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·Review·

Biocompatible and biodegradable nanoparticles for enhancement of anti-cancer activities of phytochemicals

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[ABSTRACT] Many phytochemicals show promise in cancer prevention and treatment, but their low aqueous solubility, poor stability, unfavorable bioavailability, and low target specificity make administering them at therapeutic doses unrealistic. This is particularly true for (−)-epigallocatechin gallate, curcumin, quercetin, resveratrol, and genistein. There is an increasing interest in developing novel delivery strategies for these natural products. Liposomes, micelles, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers and poly (lactide-co-glycolide) nanoparticles are biocompatible and biodegradable nanoparticles. Those nanoparticles can increase the stability and solubility of phytochemicals, exhibit a sustained release property, enhance their absorption and bioavailability, protect them from premature enzymatic degradation or metabolism, prolong their circulation time, improve their target specificity to cancer cells or tumors via passive or targeted delivery, lower toxicity or side-effects to normal cells or tissues through preventing them from prematurely interacting with the biological environment, and enhance anti-cancer activities. Nanotechnology opens a door for developing phytochemical-loaded nanoparticles for prevention and treatment of cancer.

[KEY WORDS] Nanoparticles; Cancer; Biocompatible; Biodegradable; (−)-Epigallocatechin Gallate; Curcumin; Quercetin; Resveratrol; Genistein

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Introduction

Cancer has become one of the leading causes of human morbidity and mortality worldwide, accounting for 7.6 million deaths every year [1]. There are more than 100 different types of cancer, and they are quite varied and depend on cancer location, metastasis and size [2]. In the United States and many other countries, common types of cancers are skin cancer, breast cancer, colon and rectal cancer, liver cancer, lung cancer, pancreatic cancer and prostate cancer [1, 3].

Phytochemicals are naturally occurring bioactive compounds found in vegetables, fruits, spices, grains, and other plant foods [4]. Many phytochemicals from traditional medicine have been used for the maintenance of health and prevention of diseases, especially cancer [5-6]. Over the past few decades, research evidence from cell culture and some animal studies has supported that many phytochemicals have anti-cancer activities, but inconsistent results are found in some human clinical trials [7-8]. The inconsistence may be due to the infeasibility of high doses of phytochemicals for human studies, the low level of their aqueous solubility, stability, bioavailability and target specificity to cancer cells and tumors, and the high level of degradation and metabolism by enzymes in the gastrointestinal tract, the liver and other tissues and thus short circulation time and low circulation concentrations[7, 9].

Nanotechnology involves the control of matter, generally

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in the range of 100 nm or smaller [10]. In recent years, the use of nanotechnology to enhance delivery of phytochemicals to tumors or cancer cells for improving therapeutic efficiency has received considerable attention [9, 11]. Many phytochemicals can be loaded into biocompatible and biodegradable nanoparticles, which can enhance their absorption and bioavailability, protect them from degradation by enzymes, enhance their stability, prolong their circulation time, exhibit high differential uptake efficiency in cancer cells (or tumors) over other normal cells (or normal tissues), lower toxicity through preventing them from prematurely interacting with the biological environment [12].

Biocompatible and biodegradable nanoparticles

Liposomes, nanoemulsions, micelles, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), poly (lactide-co-glycolide) (PLGA) nanoparticles are the commonly used biocompatible and biodegradable nanoparticles, and they can be administered *via* different routes including oral, intravenous, intraperitoneal, transdermal administration [12]. We illustrated the schematic structure of liposomes, emulsions, SLN, micelles, and PLGA nanoparticles in Fig. 1. Poly(ethylene glycerol) (PEG) is incorporated on the surface of most nanoparticles to maintain their integrity and stability via protecting them from degradation and metabolism by enzymes and prolong their circulation by stabilizing them against opsonization [12].

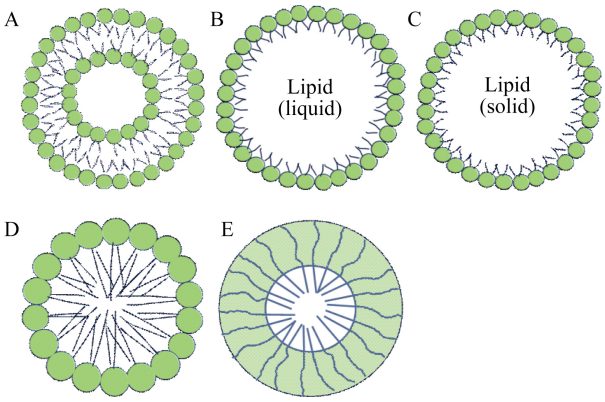

Fig. 1 Schematic structure of commonly used biocompatible and biodegradable nanoparticles. A, Liposome; B, Emulsion; C, SLN; D, Micelle; E, Polymeric micelle

