



Phytosynthesized metal oxide nanoparticles for pharmaceutical applications

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Abstract

Developments in nanotechnology field, specifically, metal oxide nanoparticles have attracted the attention of researchers due to their unique sensing, electronic, drug delivery, catalysis, optoelectronics, cosmetics, and space applications. Physicochemical methods are used to fabricate nanosized metal oxides; however, drawbacks such as high cost and toxic chemical involvement prevail. Recent researches focus on synthesizing metal oxide nanoparticles through green chemistry which helps in avoiding the involvement of toxic chemicals in the synthesis process. Bacteria, fungi, and plants are the biological sources that are utilized for the green nanoparticle synthesis. Due to drawbacks such as tedious maintenance and the time needed for the nanoparticle formation, plant extracts are widely used in nanoparticle production. In addition, plants are available all over the world and phytosynthesized nanoparticles show comparatively less toxicity towards mammalian cells. Secondary metabolites including flavonoids, terpenoids, and saponins are present in plant extracts, and these are highly responsible for nanoparticle formation and reduction of toxicity. Hence, this article gives an overview of recent developments in the phytosynthesis of metal oxide nanoparticles and their toxic analysis in various cells and animal models. Also, their possible mechanism in normal and cancer cells, pharmaceutical applications, and their efficiency in disease treatment are also discussed.

Keywords Pharmaceutical applications · Cytotoxicity · In vitro analysis · Metal oxide nanoparticles · Phytochemicals

Introduction

Plants are a source of food for several animals and humans (Burns et al. 2002) because they possess enormous nutrients required for growth (Abrahamson and Caswell 1982) and are widely available throughout the world (Daehler 1998). Plants are capable of synthesizing their own food by a process called photosynthesis, which make them a unique living organism

and a sustainable source for nutrients (Williams et al. 2015). Since the ancient period, plants have been used for medicinal purposes apart from their use as a food source or food product (Dillard and German 2000). This medicinal property of plants is due to the presence of phytochemicals including flavonoids (Nijveldt et al. 2001), phenols (Robards 2003), terpenoids (Tholl 2015), carotenoids (Farré et al. 2010), xanthophyll (Selvakumar et al. 2016), and other phytochemicals specific for certain plants (Sawada et al. 2012), which are secreted as metabolites by plants (Kennedy and Wightman 2011). In ancient times, a single phytochemical or a combination of several phytochemicals was widely used in the treatment of numerous diseases (Talib and Mahasneh 2010). However, these phytochemicals had some drawbacks. These included less stability and low adsorption in body fluids (Jeevanandam et al. 2017a). In recent times, these natural medicinal phytochemicals are fabricated into formulations and are prescribed as medicines, as an alternate to chemical-based synthetic drugs (Davatgaran-Taghipour et al. 2017). These formulated phytochemicals are used as curative agents against deadly diseases and disorders such as cancer (Lee et al. 2014), diabetes

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(Marella and Tollamadugu 2018), AIDS (Sridhar et al. 2014) and neurodegenerative (Ratheesh et al. 2017) and cardiovascular diseases (Nankar et al. 2016).

Nanoparticles, such as nanomedicines, for example, are receiving positive results from various research sectors because they are highly beneficial in biomedical and pharmaceutical applications and are believed to be the future of medical science (Nankar et al. 2016). Nanomedicines are synthesized via numerous routes, and a wide variety of nanoparticles (with unique properties) are available for use in desired applications (Lammers et al. 2011). Metal-based nanoparticles such as gold and silver have been synthesized, investigated, and proven to have potential biomedical properties (Boisselier and Astruc 2009; Durán et al. 2016). However, the most significant property required for nanomedicines to be used in biological applications is less toxicity with high stability, biocompatibility, bioactivity, and bioavailability (Tinkle et al. 2014). These properties are absent in metal nanoparticles, especially in physical- and chemical-mediated synthesis methods (Thakkar et al. 2010). This challenging setback has led to the emergence of metal oxide nanoparticles that are highly stable, compared with metal nanoparticles (Keller et al. 2010). Metal oxide nanoparticles are synthesized by chemical, physical, and biological methods. Biosynthesis methods are advantageous in yielding less toxic and highly bioactive nanoparticles (Jeevanandam et al. 2016). Bacteria, fungi, plants, certain viruses, and algae have been used extensively to generate toxic-free metal oxide nanoparticles. However, biosynthesis methods can be time consuming and difficult to scale-up and control the size and morphology (Narayanan and Sakthivel 2010; Mukherjee et al. 2001). Thus, phytochemicals from plants are utilized as an alternative to microbial-mediated biosynthesis of nanoparticles. Biomass feedstocks from plants are readily available and contain phytochemicals that can deliver unique functionalities and alter the physicochemical properties of nanoparticles (Singh et al. 2018). The combination of phytochemicals and metal oxide nanoparticles has resulted in new dimensions in drug discovery and delivery and therapeutic application of nanomedicine (Dizaj et al. 2014). Thus, this review article presents an overview of recent reports on the synthesis of metal oxide nanoparticles via phytochemicals and their *in vivo* and *in vitro* toxicity analysis. In addition, biomedical applications of phytosynthesized metal oxide nanoparticles and their possibility as a curative agent for rare diseases in future are also discussed.

In vitro analysis of phytosynthesized metal oxide nanoparticles

Recently, phytochemical extracts from various plants have been utilized for the synthesis of metal oxide nanoparticles

which include zinc oxide (ZnO), copper oxide (CuO), titanium dioxide (TiO₂), magnesium oxide (MgO), and iron oxide (Fe₃O₄) nanoparticles. *In vitro* cytotoxic analysis that is performed using cell lines as models are widely utilized to predict the preclinical response of a drug, which helps in identifying their mechanism of action for enhancing their efficiency. It can be noted that the phytosynthesized nanoparticles, in most of the cases, are less or nontoxic towards human cells, compared with chemically synthesized nanoparticles. The presence of phytochemicals as functional groups on the nanoparticle surface (Kumar et al. 2012), biocompatibility and bioavailability of these functional phytochemicals (Das et al. 2016), and phytochemical functionalization leading to spherical morphology (Patra et al. 2018) are the significant factors that reduce the toxicity of phytosynthesized nanoparticles. In phytosynthesized nanoparticles, the phytochemicals serve as the reducing and stabilizing agents that reduce their aggregation by acting as a capping agent at the interface (Kumar et al. 2012). Phytochemicals from biological sources possess enhanced biocompatibility and bioavailability compared with synthetic chemical compounds with elevated toxicity (Patra et al. 2018). Even though the nanoparticles formed are hexagonal or rod shaped, the functionalization can convert the particle into a spherical morphology (Kumar and Smita 2016). This allows internalization of nanoparticles into cell-reduced toxicity and further biodegradation of functional nanoparticles will lead to the exposure of nanoparticles with edge atoms to interact with cells (Jeevanandam et al. 2019). Contrarily, chemical-synthesized nanoparticles possess synthetic chemical compounds as a functional group on the surface of nanoparticles, resulting in more toxic side effects towards normal healthy cells. However, the toxic side effects are highly dependent on the synthesis approaches (Jeevanandam et al. 2016). The two common *in vitro* cell line models include normal lymphoblastoid and cancer cell lines that are used to analyze cyto- and genotoxic response of a drug (Niu and Wang 2015).

