Chapter 4
Nanoparticles and Their Application in Folklore Medicine as Promising Biotherapeutics

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Abstract Folklore medicines have been used to treat numerous diseases and ailments since ancient times and have been recognized for their better remedial value due to fewer side effects compared to allopathic medicines. Folkloric medicines generally include decoctions and mixtures made from the extracts of parts of medicinal plants to make these herbal drugs. Herbal drugs have been recently getting more attention because of their potential to treat almost all diseases. However, there are a few drawbacks such as poor solubility, poor bioavailability, low oral absorption, and instability which have limited their use. In order to overcome these problems, nanoparticles have come into play. Nanotechnology and herbal science are integrated to overcome the limitations of using herbal drugs in a scientific way, for the development of novel drug delivery system for herbal drugs with a nano dose which aids in increasing the biosolubility and bioavailability, protection from toxicity, and persistent delivery. These nanosized drug delivery systems have predetermined rates and site precise action. In folklore medicine, nanoparticles containing bioactive therapeutic agents have acquired a great deal of implication due to their impending site-specific action and use in drug delivery. Metallic nanoparticles can also be synthesized from plants due to the inherent ability of plants to accumulate metal ions. A number of plant sources recognized for their use in traditional medicine are being used to synthesize therapeutic nanoparticles. The current review aims to summarize the application of nanotechnology in herbal medicine and the use of nanoparticles synthesized from plants as promising biotherapeutic agents in folklore medicine and presents an overview of the aspects of folkloric medicine in India.

Keywords Folklore medicine · Herbal medicine · Metallic nanoparticles · Nanoparticles · Nanomedicine · Nanotechnology · Phytomedicine

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4.1 Introduction

Folk medicine alludes to those conventional therapeutic practices that do not form a part of formal medical training and normally involve the use of plant-extracted medication, honed specifically by one socio-geographical population. This knowledge, although not documented, is propagated verbally by our ancestors since many generations. The use of these medicines is generally confined to a particular geographical region or group of people such as a tribe or caste community. Primeval folk practitioners accomplished their expertise by observation, examination, and imitation. A number of communities belonging to rural/native/cultural societies depend on folk medicine which has a pivotal role in the remedy of illness. The vast majority of people from developing and underdeveloped countries, who do not have access to contemporary medicine, depend on the traditional/native herbal medicine for their healthcare in spite of great advancements in contemporary medicine.

Folklore medicines have been extensively used since ancient times and are recognized by general practitioners and patients for their better remedial value as they have negligible undesirable effects in correlation to allopathic medicines (Goyal et al. 2011; Thakur et al. 2011). Local communities in developing countries have depended on the exploitation of folkloric plant-derived bioactive secondary metabolite extracts for the treatment of numerous diseases and ailments. Usage of herbs and mineral products along with "enchantment" was the foundation for early folklore medication. The primeval sources like the Atharvaveda indicated the usage of plants and herbs as healing medication which dates back to the 1200 BC, subsequently by the Kahun in Egypt (Petrie collection) in 1880 BC and the Avesta from Persia (around the sixth century AD).

Simple medicinal herbs, porridges, broths, and filtrations were integrated into folk medicine for an effective medication. For example, folk medicines, viz., *Psidium guajava* leaf extract, *Azadirachta indica* (neem) leaf extract, *Ocimum sanctum* boiled with tea leaves, *Momordica charantia* extract, and *Carica papaya* leaf extract, were being used for curing numerous diseases. Folk medicine is generally practiced in secluded areas, and several folk medications are of surprisingly high curative significance. A huge percentage of inhabitants in a number of developing countries still rely on conventional practicians, including midwives, herbalists, and bone healers who are dependent on indigenous medicinal plants to gratify their primary healthcare needs.

In South Asia, despite the accessibility of a large number of practitioners with dissimilar specializations, millions of common people still rely on self-medication using indigenous remedies based on medicinal plants. In south Asian provinces, numerous indigenous plant species are used in these preparations. Many pharmaceutical companies rely on the scientific information about tribal and folk practices which assist in identifying potential lead molecules for future drug preparation, while the pharmaceutical medicines are derived from plants, almost 75% of these were discovered by screening these potential plants in folklore medicine.

In India, the use of plant extracts has been a practice since ancient times which plays a crucial role in the well-being of communities. In the Vedas, knowledge about herbal or plant extract-based treatment and their effectiveness was conveyed by word of mouth from one generation to another. In traditional medicines, for primary healthcare, plant extracts are used by nearly 80% of the world population (Sandhya et al. 2006). However, for principal healthcare, roughly 70% of rural populations are reliant on traditional medicine such as Ayurveda, Unani, Siddha, Amchi, and folk medicine (Pandey et al. 2013).

The prehistoric and primordial science of Ayurveda has an in-depth knowledge of the medicinal plants in Indian medical systems. The effectual treatment has always been endowed by ancient knowledge combined with scientific knowledge to combat and eliminate certain diseases. Folkloric knowledge of the uses of medicinal plants has provided many important drug preparations. The medical utilities of several of these plants have been documented; however, there are many more, whose potentials are yet to be explored.

As reported by the Anthropological Survey of India, the majority of India's populations consisting of more than 4635 tribes which are spread throughout the country living near the jungles, in rural areas, and in villages depend on folkloric medicine for their primary healthcare. Because India has a varied religious, cultural, and multilingual group of people, numerous medicinal systems have been developed. The development of folklore medicine is hindered by the advancement of modern allopathic medicine and facilities.

India is a domicile for a large diversity of plants with unique medicinal and pharmacological potential. The Ministry of AYUSH has provided the livelihood to tribal people by promoting Medicinal and Aromatic Plants (MAPs). Germany regulatory authority's herbal watchdog agency called "Commission E" carried out extensive literature surveys on 300 common medicinal herbs, assessing the eminence and uses of medicinally useful herbs. The enrichment of folk medicine was undertaken by reputed companies like the American Herbal Pharmacopoeia, American Botanical Council, and British Herbal Compendium. The Indian government has documented the Indian folklore knowledge, which can be obtained in the public domain and maintains the autonomy of this folklore knowledge and safeguards it from being misused in patenting on non-patentable inventions.

The "Traditional Knowledge Digital Library" (TKDL) is overseen by national and international IPR laws which is maintained and developed by the government with a joint collaboration with AYUSH and CSIR and is an exclusive digital repository of folklore medicine of India. The database is available online and is publically available and documents the in-depth information about the herbal formulations of Ayurveda, Siddha, Unani, and Yoga. The vital information in the database contains plants' names, therapeutic formulations, and Ayurvedic narration of diseases along with their contemporary names (Mukherjee et al. 2007). TKDL automatically converts the information from Sanskrit into various languages.

The utilization of recent technology like nanotechnology in the field of conventional, indigenous, or folkloric medicines has been endorsed by practitioners worldwide. Due to the lacuna in scientific justification and difficulties in processing of folklore medicines, the novel formulation development was not being considered for a long time. By developing novel drug delivery systems (NDDS) like microspheres, nanoparticles, matrix system, liposomes, and solid-lipid nanoparticles, the technical necessities of folklore medicine can be gratified by modern phytopharmaceutical research. In most of the conventional dosage forms depending on physicochemical and biochemical properties, an inadequate amount of drug administered reaches the targeted site, a greater amount of the drugs gets distributed all over the body resulting in meager therapeutic effect (Sharma et al. 2011). NDDS have potential advantage including drug-targeted delivery, thereby reducing the dosage frequency with an increased solubility, absorption, and decreased elimination (Yadav et al. 2011). Among all the NDDS, nanoparticles are considered to be a potential drug delivery system.

Nanotechnology is the creation, manipulation, and use of materials at the nanometer size scale (1 to 100 nm). Norio Taniguchi in 1974 introduced the term "nanotechnology" for the first time at the International Conference on Industrial Production in Tokyo, in order to demonstrate the super thin processing of materials with nanometer precision and the construction of nanosized mechanisms. In a lecture by Richard Feynman (known as the "father of nanotechnology") in 1959, the ideas of nanotechnological approaches were promoted, at the session of the American Physical Society, and later on in 1986, his ideas were developed by Eric Drexler. In the early 1980s, with the invention of the scanning tunneling microscope (STM), nanotechnology and nanoscience got an enhancement and led to the innovation of Fullerenes in 1985 and the structural assignment of carbon nanotubes in 1991.

Nanotechnology has a greater impact in the field of molecular manipulations whereby powder forms of the huge materials are synthesized which acquires novel properties. Such products occupy a quantum of space (<1–100 nanometers) and have prospective and precision in terms of performance, hence accepted worldwide, and applications include various fields like pharmacy, engineering, agriculture, health and medicine, economy, and day-to-day life (Nikalje 2015).

