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Smart Natural Polyphenols Nanoprodrug Conjugates

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ABSTRACT

Green chemoprevention utilizes natural polyphenols and their derivatives. Polyphenols such as curcumins, resveratrol, green tea extract, luteolin, soybeans, and pomegranate inhibit the growth of multiple cancer cell lines including the breast, prostate, thyroid, head and neck, ovarian, and cervical cancer via inhibition of IKK and suppression of NFκB activity. These compounds are also responsible for the immune response effect and they can be used as prebiotics and in the treatment of cancer or viral diseases.

Both hydrophilic and hydrophobic cargos can be incorporated into the surface polymer layer. Cargo louding depends on electrostatic attraction or repulsion, the type and composition of surface particle material, pores, etc. The electrostatic attractions between particle surface and prodrug favour the drug loadings in contrast to the repulsion. In the case of silica nanoparticles the additional drug loading is expected due NPs' pores. The loading capacity of NPs could be further enhanced by utilizing polymer gatekeeping for the entrapment of prodrugs. The prodrug-decorated particles displayed significantly higher cytotoxicity than did free prodrug.

ABBREVIATION

5-FU: 5-fluorouracil; CAC: Critical Aggregation Concentration; CAPE: Caffeic Acid Phenethyl Ester; CMC: Critical Micelle Concentration; COX2: Cyclooxygenase; CSC: Cancer Stem Cell; CTL: Cytotoxic Tlymphocytes; Cur: Curcumin; DF: Dietary Fiber; DTT: Dithiothreitol; EC: Epicatechin; ECG: Epicatechin-3-Gallate; EGC: Epigallocatechin; EGCG: Epigallocatechin 3-Gallate; EPR: Enhanced Permeation Retention; ERK1/2: Extracellular signal-Regulated Kinase 1/2; GADD 153: G1 Growth Arrest and DNA Damage-inducible gene; Gemc: Gemcitabine; GSH: Glutathione; JNK: c-Jun N-terminal protein Kinase; MAPK: Mitogen-Activated Protein Kinase; mPEG-PLA: methoxy poly(ethylene glycol)-poly(lactic acid); MTX: Methotrexate; NanoCur: Cur-PNPs nanoconjugate; NFκB: Nuclear Factor κB; NK: Natural Killers; NPs: Nanoparticles; PC-3 cells: Prostate Cancer Cells; PEI: Polyethyleneimine; PMVE-MA: Poly(Methyl Vinyl Ether-Alt-Maleic Acid); PNP: Polymer Nanoparticle; PSiNPs: 0Porous Silica Nanoparticles; ROS: Reactive Oxygen Species; SNP: Single Nucleotide Polymorphism; -SS-: Disulphide Bond; VEGF: Vascular Endothelial Growth Factor

CANCER

Modern science has proved the functional role of plants in the treatment of diseases, and this has been evident through the incorporation of modern drug therapy for many of the drugs of plant origin which have already been used for thousands of years by

the ancient civilizations. Greek and Roman therapeutic practices were preserved through the writings of Hippocrates (e.g., De herbis et curis), especially Galen (e.g., Therapeutics), which were also as the headwaters for western medicine later [1].

Interestingly in recent years, there has been an evolution in the use of medicinal plants due to the side effects of synthetic drugs, lack of new pharmaceutical remedies for microbial resistance, many chronic diseases, as well as the unprecedented investment in medicinal research and development. Additionally, the high cost of medicines and the inability of many developing countries to purchase modern drugs have forced them to search for products in the form of medicinal plants that are proved to be cheap, efficient, safe, and culturally acceptable [2].

Cancer in its simplified definition is uncontrolled growth and division of genetically unstable cells. Cancer hold many biological capabilities that can be recognized as hallmarks of cancer which are genomic instability, sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, dysregulated metabolism, tumor promoting inflammation, microenvironment, etc. [3]. Some of them are typical for the conventional diseases due to which the detection time of carcinogenesis process is postponed. However, the success rate of surviving cancer largely depends on the early detection. Sadly, that is usually not the case where cancer is often diagnosed at advanced stages. Cancer could be either hereditary (5-10% of all cancers), familial (approximately 15% of all cancers) or sporadic (70-75% of all cancers). However, cancer is initiated by mutation in either tumor suppressor genes or oncogenes. In the exposing era of new generation of sequencing and molecular profiling, the role of genetic alterations including microdeletions, micro-insertions, cytogenetic abnormalities, DNA methylation, Single Nucleotide Polymorphism (SNP), single nucleotide substitutions have been more identified. The tools of genetics have been used to systematically examine how cancers arise. Insight into the genetic and molecular horizon of cancer pathogenesis will provide a new opportunity for identification of potential prognostic, diagnostic and drug target biomarkers [4].

