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Review article

Nanoantioxidants - Potential therapeutic approaches

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Abstract

Antioxidants have been used in dermal drug deliveries since decades. Recent development in drug delivery approaches tend to use nano technology based antioxidants i.e. nano-antioxidants in treatment of various diseases such as neurodegenerative conditions, diabetes mellitus, cancer as well as in human nutrition. Nanoceria is a new antioxidant and its application has a significant importance in the medical and biological fields. By using the techniques of nanotechnology, the biologically active antioxidant substances or drugs can be encapsulated into the singular polymeric nanofibres. By this approach the biologically active substances can be entrapped as well as attached as nanoparticles. Humans have developed complex antioxidants systems that can provide protection to cells from prooxidant conditions. Deficiency in any of these components can result in depletion of the overall antioxidant status of an individual. Antioxidants agents can be endogenous or exogenous and they can be obtained through our diet or with the help of dietary supplements. Nanoantioxidants consist of inorganic nanoparticles which possess intrinsic antioxidant properties. They also consist of nanoparticles which are functionalized with antioxidants or antioxidant enzymes to function as an antioxidant delivery system. Nanoparticles which contain antioxidants have shown promise as high performance therapeutic nanomedicine in depleting oxidative stress with possible applications in treating as well as preventing numerous disease conditions. In this article we will review the various approaches related to use of nanoantioxidants as potential drug delivery systems and their applications.

Introduction

The formation of free radicals is a widely accepted pivotal mechanism leading to various reactive conditions. Free radicals are exceedingly reactive molecules with unpaired electrons. They can directly cause impairment of various structural membranes, lipids, proteins, and DNA. The degrading effects of these reactive oxygen species are induced both internally and externally. Internally it is done during normal metabolism and externally it is done through various oxidative stresses. The production of free radicals in our body escalates with age, while the endogenous defense mechanisms that counter them decline [1]. This imbalance leads up to the progressive damage of cellular structures, and thus, results in accelerated degrading of body cells.

Antioxidants are those substances that can impart protection from endogenous as well as exogenous oxidative stresses by scavenging the available free radicals. Topical antioxidants are available in multivariate combinations since decades. They are over-the-counter products that focus at preventing the clinical signs of photo- aging.

The imbalance between the production of reactive oxygen and a biological system's capacity to neutralize the reactive intermediates is the main cause of oxidative stress [2]. Both intrinsic and extrinsic mechanisms cause oxidative damage. Together, intrinsic and extrinsic damage are the primary causes of cellular degradation. The cellular mechanisms use a series of intrinsic antioxidants to protect itself from free radical damage. The extrinsic antioxidants which occur naturally have also been widely shown to offset and alleviate these cellular changes. As sunscreens have an SPF rating system which guides the consumers in their product purchasing choices but there is no universally accepted method to choose antioxidant anti-aging products. All over the world there is an accepted standard and uniform measure of the antioxidant capacity of foods which is done by ORAC (Oxygen Radical Absorbance Capacity) and ABEL-RAC (Analysis by Emitted Light-Relative Antioxidant Capacity) and these rating systems could also be applied to all antioxidant skincare products too. Thus the standardization of antioxidant products could transform the antioxidant market and would allow the physicians and consumers the ability to compare and choose effectively between various products available in the market.

What are antioxidants?

Antioxidants are substances that can block or slow the injury to cells that is caused due to the free radicals. Free radicals are those unstable molecules that our body fabricates as a reaction to the environmental as well as other pressures. Free radicals are also sometimes called "free-radical scavengers." The antioxidants are available naturally or artificially. There are certain plant-based foods that are rich in antioxidants and these plant-based antioxidants are a variety of phytonutrient or plant-based nutrient.

Endogenous antioxidants are produced by our body. Exogenous antioxidants are those that come from outside our body. The cells in our body process the food and react to the external environment thus producing waste substances called free radicals. Oxidative stress is caused when our body is not able to process and remove the free radicals efficiently out of our body and due to this our cells and body functions could be impaired. The free radicals are also known by the name reactive oxygen species (ROS). Thus oxidative stress pertains to the elevated intracellular levels of reactive oxygen species (ROS) that causes damage to the lipids, proteins and DNA. Thus a myriad of pathologies can be linked to oxidative stress. There are many factors that elevate the production of free radicals in the body which can be internal or external. Internal factor is inflammation and external factors consist of pollution, UV exposure and cigarette smoke [3].

