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Herbonanoceuticals: A New Step Towards Herbal Therapeutics

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Abstract

Herbs and herbal derivatives are of great research interest owing to their wide applications in therapeutics. Several folk evidences have been recorded in the formulations of ancient world's medicinal system, which have attracted researchers for their scientific validation. Various herbal compounds has been identified and showed their therapeutic efficiency against pathophysiological conditions. Employing these herbal compounds for synthesizing nanoparticles for biomedical applications have been ventured in recent times. Green synthesis is the procedure of synthesizing nanoparticles from herbal/ biogenic resources and several metallic nanoparticles have been synthesized by this process. The metal nanoparticle-herb combination may show better efficacy against different pathophysioloical conditions. This review tries to put forward the different metal nanoparticles formed from different herbal resources and their role in health and diseases. Although green synthesis of nanoparticle is an emerging area of research but very few data are available regarding their physiological effects, compatibility and toxicity. This review is an effort to elaborate in detail the role of medicinally important herbs in synthesizing metal nanoparticles, their physiological compatibility and therapeutic efficacy. Further, considerations and discussions are also made on limitations (toxicity) of the green synthesis of nanoparticles along with their future prospects in health and diseases. This review opens door to a completely new dimension in medicinal plant research combining the nanotechnology with herbs i.e. Herbonanoceuticals.

Introduction

Biomedical science is an ever growing field of research which has been developed with time and is still developing every day. Research and development in biomedicine utilizes realms from past cited in history of natural products used in ancient world history. Perhaps, since the origin of mankind, it has taken its own course of abrupt development with passing time, implementing old and new tools and technologies. Herbs have been an integral part of our therapeutic consideration since thousands of years, but are still under investigation and have become a part of biomedical research laboratories. Several medicinal plants and its bioactive molecules has been studied and tested for their efficacy and valediction against various diseases. The new face technology in today's world is "Nanotechnology" and it has found its application in science, engineering and medicine [1-3]. Though, evidences also exist about the use of nano-sized materials since thousands of years documented in various ancient scriptures [4,5]. Applying this modern yet old form of technology to yield metal-herb formulations can be a new paradigm in biomedicine. Considerations about choice of herbs to synthesise nanomaterials would be based on the fact of its bioactive potential and acceptability of it to the body. Such an approach can be more appealing since it would be more physiologically compatible, less toxic, cost effective, and easily available owing to its natural origin. This review tries to highlight the use of these herbs to synthesize nanomaterials for biomedical applications leading to a newer concept of "Herbonanoceuticals". Hence, this concept can be defined as engineered materials manipulated at nanoscale level using herbs for their synthesis, designed to participate in the physiological functioning of the body.

Medicinal Plants Research

Nature is a store house of different medicinal herbs containing active bio-molecules which are potential source of drug against health and diseases. Fossil record of usage of plants as medicine dated back at least to middle Paleolithic age almost 60,000 years ago [6,7]. Evidences from Indian, Chinese, Egyptian, Greek, Roman and Syrian literature showed that medicinal plants have gained its importance and was a tradition in ancient civilizations. Reviewing the history of mankind, it has been seen that herbs are integral part of world civilization and medicinal system for thousands of years [8]. According to evidences available, herbal extracts were used initially as crude drugs in the form of powder, tincture, poultice and other formulations [8,9]. These attracted researchers to extract and modify the active constituents from plants and evaluate their biological potential which finally led to drug discovery. Some of these early isolated active compounds as drugs are still in use [8,10-12]. Approximately about 119 chemical compounds derived from higher plants that have been used as medicines throughout the world [13]. The use of medicinal plants for the treatment of diseases was practiced all over the world namely from countries like China, Japan, Egypt, Brazil and India [13,14]. The World Health Organization (WHO) in its report defined traditional medicine (including herbal drugs) is comprised of therapeutic practices which exists for hundreds of years, before the development and spread of modern medicine and are in use till today [15]. In fact medicinal plants are still remains a popular choice for therapeutics in 80% of people in developing countries owing to its easy availability, cost-effectiveness, bio-compatibility, natural origin and acceptability [16]. Literature has been documented on details of folk plant remedies and its practice. There are lists on several active herbal components derived from plant sources and its therapeutic applications in various ailments [17,18]. Reports on herbal medicine, principles of herbal pharmacology treatment, validation of herbal therapeutics, issues of safety, dosage

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and dosage forms in herbal medicine have been also documented where role of herbal medicines is highlighted in patho-physiological conditions in perspectives of physiological systems and ailments such as digestive system biliary system, the hepatic system, cardiovascular system, respiratory system, urinary system, nervous system, female reproductive system, joint diseases and skin diseases [19]. Research on plants with medicinal value still remains a very attractive area of investigation among researchers owing to its diversity and therapeutic usefulness. Medicinal plants are coming in mainstream therapeutics and have become popular with time due to its eco-friendliness and lesser side effects which adds an edge over synthetic drugs [20]. Hence, the future medicine therefore will walk miles holding the hands of medicinal plants therefore research and development in this arena is required using upcoming technologies.

