MINI-REVIEW

Targeting Cancer with Nano-Bullets: Curcumin, EGCG, Resveratrol and Quercetin on Flying Carpets

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Abstract

It is becoming progressively more understandable that different phytochemicals isolated from edible plants interfere with specific stages of carcinogenesis. Cancer cells have evolved hallmark mechanisms to escape from death. Concordant with this approach, there is a disruption of spatiotemproal behaviour of signaling cascades in cancer cells, which can escape from apoptosis because of downregulation of tumor suppressor genes and over-expression of oncogenes. Genomic instability, intra-tumor heterogeneity, cellular plasticity and metastasizing potential of cancer cells all are related to molecular alterations. Data obtained through *in vitro* studies has convincingly revealed that curcumin, EGCG, resveratrol and quercetin are promising anticancer agents. Their efficacy has been tested in tumor xenografted mice and considerable experimental findings have stimulated researchers to further improve the bioavailability of these nutraceuticals. We partition this review into different sections with emphasis on how bioavailability of curcumin, EGCG, resveratrol and quercetin has improved using different nanotechnology approaches.

Introduction

Preclinical and clinical studies have shown that cancer is a genomically complex disease. It is relevant to mention that because of off target effects and modest efficacy, there is a paradigm shift in the quest for identification of bioactive ingredients with lesser off target effects. In line with this approach, there is a progressive increase in in-vitro studies which are providing relevant information regarding suppression of carcinogenesis (Sawadogo et al., 2012; Teiten et al., 2013). These started with the availability of nitrogen mustard in the late 1940s for systemic chemotherapy, and in the 1950s, with the discovery and development of vinca alkaloids, vinblastine and vincristine (Pezzuto, 1997; Fernando and Rupasinghe, 2013). In this review, four selected anticancer compounds derived from plants and their bioavailability using different nanotechnological approaches are discussed.

In nanotechnology, a particle is classified according to size: in terms of diameter, fine particles cover a range between 100 and 2500 nanometers, while ultrafine particles, on the other hand, are sized between 1 and 100 nanometers. Synthesis of metal nanoparticles has been studied since 1950s (Kreuter, 2007; Singh et al., 2011;

Huixiao et al., 2012) Nanoparticles have wide ranging applications because of specific properties resulting from both high specific surface and quantum limitation of electrons localized inside the nanoparticles (Rao et al., 2000; Kreuter, 2007; Sobczak-Kupiec et al., 2012). Nanoparticles are nowadays used in a broad range of applications such as biocompatibility enhancement (Sobczak-Kupiec et al., 2012), cancer therapy agents (Alexis et al., 2010) or cancer cell imaging (Li et al., 2009; Ahmed et al., 2013).

Silica Nanoparticles

Silicon dioxide nanoparticles, also known as silica nanoparticles or nanosilica, have emerged effectively as versatile tools in interdisciplinary research because of their stability, low toxicity and ability to be functionalized with a range of molecules and polymers (Sharma et al., 2005; Kim et al., 2006; Jiang et al., 2012). Silica particles are divided into two types according to their structure. The first type of particles is characterized by numerous nanopores and the second one has a comparatively smaller surface area (Yang et al., 2008; Fuertes et al., 2010).

SiO_2 nanoparticles are very important, especially

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their structural properties. There Non-porous silica nanoparticles have wide application in medicine as a drug delivery platform. Nonporous, nano-sized support materials as SiO_2 can offer a large external surface area for immobilization of molecule thus improving their activity by eliminating internal diffusion of a substrate. The cargos can be deliver via encapsulation or conjugation with release control by chemical linkers or degradation of silica matrix (Tang and Cheng, 2013).

Meso-porous silica nanoparticles (MSN) are also broadly used in medicine as support materials, however the mechanism of delivery of active substances differ from non-pours silica materials and based on physical and chemical adsorption (Ma et al., 2011; Tang and Cheng, 2013). Unique features of MSN, such as large surface area, tunable pore diameter, controlled particle size and morphology, excellent biocompatibility, offer great advantage (Hussain et al., 2013). MSN exhibit extremely high surface areas and pore volumes enable these matrixes to host a large amount of cargo (drugs, proteins etc...) and the regular pore structure provides a homogeneous distribution of guest molecules (e.g. drugs), followed by a sustained release. MSN pores can be tuned in the molecular size range, the best for hosting drug molecules and the pore walls can be surface functionalized to provide anchoring points for the cargo molecules and enhance drug immobilization (Lin et al., 2012). The external particle surface can be functionalized independently to regulate the release (e.g. molecular gate properties), tune the surface charge and provide suspension stability and/or attach functional moieties via standard bioconjugation reactions (Sperling and Parak, 2010; Tang and Cheng, 2013).