One of the risk factors which can initiate a cancer process is the formation of free radicals in the cells. Lipoxygenase, xanthine oxidase, and Cyclooxygenase (COX2) are the three important enzymes that are responsible for generating the Reactive Oxygen Species (ROS) in the cells [5]. ROS generated by a,b and g- radiations are able to break carbon, nitrogen chemical bonds. These radicals induce the DNA damage, strand breakage, and ionization which may lead to defects in the genes involved in proliferation and cell signaling pathways that are crucial for tumor growth and cancer progression. Antioxidants are known to inhibit the polymer degradation. A protective role in preventing cellular damage due to oxidation plays some natural compounds. Among them, for example, polyphenols have the ability to reduce the activity of xanthine oxidase and COX2, which finally decrease the level of reactive oxygen level in the cell. But sometimes the natural prodrugs increase the amount of reactive oxygen species to induce several apoptotic signaling pathways, including Mitogen-Activated Protein Kinase (MAPK), extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal protein Kinase (JNK) and Akt, as well as calcium-dependent pathways. So these different effects of aformementioned compounds, whether it increases or decreases the cellular reactive oxygen species content, depend upon the cell conditions and types. For example, berberine induces reactive oxygen species production in prostate cancer cells, but not in the normal epithelial cells. Berberine induces reactive oxygen species production, apoptosis and inhibits cell proliferation in various cell lines derived from breast, lung, colon, and liver cancer by different pathways: F as dependent pathway and p53-dependent pathway [6].

As the research progressed in the field of molecular biology, the scientific community gained deeper understanding of the process of carcinogenesis. The process of carcinogenesis can be divided into three phases, i.e., initiation, promotion and progression. As the carcinogen enters the body, it either gets activated through various metabolic pathways or gets detoxified within the human body. If activated through metabolic mechanisms, these carcinogenic agents increase the oxidative stress and thus cause DNA damage; this leads to the initiation of carcinogenesis. During promotion phase the initiated cells start proliferating actively resulting in

accumulation of preneoplastic cells. During progression stage preneoplastic cells start invading and spreading to various parts of the body. This is an irreversible phase [7,8].

NATURAL POLYPHENOLS PRODRUGS

Green chemoprevention is a term used to coin interventions that utilize derivatives of natural compounds such as curcumins, resveratrol, green tea extract, luteolin, soybeans, and pomegranate. All these aforementioned plant products have antioxidant properties secondary to the inherent polyphenols present in them [9]. Many natural products affect Nuclear Factor Kappa B (NFκB) activity, either directly or indirectly, and due to their low toxicity, they are good candidates for chemoprevention.

Polyphenol is a subgroup of phytochemicals which inhibit cancer development through different strategies, constrain the intracellular oncoprotein signaling along with the PKC/RAS/MPK or p13-kinase/AKT pathways, downregulate the pro-proliferative anti-apoptotic transcription factors NFkB and AP-1 (activator protein 1), and upregulate the carcinogen-detoxifying enzymes and DNA repair proteins [10]. Different studies show that drinking ten cups of green tea per day delay cancer onset between 4 and 7 years. Curcumin is one of many phenolic secondary metabolites isolated from rhizome of Curcuma longa, used in traditional Asian cuisine. The powder of this rhizome is known as turmeric preparation. According to the published data, curcumin might be related to the low rates of colorectal, lung, and prostate cancers in India. This compound is still in clinical trials to prove its effectiveness and safety [11]. In the laboratory, curcumin inhibits NFκB activity in ovarian, breast, head and neck, lung, and prostate cancer cell lines [12]. In the clinic, curcumin is well tolerated and has some biological activity in phase II pancreatic cancer trials [13].