Even though those nanoparticles are biocompatible and biodegradable, their toxicity and side effects should be measured. Especially, when the loading capacity and encapsulation efficiency of phytochemicals are low, a large amount of nanoparticles are administered to cells or animals [12]. Cytotoxicity assays are widely used to measure toxicity of nanoparticles to cells. The widely used cytotoxicity experiments include a trypan blue exclusion assay, a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) or (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt) (MTS) assay, a lactate dehydrogenase (LDH), a sulforhodamine B (SRB) assay and so on. In animal studies, both short- and long-term toxicity and side effects should be measured. The commonly used measurement methods are body weight, blood chemistry test, complete necropsies including full gross and microscopic evaluation of all organ-systems, histological examination and evaluation of all organs and tissues and so on. Currently, an emerging need is to set up standardized *in vitro* and *in vivo* models, safety test measures and guidelines to determine toxicity and side effects of nanoparticles [12].

Liposomes

Liposomes are particles having mono- or multi-bilayer of phospholipids structures [13]. Phospholipid is a molecule that has a hydrophilic head and two hydrophobic fatty acid tails. The head group on the surface of liposomes is attracted to water, and the fatty acid tails are repelled by water [12]. Cholesterol is another compound used in liposomes for enhancing liposome physical characteristics [14]. After phytochemicals are loaded into liposomes, their aqueous solubility, stability and circulation time can be enhanced, and their toxicity and side effects can be lowered [15]. Liposomes can entrap hydrophilic phytochemicals in their internal water compartment and hydrophobic phytochemicals into the membrane [16]. Liposomes can be used *via* oral administration, intravenous injection, subcutaneous administration and topical application [16-17].

Nanoemulsions

Emulsions are prepared by dispersing one liquid dispersed phase into the other continuous phase [12]. Oil is dispersed into water containing a surfactant or emulsifier to form oil-in-water emulsions, which have hydrophilic shells and hydrophobic cores. Nanoemulsions need high-energy input and more surfactants or co-surfactants to lower the surface tension and maintain the size less than 100 nm in diameter [18]. Oil-in-water nanoemulsions are commonly used to deliver hydrophobic phytochemicals, such as curcumin [19], quercetin [20], resveratrol [21] and genistein [22] to tumors and cancer cells. The advantages of nanoemulsions include to increase aqueous solubility of hydrophobic phytochemicals, enhance their stability and circulation time, improve their absorption and bioavailability [18, 23].

SLNs and NLCs

SLNs and NLCs are synthesized lipid particles composed of lipids, surfactants, water, maybe co-surfactants [24]. They have a hydrophilic shell and a hydrophobic lipid core. Phospholipids and surfactants are used to form the hydrophilic shell. Triglycerides, waxes, fatty acids are commonly used to form the hydrophobic lipid core. Different from emulsions, the hydrophobic lipid cores in SLNs and NLCs are solid or semi-solid. SLNs and NLCs have a perfect and imperfect lipid core structure, respectively [12]. The imperfect lipid cores of NLCs increase the loading capacity of phytochemicals [12]. Both SLNs and NLCs are colloidal carriers with an average diameter 100 nm or less [25]. SLNs are developed in the early 1990s,

serve as an alternative nanocarrier system to liposomes, nanoemulsions, and polymeric nanoparticles [26-27]. NLCs developed at the end of the 1990s [28]. As a new generation of lipid nanocarriers, NLCs can avoid many limitations of SLNs including low loading capacity, high release potential, and drug expulsion during storage [29].

Micelles

Different from liposomes, micelles have a monolayer of phospholipids (or other amphiphilic monomers or polymers) and a hydrophobic lipid core [30-31]. Many amphiphilic molecules having a polar/hydrophilic group and a nonpolar/hydrophobic group can be used to synthesize micelles [32]. Surfactants and/or co-surfactants are commonly used in preparing micelles [32]. Micelles can increase the aqueous solubility of hydrophobic phytochemicals, enhance their bioavailability, reduce adverse effects (such as toxicity), enhance permeability across the physiological barriers, and changes their biodistribution in the body [30].

PLGA nanoparticles

Synthetic polymers have many advantages including high purity and reproducibility over natural polymers [33]. The most commonly used synthetic polymer for assembling nanoparticles is PLGA. PLGA is biocompatible and biodegradable, because it yields lactic acid and glycolic acid after it undergoes hydrolysis in the body. PLGA nanoparticles have the properties of increasing drug efficacy and sustained release [34]. In particular, PLGA has been approved by FDA for human therapy [35]. PLGA nanoparticles have been used as carriers to deliver many phytochemicals such as curcumin, resveratrol, and quercetin [36-38].

Phytochemicals-loaded nanoparticles and their anti-cancer activities

In this review, we focus on some commonly consumed phytochemicals, including (−)-epigallocatechin gallate (EGCG) abundant in green tea, curcumin abundant in turmeric, quercetin abundant in red onions, resveratrol abundant in red grapes and genistein abundant in soybeans (Fig. 2), and investigate whether nanoencapsulation can enhance their characteristics and anti-cancer activities.

