

Nanoceria and Its Perspective in Cancer Treatment

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Abstract

From the birth of mankind, cancer is known as one of the most notorious and deadly diseases human kinds has ever faced on this earth. Many methods and ways are implemented to eliminate this disease and the number is still on the increasing side. It's been a couple of decades that the idea of nanotechnology was first introduced, where nanoparticle is part of that. Cerium oxide nanoparticle also known as nanoceria is one of the metal oxide nanoparticles which holds promise to treat cancer effectively. Scientists have found fruitful result ignoring the drawbacks of this particular particle and there are ongoing researches to unlock the full potential of cerium oxide nanoparticle in the case of cancer treatment as well as eliminate its drawbacks.

Keywords: Nanoparticle; Nanoceria; Cancer metal oxide

Introduction

Arguably cancer is the most complex disease, and still it is one of the principal health problems of the 21st century, since after cardiovascular diseases it is the second leading cause of death in developing countries [1-3]. Almost all cancers (stomach, liver, colon, breast etc.) are genetically rooted disease which involves the concurrent occurrence of cellular malfunctions [4,5]. Usually cancer forms as a solid tumor, which may or may not be cancerous (benign) [6]. Thus the cancerous state is a consequence of some chronological matters stimulated by factors like genetic predispositions, transformation by viruses, radiation or certain chemicals [7]. When the tumor expands big enough, some of its cells may find their pathway into the bloodstream, configuring tumors in different parts of the body, known as metastasis, which effectually increases cancer and its effects [4]. In bulk tumors, greater number of cells may be non-tumorigenic end cells, and within tumors a small population of cells is liable for tumor initiation, growth, and repetition, which are called "cancer stem cells" (CSCs) [8]. As per date different available methods of treating cancer work as a double edged sword as because it destroys both cancer and non-cancerous cells. For example, radiation therapy which has been accepted as a preferable method to treat cancer can cause damage both cancerous and normal cells equally [9]. Because of this consequence and others, different methods and materials are discovered by scientists to mimic the situation. Due to their catalytic properties nanoceria has gained concern by several researchers as a potential agent in the biomedical application [10]. These materials are versatile and may have diversified form depending on the bulk material [11] that may help to treat different disease especially cancer. In this review, we are focusing on the perspective of nanoceria in cancer treatment.

Evolution of Cancer Treatment

Traditionally cancer can be diagnosed by X-ray or CT (computed tomography) scan. But these methods are suitable when an ample amount of cancerous cells are available in the organ [12]. Other available methods are MRI (based on magnetic field and radiofrequency waves), PET (based on positron emitters labeled radiopharmaceuticals) etc. [13].

Paul Ehrlich, a German chemist was the first who invented the chemotherapy to treat cancer. Except chemotherapy, surgery and radiotherapy are other treatment methods which were used from the 1960s [14] but these methods are non-specific and may damage cancer cells as well as the healthy cells too [15]. As for example, in case of surgery the cancer-affected part are completely removed but still

there is a chance of cancer growth. In radiation therapy healthy cell may burnt along with the tumor cells and in chemotherapy necessary nutrients can stop their mechanism because of the drugs used [12] or can cause other serious side effects like cardiotoxicity which occurs in the treatment of breast cancer using doxorubicin [16]. Despite various disadvantages, chemotherapy has shown much promising result than other available methods in cancer therapy [17], though currently a combination of radiotherapy, chemotherapy, and surgery is used to treat cancer [18]. Hormonal therapy, immunotherapy, adjuvant therapy are some other available methods to treat cancer [6]. However, these are not enough because of their drawbacks and eventually use of new method or process is necessary.