Curcumin (diferuloylmethane) is a yellow polyphenol found in turmeric of the ginger family (Zingiberaceae). It has been part of folk medicine for centuries due to possessing many health benefits, including being potent analgesic, antibacterial, antiviral, antiparasitic, antioxidant, and anti-inflammatory agent. Thus, it may be able to target several hallmarks of cancer. Jaiswal et al. [14] demonstrated a dose-dependent inhibitory effect of curcumin on colon cancer cell lines. They suggested that apoptosis and cell-cycle arrest of HCT-116 cells after curcumin treatment is mediated by caspase-3-induced cleavage of β-catenin. In addition, decreasing transactivation of β-catenin/Tcf-Lef was found to lead to the inactivation of Wnt/β--catenin pathway. Moreover, treatment of HCT-116 cell line with curcumin decreased levels of c-Myc protein, a key mediator of gene regulation and differentiation that maintains self-renewal properties of embryonic stem cells. Alternatively, Ryu et al. [15] offered another mechanism of curcumin inhibitory effect on Wnt/β-catenin pathway where curcumin derivatives were able to down regulate p300, a transcriptional coactivator of Wnt/β-catenin pathway. In addition, Ryu and his group reported the suppressive effect of curcumin derivatives on β-catenin transcription that was activated by Wnt3A conditioned-medium.

Resveratrol is a polyphenol derived from red grapes and berries. Like curcumin, a significant amount of in vitro data has shown that resveratrol inhibits the growth of multiple cancer cell lines including the breast, prostate, thyroid, head and neck, ovarian, and cervical. Resveratrol appears to regulate cancer cell growth by inhibition of IKK and suppression of NFκB activity [12]. Resveratrol also inhibits IKK activity in animal models of colitis. Data from in vivo preclinical trials shows that resveratrol can prevent tumor growth or carcinogenesis in several cancer sites. Clinical trials to date, which are mostly risk assessment studies, show that resveratrol-rich products may be beneficial for cancer prevention [16].

A further chemopreventive agent that regulates NFκB activity is Epigallocatechin 3-Gallate (EGCG), the major polyphenol found in green tea. Green tea polyphenols were reported to delay the primary tumor incidence. A mouse model of prostate cancer correlated them with a substantial reduction in NFκB activity. The data from human studies suggest that green tea polyphenols may provide greater efficacy for preventing prostate cancer than for treating cancer patients. There are multiple ongoing clinical trials to access the effects of green tea on prostate, lung, bladder, esophageal, breast, and head and neck cancer. Two other natural products known to inhibit NFκB activity, dietary isothiocyanates, from watercress, and sulforaphanes, from crucifiers, are also being evaluated in clinical trials against various cancers. Other natural products known to block NFκB activity include catechins, silymarin, Caffeic Acid Phenethyl Ester (CAPE), sanguinarine, anethole, emodin, piceatannol, capsaicin, ursolic acid, betulinic acid,

flavopiridol, oleandrin, parthenolide, kambekaurin, and freeze-dried black raspberries [12,17].

In vitro and in vivo tests have shown the anticancer action of green tea from Camellia sinensis and one of its main constituents: epigallocatechin-3-gallate in several different tumor cell models [18]. Green tea is found to have potent antioxidants called catechins. These catechins are four types and recognized to be the active component to prevent carcinogenesis [19]. The four catechins are Epicatechin (EC), Epicatechin-3-Gallate (ECG), Epigallocatechin (EGC), and EGCG. One of the greatest advantages of green tea is that it is nontoxic and is outlined as one of the primary, secondary, and tertiary oral cancer prevention strategies. Green tea has a synergic effect when combined with synthetic molecular targeting chemoprevention such as COX-2 [19]. For example, the EGCG and sulindac (nonsteroidal anti-inflammatory drug) exhibit synergic anticancer effect that triggers cell apoptosis and upregulates the G1 growth arrest and DNA damage-inducible gene (GADD 153) [20]. A study revealed a potential of ~70% reduction in tumor volume after being treated with EGCG green tea catechin with NSAIDs [21].

Quercetin was intensively studied as the most abundant flavonoids in food. In vitro, quercetin inhibited the proliferation of oral cancer cell lines showing enzymatic inhibition of the thymidylate synthase, a key enzyme expressed by oral cancer cells [22,23]. Apoptotic properties of quercetin were also explained by the modulation of the Bax/ Bcl-2 (B-cell chronic lymphocytic 2-like protein 2) ratio in oral cancer cells. Quercetin was also associated with the prevention of oral cancer cell migration in several ways including the inhibiting of the expression of metalloprotease 2 and metalloprotease. The effect of quercetin extends beyond prevention; quercetin showed some cancer therapeutic potential. The combination of quercetin with cisplatin (a chemotherapeutic drug) induced apoptosis and decreased the cells' resistance to the chemotherapeutic medication.

