Chapter 6
Inorganic Particles for Delivering Natural Products

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Abstract Natural products are complex molecules that have been widely used in traditional medicine for therapeutics and diagnostics applications. Despite their long history of use, some challenges are associated with many natural product derived pharmaceuticals, like inadequate stability, poor absorption, distribution, metabolism and excretion. Medicinal chemists have been successful in addressing many of these challenges through structural modifications of the parent compound, but even so, analysis suggests that up to 20% of natural product leads are taken through unchanged as the final drug product. Even modified compounds are a challenge to administer, requiring the use of novel formulations and delivery strategies to enable the launch of an effective natural product derived drug into the market. To outwit these concerns, formulation of these natural product derived bioactive compounds using nanotechnology has been used as a potential tool in diagnostic and therapeutic applications. Compounds of organic or inorganic origin that are prepared from different metals, metal oxides, chitosan, sodium alginate, poly lactic acid, poly lactic co-glycolic acid, synthetic as well as natural origin polymers are amongst commonly used materials for development of natural product nanoformulations.

This book chapter deals in detail with the properties, synthesis, advantages and toxicity of inorganic particles like those of silver, gold, iron oxide and silica with the aim to shed light on the delivery of natural products for therapeutic and diagnostic purposes. Adjustable size and shape, large surface area, ease of functionalization and additional bioactivities associated with inorganic nanoparticles are some of the properties that give them an edge over other delivery methods. Apart from enhancing the stability of molecule, high-density surface ligands attachment enables the targeted delivery with enhanced therapeutic efficacy. Among the inorganic nanoparticles, metallic nanoparticles made up of silver or gold are increasingly being used for biomedical purposes because of their biocompatibility, versatility, broad antimicrobial activity as well as visible light extinction property. Silver and gold possesses

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peculiar properties such as Surface Plasmon Resonance associated which are not associated with other delivery vehicles like liposomes, dendrimers or micelles. Metal oxides such as Iron oxide (Fe_2O_3, Fe_3O_4) and silica (SiO_2) with various surface modifications and as hybrid are now the popular choices for delivering natural products for a variety of applications.

Keywords Natural product delivery · Gold nanoparticles · Silver nanoparticles · Iron oxide nanoparticles · Silica nanoparticles · Curcumin · Paclitaxel · Flavonoids · Quercetin

Abbreviations

FDA	Food and Drug Administration
MCM-41	Mobil composition of matter no 41
PEG	Polyethylene glycol
PEI	Polyethylenimine

6.1 Introduction

Natural products are amongst the widely used medicinal compounds for targeting and treating various bourgeoning and emerging diseases. Plants, animals and minerals are common natural source for the extraction these complex chemical molecules by various extraction processes, and/or by chemical synthesis and chemo-enzymatic synthesis. These compounds serve as the source of potential drug lead molecules. However, low bioavailability and stability limits the therapeutic application of natural products. The average calculated octanol-water partition coefficient (log P) of natural products is 2.9 while of drugs is 2.1 suggesting that natural products are more lipophilic than drugs. Natural products are more rigid than drugs because they contain larger fused ring system and on an average contain two rotatable bonds less than drugs (Wetzel et al. 2011). To circumvent these concerns, encapsulation of these bioactive compounds via nanotechnology (nanomaterials are substances having at least one dimension, 100 nm in size) has been materialized with potential applications in diagnostic and therapeutic developments. Nanomaterials can be of inorganic as well as organic origin and could be synthesized from different polymers, metals, metal oxides, chitosan, sodium alginate, poly lactic co-glycolic acid (PLGA), poly lactic acid (PLA), synthetic polymers etc. These nanomaterials protect the drug/bioactive molecule from the hazardous environment, pH and temperature variation and target the molecule to desired organ with an increase in therapeutic efficacy. Inorganic particles draw much attention due to adjustable size and shape, high surface area, ease of functionalization, high-density surface ligands attachment as well as additional bioactivities associated with them for desired applications.

Inorganic nanoparticles of non-metallic origin ($Al(OH)_3$, Fe_2O_3, ZnO, SiO_2, Fe_3O_4, CeO_2, ITO, CaO, ATO, ZrO_2) and metals and metal alloys (Pt, Cu, Pd, Fe, Ni, Co, Ag, Au, Al, Mn) have been attempted for various purposes. Metallic nanoparticles show strong plasma absorption and enhanced rayleigh as well as surface raman scattering for imaging applications. However, most of these are thermodynamically unstable and may contain some impurities such as oxides and nitrides. Most of these impurities come during synthesis and may cause irritation or toxicity or both. Among metallic nanoparticles silver or gold (Ag or Au) particles are most preferably and increasingly being used for different biomedical purposes either because of their visible light extinction behavior, versatility, antimicrobial property and good biocompatibility (Kasthuri et al. 2009a, b). Silver and gold possess specific properties such as surface plasmon resonance which dendrimers, liposomes and micelles don't. Metal oxides such as Iron oxide (Fe_2O_3, Fe_3O_4) and silica (SiO_2) with various surface modifications and as hybrid are popularly used to deliver natural products. Iron oxides exhibits super paramagnetic properties at the size range of 8–10 nm, which not only helps in targeting under the influence of magnetic field, but also governs easy synthesis, separation and hyperthermia derived cancer cell killing. On the other hand silica show high payload due to mesoporous character and easy surface functionalization. This book chapter deals in details with the properties, synthesis, advantages and toxicity of silver, gold, iron oxide and silica particles citing some examples to show delivery of natural products. Figure 6.1 shows the schematic representation of natural products delivery via inorganic nanoparticles.

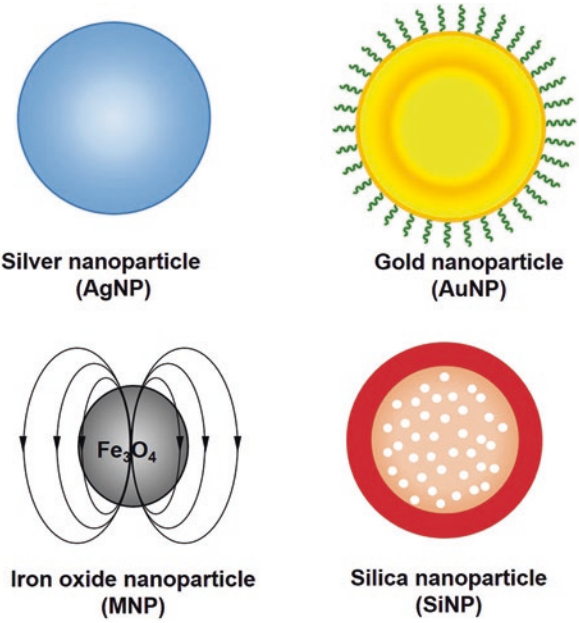

Fig. 6.1 Natural products delivery via silver, gold, iron oxide and silica nanoparticles

6.2 Inorganic Nanoparticles: Properties, Synthesis, Advantages and Toxicity

6.2.1 Metallic Nanoparticles

6.2.1.1 Silver Nanoparticles

Silver nanoparticles, due to their attractive physiochemical properties, easy to fabricate in desired size range with biological functionality, and non-toxic nature governs its extensive use in the biomedical applications. Silver based nanosystem and nanomaterials have shown antibacterial, antiviral, antifungal, antioxidant properties and used for drug/natural products delivery, tissue scaffold fabrication, wound dressing and protective coating applications. The antimicrobial properties exhibited by silver nanoparticles are related to their physiochemical properties such as shape, size, concentration, colloidal state and surface charge. Furthermore, silver nanoparticles allow the coordination of many ligands, and enabling easy surface functionalization (Tran and Le 2013; Le Ouay and Stellacci 2015; Phull et al. 2016).

Synthesis

Different methods such as chemical, physical and biological are used for the synthesis of silver nanoparticles. Using chemical method, Ag + ions are reduced to Ag (metallic silver) which agglomerates to form oligomeric clusters. Chemical synthesis is carried out using different inorganic and organic reducing agents such as sodium citrate, sodium borohydride, sodium ascorbate, elemental hydrogen, N, N-dimethylformamide and tollens method. However, different, coating agents, surfactants and polymers are used to inhibit the agglomeration of particles during chemical synthesis (Iravani et al. 2014).

Physical synthesis methods involves, ball milling, radiation, flame pyrolysis, sonication, electric arc discharge and laser ablation of silver bulk material in solution. Despite the use of highly expensive equipments, high temperature and pressure, as well as high energy consumption, physical methods are more eco-friendly as compared to chemical methods.