Cytotoxicity of ZnO nanoparticles

ZnO nanoparticles are utilized in biomedical applications due to their high bioactivity at nano size, compared with their bulk counterparts (Mishra et al. 2017). It is noteworthy that ZnO nanoparticles exhibit toxicity against various bacterial pathogens (Mostafa 2015; Reddy et al. 2014), fungal spores (Arciniegas-Grijalba et al. 2017; Jasim 2015), and viruses (Antoine et al. 2016). *In vitro* studies are extensively carried out to investigate host cell-nanoparticle interactions and to evaluate the toxicity of plant-derived ZnO nanoparticles. Song and Yang (2016) synthesized ZnO nanoparticles using *Piper betle* leaf extract and evaluated its cytotoxicity towards human osteoarthritic chondrocytes. The study reported a decrease in cell viability of osteoarthritic chondrocytes with an

increase in ZnO nanoparticle concentration. Another study by Dobrucka et al. (2018) used *Chelidonium majus* extracts to form ZnO nanoparticles and studied their in vitro cytotoxicity towards lung fibroblast cells (CCD-39Lu) and adherent epithelial cells of human lung cancer cells (A549). The cytotoxic studies revealed that the DNA replication in S-phase is different in both CCD-39Lu and A549 cells, indicating a potential toxic behavior after the addition of phytosynthesized ZnO nanoparticles. Similarly, the percentages of nonviable cells were found to be directly proportional to the phytosynthesized ZnO nanoparticle concentration in the G2/M phase of A549 cells, whereas high CCD-39Lu cell viability was observed at lower ZnO nanoparticle concentration (Dobrucka et al. 2018). These studies indicated that the phytosynthesized ZnO nanoparticles exhibited concentration and time-dependent toxicity against normal cells.

Cancer cell lines are used to elucidate the behavior of anticancer nanoparticles and to study their pharmacokinetics before clinical analysis. Chemical-synthesized ZnO nanoparticles have been proven to affect and inhibit normal cells which eventually act as a drawback in cancer treatment. Thus, phytosynthesized ZnO nanoparticles are evaluated to analyze their cell viability towards cancer cells for use as potential less toxic anticancer agents. Prashanth et al. (2015) developed ZnO nanoparticles using *Punica granatum* and *Tamarindus indica* to prove their anticancer activity against breast cancer cell lines (MCF-7). The results displayed a decline in the cancer cell viability, corresponding to an increase in *P. granatum*-synthesized ZnO nanoparticle concentration, compared with the nanoparticles from *Tamarindus indica*. Furthermore, the commercially available ZnO nanoparticles showed 66% of cancer cell viability, whereas *P. granatum*-synthesized ZnO nanoparticles exhibited cell viability around 58%. This clearly shows that the phytosynthesized ZnO nanoparticles are highly toxic towards cancer cells depending on their concentration. Another study by Suresh et al. (2018a) achieved 48% of growth inhibition towards mouse cancer cell lines using 50 µg/ml of ZnO nanoparticles synthesized via *Costus pictus* medicinal plant. This study confirms that a higher concentration of nanoparticle is vital in inhibiting the growth of cancer cells. Likewise, Ji et al. (2017) studied the anticancer activity of *Argemone mexicana* leaf extract-synthesized ZnO nanoparticles at different concentrations against cardiac cell lines of *Catla catla* fish. The results obtained indicate that the anticancer activity of ZnO nanoparticles is also dependent on the dosage. Thus, it can be concluded that the toxicity of phytosynthesized ZnO nanoparticles towards cancer is normal and is determined by the concentration and dosage of nanoparticles.

Cytotoxicity of CuO nanoparticles

Nanosized oxide form of copper (CuO) has been reported to enhance the antimicrobial property of copper; they are used as pesticides, coating material for air filtrations and has antibacterial, antifungal, and biomedical applications (Jeong and Kim 2014; Amiri et al. 2017; Shaker et al. 2016). The phytosynthesized CuO nanoparticles possess several advantageous biomedical properties, compared with chemically synthesized nanoparticles which are evaluated via in vivo cytotoxic analysis for use in pharmaceutical applications (Narasaiah et al. 2017). Like other nanoparticles, the industrial release of engineered CuO nanoparticles into the environment, land, and water is a great concern due to its toxic effects on human health (Assadian et al. 2018). Shi et al. (2017) synthesized CuO nanoparticles by utilizing *Cassia auriculata* leaf extract and evaluated their in vitro biocompatibility using rheumatoid arthritis macrophage (RAW 264.7) cell lines. The results showed that the CuO nanoparticles exhibited low cytotoxicity even at a high concentration. This shows that phytosynthesized CuO nanoparticles are suitable for use as drug delivery vehicles in rheumatoid arthritis treatment.

The study on the cancer cell lines is used to identify suitable anticancer CuO nanoparticles to inhibit cancer cells without causing a toxic effect on normal healthy cells. Rehana et al. (2017) synthesized CuO nanoparticles using five medicinal plants namely *Azadirachta indica*, *Hibiscus rosa-sinensis*, *Murraya koenigii*, *Moringa oleifera*, and *Tamarandus indica* to compare their anticancer efficiency with chemical-synthesized nanoparticles. The cytotoxic analysis was performed for biosynthesized and chemically synthesized CuO nanoparticles against four cancer cell lines: human breast (MCF-7), cervical (HeLa), epithelioma (Hep-2), and lung (A549) as well as normal human dermal fibroblast (NHDF) cell line. The results showed that cytotoxicity is dependent on the CuO nanoparticle concentration and all the phytosynthesized CuO nanoparticles exhibited appreciable anticancer activity than chemical-synthesized nanoparticles. CuO nanoparticles synthesized via *H. rosa-sinensis* and *T. indica* specifically exhibited higher anticancer activity due to the presence of anticancer phytochemicals in these medicinal plants. Likewise, Sivaraj et al. (2014) synthesized CuO nanoparticles using *Acalypha indica* leaf extracts and studied their anticancer activity against human breast MCF-7 cell lines which again proved that the anticancer activity of nanoparticles is concentration dependent. In another study, Yugandhar et al. (2017) synthesized CuO nanoparticles via stem bark extract of *Syzygium alternifolium* and estimated their efficacy against human breast cancer (MDA-MB-231) cell lines. The results displayed that 50-µg/ml concentration of phytosynthesized CuO nanoparticles has the capability to reduce 50% of cancer cells, compared with commercial cancer drug, doxorubicin, indicating their superior anticancer

activity. These studies confirmed that phytosynthesized CuO nanoparticles are better than nanoparticles yielded by chemical approaches.