Herbs and Metals in Ayurvedic Medicines

As an alternate medicinal system, folk medicine has gained popularity all over the world. Ayurveda, India's traditional medicinal system is associated with the natural sources and natural product derived preparations for the treatment of various diseases. It explores the utilization of herbs, metals and minerals for medicinal purposes [21,22]. About 6% of plant species have been screened for biological activities [7]. Ayurvedic formulations of *Samhita* period (600-1000 BC) used metals in powdered forms. They were named as *Ayaskrati*. The metals used in Ayurveda include mercury (*Parada*), gold (*Swarna*), silver (*Rajata*), copper (*Tamra*), iron (*Lauha*), tin (*Vanga*), lead (*Naga*), zinc (*Yasada*) etc. Their internal use was limited because they were not free of unwanted toxic effects. Development of *Rasashastra* in 7th century AD introduced many new pharmaceutical techniques for metal formulations of Ayurvedic preparations including *Shodana*, *Jarana* and *Marana* [23]. Techniques involved in *Rasashastra* can convert metals and minerals in very fine, absorbable, therapeutically most effective and least or non-toxic form of medicine known as *Bhasmas*. Different stages of *Bhasma* preparation brings down its size and makes it more effective therapeutic compound [23]. Preparation of *bhasmas* includes various steps. Metals are made coarse particles by hammering. Then they are purified (*Shodhana*) by heating red-hot or melted and quenched in particular liquid media for specific time. Then these purified materials are incinerated (*Marana*) and mixed with specific drugs, especially herbs, and levigated (*Bhabana*) by particular liquid media [24]. Recent literatures show that ayurvedic processing of metallic formulations may bring down its shape to nanometer size [23,25]. Chaudhary (2011) prepared different metallic bhasmas (including gold, iron, copper etc.) by ayurvedic protocol and characterize them. X-ray diffraction, transmission electron microscopy and particle size analysis revealed the synthesis of nano-sized metal particles [25]. Pavani et al (2013) made a green approach for the synthesis of iron oxide nanoparticle by modified *bhasmikaran* (method of preparing *bhasmas*) method. X-ray diffraction and transmission electron microscopy results showed the formation of nanoparticle by ayurvedic *bhasmikaran* method [26]. Being so small in size, they are more powerful because the constituent metals and minerals do not react with the tissues of the body [27]. The metals can combine with herbs which help in assimilation and delivery of the ingredients into the human body [25,27]. The above literature cited is a clear indication that metal-herb combination can work as medical wonders. Here comes the question: In what formulation or in what form should these metals be used as prodigious medical tools? Already from folk evidences it has been seen that metals in nano forms were in use. Therefore, using nanotechnology to synthesize metal nanoparticles can be one such promising approach to form metal-herb formulations whose synergistic effect can be effective against various diseases.

Green Synthesis of Nanoparticles

The term 'Green' nanoparticle not refers the colour, but the concept of synthesizing nanoparticles from metal salts by using the reducing property of biologically active compounds. The biologically active compound may derive from microorganisms (both live and dead), herbal extracts (from leaf, root, aerial part, whole body, flower, fruit, berk, latex etc.), animal extracts etc. Most of the biologically active compounds, which possess reducing capability, are biologically compatible. They are used to produce metal nanoparticles with effective therapeutic potential. From the ayurvedic point of view, it can be stated that metal nanoparticles (as in *bhasmas*), in combination with herbs may serve as a potent therapeutics. Active compounds present in herbs can reduce nanoparticle, stabilize it, and in combination they can possess a better therapeutic potential.