Even though nanoparticles are considered as the discovery of modern science, they have been documented in various ancient scriptures for thousands of years (Brill and Cahill 1988). The advancement in technologies like the synthesis and application of nanoparticles are always considered to be beneficial for humans. The synthesis of bionanoparticles is mainly dependent on medicinal plants which have the capability to integrate with metal ions and reduce them to metallic nanoparticles. The application of nanoparticles in folklore medicine when compared to allopathic medicine offers numerous advantages such as drug-targeted delivery, minimization of dose, cost-effectiveness, nontoxic, and environmental-friendly. The utilization of medicinal plant extracts for the biosynthesis of nanoparticles is primarily under exploitation.

The current review attempts to highlight the potential use of nanoparticles as biotherapeutics in folklore medicine. The review describes the different types of nanoparticles/nano drug delivery systems, properties, their biosynthesis, therapeutic activity, advantages, and disadvantages. Hence, this concept can be defined as traditional herbal medicine manipulated at the nanoscale level and integrated with folklore herbs for their potential therapeutic value for prospective drug development to combat diseases and for the proper physiology of the body.

4.2 Medicinal Plants Used in Folklore Medicine and Its Importance

In India, the most primitive records of the use of medicinal plants, documented in the Rigveda, elaborate the therapeutic properties of some herbs. Numerous medicinal plants are found to be valuable in the management and of diseases, and the medicinal properties of these folklore medications have been documented in ancient Indian literature. Beneficial medicinal activities of numerous plant species, which are rich in secondary metabolites, have been reported from various plant species which can be used to manage health. The folkloric or tribal system and Indian medicine system akin to Ayurveda, Siddha, and Unani comprehensively use medicinal plants for the well-being management all over the world. It can be predicted that nearly 75% of plant-based therapeutic entities used worldwide were included from traditional/folk medicine.

In India, nearly 70% of the modern drugs are prepared from natural resources, and a number of other synthetic analogs have been prepared from prototype compounds isolated from plants. It was reported that more than 60% of cancer drug available in the market are plant derivative (Sen et al. 2009; Pan et al. 2014). The WHO has estimated the demand for medicinal herbs and their derivatives have a profound value in the market which is around $14 billion per annum, and the demand is steeply increasing at the rate of 15–25% annually. By 2050, the trade of medicinal plants will grow up to US$ 5 trillion as estimated by the WHO.

Folklore healers from various tribes utilize up to 2500 plant species in their treatment and almost 100 species of plants which serve as a regular source of medicines in India. Sankaranarayanan (1988) documented the folklore medicines for jaundice from Coimbatore and Palghat districts of Tamilnadu and Kerala, India. Devendra et al. (2010) conducted a survey on folklore medicinal plants of Gulbarga district, Karnataka, India, and information on 36 plant species from 34 genera and 23 families. The therapeutic implications of these plants include anticancer, antidiabetic, analgesic, hepato- and cardioprotective, antispasmodic, reproductive health, and a wide range of other pharmacological properties (D'Cruz et al. 2010; Lohiya et al. 2016). Many folkloric drugs are food products which are known to have a beneficial effect on male reproductive health, including Gokhru or land caltrops (*Tribulus terrestris*), Tongkat Ali (*Eurycoma longifolia*), garlic (*Allium sativum*), onion (*Allium cepa*), marijuana (*Cannabis sativa*), chili pepper (*Capsicum frutescens*), and ginger (*Zingiber officinale*) (Tambi et al. 2012; Henkel et al. 2014; Lohiya et al. 2016; Mansouri et al. 2016). Renowned herb *Withania somnifera*, popularly known as Ashwagandha or the "Indian ginseng" is regularly used in the treatment of male infertility (Lohiya et al. 2016; Malviya et al. 2016).

The utilization of herbal medicine has been resurfacing owing to the side effects of contemporary drugs, failure of contemporary treatment against chronic diseases, and microbial resistance (Sen et al. 2010; Pan et al. 2014). The use of these herbal remedies is not only cost-effective but also safe and almost free from deleterious effects. The village elders, farmers, and tribal from several countries including China, Middle East, Africa, Egypt, South America, and other developing countries of the world have a good knowledge about well-being which started thousands of years ago and is still part of medical practices by folks of various regions of Indian subcontinents as well. Ravishankar and Shukla (2007) enlisted the medicinal plants of India and their therapeutic uses (Table 4.1).

4.3 Nanotechnology in Herbal Medicines

The potential impact of novel nano-herbal formulations in therapeutics and disease prevention is foreseen to change healthcare in an essential way. Additionally, therapeutics can be customized to every patient's profile.

The synergistic activity of herbal medicines relies on phytochemicals, rich in secondary metabolites, which improves its therapeutic value. However, most of the herbal medicines have poor solubility leading to deprived bioavailability and increased systemic clearance requiring frequent application or higher dose, making the drug a poor contender for therapeutic use. Nanotechnology and herbal science are integrated to overcome the limitations of using herbal drugs in a scientific way, for the development of novel drug delivery system which includes nano dose which aids in increasing the biosolubility and bioavailability, protection from toxicity, and persistent delivery. The novel drug delivery systems have predestined rates and site precise action.

In novel drug technology, the flow of drug circulation is aided by blending the drug into nanocarriers. Secure materials, including biodegradable polymers, lipids, and polysaccharides, are used in the preparation of nanocarriers. Nanocarriers provide the best possible surface area and maximize solubility, bioavailability, and help in accurate drug targeting when compared to micrometer-sized carriers. The amount of drug included into nanocarriers is lesser when compared to encapsulated form. Consequently, for enhancing the activity and to overcome the problems related with plant medicines, the nanosized drug delivery systems (NDDS) of herbal drugs have a potential future. The various herbal nanoparticles delivery systems are summarized in Table 4.2.

Among the various novel drug delivery systems, nanoparticles can be designed to target an individual organ which improves the selectivity, drug delivery, effectiveness, and safety, thus reducing the dose requirement and increasing patient compliance. The requirement of an ideal nanoparticulate system is that it should circulate in the bloodstream and should be small enough to reach the target cells and tissues. Nanoparticles are present in large amounts in the human body even at the cellular level; hence, it is assumed that nanoparticles can be employed to treat severe,

Table 4.1 List of some well-known Indian medicinal plants and their uses (Ravishankar and Shukla 2007)

Species name	Family	Parts used	Therapeutic uses	References
Acorus calamus	Araceae	Rhizome	Nervine tonic, antispasmodic	Bose et al. (1960); Satyavati et al. (1976)
Aegle marmelos	Rutaceae	Fruit	Hypoglycemic, chemopreventive	Vyas et al. (1979); Dixit et al. (2006)
Allium sativum	Alliaceae	Bulbs	Anti-inflammatory, antihyperlipidemic, fibrinolytic	Dixit et al. (2006)
Aloe barbadensis	Alliaceae	Gel	Skin diseases—mild sunburn, frostbite, scalds; wound healing	Baliga (2006)
Andrographis paniculata	Acanthaceae	Whole plant	Cold, flu, hepatoprotection	Koul and Kapil (1994)
Asparagus racemosus	Alliaceae	Roots	Adaptogen, galactogogue	Dahanukar et al. (1997); Gupta and Mishra (2006)
Bacopa monnieri	Scrophulariaceae	Whole plant	Antioxidant, memory enhancing	Singh and Dhawan (1997)
Berberis aristata	Berberidaceae	Bark, fruit, root, stem, wood	Antiprotozoal, hypoglycemic, anti-trachoma	Dutta and Iyer (1968)
Boerhavia diffusa	Nyctaginaceae	Roots	Diuretic, anti-inflammatory and anti-arthritic	Harvey (1966)
Boswellia serrata	Burseraceae	Oleo resin	Anti-rheumatic, anti-colitis, anti-inflammatory and anticancer	Sharma et al. (2000c)
Butea monosperma	Fabaceae	Bark, leaves, flowers, seeds and gum	Adaptogen, abortifacient, antiestrogenic, anti-gout, anti-ovulatory	Sharma et al. (2000d)
Calotropis gigantea	Asclepiadaceae	Flowers, whole plant, root, leaf	Anti-inflammatory, spasmolytic, asthma	Sharma et al. (2000e)
Callicarpa macrophylla	Verbenaceae	Leaves, roots	Uterine disorders	Sood (1995)
Cassia fistula Linn.		Resin	Laxative, antipyretic, worm infestation	Joshi (1998)
Centella asiatica	Umbelliferae	Whole plant	Tranquilizer, memory enhancer, wound healing	Suguna et al. (1996)
Chlorophytum borivilianum	Alliaceae	Roots	Aphrodisiac	Farooqi et al. (2001)

(continued)

Table 4.1 (continued)