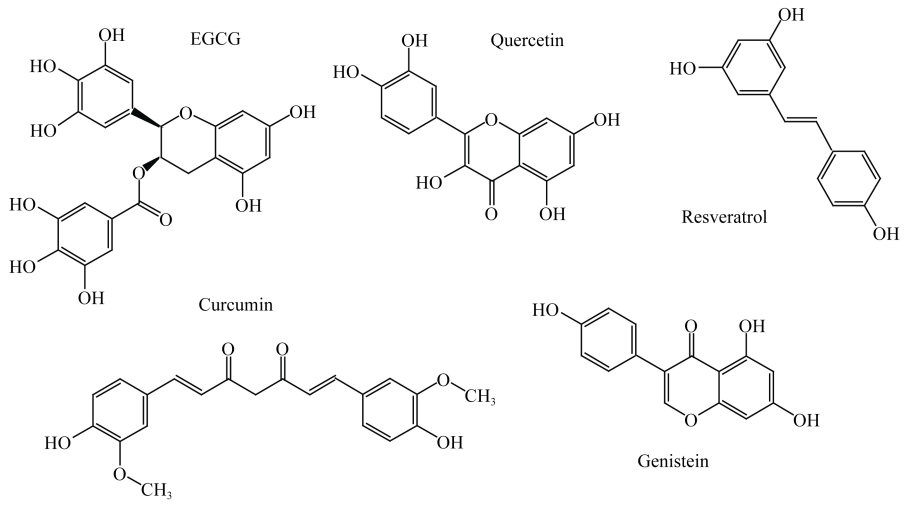

Fig. 2 Chemical structures of selected phytochemicals discussed in this review

EGCG

Green tea is made from the plant, *Camellia sinensis,* and has been taken as a healthy drink since ancient times. There are three major types of tea (with consumption rate): fermented black tea (78%−85%), unfermented green tea (14%−20%) and partially fermented oolong tea (less than 2%) [39]. Over the past few decades, scientific studies showed green tea ingestion, not black tea, might prevent many types of cancer such as breast and prostate cancer [40]. There are four major epicatechin derivatives: EGCG, epigallocathechin (EGC) and epicathechin-3 gallate (ECG) and epicatechin (EC) [39]. EGCG accounts for 25%−55% of the total catechins [39]. Green tea contains more catechins than black or oolong tea [39]. One *in vitro* study screened and determined cancer prevention effects of 10 major polyphenols found in green tea including caffeic acid (CA); gallic acid (GA); EGCG; EGC; ECG; EC; catechin (C); gallocatechin (GC); catechingallate (CG); gallocatechingallate (GCG). EGCG demonstrated the highest chemopreventive potential among them [41]. Many other studies also support these results [40, 42-43]. The underlying mechanisms of anti-cancer activities of EGCG include anti-angiogenesis, apoptosis and cell cycle arrest [37-42]. EGCG significantly inhibited new blood vessels growth and further decreases tumor progression [42]. EGCG also inhibited a crucial enzyme urokinase (uPA) for the growth of a variety of different types of tumors [40]. Moreover, EGCG induced cancer cell apoptosis and cell cycle arrest in the G1 phase, and inhibited cancer cell proliferation [41, 44].

However, EGCG has many limitations. First, EGCG is not stable in both physiological fluids and water [45]. Second, EGCG's bioavailability was extremely low in research animals and humans [46-48]. The oral bioavailability was less

than 1% reported by animal and human studies [43, 48]. The peak blood EGCG concentration was 0.15 μmol·L^{-1} after 2 cups of green tea ingestion [47]. Third, EGCG is quickly degraded or metabolized by enzymes in the liver and other tissues. Fourth, EGCG has a low level of target specificity to cancer cells or tumors. Hence, there is a critical need to overcome those problems. Many studies have demonstrated that nanoparticles can increase EGCG's stability, bioavailability and target specificity to cancer cells, and enhance its anti-cancer activities [43, 48] (Table 1). From our published articles, EGCG's stability in liposomes and NLCs was significantly increased [39, 44, 49]. Nanoparticles can also protect EGCG from premature degradation [39]. EGCG loaded in nanoparticles exhibited a sustained release manner, which lowers treatment frequency, doses and side effects. Moreover, incorporating target ligands on the surface of EGCG nanoparticles can enhance targeted delivery of EGCG to cancer cells [50]. Sanna V *et al.* incorporated target ligands on the surface of EGCG nanoparticles, which enable the targeted delivery of EGCG to prostate cancer cells expressing the prostate-specific membrane antigen (PSMA) [51]. One study used EGCG derivatives to make micellar nanocomplexes, which carriered and delivered herceptin to breast cancer cells. They found that these nanocomplexes effectively lowered cancer cell viability *in vitro* and inhibited tumor growth *in vivo* [52].