Biological synthesis are known as "green" methods and gained immense popularity due to devoid of any toxic chemical use. Using green synthesis; silver nanoparticles are prepared via bio-reduction of Ag + ions in aqueous medium using bacteria, fungi, algae, and plants. Bacterial synthesis comprises of selection and cultivation of suitable bacterial strain and maintenance of highly aseptic conditions. Culture supernatant of nonpathogenic and pathogenic microorganisms like *E. coli*, *B. indicus*, *A. flavus*, *B. cereus*, *Bacillus strain CS 11*, *P. proteolytica*, *P. meridian*, *S. aureus* etc. are used to synthesize silver nanoparticles, and can be achieved either intracellularly or extracellularly. Extracellular synthesis is easy, cheaper and required lesser time hence preferred over intracellular synthesis. However, the mechanism behind the nanoparticles formation using the microbial organisms is poorly understood which hinders the scaling laboratory technique for the industrial synthesis. (Nanda and Saravanan 2009; Shivaji et al. 2011; Das et al. 2014; Ahmed et al. 2016). Plant

based green synthesis of silver nanoparticles is gaining immense popularity because of its easy accessibility, economic feasibility, environment friendly nature, formulation simplicity along with the possibility of large scale production. Different plant extracts such as *Azadirecta Indica, Madhuca longifolia, Crocus sativus L., Calliandra haematocephala*, Grape seed, Andean blackberry fruit, Granium leaf extract and Marigold flower etc. have been reported for the green synthesis of silver nanoparticles (Patil et al. 2018; Li et al. 2007; Ahmed et al. 2016; Bagherzade et al. 2017; Raja et al. 2017; Rivera-Rangel et al. 2018). The phytochemical extracts includes flavonoids, terpenoids, saponins, phenolics, tannins, catechins, enzymes, proteins, polysaccharides and rich complex compounds which acts as reducing, stabilizing and capping agents are extensively used during "green" method of silver nanoparticles synthesis. Due to such added advantages, silver nanoparticles have been extensively investigated for targeted drug delivery and diagnostic applications.

The phytochemical composition varies significantly from plant to plant and in different parts of plants and has admissible effect on the quality of nanoparticles. For example, spherical silver nanoparticles were prepared using *Syzygium cumini* fruit extract and it has been suggested that flavonoids present in the plant extract were responsible for the reduction of Ag + to Ag which is very crucial for particle synthesis (Mittal et al. 2014). In another study, spherical silver nanoparticles were synthesized in 3–20 nm size range with leaf broth of *Arbutus unedo* which contains both reducing and stabilizing agents which are responsible for particle synthesis (Kouvaris et al. 2012), similarly, *Erythrina indica* root extract was used for silver nanoparticles synthesis in size range of 20–118 nm (Sre et al. 2015). Shail et al. reported that extract of *Origanum vulgare L.* contains mixture of flavonoids, alkaloid and terpenoids which imparts reducing and capping properties during silver nanoparticles synthesis (Shaik et al. 2018). Nanoparticle synthesis parameters such as; concentration of silver ions, plant extract concentration and phytochemical composition, temperature, pH, microwave assistance, mechanical stirring speed and time had a significant effect, it was observed that synthesis of plant extract capped silver nanoparticles were higher at 90 °C as compared to room temperature with yielding of larger size particles at higher temperature. It was also reported that, antimicrobial properties of silver nanoparticles were linearly increases with use of higher concentrations of plant extracts during synthesis as the half maximal inhibitory concentration values were decreased from 4% to 21% with increase in solubility of nanoparticles (Khan et al. 2013, 2014). After nanoparticles synthesis, characterization can be done using physicochemical properties such as shape, size, surface area, purity and coating along with the associated electrochemical properties namely; charge, zeta potential, redox, conductivity and surface plasmon resonance for the synthesis variability assessment (Li et al. 2017). Silver nanoparticles have been widely and frequently used for tumor specific drug delivery (Kajani et al. 2016). It is reported that light scattering cross section of silver nanoparticles is ~10 times greater than similar size gold nanoparticles, and are strongest light scatterers amongst the nobel metal particles. Because of these characteristics, silver nanoparticles have also been employed as photoactivated drug delivery vector and biological sensors (Brown et al. 2013). Silver nanoparticle based delivery systems facilitate

intracellular detection and controlled release of natural products through chemical or photothermal of photochemical triggers e.g. Silver nanoparticles in the size range of 60–80 nm were developed, which contains anti-sense oligonucleotides for ICAM-1 (intracellular adhesion molecule-1) silencing. Light induced release of anti-sense oligonucleotide demonstrated wound healing and therefore suggested their therapeutic potential for the treatment of Crohn's disease (Brown et al. 2013).

Toxicity Assessment of Silver Nanoparticles

Bioactive molecule incorporated surface functionalized silver nanoparticles have been exploited as promising oral formulation for improving solubility and bioavailability, reducing toxicity enhancing bioactive compound release. These formulations provide better therapeutic tool against cancer, wound healing and pathogenic microbial diseases etc. There is little information regarding exposure of silver nanoparticles to environment, animals and humans but their potential risks reporting contradictory results are available with short and long term exposure (Kittler et al. 2010; Bouwmeester et al. 2011; Loeschner et al. 2011).

Daily approximate silver intake by humans through food and/or water is 0.4–30 μg, which indicates that in the given range silver nanoparticles can be used without any sever short term toxicities for therapeutic applications (Hadrup and Lam 2014). Silver nanoparticles have demonstrated excellent antimicrobial properties and non-toxicity towards healthy mammalian cells (Stensberg et al. 2011). However, there are some reports where silver nanoparticle related toxic effects have been observed in rat hepatocytes, neuronal cells (El Mahdy et al. 2015), murine stem cells and human lung epithelial cells (Pinzaru et al. 2018). Wen H et al. has investigated the silver nanoparticles mediated acute toxicity and genotoxicity in Sprague-Dawley rats where 61.1% of nanoparticles were 27.3–106.2 nm sizes. Studies also reported that silver nanoparticles are mainly concentrated in lungs followed by spleen, liver, kidney, thymus and heart. These particles also enhance the blood urea, total bilirubin, alanine aminotransferase and creatinine which indicate abnormal liver functions. Further histopathological examination of liver, kidney, thymus and spleen after exposure with silver nanoparticles showed extensive organ damages which were also complementing the abnormal liver function tests. At the cellular level significant chromosomal breakage and polyploidy were observed which indicates silver nanoparticles derived genotoxicity (Wen et al. 2017). In an *in vivo* toxicity study using rat ear model, silver nanoparticles mediated permanent or temporary hearing loss and significant mitochondrial dysfunction was also observed. A Lower silver nanoparticles concentration has also been detected in retinal cells where these particles induced structural disruption and oxidative stress (Antony et al. 2015). Also, silver nanoparticles surface charge might modulate the particle uptake, its translocation to various tissues and organs and thereby cytotoxicity (Franci et al. 2015; Wu et al. 2017).

6.2.1.2 Gold Nanoparticles

Gold nanoparticles has garnered attention in recent biomedical field especially for ultrasensitive biomolecular detection, selective cancer cell killing by photothermal therapy, specific cells and protein labeling and cellular therapeutic delivery. Gold nanoparticles permits easy tailoring into different size, shape, and attachment of different functional groups, chemically biocompatible and have intrinsic tunable optical properties (Kumar et al. 2012). The gold nanoparticle size is related to surface plasmon resonance, by changing the thiol/gold ratio during synthesis, size of conjugated gold nanoparticles can be controlled and therefore surface plasmon resonance could be fine tune according to the application requirements. Such as particles with smaller size can be synthesized using higher amount of thiol (SH) and vice versa (Bhattacharya and Srivastava 2003). Characteristic UV absorbance at 520 nm can be observed using 10 nm gold nanoparticles, however, a blue or red shift can be observed with size variation. Figure 6.2 shows the schematic representation of different types of gold nanoparticles and effect of size on the optical properties. Gold nanorod shows the characteristic absorbance towards near infra-red range (690 nm–900 nm), these intrinsic optical properties of gold nanoparticles can be exploited for its use as composite theranostic agents in clinic (Tong et al. 2009). Gold nanoparticles of 1–100 nm, when dispersed in water are also designated as colloidal gold, these nanoparticles comprises; gold nanorods, gold nanoshells, gold nanocages, gold nanosphere and gold nanoparticles with stimuli-responsive surface enhanced raman scattering.

Synthesis

For the synthesis of gold nanoparticles, chemical method is most commonly and widely used which encompasses the reduction of gold salt (HAuCl4) with the help of reducing agents. In 1857, Michael Faraday, first reported gold nanosphere synthesis by two phase synthesis using tetraoctyl ammonium bromide having high air and thermal stability. Citrate reduction method has been used for gold nanoparticles

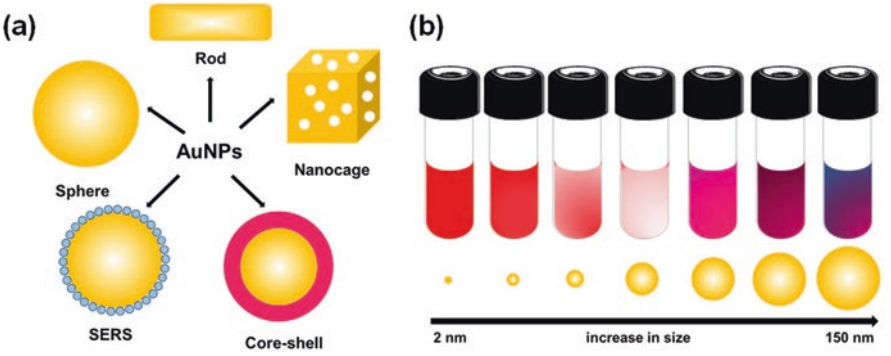

Fig. 6.2 (**a**) Types of gold nanoparticles (**b**) effect of size on the optical properties of gold nanospheres

synthesis, where the amount of citrate, a gold reducing agent, governed the yield of monodisperse gold nanospheres and it is reported that with lower amount of citrate higher amount of gold nanospheres can be obtained. In another method, in an aqueous medium, gold nanoparticles of about 20 nm were synthesized by Turkevich J et al. by single phase reduction of gold tetrachloroauric acid by sodium citrate (Turkevich et al. 1951). Bastus et al. have synthesized the gold nanoparticles of 200 nm size through kinetically controlled seed growth using same reducing agent i.e. sodium citrate (Bastus et al. 2011).