Species name	Family	Parts used	Therapeutic uses	References
Cissus quadrangularis	Vitaceae	Whole plant, root, stem and leaf	Bone fracture, inflammation	Udupa and Prasad (1964); Deka et al. (1994)
Clerodendrum serratum	Verbenaceae	Root, leaf, Stem	Malaria, anti-asthmatic, anti-allergic	Gupta and Gupta (1967)
Commiphora mukul	Burseraceae	Resin	Hypolipidemic, obesity, rheumatoid arthritis	Satyavati (1991)
Crataeva nurvala	Capparidaceae	Stem bark, leaf	Urinary disorders including stones	Anand et al. (1995)
Crocus sativus	Iridaceae	Stigma	Aphrodisiac, anti-stress, antioxidant	Billore et al. (2004a)
Curculigo orchioides	Amaryllidaceae	Root stock	Spermatogenesis enhancer	Joshi (2005)
Curcuma longa	Zingiberaceae	Rhizome	Anti-inflammatory, wound healing enhancer, chemopreventive agent, antioxidant, anticancer	Tripathi et al. (1973); Narasimhan et al. (2006)
Desmodium gangeticum	Papilionaceae	Root	Antioxidant, anti-rheumatic	Govindarajan and Vijayakumar (2006)
Eclipta alba	Compositae	Whole plant	Hepatoprotecive/promotes hair growth	Chandra (1978)
Eugenia jambolana	Myrtaceae	Seed, bark, leaf	Hypoglycemic, anti-inflammatory, antidiarrheal, antipyretic	Sharma et al. (2001)
Ficus religiosa	Urticaceae	Bark	Anti-ulcer (gastric ulcer); anti-inflammatory, hypoglycemic agent	Ambike and Rao (1967)
Gymnema sylvestre	Asclepiadaceae	Roots and leaves	Antidiabetic, antihyperglycemic	Narasimhan et al. (2006)
Gloriosa superba	Liliaceae	Tuber	Spasmolytic, oxytocic, source plant for colchicine	Sharma et al. (2002a)
Glycyrrhiza glabra	Papilionaceae	Stem	Expectorant, peptic ulcer treatment	Mitra and Rangesh (2004a)
Hedychium spicatum	Zingiberaceae	Rhizome	Soothening, expectorant, antitussive, anti-asthmatic	Chaturvedi and Sharma (1975)
Hippophae rhamnoides	Elaeagnaceae	Fruits	Extensively used in the treatment of circulatory disorders, wound healing enhancer, duodenal ulcer	Arora et al. (2006)
Holarrhena antidysenterica	Apocynaceae	Stem bark, leaf, seed	Antispasmodic, anti-colitis, hypoglycemic	Mitra and Rangesh (2004b)
Inula racemosa	Asteraceae; Compositae	Roots	Used in gastro intestinal disorders, diuretic, expectorant and allergic disorders	Mishra (2004a)

Leptadenia reticulata	Asclepiadaceae	Root, leaf, fruit	Galactogogue, vasodilator, anabolic	Anjaria et al. (1975)
Momordica charantia	Cucurbitaceae	Root, leaf, fruit, seed	Antidiabetic	Ahmed et al. (2001)
Oroxylum indicum	Bignoniaceae	Root, root bark, leaf, fruit, seed	Anti-inflammatory, diuretic	Gujral et al. (1955)
Phyllanthus amarus	Euphorbiaceae	Whole plant	Hepatoprotective	Balachandran and Govindarajan (2004)
Picrorhiza kurroa	Scrophulariaceae	Tubers	Hepatoprotective, adaptogen	Narasimhan et al. (2006)
Plumbago zeylanica	Plumbaginaceae	Root, root bark	Antipyretic, anticancer, anticoagulant, cytotoxic	Krishnaswamy and Purushothaman (1980)
Pueraria tuberosa	Fabaceae	Tuberous root	Anti-implantation, estrogenic, anti-inflammatory, dysmenorrhea, DUB	Billore et al. (2004b)
Rubia cordifolia	Rubiaceae	Root	Anti-inflammatory, antitumor, hypoglycemic	Sharma et al. (2002c)
Saussurea lappa	Asteraceae	Roots	Analgesic, aphrodisiac, asthma	Chaurasia (2006)
Swertia chirata	Gentianaceae	Whole plant	Antimalarial, hypoglycemic, febrifuge	Hamsaveni et al. (1981); Dixit et al. (2006)
Symplocos racemosa	Symplocaceae	Bark	Antidiarrheal	Sharma et al. (2002d)
Taxus baccata	Taxaceae	Source of taxol	Used in the treatment of metastatic breast cancer	Chauhan et al. (2006)
Tecomella undulata	Bignoniaceae	Bark, seeds	Antibacterial, hypoglycemic, hepatoprotective	Billore et al. (2004c)
Terminalia chebula	Combretaceae	Fruits	Laxative, antioxidant	Narasimhan et al. (2006)
Tinospora cordifolia	Menispermaceae	Stem	Adaptogen, immunomodulator	Thatte et al. (1994); Dahanukar et al. (1997)
Tribulus terrestris	Zygophyllaceae	Whole plant	Diuretic, anti-urolithiatic, cytoprotective	Chakraborty and Neogi (1978); Sangeeta et al. (1993)
Vitex negundo	Verbenaceae	Leaves, root, bark, flowers, seed	Anti-inflammatory, anti-arthritic, immunomodulator	Nair and Saraf (1995)
Withania somnifera	Solanaceae	Root	Adaptogen, antirheumatic	Sandhya and Sushil (1998)
Zingiber officinale	Zingiberaceae	Rhizome	Fever, cough, asthma, antiemetic	Sharma et al. (2002b)

Table 4.2 Herbal drug nanoparticles (Ansari et al. 2012)

Formulations	Active ingredients	Biological activity	Method of preparation	References
Artemisinin nanocapsules	Artemisinin	Anticancer	Self-assembly procedure	Chen et al. (2009)
Berberine-loaded nanoparticles	Berberine	Anticancer	Ionic gelation method	Chang et al. (2011)
Curcuminoids solid lipid nanoparticles	Curcuminoids	Anticancer and antioxidant	Micro-emulsion technique	Nayak et al. (2010)
Glycyrrhizic acid loaded nanoparticles	Glycyrrhizin acid	Anti-inflammatory antihypertensive	Rotary-evaporated film ultrasonication method	Hou and Zhou (2008)
Nanoparticles of *Cuscuta chinensis*	Flavonoids and lignans	Hepatoprotective and antioxidant effects	Nanosuspension method	Yen et al. (2008)

chronic diseases and genetic disorders. Herbal medicines can be targeted to various organs such as the brain, lungs, liver, kidneys, and gastrointestinal tract (Kostarelos 2003; Allen and Cullis 2004).

4.4 Nanoparticles in Folklore Medicines

Nanoparticles are characterized as powdered materials with particles measuring less than 100 nanometers. This diminishment in scale brings about radical changes in their physical properties compared to bulky objects. They can be metallic, mineral, polymer-based, or a blend of materials and are used in various fields like medicine, nutrition, and energy (Chandran et al. 2006). Herbal drug solubility and efficacy can be improved by utilizing nanoparticles, thereby localizing the drug at a specific site. The rich biodiversity and accessibility of plant substances have led to the increasing use of plants for the synthesis of nanomaterial blend (Mondal et al. 2011).

Nanoparticles of diverse size and shape have been biosynthesized from a range of parts of plants like seeds, leaves, fruits, flowers, stems, and roots (Prasad 2014, Prasad et al. 2018). Nanomedicine has a massive potential in curing different interminable maladie and a huge role to play in the healthcare sector in treating various chronic diseases (Cruz et al. 2010). Secondary active metabolites of plants, viz., flavonoids, tannins, and terpenoids, are highly soluble in water. Because of their high molecular weight, the absorption rates are low; hence, they are unable to cross the lipid membranes of the cells resulting in the loss of bioavailability and effectiveness. Some herbal extracts are not used clinically due to these practical problems. Encapsulating these herbal secondary metabolites in folklore medicine with nanoparticles/nanomaterials will solve these practical problems.

For effectual therapeutic activity of folklore medicine, the nanoparticles must have a size range of <50 nm, helping them to penetrate the body rapidly, and the general routes of entry are through the oral and mucous membranes which will activate diverse reactions. These nanoparticles often concentrate in sites other than those therapeutically anticipated and are vehicles for drug delivery into the body. All through the entire treatment phase, nanosystems can convey these active constituents at an optimum concentration, directing it to the preferred action site. Conventional folklore treatments do not meet these requirements.

4.5 Different Classes of Nanoparticles

Nanomaterials can be broadly classified into inorganic and organic. Organic polymers (organic nanoparticles) and/or inorganic elements (inorganic nanoparticles) are widely used to prepare nanoparticles. Liposomes, dendrimers, carbon nanomaterials, and polymeric micelles are examples of organic nanoparticles (Fig. 4.1).