Gardea-Torresdey et al. reported the synthesis of gold and silver nanoparticle by using herbal extracts [28,29]. Vitamins, sugars, plant extracts, microorganisms, biodegradable polymers etc. are being used to synthesize green metal nanoparticles. Plant extracts seemed to be the best reducing agents due to the capability of large-scale production of metal nanoparticles [30]. The key active compound in plant extracts is polyphenol. Polyphenols have reducing potential, and their side chain groups (mostly –OH group) are engaged in capping and stabilizing nanoparticles. Biocompatibility of gold nanoparticle makes it an extensively used particle in nanotechnology field [31]. Gold nanoparticles are biologically inert, but they can be engineered to possess chemical or photo-thermal functionality. This modification of gold nanoparticle can be done by altering its surface chemistry. Geetha et al. produced gold nanoparticle by using flower of *Couroupita guianensis* tree and showed that its synthesis was rapid, cost-effective and one-step process [32]. Iram et al. isolated glucoxylans from seeds of *Mimosa pudica* and used it to produce gold nanoparticle without using any stabilizing agent [33]. They showed the size of nanoparticle to be 40 nm. Phytotoxicity test of that particle did not show any significant effect on germination of radish seeds. A rapid in situ biosynthesis of gold nanoparticles was proposed using *Pelargonium zonale* leaf extract as a non-toxic reducing and stabilizing agent in a sonocatalysis process based on high-power ultrasound [34]. It took only 3.5 min in aqueous solution to reduce gold salt under ambient conditions. The particles had an average lifetime of about 8weeks at 4°C in the absence of light. 80% of the synthesized particles had diameter in the range 8-20 nm, with an average size of 12 ± 3 nm. FTIR spectrum indicated the presence of biomolecules that could be responsible for reducing and capping the gold nanoparticles. Lin et al. synthesized gold nanostructures in tea infusions and proved the presence of phytochemicals on the surface of nanostructures by using surface-assisted laser desorption/ionization mass spectrometry, Fourier transform infrared spectrometry and capillary electrophoresis coupled with UV detection. Pure crystalline structure of gold particle was revealed by energy-dispersive X-ray spectroscopy and powder X-ray diffraction data [35]. Kalmodia et al. reported a simple, rapid and robust method to synthesize surface enhanced Raman scattered gold nanoparticles by using *Vitis vinifera* leaf extract [36]. FTIR spectroscopy revealed the presence of proteins on the surface of gold nanoparticles. They proposed that the particle has potential applications in cancer diagnosis, therapy and ultra-sensitive biomarker detection. Water soluble bio molecules like polyols and proteins of aqueous extract and dried powder of *Anacardium occidentale* leaf were expected to biosynthesize gold, silver, gold-silver alloy and gold core-silver shell nanoparticles [37]. Suman et al. synthesized gold nanoparticles using aqueous root extract of *Morinda citrifolia* [38]. Arunachalam and Annamalai (2013) biosynthesized gold nanoparticles by using the reduction property of aqueous leaf extract of *Chrysopogon zizanioides* and proposed that this particle could have antibacterial, antioxidant and cytotoxic properties [39]. A simple and easy method was described by Arunachalam et al. for preparation of gold nanoparticle using aqueous extract of *Memecylon umbellatum* leaf [40]. In a study, eco-friendly, non-toxic gold nanoparticles was biologically synthesized using the leaf extract of *Euphorbia hirta* [41]. *Phoenix dactylifera* leaf extract induced reduction of gold nanoparticle was stabilized by the capping of hydroxyl and carbonyl groups in the carbohydrates, flavonoids, tannins and phenolic acids present in the extract [42]. Carboxyl group present in the aqueous extract of *Garcinia combogia* fruit was utilised to synthesize catalytically active gold nanoparticle with controllable size and shape [43]. Mohan Kumar et al. demonstrated a facile, rapid, eco-friendly method to synthesize gold nanoparticle using aqueous extract of fruits of *Terminalia arjuna*. High performance lipid chromatography revealed that ascorbic acid, gallic acid and pyrogallol present in the extract was responsible for the reduction of gold salt into gold nanoparticle [44]. Ispaghula (*Plantago ovata*) seed husk was used to synthesize and stabilize gold nanoparticle [45]. Competitive reduction of gold salt and silver salt using aqueous extract of *Piper pedicellatum* was observed by Tamuli et al. (2013) [46]. They proposed that the chemical constituents of *P. pedicellatum* (catechin, gallic acid, courmaric acid and protocatechuic acid) may act as a reducing, stabilizing and capping agent. Snitka et al. proposed that different components of honey were responsible for formation and stabilization of gold nanoparticles [47]. Glucose in honey was responsible for reduction of gold salt into gold nanoparticle, whereas fructose acted as a stabilizer. In this method, spherical, rod shaped, decahedra shaped and triangular nanoparticles were formed. This study also successfully demonstrated the separation of differently shaped nanoparticle by the simple process of centrifugation. It was found in this study that while centrifuging, the spheres sediment at the bottom of the tube, segregating from rods that form a deposit on the side wall, whereas polygons remain in the solution. In another study, honey was used as reducing agent to synthesize gold nanoparticle [48]. Various shape and size of gold nanoparticles were synthesized using citrus fruits (*Citrus limon*, *Citrus reticulata* and *Citrus sinensis*). It was observed that the size and shape of nanoparticle was in correlation with the ratio of the reactants with respect to 1.0 mM chloroauric acid solution [49]. Aqueous solution of a natural gum kondagogu (*Cochlospermum gossypium*) was utilized in synthesizing gold, silver and platinum nanoparticles, and stabilization was mediated by the gum itself [50]. Hydrolysable tannins present in the extract of *Terminalia chebula* were responsible for reductions and stabilization of gold nanoparticles [51]. Biosynthesis of gold nanoparticle was also established using aqueous extract of *Sargassum myriocystum*, phytochemicals present in garlic, fenugreek, *Gnidia glauca* flower extract, extract of cypress leaves, palm oil mill effluent, red cabbage extract, fresh/dry leaf extract of *Mangifera indica*, stem extract of *Breynia rhamnoides*, Indian propolis and its chemical constituents pinocembrin and galangin, aqueous extract of *Macrotyloma uniflorum*, ethanolic flower extract of the plant *Nyctanthes arbortristis*, *Murraya Koenigii* leaf extract, macerated extracellular aqueous dried clove buds (*Syzygium aromaticum*) solution, and *Cinnamomum zeylanicum* leaf broth [52-66].

