

Review

Antioxidants in Cancer Therapy: Recent Trends in Application of Nanotechnology for Enhanced Delivery

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Received: 5 November 2019; Accepted: 31 December 2019; Published: 21 January 2020



Abstract: Recently, the occurrence of cancer has significantly increased; it represents the second-most frequent cause of death after cardiovascular diseases. Many dietary antioxidants have shown large impact as effective agents for cancer prevention by reducing oxidative stress, which has been a part in the development of many diseases, including cancer. One of the obstacles in the delivery of antioxidant therapies into the required domain lies in the inadequate delivery of these agents to their intended site of action. Using nanotechnology in delivery of antioxidants leads to increased therapeutic index and higher drug concentration in tumor tissues, thus enhancing anticancer treatment. In this review, we discuss the role of different antioxidants in cancer therapy and their improved therapeutic effect through their formulation using nanotechnology.

Keywords: nanotechnology; antioxidants; cancer therapy

1. Introduction

Cancer is considered the second most frequent cause of death worldwide after cardiovascular disease. Although great improvements have been made in cancer therapy, it is still a major health concern and, therefore, various investigations have been done to develop new therapeutic approaches [1].

Cancer involves uncontrolled growth of cells and it can develop in any tissue. The basic process of different types of cancer is similar; it begins when a cell has a faster rate of cell division than normal cells. The initiation of cancer is highly linked to oxidative stress that results in DNA damage, instability of genome and cell proliferation [2]. Various researchers have reported the mechanism by which oxidative stress can lead to chronic inflammation, which leads to many diseases including cancer [3].

Compared to normal cells, cancer cells have a concentration of endogenous reactive oxidative stress (ROS) [4,5]. Low concentrations of ROS compounds are required for signal transduction, but a cancer cell has an accelerated metabolism, thus they need high ROS concentrations to maintain their high proliferation rate. They cause damage in mitochondrial DNA, which leads to mutation in the oxidative phosphorylation resulting in increase in production of ROS. It aids in the proliferation of cancer cells, which leads to an increase in tumor growth [6]. That is why cancer cells require high ROS concentrations to maintain their high proliferation rate.

ROS damage in cells depends on their intracellular concentration and on the equilibrium between the ROS and the endogenous antioxidant species. Oxidative stress is generated as a result of the loss of

the pro-oxidant/anti-oxidant equilibrium. This oxidative stress alters and damages many intracellular molecules such as proteins, lipids, DNA and RNA [7].

The generation of oxidative stress is caused by the imbalance between reactive oxidative stress production and the deficiency of the cell antioxidant defense system [8]. This imbalance leads to damage of important cells as it affects the whole organism. Many forms of chemotherapy and radiation therapy act through oxidative stress pathways [9–11]. Various researchers have reported the mechanism by which oxidative stress can lead to chronic inflammation, which leads to many diseases including cancer [3].

Reactive oxygen species (ROS) are products of metabolic reactions in the mitochondria of eukaryotic cells. Low concentrations of ROS compounds are required for signal transduction, but cancer cell has an accelerated metabolism, thus they need high ROS concentrations to maintain their high proliferation rate.

The generation of oxidative stress is caused by the imbalance between reactive oxidative stress production and the deficiency of the cell antioxidant defense system [8]. This imbalance leads to damage of important cells as it affects the whole organism. Many forms of chemotherapy and radiation therapy act through oxidative stress pathways [9–11].

Various studies reported that cancer patients showed low antioxidant level and increased oxidative stress, even before start of the treatment. Sharma et al. [12] has evaluated patients with tongue carcinoma, results showed that pretreatment levels of plasma lipid peroxide and conjugated dines were significantly elevated in patients with carcinoma, as compared with controls.

Antioxidants are effective in scavenging free radicals [13,14]. The first definition of antioxidant was proposed by Halliwell et al. [15] as “any substance that, present in low concentrations compared to oxidizable substrates (carbohydrates, lipids, proteins or nucleic acids), significantly delays or inhibits the oxidation of the mentioned substrates”. Antioxidants attract a huge interest in cancer therapy, where they eliminate oxidizing free radicals, thus prevent cellular damage, which is helpful in chemotherapy [16]. Different articles have investigated antioxidant supplements during chemotherapy in order to protect normal tissues without adversely influencing tumor therapy.