4.5.1 Inorganic Nanoparticles

Inorganic nanoparticles have a central core made of inorganic materials that describe their fluorescent, magnetic, electronic, and optical properties. The different types of inorganic particles include magnetic, metallic, ceramic, and nanoshells; their description and size are depicted in Table 4.3.

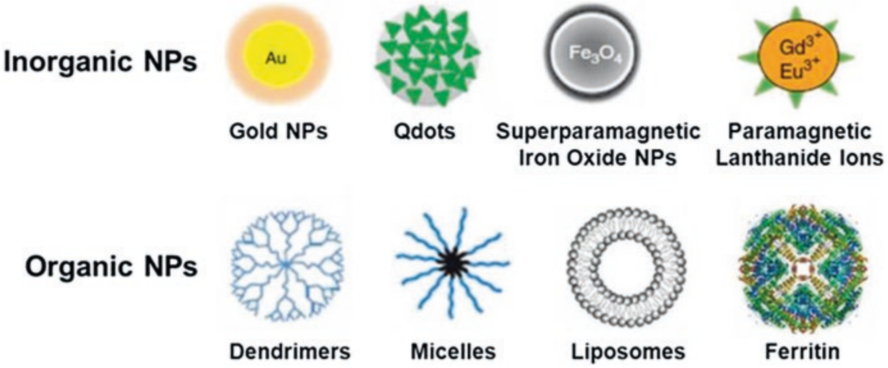

Fig. 4.1 Different types of organic and inorganic nanoparticles (https://www.nanoshel.com/organic-and-inorganic-nanoparticles)

Table 4.3 Inorganic nanoparticles

Inorganic nanomaterial	Description	Size (nm)
Ceramics	Nanoscale ceramics such as hydroxyapatite (HA), zirconia (ZrO_2), silica (SiO_2), titanium oxide (TiO_2), and alumina (Al_2O_3)	<100
Magnetic	Superparamagnetic iron oxide particles	5–100
Metallic	Gold, silver, zinc, copper particles	1–100
Nanoshells	Spherical core of a compound surrounded by a shell or outer coating of thin layer of another material	1–20

Table 4.4 Organic nanoparticles

Organic nanomaterial	Description	Size (nm)
Carbon tubes	Coaxial graphite sheets rolled up into cylinders	<100 nm
Dendrimers	Dendrimers are highly branched synthetic polymers with layered architectures constituted of a central core	<15
Liposomes	Liposomes are phospholipid vesicles that have a bilayer membrane structure	50–100
Polymers	Polymers are macromolecules composed of a large number of repeating units organized in a chain-like molecular architecture	10–1000
Quantum dots	Colloidal fluorescent semiconductor nanocrystals	2–10

4.5.2 *Organic Nanoparticles*

The various types of organic nanoparticles, namely, carbon nanotubes, quantum dots, dendrimers, liposome, and polymers, and their description and size are described in Table 4.4.

4.5.3 *Ceramic Nanoparticles*

Currently, the utilization of new ceramic materials for biomedical research has grown steadily, due to improvisation of the physicochemical properties and reduction in the cytotoxicity of biological systems; synthetic nanoscale ceramics such as alumina (Al_2O_3), hydroxyapatite (HA), silica (SiO_2), titanium oxide (TiO_2), and zirconia (ZrO_2) are being synthesized.

The employment of ceramic nanoparticles for the controlled release of drugs is one of the most exploited areas in folklore medicine. In this field, the dose and size are important. Nanoparticles in drug delivery have high stability, high load capacity, easy incorporation into hydrophobic and hydrophilic systems, and different routes of administration (oral, inhalation). In addition, a variety of organic groups which may be functionalized on its surfaces allow for a directed effect (Fadeel and Garcia-Bennett 2010).

4.5.4 Magnetic-Based

Magnetic nanoparticles can be manipulated using magnetic fields; they belong to a class of a nanoscale particle consisting of magnetic elements like iron, nickel, and cobalt, plus their chemical compounds. Recently, magnetic nanoparticles have been used in scientific research on folklore medicine as they possess unique properties that have use in medicine. Magnetic nanoparticle clusters are composed of a number of individual magnetic nanoparticles are known as magnetic nanobeads, with a diameter of 50–200 nm (Tadic et al. 2014). Magnetic nanoparticle clusters are a basis for their further magnetic assembly into magnetic nanochains (Kralj and Makovec 2015).

4.5.5 Metal-Based Materials

Metal nanoparticles are nanosized metals with a size range of 1–100 nm. Faraday in 1857 first recognized the existence of metallic nanoparticles in solution. For improving the efficacy of folklore medication, the utilization of noble metals like gold, silver, zinc, copper, and metal oxides, such as titanium dioxide, can be used (Table 4.5).

4.5.6 Nanoshells

Nanoshells consist of a spherical core of a complex bounded by a shell or outer coating of thin layer with an additional material of 1–20 nm thick which can be synthesized from semiconductors, metals, or insulators. Core-to-shell ratio used by the materials determines the property of nanoshells. Dielectric core enclosed by metallic shell, especially gold (AuNSs). In these cases, drug is encapsulated or adsorbed onto the shell surface via specific functional groups or by electrostatic stabilization. AuNSs are employed to deliver antitumor drugs (e.g., doxorubicin, paclitaxel, small interfering RNA, and single-stranded DNA) into cancer cells, which augment the efficacy of treatment. AuNSs can also be functionalized with active targeting ligands, such as antibodies, aptamers, and peptides to increase the particle's specific binding to the desired targets (Mudshinge et al. 2011).

Table 4.5 Summary of plant-derived metallic nanoparticles and its biomedical applications (Kuppuswamy et al. 2016)

Plants used	Nanoparticles	Parts of plant	Size (nm)	Shapes	Plant metabolites involved in bioreduction	Pharmacological applications	Reference
Acalypha indica	Ag, Au	Leaves	20–30	Spherical	Quercetin, plant pigment	Antibacterial	Krishnaraj et al. (2010)
Aloe vera	In_2O_3	Leaf	5–50	Spherical	Biomolecules	Optical properties	Maensiri et al. (2008)
Alternanthera sessilis	Ag	Whole	40	Spherical	Amine, carboxyl group	Antioxidant, antimicrobial	Niraimathi et al. (2013)
Andrographis paniculata	Ag	Leaves	67–88	Spherical	Alkaloids, flavonoids	Hepatocurative activity	Suriyakalaa et al. (2013)
Artemisia nilagirica	Ag	Leaves	70–90	Spherical	Secondary metabolites	Antimicrobial	Song and Kim (2008)
Boswellia serrata	Ag	Gum	7–10	Spherical	Protein, enzyme	Antibacterial	Kora et al. (2012)
Caria papaya	Ag	Fruit	15	Spherical	Hydroxyl flavones, catechins	Antimicrobial	Jain et al. (2009)
Cassia fistula	Au	Stem	55–98	Spherical	Hydroxyl group	Antihypoglycemic	Daisy and Saipriya (2012)
Cinnamon zeylanicum	Ag	Leaves	45	Spherical	Water-soluble organics	Antibacterial	Sathishkumar et al. (2009)
Citrullus colocynthis	Ag	Calli	5–70	Triangle	Polyphenols	Antioxidant, anticancer	Satyavani et al. (2011)
Citrus sinensis	Ag	Peel	35	Spherical	Water-soluble compounds	Antibacterial	Kaviya et al. (2011)
Dillenia indica	Ag	Fruit	11–24	Spherical	Biomolecules	Antibacterial	Singh et al. (2013)
Dioscorea bulbifera	Ag	Tuber	8–20	Rod, triangular	Diosgenin, ascorbic acid	Antimicrobial	Ghosh et al. (2012)
Euphorbia prostrata	Ag	Leaves	52	Rod, spherical	Protein, polyphenols	Antiplasmodial	Zahir and Rahuman (2012)
Gelsemium sempervirens	Ag	whole	112	Spherical	Protein, amide, amine group	Cytotoxicity	Das et al. (2011)
Lippia citriodora	Ag	Leaves	15–30	Spherical,	Isoverbascoside compound	Antimicrobial	Cruz et al. (2010)

Mentha piperita	Au, Ag	Leaves	90–150	Spherical	Menthol	Antibacterial	MubarakAli et al. (2011)
Mirabilis jalapa	Au	Flowers	~100	Spherical	Polysaccharides	Antimicrobial	Vankar and Bajpai (2010)
H. canadensis	Ag	Whole	113	Spherical	Phenolics, protein	Cytotoxicity	Das et al. (2011)
Iresine herbstii	Ag	Leaves	44–64	Cubic	Biomolecules phenolic compound	Biological activities	Dipankar and Murugan (2012)
Melia azedarach	Ag	Leaves	78	Irregular	Tannic acid, polyphenols	Cytotoxicity	Sukirtha et al. (2012)
Tinospora cordifolia	Ag	Leaves	34	Spherical	Phenolic compound	Antilarvicidal	Jayaseelan et al. (2011)
Trigonella foenum-graecum	Au	Seed	15–25	Spherical	Flavonoids	Catalytic	Aromal and Philip (2012)
Withania somnifera	Ag	Leaves	5–40	Irregular, spherical	Methyl-7-oxooctadecanoate	Antimicrobial	Nagati et al. (2012)

4.5.7 Carbon-Based Materials

Carbon nanotubes are made up of coaxial graphite sheets (<100 nm) which are rolled up into cylinders. They belong to the family of fullerenes, formed either as single- (one graphite sheet) or multi-walled nanotubes (numerous concentric graphite sheets). They demonstrate exceptional strength and electrical properties and are very good thermal conductors. Due to their metallic or semiconductor nature, nanotubes are frequently used as biosensors. Surface functionalization renders the carbon nanotubes water soluble. Hence, they are used as drug carriers and tissue-repair scaffolds. These nanomaterials are mainly made up of carbon made into the form of a hollow spheres, ellipsoids, or tubes. Spherical and ellipsoidal carbon nanomaterials are referred to as fullerenes, while cylindrical ones are called nanotubes.