Nanoparticles Role in Cancer Treatment

Cancer nanotechnology provides several opportunities over the conventional method of cancer diagnosis and treatment. Such as, it helps to prevent cancer, helps to detect cancer at an early stage, helps to diagnose, image and treat cancer more effectively and helps to overcome the conventional treatment problems (lack of early disease detection, non-specific systematic distribution, inadequate drug concentrations reaching the tumor etc.) by using nanomaterials or nanoparticles, which may use as a drug, imaging agents or both (multifunctional nanoparticle) with the help of a delivery system known as "nanocarrier" [12,19,20]. Nanoparticles along with the chemotherapeutic drug made nanoscale complex which helps in the treatment of cancer [18]. Surface composition and other physical and chemical properties of nanoparticles help them to detect tumor cells in a more convenient way which is either qualitative or quantitative [17]. Nanoparticles are able to permeate tumor cell easily and may retain for a longer period of time that helps them to accumulate and localize in the tumor region more preferably which helps in the enhancement of drug loading in

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the tumor area with decreased nonspecific side effects [21]. Nano-sized particles also help in the improvement of conventional MRI imaging of cancer by working as a contrasting agent like magnetic oxides, quantum dots etc. [22]. Therapies like laser thermotherapy or plasmonic photothermal therapy produce heat in tissue and cause damage to the tumor as well as non-tumor cells. But using nanoparticles in these treatments as an adjuvant could make it more specific to treat the cancer cells with fewer side effects. For example use of gold nanoparticles which is biocompatible and also have the photothermal conversion capability. Nanoparticles have the ability to overcome the barrier related shortcomings. For example, in bladder cancer, it is important to deliver the drug intravesically rather than orally. But permeability through bladder is difficult to achieve. In this case, nanoparticles could be the choice as it has the ability to penetrate the barrier more easily because of its nanosized component [23]. The unique advantage of the nanoparticle is that it can target cancer cells either in the active or passive way and it can be given locally in tumor sites which help to reduce the shortcomings of conventional chemotherapy [24]. There are lots of nanoparticles that could be used for medical as well as other perspective and cerium oxide nanoparticles is one of them.

Nanoceria

Cerium oxide nanoparticles, also known as nanoceria [10] have gained much more concern over the past decade because of their distinctive physical, chemical as well as structural properties [25]. Cerium is a rare-earth element of the lanthanide series and is available in two oxidation state, Ce^{3+} and Ce^{4+} [21]. Cerium oxide nanoparticles also are known as nanoceria can switch their oxidation state [21]. This unique property helps them to provide a wide range of applicability in biomedical and biological field i.e. they are able to interact with the disease-causing reactive oxygen species (ROS) [26]. Materials containing cerium have other uses in metallurgy, ceramics, optics etc. [21]. In order to get the desired effect or application synthesis of nanoceria in a biocompatible way is a must and that is a pretty challenging task [27].

Nanoceria Preparation

Nanoceria can be prepared by different wet chemical synthesis method i.e. sol-gel method, hydrothermal method, microwave method etc. [28]. Figure 1 shows different ways to synthesis cerium oxide nanoparticles. Methods of cerium oxide nanoparticles depend on several factors like temperature, pressure, capping agents [26]. Despite these it can be made by one other way known as the flame spray pyrolysis [29]. These prepared nanoparticles can be wrapped with a hydrophilic or hydrophobic material or not. Size may vary on the basis of their application [30,31].

Nanoceria in Cancer Therapy

Using nanoceria is a smart option for the eradication of cancer because it could eliminate cancer cells without damaging other normal tissues. Hypothesis on mechanism of action of nanoceria is that, cancerous cells are predicted as acidic and nanoceria could increase this acidic cells oxidative stress as well as apoptosis which lead to the destruction of cancer cells. Because nanoceria catalase like activity works better on acidic environment. On the other hand, surrounding tissues of the cancer remains unharmed because nanoceria works selectively only on the cancerous cells [32]. Figure 2 shows the process how nanoceria works on cancerous and non-cancerous cells.