Benefits

Antioxidants can safeguard against the oxidative stress that is caused by the free radicals onto our cells. There are many activities and processes that can lead to oxidative stress such as: mitochondrial activity, excessive exercise, tissue trauma that is caused due to inflammation and injury, ischemia and reperfusion damage, consumption of certain foods, specifically the refined and processed foods, foods that have trans fats, artificial sweeteners, and certain dyes and additives, smoking, environmental pollution, radiation, exposure to chemicals, like pesticides and drugs, including the drugs used for chemotherapy, industrial solvents.

Thus the activities and exposures mentioned above can lead to cell damage. This, in turn, may lead to: an unrestricted release of free iron ions or copper ions, an activation of phagocytes that are a type of white blood cell with help in fighting infections, an increase in those enzymes which generate free radicals, a disruption of electron transport chains.

The harm that is caused by oxidative stress has also been linked to diseases such as cancer, atherosclerosis, and vision loss. These conditions and the risks arising due to it can be minimized by using free radicals. As per a study it has been stated that antioxidants act as a radical scavenger, a hydrogen donor, an electron donor and also as a peroxide decomposer, singlet oxygen quencher and as an enzyme inhibitor, synergist and a metal-chelating agent too [4].

Conventional antioxidant therapies have been less effective in preventing cellular damage caused by oxidative stress. Nanoparticle antioxidants comprise of a new set of antioxidant therapies that help in the prevention as well as treatment of diseases which are caused by oxidative stress. It is believed that the nanoparticle antioxidants are thought to have strong and continuous interactions with biomolecules and they would be more efficient to counter free radical induced damage. They contain inorganic nanoparticles which have intrinsic antioxidant properties. The nanoparticles are used with antioxidants or antioxidant enzymes to perform the function of an antioxidant delivery system. Nanoparticles constituting antioxidants have shown high efficiency as high-performance therapeutic nanomedicine in reducing oxidative stress and their application has also been found effective in treating and preventing neurodegenerative conditions. Though to still realize the full potential of nanoantioxidants, negative characteristics that are related with the use of nanoparticles need to be conquered to substantiate their long term applications [5].

The sources of naturally produced antioxidants are profusely available from plants and animals. Antioxidants can also be synthesized by chemical processes as well as from various other agro- related wastes by using biological process. The antioxidants are broadly classified into two main groups by taking into account their solubility. The two types are water soluble and lipid soluble.

Generally the water- soluble antioxidants, for example ascorbic acid, glutathione, and uric acid, perform functions in the cell cytosol as well as the blood plasma.

The ascorbic acid in the above category is a type of redox catalyst which decreases and counteracts the reactive oxygen species (ROS) whereas glutathione consists of antioxidant properties thus acting as reducing agent and it can also be reversibly oxidized and reduced. The cell membranes are protected from lipid peroxidation by lipid-soluble antioxidants. The examples are α-tocopherol, carotenoid, and ubiquinol. They are also differentiated on the basis of their mechanism of action, that is, primary or chain-breaking antioxidants and the other being secondary or preventive antioxidants. Antioxidants can also behave as prooxidants when these are not present at the right place at a particular concentration at the right time [6], [7]. The respective importance of the antioxidant and prooxidant activities of an antioxidant are still being researched and is an area of interest. Figure 1 shows classification of antioxidants.

Numerous amounts of chemical compounds have been assessed for their antioxidant property. Based on the source of their origin, antioxidants could be categorised as exogenous or endogenous (e.g., glutathione and uric acid) but most of the antioxidants come from our diet. Natural antioxidants have the capability to effectively regulate the oxidative stress. Numerous amounts of fruits, vegetables and the fruits by-products have been recognized for antioxidant contents.