Green Synthesis Plant based materials such as; stem, root, seed, latex and leafs have been attempted for the synthesis of gold nanoparticles. Ankamwar B et al. used lemon grass extract and tamarind leaf extract for gold nanotriangle synthesis (Ankamwar et al. 2005). Spherical shaped gold nanoparticles have been synthesized using *Piper longum* extract (Yu et al. 2016). Similarly, aqueous extracts of *Citrus maxima* (Nakkala et al. 2016), aqueous extracts of neem (*Azadirachta indica*) (Anuradha et al. 2010), extract of *Allium cepa* (Parida et al. 2011) and dilute extract of *Phyllanthus amarus* (Kasthuri et al. 2009a, b), aqueous extract of *Terminalia chebula* (Edison and Sethuraman 2012), *Cassia fistula* extract (Daisy and Saipriya 2012), leaves and bark extracts of *Ficus caricaz* (Teimuri-Mofrad et al. 2017), *Plumeria Alba* (Frangipani flower) (Nagaraj et al. 2012), fruit peel extract of *Momordica charantia* (Pandey et al. 2012), extract of *Benincasa hispida* seed (Aromal and Philip 2012) and many more extracts have been used for gold nanoparticles synthesis.

Narayanan and Sakthive et al. reported gold nanoparticles of the size range 7–58 nm with different shapes such as triangular, decahaderal or spherical using *Coriandrum sativum* leaf extract (Narayanan and Sakthivel 2008). Similarly, Apiin, an ingredient present in banana leaf extract was also capable of reduction of ions to gold for nanoparticles synthesis (Kasthuri et al. 2009a, b). Nagajyothi et al. generated 8.02 nm gold nanoparticle using *Lonicera japonica* flower aqueous extract (Nagajyothi et al. 2012). Gold nanoparticles of 2.5–27.5 and 1.25–17.5 nm with an average size of 10 and 3 nm respectively were also produced using ethanolic extract of black tea and its free ethanol tannin extract, where these extracts worked as reducing and stabilizing agents during synthesis (Banoee et al. 2010).

Toxicity

Pan, Y. et al. assessed the cytotoxicity of 0.8–15 nm gold nanoparticles in different cells such as macrophages, melanoma, connective tissue fibroblast and epithelial cells and reported that these cells were sensitive to very small size of gold nanoparticles (1.4 nm) with induction of mitochondrial damage and oxidative stress, but when 15 nm particles were used instead of 1.4 nm particles, it was observed that particles are biocompatible and non-toxic (Pan et al. 2007). Gold nanoparticles cytotoxicity studies has also been performed in human cells where it has shown nontoxicity up to 250 mM, while ionic gold showed cytotoxicity at a relatively lower concentration of 25 mM (Connor et al. 2005). With surface functionalized particles it was observed that the chemical groups present at the surface of gold

nanoparticles are responsible for its effect on cells. Takahashi et al. reported the reduced cytotoxicity of gold nanorods (6.5 nm × 11 nm) in HeLa cells when cetyl trimethyl ammonium bromide (CTAB) at surface was replaced with polyethylene glycol (Niidome et al. 2006). Similarly Shukla et al. reported that 3.7 nm PEGylated gold nanoparticles of spherical size were able to enter into HeLa cell's nucleus without any toxicity due to its neutral surface (Shukla et al. 2005). Hetero biofunctionalization of gold nanoparticles with thiol polyethylene glycol acid (HS-PEG-COOH) or capping with bovine serum albumin did not produce any mortality or behavioral change in mice at the studied doses suggesting their biocompatibility (Nghiem et al. 2012). Gold nanoparticles have demonstrated size-dependent organ distributions where smaller particles of 5–15 nm showed wider organ distribution compared to large size particles of 50–100 nm. These gold nanoparticles were mainly found in liver and spleen (De Jong et al. 2008; Semmler-Behnke et al. 2008; Sonavane et al. 2008; Chen et al. 2009; Cho et al. 2009a, b; Kim et al. 2009). In another study, it was observed that coating of 20 nm gold nanoparticles with TA-terminated PEG5000 stabilized the particles and reduces the toxicity (Zhang et al. 2009; Lipka et al. 2010). Chen, Y. S. et al. conducted in vivo studies in mice by injecting different sized gold nanoparticles of 5 and 50 nm and observed lethal effects (Chen et al. 2009). A study by Cho, W.S. et al. has also reported the similar results where 13 nm PEGylated gold nanoparticles when injected intravenously into mice, were predominantly concentrated in the liver, kupffer cells, spleen macrophages and induces an acute inflammation in liver as observed in biopsy study (Cho et al. 2009a, b). Effect of route of administration on the toxicity of gold nanoparticles has also been studied and it was observed that oral administration of gold nanoparticles significantly reduces the body weight, spleen index, and red blood cells. Also, when oral, intra-peritoneal and intravenous routes were compared, it was observed that oral and intra-peritoneal dosing is more toxic than intravenous injections. Hence targeted delivery of nanoparticles using tail vain injections will be ideal for radiotherapy, photothermal therapy, and natural product or drug delivery (Shukla et al. 2005).

6.2.2 Non-Metallic Nanoparticles

6.2.2.1 Iron Oxide Nanoparticles

Recently, magnetic nanoparticles of iron oxide, also called magnetite or Fe_3O_4, have approved by U.S. Food and Drug Administration (FDA) for clinical imaging and drug delivery applications. These particles are extensively used for imaging purposes as preclinical and clinical studies proven its safety and biocompatibility. Easy synthesis, multifunctional surface modification, magnetic bio-separation along with magnetic fluid hyperthermia revolutionize the use of Fe_3O_4 magnetic nanoparticles for loading a variety of agents which are highly useful in current therapeutic and diagnostic applications. Magnetic nanoparticles allow easy tailoring of different

physical and chemical parameters such as chemical group modification, magnetism, shape, size, crystallinity and surface charge for targeting purposes. As next generation vehicles for targeted delivery of natural products and drugs, magnetic nanoparticles are amongst the preferred one due to devoid of undesired toxicities. These particles can be selectively targeted and concentrated to an organ by application of an external magnetic field (Verma et al. 2013; Ali et al. 2016). Oxidation state of iron governs its magnetic properties and hence has profound impact on magnetic properties of iron oxide nanoparticles. Use of magnetite (Fe_3O_4) is preferred over hematite, as magnetite contains both Fe^{3+} and Fe^{2+} ions and also known as ferrous-ferric oxide and has a brownish-black color with a metallic luster is known for strong magnetic properties compared to hematite (Fe_2O_3) which appears as reddish brown solid and the oxidation state of iron is (+III), for drug delivery and targeted therapeutic applications. Figure 6.3 shows the effect of oxidation state on the magnetic properties of Iron oxide nanoparticles.

Synthesis

Synthesis of iron nanoparticles can be done by thermal decomposition of Fe(N-nitrosophenyl hydroxylamine)$_3$ / Fe(acetylacetone)$_3$/ $Fe(CO)_5$ followed by oxidation. Facile decomposition of iron pentacarbonyl [$Fe(CO)_5$], which is a metastable organometallic compound, also denoted as iron carbonyl, at 140–160 °C under an inert atmospheric conditions using decalin as solvent and one of the three polymer as a surfactant and catalyst; polybutadiene, poly(styrene co-butadiene) and poly(styrene-co-4 vinylpyradine) yields magnetic iron nanoparticles (Lide 2004). Synthesis of monodispersed magnetite nanoparticles at high temperature (265 °C) using Fe(acetylacetonate)$_3$ in phenyl ether in the presence of alcohol, oleic acid, and oleylamine have been reported. In an another study, using microemulsion method, iron nanoparticles with an average size of ∽3 nm has been synthesized with the help

