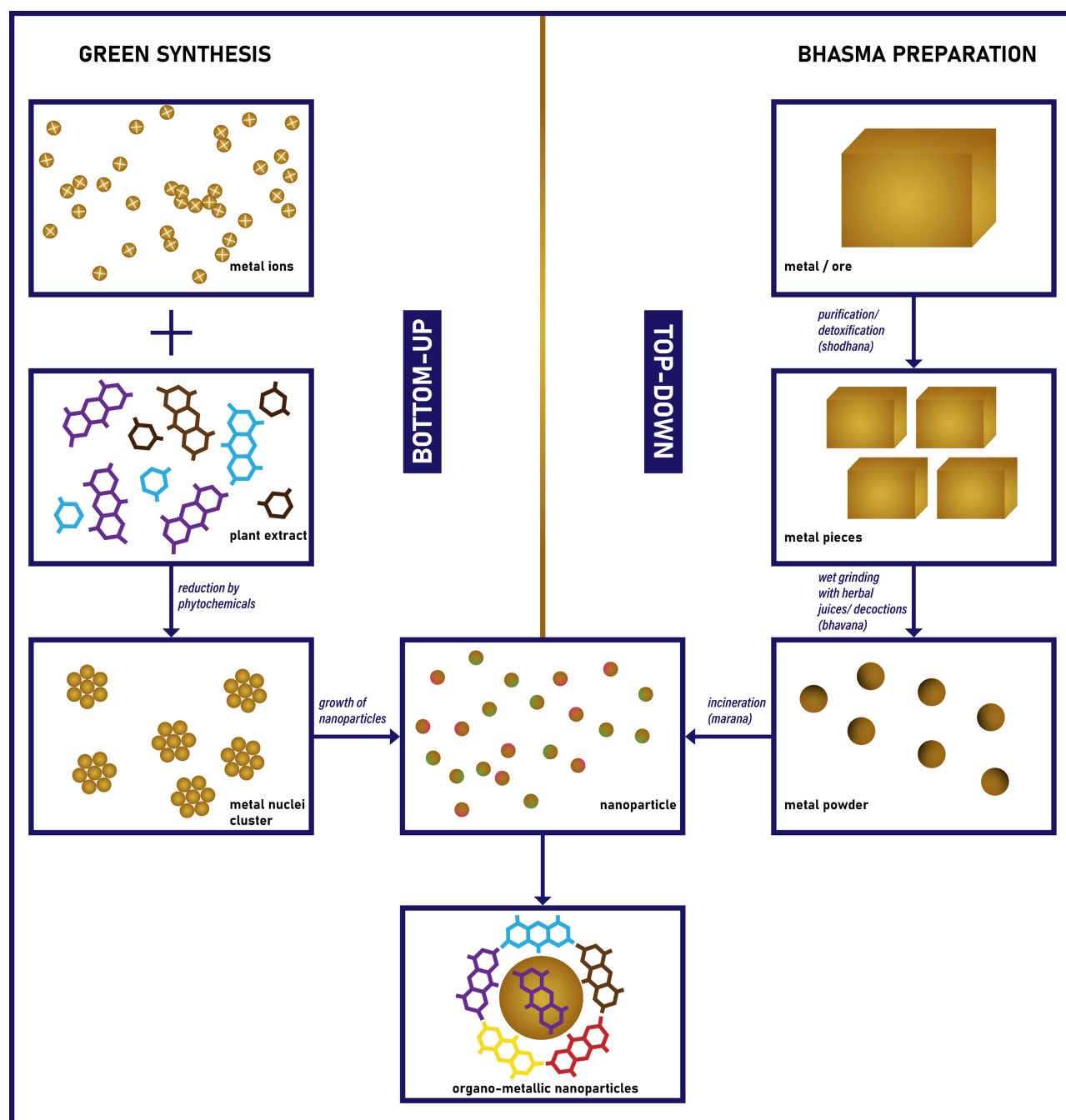


Figure 1 Schematic presentation of the nano-phytochemical complex formation in green synthesis and *bhasma* preparation.