Hence, nanoparticles can increase EGCG stability and bioavailability, enhance its sustained release and targeted delivery of EGCG to cancer cells, which may open a new door for cancer prevention and treatment.

Table 1 The characteristics and anti-cancer activities of EGCG nanoparticles

Nanoparticle type	Nanoparticle size/nm	Target Yes/No	Experiment model/dose	Cancer/tumor type	Main Outcome	Year & Ref.
Micellar nanocomplexes (comprising EGCG derivatives and a protein drug-Herceptin)	90	No	*In vitro*: BT-474 cells treated with nanocomplexes containing Herceptin: oligomerized EGCG: PEG–EGCG = 0.5: 0.024: 0.26 mg·mL^{-1}; *In vivo*: Athymic Nude-Foxn1nu female mice inoculated with BT-474 cells; intravenous injection of the nanocomplexes twice per week for five weeks	Breast cancer	↑ Anti-cancer effects *in vitro* and *in vivo* ↑ Better tumor selectivity ↓ Tumor growth ↑ Herceptin circulation time	2014 [52]
Chitosan nanoparticles	N/A	No	*In vitro*: human melanoma cells treated with 0.5−8 μmol·L^{-1} of free EGCG or nano-EGCG for 48 h *In vivo*: Athymic (nu/nu) male nude mice treated with 1XPBS, 1 mg EGCG, 100 μg EGCG, 100 μg nano-EGCG five times a week for 31 days *via* oral administration.	Human melanoma	↑ Dose advantage ↑ Mel 928 cells apoptosis ↓ The growth of Mel 928 tumor xenograft ↓ Proliferation (Ki-67 and PCNA) ↑ Apoptosis in tumors harvested	2014 [53]
Nanoliposomes; Chitosan coated nanoliposomes	55-85	No	MCF-7 cells treated with 0–10 μmol·L^{-1} of free EGCG or nano-EGCG	Breast cancer	↓ Breast cancer MCF-7 cell viability ↑ MCF-7 cell apoptosis	2013 [44]
Chitosan nanoparticles	< 200	No	*In vivo*: 22Rv1 tumor xenografts nude mice treated with void chitosan nanoparticles (control group), 40 mg/kg BW of free EGCG group, 3 mg/kg BW of Chitosan-nanoEGCG or 6 mg/kg BW of chitosan-nanoEGCG via oral intubation five times per week for 60 days	Prostate cancer	↓ Tumor growth ↑ Apoptosis	2013 [54]
PLGA–PEG nanoparticles	Around 80	Yes (PSMA-targeting ligands)	Prostate cancer (LNCaP) cells treated with 30 μmol·L^{-1} of free EGCG, targeted or non-targeted nano-EGCG	Prostate cancer	↓ Viability of LNCaP cells	2011 [51]
Gum Arabic and maltodextrin nanoparticles	Around 100	No	Human prostate carcinoma Du145 cells treated with 0–10 μmol·L^{-1} of free EGCG or nano-EGCG	Prostate cancer	↑ EGCG anti-cancer activity	2011 [55]

BW, body weight; N/A, not applicable; PEG, poly(ethylene glycerol); PLGA, poly (lactide-co-glycolide); PMSA, prostate-specific membrane antigen; ↑, increase; ↓, decrease

Curcumin

Curcumin is a hydrophobic polyphenol component abundant in the spice turmeric of ground rhizome of the herb *Curcuma longa* [56-57]. Curcumin has a potential to inhibit cancer cell proliferation, carcinogenesis, tumorigenic, and angiogenesis, hence it has been used for the prevention and treatment of many chronic diseases, especially cancer [6, 58]. However, a high level of its physical and metabolic instability and a low level of aqueous solubility of free curcumin limit its anti-cancer activities [59].

Many curcumin loaded nanoparticles have been developed to enhance its aqueous solubility, stability, bioavailability, sustained release property, targeted delivery to cancer cells and anti-cancer activities [59] (Table 2). Biocompatible and biodegradable liposomes, PLGA nanoparticles, SLNs, NLCs and micelles have been used to carry and deliver curcumin to cancer cells [66-81]. Curcumin loaded nanoparticles demonstrated a sustained release property and enhanced cellular bioavailability of curcumin, and further decreased cancer cell viability in *in vitro* studies [60-61]. Nano-curcumin compared to free curcumin decreased cell viability to a fold change of 1.5 in PC3 prostate cancer cells [62], a fold change of 1.5−2.5 in MCF-7 breast cancer cells [63] and a fold change of 1.2 in HepG2

hepatocellular carcinoma cells [64]. In murine models, nanoparticles increased bioavailability, peak blood concentrations and tumor distribution of curcumin, and suppressed tumor/ carcinoma growth and angiogenesis. Nano-curcumin compared to free curcumin resulted in a 50% reduction in prostate tumor growth [65] and a 42% reduction in pancreatic tumor volume [66]. Most of the studies used passive rather than targeted delivery strategies to deliver curcumin to cancer cells or tumors. Tumor development and progression depend on angiogenesis [67]. Curcumin nanoparticles can pass the leaky neovasculature and target to tumorigenic areas by the enhanced permeability and retention effects [68-69]. Targeted delivery of curcumin to cancer cells or tumors requires incorporation of target ligands on the surface of nanoparticles, which consequently maximize the distribution and accumulation of curcumin in cancer cells or tumors [9, 70].