There are two kinds of antioxidants doses used in cancer therapy: a preventive low dose, which provides protection of normal cells and tumor cells and a therapeutic high dose, which inhibits the growth of cancer cells without affecting normal cells. Recent reviews proved that administration of antioxidants with chemotherapy has the following advantages: (a) they do not interfere with chemotherapy and (b) they improve the cytotoxic effect of chemotherapy while protecting the normal tissue thus increase the patient survival and therapeutic response [17,18].

2. Nanotechnology for Antioxidants Delivery

Application of nanotechnology for delivery of antioxidants has been reported to enhance their therapeutic benefits in cancer therapy. Nanoparticles (NPs) have size between 1 and 100 nm. Nanoparticles for drug delivery may have different composition, size and shape. They also may differ in drug loading capacity, particle and drug stability, drug release rates, and targeted delivery ability.

Different examples of nano-systems have been reported in the literature including:

2.1. Dendrimers

Dendrimers are homogenous, symmetric around the core and consist of two shells (inner shell and an outer shell). There are different types of dendrimers with different properties including polyvalency, self-assembling, electrostatic interactions, chemical stability, low cytotoxicity and solubility. These varieties are one of the reasons to use dendrimers in the medical application [19].

Dendrimers may carry the drug by attachment of drug molecule to the functional groups on their surface or incorporation in the interior environment of the sphere [20,21]. Dendrimers are helpful in carrying both hydrophobic and hydrophilic molecules for delivery of genes, drugs and anticancer agents. Zhang et al. developed multifunctional doxorubicin conjugated poly (amidoamine) dendrimers

for pH-responsive drug release and targeted cancer therapy [22]. Another study by Liu et al. confirmed the efficacy of antioxidant response via delivery of curcumin using dendrimers as a carrier system in cancer therapy [23].

2.2. Micelles

Micelles are self assembled nanosized colloidal dispersions [24,25]. Their surfactant molecules can be aggregated either by cationic, anionic, zwitterionic or non-ionic groups [26] depending on the type of head groups and length of the alkyl chains [27,28]. They consist of both hydrophobic and hydrophilic shells, thus they are used for carrying both hydrophilic and lipophilic molecules [21].

Micelles have attracted attention for their potential use in cancer diagnosis and therapy. A study was done by Masaki et al. showed that antioxidant micelles containing catechol moieties can be used in anti-angiogenic therapy to treat various diseases including cancer [29].

Another study by Esmaili et al. reported that curcumin-loaded micelles showed an increase in curcumin solubility and bioavailability in treatment of cancer [30].

2.3. Polymeric Nanoparticles

Polymeric nanoparticles are solid colloidal systems that can carry drugs in different ways, either by dissolving, entrapping, encapsulating or adsorbing the drug onto their matrix. Depending on the formulation method, the obtained polymeric particle may be nanospheres, which are matrix systems in which the drug is dispersed throughout the particles, or nanocapsules, which are vesicular reservoir systems in which the drug is confined to an aqueous or oily cavity surrounded by a single polymeric membrane [31].

In a study by Mady and Shaker on the preparation of ellagic acid–polymeric nanoparticles using the emulsion–diffusion–evaporation method, the results showed that they were able to sustain the diffusion release of ellagic acid and enhance its cytotoxicity (6.9-fold) against the colon adenocarcinoma, thus improved ellagic acid bioavailability and its anticancer efficacy [32]. Rocha et al. also proved the efficacy of using polymeric nanoparticles in delivery of catechin for prostate cancer treatment [33].

2.4. Liposomes

Liposomes are spherical vesicles consisting of two layers of lipids with an internal aqueous cavity. They are composed of phospholipids or synthetic amphiphiles incorporated with sterols, such as cholesterol to influence membrane permeability.

Liposomal encapsulation has been reported to alter the biodistribution of compounds, such as doxorubicin [34,35] and vincristine [36] to limit systemic drug-induced toxicities. A study by Koudelka et al. was done to formulate vitamin E liposomes for treatment of cancer, where liposomes could reduce immunotoxicity, thus it was helpful for the combined chemo-and immuno-therapy [37].