The anticancerous compounds present in the Tinospora cordifolia are berberine and palmatine. Berberine is present in the stem whereas palmatine is present in both root and stem [24]. The berberine and palmatine both are protoberberine alkaloids that show anticancerous activity. Palmatine is a close structural analogue of berberine that both bear the same tetracyclic structure (7,8,13,13-tetrahydro 9,10 dimethoxy berberinium) but differ in the nature of substitutes at position 2,3 on the benzo ring, where it is dimethoxy for palmatine and methylene dioxy for berberine [25].

NANOPRODRUG CONJUGATES

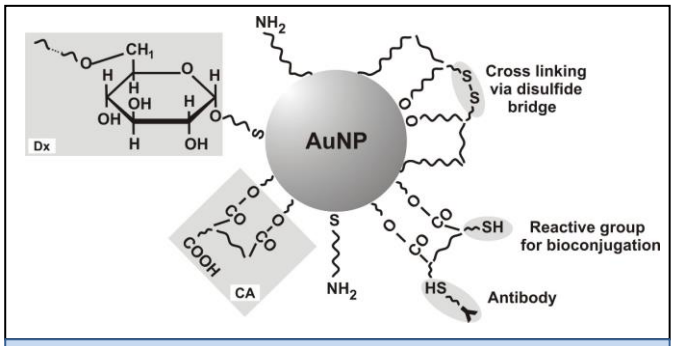

Figure 1: Schematics of nanoparticle modification - adsorption and chemisorption of ligands on the particle surface. Metal (gold, silver, etc.), silica, polymer and composite nanoparticles modified with Dextran (Dx), Citric Acid (CA), 2,3-dimercaptosuccinic acid and other capping agents (prodrugs such as polyphenols (Cur), etc.).

Nanotechnology is well equipped to provide a remarkable natural system for drug delivery mediated through nanocarriers/Nanoparticles (NPs). In some cases, the natural prodrug itself can work as its own carrier as it can be formulated into nanoscale dimensions. An assembly between the nanocarrier and the (pro) drug tend to maximize the benefits over risk ratio. Furthermore, this assembly enhances the solubility as well as the bioavailability of the prodrug. It also reduces the rate of drug degradation rate within the body and control the drug release, thus allowing to more sustained release over specific time interval. In addition, drug delivery via NPs increases specificity as they deliver a specific cargo drug to an exact location without compromising the drug dose concentration through crossing the body natural barriers. NP-mediated drug delivery also reduces toxicity (and thus side effects) as much lower doses of drugs are now utilized (Figure 1) [26]. The capping agent interact with the subnanoparticles via physi- and chemisorption due to which they can block the particle aggregation as well. They can be modified with compounds carrying functional groups, such as Cyano (-CN), thiol (-SH) and amino (-NH2) groups, known for their high affinity for some particles (Figure 1). Prodrugs having these

functional groups can be used as capping agents for nanoparticles. The nanoscale particles, nanoparticles, except of nanocarrier, are often used for a wide range of applications. Most of those applications make use of the fact that NP's high surface area to mass ratio provides a large functional surface which is able to bind, adsorb, and carry other compounds. NPs are commonly classified based on their origins as the source material can be biological (such as phospholipids, lipids, lactic acid, etc.) or chemical (such as carbon nanotubes and dots, silica, gold, silver, and other metals) [27].

Nontraditional features (chemical and physical) of nonmaterial's result from the small size and account for their particle size. Chemical properties include total chemical composition, mixing state (internal/external), surface composition, electrochemistry, and oxidation state while number and mass concentration, size, surface area, total mass, morphology, and optical properties are essential physical properties [28]. Particle size distribution helps determining the biodistribution and the retention of nanoparticle within target tissues [29]. The particle size inversely affects the surface area and hence drug carrying capacity. Surface charge (zeta potential) is the electrostatic potential of nanoparticle which regulates its diffusive characteristics and interaction with surrounding species in solution including cell membranes. This property is associated with the nanoparticle dispersion stability and the particle surface morphology, both of which are crucial for evaluating the NP's stability and surface adsorption [30]. Generally, dispersions (nanoparticles) are stabilized by two mechanisms: steric and electrostatic. In the former NPs are neutral that is, their zeta potential ranges between -10 mV and +10 mV. However, in the latter NPs are either cationic or strongly anionic and their zeta potential is greater than +30 mV or less than -30 mV, respectively [31].