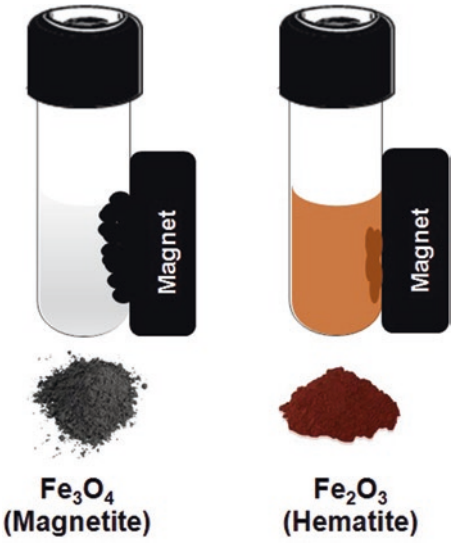

Fig. 6.3 Magnetite and hematite iron oxide nanoparticles

of trioctyl phosphine oxide as a stabilizing agent (Guo et al. 2001). Magnetic nanoparticles of monodisperse maghemite in a size range of 3.5 ± 0.6 nm with high magnetization saturation values along with monolayer oleic acid capping have been reported by Vidal et al. using one-pot microemulsion method (Vidal-Vidal et al. 2006), although this method is rarely used as a matters of convenience. Ionic surfactant such as quaternary ammonium compound (Martino et al. 1997; Seip and O'Connor 1999; Li et al. 2003) and nonionic e.g., polyether-based (Martino et al. 1997) long-chain surfactants are commonly used in micellar synthesis. Reduction of iron salts and its oxides using widely used reducing agents such as hydrazide (Seip and O'Connor 1999), sodium borohydride (Luborsky and Paine 1960; Glavee et al. 1995; Li et al. 2003), and lithium borohydride for the iron nanoparticles precipitation during synthesis is also reported. Use of surfactant during nanoparticles precipitation helps to prevent particle agglomeration. Likewise, co-precipitation is the other conventional method used for Fe_3O_4 or γ-Fe_2O_3 nanoparticles fabrication; which involves 1:2 molar ratios of ferrous and ferric ion salts. The above mentioned molar ratios are first mixed and then precipitated at room temperature or higher temperature using the highly basic solutions such as sodium hydroxide. Different synthesis conditions; temperature, stirring rate, precipitating agents, type of salts used, the ratio of ferrous and ferric ions, pH value affects the size and shape of magnetic nanoparticles (Wu et al. 2008).

Besides the above mention methods, *hydrothermal synthesis* is used for the synthesis of iron oxide nanoparticles with controlled shape and size. The method use high vapor pressure (0.3–4 MPa) and temperature (130–250 °C) for nanoparticles crystallization. Wang et al. obtained 40 nm particles with saturation magnetization (85.8 emu·g^{-1}) and high crystallinity using Fe_3O_4 at high temperature for 6 h (Wang et al. 2003). Similarly, with help of sodium bis(2-ethylhexyl) sulfosuccinate surfactant, Zheng et al. synthesized 27 nm magnetite nanoparticles using the hydrothermal synthesis (Zheng et al. 2006) which exhibited a superparamagnetic behavior at room temperature. Magnetic nanoparticles can also be synthesized using mechanical methods such as high-energy milling (Kerekes et al. 2002). But this method is not generally employed due to production of high poly dispersity and irregular shape and size.

Green biosynthesis is generally preferred over other method because the magnetite nanoparticles generated using this method possesses higher biocompatibility and biodegradability, due to the special non-toxic surface coating of green materials. Phumying et al. prepared magnetite nanoparticles using *Aloe vera* extract at different conditions (Phumying et al. 2013). In another study brown seaweed (*Sargassum muticum*) were used to synthesize magnetite nanoparticles (El-Kassas et al. 2016), similarly Rajendran et al. described the synthesis of magnetite nanoparticles using *Sesbania grandiflora* leaf extract as a photocatalyst (Rajendran and Sengodan 2017). Similar attempts were made by different groups using green biosynthesis such as, magnetite nanoparticles of 40–70 nm were synthesized using *Rubus glacus Benth* or *Andean blackberry* leaves (Kumar et al. 2016), nanoparticles has also been synthesized using *Syzygium cumini* seed extract (Venkateswarlu et al. 2014, 2019), *Punica Granatum* rind extract (Venkateswarlu et al. 2014, 2019),

plantain peel extract (Venkateswarlu et al. 2013) and lemon juice (Bahadur et al. 2017). In many green synthesis approaches Lemon juice was used where it serves as the source of citric acid for surface capping and particle size control of magnetic nanoparticles. Other natural products such as potato (Buazar et al. 2016), *Mimosa pudica* root (Niraimathee et al. 2016), arabic gum (Horst et al. 2017) has also been attempted for iron nanoparticles synthesis.

Magnetic nanoparticles has also been prepared using waste materials such as tea residue, coffee waste hydrochar and aqueous corn leaf extract and used for arsenic removal (Lunge et al. 2014), acid red 17 (azo dye) removal (Khataee et al. 2017) and in drug delivery due to antioxidant and antibacterial activities (Khataee et al. 2017). Iron nanoparticles has not only been synthesized using plants but also other green materials such as natural polymer (Sodium alginate (Gao et al. 2008), chitosan (Shrifian-Esfahni et al. 2015), polysaccharides (pectin) (Namanga et al. 2013), glucose (D-maltose) (Demir et al. 2013), amino acid (arginine) (Wang et al. 2009), vitamin (Nicotinic acid) (Attallah et al. 2016), enzyme (Urease) (Shi et al. 2014) and fungi (yeast) (Zhou et al. 2009) were also used.

Toxicity

Use of iron oxide nanoparticles were increasing day by day for various biomedical applications. U.S. Food and Drug Administration (FDA) has approved Feridex® (ferumoxides), a dextran-coated magnetic nanoparticles as a imaging contrast agent for the detection of liver lesions (Bulte 2009) and Feraheme® (ferumoxytol) for the treatment of anemia i.e. iron deficiency in adult patients with chronic kidney disease (Wang 2015). Therefore, concerns have been raised regarding its safety, distribution and clearance. Feng Q et al. has analyzed the *in vitro* cellular uptake, bio-distribution, clearance and toxicity of iron oxide nanoparticles which are well characterized and commercially available. The average size, hydrodynamic size, method of preparation, type of coating, surface functionalization affects the efficacy and toxicity of iron oxide nanoparticles (Nel et al. 2009). Similarly effect of particle size and different surface coating on blood half-life and magnetic behavior of iron oxide nanoparticles have been reported by Roohi F et al. They have found the inverse relationship of pharmacokinetic properties with particle size, as the hydrodynamic radius of nanoparticles gets decreased, a significant increase in blood half-life time and biodistribution of iron oxide nanoparticles were observed, thus affecting uptake of these particles by different organs and ultimately toxicity. In an another study, effect of different coating materials, polyacrylic acid, carboxy dextran, polyethylene glycol (PEG) and starch on 50 nm magnetic nanoparticles were observed and it was reported that polyacrylic acid-iron oxide nanoparticles displayed the shortest blood half-life, followed by carboxy dextran-iron oxide nanoparticles, starch-iron oxide nanoparticles, and PEG-iron oxide nanoparticles. These differences were ascribed by different ionic characteristics of the coating agents (Roohi et al. 2012). Feng Q et al. has compared the toxicity and uptake of Polyethylenimine-coated iron oxide nanoparticles (PEI-iron oxide nanoparticles) with the PEGylated one (PEG-iron oxide nanoparticles). PEI-iron oxide nanoparticles displayed significantly higher uptake by macrophages and cancer cells than PEG- iron oxide nanoparticles.

PEI-iron oxide nanoparticles displayed severe cytotoxicity than PEG-iron oxide nanoparticles also. This may be due to reactive oxygen species production and apoptosis. Whereas PEG- iron oxide nanoparticles did not exhibited toxicity but it induces autophagy, which imparts biocompatibility and reduces the cytotoxicity. The bio-distribution studies signifies that, iron oxide nanoparticles larger than 100 nm in size are rapidly concentrated in liver and spleen via macrophage phagocytosis whereas particles smaller than 10 nm are likely to be eliminated through renal clearance. (Kumar et al. 2011). *In vivo* studies in BALB/c mice displayed no obvious toxicity with PEG-iron oxide nanoparticles, whereas dose dependent toxicity was observed in PEI-iron oxide nanoparticles which signify the importance of coating materials (Feng et al. 2018). Gokduman K et al. has performed the dose (0–400 μg/ml) treatment (single dosing vs. cumulative dosing) and time-dependent toxicity of super-paramagnetic iron oxide nanoparticles of 10 nm size on primary rat hepatocytes, which state that toxicity was increases significantly with increasing concentration and treatment duration (Gokduman et al. 2018). Apart from biomedical applications, iron oxide nanoparticles can be used for removal of metal contamination from aqueous solutions (Ge et al. 2012). Therefore, toxicity assessment studies were also performed in Zebrafish to study the effect of these particles on developmental toxicity in fish in aquatic environments where developmental toxicity were observed as presence of mortality, hatching delay, and malformation at higher concentrations (≥10 mg/L) of iron oxide nanoparticles (Zhu et al. 2012).

6.2.2.2 Silica Nanoparticles

Mesoporous silica nanoparticles, because of high surface area, well ordered mesopores with larger pore volume have been used as multifunctional drug delivery system. The particle size, shape and surface can be easily modified depending upon the desired purpose (Vallet-Regi et al. 2007; Fernandez-Fernandez et al. 2011; Rosenholm et al. 2011; Baeza et al. 2015). Functionalization is generally performed over silanol-containing surface for controlled drug release and drug loading. Since the first use of silica based material, MCM-41 for drug delivery by Vallet-Regí et al. in 2001 (Vallet-Regi et al. 2001), other silica materials, such as SBA-15 or MCM-48, and some metal-organic hybrid and their nanoparticles with modifications have been developed for loading of different biologically active compounds. Silica oxide is widely used in dentist industry for many purposes such as tooth and bone implants, ceramic plates (Lührs and Geurtsen 2009), orthopedics (scaffolds) (Zhu et al. 2014; Zhou et al. 2017) and for specialized medical device manufacturing (Brunner et al. 2009; Cao and Zhu 2014). Additional advantages associated with the use of silica are: high thermal stability, chemical inactivity, resistance to microbial attack, high hydrophilicity and biocompatibility, high loading capacity making it an attractive material for biomedical purposes (Gonçalves 2018). Furthermore, U.S. Food and Drug Administration (FDA) have recommended amorphous silica and silicates as safe at the oral intake up to 1500 mg per day. Amorphous silica is widely used in

cosmetic product manufacturing, for foods and oral delivery of drugs (Kasaai 2015; Go et al. 2017; Gonçalves 2018).