Taken together, many studies have suggested that nanoparticles (liposomes, SLNs, NLCs and PLGA nanoparticles) can improve characteristics of curcumin including solubility, stability and bioavailability, and its anti-cancer activities, and might be a good strategy for cancer prevention and treatment [18, 59, 71].

Table 2 The characteristics and anti-cancer activities of curcumin nanoparticles

Nanoparticle type	Nanoparticles size /nm	Target Yes/No	Experiment model/dose	Cancer type	Main Outcome	Year & Ref.
Lipid–polymer nanoparticles	Around 172	No	MDA-MB-231 breast cancer cells treated with 0−40 μmol·L^{-1} of free curcumin or nano-curcumin	Breast cancer	↓ Metastasis ↓ Inflammation	2014 [72]
Thiolated chitosan nanoparticles	Around 150	No	HT29 cells treated with 20 μmol·L^{-1} of free curcumin or nano-curcumin and Swiss Albino mice treated with 25 mg/kg BW of free curcumin or nano-curcumin	Colon cancer	↑ Sustained release ↑ Cellular uptake ↓ Cell viability ↑ Apoptosis ↑ Anti-cancer activities ↑ Bioavailability *in vivo*	2014 [73]
PLGA nanoparticles	N/A	Yes (PSMA antibody as a target ligand)	Prostate cancer xenograft mice model and prostate cancer cells (C4-2, DU-145, PC-3) treated with free or nano-curcumin (2.5−40 μmol·L^{-1}). PSMA antibody conjugated on the nanoparticles for targeting to cancer cells.	Prostate cancer	↓ Proliferation of cancer cells ↓ Tumor growth ↓ Key oncogenic proteins ↑ Apoptosis ↓ Oncogenic miR21 ↑ miR-205	2014 [65]
NLCs	Around 108	No	PC3 cells treated with 20 μmol·L^{-1} of free or nano-curcumin	Prostate Cancer	↑ Sustained release ↓ Cell viability ↑ Anti-cancer activities	2013 [62]
SLNs	Around 153	No	MCF-7 cells treated with 5 μg·mL^{-1} and Male Sprague-Dawley rats (2 mg·kg^{-1}) treated with free or nano-curcumin via intravenous administration	Breast cancer	↑ Intracellular uptake ↑ Bioavailability of curcumin ↑ Anti-cancer activities	2013 [63]
SLNs	100	No	SMMC-7721 cells treated with 20−64 μg·mL^{-1} of free curcumin or nano-curcumin	Liver cancer	↑ Sustained release ↓ Cell viability ↑ Apoptosis	2013 [74]
SLNs	20−80	No	A549 cells treated with 4−100 μmol·L^{-1} of free curcumin or nano-curcumin. Nude mice bearing A549 cells xenografts treated with 200 mg/kg BW of free curcumin or nano-curcumin via intraperitoneal injection	Lung cancer	↑ Stability of curcumin ↓ Growth of lung cancer cells ↑ Apoptosis of A549 lung cancer cells ↑ Blood plasma of curcumin *in vivo* ↑ Tumor distribution of curcumin ↓ Tumor volume	2013 [75]
Liposomes	Around 100	No	Human MiaPaCa pancreatic cancer cells treated with 0–30 μmol·L^{-1} of free curcumin or nano-curcumin and in the pancreatic tumor xenograft study (20 mg/kg BW).	Pancreatic cancer	↓ Cell viability ↓ Tumor growth ↓ Angiogenesis	2013 [66]
PLGA nanoparticles	Around 130	Yes (APgp as a target ligand)	Multidrug resistant (KB-V1) and drug sensitive (KB-3-1) cervical carcinoma cells treated with 5–30 μmol·L^{-1} of free curcumin or nano-curcumin	Cervical cancer	↑ Targeting to cancer cells ↑ Cellular uptake ↓ Cell viability	2012 [76]
PLGA nanoparticles	120–190	No	HeLa cells treated with 5–25 μmol·L^{-1} of free curcumin or nano-curcumin	Liver cancer	↑ Aqueous solubility and sustained release ↑ Cellular uptake ↑ Anti-cancer efficacy	2012 [77]
MPEG-PCL micelles	Around 27	No	BALB/c mice were given curcumin/ MPEG-PCL micelle (25 mg/kg BW curcumin) via intravenously injection	Colon cancer	↓ Tumor cell-induced angiogenesis ↓ Growth of colon carcinoma	2011 [78]

Anti-P-glycoprotein, APgp; BW, body weight; MPEG-PCL, monomethoxy poly(ethylene glycol)-poly(3-caprolactone); N/A, not applicable; NLCs, nanostructured lipid carriers; PSMA, prostate specific membrane antigen; PEG, poly(ethylene glycerol); PLGA, (poly lactide-co-glycolide); SLNs, solid lipid nanoparticles; ↑, increase; ↓, decrease.

