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Research review paper

Advances in phytochemical delivery systems for improved anticancer activity

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ABSTRACT

Natural compounds have significant anticancer pharmacological activities, but often suffer from low bioavailability and selectivity that limit therapeutic use. The present work critically analyzes the latest advances on drug delivery systems designed to enhance pharmacokinetics, targeting, cellular uptake and efficacy of anticancer phytoconstituents. Various phytochemicals, including flavonoids, resveratrol, celastrol, curcumin, berberine and camptothecins, carried by liposomes, nanoparticles, nanoemulsions and films showed promising results. Strategies to avoid drug metabolism, overcome physiological barriers and achieve higher concentration at cancer sites through skin, buccal, nasal, vaginal, pulmonary and colon targeted delivery are presented. Current limitations, challenges and future research directions are also discussed.

1. Introduction

Plants have been invaluable sources for the discovery of anticancer drugs, such as paclitaxel (taxol) and vinca alkaloids, and various liposomal and nanoparticles (NPs) delivery systems of doxorubicin and paclitaxel have been approved in recent years broadening the use of these classic chemotherapeutics (Farooqi et al., 2018; Newman and Cragg, 2016; Xie et al., 2016).

Several other bioactive phytochemicals, such as berberine, camptothecins, catechins, celastrol, curcumin, quercetin and resveratrol, show promising anticancer pharmacological activities (Anand et al., 2008; Bishayee, 2009; Jang et al., 1997; Kabary et al., 2018; Kashyap et al., 2018; Khan et al., 2016; Singh et al., 2011; Wang et al., 2017). However, various physicochemical and pharmacokinetic limitations, such as low water solubility, bioavailability and deficient targeting, restrain the use of those compounds in clinics, and many drug delivery systems are being conceived to enhance their anticancer efficacy.

Several groups have reviewed developments in phytochemical delivery systems for cancer therapy, but those reviews were mainly focused on specific types of delivery systems (Mouhid et al., 2017) or compounds, e.g. polyphenols (Davatgaran-Taghipour et al., 2017). Xie et al. (2016) have provided a summary of the properties and clinical development of paclitaxel and vincristine nanoformulations already in clinical use. However, a comprehensive review covering various delivery strategies of compounds in preclinical stage is not available to the best of our knowledge. Moreover, connecting the observed efficacies of novel formulations with bioactivity of phytochemicals may offer new treatment modalities.

The aims of the present review were to summarize and critically analyze the recent development of delivery systems for promising anticancer phytochemicals, identify the delivery systems and therapeutic applications supported by experimental evidence, and discuss the opportunities for further improvement.

2. Methodology for literature search and study selection

The literature search was performed using PubMed, Scopus and ScienceDirect databases for studies (January 2015–March 2019), combining a detailed description of preparation and characterization of the delivery system with an *in vivo* evaluation of the anticancer activity. An initial group of compounds with higher therapeutic potential was identified using the keywords “cancer” AND “in vivo” (OR “animal” OR “rat”) AND “delivery system” (OR “nano” OR “controlled release”) AND “phytochemical” (OR several other designations, e.g. flavonoid or curcumin, to embrace phytochemical diversity). However, delivery systems lacking a safety evaluation were excluded at this first stage. Afterwards, specific searches for additional studies with those compounds or similar delivery systems were performed to display the recent

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advances in the field. Studies comparing the efficacy of carried *versus* free drug or elucidating the mechanism of action of the phytochemical deserved a particular attention. In the case of applications less explored (i.e., few published studies) or when useful to better interpret *in vivo* results, other studies with compounds already used in clinics or *in vitro* data are also discussed. Studies published in English language only were included in this review. Conference abstracts, book chapters and unpublished results were excluded.

3. Anticancer phytochemicals and their modes of action

3.1. Diversity of plant-derived anticancer compounds

The chemopreventive potential of phytochemicals gained a great attention since epidemiological data indicated that consumption of plant-based foods is associated with a reduced risk of cancer (Amin et al., 2009; Gullett et al., 2010). Medicinal and dietary plant-derived bioactive compounds can have a low cost, be well tolerated, and countless *in vitro* and *in vivo* studies encourage the development of natural compounds for prevention and treatment of major diseases, such as cancer (Asensi et al., 2011; Bishayee et al., 2012; Bishayee and Sethi, 2016; Gullett et al., 2010; Kaur et al., 2018; Liu et al., 2015; Mahbub et al., 2015; Wong et al., 2016).