Cytotoxicity of TiO₂ nanoparticles

TiO₂ gained its importance in the biomedical field as an implant material for decades due to its beneficial surface properties (Patel et al. 2017). Based on the literatures, TiO₂ nanoparticle is undoubtedly a potential material for consumer products and biological applications, as their biocompatible nature is highly beneficial in the medical field. However, it is important to evaluate the toxicity of commercially available TiO₂ nanoparticles, as most commercial TiO₂ nanoparticles are synthesized using toxic chemicals (Czajka et al. 2015). TiO₂ shows cytotoxic effects towards numerous cancer cells (Ahamed et al. 2017; Lotfian and Nemati 2016); however, chemically fabricated TiO₂ nanoparticles showed cytotoxic effects towards normal cells due to the presence and absorption of chemicals on the nanoparticle surface. Hariharan et al. (2017) studied the anticancer activity of TiO₂ nanoparticles produced by phytochemical mixture of *Cynodon dactylon* towards lung cancer (A549) cell lines. The results showed the phytosynthesized TiO₂ nanoparticles leads to 50% of cytotoxicity towards lung cancer cells at a low concentration (IC₅₀ = 140 µg/ml), compared with commercial TiO₂ nanoparticles. Similarly, He et al. (2017), utilized *Cinnamomum tanala* leaf extracts to synthesize TiO₂ nanoparticles and examined their cytotoxicity towards human prostate cancer (D 145) cell lines. The phytosynthesized TiO₂ nanoparticles inhibit 88% of cancer cell growth at a low concentration of 0.05 µg/ml which proved their anticancer activity. Recently, Senthilkumar and Rajendran (2018) synthesized TiO₂ nanoparticles using *Justicia gendarussa* leaf extract and studied their anticancer activity towards MCF-7 and MDA-MB-231 breast cancer cell lines. The results revealed that the cell viability of MCF-7 was reduced 55.64%, while the cell viability of MDA-MB-231 was dropped to 53.82% at 1-µM concentration after 24 h of incubation. This shows that TiO₂ nanoparticles are toxic to MDA-MB-231 cells and can be a better alternative for chemical-synthesized TiO₂ nanoparticles. All these data demonstrated that the phytosynthesized TiO₂ nanoparticles show time- and dose-dependent cytotoxicity towards cancer cells. However, in vitro cytotoxic analysis of phytosynthesized TiO₂ nanoparticles in normal cells has to be performed in the future to evaluate their side effects and utilize them in other biomedical applications.

Cytotoxicity of MgO nanoparticles

Among all other metal oxide nanoparticles, MgO nanoparticles have been widely used in pharmaceutical applications such as cancer therapy, nano-cryosurgery, and hyperthermia

and as an antimicrobial agent towards various drug-resistant pathogens (Jeevanandam et al. 2017b). Additionally, they inhibit bacterial and cancer cells by ultrasound-induced lipid peroxidation in the lipid membrane (Akram et al. 2018). Due to their extensive clinical usage, the chemically modified MgO nanoparticles have been restricted for medical purposes due to their toxic nature. Hence, current research works are focused on producing biocompatible, less toxic MgO nanoparticles via plant extracts. Recently, Suresh et al. (2018b) synthesized MgO nanoparticles using *Costus pictus* leaf extract and analyzed their anticancer activity against mice DLA cell lines. The results implied that the cancer cell inhibition rate increases with an increase in nanoparticle concentration. This study confirms the superior anticancer activity of phytosynthesized MgO nanoparticles which have the potential to replace toxic chemical-synthesized nanoparticles in biological applications. Likewise, Sugirtha et al. (2015) studied the anticancer activity of MgO nanoparticles that are synthesized using two plant extracts, namely *Brassica oleracea* and *Punica granatum*. The HeLa cell lines were used to examine the anticancer activity of nanoparticles, and the results showed a significant decrement in the cell viability with an increase in the concentration of phytosynthesized MgO nanoparticles. In another study by Majeed et al. (2018), MgO nanoparticles were fabricated through aqueous extract of *Penicillium* species and their cytotoxicity was evaluated using normal (Vero) and cancer cells (A-549). This study revealed that the phytosynthesized MgO nanoparticles are highly toxic towards cancer cells with less cytotoxic side effects towards normal cells. Likewise, Jeevanandam et al. (2018) analyzed the cytotoxicity of MgO nanoparticles synthesized via a sol-gel approach and *Amaranthus tricolor* leaf extract towards normal (Vero) and diabetic (3T3-L1 adipose) cell lines. The study revealed that the sol-gel-synthesized nanoparticles are highly toxic compared with phytosynthesized counterpart along with antidiabetic property (Jeevanandam 2017). It is evident from these literatures that phytosynthesized MgO nanoparticles are less toxic with enhanced biological properties than chemical-synthesized nanoparticles.

Cytotoxicity of iron oxide nanoparticles

Generally, iron is involved in the biological processes such as mitochondrial electron transporting chain and also in drug metabolism (Balas et al. 2017). These conventional properties of iron make iron oxide nanoparticles, mostly Fe₃O₄, a potential drug carrier candidate for targeted and controlled drug delivery (Hola et al. 2015), biosensors (Peterson et al. 2015), and diagnostic medical devices (Magro et al. 2018). These magnetic nanoparticles are extensively used as they are inexpensive and play a crucial role in biomedical applications due to their superparamagnetic properties (Sharma et al. 2018). These oxide nanoparticles are under stringent research to

determine if they can be utilized in cancer imaging, drug delivery, and therapeutic applications (Ali et al. 2016). However, these magnetic nanoparticles synthesized via chemical routes are restricted to biomedical usages due to their toxic reactions towards human cells. Meanwhile, phytosynthesized magnetic nanoparticles showed low toxicity and high biodegradability compared with the chemically synthesized nanoparticles (Yew et al. 2018). This favors phytosynthesized iron oxide nanoparticles to be a utilizable anticancer agent without affecting normal cells. Recently, the effect of *Sargassum muticum*–phytosynthesized iron oxide nanoparticles on cancer cell lines was analyzed by Namvar et al. (2014). The in vitro anticancer activity of iron oxide nanoparticles was tested against various human cancer cell lines, namely, human cell lines for leukemia (Jurkat cells), breast cancer (MCF-7 cells), cervical cancer (HeLa cells), and liver cancer (HepG2 cells) after 72 h of exposure. The results showed that the iron oxide nanoparticles fabricated by phytochemical showed toxicity only towards cancer cells and helped the growth of normal cells. Similarly, Sathishkumar et al. (2018) prepared iron oxide nanoparticles using *Couroupita guianensis* fruit extract and evaluated their in vitro anticancer activity against human hepatocellular carcinoma cells (HepG2). The crude extract and the magnetic nanoparticle showed increment in the cytotoxicity towards HepG2 cells. Both extract and the nanoparticle induced apoptosis to inhibit cancer cell growth which was noticed by the cellular morphological changes. The results showcased that the fruit extract–mediated iron oxide nanoparticles exhibit a synergistic cytotoxicity effect towards HepG2 cells, compared with crude fruit extract.