Iram et al. isolated glucoxylans from *Mimosa pudica* seeds and used it to produce silver nanoparticle of 6 nm diameter [33]. Phytotoxicity test of these particles did not show any significant effect on germination of radish seeds. Bioreduction of silver salt was also reported using aqueous sorghum bran extracts [67].

Commercial production of magneto-sensitive nanoparticle by green method is now an emerging trend producing targeted drug-delivery carriers. Several plant extracts, bacteria and fungus were utilized to synthesize iron nanoparticle by bioreduction method. Machado et al. studied the green production of zero valent iron nanoparticle using different tree (oak, pomegranate and green tea) leaf extract which are capable of reducing iron (III) to zero valent iron in aqueous solution [68]. Their results showed that dried leaves produce extracts with higher antioxidant capacities than non-dried leaves. They worked out the most favourable extraction conditions (temperature, contact time, and volume: mass ratio) for each leaf extracts and selected water as a solvent with the aim of developing a green, but also low-cost method. Reducing capability of polyphenols of eucalyptus leaf extract was utilized by Wang et al. to produce spherical iron nanoparticle [69].

Very few studies have done regarding the environmentally benign synthesis of zinc nanoparticle. Nagarajan and Arumugam Kuppusamy (2013) synthesized zinc oxide nanoparticle by using marine sea weeds (green *Caulerpa peltata*, red *Hypnea Valencia* and brown *Sargassum myriocystum*) [70]. FT-IR spectrometry showed the involvement of fucoidan pigment in synthesis of nanoparticle. Rajiv et al. (2013) reported the synthesis of zinc oxide nanoparticle from leaf extract of a weed, *Parthenium hysterophorus L.* and showed its size-dependent antifungal activity against *Aspergillus flavus* and *Aspergillus niger* [71]. Mixed copper and zinc oxide nanoparticle was synthesized using *Brassica juncea L.* plant and it was found that the ZnO nanoparticles were non-uniform in shape [72].

Copper has an effective biocidal activity [73-75], and products with copper containing surfaces may be used for sterilizing processes in hospitals [76,77]. Cupper ion possesses toxic behaviour towards biological systems. Zero valent copper nanoparticle production in nature is a common phenomenon. Plants can convert excess copper ions of contaminated soil into metallic nanoparticle in and near their roots with the help of endomycorrhizal fungi naturally [78]. Copper oxide nanoparticle can be synthesized using different herbal extracts also. Sankar et al. synthesized rod shaped CuO nanoparticle using *Carica papaya* leaf extract [79]. Thekkae Padil and Cernik (2013) prepared CuO nanoparticle using gum karaya, a natural nontoxic hydrocolloid [80]. Harne et al. synthesized copper nanoparticle using the aqueous extract of latex of *Calotropis procera L.* and showed its excellent long term stability [81].