4.5.8 Dendrimers

Dendrimers have a central core which are highly branched synthetic polymers (<15 nm) with layered architectures. The surface of a dendrimer has numerous chain ends, which can be tailored to perform specific chemical functions. This property could also be useful for catalysis as three-dimensional dendrimers contain interior cavities into which other molecules could be placed, they may be useful for drug delivery. Dendrimers demonstrate intrinsic drug properties and are used as tissue-repair scaffolds. Furthermore, dendrimers are excellent drug and diagnostic imaging agent.

4.5.9 Liposome-Based

Liposomes are phospholipid vesicles (50–100 nm) made up of a bilayer membrane structure comparable to that of biological membranes having an internal aqueous phase. Based on the size and number of layers, liposomes are classified into multi-oligo or uni-lamellar. Liposomes are nanoparticulate systems that have been developed for more than four decades for drug delivery to a specific site in the body (Samaligy et al. 2006).

Their amphiphilic nature allows them to convey hydrophilic drugs entangled within their aqueous interior and hydrophobic drugs dissolved into the membrane. Liposomes demonstrate exceptional penetration, circulation, and diffusion properties, and the liposome surface can also be customized with ligands and/or polymers to boost the specificity of drug delivery.

4.5.10 Polymeric Nanoparticles

Polymeric nanoparticles are macromolecules made up of repeated subunits of chain-like molecular architecture which brings about the variations in composition, structure, and properties. A polymeric nanoparticle ranges from 10–1000 nm in diameter, protecting drugs efficiently. They can materialize as nanocapsules (NCs) and nanospheres (NSs); these structures have varied composition and structural organization. Nanocapsules enclose an oily core bounded by a polymeric membrane; the active ingredient can be adsorbed to the polymeric membrane and/or dissolved in the oily core. This active component has better adsorption on nanospheres manufactured from polymeric substrates. Although there is an increasing demand for the new types of polymers, some of them have already been used extensively for polymeric nanoparticles, including poly-L-lactic acid (PLA) and copolymers with glycolic acid (PLGA) (Schaffazick et al. 2003; Alexis et al. 2008; Ajazuddin 2010; Prasad et al. 2017). Because of this diversity of structures, properties, and compositions, polymers are mainly utilized in nanoparticle systems to produce nanoparticles suitable for a specific folklore medication.

4.5.11 Natural and Synthetic Polymeric Nanoparticles

Chitosan, albumin, and heparin are the naturally occurring nanoparticles which have been extensively used for the delivery of drugs, DNA, and proteins. In addition, the use of hydroxypropyl-methacrylamide (HPMA), polyethylene glycol (PEG), polylactic acid-glycolic acid (PLGA), and polylactic acid (PLA) nanoparticles as natural and synthetic polymers has been recognized. The use of conjugated polymeric nanoparticles with chemotherapeutic drugs can minimize the damaging effects of the free drug administration (Cho et al. 2008).

4.5.12 Quantum Dots

Quantum dots are photostable colloidal fluorescent semiconductor nanocrystals (2–10 nm). The central core of quantum dots is made up of an amalgamation of elements from groups II–VI of the periodic system (CdSe, CdTe, CdS, PbSe, ZnS, and ZnSe) or III–V (GaAs, GaN, InP, and InAs), which are coated with a layer of ZnS. They demonstrate high quantum yield and composition-tunable emission spectra and are extremely resistant to photo and chemical degradation. All these features make quantum dots good candidates for drug delivery in folklore medicine.

4.6 Choice of Nanoparticles in Folklore Medicine

The application of metallic nanoparticles in folklore medicine has gained a tremendous interest due to the emerging significance of targeted drug delivery of medicine. Primitive Indian medical sciences made use of herbs or an amalgamation of mineral-herb preparations. Gold, silver, lead, tin, copper, iron, mercury, and zinc are the most commonly used therapeutic metals used in herbal medicines. The term "Bhasmikaran" often used in Indian medicine refers to the transition of non-biocompatible herbo-mineral material to a biocompatible form. The process of preparation of Bhasma (metal ash) enhances the medicinal value by transforming the metal from to its zero-valent state to an advanced oxidation state forming a metal oxide. These metals are maximally processed and are changed into their therapeutic form which can be utilized to enhance the medicinal value of folklore medicine.

In conservative Ayurvedic practices and medicine, "Swarna Bhasma" aka "gold ash" is frequently given as a potent treatment. Gold ash has been utilized in various folklore medicines to improve human health. Nanosized gold particles, oxidized form of gold ash, has superior medicinal properties when compared to the native state metallic gold. In Indian literature of 2500 BC, there occurs evidence of the therapeutic use of gold nanoparticles, and these practices are still being followed to date. There are great prospects for gold nanoparticles (GNPs) to be used in human health and cosmetics applications (Alanazi et al. 2010).

Gold nanoparticles have been extensively employed in biomedical applications (Bhattacharya and Mukherjee 2008; Sperling et al. 2008; Puvanakrishnan et al. 2012), separation sciences (Sýkora et al. 2010), disease diagnostics (Torres-Chavolla et al. 2010), and pharmaceuticals (Bhumkar et al. 2007; Cai et al. 2008).

The antibacterial and anti-inflammatory properties of silver nanoparticles promote faster wound healing. Because of these attributes, silver nanoparticles have been integrated into the already available wound dressings, antiseptic formulations, and medical implant coatings (Cohen et al. 2007; Huang et al. 2007; Asha Rani et al. 2008; Cox et al. 2011; Li et al. 2011a, b; Pollini et al. 2011; Aziz et al. 2016).

Platinum nanoparticles have been employed extensively in biomedical applications in either pure or alloyed form with other nanoparticles (Hrapovic et al. 2004) and palladium nanoparticles in catalysis and electro-catalysis applications (Akhtar et al. 2013; Gopidas et al. 2003), chemical sensors (Coccia et al. 2012), optoelectronics (Chen et al. 2007), and antibacterial applications (West et al. 2010).

Metallic nanoparticles including iron (Pankhurst et al. 2003; Njagi et al. 2010), copper (Lee et al. 2011; Yadav et al. 2017), zinc oxide (Brayner et al. 2006), and selenium (Prasad et al. 2013) have applications in medical treatments and antimicrobial formulations.

Numerous diseases from infertility to asthma, diabetes, and cancer can be treated by administering gold nanoparticles along with herbs. The gold acting as a catalyst transports the herbal medicine to the target organ thereby enhancing its activity and also helping to restore the normal function of the diseased organ.

Phenolic acids, flavonoids, alkaloids, and terpenoids are secondary metabolites found in crude plant extracts, and these biocompounds are primarily used in the ionic reduction of bulk metallic nanoparticles (Aromal and Philip 2012). Eco-friendly nanoparticles produced from these primary and secondary metabolites are involved in the redox reaction. Numerous reports showed that the biosynthesized nanoparticles effectively controlled oxidative stress, genotoxicity, and apoptosis-associated changes (Kim et al. 2007). In the field of agriculture industry and plant sciences, nanoparticles are being used to convert the agricultural and food wastes into energy and useful by-products.

4.7 Need of the Nanoparticles in Folklore Remedies

To overcome the flaws of using traditional herbal drugs, nanoparticles are incorporated due to the following reasons: Nanoparticles can target the herbal medicine to specific organ, improving the selectivity, drug delivery, effectiveness, and safety. Nanoparticles improve the efficacy by increasing the solubility of herbal drug and target the drug to a specific site (Sharma et al. 2014). Owing to their unique size and high-loading capacities, nanoparticles can convey high concentrations of drugs to disease sites. Delivering the drug in nanosize boosts the surface area of the drugs consequently, allowing rapid distribution in the bloodstream, and shows enhanced permeation and retention effect, i.e., improved permeation through the barriers and retention due to meager lymphatic drainage (Jayaseelan et al. 2013). Displays decreased the side effects by submissively targeting the site of action without the addition of any particular ligand moiety (Ansari et al. 2012).