Different investigation have shown that cerium oxide nanoparticles can play a key role to detect cancer biomarker, known as cerium oxide nanoparticle based colorimetric ELISA which is less time consuming, reliable and effective rather than traditional ELISA method [33]. The main advantage of using nanoceria is because of its selective nature towards human cancer cells. Pesic et al. proved that by using nanoceria suspension and tested *in vitro* in different human cancer cell lines [34]. In a recent study Giri et al. have demonstrated that nanoceria prepared by wet chemical synthesis can play a vital role in the treatment of ovarian cancer by inhibiting different growth factor like vascular endothelial growth factor. Synthesis of nanoceria was carried out by using cerium nitrate hexahydrate. Hydrogen peroxide and ammonium hydroxide

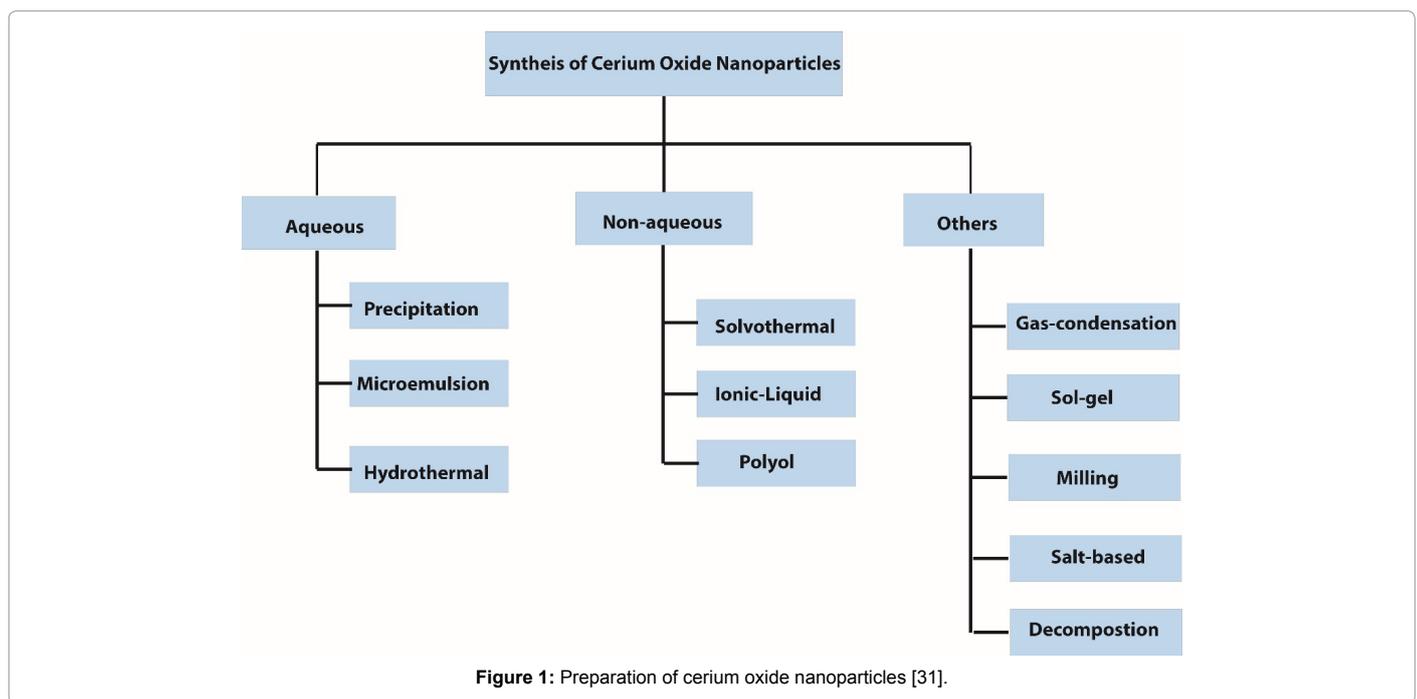


Figure 1: Preparation of cerium oxide nanoparticles [31].