Muthu et al. incorporated vitamin E in liposomal formulation for the delivery of vitamin E to target brain cancer cells. Their results showed that liposomes had a great efficacy in targeting cancer cells as a multifunctional carrier [38].

2.5. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are lipid-based nanocarriers, which are solid in the body temperature and stabilized by emulsifiers [8]. SLNs can protect the incorporated drug from the surrounding harsh environmental situations. Their biodegradability and biocompatibility also make them suitable to be used as a drug carrier systems [39]. They can overcome some of the obstacles of other nano-systems, where their large scale production is lower in cost, and have fewer storage and drug leakage problems in comparison to liposomes [8,40,41].

Various reviews have described the different types of SLNs, characterization methods, preparation techniques, structural properties, factors that may affect their formation and storage stability, drug loading and drug release principles [8,42,43].

3. Methods of Preparation of SLNs

Several methods have been adapted for the preparation of SLNs, including:

3.1. High Pressure Homogenization Technique

This technique includes two strategies, hot homogenization and cold homogenization.

Hot homogenization is carried out at temperatures above the melting point of the lipid, while in the cold homogenization process, solubilization of the drug in the lipid is first done, followed by rapid cooling [44]. The cold homogenization can overcome the obstacles of hot pressure homogenization such as degradation [44]. Müller et al. suggested using cold homogenization technique, which is performed at room temperature to increase aqueous solubility of the drug [45,46].

3.2. Microemulsion Technique

The concept of microemulsion technique was introduced in the early 1940s by Hoar and Schulman [47]. Microemulsions are thermodynamically stable systems composed of a hydrophilic, a hydrophobic and an amphiphilic component, with the globules are in the nano-size range [48].

3.3. Solvent Emulsification Evaporation Technique

In this technique, a water immiscible organic phase containing the lipophilic material (lipid) and the lipophilic drug is emulsified by homogenization in an aqueous phase followed by evaporation of the organic solvent by mechanical stirring at room temperature, resulting in the formation of lipid precipitates as SLNs [49,50].

3.4. Solvent Emulsification Diffusion Technique

This technique depends on dissolving the lipid and the drug in a partially water miscible organic solvent (e.g., benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate and methyl acetate), then the organic solvent is emulsified using an emulsifying agent dissolved in an aqueous phase under agitation. Once emulsion is formed, SLNs are obtained by evaporation of the solvent under low pressure [51].

3.5. Ultrasonication Technique

In this technique, the drug is added to the dissolved lipid, then the aqueous phase added to the dissolved lipid phase and emulsified by sonication at high speed stirring. Ultrasonication technique was initially used for the production of solid lipid nanodispersion [52]. However, one of the drawbacks of this method is the physical instability of the prepared SLNs [53].

3.6. Melting Dispersion Technique (Hot Melt Encapsulation Method)

In this technique, the molten solid lipid containing the drug is emulsified into the heated aqueous phase. Following this, the system is allowed to cool down to room temperature resulting in the formation of SLNs. This method is better than the ultrasonication method, but less than the solvent emulsification evaporation method in terms of reproducibility [54,55].

3.7. Double Emulsion Technique

Production of SLNs by double emulsion technique involves the dissolution of the drug (mainly hydrophilic drug) in an aqueous solvent (inner aqueous phase) followed by dispersion in lipid containing emulsifier/stabilizer, known as oil phase, to produce primary emulsion (w/o). Following this, a double emulsion (w/o/w) is formed through the introduction of an aqueous solution containing the hydrophilic emulsifier under stirring and finally isolated by filtration [56,57]. Double emulsion technique is suitable for the preparation of protein and peptide-loaded lipid nanoparticles, as it does not involve a heating process. Moreover, the surface of the nanoparticles can be modified to sterically

stabilize them through the incorporation of a lipid-PEG derivative, resulting in improved resistance in the gastrointestinal fluids [58].

3.8. Solvent Injection Technique

In this technique, the lipid and drug are first dissolved in a water miscible solvent, and then the mixture is injected in an aqueous phase through an injection needle. The resulting dispersion is filtered to obtain the prepared SLNs [53]. Solvent injection technique has several advantages such as the ability of using pharmacologically acceptable organic solvent, easy to handle and fast production process.