Alkaloids, terpenoids, polyphenols and organosulfur compounds are the most promising groups of phytochemicals for cancer prevention and therapy (Kaur et al., 2018; Krajka-Kuźniak et al., 2015; Rothwell et al., 2017; Thoppil and Bishayee, 2011). Camptothecin is a naturally occurring quinoline alkaloid extracted from the tree *Camptotheca acuminata* that inhibits DNA topoisomerase I. This enzyme is also inhibited by the semisynthetic derivatives and accepted drugs topotecan and irinotecan (and the active metabolite 7-ethyl-10-hydroxycamptothecin). The terpenoid celastrol exhibits antitumor effects through a range of biological actions, including regulation of several transcription factors, proteases, angiogenesis, cell cycle and apoptotic processes (Shanmugam et al., 2016; Kashyap et al., 2018; Zhang et al., 2019). Genistein is the soy phytoestrogen most studied for cancer therapies, frequently in combination with standard chemotherapy, and results are expected from clinical trials for prostate and lung cancer (Section 6). This isoflavone inhibits the growth of hormone-dependent cancers, affects redox homeostasis, and alters the expression of various estrogen receptors, tumor suppressors and transcription factors in cancer cells (Shanmugam et al., 2016; Pool et al., 2018). However, polyphenols and antioxidant phytochemicals in general don't have a definite therapeutic target and exhibit multifunctional actions that can contribute to their anticancer activity.

3.2. Antioxidant, anti-inflammatory and carcinogen-detoxifying actions

The antioxidant and anti-inflammatory actions of polyphenols, such as curcumin, epigallocatechin-3-gallate (EGCG) and resveratrol, have key roles against different stages of the carcinogenesis process and metastasis (Asensi et al., 2011; Bishayee, 2009; Gullett et al., 2010; Kasi et al., 2016; Mahbub et al., 2015; Sinha et al., 2017; Sznarkowska et al., 2017). Reactive oxygen species (ROS) and chronic inflammation combined with genetic alterations causing transcriptional reprogramming drives multistage carcinogenesis process, including initiation, promotion and progression (Jang et al., 1997; Kaur et al., 2018; Sznarkowska et al., 2017; Taniguchi and Karin, 2018). In these conditions, prevention of carcinogenesis by antioxidant and anti-inflammatory phytochemicals is associated with their ability to modulate oxidative stress and inflammatory signaling in healthy cells, decrease ROS production, mitigate damage to DNA and other cellular components, inhibit nuclear factor-κB (NF-κB) pathway, and activate nuclear factor erythroid 2–related factor 2 (Nrf2)-mediated antioxidant response (Gullett et al., 2010; Krajka-Kuźniak et al., 2015; Samadi et al., 2015; Suphim et al., 2010; Sznarkowska et al., 2017).

Inflammation has a critical role in the initiation of cancer and aberrantly activated NF-κB in tumor microenvironments induces the transcription of various pro-proliferative and anti-apoptotic genes, which supports the use of potent NF-κB suppressor phytochemicals, such as curcumin, resveratrol, lycopene, EGCG and genistein in cancer prevention and therapy (Gullett et al., 2010; Shanmugam et al., 2016; Taniguchi and Karin, 2018).

The inhibition of phase I xenobiotic metabolizing enzymes (e.g., cytochrome P450) implicated in carcinogen activation and the induction of phase II detoxifying and antioxidant enzymes by various phytochemicals are other important chemopreventive mechanisms, minimizing the window in which carcinogens are active (Asensi et al., 2011; Kaur et al., 2018). Several compounds including isothiocyanates, indoles and polyphenols, such as EGCG, protocatechuic and tannic acids, induce expression of phase II and antioxidant genes through the Nrf2 pathway (Jang et al., 1997; Krajka-Kuźniak et al., 2015; Lambert and Elias, 2010; Shanmugam et al., 2016). The redox-sensitive transcription factor Nrf2 can activate the expression of many antioxidant and detoxifying enzymes, such as heme oxygenase (HO), glutathione S-transferase (GST), superoxide dismutase (SOD) and catalase (Krajka-Kuźniak et al., 2015; Shanmugam et al., 2016).