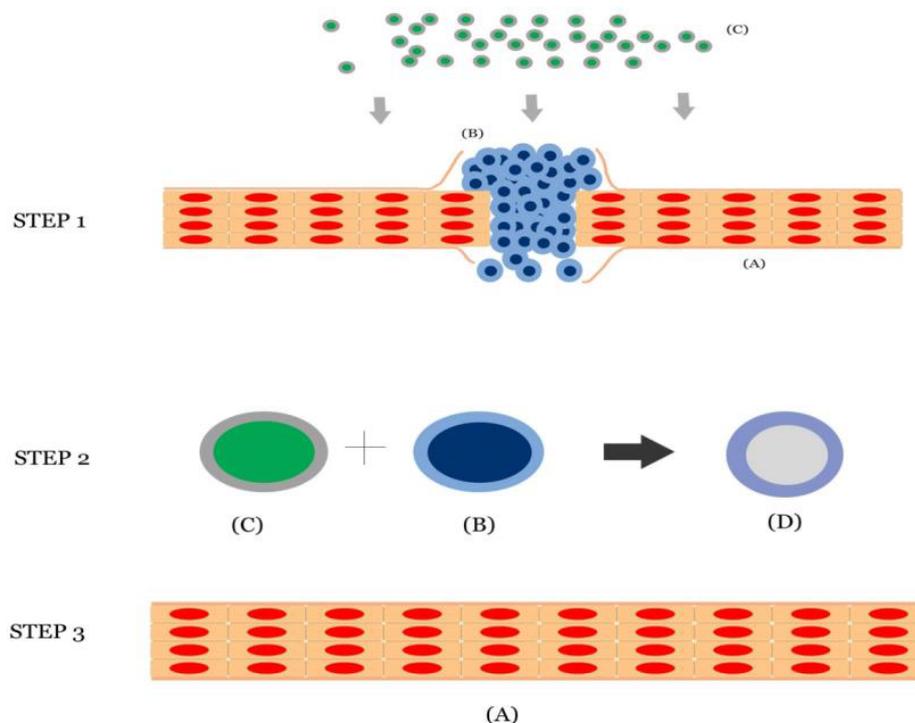


Figure 2: In step 1 nanoparticles are given both in cancer and non-cancer cells. Step 2 shows nanoceria works on cancer cells selectively and leads to the increased oxidative stress and apoptosis of cancer cells. Step 3 shows normal cells remain unharmed. (A)=normal cell, (B)=Cancer cell, (C)=nanoceria, (D)=apoptosis of cancer cell.

were used as oxidizing agent and pH adjustment. The experiment also proved that nanoceria could be attached with other chemotherapeutic drugs in order to improve the efficacy as well as potency with decreased level of side effect [35]. For the identification of tumor cells Perez et al. developed a method by using polyacrylic acid coated cerium oxide nanoparticles with folic acid. This folic acid combined nanoceria can be easily taken by tumor cells which help to identify them easily rather than other available method [30] and was tested in case of lung carcinoma [33]. Other studies have shown that nanoceria prepared by hydrothermal (have a morphology of flaky kind) and hydrolysis (have a morphology of spherical) method can be attached successfully with transferrin, a tumor marker in order to improve the antitumor therapy [21]. Some clinical reports have also shown that cerium iodide may be able to shrink the tumor and assist to improve the quality of life. Reports have also shown that nanoceria helps to protect the normal cells and assist in the destruction of tumor cells where oxidative stress is induced and lipid peroxidation, cell membrane leakage has caused. This ability of nanoceria works better in acidic conditions. It was also observed that nanoceria are able to assist in the radiation therapy, working as an adjuvant by protecting the normal cells as well as increasing the toxicity towards the cancer cells [30]. Alili et al. and his groups have shown that polymer (Dextran) coated nanoceria has the ability to combat with a certain type of skin cancer known as malignant melanoma. They have shown both *in vivo* and *in vitro* that nanoceria concentrations are nontoxic to normal cells and have cytotoxic and anti-invasive effects on melanoma cells. The nanoceria concentrations they used was low as it has a protective effect on normal cells [36]. In another study Montfort et al. have confirmed that nanoceria prepared by using dextran, water, hydrogen peroxide and ammonium peroxide can be used to treat squamous cell carcinoma and human dermal fibroblasts;

