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Review

Nanoparticle formulations to enhance tumor targeting of poorly soluble polyphenols with potential anticancer properties

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ABSTRACT

Polyphenols have been extensively studied for their relevant anticancer activity. Quite often however their instability, extensive metabolization, low bioavailability and poor solubility limit their application in cancer prevention and therapy. Formulation in nanoparticles has been widely proposed as a means to overcome these limits, maximize localization and specific activity at tumor site. The present review is intended as an update of literature regarding nanoparticulate carriers aimed to deliver polyphenols to the cancer site. Three molecules were chosen, all of which were hydrophobic and poorly soluble, representative of different polyphenol classes: quercetin (QT) among the flavonoid group, curcumin (CUR) as representative of curcuminoids, and resveratrol (RSV) among the stilbenes. In particular, nanoparticulate systems suitable for poorly soluble drugs will be described and attention will be paid to characteristics designed to improve tumor targeting, specific delivery and interaction with tumor cells.

1. Introduction

A lot of recent literature indicates polyphenols as effective anticancer agents. This activity seems to be supported by the number of strong biological actions of this class of molecules, mainly related to the defense role in which they are involved in plants [1]. A role has also been recognized in modulating the immune system, reducing angiogenesis, attenuating adhesiveness and invasiveness of cancer cells and reducing inflammation response [2].

Moreover, the generally recognized relationship between polyphenol anti-cancer activity and their involvement in cell redox balance is especially important. Polyphenols are well known as strong ROS scavenging anti-oxidant agents and this is quite often related to protection towards cancer occurrence. It is known that faster ROS production occurs in cancer cells due to abnormal regulation of redox processes. On the other hand, the role of polyphenols in anti-cancer therapy is also related to the apoptosis of cancer cells due to a pro-oxidant effect. It has been reported that some catechins, for example, are not only able to quench free radical species but are also characterized by pro-oxidant effects which are responsible for the induction of protective endogenous antioxidant systems in normal tissues and for the induction of apoptosis in tumor cells [3]. These opposing activities are, however, not in contrast. The prevalence either of anti-oxidant action and chemopreventive effect or of pro-oxidant action and apoptotic effect depends on the cancer cell environment, acute or chronic treatment, and polyphenol concentration. Chemopreventive prophylactic activity can be usually envisaged at low concentrations, while therapeutic effects can be obtained at high levels [4]. The effect of redox environment of the tumor can be the reason for the specificity described in polyphenols that interact with cancer cells in a different way than with healthy ones [4,1]. It is necessary, however, to consider that intermediate ROS concentrations present risks of toxic cancerogenic effects, as illustrated in Fig. 1 [4].

These considerations place attention on the importance of a good knowledge of the polyphenol dose-effect relationship. This represents a relevant concern for a class of molecules whose bioavailability barriers can strongly limit the occurrence of useful concentrations at the target tissue or organ. An extensive review regarding polyphenol bioavailability has put in evidence the complexity of the scenario for such a broad class of different molecules [5]. They greatly differ not only for gastrointestinal absorption but also for pre-systemic metabolization, which often involves degradation by intestinal flora and conjugation in small intestine and liver. The differences in chemical structure also affect the affinity of polyphenols for albumin and the partitioning between aqueous environment and cellular membranes. Tissue uptake behavior is even less clear, with some evidence of regional selectivity that seems to suggest a not always linear correlation between plasma and tissue concentrations [5].

Furthermore, quite often polyphenols, besides low bioavailability, also present stability concerns, as in the case of epigallocatechin gallate

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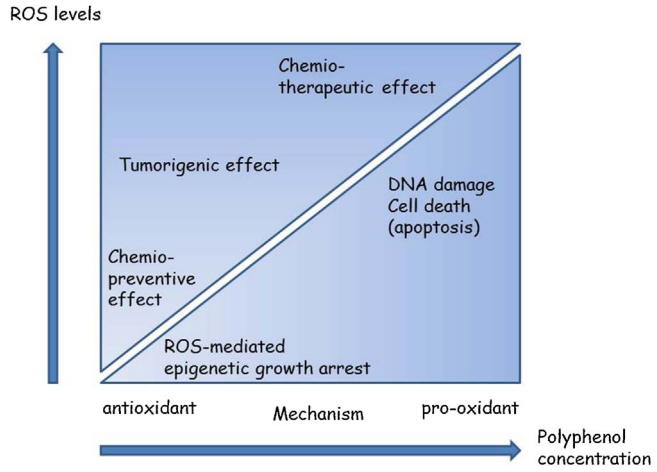

Fig 1. Cellular redox status and polyphenol anti-cancer activity (modified from [4]).

(EGCG); although stable at acidic pH values, it degrades at the physiological pH of 7.4. Other polyphenols, largely studied for their promising anticancer activity, present poor solubility together with bioavailability and stability problems. Hydrophobicity and low solubility involve formulation and administration concerns and can further decrease absorption and therefore efficacy.

In this scenario, a correct choice of carrier formulations, able not only to increase polyphenol concentration by colloidal solubilization but also to improve absorption and stability and to target cancer cells, is of paramount importance to achieve the best safety to effect ratios. Nanoparticulate carriers (NPs) have been largely described to this aim.