Synthesis

Silica nanoparticles are generally synthesized by sol-gel, flame decomposition and reverse micro-emulsion methods. Reverse micelles are formed when organic solvent containing surfactant is added to aqueous phase, polar head group orient themselves to form microcavities containing water using reverse micro-emulsion method (Tan et al. 2011). Silica nanoparticles are also formed in the same manner when silicon alkoxides and catalyst addition results in particle synthesis inside the microcavities. Like the other methods which have several limitation, major challenge associated with this method is high cost and difficulties in surfactant removal (Bagwe et al. 2006; Liu and Han 2010; Wang et al. 2014). Naka Y et al. has reported one-pot water-oil-microemulsion technique for manufacturing of organo-unctionalized silica nanoparticles. Use of mixture of organosilane (3-aminopropyltriethoxysilane), phenyltrimethoxysilane, 3-mercaptopropyltrimethoxysilane, vinyltriethoxysilane, 3-cyanoethyltriethoxysilane and polyoxyethylene nonylphenol ether in the solution of tetraethyl orthosilicate is employed to synthesize monodisperse silica nanoparticles in the size range 25–200 nm (Naka et al. 2010). Kozlecki et al. has reported silica nanoparticle synthesis using modified oil-in-water microemulsion. Silica nanoparticles in the size range of 170–422 nm with high surface area (>300 m^2/g) were reported using heptanes, 2-ethylhexanole, Tween®85 non-ionic surfactant, tetraethyl orthosilicate and ammonium hydroxide. Similarly, precipitation of β-cyclodextrin and hydroxyethylcellulose have been used to obtain particles with similar characteristics (Koźlecki et al. 2016).

Silica nanoparticles can also be synthesized from metal organic precursors through high temperature flame decomposition technique, which is also known as chemical vapor decomposition (Silva 2004). Chemical reaction of silicon tetrachloride with hydrogen and oxygen is also used for silica nanoparticles synthesis, but desired particles size, shape and morphology are major limitations which are difficult to control, also this method is mainly used to produce particles in powder form. Yan F et al. have also prepared silica nanoparticles in the same manner where water vapors at ∼150 °C were used to hydrolyzed silicon tetrachloride vapors. The obtained porous amorphous silica were having a large specific surface area (342.44 m^2/g), with broad size distribution of 162.8 ± 41.0 nm (Yan et al. 2014).

Sol-gel process which involves hydrolysis and condensation of metal alkoxide such as tetraethyl orthosilicate or inorganic salts e.g. sodium silicate in the presence of mineral acid e.g. hydrochloric acid or base e.g. ammonia as catalyst under mild conditions, is/are commonly used for the synthesis of silica and silica nanoparticles for different therapeutic and diagnostic applications (Stöber et al. 1968; Hench and West 1990; Klabunde et al. 1996). In the course of sol-gel based synthesis, in the first step, silanol groups were generated using tetraethyl orthosilicate hydrolysis, in the second step, condensation/polymerization is carried out between silanol group and ethoxy group for siloxane bridge formation, which results in the formation of

silica structure. Further, nucleation followed by growth are the remaining two stages in silica nanoparticles synthesis (Matsoukas and Gulari 1988).

Stober et al. has reported the synthesis of spherical and mono-dispersed silica nanoparticles for the first time in 1968 (Stöber et al. 1968). Using this method silica particles in the size range of 5–2000 nm could be synthesized by the addition of ammonia to aqueous alcohol solution of silica. Later, modified Stober methods were developed for silica nanoparticles synthesis. Rao KS obtained silica nanoparticles in the size range of 20–460 nm via the hydrolysis of tetraethyl orthosilicate in ethanol medium (Rao et al. 2005). Silica particles were also synthesized from low cost precursors such as sodium silicate solution, in the process, precipitation were carried out by the addition of acids such as hydrochloric acid with carbon dioxide (Stöber et al. 1968). Bentonite clay has also been reported to prepare silica nanoparticles via generation of sodium silicate which is then converted into sodium silicate solution with sodium hydroxide treatment further hydrolysis of this solution in the presence of nitric acid and ethanol were resulted in different size silica nanoparticle synthesis. The particle size was controlled by monitoring the concentration of silica rich clay and nitric acid (Zulfiqar et al. 2016).

Agricultural wastes such as, rice husk, rice hull, semi burned rice straw, sugarcane waste and Vietnamese rice husk are used for the green synthesis of silica nanoparticles (Zaky et al. 2008; Zhang et al. 2010; Liu et al. 2011; Rovani et al. 2018). Silica nanoparticle synthesis attempts have been made by Rovani S et al. using sugarcane waste ash, and the particles obtained were 20 nm to several micrometers range with specific surface area of 131 $m^2\ g^{-1}$ and ~230 mg g^{-1} acid orange eight dye adsorption capacity (Rovani et al. 2018). Nanosized silica was synthesized using sol-gel method from Vietnamese rise husk with heat treatment, for this, ash was generated from the rise husk with thermal treatment at 600 °C for 4 h. Then sodium silicate solution were obtained from rice husk ash by treating it with sodium hydroxide solution and finally silica nanoparticles were precipitated by addition of sulphuric acid at pH 4 in the water/butanol with cationic presence. The particles with highest specific surface area (340 m^2/g) and an average size of 3 nm were also reported (Thuc and Thuc 2013).

Surface modification of silica nanoparticles are generally carried out for incorporation of a variety of structurally diverse molecules. The reagents used for surface modifications are silane coupling agents such as amino propyl methyl diethoxy silane and methacryloxy propyl triethoxy silane under non-aqueous and aqueous conditions (Kang et al. 2001; Yu et al. 2003). Kobler and Bein et al. reported formulation of highly small mesoporous silica nanoparticles by co-condensation process with phenyl triethoxysilane in the presence of triethanolamine catalyst (Kobler and Bein 2008). Silica particles of different shapes, size and pore size have been synthesized. Wang et al. has synthesized cubic shaped silica nanoparticles with the help of tartaric acid (Yu et al. 2005). Nanosized MCM-41 silica particles with several morphologies such as hexagonal shape under basic conditions have also been reported (Cai et al. 2001). Ikari et al. reported the hexagonally arrayed mesoporous silica nanoparticles with the help of binary surfactant method (Ikari et al. 2006). Mesoporous silica containing hexagonally ordered mesopores of 2 nm were synthesized using a

cationic surfactant cetyl trimethyl ammonium bromide, while silica nanoparticles having bigger mesopores (20–50 nm) were designed by sulphonated aromatic polyether ether ketone (Pang et al. 2005). Sugar molecules such as glucose and fructose have been used for eco-friendly production of silica nanoparticles of mesoporous and mono-dispersed nature (Mukherjee et al. 2009), the obtained particles were of 50–1140 nm size, which were produced by reaction mixture of phenyltriethoxysilane, ammonia, water, ethanol and the non-surfactant sugar template.

Toxicity

Several reports have been published related to silica effect on human health, in a detailed study related to its toxicity, it was observed that, exposure to crystalline silica cause the fibrotic lung disease, also known as silicosis, lung cancer, emphysema and pulmonary tuberculosis (Zhang et al. 2012). Conversely amorphous form of silica is considered as safe and hence it has been a part of human diet as medical clay or as food additive (labelled E551) (Sripanyakorn et al. 2009; Jurkić et al. 2013). When used *in vivo*, amorphous form of silica is cleared more rapidly as compared to its crystalline form from the lungs which may be responsible for its lower toxicity and its use for human applications *in vivo* (Arts et al. 2007). The *in vivo* as well as *in vitro* use of mesoporous silica nanoparticles are well tolerated, when used *in vitro*, it is considered safe at lower than 100 μg/ml concentrations (Huang et al. 2008; Hudson et al. 2008; Tao et al. 2008; Lu et al. 2010), whereas lower than 200 mg/kg doses are considered safe for *in vivo* use (Lu et al. 2010). Although there is conflicting reports regarding the relationship between silica nanoparticles size and toxicity, even most of these reports indicate that physicochemical property such as, size, surface groups, dose and cell type governs the cytotoxicity of these particles. In one study, effect of different size silica nanoparticles such as 30, 48, 118 and 535 nm on viability of mouse keratinocytes was investigated and reduction in cell viability with decrease in size at 10–200 μg/ml doses was observed (Kyung et al. 2009). While in another study on human hepatocytes, the effect of 7, 20, 50 nm silica nanoparticles on cell viability at 20–640 μg/ml doses was investigated and it was found that cell viability with 20 nm particles was highest followed by 7 nm and 50 nm size particles (Lu et al. 2011). Kim and in-Yon et al. studied the biocompatibility of 20–200 nm silica nanoparticles on mouse embryonic fibroblast (NIH/3 T3), human hepatoma (HepG2) and human alveolar carcinoma (A549) cells and reported that, all the three cell type preferentially engulf silica nanoparticles of 60 nm at high doses, these particles led to disproportionate decrease in cell viability when compared with other size particles (Kim et al. 2015). Cytotoxicity and cell dysfunction is most commonly observed in dendritic cells, mast cells, lymphocytes, monocytes, macrophages and kupffer cells upon exposure to silica nanoparticles. In organ specific immunotoxicity studies, lymphocytes infiltration, granuloma formation and hydropic degeneration (condition in which cells absorb more water) in liver hepatocyte were observed, whereas in the spleen, decreased proliferation in immune cells such as B and T cells along with the altered serum IgG and IgM levels were observed, similarly in the lungs, neutrophil infiltration and in heart inflammation was observed (Chen et al. 2018). Zhao Y et al. observed that, when red blood cells were treated