4.8 Mechanism of Nanoparticle Formation

A number of methods are used for the synthesis of nanoparticles (NPs) including physical, chemical, enzymatic, and biological. Physical methods include plasma arcing, ball milling, thermal evaporate, spray pyrolysis, ultrathin films, pulsed laser desorption, lithographic techniques, sputter deposition, layer-by-layer growth, molecular beam epistaxis, and diffusion flame synthesis of nanoparticles (Joerger et al. 2000), while chemical methods used are electrodeposition, sol-gel process, chemical solution deposition, chemical vapor deposition (Panigrahi et al. 2006; Oliveira et al. 2005), soft chemical method, Langmuir Blodgett method, catalytic route, hydrolysis (Pileni 1997), co-precipitation method, and wet chemical method (Gan et al. 2012). Physical and chemical methods are hazardous to the environment and to human health because of the use of high radiation and highly concentrated reductants and stabilizing agents. A single-step bioreduction process is involved in the biosynthesis of nanoparticles; hence, a lesser amount of energy is utilized to synthesize eco-friendly NPs (Sathishkumar et al. 2009). Environmentally sustainable resources like plant extracts, bacteria, fungi, microalgae such as cyanobacteria, diatoms, seaweed (macroalgae), and enzymes (Iravani 2011) are used in biological methods (Prasad et al. 2016).

4.8.1 Bioreduction Mechanism

In the synthesis of nanoparticles, the intracellular or extracellular extract of organisms is merely combined with a solution of the metal salt at room temperature. The reaction is completed within minutes. The nature of the extract, its concentration, the concentration of the metal salt, the pH, temperature, and contact time all determine the rate of production of the nanoparticles, their quantity, and other characteristics. Figure 4.2 depicts the biosynthesis of nanoparticles using various organisms.

4.8.2 Plant-Mediated Synthesis of Nanoparticles

A plethora of organisms including fungi, bacteria, and yeast have been recognized for the synthesis of safe noble nanoparticles. But this is not industrially feasible as the microbial mediated synthesis of nanoparticles requires costly medium and aseptic conditions. Thus, the potential usage of plant systems for nanoparticle synthesis has garnered great interest (Prasad 2014). Henceforth, plant systems have

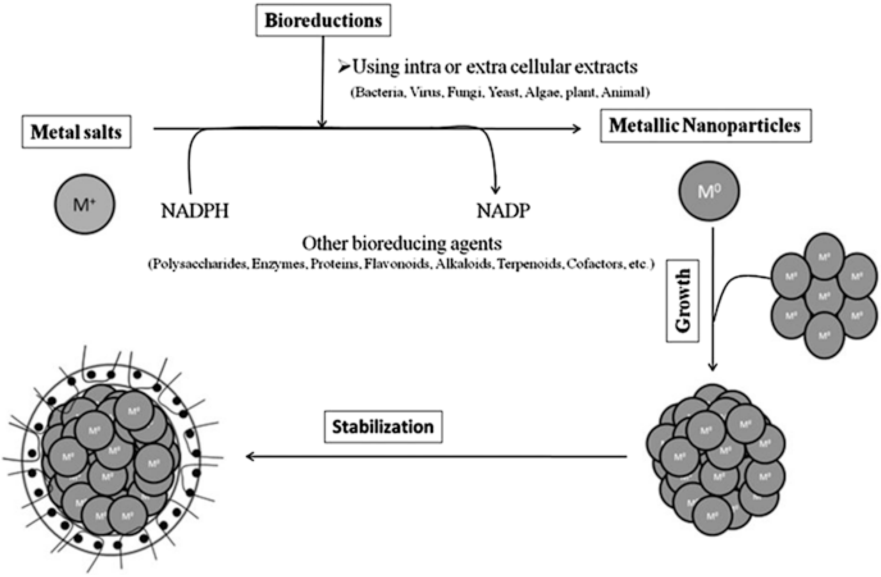

Fig. 4.2 The proposed mechanism of biological synthesis of nanoparticles (Velusamy et al. 2015)

been considered as ideal bioreactors for the synthesis of metal nanoparticles without using toxic chemicals.

Proposed mechanism of nanoparticle synthesis using plant extracts:

Gold: a number of biomolecules like proteins, sugars, amino acids, enzymes, and other traces of metals can be extracted from plants. These metabolites are involved in the bioreduction process. Thakkar et al. (2010) proposed the reaction of Au^+ ions reduction into metallic Au nanoparticles in the presence of metabolites and redox enzymes. The reaction is given below:

$$\mathrm{HAu}+\mathrm{Cl}_4\cdot 4\mathrm{H}_2\mathrm{O}+\text{plant extracts}\rightarrow \mathrm{AuoNPs}+\text{by}-\text{products.}$$

Platinum: platinum nanoparticles are produced by the general reaction below:

$$\mathrm{H}_2\mathrm{Pt}+\mathrm{Cl}_2\cdot 6\mathrm{H}_2\mathrm{O}+\text{plant extracts}\rightarrow \mathrm{PtoNPs}+\text{by}-\text{products.}$$

Copper: copper nanoparticles are synthesized from plant extracts, and the reduction mechanism was proposed by Ramanathan et al. (2013):

$$\mathrm{CuSO}_4\cdot 5\mathrm{H}_2\mathrm{O}+\text{plant metabolites}\rightarrow \mathrm{CuoNPs}+\text{by}-\text{products.}$$

Silver: the biochemical reaction of $AgNO_3$ reacting with plant broth to produce silver nanoparticles was proposed by Tripathy et al. (2010):

$$\mathrm{Ag}+\mathrm{NO}_3^-+\text{plant extract}\rightarrow \mathrm{AgoNPs}+\text{by}-\text{products.}$$

4.8.3 Biological Synthesis of Metal Nanoparticles via Plants

Plants have long been known to have the potential to hyper-accumulate and reduce metallic ions (Kale et al. 2013). Plants are considered a more environment-friendly route for biologically synthesizing metallic nanoparticles and as detoxifying agents (Kale et al. 2013; Khan et al. 2013; Prasad 2014; Prasad et al. 2018). Bioactive alkaloids, phenolic acids, polyphenols, proteins, sugars, and terpenoids from plants have a pivotal role in first reducing the metallic ions and then stabilizing them (Marshall et al. 2007; Castro et al. 2011). The variability in the composition and concentration of these active biomolecules among different plants and their subsequent interaction with aqueous metal ions is said to contribute to the diversity of nanoparticle sizes and shapes produced. The synthesis of nanoparticles via plants by reducing metal salts is a direct process occurring at room temperature and starts by combining a plant extract sample with a solution containing metal salt. Biochemical reduction of the salts proceeds instantaneously, and the formation of nanoparticles is indicated by a change in the color of reaction mixture. An initial activation period occurs during the synthesis, where processed metal ions are altered from their mono- or divalent oxidation states to zero-valent states followed by the nucleation of the reduced metal atoms (Malik et al. 2014). This is instantaneously followed by a growth phase where smaller adjacent particles merge to form thermodynamically stable larger nanoparticles while further biological reduction of metal ions takes place. As growth spurts, nanoparticles aggregate to form diverse morphologies like cubes, spheres, triangles, hexagons, pentagons, rods, and wires (Akhtar et al. 2013). The plant extract's ability to stabilize the nanoparticle determines it's most thermodynamically favorable and stable morphology during the final stage of synthesis. The metal salt concentration, reaction time, reaction solution pH, and temperature of plant extracts drastically influence the quality, size, and morphology of the synthesized nanoparticles (Dwivedi and Gopal 2010; Mittal et al. 2013).

Kesarwani and Gupta (2013) had reviewed several studies on nanostructured systems to optimize the properties of plant extracts. Bhattacharya and Ghosh (2009) devised and used lipid-based systems with green tea and ginseng (*Panax ginseng* CA Meyer) (Araliaceae) extracts, in various formulations, to optimize the absorption of the active components. The use of herbal extracts to synthesize gold and silver nanoparticle was reported by Gardea-Torresdey et al. (2002). Plant extracts contain polyphenols which act as reducing agents whose side chains (mostly –OH group) help in capping and stabilizing nanoparticles and are thus used in the synthesis of metal nanoparticles in large scale.

Gold nanoparticles are extensively used in nanotechnology due to their biocompatibility but are biologically inert; to solve this, they can be engineered to possess chemical or photothermal functionality. This alteration of gold nanoparticle can be done by changing its surface chemistry. Geetha et al. (2013) synthesized gold nanoparticles using the flower of *Couroupita guianensis* tree by a rapid, cost-effective, one-step process. Gold nanoparticles were synthesized without using any stabilizing agent from glucoxylans isolated from the seeds of *Mimosa pudica* (Iram et al. 2014).