that is non-toxic to stromal cells [37]. Studies have shown that radiation therapy of cancer is a painful way to treat cancer that may cause cell damage of the gastrointestinal tract, lung, breast etc., side effects like nausea, dermatitis, fatigue etc. and nanoceria can assist in this therapy to minimize this effect [38] depending on the X-ray radiation spectra [39]. As for example amifostine is the only radioprotectant clinically available for the cancer therapy [38]; i.e. head and neck cancer [40] but it causes nausea and hypotension. Nanoceria can fix this issue by minimizing the side effects [38]. For this characteristic nanoceria is known as smart radio-protecting as well as radio-sensitizing agent [41]. In a study Baker et al. have reported that nanoceria can work as a radioprotective compound in head and neck cancer therapy [40]. Ting et al. and his groups have shown that nanoceria synthesized by using flame spray method bounded with heparin, that helps to enhance the biological properties of nanoceria in comparison with nanoceria only can play an important role in tumor therapy by enhancing the ROS-modulating activity in monocyte cell line [42] that helps in the controlling of cancer angiogenesis. Studies have shown that nanoceria helps in the elimination of tumor cells by increasing the level of ROS (reactive oxygen species). Many studies have also proved that nanoceria can induce apoptosis selectively and helps in the suppression of tumor cell proliferation [29]. It has been reported that nanoceria which is anionic in nature are toxic to lung cancer cells A549 [43] and nanoceria particles size of 20 nm are toxic to CLR5883 cells [44]. Lin et al. have demonstrated that depending on the time and dose cerium oxide nanoparticles can be cytotoxic to human lung cancer cells [45-49]. Nanoceria is under investigation from the past couple of years as a potent anticancer agent in order to get rid of cancer. More researches need to be done to unlock its full potential. Table 1 shows nanoceria research towards different types of cancer.

Functionalization of Cerium oxide Nanoparticles (CONPs)

Synthesized metal oxide nanoparticles such as nanoceria are applicable in different ways but their main drawback is they are unstable or stable in a low range of pH which hampers its effectiveness a lot. Approaches were taken to improve this condition like incorporation of PEG with nanoceria help to increase its stability range [49]. Studies have shown that in order to functionalize the CO nanoparticles in a more useful way, specifically targeted and to improve biological response as well as reduced toxicity they have been encapsulated with different natural polysaccharides, polymers like heparin, PEG, hyaluronan and many others. Ting et al. and others have demonstrated that a combination of heparin and nanoceria produced by flame spray pyrolysis method have shown superior ROS scavenging effect in activated U937 cells over a prolonged period of time rather than bare nanoceria which was tested by ATR-FTIR, NMR and TGA. It was experimented that heparin as well as heparin sulphate proteoglycans has cell proliferation changing capability by interactions using a ligand growth factor and receptor of the cell surface. This study also proved that heparin combined nanoceria also increases the cellular uptake process [42]. In another study Lord et al. successfully able to functionalize nanoceria with different level of heparin which shown enhanced cellular uptake as well as stronger anti-angiogenic effect. Nanoceria was prepared by using flame spray pyrolysis and number of unfractionated heparin molecules was either 130 or 880. Functionalization of heparin-

conjugated nanoceria was confirmed by TGA and it was also proved that both nanoceria and heparin were non-cytotoxic [43]. Alili et al. observed *in vitro* and *in vivo* that dextran-coated cerium oxide nanoparticles have hold a promising future to lower the invasion of tumor [36]. In order to improve the stability of the nanoceria dextran could play a major role which was observed by Perez et al. They have used cerium salt and dextran to make the dextran-coated nanoceria and different tests were performed like TEM, DLS, XRD, FTIR etc. to ensure the stability [50-52]. These functionalization surely help to minimize the toxic effects of the metallic nanoparticles like nanoceria and increase its efficacy. Functionalization of nanoceria with various types of materials are shown in Tables 2 and 3.