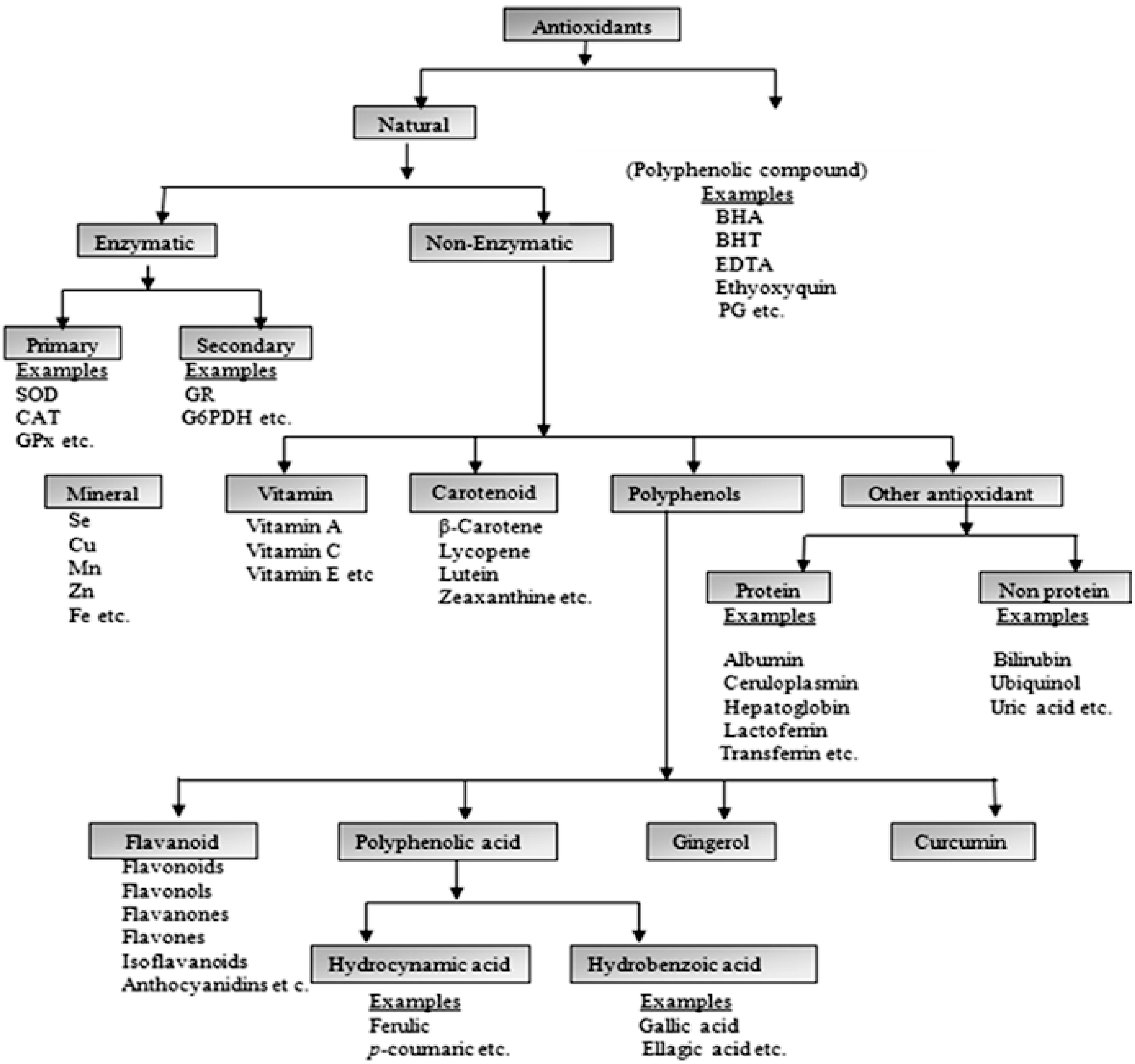

Figure 1. Classification of antioxidants [26].

These antioxidant contents are in the form of vitamins (ascorbic acid), carotenoids (lutein), polyphenols (3,6-dihydroxyflavone), and metabolic sensitizers (methyl selenocysteine), which have shown the capability to scavenge the surplus of free radicals in the human body. Additionally, antioxidants for example, gallic acid (GA) that are obtained from natural resources (dried rose flower extracts—Rosa rugosa), as well as other bioactive compounds derived from various other sources, have also depicted antioxidant capacity and the ability of scavenge active species of oxygen as well as electrophiles and in the decline of lipid peroxidation level [8]. Still natural antioxidants are susceptible to degradation and their bioavailability is also limited due to the low absorption and degradation during delivery. The synthetic compounds like butylated hydroxyanisole also called as BHA as well as butylated hydroxytoluene (BHT), BHT analogs, and also GA esters are also being utilized as antioxidants. These antioxidants have shown depleting health influences and thus their application is restricted and the naturally occurring dietary antioxidants are given in their place.