To develop successful nanomedicine prodrugs, stability of the NPs is an essence. These colloids should be stable and capable of retaining the drug in the bloodstream until they properly release the drug in target tissues. Instability of polymer dispersions is often reflected by aggregation, degradation, or unintended (pro) drug release. Techniques such as determination of critical aggregation/micelle concentration (CAC/CMC), determination of low critical solution temperature, cloud point, gel permeation chromatography, dispersion viscosity, forster resonance energy transfer technique, etc. are often adopted to investigate nanoparticle's stability in vitro before ultimately testing it out in vivo. The CMC, for example, provides the data on the free/complexed stabilizer ratio in the bloodstream [29].

Herbal nanomedicine provides less toxic and cheaper novel therapeutics. Curcumin's health-promoting benefits are well known. Especially, it acts as an anti-cancer agent, as prevention of tumor initiation, promotion, metastasis, and angiogenesis in numerous cancer types [32]. However, the low water-solubility/natural therapeutics's poor bioavailability disfavour their clinical applications. For example, a daily 3.6 g oral curcumin administrated for approximately 4 months resulted in 10 nM concentration of curcumin in the peripheral blood (clinical trials on advanced colon cancer patients concluded curcumin's poor bioavailability). Hence, to overcome this challenge, nanomedicine was employed. The nanoparticles are able to bind, adsorb, and carry curcumin prodrugs. The reduced particle and the increased surface area significantly increase both curcumin's solubility and bioavailability. Bisht and his colleagues [33] have fabricated Curcumin (Cur) decorated polymeric nanoparticles. Their pharmacokinetic studies confirmed a remarkable increase in the bioavailability of curcumin as Cur-loaded NPs in plasma and tissues when compared to the free curcumin. In addition, the administrated Cur-PNPs Nanoconjugate (NanoCur) solution to pancreatic cancer tissues exhibited significant primary tumor growth inhibition. The synergistic effects was observed in Nano Curc-Gemc (gemcitabine) conjugate which strongly enhanced the tumor growth inhibition more effectively compared to either NanoCurc alone or NanoGemc alone. Similar data were also obtained on other Nano Natural Prodrugs indicating their neuroprotective abilities, and breast cancer chemoprevention activities [34].

Paclitaxel-decorated albumin-coated nanoparticle formulation is effective to inhibit the cancer progression [35]. Nowadays its sale controls 50–60% of the total paclitaxel market in the USA. Cabazitaxel, is another semisynthetic taxane anticancer agent, combined with prednisone provides effective nanoprodrug system. Since then, other technologies have been advanced to improve solubility, facilitate administration, and enhance the pharmacological profile and bioavailability.

A wide range of nanoparticles including synthetic hydrophobic polymer, quatum dots, noble metal and magnetic nanoparticles, etc. can be used to increase the therapeutic index of natural prodrugs. Assemblies of amphiphilic water-soluble (bio) polymers can directly adsorb prodrugs but this is not the case with hydrophobic synthetic nanoparticles, inorganic nanoparticles, carbon nanoparticles, whose surface is not able to adsorb hydrophilic agents. For example, magnetite nanoparticles are first functionalized or loaded with dextran. The surface dextran coating was futher fastened to particle by crosslinking with crocin. These developed NPs were then tested out both in vitro and in vivo where mice were injected with carcinogenic agent to induce liver cancer. The developed crocin-coated NPs exhibited improved anti-tumorigenic activities compared to free crocin in both in vitro and in vivo systems. To improve particle's stability, Rahaiee and his group [36] have encapsulated crocin into chitosan-decorated sodium alginate nanoparticles. The fabricated NPs with the zeta potential ca -33 mV were relatively stable under such, otherwise, unfavorable environmental conditions. However, the electrostatic repulsion between the negatively charged cell membranes and prodrug nanoconjugates might somewhat disfavour the specific cell targeting.

Anti-Cancer Stem Cell (CSC) agents via Nano Prodrugs are set up to deliver the prodrugs. This approach will boast the bioavailability and the biological activity. The NPs may accumulate either passively due to Enhanced Permeation Retention (EPR) by exploiting the abnormal vascular nature of tumors or positively due to specific targeting where NPs can be decorated with antibodies against CSCs [37]. Developing NPs with optimum size and surface charge to target CSCs can effectively reach the CSCs niches and eradicate them, providing the perfect opportunity to focus on nanotechnological approach for CSCs treatment.