The physicochemical properties, i.e. size and surface charge, are the two main determining factors that influence nanoparticles behavior. It is controlled during synthesis by Stober process for non-porous and meso-porous silica nanoparticles (Park et al., 2002; Rao et al., 2005). Preparation of silica nanoparticles consist of hydrolysis and polycondensation process tetraethylorthosilicate (TEOS) under alkaline conditions in ethanol (Stober et al., 1968).

Poly (2-hydroxyethyl methacrylate) (PHEMA) Nanoparticles

Hydrophilic polymers based on PHEMA are suitable for biomedical engineering applications because of their properties such as: high water content, non-toxicity, softness, flexibility and good compatibility with skin and human tissue and also easy modification of these properties via chemical formulation (Zhu and Marchant, 2011; Dobic et al., 2012). PHEMA-based materials are widely used in ophthalomology-contact lenses and orbital implants (Allan, 1999; Lloyd et al., 2001). PHEMA has been used as tissue engineering scaffold. The crosslinked networks of hydrophilic co-polymers which swell in water are permeable to gases, nutrients and growth-promoting factors and entrapment of cells. PHEMA could be modified with different agent such as protein-derived peptides, collagen, charged functional groups (He et al., 2012).

Among various polymers, group of polymers 2-hydroxyetyhyl methacrylate (PHEMA) is widely used in biomedical research because of their useful physicochemical properties and suitability for controlled drug delivery applications (Coelho et al., 2010). The poly (2-hydroxyethyl methacrylate) nanoparticles could be used as a carries for the drugs, which could be linked to chain via functional groups. However, in many situations, drugs chemically bound to the polymer chain exhibit reduced biological activity. Therefore, drugs should be separated from the polymer chain by means of a spacer, ie. transformed polymer into a suitable derivative by interconnection with PHEMA and to introduce a spacer between the carrier and the bioactive components (Jantas and Herczynska, 2010).

Chouhan and Bajpai,(2009) describe release of anticancer drug - 5-fluorouracil from the PHEMA nanoparticles and the influence of environmental conditions, such as temperature, pH as well as chemical structure i.e. percent loading of the drug. Tsou et al.,(2005) described an application PHEMA loaded ciprofloxacin as wound dressing. In this case poly (2-hydroxyethyl methacrylate) was used because of physicochemical properties such as: easy oxygen permeability, good water transmission, and absorption, high biocompatibility and non-toxicity.

PLGA Nanoparticles

Poly (lactic-co-glycolic acid) (PLGA) is widely used in medicine and pharmacology because of its biocompatibility and biodegradable nature. PLGA are approved by the US FDA and European Medicine Agency (EMA) (Danhier et al., 2012). Its hydrolysis leads to metabolite monomers, lactic and glycolic acids, which are endogenous and easily metabolized by the body via the Krebs cycle (Danhier et al., 2012). This polymer has been used to form polymeric nanoparticles (NPs) to encapsulate a variety of therapeutic compounds, such as: nonsteroidal anti-inflammatory drugs (NSAIDs), anticancer drugs, peptides and steroid hormones, siRNA (Giteau et al., 2008; Campolongo and Luo, 2009; Sameni et al., 2009). A numbers of different molecular weight of poly (lactic-co-glycolic acid) and its copolymers are used, which determine physicochemical properties among others degradation time (Asghar et al., 2012; Danhier et al., 2012; Hussein and Abdullah, 2013). The size of polymer particles has strong influence on drug releasing, influences circulating half-life, cellular uptake and biodistribution; the nanoparticles particles are taken up by cells much faster than micron size (Mohanraj and Chen, 2006; Gratton et al., 2008). PGLA can be applied as carrier for sustained drug release, targeting delivery of drugs to specific tissues, vascular beds, and cells (Miladi et al., 2013; Vanic and Skalko-Basnet, 2013). PLGA nanoparticles targeted to dendritic cells with an antibody are taken up specifically, but microparticles targeted with the same antibody are taken up non-specifically (Cruz et al., 2010).