microscope (TEM) and scanning electron microscope (SEM) analyses revealed that *Vanga Bhasma* is polycrystalline and less than 100 nm in size.²² SEM analysis of *Krishna Vajra Abhraka Bhasma* showed that the *Bhasma* is square shaped with a mean size of 92.3 nm.⁴⁴ SEM and X-ray diffraction analysis showed that *Swarna Bhasma* are large aggregates of smaller nanoparticles of about 60 nm in size.⁴⁵

Immunomodulation, nontoxicity and the ability to target drugs to the site of action are characteristics of a properly prepared *Bhasma*.¹⁹ Medicinal plants used in the various stages of *Bhasma* preparation are believed to reduce the toxicity of metals (Table 1). Decoction of horse gram used in the purification (*shodana*) phase of *Lauha Bhasma* (Fe) preparation removed Fe^{3+} from the raw material.⁴⁶ Further purification with decoction of three fruits (*Phyllanthus*

Table 1 Medicinal Plants Used in Various Steps of *Bhasma* Preparation

Plant Species Used	Purpose	Bhasma	Reference
<i>Vitex negundo</i> L.	Shodhana	Vanga Bhasma, Yashada Bhasma, Naga Bhasma	[22,23,25]
<i>Curcuma longa</i> L.			
<i>Citrus jambhiri</i> Lush.		Tamra Bhasma	[49]
<i>Dolichos biflorus</i> L.		Vaikrānta Bhasma, Swarna Bhasma, Lauha Bhasma	[50–52]
<i>Bauhinia variegata</i> L.		Swarna Bhasma	[50]
<i>P. emblica</i>		Lauha Bhasma	[46]
<i>T. chebula</i>			
<i>T. bellirica</i>			
<i>Aloe Vera</i> Tourn. ex Linn.	Bhavana	Vanga Bhasma	[22]
<i>Amorphophallus campanulatus</i> (Roxb.) Blume ex Decne.		Tamra Bhasma	[49]
<i>Ficus benghalensis</i> L.		Ras-Sindoor	[53]
<i>Plectranthus coesta</i> Buch-Ham		Naga Bhasma	[23]
<i>Azadirachta indica</i> A. Juss.			
<i>Citrus medica</i> L.	Marana	Vaikrānta Bhasma	[52]
<i>A. Vera</i>		Yashada Bhasma, Rajata Bhasma	[25,54]
<i>Calotropis procera</i> (Ait.) R.Br.		Abhraka Bhasma	[55]
<i>Ricinus communis</i> L.			
<i>Cyperus rotundus</i> L.			
<i>Adhatoda vasica</i> Nees.		Naga Bhasma	[23]

emblica L. *Terminalia chebula* Retz. and *Terminalia bellirica* (Gaertn.) Roxb. kept the Fe in Fe²⁺ form and removed any remaining Fe³⁺ in the sample.⁴⁶ *Tinospora cordifolia* (Thunb.) Miers (Giloy), known for its efficacy in the treatment of cancer and hypersensitivity due to the presence of isoquinolone alkaloids, was used for the preparation of *Kamdudha ras Bhasma* - Au and Ag ash.⁴⁷ Similarly, *Rosa centifolia* L., a plant species with tremendous antioxidant potential⁴⁸ is used for the preparation of Hg ash/ *Kaharva pishti Bhasma*.¹⁹

Bhasma are used in the successful treatment of various types of cancer, autoimmune diseases, tonsillitis, jaundice, anemia, chronic urinary tract infections, ovarian cysts and some other infectious diseases.^{19,56} Some of the *Bhasma* used in the treatment of different diseases are listed in Table 2.