In malignant cells, moderate or localized levels of ROS support proliferation and migration, therefore contributing for tumor development and metastasis. Consequently, phytochemicals inhibiting specific ROS sources, particularly at mitochondria, have been postulated as preventive and therapeutic anticancer strategies (Baran et al., 2014; Lagoa et al., 2011; Sznarkowska et al., 2017). The antiproliferative activity of genistein in free form and loaded into NPs was recently associated with the decrease in hydrogen peroxide production by human colon cancer cells (Pool et al., 2018). However, assessments of cellular overall redox status may display apparently contradictory effects as illustrated with inhibition of mitochondrial complex I (Baran et al., 2014; Branco et al., 2015), and current methods are still unable to discriminate the role of each ROS source.

Adaptations of redox homeostasis in tumor cells to the increased ROS that drive their growth and metastasis include enhancing the antioxidative defense systems by elevation of the basal Nrf2 program and glutathione synthesis (Branco et al., 2015; Mahbub et al., 2015; Sznarkowska et al., 2017). Suphim et al. (2010) also noticed the constitutive activity of NF-κB in cholangiocarcinoma cells. Excluding melanoma, many cancers were reported to have high levels of glutathione, which increases the antioxidant capacity of the cancerous cells, preventing oxidative stress and DNA damage, and inhibits cell death at different checkpoints, thus it is associated with resistance to treatments (Mahbub et al., 2015; Sznarkowska et al., 2017). Mahbub et al. (2015) showed that the basal glutathione levels of leukemia cells were inversely correlated with their sensitivity to doxorubicin, etoposide and polyphenol actions. Taking into account the dependence of cancer cells on ROS signaling, they might be more vulnerable to disturbance of the redox mechanisms than normal cells (Sznarkowska et al., 2017).

3.3. Regulation of various cell death pathways

Analogous to classical antineoplastic agents, such as doxorubicin or mitomycin C, several phytochemicals and their derivatives can also act as prooxidants, and this is the case of etoposide, camptothecins and polyphenols, which are able to increase the concentration of ROS, leading to cell death (Kaur et al., 2018; Suphim et al., 2010). The prooxidant behavior of polyphenols depends on several conditions, namely pH, levels of transition metal ions and O_2, but it seems evident that only high micromolar concentrations of polyphenols cause necrosis of cancer cells (Kaur et al., 2018; Lambert and Elias, 2010; Rengasamy et al., 2019; Suphim et al., 2010).

EGCG triggered apoptosis in various cancer models by increasing the ratio between Bax and Bcl-2 proteins (Khan et al., 2014; Siddiqui

et al., 2014). Bcl-2 and Bcl-xL are antiapoptotic proteins of the Bcl-2 family that inhibit mitochondrial release of cytochrome c by interacting with proapoptotic Bax and Bad, and are overexpressed in several malignancies (Maji et al., 2018). Gallic acid can induce apoptosis through both intrinsic and extrinsic pathways as supported by increases in initiator caspase-8 and caspase-9 in cancer cell lines (Kaur et al., 2018). The anticancer activity of celastrol has also been associated with the apoptosis-inducing capacity observed both *in vitro* and *in vivo*, mediated by different possible pathways, including upregulation of Bax and p53 and inhibition of Bcl-2 and NF-κB signaling (Aqil et al., 2016; Kashyap et al., 2018; Zhang et al., 2019). The NF-κB proteins promote cell proliferation and inhibit apoptosis by upregulating several genes, such as Bcl-2 and Bcl-xL, and antagonizing p53, hence the NF-κB regulatory network is an attractive antitumor target (Taniguchi and Karin, 2018). It is worth noting that nanoformulations increased the *in vivo* therapeutic efficacy of quercetin and EGCG to prevent the activation of NF-κβ and induce apoptosis in inflammation and cancer models (Chakraborty et al., 2012; Khan et al., 2014; Siddiqui et al., 2014).

Functional genomic studies are providing valuable perspectives to chemopreventive and anticancer actions of phytochemicals. In addition to the p53 pathway, resveratrol is commonly observed to alter the expression of genes involved in apoptosis, cell-cycle control and androgen pathway, whereas more intense studies on epigenetic remodeling and microRNA profiling are needed (Huminiecki and Horbańczuk, 2018; Xie et al., 2016).