Toxicity of CeO₂ Nanoparticles

Several researches has been done through Leung et al. and his team performed an experiment on different species i.e. bacteria, algae using three types of commercially available cerium oxide nanoparticles and found different behavior towards different organisms. Such as the samples show higher toxicity toward *E. coli* and lower toxicity towards *S. costatum* [53]. Another study demonstrated by Srinivas et al. observed that pulmonary toxicity may occur in rats when CeO₂ nanoparticles, the size of 15 nm to 30 nm, are in nasal exposure for 4 hrs [54]. An *in vivo* study performed by Zhang et al. shown that CeO₂ nanoparticle, the size of 8.5 nm can cause inducement of oxidative damage and ROS accumulation in *C. elegans* [55]. Brunner et al. have found that CeO₂ show modest toxicity after 3 days of exposure *in vitro*

Name of Cancer	Developed by	Preparation Method	Particle Size	Model	Result	Effect	Ref.
Ovarian	Giri et al.	Wet chemical synthesis	(3-5) nm	Mice	Inhibit ROS and different growth factor like SDF-1, HB-EGF, VEGF, HGF	<i>In vivo</i> and <i>In vitro</i>	[33]
Prostate	Renu et al.	Hydrothermal and hydrolysis	(100-200) nm	Human and mouse cell line	Cytotoxic towards PC-3	<i>In vitro</i>	[21]
Pancreatic	Wason et al.	Direct synthesis	10 μm	Mice	Sensitizer and protectant	<i>In vitro</i>	[44]
Human dermal fibroblast	Montfort et al.	Direct synthesis	150 μm	Human cell line	Lower the effect of SCL-1	N/A	[35]
Lung	Lin et al.	Homogeneous nucleation	20 nm	Human lung cell line	Cytotoxic to A459 cells	<i>In vitro</i>	[45]
Colon	Jana et al.	Micro-emulsion	(10-100) μm	Human colon cell line	Interferes with colon cancer metastatic activity.	N/A	[46]
Melanoma	Alili et al.	Direct synthesis	(3-5) nm	Human melanoma cell	Shows ROS-dependent cytotoxicity and anti-invasive property toward melanoma cells	<i>In vitro</i> and <i>in vivo</i>	[34]

Table 1: Nanoceria in different cancer.

Functionalized with	Name of researchers	Number of molecules/nanoparticles	Synthesis method	Linker	Degradation time in hour	Tested in	Aim	Ref
Heparin	Ting et al.	130	Flame spray pyrolysis	3 aminopropyl triethoxysila	48 h	Human monocyte cell line	Improve biological property	[40]
Heparin	Lord et al.	130 or 880	Flame spray pyrolysis	3 aminopropyl triethoxysilane	>72 h	Primary human coronary artery endothelial cells	Increase potency	[41]

Table 2: Functionalization of cerium oxide nanoparticles with heparin.

Material Name	Researcher	Aim	Characteristics	Ref.
Phosphonated PEG-oligomers	Qi et al.	Stability increase	1. Capability of strong UV absorption 2. Re-dispersion ability in aqueous or organic solvents after freeze drying as powder	[47]
Dextran	Alili et al.	Increase stability and affectivity	1. Stable in alkaline and neutral medium 2. Particles do not agglomerate	[34]
Dextran	Perez et al.	Increase stability	1. Do not have any impact on the autocatalytic properties of nanoceria 2. Reduced antioxidant activity at acidic pH	[48]
Dextran	Asati et al.	Increase oxidative activity	Shows pH dependent result where acidic pH suits the most	[49]
Poly acrylic acid	Sehgal et al.	Stability increase	1. Process doesn't need any kind of mechanical stimulation	[50]

Table 3: Functionalization of cerium oxide nanoparticles with other material.