Yashada (Zn) *Bhasma* is commonly used in the treatment of diabetes, urinary disorder, eye diseases, etc.²⁵

A. vera is used in the *marana* process of *Yashada Bhasma* and both *A. vera* and Zn have the potential to lower blood sugar level. The authors suggest that both metallic Zn and organic compounds present in *A. vera* may form a coordination bond between them to enhance the medicinal property.²⁵ *Shankh Bhasma*, prepared with *A. vera* and calcium carbonate, is used for stomach-related disorders such as indigestion, flatulence, abdominal pain, vomiting, belching, diarrhea, and gastritis.⁵⁸ It should be noted that calcium carbonate is used in the modern medicine as an antacid to relieve heartburn, acid indigestion, and stomach upset.⁵⁹ *A. vera* is also reported to reduce the symptoms of gastroesophageal reflux disease.⁶⁰ However, no correlation between *A. vera* and calcium carbonate has been experimentally demonstrated for the medical use of *Shankh Bhasma*.^{58,61} Although organic compounds could be burnt out at higher temperatures used in *Bhasma* preparations, the presence of organic molecules has been

Table 2 Some of the *Bhasma* Preparations Used in the Treatment of Diseases

<i>Bhasma</i>	Material Used	Treatment	Reference
<i>Abhraka Bhasma</i>	Mica	Chronic cough, anemia and tropical sprue	[55]
<i>Lauha Bhasma</i>	Fe	Hematinic, chronic fever, breathlessness, anti-aging	[51,57]
<i>Naga Bhasma</i>	Pb	Diarrhea, spleen enlargement and diabetes	[23]
<i>Rajata Bhasma</i>	Ag	Irritable bowel syndrome, acidity, pitta disorders	[19,54]
<i>Ras-Sindoor</i>	Hg	Syphilis, genital disorders and for rejuvenation	[53]
<i>Shankh Bhasma</i>	Conch shells (Calcium carbonate or oxide)	Indigestion, flatulence, abdominal pain, vomiting belching, diarrhea, belching and gastritis	[58]
<i>Swarna Bhasma</i>	Au	Tuberculosis, diabetes mellitus, rheumatoid arthritis and nervous diseases	[45,50]
<i>Swarn makshik Bhasma</i>	Copper pyrite	Anemia, jaundice, convulsions, insomnia, stomatitis, chronic fever and skin diseases	[19,56]
<i>Tamra Bhasma</i>	Cu	Ascites, anemia, asthma, hyperacidity	[49]
<i>Trivanga Bhasma</i>	Pb, Zn, and Sn	Diabetes mellitus and urinary disorders	[24]
<i>Vanga Bhasma</i>	SnO ₂	Genitourinary disorder, diabetes, anemia, asthma, gastric ulcers and urinary diseases	[22]
<i>Vaikrānta Bhasma</i>	Black tourmaline	Diabetes	[19,52]
<i>Yashada Bhasma</i>	Zn	Diabetes, eye disorder, urinary disorder	[25]
<i>Krishna Vajra Abhraka Bhasma</i>	Biotite mica	Respiratory diseases	[44]

observed in *Naga Bhasma* and this could be attributed to the organometallic complexes formed at various stages of *Bhasma* preparation and may be retained even at higher temperatures.²³ It is believed that *Naga Bhasma* acts as a carrier for the medicinal properties of various medicinal plants used in different stages of *Bhasma* preparation such as *V. negundo*, *C. longa*, *A. indica* and *A. vasica*.²³ However, the role of these medicinal plants in the treatment efficacy of *Bhashmas* in various diseases has not been experimentally validated.

Although *Bhasma* is used in traditional medicine for centuries to treat various ailments, concerns have been raised about its toxicity. Various steps in the preparation of *Bhasma* play an important and crucial role in detoxification of metals. After the preparation of *Bhasma*, it has to undergo a series of tests so that it can be used as medicine. The test for toxicity is called “Varitara” and those *Bhasma* preparations which have passed the *Varitara* test are free from toxic metals and can be used as medicine.⁶² Recently, many toxicity studies have been conducted on animal models that showed no toxic effect even at higher