Green Nanoparticle and its Applications

Properties of metals in their bulk form significantly differ from the properties in nanoscale dimension. Metals and their nanoparticles have various roles in human body [82]. When conjugated with biologically active compounds, they exhibit the active potential of the compound. Sometimes the synergistic effects of nanoparticle and conjugated compounds are also seen. Generally the extracts that are selected for green synthesis have medicinal values. Nanoparticle conjugation makes the herbal extracts more effective. Anti-cancer, drug delivery, anti-microbial, anti-anemic, anti-arthritic, anti-diabetic, antioxidant properties of green nanoparticles have been established till date [32,88,89,94-96] (Table 1).

Anti-cancer activity of green nanoparticle

Geetha et al. produced gold nanoparticle by using flower of *Couroupita guianensis* tree and its anticancer activity was explored using MTT assay, DNA fragmentation, apoptosis by DAPI staining and comet assay for DNA damage [32]. Karuppaiya et al. synthesized gold nanoparticle of 127 nm by using aqueous extract of the

Type of Green Nanoparticle	Herbs and Herbal Compounds Used	Biological Activity	Reference
Gold	*Couroupita guianensis* (Flower)	Anticancer	Geetha et al., 2013 [32]
	Dysosma pleiantha (Rhizome)	Antimetastatic	Karuppaiya et al., 2013 [83]
	Pleurotus florida	Anticancer	Bhat et al., 2013 [84]
	Eclipta Alba (Leaves)	Anticancer (breast cell line)	Mukherjee et al., 2012 [85]
	Cinnamomum zeylanicum (Bark)	Anticancer	Chanda et al., 2011 [87]
	Mimosa pudica (Glucoxylans from seeds)	Drug delivery	Iram et al., 2014, 2014 [33]
	Punica granutum (Fruit peel)	Drug delivery	Ganesh kumar et al., 2013 [88]
	Xylose from straw, corncobs, pecan shells and cottonseed hulls	Antimicrobial	Badwaik et al., 2013 [89]
	Cinnamomum zeylanicum (Leaf)	Antimicrobial	Smitha and Gopchandran, 2013 [90]
	Terminalia chebula	Antimicrobial	Kumar et al., 2012 [51]
	Banana peel	Antimicrobial	Bankar et al., 2010 [91]
	Trigonella foenum-graecum (seed)	Antianemic	Ghosh et al, 2014 [94]
	Methotrexate	Antiarthritic	Gomes et al., 2012 [95]
	Propanoic acid 2-(3-acetoxy-4,4,14-trimethylandrost-8-en-17-yl) isolated from Cassia auriculata	Antidiabetic	Venkatachalam et al., 2013 [96]
Silver	*Helitropium indicum* (Leaves)	Larvicidal	Veerakumar et al., 2014 [98]
	Cocous nucifera (Inflorescence)	Antimicrobial	Mariselvam et al., 2014 [92]
	Achillea biebersteinii (Flowers)	Anti-angiogenic	Baharara et al., 2014 [97]
	Plectranthus amboinicus (Leaf)	Antimicrobial	Ajitha et al., 2014 [93]
Zinc	*Parthenium hysterophorus*	Antifungal	Rajiv et al., 2013 [71]
	Caulerpa peltata, Hypnea Valencia, Sargassum myriocystum	Not explored	Nagarajan and Arumugam Kuppusamy, 2013 [70]
Copper	*Carica papaya* (Leaf)	Not explored	Sankar et al., 2014 [79]
	Calotropis procera (Latex)	Not explored	Harne et al., 2012 [81]
Iron	Oak, pomegranate and green tea (Leaf)	Not explored	Machado et al., 2013 [68]
	Eucalyptus (Leaf)	Not explored	Wang et al., 2014 [69]

Table 1: Biological activity of green nano particle synthesized using herbs and herbal compounds.