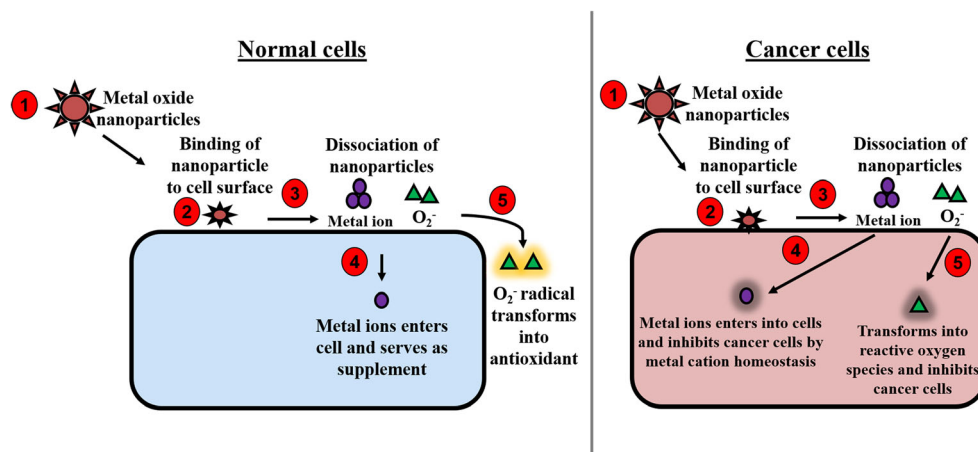
Furthermore, Nagajyothi et al. (2017) synthesized iron oxide nanoparticles using *Psoralea corylifolia* seed extract and evaluated their cytotoxic effect towards renal carcinoma (Caki-2 cells) and normal Madin-Darby canine kidney epithelial cells (MDCK). The result indicated that the phytosynthesized magnetic nanoparticles exhibited dose-dependent cytotoxicity towards both cells. The caspase activity in the MDCK and Caki-2 cells upon exposure of

phytosynthesized iron oxide nanoparticles for 48 h displayed that the fluorescence gradually increased with the increase in nanoparticle concentration which shows the occurrence of apoptosis. Likewise, Saranya et al. (2017) studied the cytotoxicity of phytosynthesized iron oxide nanoparticles through *Musa ornate* and *Zea mays* towards various normal cells such as kidney epithelial (Vero), pig kidney (PK 15), Madin-Darby bovine kidney (MDBK) cell lines. The results indicated that the cell viability depends on the type of cells, concentration, and exposure time of nanoparticles. In another study, the toxicity of *Juglans regia* husk extract–synthesized nanosized iron oxides towards normal human colorectal adenocarcinoma cells was evaluated by Izadiyan et al. (2018). The results confirmed that the phytosynthesized iron oxide nanoparticles are nontoxic even at a high concentration (1000 µg/ml) (Izadiyan et al. 2018). Thus, these studies proved that it is better to use phytosynthesized iron oxide nanoparticles for biomedical applications than a chemical-mediated approach.

Proposed cytotoxic mechanism of metal oxide nanoparticles

It is apparent from the in vitro analysis that the metal oxide nanoparticles are nontoxic to normal cells and show toxic reactions to cancer cells. The toxicity of the phytosynthesized nanoparticles towards normal and cancer cells depends on their chemical structure (Yang and Yu 2016), size (Tammina et al. 2017), morphology (Ann et al. 2015), and functional phytochemical-based surface charge (Saikia et al. 2016). This may be due to the different mechanisms of nanoparticles that are showcased towards diseased and healthy cells. The most common mechanisms of nanoparticle interaction with the normal and cancer cells that are proposed in several literatures are mentioned as schematic in Fig. 1. Due to electrostatic force of attraction, the metal oxide nanoparticles possess the capability to bind with the surface of both normal and cancer cells (Mashitah et al. 2016). Upon binding with the cell surface, the phytosynthesized nanoparticles dissociated into

Fig. 1 Mechanism of phytosynthesized metal oxide nanoparticles in normal and cancer cells



their ionic state such as metal and oxygen radical, due to the interaction of biomolecules present in the nanoparticles as a capping agent with the body fluid (Verma and Stellacci 2010). In normal cells, the metal ions may enter to the cells through passive, selective ion transport and act as an ion supplement which supports cell development. Further, the oxygen radical is removed by superoxide dismutase (SOD) to form hydrogen peroxide and catalases in peroxisomes as well as phytochemicals help to convert these hydrogen peroxides into water and oxygen. Thus, the superoxide radical is transformed into antioxidants before the formation of reactive oxygen species in normal cells (Aruoma 1998). In the case of cancer cells, proper cell membrane, SOD, and peroxisomes are absent due to abnormal (tumorous) growth (Reya et al. 2001). This led the dissociated ions to easily enter the cells. The increased metal ion concentration is proven to inhibit cancer cell growth by altering its metal cation homeostasis. Meanwhile, the oxygen radical transforms into reactive oxygen species which eventually forms hydrogen peroxide and leads to oxidative stress and mortality to cancer cells (Chang et al. 2012). However, there is no experimental confirmation to prove these mechanisms which drive forward the research to clarify the cytotoxic mechanism of phytosynthesized metal oxide nanoparticles in both normal and cancer cells.

Characteristics of metal oxide synthesis approaches

Metal oxide nanoparticles are usually synthesized by physical (Zhao et al. 2016), chemical (Ling et al. 2015), and biological (Shah et al. 2015) methods. Precursors and stabilizing and reducing agents play a significant role in initiating the nanoparticle formation process (Imran Din and Rani 2016). In physical approaches, the bulk or micro-sized precursors are downsized into ions or atoms via evaporation, laser ablation, molecular beam, and sputtering processes. These ions or atoms are deposited over a substrate and stabilized via pH, temperature, and pressure alterations to form nanosized particles. Physical synthesis approaches mostly yield monodispersed, pure metal oxide nanoparticles, and their toxicity towards living organisms is due to potential disintegration into ionic states in biological fluids (Guozhong 2004). In addition, the separation of nanoparticles from the substrate requires the use of toxic chemicals such as ethanol, acetone, methanol, and chemical buffers. These alcohols may be present and associated with the functional surface groups of the nanoparticles and can lead to toxic reactions (Wu and Cederbaum 2003). Similarly, cetyltrimethylammonium bromide (CTAB) and cetylpyridinium chloride (CPC) chemicals are used as a stabilizing agent to avoid agglomeration of nanoparticles (Begletsova et al. 2017). It is noteworthy that these complex chemical-stabilizing agents are highly toxic to living cells (Park et al. 2016; Lau et al. 2012). Further, the nature and

purity of the precursor can affect the toxicity of the nanoparticles (Sirelkhatim et al. 2015).

There are a number of chemical-based metal oxide nanoparticle synthesis approaches. These include solvothermal, hydrothermal, polyol, sol-gel, and colloidal methods (Ali et al. 2016). Among these methods, the initial formation of metal hydroxide (and organic or inorganic components as byproducts) with heat treatment at high temperatures to form metal oxide nanoparticle is a common reaction route (Jeevanandam et al. 2017b). However, the type and extent of utilization of reducing and stabilizing agents and solvents as well as the conditions of pH, reduction of byproducts, and the application of external energy sources to increase reaction rates via calcination, annealing, microwave, and ultrasound differentiate these methods and the yield of nanoparticles (Schmidt 2001). The presence of synthetic functional groups with the nanoparticles is due to the use of toxic chemicals as reducing and stabilizing agents, for pH adjustments and washing. Synthetic organic or inorganic precursors are mixed with toxic chemicals to reduce and stabilize bulk particles for the formation of nanoparticles, and this adds toxic functional groups and contaminants to the nanoparticle surface (Iravani 2011). Some of the toxic functional groups and contaminants may be vaporized off during high temperature conversion of metal hydroxides to oxides (Van Hoecke et al. 2011; Hussain et al. 2009). However, trace amounts of toxic elements will be present on the surface of the nanoparticles due to insufficient temperature and heating duration to completely remove toxic functional groups. This eventually leads to the disintegration of ions from the nanoparticles into biofluids and cause toxicity to cells (Hussain et al. 2009). Thus, compared with powders (nanoparticles prepared at high temperatures), nanoparticles synthesized as colloids are highly toxic due to the presence of toxic functional groups on their surface (Srivastava et al. 2015).