The drug loading can be increased by the choose of particle type such as porous silica nanoparticles (PSiNPs). PSiNPs are able to encapsulate both hydrophilic and hydrophobic cargos via their pores. Owing to their large pore volume, PSiNPs inherently possess greater loading capacity compared to other carriers. The loading capacity of PSiNPs could be further enhanced by utilizing polymer gatekeeping for the entrapment of hydrophobic drugs [38]. Consecutive drug loading process which increases the intermolecular interactions can also lead to improved loading of the drugs [39]. An increase in the drug feeding ratio was also found to have a profound influence on the loading capacity of PSiNPs [40]. The pore volume of PSiNPs is the major factor which dictates the loading of the drug.

The strong cellular association of the functional polymers (such as Polyethyleneimine (PEI), poly(methyl vinyl ether-alt-maleic acid) (PMVE-MA),etc.)-functionalized silica nanoparticles can be attributed to the high dispersibility of these NPs as well as bioadhesive properties of the polymers [41]. In line with these results, there have been evidences of high uptake of negatively charged particles in different cell lines [42], despite the unfavorable interaction between them and the negatively charged cell membranes [43].

The unique property of some drugs can enhance the probability of their interaction with the functional (amine, carboxyl, etc.) groups of the polymers conjugated to the SiNPs and, consequently, increase their loading degree in the PSiNPs. For example, the loading degree of methotrexate (MTX) in the bare PSiNPs was ~6.4%, whereas PEI and PMVE-MA conjugation improved the MTX loading degree to ~12.6 and ~14.0%, respectively [44]. This suggests that the polymer conjugation increase the loading of the drug due to the more interactions of the drug's functional groups with the free amine and carboxyl groups of the polymer-conjugated PSiNPs.

Biodegradable methoxy poly (ethylene glycol)-poly(lactic acid) (mPEG-PLA) nanoparticles was utilized as the amphiphilic polymer to model the curcumin delivery via a disulphide bond ((mPEG-PLA-SS-Cur)) [45]. The redox-responsive mPEG-PLA-SS-Cur conjugates self-assemble into micellar nanoparticles. The surface charge analysis showed that the sample exhibited a negative zeta potential at ca. -10.6 mV (mPEG-PLA-SS-Cur). The hydrodynamic size of the redox-liable sample determined by DLS was ~115.6 nm. The presence of DTT in the receiver fluid is to mimic the role of Glutathione (GSH) in the cells. DTT usually broke down the disulfide bond more efficiently than GSH and had been widely used to test the redox-sensitive systems in vitro [46]. The IC50 of mPEG-PLA-SS-Cur micelles was ~ 18.5 (μg mL-1). In contrast the IC50 of free curcumin was ~ 13.2 (μg mL-1). The redox-sensitive curcumin-decorated

particles displayed significantly higher cytotoxicity than did free curcumin.

CONCLUSION

Nontraditional features of nanomaterials result from the small size and account for their large surface area. Nanoparticles (NPs) can be easily functionalized and then adsorb and bind various bioagents/drugs. Natural prodrugs act as an anti-cancer agent, as prevention of tumor initiation, promotion, metastasis, and angiogenesis in numerous cancer types. Herbal medicine provides less toxic and cheaper novel therapeutics. A wide range of surface-modified nanoparticles including polymer, quatum dots, noble metal and magnetic nanoparticles, etc. can be used to increase the therapeutic index of natural prodrugs.

The prodrug-decorated nanoparticles colloids should be stable and capable of retaining the drug in the bloodstream until they properly release the drug in target tissues. The hydrophilic agent-decorated hydrophobic nanoparticles may accumulate either passively due to enhanced permeation retention by exploiting the abnormal vascular nature of tumors or positively due specific targeting where NPs can be decorated with antibodies against cancer tissues.

The drug loading is mainly based on the adsorptive properties of nature- or synthetic nanoparticles. Both hydrophilic and hydrophobic cargos can be incorporated into the surface polymer layer. The electrostatic attractions between particle surface and prodrug favours the drug loadings. The additional drug loading in some nanoparticles is expected due NPs' pores. The loading capacity of NPs could be further enhanced by utilizing polymer gatekeeping for the entrapment of prodrugs. The prodrug-decorated particles displayed significantly higher cytotoxicity than did free prodrugs.

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