Dysosma pleiantha rhizome and showed its anti-metastatic activity of biosynthesized gold nanoparticles against HT-1080 cells (human fibrosarcoma cancer cell line). Gold nanoparticles prepared by this method were non-toxic to cell proliferation and, also it can inhibit the chemo-attractant cell migration of HT-1080 cells by interfering the actin polymerization pathway [83]. Green synthesis of gold nanoparticle using edible mushroom *Pleurotus florida* exhibited effective anticancer property against A-549 (Human lung carcinoma), K-562 (Human chronic myelogenous leukemia bone marrow), HeLa (Human cervix) and MDA-MB (Human adenocarcinoma mammary gland) cell line and no lethal effect was observed in Vero (African green monkey kidney normal cell) cell lines [84]. Mukherjee et al. developed a simple, fast, clean, efficient, low-cost and eco-friendly approach to synthesize biocompatible gold nanoparticles using aqueous extract of *Eclipta Alba* leaves and showed its inhibiting property in breast cancer cells (MCF-7 and MDA-MB-231) proliferation when combined with doxorubicin [85]. Venkatpurwar et al. synthesized green gold nanoparticle by using porphyran as a reducing agent and it was utilized as a carrier for delivery of the anticancer drug doxorubicin hydrochloride [86]. Spectroscopic examination revealed that hydrogen bonding was responsible for conjugation of doxorubicin hydrochloride and gold nanoparticle. The release of doxorubicin hydrochloride from nanoparticle was found to be six fold higher in acetate buffer (pH 4.5) as compared to physiological buffer (pH 7.4). It exhibited higher cytotoxicity on LN-229 cell line (human glioma cell line) as compared with an equal dose of native doxorubicin hydrochloride solution. Uptake of cinnamon phytochemical-reduced gold nanoparticle by normal human fibroblast and cancerous (PC-3 and MCF-7) cells are evident with detectable photoacoustic signals, and can serve as excellent cytotoxic/ photoacoustic contrast-enhancement agents [87].

Drug delivery using green nanoparticle

Owing to very high surface area-to-volume ratio, metal nanoparticles possess effectiveness to carry drugs to specific target organs. Nanoparticles with very small volume can reach target site carrying the drugs and mediate their effects. Drugs can be tagged with the surface, or loaded inside the hollow sphere of metal nanoparticles. They show sustained release procedures of drugs. Green gold nanoparticle of 40 nm is suitable for drug delivery as they are non-cytotoxic [33]. Targeted drug delivery in cancer also may be possible by using green gold nanoparticle synthesized using fruit peel extract of *Punica granutum* [88].

Antimicrobial activity of green nanoparticle

Xylose, a monosaccharide found in straw, corncobs, pecan shells and cottonseed hulls was used to synthesize and cap gold nanoparticle with effective antibacterial activity against gram positive bacteria [89]. Gold nanoparticle synthesized using *Cinnamomum zeylanicum* leaf broth exhibited efficient antibacterial activity against gram negative *Escherichia coli*, gram positive *Staphylococcus aureus*, and antifungal activity against *Aspergillus niger* and *Fusarium oxysporum* [90]. Gold nanoparticle synthesized from aqueous extract of *Terminalia chebula* showed better antimicrobial activity towards gram positive *S. aureus* compared to gram negative *E. coli* using standard well diffusion method [51]. Banana peel extract mediated synthesis of gold nanoparticle showed efficient antimicrobial activity towards most of the tested fungal and bacterial cultures [91]. Silver nanoparticle synthesized using methanol and ethyl acetate extracts of the inflorescence of the tree *Cocous nucifera* showed antimicrobial activity against human bacterial pathogens including *Klebsiella pneumoniae*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Salmonella paratyphi* [92]. Ajitha et al.

synthesized silver nanoparticle from *Plectranthus amboinicus* leaf extract and showed its antimicrobial potential [93].

Other applications of green nanoparticle

Apart from being synthesized from herbal sources, the therapeutic applications of these metal nanoparticles have been also evaluated. Ghosh et al. explored potential hematopoietic and antioxidant property of gold nanoparticle synthesized using fenugreek seed aqueous extract. In this study, iron deficiency anemia in experimental animal model was antagonized with the treatment of herbal gold nanoparticle [94]. Gomes et al. reported anti-arthritic potential of methotrexate-capped gold nanoparticle in experimental rat model [95]. In a noble study, Venkatachalam et al. explored antidiabetic property of gold nanoparticle produced by the reducing capacity of propanoic acid 2-(3-acetoxy-4,4,14-trimethylandrost-8-en-17-yl) isolated from *Cassia auriculata* [96]. In this study, alloxan (150 mg/kg body weight) induced diabetic male albino rats were treated with different doses (0.25, 0.5, 0.75 and 1.0mg/kg body weight) for 28 days. It was observed that plasma glucose level, cholesterol and triglyceride were reduced and plasma insulin level increased after treatment with gold nanoparticle at dosage of 0.5mg/kg body weight. It also exhibited remarkable protein tyrosine phosphatase 1B inhibitory activity. Silver nanoparticle synthesized from *Achillea biebersteinii* flowers extract showed anti-angiogenic potential in rat aortic ring model [97].