Antiproliferative or apoptosis-inducing low concentrations of curcumin rapidly inhibited NF-κB signaling, decreased Bcl-xL levels, and caused partial depolarization of mitochondria, but without detectable oxidative stress (ROS and intracellular GSH levels) in cholangiocarcinoma *in vitro* (Suphim et al., 2010). The same concentrations of curcumin also increased the levels of proapoptotic proteins Bax and p53 related to cell death, whilst higher concentrations failed to alter these proteins, but caused ROS generation, mitochondrial collapse and massive cell death. Data from different studies with EGCG also associate its cytotoxicity to relatively high and prooxidant concentrations (Branco et al., 2015; Lambert and Elias, 2010), although activity of this catechin-type flavonoid against melanoma cells is apparently stronger than observed with curcumin (Fig. 1). While low concentrations are able to modulate cell signaling pathways implicated in carcinogenesis initiation and promotion as well as in migration and invasive phenotypes, the data on the cytotoxicity or antiproliferative effects of anticancer polyphenols generally indicate that relatively high concentrations

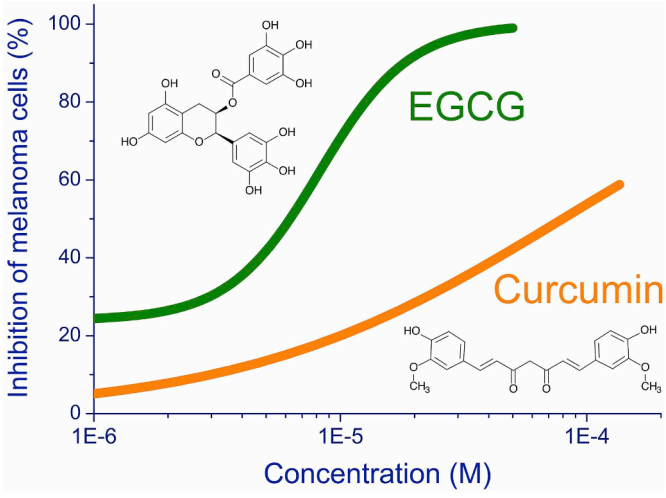

Fig. 1. Concentration-dependent bioactivity of epigallocatechin-3-gallate (EGCG) and curcumin against melanoma cells according to *in vitro* assessments. Data for EGCG (with permission from Silva et al., 2017) and curcumin cytotoxicity (with permission from Muddineti et al., 2017) were modeled using a Hill function.

are needed for effective antitumor activity. Since high doses of these compounds also raise safety concerns, for example hepatotoxicity of tea catechins (Kaur et al., 2018; Lambert and Elias, 2010; Rengasamy et al., 2019), targeted delivery to tumor sites and cancer cells is an obvious advantage.

Autophagy is a tightly regulated process involved in the degradation of damaged proteins and organelles in eukaryotic cells. The role of this process in cellular transformation and cancer progression is still debated (Sznarkowska et al., 2017). Various phytochemicals, including celastrol, curcumin, resveratrol, thymoquinone, γ-tocotrienol and ursolic acid, have been shown to induce autophagy in diverse cancer models (Deng et al., 2019). In addition to apoptosis and autophagy, other cell death modalities, such as non-canonical programmed cell death mechanisms, may provide efficient therapeutic outcomes (Diederich and Cerella, 2016).

3.4. Suppression of angiogenesis

Angiogenesis represents a critical hallmark of cancer enabling tumor progression, invasion and metastasis. Vascular endothelial growth factor (VEGF) is regarded as the most important pro-angiogenic growth factor as it triggers a cascade that induces the production of other factors that stimulate endothelial cell proliferation and formation of blood vessels. Hypoxia-inducible factor-1 (HIF-1) plays a pivotal role in the process of angiogenesis. HIF signaling mediates the expression of VEGF and becomes even more important if we consider that it is implicated in redox and metabolic remodeling in cancer cells (Kaur et al., 2018). Curcumin, EGCG and resveratrol have been shown to inhibit VEGF and HIF-1α expression and angiogenesis in various cancer models (Bishayee, 2009; Bishayee and Darvesh, 2012; Reuben et al., 2012). As discussed in Section 4, the potential of various delivery systems of phytochemicals to act as inhibitors of VEGF signaling and angiogenesis is increasingly investigated *in vivo*.