Suman et al. (2014) produced gold nanoparticles from aqueous root extract of *Morinda citrifolia.* Arunachalam and Annamalai (2013) using the reducing property of aqueous leaf extract of *Chrysopogon zizanioides* biosynthesized gold nanoparticles with antibacterial, antioxidant, and cytotoxic properties. Very few studies have been conducted on the environmentally benign synthesis of zinc nanoparticle. Nagarajan et al. (2013) made zinc oxide nanoparticle using green *Caulerpa peltata*, red *Hypnea valencia*, and brown *Sargassum myriocystum* which are marine seaweeds. FT-IR spectrometry showed the contribution of fucoidan pigment in the synthesis of nanoparticle.

Rajiv et al. (2013) reported the synthesis of zinc oxide nanoparticle from the leaf extract of the weed, *Parthenium hysterophorus* L. which displayed the size-dependent antifungal activity against *Aspergillus flavus* and *Aspergillus niger.* Mixed copper and zinc oxide nanoparticle were synthesized using *Brassica juncea* L. plant, and it was found that the ZnO nanoparticles were nonuniform in shape (Qu et al. 2012). Sankar et al. (2014) synthesized a rod-shaped CuO nanoparticle using *Carica papaya* leaf extract. Padil and Černík (2013) used gum karaya, a natural nontoxic hydrocolloid, to formulate CuO nanoparticles. Harne et al. (2012)

synthesized copper nanoparticles with excellent long-term stability using the aqueous extract of latex of *Calotropis procera* L.

4.8.4 Synthesis of Metallic NPs From Plants

Lately, plant-derived nanomaterials have drawn intrigue in many fields due to their diverse physicochemical properties. The various parts of plant such as the stem, root, fruit, seed, callus, peel, leaves, and flower are being utilized to synthesize metallic nanoparticles like gold, silver, platinum, zinc, copper, titanium oxide, magnetite, and nickel in various shapes and sizes by biological approaches. The biosynthesis reaction can be modified to fit a wide range of metal concentration and amount of plant extract in the reaction medium; it may transform the shape and size of the nanoparticles (Chandran et al. 2006; Dubey et al. 2010).

4.8.5 Stem as Source for Nanoparticle Synthesis

Shameli et al. (2012) synthesized silver nanoparticles using *Callicarpa maingayi* stem methanolic extract and formed [Ag (*Callicarpa maingayi*)] + complex. Aldehyde groups present in the plant extract are involved in the reduction of silver ions into metallic Ag nanoparticles. The phytosynthesis of silver nanoparticles using *Cissus quadrangularis* extracts at room temperature was reported by Vanaja et al. (2013). Diverse functional groups, like carboxyl, amine, and phenolic compounds, were involved in the reduction of silver ions extracted from the stem part of plant extract. Thus, synthesized silver nanoparticles revealed a good antibacterial activity against the pathogenic bacteria, viz., *Klebsiella planticola* and *Bacillus subtilis*.

4.8.6 Leaves-Mediated Synthesis of NPs

Many plant leaf extracts including *Centella asiatica*, *Murraya koenigii*, and *Alternanthera sessilis* have been investigated as mediators for the synthesis of nanoparticles. AgNPs form potent medicines in cancer treatment and other dreadful diseases. Leaf extracts of *P. nigrum* having longumine and piper longminine are utilized as capping agents for the synthesis of silver nanoparticles and may augment the cytotoxic effects on tumor cells (Jacob et al. 2012).

Vijayakumar et al. (2013) described a green synthesis approach for silver nanoparticles with the *Artemisia nilagirica* plant leaf extract. Leaf-mediated nanoparticles in folklore medicine have a potential use as antimicrobial agents in the present and the near future.

4.8.7 Flowers as Source for NPs Production

Noruzi et al. (2011) explored the usage of rose petals for the eco-friendly synthesis of gold nanoparticles. The extract medium contains a surplus of sugars and proteins which are the main sources for the reduction of tetrachloroaurate salt into bulk GNPs. Similarly, *Catharanthus roseus* and *Clitoria ternatea* are used to synthesize metallic nanoparticle with the desired sizes and shapes. Flower-mediated synthesis of nanoparticles have been very useful in controlling harmful pathogenic bacteria. Vankar and Bajpai (2010) used an eco-friendly method to produce gold nanoparticles using the aqueous extract of *Mirabilis jalapa* flowers which acts as reducing agents.

4.9 Use of Nanoparticles as a Therapeutic in Folklore Medicine

Biological entities can be used in the synthesis of nanoparticles in folklore medicine which can deliver new sources of medicines that are cost-effective, stable, nontoxic, eco-friendly, and synthesized using the approach of green chemistry. Although biological entities have been extensively used to produce nanoparticles, bacteria- and fungi-based techniques need a special culture preparation or isolation techniques, while the use of plants offers a straightforward, inexpensive, easily scaled up, clean, nontoxic, and robust procedure that does not need any such special procedures. Nanoparticles with a specific size, shape, and composition can be potentially produced from plant extracts that can be extensively used in the present medical procedures involving nanoparticles like immunoassays fluorescent labeling, targeted drug delivery, and in bandages as antibacterial agents.

Herbal and folklore researchers have established that therapeutic nanoparticles (NPs) are more effective drug delivery systems when compared to the conventional forms of drugs. Nanocarriers transdermal gel (NCTG) was made from optimized nanotransfersomes of diclofenac diethylamine (DDEA) and curcumin (CRM) for a sustained release and targeted effect. Greater absorption of the drug with coadministration of lecithin was achieved due to the nanosize of NCTG, also giving vesicles a hydration gradient, increased permeability, decreased degradation, and clearance by surfactant compared to marketed gel and plain curcumin gel (Chaudhary et al. 2014). Chaudhary et al. (2013) formulated and optimized nanotransfersomes of DDEA and CRM which provided a large surface area with high penetration potential and achieved high bioavailability. A potential treatment scheme for uncreative colitis was through a synthesis of pH-sensitive nanoparticles of curcumin-celecoxib combination (Gugulothu et al. 2014). The preparation of curcumin solid lipid nanoparticles (CRM-SLN) with a high-loading capacity and chemical stability for the treatment of oral mucosal infections was reported by Hazzah et al. (2015). Dandekar et al. (2010) successfully demonstrated an effective antimalarial action with curcumin-loaded hydrogel nanoparticles of hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP).

Prabakar et al. (2013) established the biosynthesis of silver nanoparticles (AgNPs) using *Mukia scabrella* leaf extract; it showed noteworthy antimicrobial activity against MDR-GNB nosocomial pathogens. AgNPs from the aqueous leaf extract of *Bauhinia tomentosa* Linn. were produced, and their in vitro anticancer activity was studied by Mukundan et al. (2015). Khatoon et al. (2015) prepared fluorescent AgNPs with a significant fluorescence and antibacterial activity by using *Artemisia annua* leaf extract, and their biocompatibility was confirmed by checking for cytotoxicity against human erythrocytes.

Islam et al. (2015) synthesized gold nanoparticles (AuNPs) from the gall extract of *Pistacia integerrima* which displayed a notable antifungal and antinociceptive activity. *Aegle marmelos* Correa (AMC) was investigated for the phytofabrication of nickel nanoparticles (NiNPs) from the aqueous leaf extract of AMC. NiNPs are very good anti-inflammatory agents and drug carriers (Angajala et al. 2014). Magnetic nanoparticles (MNPs)-based drug delivery approach for the co-delivery of curcumin and temozolomide was found to be capable of provoking great anticancerous activity (Dilnawaz and Sahoo 2013).

Bitencourt et al. (2016) confirmed the in vitro efficacy against the complications of diabetes mellitus (DM), and the in vivo toxicity was assessed by using an aqueous extract of *Syzygium cumini* seed (ASc) and polymeric nanoparticles containing ASc (NPASc) which showed a high in vitro activity and potential inhibitory activity against ox-LDL particles. Solid lipid nanoparticles (SLNPs) can be utilized as carriers for the extract's phenolic compounds. For the synthesis of SLNPs, witepsol and carnauba (WSLNPs and CSLNPs) loaded with medicinal herbs, extracts of savory, and sage were used. WSLNPs was a more appropriate vehicle for herbal extracts, with a greater stability during digestion and a high release percentage of phenolic compounds self-nanoemulsifying in the small intestine (Campos et al. 2015).

Li et al. (2011a, b) successfully synthesized a stable drug delivery system (SNEDDS) formulation with persimmon leaf extract with a noteworthy improvement in solubility, in vitro release, and bioavailability compared with the Naoxinqing tablets. SNEDDS optimized quercetin (QT) formulae presented an optimum shield against liver damage, compared with QT against hepatotoxicity induced by paracetamol.