As a metal, sliver has effective larvicidal activity. In nanosized form also it shows larvicidal activity. Silver nanoparticle synthesized using *Helitropium indicum* plant leaves showed significant larvicidal property against late third instar larvae of *Aedes aegypti*, *Anopheles stephensi* and *Culex quinquefasciatus* [98]. Rajiv et al. synthesized zinc nanoparticle using *Parthenium hysterophorus* and showed its size-dependent antifungal activity against plant fungal pathogens [71].

Nanoparticles synthesized by green method do not produce toxic bi-products and are environmentally compatible. Moreover, some green nanoparticles reduce environmental pollution, and may serve as effective tool to sustain our life in a better way. Gold nanoparticle loaded graphitic carbon nitride nanosheets prepared by green photoreduction of gold shows effective degradation of organic pollutants [99]. In a study, citric acid and ascorbic acid present in aqueous red tomato (*Lycopersicon esculentum*) juice were responsible for the formation and stabilization of gold nanoparticle, and its efficacy to detect and estimate the presence of pesticide methyl parathion was established [100]. Gold nanoparticle synthesized using guar gum was capable of sensing aqueous ammonia [101]. Chondroitin sulphate-reduced gold nanoparticles were capable of sensing melamine at micro molar level [102]. Iron nanoparticle, synthesized using oolong tea extract was capable of degrading malachite green upto 75.5%, and may serve as a green nanomaterial for environmental remediation [103]. Kuang et al. demonstrated the preparation of iron nanoparticle using green tea extract, oolong tea extract and black tea extract, and showed their effectiveness as a catalyst for the Fenton-like oxidation of monochlorobenzene, an environmental pollutant [104]. Iron nanoparticle synthesized using green tea extract was capable of removing monochlorobenzene from wastewater. They proposed that monochlorobenzene adsorbed on the surface of nanoparticles and oxidized by the hydroxyl radical. Iron nanoparticle synthesized using eucalyptus leaf extract caused removal of 71.7% of total nitrogen and 84.5% of chemical oxygen demand [69].

Gold nanoparticles synthesized using the reducing property of sialic acid showed target-specific aggregation with influenza virus via hemagglutinin-sialic acid binding. A linear correlation was observed between the dilution of chemically inactivated influenza B/Victoria and influenza B/Yamagata and the change in optical density of gold nanoparticle. Very low virus dilution (hemagglutination assay titer, 512) of 0.156 vol% was readily detected by this formulation [105]. Chitosan-reduced gold nanoparticle is capable of sensing caffeic acid and may open up new routes in the design of highly efficient sensors. It possesses great applications in analyzing complex matrices such as wine, soft drinks, and fruit beverages [106]. Tannic acid was used as a reducing agent to synthesize gold nanoparticle and a glucose biosensor was further fabricated by immobilizing glucose oxidase into chitosan-gold nanoplate composites film on the surface of glassy carbon electrode. This sensor exhibited good response to glucose sensing [107]. Magnetite-gold hybrid nanoparticle, synthesized using grape seed proanthocyanidin as the reducing agent was used as a contrast agent for MRI and CT bioimaging [108]. Fowles et al. proposed that gold nanoparticle prepared from zeatin (a plant phytohormone) nanostructures could be used for facile preparation of shape controlled nanoparticles and may open up new avenues for device fabrications in optoelectronics and sensors [109].

Physiological Compatibility of Green Nanoparticle

According to Williams (2008), biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy [110]. The main aims of producing green nanoparticle were environmental safety and biological compatibility. Most of the ionic metals are toxic to our body. In nanoscale range they produce lesser toxicity than ionic forms. Studies showed the blood compatibility of ayurvedic bhasmas (reference). Metal nanoparticles synthesized by biological compounds do not require any synthetic/extra capping agent. The compounds present in the solution of biological reducing agent itself cap the newly synthesized nanoparticles. In most of the cases, the biological reducing agents have medicinal value, or have some active components that are used for years. These extracts and components are proven to be biologically compatible since ancient times. Conjugation of these compounds with metal nanoparticles makes the nanoparticle biologically compatible. Thus the synthesized nanoparticle becomes less cytotoxic to physiological systems. Flower shaped gold nanoparticles synthesized using the reducing property of ascorbic acid possessed low level of cytotoxicity on a human retinal pigment epithelial cell line [111]. Green gold nanoparticle prepared using Korean red ginseng root (*Panax ginseng*) was nontoxic to normal cervical cells lines [112]. Gold nanoparticle synthesized using *Zingiber officinale* aqueous extract showed good blood compatibility. This gold nanoparticle was stable at physiological conditions and did not initiate any cellular aggregation and platelet activation. It did not activate the complement system in body also [113]. Iron oxide nanoparticle produced using grape seed proanthocyanidin showed good biocompatibility on human Mesenchymal Stem Cells. It was observed that the nanoparticle showed good biocompatibility even at high concentrations (500 µg/mL) and up to 48 h incubation, with no apoptotic signals or reactive oxygen species generation [108]. Hence, nanoparticles synthesized from herbal sources showed better therapeutic potential, better biocompatibility and less toxicity which brings forward the concept of "Herbonanoceuticals".

