



Nano-Delivery Carriers for Enhanced Bioavailability of Antitumor Phytochemicals

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Abstract

Phytochemicals, the plant derived natural products or bioactive compounds, exhibit immense diversity regarding origin and mechanism of action. The recent two decades have witnessed renaissance in anti-cancer therapeutics stressing identification of anti-neoplastic or anti-cancer properties of different phytochemicals/plant nutraceuticals. However, the available formulations of these phytochemicals exhibit pharmacological limitations such as low water solubility and reduced bioavailability. These aspects can be possibly improved by developing nano-enabled formulations of these phytochemicals. Various nano-scale delivery vehicles which include branched globular polymeric particles (dendrimers), unilamellar micelles, double layered liposomes, and other zero-dimensional nanomaterials have been developed to address the low water solubility and poor uptake issues. The phytochemical of interest can be encapsulated, embedded, or adsorbed on these nano-scale carriers. The nano-scale dimensions of these engineered delivery vehicles could help enhance the stability of water dispersed formulations. Further, the nano-size enables easy infiltration to cancer cells at rates higher than the non-nano-formulations of the same anti-cancer phytochemical thereby reducing the dosage required to achieve effective anti-cancer action. The amenability to multiple surface functionalization of these nano-delivery vehicles can ensure decoration with ligands that can lead to targeted delivery of the phytochemical to cancer cells leading to decreased

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cyto-toxicity to normal tissues. This manuscript describes the various types of phytochemical payloaded nano-carriers for targeted or site-specific delivery of active anti-cancer chemical(s) to reduce undesirable side effects of chemotherapeutic agents on application in cancer subjects.

Keywords

Anti-cancer drug · Bioactive compounds · Nano-carriers · Nanoparticles · Natural products

8.1 Introduction

Cancer has emerged as the second most dreaded cause of human deaths claiming every one in six individuals globally. Cancer is characterized by rapid and uncontrolled growth of abnormal cells exhibiting omission of the contact inhibition phenomena followed by invasion of adjoining tissues and other visceral organs of the body leading to metastasis and ultimately death [1]. International Agency for Research on Cancer (IARC) through its World Cancer Report (2014) has predicted an upsurge in the reported cancer cases to 25 million by the year 2035. In 2018, 9.6 million deaths have been reported due to cancer with the under-developed and developing countries being the prima foci accounting for nearly 70% of the cancer related deaths. Due to expensive treatment options and post-treatment patient care costs, the economic impact of cancer is immense. In 2010, approximately US\$ 1.16 trillion was the estimated gross annual economic cost of cancer [2]. Cancer Prevention and Control through an Integrated Approach (WHA70.12), a resolution passed by WHO in 2017 aims to accelerate designing strategies; conventional, alternative, and advanced, to reduce premature mortality due to cancer.

8.2 Use of Phytochemicals for Treatment of Cancer

Use of products of natural origin as remedies has been practiced since ancient time. Various ancient scriptures like *Charaka Samhita* from India and *Wu Shi Er Bing Fang* from China include illustrative documentation of more than 200 natural products of therapeutic relevance. *Ben Cao Gang Mu* published in sixteenth century documented more than 1000 natural bioactive agents [3]. Early nineteenth century marked the isolation of morphine from *Opium* plant by a German pharmacist, Friedrich Serturmer, and since then it has been widely applied in the medical field as anesthesia [4]. A plethora of natural bioactive compounds have since been isolated including alkaloids, glycosides, and flavonoids. Plant based pharmaceuticals have been extensively studied as treatment options for cancer and currently over 60% of the total anti-cancer drugs in use have been derived from plants [5]. For example, curcumin, a polyphenol extracted from *Curcuma longa* (turmeric), possesses remarkable anti-cancer properties [6]. Similar anti-cancer potential has also been reported for secondary metabolites derived from actinobacteria [7]. However, it is earlier to obtain scaled up quantities of the plant

based anticancer [8]. The non-edible or even edible tissues/organs of diverse plant genera including fruits, vegetables, and medicinal plants contain anti-neoplastic phytochemicals. Relative safety of these drugs and their easy availability makes these phytochemicals a promising alternative treatment for cancer.

Common anti-neoplastic phytochemicals include original compounds or their derivatives namely taxanes, podophyllotoxin, vinca alkaloids, camptothecin, anthracyclines, and many others. The action mechanism of these drugs is not just limited to anti-oxidative and immune-modulatory roles, but they have been observed to actively target cancer related metabolic pathways [7]. Genistein, a plant based estrogen homolog obtained from legumes, is being tested for its therapeutic effects against cancers of pancreas, kidneys, rectum, and ovaries [9]. Likewise, lycopene (beta carotenoid), a lipophilic hydrocarbon isolated from tomatoes, papaya, watermelon, and carrots can prevent Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) mediated DNA damage. Apart from the preventative effects, lycopene also directly affects cancer related metabolic pathways in prostate cancer [10]. The phytochemicals with more targeted effect on cancer such as paclitaxel isolated from Pacific yew, *Taxus brevifolia* acts as a mitotic inhibitor and thus can prevent cancer cell division by stabilizing the microtubules. Both paclitaxel and its derivative compound, docetaxel, have been approved by FDA to be used as anti-cancer drugs against breast, lung, and ovarian cancers [11].