A biosynthesis approach also uses a synthetic chemical as a precursor and other parameters including reducing and stabilizing activities as well as pH alterations are managed via biological entities (Kahani and Yagini 2014). In phytosynthesized metal oxide nanoparticles, the precursor is either an organic or inorganic chemical and it is mixed with extracted phytochemicals from plant biomass that can act as both reducing and stabilizing agents (Ramanathan and Aqra 2019). The concentrations of the precursor and the phytochemical extract, as well as the conditions of temperature and pH, are the crucial factors that affect the nanoparticle synthesis process (Jeevanandam et al. 2017c). A balance in the concentration of precursor and the phytochemical can result in the generation of nanoparticles with the desired size and stability (Padil and Černík 2013). The process temperature affects the dissociation of complex phytochemicals into simpler forms. This simpler forms bind as capping agents with effective reducing capability for the formation of metal oxides

as well as being a stabilization agent to avoid aggregation (Jeevanandam et al. 2018). The morphology and surface charge of the nanoparticles can be modified via pH alterations, and this can be exploited to increase the stability of the nanoparticles (Jeevanandam et al. 2019). Toxicity associated with phytosynthesized nanoparticles may be due to byproducts from the heating process, resulting from potential reaction between unreacted organic and inorganic components of the precursor and dissociated phytochemicals. These molecular entities may be present as a capping agent, surface functional groups, of nanoparticles or contaminants to cause cytotoxicity by inducing ionization (Sabir et al. 2014). Further, the application of phytochemical extracts to adjust pH, as opposed to the addition of synthetic chemicals, reduces byproduct reaction-mediated toxic effect and well as morphology and surface charge-related toxic reactions (Kominkova et al. 2017). Washing of phytosynthesized nanoparticles is performed with water instead of detergents or alcohols to eliminate toxicity to live cells (Thakur and Joshi 2012). Thus, it is evident that the formation of toxic nanoparticles and byproducts can be reduced quite significantly in phytosynthesis approaches compared with the other synthesis methods.

In vivo analysis of phytosynthesized metal oxide nanoparticles

In vivo toxicity analysis has to be performed for nanoparticles before it is marketized as a commercial material for human convenience and is necessary to understand their biological interactions with the animal models. Various animal models such as mice, rats, hamsters, rabbits, fishes, birds, guinea pigs, amphibians, and primates are used to examine the in vivo toxicology of nanomaterials. Other than these mammals, a zebrafish model is another commonly used transparent, easy to maintain, and effective animal model to study for its toxicology. Likewise, *Drosophila melanogaster*, also called fruit fly, is a widely accepted animal model used to evaluate the genotoxicity of nanomaterials. Hence, this section broadly focuses on the recent updates of plant extracts, derived synthesis of metal oxide nanoparticles, and their toxicology studies in in vivo animal models.

Mouse model

Bala et al. (2015) synthesized two (12–46 nm, 190–250 nm) different sizes of ZnO nanoparticles using *Hibiscus subdariffa* extract and performed an antidiabetic analysis using Swiss albino mice. The smaller ZnO nanoparticles showed effective penetration than large-sized nanoparticles due to its large surface area with decent antidiabetic property. It is also observed that the zinc ions can increase the fasting insulin level and

fasting glucose level in the in vivo animal model (Bala et al. 2015). Likewise, Vimala et al. (2014) examined the toxicity of doxorubicin-loaded ZnO nanoparticles with different shapes fabricated via *Borassus flabellifer* by using the same animal model. The results revealed that there is no notable toxic effect during the drug delivery process in the in vivo condition (Vimala et al. 2014). In another in vivo study, Swiss albino male adult mice were used to analyze the toxicity of *Ochradenus baccatus*-synthesized ZnO nanoparticles that were injected into the mice's skin four times in a week and were sacrificed after the 28th day. The results showed that even at higher dosage of phytosynthesized ZnO nanoparticles, the toxicity level was very low in the animal model (Al-Shabib et al. 2018).

Additionally, Sulaiman et al. (2018) evaluated the toxicity of *Olea europaea*-phytosynthesized CuO nanoparticles using 25 male Swiss albino mice. The final report reveals that the nanoparticle induces weight loss in animals which may be due to the over dosage of CuONPs that affects the digestive system. The result also unveiled that the CuO nanoparticles exhibited dose-dependent toxicity in mouse models (Sulaiman et al. 2018). Another study by Sankar et al. (2014) which involved TiO₂ nanoparticles synthesized by using *Origanum vulgare* extract showed that these phytosynthesized nanoparticles are beneficial in wound healing treatment on Wistar male albino rats. The results demonstrated that the phytosynthesis yielded nontoxic nanoparticles that do not cause pus formation, bleeding, and microbial infections in the animal model. This study confirms that the phytosynthesized nanoparticles are highly significant as therapeutic agents for wound-healing applications due to their eco-friendly, nontoxic nature, and specific wound-healing properties (Sankar et al. 2014). Further, TiO₂ nanoparticles synthesized by both chemical (sol-gel) and *Desmodium gangeticum* root extract were subjected to in vivo toxicity analysis. The results showed the phytosynthesized nanoparticle exhibited less nephrotoxicity than chemical-synthesized nanoparticles in the Wistar rat model, due to the presence of biomolecules. At the mitochondria level, there were no major alterations due to the toxicity observed when both chemical and phytosynthesized TiO₂ nanoparticles are exposed to the animal (Ansari and Kurian 2017). These studies concluded that the plant extract-mediated nanoparticle synthesis can be effectively used in medical applications. The advantage of this animal model is that the effect of nanoparticles towards different organs is possible to evaluate which is significant for targeted drug delivery applications. Figure 2 represents the possibility of specific organ-based toxicity evaluation via in vivo nanoparticle toxicity analysis using mouse models.