Curcumin

Curcumin is a well studied natural anticancer agent. Despite its multifunctional activities in cancer cells, there are some challenges which need to be overcome. Poor bioavailability of curcumin because of limited solubility in water is a major stumbling block. Interdisciplinary approaches are being used to improve its bioavailability.

Curcumin has been shown to induce apoptosis in drug resistant cancer cells (Roy and Mukherjee, 2014). It functionalizes intrinsic pathway and regulates Bcl-2/Bax ratio in A549 cancer cells (Li et al., 2013). Curcumin liposomes effectively induced apoptosis and there was notably reduced angiogenesis in the LL/2 model (Tang et al., 2013). Another contemporary study revealed that curcumin-loaded nanoparticles prepared with amphilic methoxy PEG-polycaprolactone (PCL) block copolymers substantially inhibited cancer growth in mice transplanted with A549 (Yin et al., 2013b). Curcumin has also been shown to exert its cancer suppressing effects in mice xenografted with HepG2 cells (Dai et al., 2013).

Silica nanoparticles conjugated to curcumin have recently been studied for efficacy in cervical cancer cells (Gangwar et al., 2013). Curcumin-loaded solid lipid nanoparticles (SLNs) have also been shown to display controlled release of the compund. Another characterisitic feature of solid lipid nanoparticles noted was considrably higher efficiency of drug entrapment and loading capacity (Chen et al., 2013). Encapsulation of curcumin in SLN was also tested in a coculture system of consisitng of absorptive Caco-2 and mucus secreting HT29-MTX cells that provided proof-of-concept that curcumin was delivered efficiently (Guri et al., 2013). Intravenous administration of Curcumin-loaded SLNs into rats underscored the fact that there was 1.25-fold increase in bioavailability of curcumin (Sun et al., 2013).

Loading of curcumin into hydrophilic polymeric core has also been pursued optimistically and it has been shown that poly(2-hydroxyethyl methacrylate) (PHEMA) nanoparticles might serve as efficient carriers of curcumin. There is a direct piece of evidence that suggests that encapsulation of curcumin into the hydrogel nanoparticles resulted in homogenously distributed curcumin in aqueous solution (Guzman-Villanueva et al., 2013). PHEMA nanoparticles loaded with curcumin have been tested in ovarian cancer cells (SKOV-3) (Kumar et al., 2014). Magnetic nanoparticles (MNPs) are also notable carriers of drugs and a recent study revealed synergistic delivery of curcumin and temozolomide to evaluate anticancer activity in glioblastoma spheroid model. MNPs conjugated curcumin and temozolomide effectively induced apoptosis as evidenced by cell death assays (Dilnawaz and Sahoo, 2013).

It is getting successively more comprehensible that cancer cells have developed mechanisms to escape from retention of cytotoxic drugs in the cell. Mounting evidence suggests that Poloxamers and D-alpha-Tocopheryl polyethylene glycol succinate (TPGS) have shown efficacy in overcoming drug resistance.

In accordance with this concept, a recent study highlighted Poloxamer/TPGS mixed micelles as an effective delivery system for curcumin for targeting of multidrug resistant ovarian cancer cells (Saxena and Hussain, 2013). Water-soluble PLGA nanoparticles conjugated to curcumin dramatically induced apoptosis in cisplatin resistant oral cancer cells via activation of intrinsic pathway (Chang et al., 2013).

There is a rapidly growing interest in using N-isopropylacrylamide (NIPAAM)/N-vinyl-2-pyrrolidone (VP)/Polyethylene glycol monoacrylate (PEG-A) polymeric nanoparticles to encapsulate curcumin to improve its biodistribution. NIPAAM/VP/PEG-A nanoparticles loaded with curcumin were tested in prostate cancer cells and results indicated that optimial activity was notable at 400 µg/mL that induced apoptosis in almost 92% of cells (Salehi et al., 2013). Poly (ε-Caprolactone)-PEG-poly (ε-Caprolactone) (PCL-PEG-PCL) triblock copolymers have also emerged as drug delivery systems with impressive efficiency. Consistent with this approach, curcumin was loaded into PCL-PEG-PCL triblock copolymeric nanoparticles and it was observed that these NPs released curcumin in a controlled manner (Feng et al., 2012).