therapeutic concentrations.^{49–51,63–65} A study of commercial Ayurvedic formulations (*Energetic-31* capsule and *Basanta Kusumakara Rasa*) containing various combinations of different *Bhasma* showed no adverse/toxic effects in rats.⁶² Similarly, toxicity study of *Naga Bhasma* and *Trivanga Bhasma* which contains Lead also showed no toxicity in rats for up to the treatment concentration 60 and 78 mg/kg, respectively.^{23,24} However, administration of higher than therapeutic dose of *Tamra Bhasma* for 28 days to rats showed mild toxicity in kidney, liver, thymus and heart.⁴⁹ On the other hand, few case reports claim that *Bhasma* has toxic effects due to higher concentration of metals.^{66,67} A recent case study reported intake of *Dahana Bhasma* for severe dyspepsia and loss of appetite caused severe liver injury.⁶⁸

Medicinal Plants and Metals in Green Synthesis of Nanoparticles

Green synthesis is mainly based on the redox process, in which metal ions are first reduced to a cluster of crystallites and then stabilized by the reactive phytochemicals.^{34,69} The

process of green synthesis involves the preparation of aqueous solutions of metal salt and plant extract and finally mixing.^{70–72} In an aqueous solution, the metal salt dissociates into positive metal ions, which can become supersaturated and form a hydroxyl complex (metal- OH). When the plant extract is added slowly to the metal salt solution, the hydroxyl complexes are reduced and then the metal crystallite planes grow. When the crystallite planes are in the higher energy growth phase, secondary metabolites with compatible opposite charge and free activation energy for the reaction would probably come into action and perform a capping action around the high-energy planes.⁴ Several classes of organic compounds have been proposed to be involved in the green synthesis process and a detailed review in this regard has been published recently.⁴ Various classes of plant compounds, namely, alcoholic compounds, terpenoids, quinines, polyphenols (flavones, taxifolin and catechin derivatives), alkaloids, amino acids, polysaccharides, glutathiones, antioxidants, succinic acid, ascorbic acid, tartaric acid, oxalic acid, dihydroxybenzoic acid, etc, were found in the extracts used for green synthesis.⁴ Allicin from *Allium sativum* L. and curcumin from *Curcuma longa* L. were successfully used as organic components in the preparation of copper hybrid nanostructures.^{73,74} In addition, heavy molecules such as proteins, glycoproteins and lipids were also found. However, there is evidence in the literature of the involvement of some flavonoids such as rutin, quercetin, etc as reducing or capping agents.⁴ Although many compounds are capable of reducing metal ions to nanoparticles, what is known about whether there is a preference for certain classes of compounds exist, what role these compounds play in forming the nanoparticles, and which compounds in a complex mixture are involved in this process is not clear.

Green synthesized nanoparticles show great promise in pharmacological or therapeutic applications. For example, a number of reports show that green synthesized nanoparticles could fight various types of cancer.^{40,75–77} However, the biological activity of nanoparticles depends on many factors, such as size, shape, capping agent, etc.^{78,79} The presence of plant extract derived capping agents in the nanoparticles may reduce their non-specific toxic behavior. For example, nanoparticles prepared with plant extract were found to be biocompatible for healthy cells, whereas they were lethal for pathogens and tumor growth.^{80,81} Green synthesized Au nanoparticles with *Ocimum tenuiflorum* L. extract showed higher anticancer activity than the chemically synthesized Au nanoparticles in several cell

lines.⁸¹ Similarly, Ag nanoparticles synthesized using *A. indica* extract have less toxic effects against human red blood cells compared to chemically synthesized Ag nanoparticles.⁸² Green synthesised nanoparticles were tested for toxicity in animal models. The silver nanoparticles synthesised using *Solanum nigrum* L. extract showed lower toxicity to vertebrates and aquatic invertebrates compared to the ionic form of silver.⁸³ No adverse or toxic effects on kidney, liver, heart and brain of rats were observed after treatment with silver nanoparticles synthesised using *Ficus carica* L. fruit extract.⁸⁴ Some of the important medicinal plants used for green synthesis of nanoparticles, their pharmacological properties and corresponding bioactivities of the nanoparticles are listed in Table 3.