Nanoantioxidants

Advancement in nanotechnology has revealed several nanoparticles either from inorganic or biological origins, like melanin nanoparticles as potent antioxidants by themselves. The novel metal nanoparticles (Au, Ag, Pt) as well as the transition metal oxides (CuO, NiO) are often used and are also tested for their antioxidant activity. Additionally, nanocomposites are also evaluated for antioxidant activity. They can be either in single or bi-metallic combination or synthesized via chemical or green techniques by employing different phytochemicals (leaf extracts). Still the antioxidant properties of these nanoparticles are dependent on their nature, their chemical composition, their surface charge, particle size and surface to volume ratio as well as surface coating [9], [10]. Nanoparticle antioxidants have several advantages over the conventional forms such as they give environmental protection to bioactive components, increased bioavailability, and targeted delivery of antioxidants, as well as controlled release at the site of action as compared to the traditional antioxidant delivery methods.

However, achieving high specificity against the ROS is the main hurdle to these antioxidants, hence may fail to prevent oxidative damage completely. Besides, there are some crucial challenging issues for in vivo applications of these exogenous nanomaterials such as the oxidative stress, immune cell activation, mitochondrial respiration & genotoxicity, which may cause potential deleterious health effects [11].

Recently the engineered nanostructured particles have been thought of as an innovative strategy to deliver the novel antioxidants with enhanced characteristics. Nanoparticles functionalized with natural antioxidants or with antioxidant enzymes where nanoparticles are the ones that act as the carrier or antioxidant delivery vehicle were found to be efficient in enhancing the antioxidant activity and also for providing targeted delivery of a certain type of antioxidants that exhibit poor permeation across cell membranes and also cell internalization. The term nanoantioxidant was used for the first time by Sharpe et al., who classified the nanoparticle antioxidants into two categories which were (i) inorganic nanoparticles witch have intrinsic antioxidant properties, and (ii) functionalized as well as composite inorganic nanoparticle antioxidant. The latter one based on the mode of integration of the antioxidants, was subdivided into three classes. Those three classes were antioxidant functionalized nanoparticles, nanoencapsulated antioxidant, and magnetically responsive antioxidant nanocarrier. A higher amount of antioxidant activity and bioavailability has been demonstrated by Surface antioxidants-functionalized nanomaterials. Biodegradable nanoparticles have been utilised to improve the bioavailability of natural antioxidants. Moreover, inorganic nanoparticles are thermally stable and chemically inert, which facilitate exploiting the potential, also the immobilization of natural antioxidants. The nanoparticles that are conjugated natural antioxidants also facilitate chemical stability of the antioxidants in the physiological conditions and they also deliver the product in complete molecular form in a more widespread concentration range, and specifically offer slow and continuous release [11], [12]. There are a lot of studies available on natural, synthetic, and nanoparticle antioxidants and their potentials in varied applications. They are applied or utilized for gene delivery, for theranostics in neurodegenerative as well as cardiovascular diseases. They also have biomedical applications and are also used in therapies for different environmental pollutants-induced toxicities [13].

Although, as per our knowledge, there is no availability of any study yet on the scope of nanoparticles and their antioxidant integration to have a complete and informed knowledge about this field in a wider context [14]. That is why this review is focused on the various strategies that are needed for the functionalization of nanoparticles with antioxidants or compounds that possess antioxidant properties, so that their efficiency and targeted delivery can be at par with the sustained release properties [16]. There are many commonly used techniques for the incorporation of the antioxidants with the help of methods such as nanostructures surface loading, encapsulation, entrapment in the nanogel or in the core and/or core-shell spaces of hollow nanospheres, alongside the subsequent effects on the properties of antioxidants and their targeted delivery, have been talked about in this article. The elaborate discussion about the properties, stability, potency, and essentially about the, delivery strategies have been outlined [15, 17].

(A) Antioxidant Functionalized Nanoparticles

1. SiO2 Nanoantioxidant (SiO2 cross linked with gallic acid)
2. AuNPs Nanoantioxidant (Gold nanoparticles)
3. Silver Nanoparticles (AgNPs) Nanoantioxidant
4. Iron-Oxide Magnetic Nanoparticles (Fe2O3NPs) Nanoantioxidant
5. Cerium Oxide Nanoparticles Nanoantioxidant
6. Dual Nanoparticles Nanoantioxidant
7. Polymeric Nanoantioxidant

(B) Nanogel Entrapped Antioxidant

(C) Hollow Nanosphere Tagged Nanoantioxidant

(D) Nanoparticles Mediated Antioxidant Encapsulation

1. Polymeric Encapsulation
    - 1.1 Poly-d,l-lactide-Based Nanoparticles
    - 1.2 PLGA-Based Nanoparticles
    - 1.3 Poly(ε-caprolactone)
    - 1.4 Polyanhydride Nanoparticles
    - 1.5 Prodrug Approaches
2. Polysaccharide-Based Nanoparticles
    - 2.1 Chitosan Originated Nanocarrier
    - 2.2 Starch Nanoparticles
    - 2.3 Alginate
3. Protein-Based Nanoparticles

Figure 2 shows various nanoparticle functionalised antioxidants.