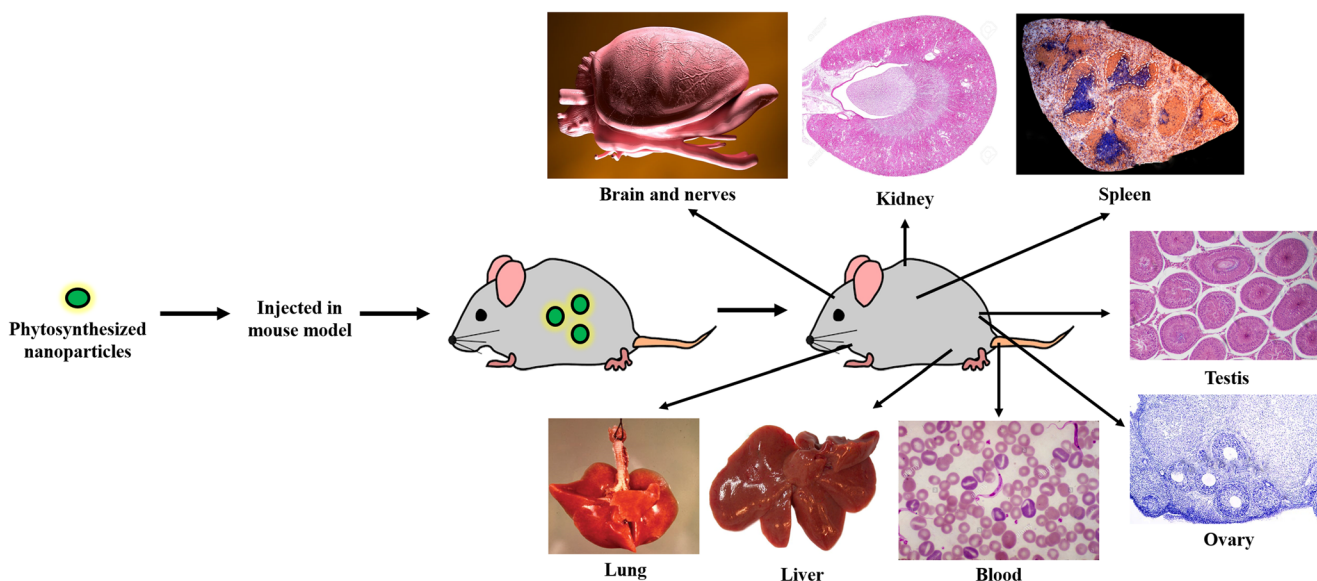


Fig. 2 In vivo toxicity analysis using mouse as model organism

Drosophila melanogaster model

A fly species, named *Drosophila melanogaster*, is usually used to study in vivo genetic variations or mutations that are caused by a drug material in a living organism (Meigen and Loew 1824; Lindsley and Grell 1968). *Drosophila* has gained enormous importance to the analysis of the in vivo genotoxicity of nanoparticles in recent times. Currently, the central nervous system (CNS) of this animal model was used to study the neurotoxic effect of phyto- and chemical-synthesized ZnO nanoparticles. The results revealed that both ZnO nanoparticles at higher concentrations (100 mg/ml) showed specific crawling inability in the animal due to the damage of neuromuscular coordination (Sood et al. 2017). Similarly, the genotoxic behavior of zinc ions in ZnO nanoparticles and ZnCl₂ was examined using the *Drosophila* model and the results revealed that the genotoxic behavior was due to the expression of altered gene and does not depend on zinc ions (Alaraby et al. 2015). Another study utilized 50–80 nm-sized ZnO nanoparticles to evaluate its toxicity towards *Drosophila melanogaster* and showed no toxic observations in any organ of the animal model (Ng et al. 2017). The *Drosophila* model was also used to evaluate the toxicity of CuO nanoparticles and copper sulfate. The results established that the CuO nanoparticles exhibited low toxicity even at a higher concentration (10 mM), whereas low concentrations (5 mM) of copper sulfate displayed higher toxicity (Alaraby et al. 2017). Likewise, copper-doped ZnO nanoparticles were synthesized to evaluate its toxicity at different feeding durations towards male drosophila models. The climbing ability, activity pattern, activity of acetylcholinesterase, glutathione-S-transferase, glutathione, lipid peroxidation, caspases, and total protein content of the model were analyzed, and it

revealed no significant change in their climbing activity and no toxic effects were observed in the *Drosophila* model even at a higher (8 µg/µl) concentrations (Siddique et al. 2015). Figure 3 displays the toxicity of nanoparticles that are observed in different life stages of *Drosophila*. Thus, this model is highly beneficial in evaluating the effect of nanoparticles in subsequent generations of an organism. However, the major drawback in using *Drosophila* as an animal model is its scientific acceptance and inability to evaluate cytotoxicity and bioavailability in different organs.

Zebrafish model

Zebrafish (*Danio rerio*) is an alternative for mouse models to assess the toxicity of nanoparticles as they do not require an animal facility center and are smaller in size (Strähle et al. 2012). Kumari et al. (2017) used zebrafish models for the in vivo analysis of *Calotropis gigantea*-synthesized CuO nanoparticles, and the final results revealed that the fish embryo gets swelled up due to the CuO nanoparticle toxicity which is dependent on their concentration (Kumari et al. 2017). Meanwhile, George et al. (2014) investigated the toxicity of TiO₂ nanoparticles in the *Danio rerio* model, and the results suggested that the nanoparticle exhibited no toxic effect in the dark. The increment in the solar light exposure towards nanoparticle leads to their physicochemical transformation and increases their toxicity in fish models (George et al. 2014). Another study by Vicario-Parés et al. (2014) investigated the toxicity of three different metal oxide nanoparticles such as CuO, ZnO, and TiO₂ nanoparticles using zebrafish larvae. The study observed that CuO nanoparticles were highly toxic to fish larvae and TiO₂ nanoparticles were least toxic, among other metal oxides. Besides, it is

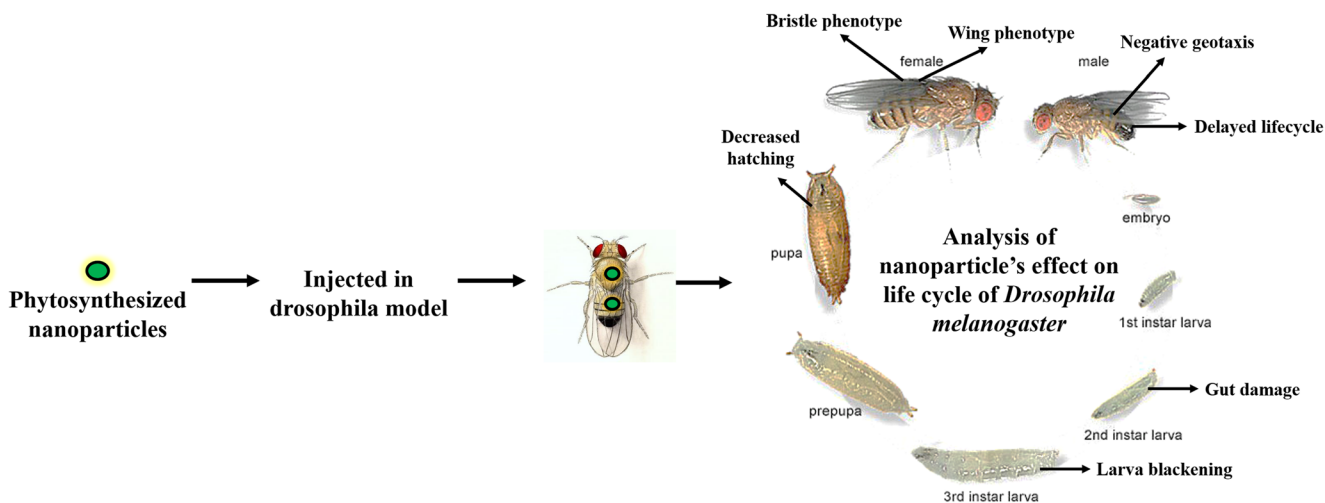


Fig. 3 Evaluation of nanoparticle’s toxic effects towards life stages of *Drosophila melanogaster*

noteworthy that all these three nanoparticles affect the hatching rate of zebrafish larvae (Vicario-Parés et al. 2014). Also, Hua et al. (2014) reported the morphology-mediated toxic effect of nanoparticle in the zebrafish model, and the results revealed that the ZnO nanosticks are highly toxic than nanospheres (Hua et al. 2014). Furthermore, the histopathological analysis of cobalt oxide nanoparticles and cobalt ions using the zebrafish model showed less toxicity of nanoparticles. However, there was damage in the zebrafish gills upon aggregation and precipitation of cobalt oxide nanoparticles. Thus, it is advised that care should be taken for the synthesis of stable cobalt oxide nanoparticles to avoid aggregation (Mansouri et al. 2015). Figure 4 shows the possible toxicity exhibited by nanoparticles in the life stages of zebrafish. Even though zebrafish is extensively used for in vivo toxic analysis of nanoparticles, it is not considered an alternative to the mouse model as fish is an aquatic animal model. Hence, it is used

only for lab-scale toxic analysis to screen and select less toxic nanoparticle samples for drug delivery applications.