Other methods used for preparation of nanoparticles (Table 1).

3.8.1. Desolvation Technique

This technology is applicable for a wide range of polymers by changing the charge and pH by addition of a desolvating agent like ethanol or concentrated organic salt solution [59].

3.8.2. Dialysis Technique

Dialysis technique is a simple and effective technique for preparation of polymeric nanoparticles with narrow distribution. Briefly, drug and polymers are placed inside a dialysis tube/membrane after dissolving with water miscible organic solvents with appropriate molecular weight cut off. The organic phase diffuses out through the dialysis tube/membrane into the aqueous phase which decrease the interfacial tension between them [60].

3.8.3. Nanoprecipitation Technique

Nanoprecipitation technique was first introduced by fessi for preparation of polymeric nanoparticles, where formation of particles is based on the precipitation and subsequent solidification of the polymers due to the interfacial deposition of polymer after displacement of semi polar solvents miscible with water, from a lipophilic solution [61].

3.8.4. Solvent Evaporation Technique

Solvent evaporation technique is commonly used for preparation of polymeric nanoparticles. Briefly, the polymer is dissolved in an organic solvent into which the drug is dissolved/dispersed [62].

4. Examples on Utilizing Nanotechnology in the Delivery of Antioxidants for Cancer Therapy

The therapeutic benefits of applying nanosystems fabrication techniques in delivering various antioxidants have been listed in Table 2.

4.1. Vitamin E

Vitamin E is a lipophilic component in the cell antioxidant defense system and can be obtained from the diet, its important role in the body is related to its antioxidant activity [63]. It has been shown to enhance the cytotoxic effect of anticancer drugs, including 5-fluorouracil [64], vincristine [65] and doxorubicin [66,67]. Studies on animals have shown that parenteral administration of vitamin E resulted in enhancing the anticancer effect of 5-FU [68] and cisplatin [69]. Feng et al. have developed systems of nanoparticles of biodegradable polymers for oral administration of anticancer drugs, with the incorporation of vitamin E using modified solvent extraction/evaporation [70].

4.2. Coenzyme Q10 (Ubiquinone)

Co-enzyme Q10 (Co-Q10) is a lipophilic antioxidant that has the ability to prevent lipid peroxidative damage of mitochondrial membranes. A study done by Hurley et al. showed that parenteral administration of Co-Q10 was able to prevent acute doxorubicin-induced cardiotoxicity in animals [71]. In a study done by Nehilla et al. Co-Q10-loaded surfactant-free biodegradable poly (lactic-coglycolic

acid) (PLGA) nanoparticles were prepared using nanoprecipitation method, which resulted in sustained drug delivery due to the extended C-oQ10 release [72].

4.3. Vitamin C

Vitamin C is a versatile hydrophilic antioxidant that can protect against lipid peroxidation by scavenging ROS in the aqueous phase before initiation of lipid peroxidation. Pohl and Reidy have proven that oral administration of vitamin C to human volunteers lead to protection against chemotherapy induced mutagenesis [73]. Supplementation with vitamin C has significantly reduced the chromosomal damage, indicating that vitamin C could reduce the chemotherapy-induced carcinogenesis. In their study, Duarah et al. [74] studied the loading of Vitamin C into ethyl cellulose nanoparticles by the solvent evaporation method for effective delivery to the skin layers.

4.4. β -Carotene

β -carotene is a lipophilic antioxidant produced by microorganisms and plants. In a study done by Teicher et al. β -carotene was found to improve the cytotoxicity effect of melphalan on human carcinoma cells [75] and of cisplatin and dacarbazine on melanoma cells [76]. Another study by Seang Chu et al. reported that β -carotene nanodispersions prepared by emulsification–evaporation method could increase the gastrointestinal absorption of lipophilic drugs [77].