Summary and Conclusions

Green nanotechnology is one of the upcoming challenging areas of nanotechnology having a wide area of application in pharmaceutical industry, health /cosmetic products and in research. There are several hurdles that need attention for better utilization of these wonder molecules. The herbs which are the backbone of these molecules need a close look before their selection. The selection criteria should be focussed on the biological activity, structural advantages, conjugation potential, toxicity profile, stability, etc.

The scientific way to chose and determine the herb or plant of interest would be to look at the background of the plants, it's till date information on active constituents identified, scientific evidences on its biological interaction, clues of its therapeutic potential, etc. Plants already recognized to have biological and therapeutic potential should be given preference. This systematic approach may yield better nanoparticles in terms of stability, acceptability and therapeutic value owing to its herbal origin. Even a more precise and better approach could be to identify the active constituent of the plant/herb responsible for the therapeutic value and use it for nanoparticle synthesis rather than using the whole crude extract of the plant. This way of approach can avoid the unnecessary side effects and interfering constituents present in the crude extract which may interfere with the synthesis process and activity.

The synthesis of different nanoparticles is done by different techniques and these techniques vary greatly with the type of particle synthesized. Till date, multiple approaches of synthesis are followed; therefore, an initiative to establish a set of conventional standardized technique development for nanoparticle synthesis should be of concern to researchers. This development can take the technology a step further since conventional ways and standardization can finally categorize the nanoparticles and therefore, give them a more scientific way of nomenclature. To be more precise it will lead to better understanding and yield of nanoparticles.

Characterization techniques also need to be standardized for conventional physico-chemical characterization of the green nano particles. The available characterization methods come with their own limitations and a multiple number of methods have to be followed for a single nanoparticle. Therefore, development of a single yet confirmed analysed nanoparticle characterization technique is needed to be established. The issue of stability still remains a biggest challenge to the researchers, since stability greatly varies with physical and chemical conditions. And when the nanoparticle is meant for drug delivery then the concern is to keep the particle stable until it hits the target functional area within the body system. Size is another important issue which has to be kept in mind while designing particle for biomedical purpose. Previously it was thought, smaller the size better is its interaction and clearance but with advent of research it has been seen that small size of nanoparticles also makes them highly reactive. Therefore, owing to their extreme reactivity it can hence produce some undesired effects at the molecular level. The chances of these particles to compartmentalize in different compartments of the body also depend on the particle size. Smaller the particle size higher will be its chance for translocation across tissue compartments especially for metal nanoparticles. With bigger particle size arise the problem of body retention and poor clearance. So, it has to be intelligently chalked out for what purpose the particle will be used based on which design of the particle has to be done giving priorities to the issues of size dependent complexities.

While talking about clearance, a more scientific and safe approach would be designing bio-degradable nanoparticles. Consideration can also be given to tag or attach with another third compound/element which can scavenge these nanoparticles out of the body after their desired targeted action. It would be rather a total nanoparticle system design which will help in better clearance thereby flushing out nanoparticles to avoid unnecessary side effects caused by particle retention.

One of the important concerns would be issues of toxicity since most of the studies are done in vitro/ex vivo systems therefore, overall system toxicity evaluation in *in vivo* models should be given priority. Most of the nanoparticles formed are from crude extracts of the herbal sources; therefore, it becomes very difficult to actually say which particular compound acted as the reducing agent, what the capping material is, and which nano-biomolecule is actually responsible for the therapeutic efficacy. Another important consideration is dosage which is difficult to determine since the herbo-nano-metal formulation has both herb and nanometal, therefore, deciding dose will be challenging as it would different from the reported dose of the herb and of the bulk metal.

To conclude, with a new technology come new challenges which has both pros and cons. Resolving these challenges can make this technology survive for years in research, development and applications. Initiatives need to be taken to solve these issues so that herbo nano-metal formulation i.e., herbonanoceuticals can be a wonder drug for future therapeutics.

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Conflict of Interest

The authors declare no conflict interest.

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