Quercetin

Quercetin (3,3',4',5'-7-pentahydroxy flavone) is a polyphenolic compound found in onion, apple, berries, tea and brassica vegetables, as well as many nuts, seeds, barks, flowers and leaves [79]. The underlying mechanisms of quercetin as a potential natural anti-cancer agent include apoptosis induction, suppression of proliferation and metastasis [80]. Anti-proliferative activities of quercetin have been demonstrated in breast [81], leukemia [82], colon [83], squamous cell [84], endometrial [85], gastric [86] and non-small cell lung [87] cancer cells. Despite its promising anti-cancer activities, the clinical application of quercetin in cancer treatment is restricted due to its low level of aqueous solubility and tumor-targeting specificity [47].

Many quercetin-loaded nanoparticles have been developed to increase the bioavailability and biopotency of quercetin to improve its anti-cancer activities [95-99] (Table 3). The quercetin loaded nanoliposomes enhanced the cytotoxic effects on C6 glioma cells and induced necrotic death of those cells [88]. Rezaei-Sadabady *et al* reported that liposomes significantly improved aqueous solubility and bioavailability of quercetin [89]. Its antioxidant capacity and effectiveness for removing reactive oxygen species (ROS) was increased and the cellular uptake by human MCF-7 breast cancer cells was enhanced when encapsulating quercetin in a liposomal delivery system [90]. Nano-quercetin compared to free quercetin significantly decreased the viability of A549 lung cancer cells *in vitro*. Nano-quercetin and free quercetin at 100 μmol·L^{-1} decreased the cell viability of A549 lung cancer cells by 60% and 100%, respectively [98]. *In vivo* anti-cancer efficacy of nanomicellar quercetin was evaluated in human A549 lung tumor xenograft mice received 30 mg/kg body weight of free or nanomicellar quercetin via oral gavage three times per week for three weeks [91]. At the end of this study, nanomicellar quercetin had more than 1.5-fold higher tumor growth inhibition than free quercetin. Importantly, nanomicellar quercetin treatment did not result in weight loss [91]. Chemically modified polymeric nanocapsules as quercetin carriers were described and characterized for the passive and active targeting to cancer cells and tumors [92]. The active targeting to HeLa cells or mice IGROV-1 tumor expressing folate receptors was achieved by conjugating folic acid to PLGA utilizing PEG as a spacer in polymeric nanocapsules [92]. Biocompatible quercetin encapsulated NLCs (Q-NLCs), which consist of natural lipid, vitamin E acetate, surfactant and free quercetin, were successfully synthesized in our group by using a novel phase inversion-based process method [89]. The aqueous solubility of quercetin was improved more than 1 000 times when using NLCs as carriers for quercetin. Compared to free quercetin and void NLCs, Q-NLCs significantly enhanced cytotoxicity and apoptosis of MCF-7 and MDA-MB-231 breast cancer cells, and increased cellular uptake of quercetin by those cells. Importantly, void NLCs and phosphate buffered saline treatments showed similar low cytotoxicity to those cells [89].

In summary, nanotechnology may overcome many characteristic limitations of quercetin and enhance its anti-cancer activities.

Table 3 The characteristics and anti-cancer activities of quercetin nanoparticles

Nanoparticle type	Nanoparticles size/nm	Target Yes/No	Experiment model/dose	Cancer type	Main Outcome	Year & Ref.
Folic acid-PEG-PLGA	150	Yes (Folic acid as a target ligand)	*In vitro*: HeLa Cells; *In vivo* intravenous administration in HeLa or IGROV-1 tumor-bearing mice	Cervical and ovarian cancer	↑Anti-cancer activities ↑Target specificity to cancer cells and tumors	2014 [92]
NLCs	Around 30	No	MCF-7 and MDA-MB-231 breast cancer cells treated with 0–50 μmol·L^{-1} of free quercetin or nano-quercetin	Breast cancer	↑Apoptosis ↑Aqueous solubility improved by 1 000 folds ↓ Viability of cancer cells	2014 [90]
Liposomes	Around 100	No	MCF-7 breast cancer cells treated with 0− 50 μmol·L^{-1} of free quercetin or nano-quercetin	Breast cancer	↑Cellular uptake ↑Antioxidant activities	2014 [89]
Nanoliposomes	62−192	No	C6 glioma cell treated with 0–400 μmol·L^{-1} of free quercetin or nano-quercetin	C6 glioma cells	↓Viability of C6 glioma cells ↑Necrotic cell death	2012 [88]
Nanomicelles	Around 16	No	Lung tumor mice were given 30 mg/kg BW of free quercetin or nano-quercetin *via* oral gavage 3 times per week for 3 weeks	Lung cancer	↑Stability ↓Viability of cancer cells ↓Tumor size	2012 [91]

BW, body weight; NLCs, Nanostructured lipid carriers; PEG, poly(ethylene glycerol); PLGA, poly (lactide-co-glycolide); ↑, increase; ↓, decrease.