4.5. Resveratrol

Resveratrol is a natural polyphenol and phytoalexin, it has numerous therapeutic effects including anticancer, antioxidant and anti-inflammatory effects. However, its poor pharmacokinetic properties, low aqueous solubility, low photostability and extensive first pass metabolism, resulted in its poor bioavailability. In their study, Kampa et al. reported that resveratrol could effectively inhibit the growth of prostate cancer cells [78]. Manna et al. have shown that resveratrol is capable of inhibiting reactive oxidative stress and lipid peroxidation induced by tumor necrosis factor in wide variety of cells [79]. Several studies reported the nanoencapsulation of resveratrol in order to enhance its anti-tumor activity. In their study, Thiye et al. [80] reported the preparation of resveratrol-conjugated gold nanoparticles: in order to increase the anti-tumor efficacy against breast, pancreatic and prostate cancers. Another study by Penalva et al. [81] reported the enhanced oral bioavailability of resveratrol through its encapsulation of casein nanoparticles.

4.6. Curcumin

Curcumin is extracted from curcuma rhizomes, through crystallization by extraction with solvent and extract purification. Since inflammation is highly linked to tumor promotion, curcumin is considered as a chemopreventive agent due to its anti-inflammatory and antioxidant effects on carcinogenesis [82]. Although it is a great bioactive agent and natural antioxidant but it has some disadvantages such as water insolubility and low bioavailability [83]. To overcome this problem, curcumin nanoparticles were formulated [84]. Das, Kasoju developed curcumin-loaded tripolymeric composite nanoparticles using ionotropic pre-gelation followed by polycationic cross-linking for the delivery to cancer cells. Results showed that these composite nanoparticles could successfully deliver curcumin into cancer cells [85].

4.7. Catechin

Catechin is a herbal flavonoid with great antioxidant activities [86]. However, only few clinical studies are carried out on humans, owing to its very low bioavailability due to rapid elimination from liver by biliary excretion, when administered in vivo [87]. In a study done by Kaur et al. results showed that treatment of mammary adenocarcinoma mice with catechin from green or black tea resulted in an increase in the survival time and decreased the tumor load [88]. Hu, Pan et al. have developed

chitosan-tripolyphosphate nanoparticles using cross linking technique as carriers for delivering tea catechins successfully in a controlled manner [89].

4.8. Rutin

Rutin (RT) is a natural flavonoid widely distributed in medicinal herbs, food and other products, and possess powerful antioxidant, anti-inflammatory and anticancer properties. Owing to its immense antioxidant potential, it has been reported to exhibit therapeutic potential in diverse variety of cancers including hepatic cancer. Despite its diverse therapeutic merits, RT shows poor aqueous solubility, which results in low oral bioavailability, which further limits its therapeutic potential in cancer therapy. A study which was done to investigate the chemoprotective effects of RT, reported that this antioxidant induced favorable changes in the antioxidant defense system in cancer therapy [90]. In a study by Zhang et al. [91], the antioxidant activity of rutin was improved via incorporation into zein-sodium caseinate nanoparticles.

4.9. Baicalin

Baicalin (BA) is a flavonoid extracted from *Scutellaria baicalensis* Georgi. It has numerous biological activities including anti-inflammatory, antibacterial, antioxidant and anticancer effects [92,93]. Increasing evidence suggests that BA has strong capacity to inhibit tumor growth in various cancers [94,95]. A study by Chen et al. reported that BA effectively inhibited viability of ovarian cancer cells [96]. In addition, BA could retard cancer progression by inhibiting invasion and metastasis of cancer cells [97].

Studies reported that concomitant administration of BA and vitamin C could suppress lung carcinoma and lung metastasis [98,99], and suppress tumor growth in hepatic cancer [100]. Zhao et al. have developed BA loaded cationic solid lipid nanoparticles prepared by emulsion evaporation–solidification at low temperature method for brain targeting as a carrier for drugs through blood brain barrier [23].

5. Conclusions

Various studies have proved that using antioxidants during cancer therapy is a promising trend to improve response to chemotherapy, avoid/reduce side effects associated with chemotherapy and maintain the cellular integrity, thus maintain the homeostasis of the host immune system. In this review, several antioxidants with different therapeutic benefits in cancer therapy have been discussed. Moreover, several studies focusing on the application of nanotechnology in delivery of these antioxidants have been shown and proven promising results in enhancing their therapeutic benefits in cancer therapy. Therefore, further preclinical and clinical studies are needed to establish the clinical implications of antioxidants doses and timings.

Table 1. Advantages and disadvantages of different methods of preparation of solid lipid nanoparticles (SLNs).