Future aspects of nano-antioxidants

1. Anti-aging application: The nanoparticles showed narrow size of about 140 nm and their pH was close to neutral and thus they were appropriate for cutaneous application. It was determined by the alternative tests that they did not cause any skin irritant effects, cytotoxicity or produce oxidative stress [18]. The nanoantioxidants showed notable decrease in wrinkle degree after 21 days of application as compared to the control product. The volunteers used subjective analysis to differentiate between the nanoparticles and the control product. Finally the conclusion was formed that the nanoparticles that contain antioxidant actives were safe for topical application and also showed anti-aging activity in vivo and it was also determined that they are suitable as a cosmetic ingredient too [19], [20]. The naringin nano-ethosomal novel sunscreen creams are used to decrease skin ageing.[28]
2. The promising future of nano-antioxidant therapy against the toxicities induced by environmental pollutants: This has become a major health concern these days. The increase in the formation of Reactive Oxygen Species (ROS) is caused mainly due to man-made chemicals such as xenoestrogens, pesticides, heavy metals, polycyclic aromatic hydrocarbons (PAHs), etc. and they also adversely impact the endogen antioxidant defense.
3. An emerging strategy for interference against neurodegenerative conditions: In many neurodegenerative conditions, oxidative stress has been associated to the neuronal cell death for a long time. Since the conventional antioxidant therapies cannot cross the blood brain barrier, therefore they have been less effective. It is believed that they possess strong and lasting interactions with biomolecules and thus they would be more efficacious against free radical induced damage. Nanoparticles which contain antioxidants have exhibited that the high-performance therapeutic nanomedicine help in depleting oxidative stress thus having possible applications in treating as well as preventing neurodegenerative conditions [21], [22].

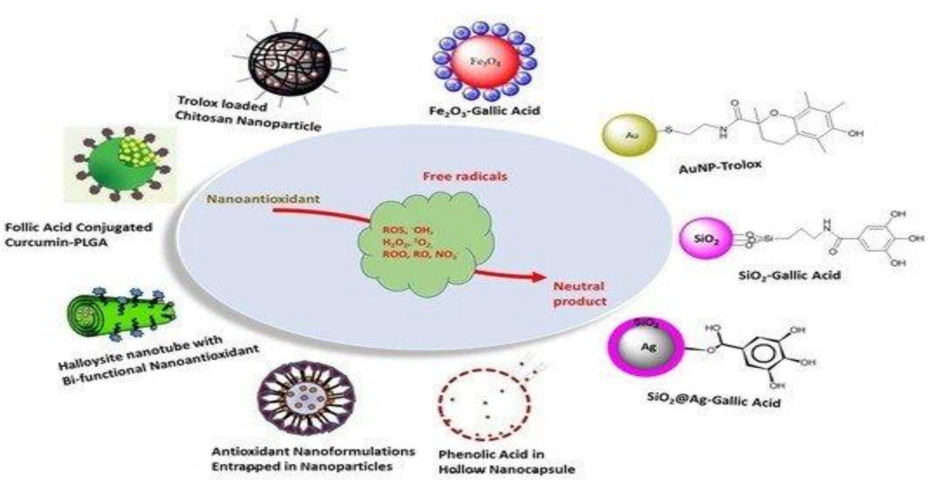

Figure 2. Various nanoparticle functionalised antioxidants [27].