Resveratrol

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a natural polyphenolic compound produced by the enzyme stilbene synthase in response to environmental stress like sunlight, heavy metals, fungal infection, injuries or UV irradiation [93], and acts as a natural inhibitor of cell proliferation [94]. Resveratrol is abundant in grapes, red wine, raspberries, mulberries, blueberries and knotweed. Resveratrol has two isomeric forms: *cis*- and *trans*-resveratrol, which can convert to each other by yeast during fermentation or UV irradiation. One gram of fresh grape skin contains about 50 to 100 μg of *trans*-resveratrol, which contributes to high resveratrol concentrations in red wine and grape juice [95].

Many *in vitro* and animal studies have demonstrated that resveratrol has anti-cancer activities [96-97]. However, the evidence is inconclusive regarding the effectiveness for

cancer prevention or treatment in human studies. The major problems are its low level of bioavailability, aqueous solubility and target specificity to cancer cells. In order to overcome those limitations and to enhance anti-cancer activities, scientists have developed many biocompatible and biodegradable nanoparticles including liposomes, albumin nanoparticles, SLNs, NLCs, chitosan nanoparticles and gelatin nanoparticles [98-99] (Table 4). Nano-resveratrol compared to free resveratrol resulted in higher cellular uptake of resveratrol by NCI-H460 lung cancer cells, which was associated with greater DNA damage and apoptotic incidence [100]. The underlying mechanisms for nano-resveratrol included cancer cell apoptosis include the down-regulation of Bcl-2 and NF-κB expression and the up-regulation of Bax, p53, p21 and caspase-3 expression [101]. Other studies also reported that nano-resveratrol activated apoptotic pathways in human lung A549/cDDP cancer cells [99], ovarian carcinoma cells [102], MCF-7 breast cancer cells [103] and PC-3, DU-145, and LNCaP prostate cancer cells [104]. Nano-resveratrol compared to free resveratrol also significantly decreased prostatic cancer incidence [98] and colon cancer growth [105] in animal studies.

Bu L *et al* modified the surface of nanoparticles by two ligands, avidin (A) and biotin (B) to make targeted nanoparticles to enhance target specificity of resveratrol-loaded chitosan nanoparticles to hepatic carcinoma [106]. Targeted compared to non-targeted resveratrol loaded nanoparticles had the higher liver targeting index and more potent cytotoxicity against HepG2 cells.

Overall, biocompatible and biodegradable nanoparticles can enhance aqueous solubility, stability and bioavailability of resveratrol and increase its anti-cancer activities.

Table 4 The characteristics and anti-cancer activities of resveratrol nanoparticles

Nanoparticle type	Nanoparticles size/nm	Target Yes/No	Experiment model/dose	Cancer type	Main Outcome	Year & Ref.
Gelatin nanoparticles	294	No	NCI-H460 cells treated with 5−10 mg·mL^{-1} of free resveratrol or nano-resveratrol	Lung cancer	↑Cell cycle arrest ↑Anti-cancer efficacy	2015 [101]
PEG–PLA nanoparticles	120−260	No	*In vitro:* CT26 colon cancer cells treated with 20 and 40 μmol·L^{-1} of free resveratrol or nano- resveratrol *In vivo:* CT26 tumor bearing mice treated with 100 mg/kg BW of void nanoparticles and nano- resveratrol twice per week for 3 weeks	Colon cancer	↓CT26 colon cancer cell number ↑Apoptotic cell death ↓Tumor size	2015 [105]
SLNs	Around 250	No	Female Wistar rats treated with 5 mg/kg BW of free resveratrol and nano-resveratrol through intra-peritoneal injection	Brain cancer	↑Brain resveratrol con-centrations	2014 [107]
Chitosan nanoparticles	200−300	Yes (avidin and biotin used as target ligands)	*In vitro:* HepG2 cells treated with 0−6 μg·mL^{-1} of free resveratrol or nano-resveratrol *In vivo:* Kunming mice treated with 0.25 mg/kg BW of free resveratrol or nano-resveratrol via tail vein injection	Hepatic carcinoma	↑Target specificity to liver ↑Anti-cancer activity ↑Cytotoxicity	2013 [106]
Bovine serum albumin nanoparticles	N/A	No	The tumor-bearing mice treated with 50−200 mg/kg BW of free resveratrol or nano- resveratrol once a week for 4 weeks	Ovarian cancer	↓Tumor growth ↑Apoptotic and necrotic characteristics in the tumor tissues	2010 [102]

BW, body weight; N/A, not applicable; PEG, poly(ethylene glycerol); PLA, poly (D,L-lactide); SLNs, solid lipid nanoparticles; ↑, increase; ↓, decrease.