Other animal models

Very recently, *Daphnia magna*, a small crustacean plankton, was used to analyze the in vivo toxicity of both chemical and phytosynthesized CuO nanoparticles. The CuO nanoparticles prepared by phytochemicals were proven to be highly stable with slow ion release mechanism, compared with chemical-synthesized CuO nanoparticles. This is a pioneer work to prove that in vivo toxicity of phytosynthesized nanoparticles shows low using *Daphnia magna* as an animal model (Saif et al. 2016). Likewise, *Morinda citrifolia* root extracts were used to synthesize TiO₂ nanoparticles, and their larvicidal activity was studied using *Anopheles stephensi*, *Aedes aegypti*, and *Culex quinquefasciatus*. The results revealed that the

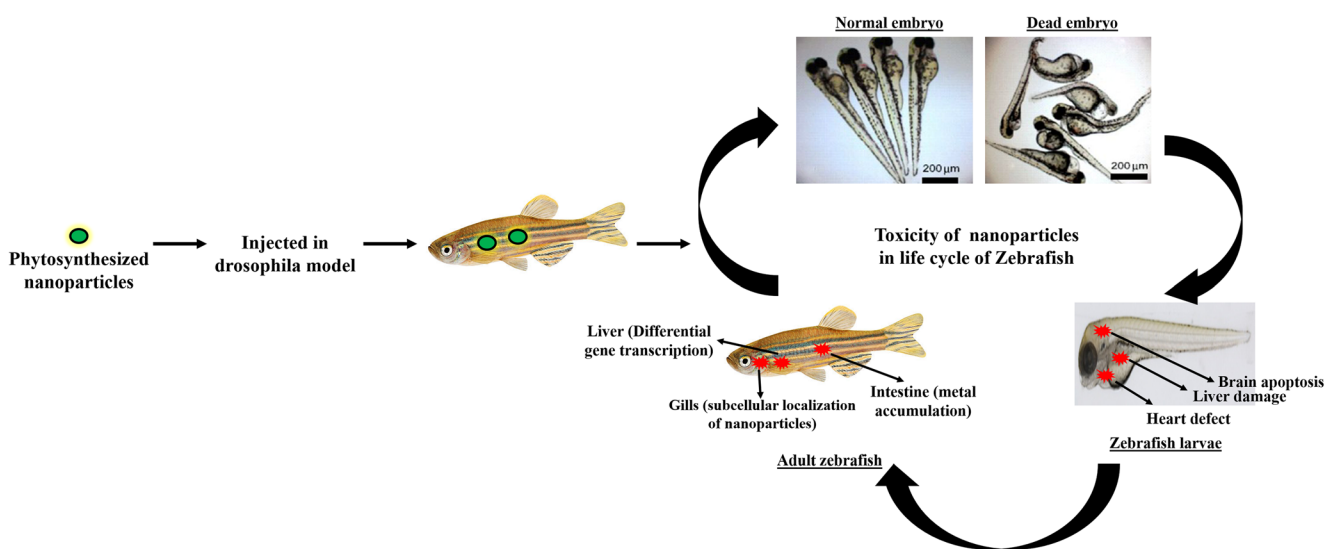


Fig. 4 Toxicity of nanoparticles in the life stages of zebrafish

phytosynthesized TiO₂ nanoparticles exhibited excellent larvicidal activity, compared with crude root extract. In addition, the in vivo toxicity analysis of these nanoparticles in *Poecilia reticulata* fish models also confirms their nontoxicity towards aquatic organisms. Thus, phytosynthesized TiO₂ nanoparticles are proposed to be a better larvicidal agent against mosquito larval that is nontoxic to aquatic organisms (Suman et al. 2015). Furthermore, aluminum oxide nanoparticles were exposed to healthy adult fresh water *Oreochromis mossambicus* fishes at different concentrations for 96 h and the results revealed that the oxide nanoparticles induce histological alterations such as liver damage, morphological changes in veins, aggregation of blood cells, and shrinkage of pancreatic tissue (Murali et al. 2017). In another study, mussels (*Mytilus galloprovincialis*) were used to monitor the toxicity of iron oxide nanoparticles. After 1 week of exposure towards nanoparticles, mussels were found with oxidative stress due to the toxicity of iron oxide nanoparticles (Taze et al. 2016). Table 1 is the summary of recent in vivo toxicological analysis of various metal oxide nanoparticles using animal models. From these studies, it is notable that in vivo toxicity analysis is slowly being introduced to evaluate the interaction of nanoparticles towards live organisms. However, there are no specific protocols to regulate these studies which are a major drawback to utilize in vivo analysis as preclinical studies for nanoparticles. The regulation and proper guidelines for in vivo analysis of nanoparticles will be highly beneficial in future for utilizing nanoparticles in biomedical applications.

Biomedical applications of phytosynthesized metal oxide nanoparticles

The reduction in the cytotoxicity of green-synthesized metal oxide nanoparticles as reported in literatures, compared with chemical-synthesized nanoparticles, leads to the utilization of these oxide nanoparticles in various biomedical and pharmaceutical applications. These phytosynthesized nanoparticles are extensively used in applications such as cancer treatment (Ashokan et al. 2017; Rajeshkumar et al. 2018; Dey et al. 2018), diagnosis, and treatment of numerous other diseases such as microbial infections (Thatoi et al. 2016; Sutradhar et al. 2014), diabetes (Rajakumar et al. 2018), neurodegenerative and cardiovascular diseases (Ashraf et al. 2018; Groiss et al. 2017), fabrication of dental and orthopedic implants (Gopi et al. 2015; Zhang et al. 2018a), bioimaging (Eriksson et al. 2018; Alwi et al. 2012), and biosensors (Singh et al. 2017; Reddy et al. 2018). The reactive oxygen species released from oxide nanoparticles in combination with antioxidant phytochemicals are highly beneficial in inhibiting the growth of diseased cells, especially cancer cells. Moreover, metal oxide nanoparticles synthesized via phytochemicals were also highly useful as antimalarial (Gandhi et al. 2018),

antilarval (Rajakumar et al. 2015), anti-inflammatory (Nagajyothi et al. 2015), and acaricidal (Banumathi et al. 2016) properties which help in avoiding the spread of harmful diseases. Thus, phytosynthesized metal oxide nanoparticles with bioavailability and stability will help to overcome the challenges of disease treatment in future. In addition, these phytosynthesized nanoparticles will reduce the cytotoxicity and even if they disintegrate into their ionic state, they will be utilized as micronutrient supplements for cellular development.