Plant based anti-cancer drugs, therefore, show a range of possibilities, from their anti-oxidative and immune-modulating activities to directly acting as anti-mitotic agents. Their low toxicity, higher tolerance, and easy availability signify their role and potential in cancer therapy. However, their use has been limited by some factors discussed below.

8.3 Phytochemical Use: Possible Limitations

Plant based drugs encounter many limitations in terms of their pharmacological activities. One of the major challenges is low solubility of phytochemicals which hinders development of drug formulation. Such poorly formulated drugs exhibit inferior blood circulation. Some of these drugs may show low gastrointestinal absorption, while others get quickly metabolized and does not remain effective for longer durations. When the drugs have faster clearance rate, higher doses have to be applied at frequent intervals, making the process very tedious (Table 8.1).

Table 8.1 Lists of the some common phytochemicals and their limitations when applied as anti-cancer drugs

Phytochemical or its derivative	Limitation	Reference
Paclitaxel, docetaxel	Low solubility and poor penetration	[12, 13]
Taxol and taxotere	Hypersensitivity, toxicity	[14]
Cremophor®EL	Hepatic disposition	[15]
Vincristine	Short terminal elimination half-life	[16]
Docetaxel and paclitaxel	Multi-drug resistance	[17]

8.4 Nano-Enabled Approaches for Phytochemical Application: Can Nanotechnology Help Circumvent Possible Pharmacological Limitations of Phytochemicals?

As discussed in Sect. 8.3, the pharmacological limitations of phytochemicals need to be addressed by use of appropriate delivery systems. One of the convergent disciplines, Nanomedicine—the nanotechnological applications for biomedicine, has gained tremendous interest involving use of nanomaterials as novel drug delivery vehicles. Likewise, nano-enabled devices can ensure improved targeting, high efficacy, and decreased side effects to patient under treatment. The phytochemicals can be loaded on to nano-carriers to achieve improved solubility, better stability, bioavailability, and target specificity on application. The bio-safety of the nano-vehicles can be ensured if these carriers can be fabricated or encapsulated using biodegradable compounds [18, 19].

One of the main characters of cancerous tissue is angiogenesis. Tumors generate defective and leaky blood vessels that continuously leak fluids into interstitial spaces. From here, the fluids are drained by poorly formed lymphatic system. By targeting this phenomenon, a nano-sized drug carrier can be applied that can easily invade the tumor and accumulate there. This is called Enhanced Permeability and Retention effect or EPR effect [14]. The challenge of multi-drug resistance in tumor cells can also be averted by modifying the surface of the nano-carriers through chemical functionalization. These modifications will alter the interactions between drug carriers and cell membranes [20]. Some of the FDA approved nano-carrier based delivery systems are discussed in the following text.

8.4.1 Antibodies Drug Conjugation (ADC)

The conventional unconjugated anti-cancer drugs exhibit high cellular toxicity causing death of normal body cells besides the tumor cells due to low specificity to target the cancerous tissue alone. Therefore, one of the novel biopharmaceutical drugs, the Antibody drug conjugation (ADC), which combine the specific immunogenicity feature of monoclonal antibodies with the higher toxicity of the drug molecule can effectively ensure improved targeting of the cancer cells [21]. The monoclonal antibody(ies) is/are raised against specific surface antigens produced and secreted by the tumor cells. These antigenic moieties exist on the outer end of the cell membrane of tumor cell. Monoclonal antibodies against these specific tumor cell surface antigens are then attached to highly potent anti-cancer agents or drug molecules via a chemical linker domain. The size of the final bioconjugate remains in nano-scale dimensions; however, ADCs are considered to be non-nano anti-cancer agents. The common anti-cancer agents used include two types of cytotoxins viz., DNA damaging agents and microtubule inhibitors. Microtubule inhibitors can be further of two types: maytansinoids and auristatins. Maytansinoids are derivatives of maytansine, a phytochemical isolated from African shrub *Maytenus serrata* [22, 23]. Selection of suitable cytotoxin, linkers, and target antibodies are key components to be considered while designing ADCs.

8.4.2 Nanoparticles

Nanoparticle is a term used in nanopharmaceutics to identify zero-dimensional particles falling in size range of 10–1000 nm. The drug of interest can either be embedded or coated in these nanoparticles. Chemically, the origin of nanoparticles is diverse and include metal/ non-metal oxides/sulfides/nitrides, polymers, and carbon nanomaterials. Among these nano-delivery vehicles, the polymeric nanoparticles represent a very diverse group including the nanoparticles derived or formulated from biodegradable high molecular weight polymer compounds (e.g., poly(lactic-co-glycolic acid (PLGA) nanoparticles), and natural polymers (e.g., albumin nanoparticles, gelatin cellulose nanoparticles, and chitosan nanoparticles) [24]. These nanoparticles have high storage stability. PGLA and poly lactic acid (PLA) based nanoparticles have been synthesized using formulation of ginsenoside and luteolin, and have been found to be effective against lung cancer cells [25, 26].