Despite a large number of important medicinal plants have been used for green synthesis, many studies have not tested the pharmacological potential of the synthesized nanoparticles.^{88,96,120,136} Moreover, although the extracts of plants with diverse array of medicinal values have been used, the pharmacological properties attributed to these plants/extracts have not been tested in the resulting nanoparticles (Table 3). For example, ZnO and Ag nanoparticles synthesized using extracts of *C. roseus*, a well-known medicinal plant in cancer treatment, were not tested for anticancer activities but for antimicrobial activities.^{100,101} Antiplatelet, anti-inflammatory and analgesic activities attributed to *Z. officinale* were not tested in the synthesized Ag nanoparticles.¹⁷⁰ Similarly, Au nanoparticles synthesized with *R. communis* extract were tested only for anticancer and antimicrobial properties; other pharmacological properties, including prophylactic, purgative, anti-inflammatory, and antidiabetic activities, were not tested.¹⁵⁸ Aqueous extract of *A. indica* leaves has been reported to exhibit significant immunostimulatory activity.¹⁷² However, three nanoparticles synthesized with the aqueous leaf extract of *A. indica*, namely Ag, CeO₂, and CuO, have not been evaluated for their immunostimulatory activity.^{94–96}

Although many studies showed the antioxidant, anticancer and antimicrobial potential of the green synthesized nanoparticles (Table 3), the basis of these properties was not revealed in most of the studies. Although *L. nobilis* has anticancer activity, how the ZnO nanoparticles green synthesized with its extract exerted the anticancer activity and the principles of action behind it were not explained.¹³¹

Table 3 The Pharmacological Properties of the Medicinal Plants Used for Green Synthesis of Metal Nanoparticles and the Bioactivities Tested for the Nanoparticles

Plant Species	Pharmacological Properties of Plant	Nanoparticles Synthesized	Bioactivities Tested	Reference
<i>A. vasica</i>	Antiallergic, antiasthmatic, antiinflammatory, antimicrobial	Ag, CuO/C	Antimicrobial	[85–87]
<i>Agathosma betulina</i> (Berg.) Pillans	Antiseptic, antiinflammatory	NiO	None tested	[88]
<i>Allium ampeloprasum</i> L.	Antiseptic, antiasthma, diuretic and expectorant	Ag	Antioxidant	[89]
<i>A. vera</i>	Antimicrobial, antiinflammatory, antiulcer and antiarthritic	Ag	Antibacterial	[90]
		Fe ₂ O ₃	None tested	[91]
<i>Annona muricata</i> L.	Used in the treatment of cancer and parasitic infections	Ag	Anticancer	[92]
<i>Artemisia annua</i> L.	Antimicrobial, allelopathic, antiinflammatory, antifeedant and antitumour	Ag	Antibacterial	[93]
<i>A. indica</i>	Immunostimulant, antibacterial, antioxidant, antiinflammatory and anticancer	Ag	Antimicrobial	[94]
		CeO ₂ , Cu	None tested	[95,96]
<i>Bergenia ciliata</i> (Haw.) Sternb.	Antitussive, antiulcer, antioxidant, antibacterial and anticancer	ZnO	Anticancer and antibacterial	[97]
<i>Calotropis gigantea</i> (L.) Dryand.	Purgative, anthelmintic, anticonvulsant, sedative and antipyretic	CdS	Antimicrobial	[98]
		MgO	None tested	[70]
<i>Carissa carandas</i> L.	Used in the treatment of scabies, intestinal worms, pruritus, antiscorbutic, anthelmintic, pain relieving, cancer and hepatoprotective	Ag	Antioxidant, anticancer and antibacterial	[99]
<i>Catharanthus roseus</i> (L.) G. Don	Anticancer, astringent, antibacterial, antidiabetic, antifungal, and antimalarial	Ag, ZnO	Antimicrobial	[100,101]
<i>Catunaregam spinosa</i> (Thunb.) Tirveng.	Stem bark to treat muscle pain, root bark to treat dandruff, leaves to cure fever	SnO ₂	None tested	[71]
<i>Citrullus colocynthis</i> (L.) Schrad.	Antibacterial, antiinflammatory, antioxidant and anticancer	ZnO	Antibacterial, antioxidant	[102]
<i>Clitoria ternatea</i> L.	Diuretic, nootropic, antiasthmatic, anti-inflammatory, analgesic, antipyretic, antidiabetic, antilipidemic, antiarthritic and antioxidant	MgO	Antioxidant	[103]
		SnO ₂	None tested	[104]
<i>Coleus aromaticus</i> Benth.	Antilithic, antispasmodic, cathartic and stimulant	Ag	Antibacterial, antioxidant	[105]
		Pd		[106]
<i>Coptis chinensis</i> Franch.	Antioxidant and antiinflammatory	Au	Antibacterial	[107]
<i>Costus speciosus</i> (J. Koenig) Sm.	Antioxidant, antiinflammatory, antibacterial, antifungal, analgesic, antipyretic, antidiuretic, larvicidal, and antistress	Ag and Au	Antibacterial, antioxidant	[108]
<i>Crocus sativus</i> L.	Anti-inflammatory, sedative, antiasthma, antioxidant and adaptogenic agent.	Ag	Antibacterial	[109]