Genistein

Genistein (4,5,7-trihydroxyisoflavone, GEN) has been identified as the main isoflavone found in soybeans enriched foods. Genistein intake is high in some Asian countries, especially Japan and China [108]. Some studies have demonstrated that GEN has anti-cancer activities [108-110]. However, only several papers investigated anti-cancer properties of GEN nanoparticles (GEN-NP).

In Table 5, Mendes *et al* [111] treated Ehrlich Ascites Tumor (EAT) bearing Swiss mice using multicompartimental nanoparticles containing paclitaxel (PTX) and GEN, and found 0.2 mg/kg body weight/day of PTX resulted in 11% of tumor inhibition, but 12 mg/kg body weight/day of GEN caused 44% of tumor inhibition. De Zampieri *et al* [112] found that GEN-nanoparticles resulted in a higher amount of GEN accumulation in deeper layers of the skin and GEN-nanoparticles might be a promising nanocarrier system for skin delivery of GEN and skin cancer prevention and treatment. Other studies have demonstrated that nano-GEN demonstrated a sustained release manner, increased GEN uptake by cancer cells and enhanced anti-cancer activities of GEN in different cancer cells [113, 114].

Future perspectives

Although nanoparticles can enhance anti-cancer activities of phytochemicals reported in many *in vitro* and *in vivo* studies, there are still some concerns regarding their cost, safety, side-effects and long-term toxicity. Hence, a new subdiscipline of nanotechnology called nanotoxicology has emerged [18, 115-116]. Even though the oral administration route is preferred [18], most nanoencapsulated phytochemicals,

Table 5 The characteristics and anti-cancer activities of genistein (GEN) nanoparticles

Nanoparticle Type	Nanoparticle size/nm	Target Yes/No	Experiment Model/Dose	Cancer Type	Main Outcome	Year & Ref.
Polymeric nanocapsules	Around 160	No	Ehrlich Ascites Tumor (EAT)-bearing mice treated with free GEN or nano-GEN	Ehrlich Ascites Tumor	↑ Tumor inhibition	2014 [111]
PLA nanoparticles	Around 140	No	Franz-type diffusion cells with porcine ear skin treated with free GEN or nano-GEN	Skin Cancer	↑ Skin delivery of GEN.	2013 [112]
NLCs	Around 110	No	Prostate cancer cells treated with nano-GEN	Prostate Cancer	↑ Sustained release ↓ Cell viability	2013 [62]
Liposomes	Around 161	No	PC-3 and OVCAR-3 cancer cells treated with 0−80 μmol·L^{-1} of free GEN or nano-GEN	Ovarian and Prostate Carcinomas	↑ Cellular delivery ↑ Cytotoxicity ↑ Apoptosis	2013 [113]
Lipidic micelles and nanoemulsions	20−200	Target	CT26 and HepG2 cells treated with 0−400 μmol·L^{-1} of free GEN or nano-GEN	Hepatic and Colon Carcinomas	↑ Cytotoxicity ↑ Anti-cancer activities	2013 [114]

NLCs, Nanostructured lipid carriers; PLA, poly (D,L-lactide); ↑, increase; ↓, decrease.

especially tumor-targeting nanoparticles, are delivered to animals mainly by intravenous, subcutaneous, intraperitoneal administration. Due to gastrointestinal digestion and degradation, developing nano-delivery systems for the oral administration of phytochemicals remains challenging [115]. Improving cancer cell- or tumor-targeting efficiency and specificity of phytochemical nanoparticles is a promising and emerging research area, because they can increase anti-cancer efficacy and effectiveness of phytochemicals, and lower their toxicity and side effects to normal cells and tissues. After finishing cell and animal studies, prospective clinical studies are needed to evaluate their anti-cancer activities and measure toxicity and side effects in humans[14, 117]. Furthermore, there is an urgent need to finalize occupational and environmental safety guidelines for synthesizing and using nanoparticles by the government [118].

Conclusions

In conclusion, liposomes, nanoemulsions, micelles, SLNs, NLCs and PLGA nanoparticles are commonly used biocompatible and biodegradable nanoparticles and used as phytochemical carriers. Nanotechnology has a great potential for improving solubility, stability, bioavailability and anti-cancer activities of EGCG, curcumin, quercetin, resveratrol and genistein. More studies are required to optimize formulations of nanoparticles for enhancing their anti-cancer effectiveness and efficacy and tumor-targeting specificity, and lowering their cost, side-effects, and toxicity.

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