Astonishingly, curcumin complexed with β-Cyclodextrin nanoparticles was noted to improve permeability of curcumin acrossed skin model tissue (Rachmawati et al., 2013).

Quercetin

Quercetin is a polyphenolic compound widely distributed in many vegetals, such as capers, lovage, dill, apple and tea (Gao et al., 2012; Kulisic-Bilusic et al., 2012; Michaud-Levesque et al., 2012). Current researches indicated that quercetin has promising anti-cancer as well anti-inflammatory properties. Some studies reported that quercetin could stifle the growth of cancer cells through inducing apoptosis in a variety of cancer cell lines. Even though the promising application of quercetin in cancer therapy, its use is restricted because of the poor water solubility. Thus novels formulation of quercetin are desirable (Gao et al., 2012).

There are some exciting pieces of evidence which substantiate the fact that quercetin-loaded nanoliposomes (QUE-NLs) have remarkable anticancer activity and variation in the concentration determined mode of death. QUE-NLs at a concentration of (200 µM) induced non-apoptotic cell death in glioma cells (Wang et al., 2012). However, QUE-NLs at a concentration of (100 µM) induced apoptotic cell death in glioma cells (Wang et al., 2013).

Polylactic Acid (PLA) and PLGA are biodegradable polymers. Poly(lactic-co-glycolic acid) (PLGA) is a better biodegradable polymer and undergoes hydrolysis in human body producing metabolites including lactic acid and glycolic acid. Confluence of information suggested that delivery of quercetin and tamoxifen encapsulated in PLGA strongly induced apoptosis in breast cancer cells (Jain et al., 2013). Nanoparticles prepared from polylactic acid-hyperbranched polyglycerol (HPG-PLA) have also proved to be novel carriers of drugs (Gao et al., 2011)

Another drug delivery system particularly, PEG

(660)-12-hydroxystearate (PEG 660-stearate) has also persuasively revealed a considerably improved solubilization of quercetin upto five times (Dora et al., 2012). Increasingly it is being realized that nanoemulsion-based delivery systems are effective in enhancing bioaccessibility of drugs. In agreement with this approach, it has recently been shown that bioaccessibility of crystalline quercetin was comparatively lesser than that of dissolved quercetin (Pool et al., 2013).

Resveratrol

Resveratrol (3, 5, 4'-trihydroxystilbene or 3, 5, 4'-stilbe- netriol; MW: 228.25) is found in more than seventy plant species, primarily in red grape and red wine, peanuts, some berries, dark chocolate and other cocoa products.

Rapidly increasing studies have focused on the potential anti-cancer activity of resveratrol in various kinds of cancers This natural polyphenol possesses a strong anti-cancer property *in vitro* and also in various animal models *in vivo* (Wu et al., 2013a). Poor bioavailability of resveratrol is a major issue and in this context, an increasing number of recent studies have aimed at designing novel resveratrol formulations to overcome these barriers (Amri et al., 2012). It has previously been shown that resveratrol efficiently inhibited in-vitro invasion of NuTu-19 ovarian cancer cells. However, these effects were not observed in mice xenografted with NuTu-19 ovarian cancer cells (Stakleff et al., 2012). Resveratrol induced apoptosis in HT- 29 cells via regulation of PKCα and ERK1/2 (Fang et al., 2012). Resveratrol considerably inhibited cancer growth in mice xenografted with A549 cells (Yin et al., 2013a). Mechanistically it was shown that resveratrol inhibited proliferation of oesophageal adenocarcinoma cells (Sjaarda et al., 2013). Deatiled mechanistic insights revealed that resveratrol inhibited Skp2-mediated ubiquitylation and proteasomal degradation of p27Kip1. Gene silencing strategy provided evidence that p27Kip1 silencing impaired resveratrol mediated suppression of proliferation (Fan et al., 2014).

Resveratrol loaded cationic chitosan-and anionic alginate-coated poly(D, L-lactide-co-glycolide) nanoparticles demonstrate protection against light-exposure degradation, thus opening new perspectives for improving biodistribution of phytochemicals for (nano)chemoprevention/chemotherapy (Sanna et al., 2012). In addition of light protection, resveratrol-loaded nanoparticles based on poly (D, L-lactide-co-glycolide)-poly(ethylene glycol) and poly(epsilon-caprolactone) blend significantly improved the cytotoxicity compared to that of free RSV toward prostate carcinoma cell lines (Sanna et al., 2013).