with different size mesoporous silica nanoparticles such as MCM-41 of ~100 nm and SBA-15 of ~600 nm, small size particles (~100 nm) readily adsorb on red blood cell surface without any cell membrane disruption whereas larger size particles (~600 nm) adsorb on cell membrane, internalized by the cells and induced cell membrane disruption which eventually leads to red blood cells hemolysis (Huang et al. 2008). It is also reported that silica nanoparticles are able to freely pass through the blood-brain barrier (BBB), and can enter into the central nervous system (Klejbor et al. 2007) hence, adverse central nervous system effects such as neurotoxicity, neuro-inflammation, neuro-degeneration were observed. Along with this, enhanced levels of amyloid beta protein were also reported which is the hallmark of Alzheimer's disease. When, silica nanoparticles were incubated with primary cultured hippocampal neurons, a rapid and persistent decalcification of endolysosome was observed which was correlated with brain amyloidogenesis and Alzheimer's disease. Therefore, use of silica nanoparticles for the treatment of Alzheimer's and other neurological disorders were not recommended (Ye et al. 2018).

6.3 Recent Advances in Inorganic Nanoparticles Mediated Natural Products Delivery

Different formulations such as liposomes, solid lipid nanoparticles, polymeric nanoparticles and/or inorganic nanoparticles are known for the delivery of natural products. Various advantages of inorganic nanoparticles are highlighted about enhancement of therapeutic potential of natural products. Figure 6.4 shows the chemical structure and Table 6.1 shows the compiled list of some natural compounds that have been delivered via inorganic nanoparticles and their efficacy has been tested *in vitro* and/or *in vivo* with positive effects.

6.3.1 Curcumin

Curcumin or diferuloylmethane, which is known as folk medicine, is a major bioactive polyphenol constituent found in the rhizome of *Curcuma longa* (Turmeric). Curcumin acts as potent anti-inflammatory and antioxidant agent and is used to specifically kill cancer cells; it can suppress tumor genesis, tumor promotion, and metastasis as reported in several preclinical studies (Shanmugam et al. 2015). The problem with the use of curcumin is that it is not soluble in water and shows low bioavailability. Attempts to improve the bioavailability of curcumin are underway employing various processes. Nanocurcumin shows improvement in bioavailability compared to conventional curcumin.

To circumvent the antibiotic resistance associated with existing antibacterials, silver nanoparticles of 25–35 nm, which contains curcumin natural product, were

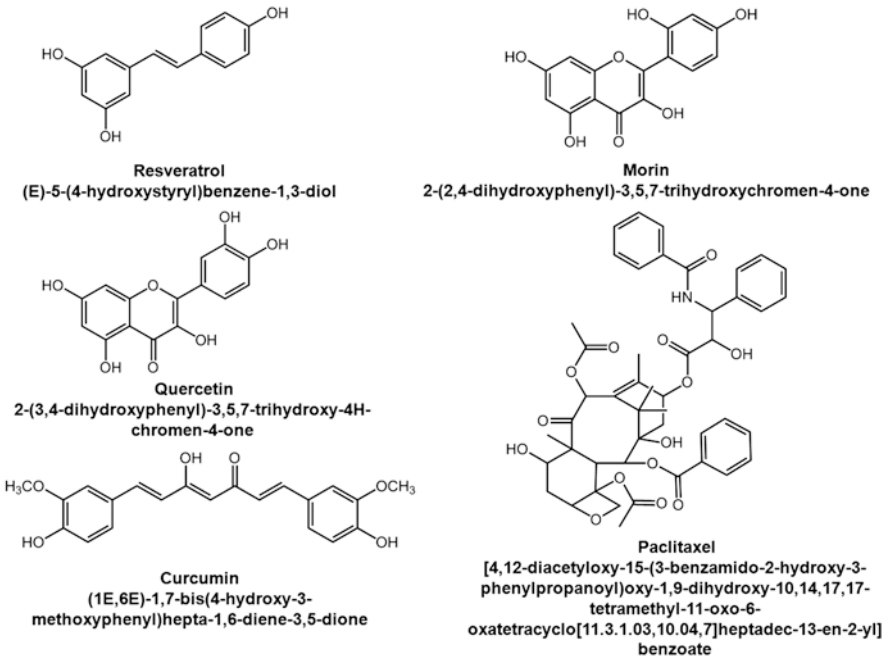

Fig. 6.4 Chemical structure of resveratrol, morin, quercetin, curcumin and paclitaxel natural products

synthesized. These curcumin silver nanoparticles were effective against wide range of microbes such as gram-positive and gram-negative bacteria and reduce the minimum effective curcumin concentration by fourfold (20 mg/L to 5 mg/L). Skin biocompatibility studies on keratinocytes (HaCaT) showed slight toxicity, whereas as an antimicrobial, curcumin silver nanoparticles showed selective toxicity towards bacteria and induces anti-inflammatory effect on human macrophages (THP-1) (Jaiswal and Mishra 2018). Abdellah et al. also studied the antibacterial effect of curcumin silver nanoparticles against *Escherichia coli* and observed improved photostability and antibacterial activity with minimal toxicity to skin cells (Abdellah et al. 2018). For the enhancement of anticancer potential of curcumin, its silver nanoformulations with average size of 17.98 nm were reported, study showed that curcumin silver nanoparticles induces cell toxicity in concentration dependent manner and had a greater cytotoxic effect on the tumor cells in comparison to plain curcumin (Garg and Garg 2018). Increased water solubility and loading efficiency was also reported with a novel in situ synthesis method in which curcumin conjugate to gold quantum cluster were developed. *In vitro* apoptotic potential in cancer cells were also supported by the *in vivo* studies in SCID cancer mouse model without showing any severe toxicity to internal organs, this showed that silver nanoparticles as an delivery vehicle for natural product could be advantageous (Khandelwal et al. 2018).

Table 6.1 Applications of metallic nanoparticles in delivering natural products

	Natural Product	Metallic nanoparticle and its modification	Purpose/Outcome	References
Inorganic metallic particles				
Silver nanoparticles				
1.	Curcumin	Silver nanoparticles	Antimicrobial and antibiofilm activity enhancement	Abdellah et al. (2018) and Jaiswal and Mishra (2018)
2.	Curcumin	Silver nanoparticles	Anticancer activity/ enhancement of anticancer activity	Garg and Garg (2018)
3.	Paclitaxel	Polyethylenimine-functionalized silver nanoparticles	HepG2 cell apoptosis	Paciotti et al. (2016)
4.	Flavonoid	Silver nanoparticles	Wound healing bio-efficacy	Sharma et al. (2019)
5.	Quercetin	Silver nanoparticles	Antibacterial and antibiofilm activities	Yu et al. (2018)
Gold nanoparticles				
6.	Curcumin	Gold- quantum clusters	Anticancer activity/ enhancement	Khandelwal et al. (2018)
7.	Paclitaxel	Gold nanoparticles	Anticancer activity	Paciotti et al. (2016)
8.	Flavonoid	Gold nanoparticles and Au-Ag bimetallic nanoparticles	Wound healing bio-efficacy	Sharma et al. (2019)
9.	Anthocyanin	PEG-gold nanoparticles	Enhanced neuroprotection	Kim et al. (2017)
10.	Rutin	Rutin conjugated gold nanoparticles	Treatment of rheumatoid arthritis	Gul et al. (2018)
11.	Vincristine sulfate	Vincristine sulfate conjugated gold nanoparticles	Enhanced antitumor efficiency	Liu et al. (2015)
12.	Betulin	Gold nanoparticles	Anti-tumor effect	Mioc et al. (2018)
13.	Quercetin	Gold nanoparticles	Anti-tumor effect, breast cancer	Balakrishnan et al. (2016) and Yilmaz et al. (2019)

(continued)

Table 6.1 (continued)