(Continued)

Table 3 (Continued).

Plant Species	Pharmacological Properties of Plant	Nanoparticles Synthesized	Bioactivities Tested	Reference
<i>Cyclopia intermedia</i> E. Mey.	Antidiabetic, anticancer, antiobesity, antioxidant and antimicrobial activities	Au	Anticancer	[110]
<i>Cynara cardunculus</i> L.	Antioxidant	Ag	Antibacterial	[111]
<i>C. rotundus</i>	Analgesic, anthelmintic and antifungal activity	CuO	Antibacterial	[112]
<i>Dodonaea viscosa</i> (L.) Jacq	Antibacterial activity, antifungal property, antiviral activity and antiplasmodial activity.	Ag	Antibacterial and anticancer	[113]
<i>Eriobotrya japonica</i> (Thunb.) Lindl.	Anticancer, antioxidant, antiinflammatory, antidiabetic and antimicrobial	Ag	Anticancer, antiallergic and antiinflammatory	[114]
<i>Elephantopus scaber</i> L.	Wound healing, anticancer and antimicrobial	Ag	Antioxidant, anticancer and antimicrobial	[115]
<i>Eleutherococcus senticosus</i> (Rupr. & Maxim.) Maxim.	Anticancer, antioxidant, and antimicrobial	Ag, Au	Antioxidant, anticancer and antibacterial	[116]
<i>Eucalyptus globulus</i> Labill.	Antibacterial, antioxidant, analgesic, anti-pyretic and antiinflammatory	TiO ₂ , Ag	None tested	[117,118]
		ZnO	Antifungal	[119]
<i>F. carica</i>	Antiinflammatory and antispasmodic; to treat various ailments such as gastrointestinal, respiratory, and cardiovascular disorders	Fe	None tested	[120]
		Ag	Anticancer and animal toxicity	[84]
<i>Gloriosa superba</i> L.	Used as germicide, to cure ulcers, piles, haemorrhoids, inflammation, scrofula, leprosy, dyspepsia, worm's infestation, flatulence, intermittent fevers, debility, arthritis, and against snake poison	Ag and Au	Antibacterial, and antibiofilm	[121]
		CuO	Antibacterial	[122]
		Pt and Pd	Anticancer	[123]
<i>Hibiscus sabdariffa</i> L.	Antibacterial and antioxidant	Au	Inhibit formation of amyloid fibrils	[124]
<i>Holoptelea integrifolia</i> (Roxb.) Planch.	Antioxidant, antibacterial, antimutagenic, antivenom and antitumor	Ag	Antioxidant, antiinflammatory, antidiabetic and antibacterial	[125]
<i>Hyptis suaveolens</i> (L.) Poit.	Antirheumatic, antiinflammatory, antifertility	Ag	Anticancer	[126]
<i>Impatiens balsamina</i> L.	Wound healing	Ag	Antimicrobial	[127]
<i>Ipomoea asarifolia</i> (Desr.) Roem. & Schult.	Diuretic, emmenagogue and purgative	Ag	Antibacterial	[128]
<i>Justicia adhatoda</i> L.	Antiinflammatory, antipyretic	ZnO	Antimicrobial	[129]

(Continued)

Table 3 (Continued).