Zhao et al. (2010) synthesized a SNEDDS from the rhizome of *Curcuma zedoaria* and formulated a Zedoary turmeric oil (ZTO) having better bioavailability and aqueous dispersion. The manufactured ZTO-SNEDDS could serve as a partial lipid phase with double advantages of increasing drug loading and also curbing the requirement of inert oils. A multiunit drug delivery system (MUDDS) was prepared for a Chinese medicine: Niuhuang Xingxiao Wan (NXW) to supplement the drug bioavailability and effectiveness. The in vivo assay for antitumor activity showed the potential efficacy of NXW-MUDDS compared to NXW (Shi et al. 2015).

Suganya et al. (2011) studied and prepared topical administration anti-inflammatory agents from nanoemulsion and poly lactic-co-glycolic acid (PLGA) NPs by mixing of four prenylated flavanones isolated from *Eysenhardtia platycarpa* leaves. A nanofiber mat of polycaprolactone (PCL)/polyvinylpyrrolidone (PVP) was created from crude bark extract of *Tecomella undulata* and evaluated for their antibacterial activities. The extract loaded with nanofiber mat of PCL/PVP showed wound healing properties and reduced dermal bacterial infections, inhibiting the growth of such bacterial strains. To improve wound healing in a rat model, Yao et al. (2017) successfully incorporated *Centella asiatica* (CA) extract into electrospun membranes. The wound areas covered with electrospun gelatin membranes containing CA (EGC) membranes showed more collagen deposition and more capillaries than the wound areas to which the other treatments were applied demonstrating the potentiality of EGC membranes in wound dressings.

The use of capsaicin for topical treatment in nanoparticle, microemulsion, or nanocapsule form was demonstrated as a treatment/modulation in specific receptor activity in vivo or in vitro to treat chronic or acute pain and neuropathic pain (Bakthavatchatam et al. 2003, 2004).

Kanazawa (2009) synthesized a nanoparticle comprising of 0.1–100% w/w of a blood circulation promoter such as tocopherol derivative, a nicotinic acid derivative (niacin, vitamin B3), *Swertia japonica* extract (Makino), sunflower, tocopherols (vitamin E), olive oil (tocotrienols), palm oil, and a biodegradable polymer-like protein, such as collagen, gelatin, albumin, casein, acid-treated gelatin, ovalbumin, sodium casein, and so on. An α-, β-, γ-, and κ-casein was also used alone or in combination. The protein was then subjected to a cross-linking treatment after the formation of a nanoparticle by using transglutaminase obtained from guinea pig liver, goat, rabbit, or human liver and treated with organic solvents like ethanol, acetone, and isopropanol. This formulation can be used as a transdermal absorbable agent, topical therapeutic agent, oral therapeutic agent, intradermal parenteral injection, subcutaneous parenteral injection, cosmetic, functional food, supplement, or a quasi-drug.

Leighton and Frangakis (2013) established a method for the treatment of herpes simplex virus-induced inflammation by the topical application of a mixture containing an effective dose of antihistamine, with the base composition containing essential extracts of lemon balm (*Melissa officinalis*), calendula flowers (*Calendula officinalis*), green tea gunpowder (*Camellia sinensis*), and green rooibos (*Aspalathus linearis*) as emulsions, nanoparticles, suspensions, and patches. A nanoformulation of *Butea monosperma* extract was prepared to treat/prevent bone disorders like osteoporosis. The formulation was available as a microemulsion, nanoparticle, nanoemulsion, and microparticle with a dose of 0.1–5000 mg (Maurya et al. 2007).

Mousa et al. (2013) put forth a method and composition to prepare nanoformulations of active ingredients like *Lepidium sativum*, green tea extract, pomegranate extract, or other lepidium extracts; calcium; vitamin D; and antioxidants like flavonoids and/or isoflavones, lycopene, and a combination that is used for the treatment of osteoporosis in animals. The active ingredient is encapsulated within the nanoparticles selected from a group of chitosan nanoparticles, poly(lactic-co-glycolic acid) (PLGA) nanoparticles, chitosan cross-linked to fatty/bile acids, alginate-chitosan nanoparticles, polyvinylpyrrolidone (PVP) hydrogel nanoparticles, and so on. The present composition was meant for oral, topical, injectable, via toothpaste, and in combination, in cases of osteoporosis and bone fracture in animals.

Shen et al. (2012) prepared a polyester nanoparticles unit containing curcumin and pyromellitic anhydride monomer residues, and a polyethylene glycol monomethyl ether side chain, bound to the polymer backbone and also prepared polyester which possessed an antitumor, antioxidant, anti-inflammatory, and antibacterial properties in the form of nanoparticles, colloidal particles, and vesicles. An herbal composition of a therapeutically effective amount of *Scutellaria baicalensis*, *Glycyrrhiza uralensis*, *Ziziphus jujuba*, and *Paeonia lactiflora* with a chemotherapeutic compound used to treat cancer in mammals was developed by Liu et al. (2013).

DiMauro and Codman (2013) developed methylated curcumin-methoxystilbene hybrid molecules, used in treating cancer. Less than 1% of oral curcumin enters the plasma and undergoes intestine-based metabolism and rejection. The small amount of curcumin that enters the bloodstream is quickly metabolized by the kidney and liver. The intranasal administration of a formulation with an effective amount of curcumin to the olfactory mucosa across the cribriform plate and into the brain can be used to treat neurodegenerative diseases like Alzheimer's disease.

4.10 Advantages and Disadvantages of Nanoparticles From Herbal Extracts in Folklore Medicine

Nanoparticles synthesized using plant extracts are advantageous to the conventional folklore methods of synthesis due to their low cost of production, fewer accidents, and safer products with less waste. All these characteristics make biosynthesis an almost ideal method for making nanoparticles. However, the change in the physicochemical and structural properties of nanomaterials with a decrease in size could be responsible for a number of material interactions that could lead to toxicological effects. These attributes have to be considered when developing a method of synthesis of nanoparticles and formulating nanodrugs.

4.11 Conclusion

In recent decades, folklore medicines are getting popular and have been getting more consideration because of their potential to treat numerous diseases. However, quite a few problems such as poor solubility, poor bioavailability, low oral absorption, instability, and unpredictable toxicity of herbal medicines limit their use.

In order to overcome such problems, nanoparticles can play a vital role in folklore medicine. Development and synthesis of herbal nanoparticles has become a cutting-edge research in the folklore nanoformulation area. The use of nanoparticles of folklore medicine is gaining popularity and has been getting more consideration because of the fact that nanoparticles can be potentially designed to treat various ailments and diseases. Nanotechnology makes use of nanoparticles that have a high surface area and can reach the targeted site because of its extremely small size. Nanotechnology and folklore can be integrated to overcome the limitations of herbal drugs and to optimize its biotherapeutic effects.

Nanoparticles, especially metallic nanoparticles, have attracted a substantial interest in diverse fields such as medicine and agriculture. This review summarizes the application of nanoparticles from plants as promising biotherapeutic agents in folklore medicine. However, the massive diversity of biological entities ranging from microorganisms to plants renders the field largely unexplored. The production of nanoparticles from plants to serve as stable drug delivery agents is due to the fact that these particles are nontoxic, cost-effective, easily scaled up, environment-friendly, and synthesized using the bioreduction approach. Plant extracts can be used to produce nanoparticles with a specific size, shape, and composition.

Plant-synthesized nanoparticles can be used in the current medical procedures involving nanoparticles such as fluorescent labeling in immunoassays, targeted delivery of therapeutic drugs, tumor destruction via heating (hyperthermia), and antibacterial agents in bandages. On another front, plant-synthesized nanoparticles also are potential delivery agents of antimicrobial compounds for use as pesticides for agricultural crops. Metallic nanoparticles prepared from the extracts of many medicinal plants have been combined with folklore medicinal preparations to increase the efficacy of the herbal drugs. Despite the environmental advantages of using biological synthesis over the traditional methods, there are some unaddressed issues such as particle size and shape consistency, reproducibility of the synthesis, and knowledge of the process of synthesizing metallic nanoparticles. Therefore, a more thorough investigation is due, to evaluate and understand the actual plant-dependent materials and involved mechanisms. Nanosized drug delivery systems for herbal drugs can potentially enhance the biological activity and overcome problems associated with plant medicines. However, monumental challenges remain on the implementation of clinically viable therapies in this field. Trials for novel methods to control the interactions of nanomaterials within biological systems are one of the current challenges to translating these technologies into therapies.

The use of nanoparticles in folklore medicine can be potentially designed to increase its bioavailability and for treatment of various ailments and diseases. The review has also demonstrated that folklore medicine biosynthesized in the form of nanoparticle not only increases the solubility and bioavailability of poorly soluble herbals but can also improve biotherapeutic activity of novel herbs.

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