	Natural Product	Metallic nanoparticle and its modification	Purpose/Outcome	References
Inorganic non-metallic particles				
Iron oxide nanoparticles				
14.	Trans-resveratrol	Superparamagnetic Iron oxide nanoparticles	Glioma treatment/ potential cytotoxic effect	Sallem et al. (2019)
15.	Curcumin	Magnetic nanoparticles	Breast cancer therapeutics and imaging applications	Yallapu et al. (2012)
16.	Curcumin	Magnetic nanoparticles	Pancreatic cancer	Yallapu et al. (2013)
17.	Curcumin	Folate-modified and curcumin-loaded dendritic magnetite nanocarriers	Thermo-chemotherapy of cancer cells	Montazerabadi et al. (2019)
18.	Quercetin	Superparamagnetic iron oxide nanoparticles	Enhance bioavailability of quercetin, and ameliorates diabetes-related memory impairment.	Ebrahimpour et al. (2018) and Enteshari Najafabadi et al. (2018)
19.	Paclitaxel	Iron oxide nanoparticles	Breast Cancer therapy	Lugert et al. (2019)
20.	Etoposide	Magnetic polymeric microparticles	Anticancer activity	Sundar et al. (2014)
Silica nanoparticles				
21.	Curcumin	Amino-functionalized silica nanoparticles	Anticancer activity	de Oliveira et al. (2016)
22.	Carvacrol	Hybrid-silica nanoparticles	Antibacterial activity	Sokolik and Lellouche (2018)
23.	Eugenol	Mesoporous silica nanoparticles	Antimicrobial activity	Melendez-Rodriguez et al. (2019)
24.	Thymol	Biogenic silica	Biopesticide	Mattos et al. (2018)
25.	Quercetin and doxorubicin	Mesoporous silica nanoparticles	Gastric carcinoma chemotherapy	Fang et al. (2018)
26.	Morin (2′,3, 4′,5,7-pentahydroxyflavone)	Mesoporous silica	Antioxidant properties	Arriagada et al. (2016)
27.	Flavonoid	Titania-functionalized silica nanoparticles	Anti-oxidant and anti-inflammatory properties	Sokolik and Lellouche (2018)
28.	Paclitaxel	Mesoporous silica nanoparticles	Anticancer activity against human lung cancer cell line A549	Wang et al. (2017)

6.3.2 Taxol or Paclitaxel

Taxol or Paclitaxel is first discovered by Mrs. Monroe E. Wall and Mansukh C. Wani. It is a white crystalline powder which melts at ~210 °C. Since its first isolation from the bark of Pacific yew (*Taxus brevifolia*), it still remains the drug of choice for cancer treatments. Paclitaxel was the first chemotherapeutic agent which was obtained from natural products and approved by U.S. Food and Drug Administration (FDA) for clinical use. As an potent anticancer agent, it is used for variety of cancers such as leukemia and number of solid tumors including breast, lung, ovary, gastric, brain, and prostate cancer (Jordan and Wilson 2004; Gupta et al. 2010). ***Paclitaxel*** is known for cell cycle arrest through tubulin-microtubulin equilibrium disruption and induces cancer cell death (Horinouchi et al. 2014). However paclitaxel suffers with low water solubility (~0.4 μg/ml) due to its hydrophobic nature, low permeability and serious adverse effects. Therefore, in the ***paclitaxel*** trademark formulation "Taxol" organic solvents such as polyoxyethylated castor oil (Cremophor EL) and dehydrated ethanol (50/50, v/v) have been used as solvent system for the preparation of commercial formulation, because of this it has shown its own side effects and nonlinear pharmacokinetics (Sparreboom et al. 1996). Albumin nanoparticles bound paclitaxel formulation (Abraxane) with a particle size of 130 nm is approved clinically about a decade ago for the treatment of metastatic breast cancer, and further attempts have been made for its solubility improvements along with pharmacokinetic and pharmacodynamics studies. A novel nanosystem based on polyethylenimine (PEI) decorated silver nanoparticles encapsulating ***paclitaxel*** have been synthesized and its cytotoxic effect was assessed against hepatocarcinoma (HepG2 cells), which is the third leading cause of cancer related deaths around the world. The particles were 2–3 nm in size having zeta potential values of 23 mV, which induced HepG2 cell apoptosis, triggered intracellular reactive oxygen species; thus can be used in the chemotherapy of cancer (Li et al. 2016). Gibson et al. has covalently attached ***paclitaxel*** to phenol-terminated gold nanoparticles of 2 nm size with a hexaethylene glycol linker (Gibson et al. 2007). Oh et al. developed a composite system based on gold/chitosan/pluronic nanoparticles for ***paclitaxel*** loading. For controlled release of ***paclitaxel***, gold nanoparticle synthesis with citrate reduction method were also described (Oh et al. 2008). Heo and co-workers described ***paclitaxel*** loaded gold nanoparticles synthesis with desired surface functionalization using PEG, biotin and rhodamine B linked beta-cyclodextrin, where ***paclitaxel*** formed an inclusion complex with beta-cyclodextrin. Physical characteristics of the particles showed that the gold nanoparticles were almost spherical and were in the size range of 20–40 nm. These particles had shown cytotoxicity towards HeLa, A549 and MG63 cancer cell as compared to NIH3T3 normal cells (Heo et al. 2012). Hua et al. synthesized poly(aniline-co-sodium N-(1-one-butyric acid) aniline coated Fe_3O_4 magnetic nanoparticles for paclitaxel loading in which drug was immobilized onto the surface of particles. These particles were more effective in killing PC3 and CWR22R prostate cancer cells compared to free ***paclitaxel*** and improved the aqueous solubility of ***paclitaxel*** to 312 μg/ml from

0.4 μg/ml (Hua et al. 2010). Hwu J.R. et al. have reported the conjugated ***paclitaxel*** containing gold nanoparticles and Fe_3O_4 magnetic nanoparticles tailored with maleimidyl 3-succinimidopropionate ligands for anti-cancer activity (Hwu et al. 2009). Similarly, for lung cancer delivery of ***paclitaxel***, mesoporous silica nanoparticles with a core-shell structure were reported. *In vitro* and *in vivo* studies report that ***paclitaxel*** delivery via particles not only led to an increase in dissolution rate but also improved the lung absorption of ***paclitaxel***. Nanoparticulate delivery of ***paclitaxel*** showed 2.68-fold higher concentration in the area under concentration time curve in a pulmonary inhalation study in rabbit as compared to free ***paclitaxel*** and were effective in killing human lung cancer cells (A549) (Wang et al. 2017).

6.3.3 Trans-Resveratrol

Several *in vivo* and *in vitro* reports in animal models have shown the beneficial effects of ***resveratrol***, a 3,4′,5-trihydroxy-trans-stilbene which naturally occur as polyphenolic compound in red wine, peanuts, grapes, soyabean, pomegranates and barriers (Wallerath et al. 2002; Wenzel and Somoza 2005). Studies in animals have shown that resveratrol, acts as antioxidant (Stivala et al. 2001), anti-microbial (Chalal et al. 2014), anti-inflammatory (Tili et al. 2010), estrogenomimetic and chemopreventive. Because of its antioxidant properties, it has demonstrated its therapeutic potential against skin, breast, lung, prostate, and pancreatic cancers (Aggarwal et al. 2004; Athar et al. 2007). Neuroprotective role of ***resveratrol*** has also been observed in Alzheimer's, Parkinson's disease and stroke (Ignatowicz and Baer-Dubowska 2001; Singh et al. 2019). However, poor systemic bioavailability due to its low water solubility along with very short half-life (30–45 min) limits clinical efficacy of ***resveratrol***. Various ***resveratrol*** nanoformulations have been developed to overcome these limitations, such as, gold nanoparticles and silver nanoparticles using eco-friendly synthesis methods in order to enhance their bioavailability and antibacterial efficacy. Using ***resveratrol,*** which served as reducing agent, spherical-shaped nanoparticles having size range of 8.32–21.84 nm, exhibiting surface plasmon resonance at 547 nm and 412–417 nm for gold and silver respectively were reported. Antibacterial activity was observed against both gram-positive and gram-negative bacteria, the ***resveratrol*** conjugated nanocarriers exhibited enhanced antibacterial activity compared to resveratrol alone. ***Resveratrol gold nanoparticles*** demonstrated the superior antibacterial activity against *Streptococcus pneumonia* (Park et al. 2016). For the treatment of brain tumor, with the help of ***resveratrol*** derivative, Sallem et al. has reported the synthesis of surface modified superparamagnetic iron oxide nanoparticles. In the study, ***resveratrol*** derivative molecule (4′-hydroxy-4-(3-aminopropoxy) trans-stilbene was chemically synthesized and then this was grafted onto superparamagnetic iron oxide nanoparticle surface using an organosilane coupling agent and obtained particles were in the size range of 9.0 nm as reported by transmission electron microscopy. *In vitro* biological efficacy

assessment showed that these particles were able to damage the plasma membrane, and limited the proliferation of cancerous cells (C6 rat glioma cells) as observed in clonogenic test (Sallem et al. 2019). Popova et al. has synthesized Trans-resveratrol encapsulated nanoporous silica particles of different structures. Nanosized BEA zeolite, nanoporous MCM-41and KIL-2 silica were used as carrier material. High loading of ***resveratrol*** were achieved in nanoparticles using solid state dry mixing and with ethanol solution, both methods were good in high ***resveratrol*** loading however, solid state dry mixing were more effective in stabilizing trans-resveratrol (Popova et al. 2014). In another study colloidal mesoporous silica nanoparticles of an average size of 283 nm encapsulating resveratrol were prepared. ***Resveratrol*** encapsulation led to solubility enhancement by ~95% and increased in vitro release as compared to pure resveratrol. The in vitro efficacy studies performed on LS147T and HT-29 colon cancer cell lines with ***resveratrol*** loaded mesoporous silica nanoparticles induces cancer cell apoptosis through PARP and cIAP1 pathways. These nanoparticle formulations also exhibited anti-inflammatory potential in lipopolysaccharide-induced NF-κB activation in RAW264.7 cells (Summerlin et al. 2016).