Plant Species	Pharmacological Properties of Plant	Nanoparticles Synthesized	Bioactivities Tested	Reference
<i>Lantana camara</i> L.	Antimicrobial	Ag	Antioxidant, anticancer and antimicrobial	[127,130]
<i>Laurus nobilis</i> L.	Antiseptic, antioxidant, digestive and anticancer	ZnO	Anticancer and antibacterial	[131]
<i>Lavandula stoechas</i> L.	Antibacterial, anticholinesterase inhibition and antioxidant	Ag	Antibacterial, antioxidant	[132]
<i>Matricaria chamomilla</i> L.	Antifungal, anti-inflammatory, antimicrobial and antioxidant	Ag	Anticancer	[133]
			Antimicrobial	[134]
		CuO	Antioxidant and DNA cleavage	[135]
<i>M. pulegium</i>	Carminative, antitussive, antimicrobial, antioxidant and antiseptic effects	Ag	Antimicrobial and anticancer	[80]
		Fe	None tested	[136]
<i>Morinda citrifolia</i> L.	Anticancer, analgesic, antimicrobial, and antiinflammatory activity	Ag	Antibacterial	[137]
<i>Moringa oleifera</i> Lam.	Antipyretic, antitumor, antiepileptic, antiulcer, antiinflammatory, antispasmodic, antihypertensive, diuretic, antidiabetic, antioxidant and antimicrobial	Pd, Ag, Fe	Antimicrobial	[138–140]
		Bi, Cu,	Antimicrobial and antioxidant	[141,142]
<i>Morus alba</i> L.	Antioxidant, hypolipidemic and anti-hyperglycaemic	Ag	Antibacterial	[143]
<i>Nervalia zeylanica</i> (L.) DC.	Cure wounds, colic, ulcers, headache, intestinal worms, inflammations, rheumatic pain, skin diseases, and leprosy	Ag	Antimicrobial and antioxidant	[144]
<i>Mussaenda glabrata</i> (Hook.f.) Hutch. ex Gamble	Cure ulcers and asthma	Ag and Au	Antimicrobial	[145]
<i>Naregamia alata</i> Wight & Arn.	Used to cure ulcers, wounds, skin diseases, asthma, arthritis and fever	Ag and Au	Antimicrobial	[146]
<i>Ocimum sanctum</i> L.	Antioxidant, antibiotic, antidiabetic, antiatherogenic, immunomodulatory, antiinflammatory, analgesic, antiulcer, chemo-preventive and antipyretic	Ag	Antibacterial	[147]
		Ni	None tested	[148]
<i>Olea europaea</i> L.	Antimalarial, antibacterial, antioxidant, antiinflammatory and antimycoplasma	Ag	Anticancer and antibacterial	[149]
<i>Pelargonium endlicherianum</i> Fenzl.	Used to treat cough, sore throat, congestion and other respiratory ailments	Ag	Antimicrobial	[150]
<i>Phyla dulcis</i> (Trevir.) Moldenke	Antiproliferative and antiviral	Ag	Antimicrobial	[151]

(Continued)

Table 3 (Continued).