2. Nanoparticles in cancer therapy

In recent years, NPs have been widely studied to improve selective delivery of drugs to the tumor site. Selectivity can optimize dose regimen and reduce systemic toxicity that represents one of the most relevant limits of anticancer drugs. NPs achieve this objective thanks to their ability to accumulate in the solid tumor mass by targeting mechanisms that can be either passive or active and to specifically trigger internalization inside tumor cells. These properties have made NPs a unique tool for cancer therapy, imaging, and a combination of the two in the more recent theranostic approach [6–8]. Passive targeting relies on a phenomenon discovered in 1986, known as Enhanced Permeability and Retention (EPR) effect [9–11]. This effect is based on abnormal features of blood vessels in solid tumors, where enhanced angiogenesis leads to a rapid proliferation of irregular vessels characterized by anomalous fenestrations between endothelial capillary cells, larger than in normal tissues. The resultant effect is higher extravasation of macromolecules and NPs. However, the lymphatic drainage is less efficient in tumors, resulting in prolonged retention of NPs inside the tumor mass and increased concentrations up to 10–50 fold with respect to normal tissues [12,13].

For NPs, both extravasation and retention depend on dimensions. Dimensions that are too large impair extravasation, which in the case of most tumors is considered good for carriers smaller than 200 nm. In less permeable tumors, such as human pancreatic adenocarcinoma, nanocarriers should be smaller than 70 nm to achieve optimal extravasation. On the other hand, retention is reduced for too small NPs, again limiting accumulation inside the tumor tissue [14–16].

Charge and surface properties are among the NP characteristics crucial for successful concentration in tumors by EPR effect. After intravascular administration, circulating NPs are usually prone to opsonization and reticuloendothelial system (RES) recognition, which strongly limits their blood half-life and possibility to arrive in the proximity of the tumor. Escape to RES and consequent increase in circulation time is generally greater for neutrally charged particles in comparison with positively charged ones and for hydrophilic surfaces with respect to hydrophobic ones [13,17,18].

Carrier dimensions and surface properties are also generally recognized as especially relevant factors for the interaction with the cell surface and consequent cell internalization [19,20]. The advent of the NP era is changing the idea that a strict relationship exists between drug dissolution and drug absorption, since for nanocarriers not only phagocytosis, but also endocytosis becomes a useful pathway for cell penetration and possibly translocation or localization in different subcellular organelles. This behavior can raise concerns about toxicity effects that have been observed as a consequence of NPs interaction with cells, opening a new area of nanotoxicology [19]. The same mechanisms, however, also open new perspectives for improvement of efficacy and selectivity in cancer therapy. The cell uptake of nanoparticles by endocytosis assumes particular importance for those molecules, such as some polyphenols, whose potential anti-cancer activity is limited by poor solubility.

While phagocytosis mainly occurs in immune system cells such as neutrophils and macrophages, endocytosis characterizes every type of cell. Three endocytic mechanisms can usually be identified, that is clathrin mediated, caveolae-mediated, and clathrin/caveolin-independent ones [21,22]. Research is still in progress to completely understand the carrier characteristics that are responsible for the prevalence of one of these ways and for the consequent intracellular fate. So far, even for this aspect, some evidence proves the relevance of particle dimension. Better internalization due to clathrin-mediated endocytosis occurs for NPs under 200 nm, whereas lower dimensions, under 100 nm, seem to be generally required to activate caveolae-mediated endocytosis [23]. Adsorption of NPs at the cell surface is the first step for internalization. This explains why the positive charge of NPs can enhance internalization by inducing uptake through endocytosis, thanks to electrostatic interaction with the negatively charged cell surface [24,22].

Ligand decorated NPs represent an ulterior generation of carriers intended to improve localization inside the tumor by means of active targeting. It is quite clear nowadays that, although some successes have been registered, this strategy is often quite disappointing in terms of drug accumulation at the tumor target [17]. However, it determines relevant advantages due to the specific interaction of the carrier with cell receptors that, in turn, causes a triggering of cell internalization and results in enriched cellular uptake [25,26]. The number of potential ligands proposed for the design of tumor targeted NPs is quite high and is still increasing, encompassing monoclonal antibodies, aptamers, proteins and peptides, carbohydrates and small molecules such as folic acid. The strategy relies on the over-expression in tumor cells of specific receptors [26,27], so that the concentration in these cells results much higher than in normal ones. Folate receptor is a glycosylphosphatidylinositol-linked protein over-expressed in epithelial, ovarian, cervical, breast, lung, kidney, colorectal, and brain tumors. This receptor is largely proposed in literature to target drug release by activating caveolae-mediated endocytosis [28,29]. Besides the choice of ligand and the NP characteristics already mentioned as relevant for EPR effect, ligand concentration on NP surface and surface modification in terms of hydrophobicity and charge can also play a decisive role in the therapeutic success of ligand decorated NPs [30]. More recently, a new generation of NPs has been developed, that does not rely only on passive retention or on endogenous tumor ligands, but is based on “environment-responsive” properties. In these cases, environmental conditions specifically induced by the presence of the tumor, trigger the drug release, thus maximizing tumor delivery. One of the approaches most commonly found in literature relies on the lower pH in proximity of tumors with respect to normal tissues, due to acidic metabolites accumulated in hypoxia conditions [17].

In all these cases it is quite important to verify that the release occurs only at the tumor site in response to different stimuli, and that polyphenols are retained inside the NPs during their circulation in