4. Imaging and targeted drug delivery: The antioxidants can be prevented from getting destroyed in the human gut by using a nano-encapsulated antioxidant as a protective vehicle and it also makes sure that they are better absorbed in the digestive tract. Actually, the nano-capsules attach themselves to the intestinal walls and the antioxidants are poured directly into the intestinal cells and thus they get absorbed directly into the blood stream. Nano-polymers known as Dendrimers are another well-known and popular mode for delivering antioxidants. Dendrimers have multiple branches as well as sub-branches of atoms that are radiating out from a central core. Dendrimers impart extreme control over their architectural design, which also includes their size, shape, branching length or density, and their surface functionality. Due to this flexibility shown by these nanostructures, they have become an ideal carrier for biomedical applications like targeted drug delivery, gene transfection, and imaging.
5. Metallic Nanoantioxidants used as Potential Therapeutics for Type 2 Diabetes: An important contributor to Type 2 diabetes (T2D) pathogenesis is the overproduction of reactive oxygen species (ROS) that is caused due to hyperglycemia. However the common antioxidant therapy is ineffective for its treatment. This may be due to narrow absorption profiles as well as low bioavailability of antioxidants that are orally administered. Thus, novel antioxidant agents that can be delivered to specific target organs are vigorously developed these days. Thus, metallic nanoparticles (NPs) which are nanosized materials with a dimension of 1–100 nm are proving to be effective in the treatment of T2D. This was possible because of their tuned physicochemical properties as well as their ability to modulate the level of oxidative stress [22].
6. Nano-antioxidant experiment to launch in the International Space Station: Nanoparticles exhibit promising properties down to its microscopic level. A group of experts in Italy have spent years modifying tiny inorganic materials and also analyzing their behavior. A few of them exhibit magnetic properties and the others are able to give electrical stimuli. These ceramic particles which are called ***nanoceria,*** are designed chemically in a laboratory and they display a powerful antioxidant activity. These tiny, smart particles can protect organisms from the damage that is caused due to oxidative stress and thus they could be essential in fighting chronic diseases. As prolonged exposure to microgravity as well as radiation increases the damage to the muscle cells, the Space Station is an ideal scenario where we can study how the cells deteriorate and how we can fight this. Since on Earth, in the field of medicine, we have explored nanotechnology a lot therefore now it is on its way to space to find and determine more answers [23].
7. Using nanoparticles to get the most out of antioxidants in our food: The application of nanotechnology in the food industry is a current approach as compared to the biomedical and information technology industries. There are several opportunities for the utilization of nanotechnology in the foodstuff, for example in processing products, in food security, biosecurity as well as innovative materials (e.g., nanoparticles). The development of nanomaterials (such as the nanoparticles for bioactive loading) is mainly focused on the physicochemical protection of sensitive compounds thus strengthening their stability and/or masking their odor or taste. In the development of functional foods, the control of the release properties of certain bioactives has also received much attention. Functional foods are those foods whose elements consist of some physiological function which is beyond their nutritional values. For example, polyunsaturated fatty acids, carotenoids, vitamins, coenzymes as well as polyphenols [24].
8. Delivering chemotherapy: The application of nanotechnology in cancer therapeutics helps in improving pharmacokinetics as well as reduces the systemic toxicities of chemotherapies with the help of selective targeting and delivery of these anticancer drugs to the tumor tissues. The nanosized carriers have an advantage that they can enhance the delivered drugs overall therapeutic index with the help of nanoformulations of the chemotherapeutics that are either encapsulated or conjugated to the surfaces of nanoparticles.

Conclusions and future perspectives

Natural and synthetic antioxidants are now-a-days considered outdated technologies for managing oxidative stress-induced diseases. In the past few decades, the inorganic nanoparticles have been assessed successfully for their antioxidant properties. Recently nanoantioxidants have shown the potential of depleting oxidative stress with considerable sensitivity, cellular antioxidant activity, slight cytotoxic effects, as well as targeted delivery. The covalent attachment or encapsulation of antioxidants with nanospheres of various origins like inorganic nanoparticles, metal nanoparticles, natural polymer-based nanoparticles, liposomes, protein-polysaccharide-based nanoparticles, and a lot of other combinations have been tested as per the above conditions and thus are under consideration for lots of applications. We also need to understand the nature, physicochemical properties and mechanism of actions of the nanoantioxidant composites to obtain the highest benefits in terms of the catalytic and biological activity of the composites. Besides, extensive toxicity evaluation must be performed specifically for the non-biodegradable as well as insoluble nanoparticles prior to conducting any future biomedical application. Additionally, we also need to identify and evaluate the beneficial aspects as well as the side effects of the fabricated nanoantioxidants, so that they can be used safely for in vivo application, particularly for long term treatment. Thus the development of novel as well as efficient delivery of therapeutic nanoantioxidants and the design of novel antioxidant activity assays for accurate and reliable measurements are also necessary [24, 25]. Therefore, greater understanding of new molecules as well as well-developed nanostructures and nanotechnology and their combination into a unique form with considerable antioxidant properties, will carve the future for nanoantioxidant-mediated treatments.

Author contributions

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that there are no competing conflicts of interest.

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