Future perspective

There are numerous biomedical applications in which metal oxide nanoparticles are utilized and some of these have been investigated by researchers as reported in literatures. However, lack of awareness and the tediousness in large-scale fabrication of green-synthesized nanoparticles leads to the extensive utilization of chemical-synthesized nanoparticles for applications, even after the emergence of stable and biocompatible biosynthesized nanoparticles. Currently, computer modeling and simulation named as in silico analysis are gaining the interest among researchers as they seek to analyze the toxicity of nanoparticles (Cohen et al. 2012). Those in silico modeling and simulations are highly helpful in designing and analyzing personalized nanoparticle delivery (Hossain et al. 2013) and cell diffusion transfer (Labowsky et al. 2015) mechanisms of phytosynthesized metal oxide nanoparticles to enhance their ability to be a useful nanomedicine entity. These phytosynthesized metal oxide nanoparticles possess high potential to be useful as drug molecules to cure rare diseases such as progeria and lafora. Progeria is an autosomal dominant genetic disorder which leads to aging at a very early stage (Scaffidi and Misteli 2005), whereas lafora is a progressive myoclonic epilepsy which is a fatal autosomal recessive genetic disorder characterized by the presence of inclusions called lafora bodies in the cellular cytoplasm of organs such as the liver, skin, heart, and muscles (Tagliabracci et al. 2008). Common protein deficiency syndromes such as marasmus and kwashiorkor (Ramírez Prada et al. 2011) and diseases such as Alzheimer's (Masters et al. 1985) and Parkinson's (Hughes et al. 1992) also require a drug molecule which can cure them without any side effects. Phytochemicals from plants with antioxidant properties have proved to be useful in curing these diseases (Zhang et al. 2018b; Liu et al. 2017). Thus, phytochemical-encapsulated metal oxide nanoparticles will be significantly beneficial as a curative agent for these diseases without any additional complications in future. In addition, multicompartamental encapsulation and nanocomposites of phytosynthesized metal oxide nanoparticles with various biological properties will be significant in fabricating smart nanomaterials that can monitor, sense deficiency or

Table 1 Summary of recent in vivo toxicity analysis of metal oxide nanoparticles in animal models

Metal oxide nanoparticles	Size and morphology	Animal model	Result	Reference
ZnO	12–46 nm size of spherical nanoparticles and 50–60 nm breadth of dumbbell-shaped nanoparticles	Swiss albino mice	Good antidiabetic property with effective penetration.	(Bala et al. 2015)
ZnO	55 nm of rod-shaped nanoparticles	Swiss albino mice	Nontoxic	(Vimala et al. 2014)
ZnO	Poly-morphology with size above 100 nm	<i>Drosophila melanogaster</i>	Neurotoxic at 100 mg/ml	(Sood et al. 2017)
ZnO	50–80 nm-sized agglomerated spherical nanoparticles	<i>Drosophila melanogaster</i>	Nontoxic	(Alaraby et al. 2015)
ZnO	Mixture of circular, elliptical, and hexagonal with size below 50 nm	Swiss albino male adult mice	Less toxic even at high concentrations	(Al-Shabib et al. 2018)
ZnO	70 nm-sized spherical nanoparticles	<i>Drosophila melanogaster</i>	Less toxic	(Ng et al. 2017)
ZnO	Nanospheres, nanosticks, and cuboidal submicron particles	Zebrafish	ZnO nanosticks are more toxic than nanospheres	(Hua et al. 2014)
CuO, TiO ₂ , ZnO	Below 100 nm-sized nanoparticles	Zebrafish	Toxicity—CuO < ZnO < TiO ₂	(Vicario-Parés et al. 2014)
Cu-doped ZnO	Agglomerated nanoparticles	<i>Drosophila melanogaster</i>	Nontoxic	(Siddique et al. 2015)
TiO ₂	Average particle size of 341 nm and spherical shape	Wistar male albino rats	Effective wound healing property	(Sankar et al. 2014)
TiO ₂	Spherical above 100 nm in size	Zebra fish	Nontoxic in dark, toxic in solar light condition	(George et al. 2014)
TiO ₂	0.70 nm of grain size	Wister rat	Less nephrotoxic than commercial TiO ₂ nanoparticles	(Ansari and Kurian 2017)
TiO ₂	20–40 nm-sized spherical nanoparticles	Mosquito larvae (<i>Anopheles stephensi</i> , <i>Aedes aegypti</i> , <i>Culex quinquefasciatus</i>) and non-target fish	Toxic to mosquito larvae and less toxic to non-target fish named <i>Poecilia reticulata</i>	(Suman et al. 2015)
CuO	25–35 nm size with spherical shape	Zebrafish	Toxic	(Kumari et al. 2017)
CuO	Oval-shaped, 100–125 nm-sized nanoparticles	<i>Daphnia magna</i>	Less toxic	(Saif et al. 2016)
CuO	20–50 nm-sized spherical shape	Swiss albino mice	Toxic	(Sulaiman et al. 2018)
CuO	50 nm-sized agglomerated spherical shape	<i>Drosophila melanogaster</i>	Toxic above 10 mM	(Alaraby et al. 2017)
Al ₂ O ₃	40 nm-sized coral-like morphology	<i>Oreochromis mossambicus</i>	Toxic	(Murali et al. 2017)
Fe ₂ O ₃	20–40 nm-sized nanoparticles	<i>Mytilus galloprovincialis</i>	Toxic	(Taze et al. 2016)
Cobalt oxide	50 nm-sized spherical nanoparticles	Zebrafish	Less toxic	(Mansouri et al. 2015)

disorder, and release drug molecules to cure them. These types of nontoxic and non-mechanical molecular nano-robots or smart bio-nanomaterials are possible via phytochemical-mediated metal oxide nanoparticle synthesis.

Conclusions

Metal oxide nanoparticles are slowly capturing the place of metal nanoparticles in biomedical applications due to their enhanced stability and bioactivity in body fluids. In recent times, plant extracts are extensively used to synthesize a wide variety of nanoparticles, especially metal and metal oxide nanoparticles, due to their user-friendly synthesis approach and its large-scale production tendency. Since, phytochemicals contain biomolecules that help in nanoparticle formation, these phytosynthesized nanoparticles are believed to be less cytotoxic towards human cells. However, the *in vitro* and *in vivo* toxicity analysis—as mentioned in this article—reveals that phytosynthesized nanoparticles exhibit dosage-, time-, and concentration-dependent toxicity towards cells and organs. In comparison with chemical-synthesized nanoparticles, the phytosynthesis approach is beneficial in biomedical application and hence, toxicity analysis plays a key role in selecting nontoxic nanoparticles with unique biological properties. It is evident from this article that there is no regulation for *in vitro* and *in vivo* nanoparticle analysis, which is a drawback in using them as a potential preclinical analysis method. In the future, specific regulations and procedures should be provided with existing literatures to carry out a toxicological analysis in cell and animal models and to promote less toxic nanoparticles for clinical studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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