Method	Advantages	Disadvantages
High pressure homogenization Technique	<ul style="list-style-type: none"> -Low impact on the environment -Sustainable -Saving energy, time and additional costs [101] -Hot homogenization has a problem of drug entrapment and crystallization, Cold homogenization minimizes thermal exposure of the drug but does not avoid it completely, due to the melting of the drug-lipid mixture in the initial step [102]. 	Low efficiency of the process [103]
Microemulsion Technique	<ul style="list-style-type: none"> -Spontaneous formation -Ease of manufacturing -Scale-up -Thermodynamic stability -Improved drug solubilization and bioavailability [104] 	Their formation requires large amounts of surfactant which are irritating at high concentrations [105]

Table 1. Cont.

Method	Advantages	Disadvantages
Solvent evaporation method	-Controlled delivery of peptide -Drugs and vaccines -Controlled delivery of peptide -Drugs and vaccines -Controlled delivery of peptides, drugs and vaccines [51]	Difficulty of controlling the evaporation rate (and hence the growth rate), and the poisonous and corrosive nature of the solvent vapor released [106]
Solvent Emulsification Diffusion Technique	-Avoidance of any heat [102] -Possible incorporation of high amounts of polymer and drug -The excellent yields generally obtained -The easy scaling-up of the process [107]	Solvents used may cause toxicity [107]
Ultrasonication method	-It can reduce the separation time to less than 30 min. -It helps to decrease the amount of catalyst required by 50–60% due to the increased chemical activity in the presence of cavitation -Increase in purity of the glycerol	Misreading of signals, can result in unnecessary repairs [108]
Melting Dispersion Technique (Hot Melt Encapsulation Method)	-More efficient time to achieve the final product -Environmental advantages due to the elimination of solvent use -Increased efficiency of drug delivery to the patient [109]	-Use of a limited number of polymers -Not suitable for high heat sensitive molecules such as microbial species and proteins -Thermal process (drug/polymer) stability [110]
Solvent Injection Technique	-Use of pharmaceutically acceptable organic solvents -No need for high pressure homogenization -Easy handling and a fast production process without technically sophisticated equipment [111]	-Population is heterogeneous (70 to 200 nm) -Exposure of compounds to be encapsulated to organic solvents at high temperature [112,113]

Table 2. Different antioxidants and their fabricated nanosystems in cancer therapy.

Antioxidant	Nano-System	Result	Reference
Coenzyme Q10	Ubiquinone (CoQ10)-loaded biodegradable nanoparticles prepared by nanoprecipitation	Sustained drug release	Nehilla et al., 2008 [72]
Vitamin C	Chitosan/vitamin C nanoparticles were prepared via ionotropic gelation between the amino groups of chitosan and vitamin C	Enhancement of delivery of Vitamin C and increase of shelf life	Alishahi et al., 2011 [114]
Curcumin	Composite nanoparticles of three biocompatible polymers (Alginate, chitosan and pluronic)	Delivery of hydrophobic drugs into cancer cells	Das et al., 2010 [85]
	Micelles	Increase in curcumin solubility and bioavailability	Esmaili et al., 2011 [30]
Catechin	Chitosan-tripolyphosphate nanoparticles prepared by polyanion-initiated gelation process	Controlled release of catechin	Hu et al., 2008 [89]
	Polymeric nanoparticles	Increased stability of catechin during storage and after administration	Rocha et al., 2011 [33]
Baicalin	PEGylated cationic solid lipid nanoparticles prepared by emulsion evaporation-solidification at low temperature method	Crossing blood brain barrier	Liu et al., 2015 [23]
B-carotene	Protein-Stabilized β -Carotene nanodispersions prepared by emulsification–evaporation method	Increased gastrointestinal absorption of lipophilic drugs	Chu et al., 2007 [77]
Vitamin E	Nanoparticles prepared by modified solvent extraction/evaporation method	Enhancement of oral chemotherapy	Feng et al., 2009 [70]
	Liposomes	Enhancement in targeting brain cancer cells	Muthu et al., 2011 [38]
Rutin	Nanoparticles prepared by nanoprecipitation technique	Sustained release of rutin	Banjare and Ghillare, 2012 [115]

Conflicts of Interest: The authors declare no conflict of interest.

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