Plant Species	Pharmacological Properties of Plant	Nanoparticles Synthesized	Bioactivities Tested	Reference
<i>P. emblica</i>	Antioxidant activity, antiaging, antipuretic, and antiinflammatory	Pd	Anticancer and antibacterial	[152]
		Ag	Antibacterial	[153]
<i>Phyllanthus Niruri</i> L.	Used in the treatment of jaundice, diarrhea, kidney ailments, constipation, ulcers, malaria, hemorrhoids, ringworm and hemorrhoids	TiO ₂	None tested	[154]
<i>Pimpinella anisum</i> L.	Antioxidant, antibacterial, antifungal, anticonvulsant, antiinflammatory, analgesic, gastro-protective, antidiabetic, and antiviral activities	Ag	Anticancer and antibacterial	[155]
<i>Piper nigrum</i> L.	Antipyretic, analgesic, hepatoprotective, antioxidant and anti-inflammatory	Ag	Antioxidant and toxicity in animal	[156]
<i>Pongamia pinnata</i> L.	Anti-inflammatory, analgesic	Au	Antifungal	[157]
<i>R. communis</i>	Prophylactic, purgative, antimicrobial, antiinflammatory and antidiabetic	Au	Anticancer and antimicrobial	[158]
<i>Rosa canina</i> L.	Anti-inflammatory, antioxidants	ZnO	Anticancer and antibacterial	[159]
<i>Saraca indica</i> L.	To cure gynaecological disorders like pelvic pain, endometriosis, menorrhagia, uterine fibroids, haemorrhagic dysentery	Ag	Antimicrobial	[160]
<i>Salvadora persica</i> L.	Abrasive, astringent, antiseptic and detergent	Ag	Antimicrobial	[161,162]
		ZnO	Anticancer	[163]
<i>S. nigrum</i>	Used for treating inflammation, pain and fever	Ag	Toxicity in animals	[83]
<i>Stereospermum suaveolens</i> (Roxb.) DC.	Used for treating vomiting, fever, asthma, blood and heart infections	Ag and Au	Antioxidant, anticancer and antibacterial	[164]
<i>Syzygium aromaticum</i> (L.) Merr. & L.M.Perry	Antiseptic, antibacterial, antifungal and antiviral	Ag	Antimicrobial	[165]
<i>T. bellirica</i>	Laxative, astringent, anthelmintic and antipyretic	Ag	Antimicrobial	[166]
<i>T. cordifolia</i>	Anticancer, antileprotic, antihyperglycemic, antiallergic and antidiabetic	Ag	Antioxidant and antibacterial	[167]
<i>Withania coagulans</i> (Stocks) Dunal	Antihyperglycaemic, anti hypercholesterolemic, antifungal, antibacterial and anticancer	Ag	Antioxidant, anticancer and antibacterial	[168]
<i>Withania somnifera</i> (L.) Dunal	Antioxidant, antiInflammatory, antitumor and antistress	Se	Antioxidant, anticancer and antibacterial	[169]
		Ag	Antimicrobial	[72]
<i>Zingiber officinale</i> Roscoe	Antiplatelet, antiinflammatory and analgesic	Ag	Antibacterial	[170]
<i>Ziziphus zizyphus</i> (L.) H. Karst.	Antifungal, antibacterial, antiulcer, and antiinflammatory	Au	Antimicrobial	[171]

Conclusion

The organometallic nature and biocompatibility of the green synthesized nanoparticles indicate the possibility of their application as ideal candidates for the development of phytonanomedicines. Despite a large number of medicinal plants with important pharmacological properties were used in green synthesis, most studies have not tested the pharmacological properties attributed to those plants/extracts or the bioactivity of the nanoparticles at all, making it difficult to establish a correlation between the medicinal plants used in the process and the nanoparticles. Therefore, testing the pharmacological properties corresponding to the plant extracts in green synthesized nanoparticles would be very useful to advance this field of nanomedicine. Similarly, comparative analyses of the pharmacological properties of green synthesized nanoparticles and *Bhasma* prepared using the same plants/extracts would provide new clues. Since green synthesis imparts novel pharmacological properties to the resulting nanoparticles, a clear understanding of the specific compounds involved in the reduction and capping processes would further advance this area of research. Detailed toxicity studies are required before green synthesized nanoparticles are considered for medical applications.

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Disclosure

The authors report no conflicts of interest in this work.

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