8.4.2.1 Liposomes

Liposome-polymeric nanoparticles were the first well-explored and prudently commercialized nano-based drug delivery system used in cancer therapeutics [27]. Structurally, liposomes are comprised of a hydrophobic shell and hydrophilic core. Therefore, the polar drugs can be loaded in the core while the non-polar drugs can be loaded in the shell. The properties of a liposome can be suitably altered by simply modifying the composition of the phospholipid bilayer. A commercial preparation under the name Lipusu[®] has been developed as a more stable and less toxic substitute for Taxol[®] using liposome based delivery. Lipusu[®] showed higher retention in tumor tissues in mice compared to Taxol[®] [28].

8.4.2.2 Micelles

Micelles are the smallest nano-vehicles (~10 to 400 nm) that can be utilized for efficient drug delivery. These are formed when the concentration of a surfactant gets higher than critical micelle concentration (CMC). Polymeric micelles are being increasingly used for the development of several drug formulations. These micelles can be prepared by polymerization of the natural organic or synthetic compounds (monomer). Most commonly used compounds include the hydrophilic monomer PEG while the core-forming compounds include poly(propyleneoxide), poly(caprolactone), poly(D, L-lactic acid), and poly(L-aspartic acid) compounds [29]. An example of polymeric micelle formulation of a known anti-cancer drug containing Paclitaxel, Genexol-PM, has a size dimension in nano-regime (24 nm). In clinical trials for cancer, this drug has shown higher inhibition of tumor cell growth compared to Taxol [24].

8.4.2.3 Dendrimers

Dendrimers are nanoscopic, radially symmetric large molecular weight polymer molecules that exhibit extensive branched structure [30]. The peripheral groups present on the branched structure can be easily modified to help in binding of

hydrophobic drug molecules [30]. The distinct physical-chemical and structural properties of dendrimers can be very useful for their role as 'Excipients' [31]. Dendrimers of gallic acid with polyamidoamine (PAMAM) have been formulated and found to be active against breast cancer cell lines [32].

8.4.2.4 Metal Nanoparticles

Metal nanoparticles can be synthesized using green nanotechnology approaches where solutions of desired metals are treated with suitable phytochemical solution. Phenolic compound rich extracts of plant *Albizia adianthifolia* were used to synthesize silver nanoparticles (AgNPs). Similarly, stem latex of *Euphorbia nivulia* plant have been used to generate AgNPs. Both of these nanoparticles showed anti-cancer effects against A-549 cancer cells [33]. Gold, copper, and titanium based nanoparticles have been synthesized and tried at pre-clinical levels for their effects against cancer cells.

Shape of nanoparticles is also an important aspect ensuring efficacy and uptake of the loaded anti-cancer drug. It has been demonstrated that nano-rods have 1.6-fold higher uptake by cancer cells compared to nano-spheres [34]. While larger particles are cleared quickly from the body, smaller ones are harder to filter. For EPR, 5–100 nm size has been found to be most suitable.

Application of nanoparticles is limited due to unavailability of substantial information regarding their toxic effects. The small size that makes nanoparticles suitable for therapeutic use can also create problems inside the body. The nanoparticles can cross barriers and get accumulated in vital organs like heart, lungs, brain, and liver. This can lead to complications such as systemic failure or inactivation of immune cells, inflammation, edema, etc. [35].

8.4.2.5 Carbon Nanotubes

Carbon nanotubes are hollow, rolled cylindrical tubes derived from single C-atom sheets, graphene. These long and thin cylinders exhibit remarkable mechanical and physical properties. The walls of these nanotubes can be functionalized with desired drug [36]. Multi-walled carbon nanotubes functionalized by PTX have been shown to be effective against HeLa cell lines [37].

8.5 Conclusion

Plant based anti-cancer drugs have a unique potential for use in cancer therapy. However, the efficacy of these phytochemicals get limited due to issues regarding the stability of the formulation and its bioavailability. Therefore, among the other alternatives that have been explored for addressing these issues, use of nano-inspired or -enabled phytochemical delivery systems can possibly circumvent the pharmacological limitations of these natural products. Nano-carriers can improve the solubility due to decrease in size dimensions, bioavailability, and uptake owing to larger surface area on nano-scaling, target specificity, and kinetics of these drugs besides

lowering the toxicity of these drugs [38]. Further, analysis of advanced toxicity studies can ensure the safer administration of these drugs.

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Conflict of Interest The authors declare no conflict of interest.

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