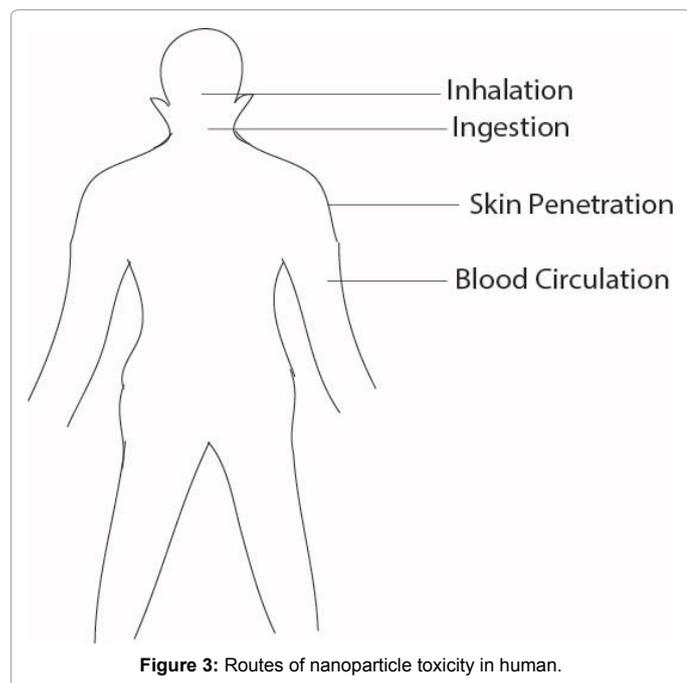


Figure 3: Routes of nanoparticle toxicity in human.

in mesothelioma cells [56]. García et al. shown CeO₂ nanoparticles also shown toxicity towards *Allium porrum*, *Capsicum annum*, *D. magna* seeds [57]. Park et al. and Cho et al. and many other scientists have done experiment both *in vivo* and *in vitro* and found out that the CeO₂ nanoparticles are responsible for acute inflammation of lung cancer cells in case of both [58]. There is one other study where Gaiser et al. proved that CeO₂ nanoparticles can cause hepatocyte toxicity to fish cell line [59]. Another study has proved that CeO₂ nanoparticles are responsible for roundworm lifespan reduction, moderate toxicity towards different human muscle tissues. Evidence of the toxicological effects of CeO₂ nanoparticles doesn't conclude anything as number of evidences are quite limited and the mechanism of these particular types of nanoparticles are not well known [60]. However, many more experiment needs to be performed in order to understand the potential of CeO₂ nanoparticles application and its toxicological effects. Figure 3 represents different routes of human body where the nanoparticles could enter into the system and make toxicological response are shown in.

Recent Trends and Future Perspective

As nanoceria is a noble way to deal with cancer and many other diseases there are plenty of drawbacks that need to be fixed. For this, scientists have been researching to find a different suitable way to make the right use of it. For example, to increase the interaction with cells and as well as to make it more stable spherical brush made of the polymer can be coated with nanoceria. Qiu et al. have made an experiment of modified nanoceria and found out that the modification hasn't alter the antioxidant properties of nanoceria and works better than the non-modified one [61]. Scientists are also concerned about the fate of nanoceria in the cell as there is a chance of accumulation of nanoparticles due to its small size. Strobel et al. have found that endothelial cells have the ability to clear up the nanoceria through a process called exocytosis which helps to reduce the adverse effect of it [62]. But as the use of different types of nanoceria are still in developing stage more research needs to be done about the fate, transformation, transport, toxicity, the interaction of nanoceria [63].

Conclusion

Among other metal oxide nanoparticles, cerium oxide nanoparticle holds promise in the different field of science and technology. Like various nanoparticulate substance, it has also been testified for its affectivity in cancer treatment. But it's been a tough choice since this particular nanoparticle has stability drawback which is now a major concern that holds its full potential. Many researches have been done and there are lots of ongoing to minimize or fully remove its drawback without hampering its original activity.

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