There are evidences that nanoencapsulated resveratrol could be more effective than no encapsulated. Resveratrol-loaded lipid-core nanocapsules treatment reduces *In vitro* (C6 glioma cell line) and *In vivo* (brain-implanted C6 cells) glioma growth more effectively than resveratrol in solution (Figueiro et al., 2013). The anticancer activity of resveratrol-loaded gelatin nanoparticles on NCI-H460 non-small cell lung cancer cells was evaluated. The prepared resveratrol-gelatin nanoparticles exhibited very rapid and more efficient cellular uptake and showed greater antiproliferative efficacy treatment in NCI-H460 cells than free resveratrol (Karthikeyan et al., 2013).

Still, based on the fact that nanoparticles bound with either biotin or avidin tend to accumulate in tumors and avidin-attached reagents were quickly eliminated from blood circulation and assembled in liver, trans-resveratrol loaded chitosan nanoparticles, with the surface modified either by biotin or by both biotin and avidin were studied. Inhibitory study on HepG2 cells showed that compared to trans-resveratrol solution and no-modified biotin or avidin nanoparticles, both resveratrol loaded chitosan biotin and avidin modified surface significantly improved the anticancer activity (Bu et al., 2013).

Not only through polymer or lipid nanosctrutures resveratrol could be applied in drug delivery systems. Resveratrol loaded clay nanotubes added to breast cell culture (MCF-7) strongly increase the toxicity leading to cell apoptosis, showing that halloysite clay can be considered as green and natural nanocarriers for hydrophobic drugs encapsulation (Vergaro et al., 2012).

In this way, it can be concluded that resveratrol is a drug that can be better released by nanotechnological approaches to the target site.

Epigallocatechin Gallate (EGCG)

EGCG is a potent phytochemical reported to be involved in regulation of apoptosis and carcinogenesis. However, minimal bioavailability of EGCG considerably reduced EGCG mediated biological effects *in vivo*. EGCG has been shown to exert its inhibitory effects on invasion and migration of HeLa cells (Sharma et al., 2012). There is a recent report highlighting mechanisms by which EGCG inhibits activation of NFK B and of MMP- 9 in human T-cell lymphotropic virus-1 positive leukemia cells. The results revealed that EGCG treated cancer cells had notably reduced nuclear distribution of NFKB (Harakeh et al., 2014).

Different approaches have been used to improve the biodistribution by encapsulating EGCG with bioactive caseinophosphopeptides and chitosan (Hu et al., 2012). Encouraging results have been noted by oral administration of nanoformulated EGCG in athymic nude mice subcutaneously implanted with 22Rv1 tumor xenografts. Drug release was studied and results revealed sustained release of EGCG in simulated gastric juice acidic pH. In simulated intestinal fluid release of EGCG was notably higher (Khan et al., 2013). In line with this approach, another circumstantial study suggested increased protonation of EGCG at gastric juice pH (1.0). It was observed that EGCG-dispersed selenium nanoparticles did not mediate notable anticancer activity *in vivo* (Wu et al., 2013b). It is noteworthy that nanoparticle conjugated EGCG promoted DNA damage in lymphocytes however, EGCG in bulk dramatically reduced DNA damage in concentration dependent manner (Alotaibi et al., 2013). Cell receptor targeted nanoparticle mediated delivery of chemotherapeutic drugs has also attracted considerable attention. Targeted delivery of drugs using self-assembled

6-O-(3-hexadecyloxy-2-hydroxypropyl)-hyaluronic acid (HDHA) nanoparticles has recently been tested in swiss albino mice grafted with Ehrlich's ascites carcinoma (EAC) cells. Moreover, O-hexadecylated dextran (HDD) nanoparticles loaded with chemotherapeutic drug were also evalauted for efficacy. The results confirmed that drug loaded HDHA NPs were more effective in delivery of drug to the target site as compared to drug loaded HDD NPs. It was further highlighted that instead of delivering single therapeutic agent, combinatorial approach, using EGCG with targeted delivery of drug proved to be more efficient in restricting growth of tumor cells in mice (Ray et al., 2013). EGCG functionalized with laminin receptor specific gold nanoparticles has also been tested for efficacy in SCID mice xenografted with PC-3 cells (Shukla et al., 2012).

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