6.3.4 Quercetin (3, 5, 7, 3′, 4′-Pentahydroxyflavone)

Citrus fruits, green leafy vegetables as well as many seeds such as nuts, buckwheat, flowers, barks, broccoli, olive oil, apples, onions, green tea, red grapes, red wine, dark cherries and berries such as blueberries and cranberries are highly abundant with dietary bioflavonoid Quercetin. It is known for its beneficial effects such as antioxidant, antitumor and antibacterial activities, cardioprotection, anticancer, antiulcer, anti-allergic, anti-inflammatory, antiviral, and antiproliferative (D'Andrea 2015; Anand David et al. 2016). Verma et al. synthesized the poly(lactic-co-glycolic acid) coated Fe_3O_4 nanoparticles with quercetin for aerosol delivery by nebulization. Anticancer activity of quercetin was improved when formulated as magnetic core-shell nanoparticles as observed against A549 lung cancer cells. Quercetin magnetic nanoparticles enhance its water solubility and bioavailability and therefore improve the anticancer activity of the quercetin natural compound. Intranasal administration of quercetin loaded magnetic nanoparticles *in vivo* in mice reduced the viability of A549 cells significantly. In addition, development of quercetin as nanoparticles helps in enhanced solubility and dispersion along with stability against oxidation and improved biocompatibility (Verma et al. 2013). Quercetin loaded silver nanoparticles were synthesized for high antibacterial and anti-biofilm activities for the therapeutics of bovine mastitis caused by *E. coli*. The composite material developed by combining silver nanoparticles and quercetin, exhibited super antibacterial and anti-biofilm properties against multi-drug resistant *E. coli* strain, compared to free silver nanoparticles and quercetin alone (Yu et al. 2018). Gold nanoparticles conjugated with quercetin were synthesized to target breast cancer cells with specific and selective anticancer activities. These particles inhibited

epithelial-mesenchymal transition and decreased angiogenesis. In Sprague-Dawely rats, quercetin conjugated gold nanoparticles inhibited breast tumor growth in 7, 12-dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma as compared to free quercetin (Balakrishnan et al. 2016). Yilmaz M et al. encapsulated quercetin in a macrocycle, p-sulfonatocalix[4]arene, which led to an increase in aqueous solubility to 62 thousand-fold with a 2.9-fold enhancement in its cytotoxicity with respect to free quercetin in SW-620 colon cancer cells. A nanohybrid system consisting of nanoparticle gold core decorated with calixarene hosts were synthesized for pH responsive quercetin release. The quercetin loaded nanohybrid significantly enhanced the colon cancer cells cytotoxicity (>50-fold). Also quercetin loaded nanoparticles showed a reduction in tumor volume in *In vivo* studies in a mouse 4T1 tumor model with no apparent particles related toxicity (Yilmaz et al. 2019). Quercetin was also conjugated to silica nanoparticles where these nanoparticles inhibit MCF-7 breast cancer cell growth through enhanced cancer cell apoptosis and cell cycle arrest (Aghapour et al. 2018). Silica/quercetin sol-gel hybrid was developed by Catauro M et al. as antioxidant dental implant material. This material was able to encapsulate high amount of quercetin with notable anti-oxidant properties (Catauro et al. 2015).

6.3.5 Flavonoids

Wound healing activates were reported using the aqueous alcoholic extract of the seeds of *Madhuca longifolia* plant. Therefore, *Madhuca longifolia* flavonoid-loaded gold, silver and gold-silver dual metallic nanoparticle formulations were reported with enhanced wound healing activities (Sharma et al. 2019). Flavonoid dihydromyricetin-conjugated silver nanoparticles for the treatment of fungal pathogenic infections caused in immunocompromised patients were also reported. The antifungal activities of these nanoparticles against *Aspergillus fumigates, Aspergillus niger, Paecilomyces formosus, Candida albicans* and *Candida parapsilosis*, as elucidated by zone of inhibition assay, were promising with reduced minimal inhibitory concentration as compared to free flavonoid which highlight the advantage of nanotechnology in natural product delivery. The results concluded that dihydromyricetin-conjugated silver nanoparticles can be used as potential alternative to commercially available antifungal agents (Ameen et al. 2018). Similarly, Morin (2′,3,4′,5,7-pentahydroxyflavone), a polyphenolic compound present in plants and vegetables (Gopal 2013), also known for several therapeutic activities such as anticancer (Sivaramakrishnan and Devaraj 2010), anti-inflammatory (Iglesias et al. 2005) and cardioprotective effects (Wu et al. 1995; Prahalathan et al. 2012; Govindasamy et al. 2014). Moreover, morin has shown skin protective effects against harmful radiations like UV-B radiation, therefore its topical formulation has been attempted for therapeutics (Lee et al. 2014; Shetty et al. 2015). However, degradation of morin in the presence of sunlight, oxygen and pH, limited its use in pharmaceutical and cosmetic formulations (Parisi et al. 2014). Therefore, amino

propyl modified mesoporous silica nanoparticles loaded with morin were synthesized. The particles were ~150 nm in size and demonstrated maximum adsorption capacity for morin (20 mg g^{-1}). The amino propyl modified mesoporous silica nanoparticles also exhibited a synergistic effect i.e. antioxidant property against hydroxyl radical (Arriagada et al. 2016).

6.4 Other Natural Products Delivered Using Inorganic Particles

Camptothecin is a highly cytotoxic natural alkaloid, which acts against a broad spectrum of tumors by inhibiting the nuclear enzyme topoisomerase, but because of its poor water solubility and chemical instability its therapeutic use is limited. Therefore attempts have been made to develop camptothecin metallic nanoparticles. In such attempts, Castillo et al. has developed PEG coated iron oxide nanoparticle for camptothecin delivery to H460 lung cancer cell line. Camptothecin loaded nanoparticles exhibited remarkable pro-apoptotic activity with an increase in therapeutic efficacy (Castillo et al. 2014). Essential oils and essential oil derived compounds are usually classified as Generally Recognized As Safe (GRAS) by U.S. Food and Drug Administration and serve as biocide or antimicrobial. Carvacrol which is also a major ingredient of oregano and thyme essential oils, also bear limitations such as low aqueous solubility, easy phenol oxidation, heat/light inactivation, distinct odor, which limit its use for therapeutic applications. Therefore, hybrid silica nanoparticles with carvacrol attachment via covalent bond were prepared with great antibacterial effect against *Escherichia coli* (*E. coli*) (Sokolik and Lellouche 2018). Similarly, volatile oils such as eugenol, thymol and vanillin formulations were also reported where these were grafted onto the surface of three silica supports (fumed silica, amorphous silica and MCM-41) via aldehyde derivatization. Incorporation of essential oil into silica nanoparticles greatly enhanced their antimicrobial activity against *Listeria innocua* and *E. coli* compared to their free counterparts (Ruiz-Rico et al. 2017). Rutin, a another flavonol, abundantly found in plants, such as passion flower, buckwheat, tea, and apple. The use of rutin for various medical applications has been proposed because of its antioxidant, cytoprotective, vasoprotective, anticarcinogenic, neuroprotective and cardioprotective activities (Ganeshpurkar and Saluja 2017). Rutin conjugated gold nanoparticles were fabricated and their efficacy was tested in collagen induced arthritis in rats. It was found that these particles reduced the inflammatory response by down regulating nuclear factor-κB (NF-κB) and inducible nitric oxide synthase expression levels (Gul et al. 2018).

Another natural poly phenolic compound, Anthocyanins found in fruits, grains, and flowers, have shown antioxidant, anti-inflammatory, and anti-apoptosis properties in different preclinical studies (Ghosh and Konishi 2007; Zafra-Stone et al. 2007) hence anthocyanin-loaded PEG-gold nanoparticles were prepared and tested

in $A\beta_{1-42}$-injected mouse models of Alzheimer's disease. These particles demonstrated reduction of neuroinflammation with enhanced neuroapoptotic markers suggesting its potential for the treatment of neurodegenerative diseases (Kim et al. 2017).

6.5 Conclusion

Natural product delivery via inorganic nanoparticles showed enhancement of efficacy and ameliorated problem of solubility and bioavailability. Natural products have a wide spectrum of activities and inorganic particles itself possesses antibacterial, cancer cell killing and anti-inflammatory properties. Therefore use of inorganic nanoparticles, for natural product delivery or active ingredient of natural product origin, will not only helpful in overcoming the several limitations associated with natural products but also enhance their therapeutic potential due to several associated benefits. A combination of natural product along with inorganic nanoparticles were attempted and elaborated in this chapter. These facts and reports implies the possibility of natural product-loaded inorganic nanoparticles as a therapeutic agent for the treatment of several diseases such as cancer, infections, rheumatoid arthritis and have antibacterial and antibiofilm activities. However, toxicity is a concern; therefore selection of specific delivery system or appropriate combination of natural product and formulation is very crucial desired purposes.

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