3.5. Synergistic effects of phytochemicals in combinations with classical antineoplastic agents

Combination of anticancer phytochemicals with standard chemotherapeutics is also an attractive hypothesis to reduce the therapeutic doses and toxicity concerns. An interesting study investigated the effects of combinations of polyphenols with doxorubicin or etoposide in lymphoid and myeloid leukemia cells (Mahbub et al., 2015). Combinations of low concentrations of doxorubicin or etoposide with the flavonoids, such as quercetin or apigenin, additively or synergistically reduced ATP levels, induced apoptosis (caspase-3, caspase-8 and caspase-9 activation) and increased S and/or G2/M phase cell cycle arrest in the malignant cell lines. It is remarkable that these combinations caused synergistic decreases in glutathione levels and increases in DNA damage, whereas the drugs alone had only moderate effects in these parameters. Other antioxidant polyphenols, namely emodin, *cis*-stilbene and rhein, were also studied in combination with chemotherapeutic drugs, but the anticancer results were less pronounced compared to flavonoids. The synergistic responses seemed dependent on activation of caspase-9 in particular, therefore on intrinsic apoptosis, yet these cell lines were p53 null, suggesting that the polyphenols affect a mitochondrial target in the cancer cells, as it was also hypothesized in the synergistic killing of Jurkat cells by menadione plus quercetin (Baran et al., 2014). Very importantly, the polyphenols alone or combined with doxorubicin or etoposide showed no toxicity to non-cancerous cells, and in most cases protected these cells from the adverse actions of chemotherapeutic agents (Mahbub et al., 2015).

Ameliorating adverse toxic effects of chemo- and radio-therapies is an additional pharmacological action of antioxidants and natural compounds (Asensi et al., 2011), and delivery systems may be useful to improve drug effects at the target tissues. The cardiotoxicity of chemotherapeutic agents has been the preferred experimental model to

evaluate this hypothesis, and studies with tumor-bearing mice showed that controlled release of thymoquinone and ginsenoside Rg3 could attenuate early markers of doxorubicin cardiotoxicity, such as heart lipid peroxidation and creatine kinase leakage (El-Ashmawy et al., 2017; Lagoa et al., 2014; Li et al., 2017).

Successful combinations can enhance the therapeutic efficiency of classical antineoplastic agents employing phytochemicals that inhibit multidrug resistance proteins, P-glycoprotein, breast cancer resistance protein, and other pathways underlying chemo- and radio-resistance of cancer cells (Asensi et al., 2011; Mercader and Pomilio, 2012). In this line, a micellar delivery system increased the capacity of curcumin to reduce drug efflux in drug-resistant cancer cells and its therapeutic efficacy *in vivo* (Muddineti et al., 2017). The chemopreventive and therapeutic potential of phytochemicals can be related to inhibition of diverse oncogenes and promotion of tumor suppressor genes. A particular attention has been paid to regulation of p53, and several compounds were reported to promote the expression of *TP53* and induce apoptosis in cancer cells (Gullett et al., 2010; Suphim et al., 2010).

4. Delivery systems for enhanced bioavailability and therapeutic efficacy of anticancer phytochemicals

In spite of the encouraging pharmacological activities of various phytochemicals, there are several difficulties in the clinical translation of the beneficial effects, especially with polyphenols. Many of those compounds have a poor aqueous solubility or cannot be effectively retained in circulation. Low gastrointestinal absorption, high metabolism, chemical degradation and rapid clearance can hamper pharmacological concentrations being achieved in blood or in tumor tissues. For example, resveratrol has a circulation half-life of several minutes (Jung et al., 2015), and flavonoids quercetin and EGCG usually achieve low micromolar concentrations in blood that can be enough for cytoprotective actions (Lagoa et al., 2017), but are considered inadequate for potent antitumor activity as discussed in Section 3.3 (Fig. 1).

Significant efforts have been devoted in developing delivery systems able to overcome these critical drawbacks by increasing the stability and solubility of the bioactive phytochemicals, improving oral bioavailability, and specifically targeting the tumor cells (Fig. 2). This section focuses on delivery systems designed for more usual routes of administration, such as oral or intravenous (IV), mostly tested *in vivo*, while systems for alternative administration routes are discussed in Section 5.

4.1. Delivery systems for enhanced bioavailability of phytochemicals

Table 1 presents recent delivery systems aimed at circumventing bioavailability limitations of anticancer phytochemicals. Lipid-based systems are very successful, presumably because they can increase the solubility and intestinal uptake of hydrophobic compounds.

In the case of resveratrol, different delivery systems have been envisioned and a recent review specifically concerning stilbenes is available (Peng et al., 2018a). Berberine has therapeutic interest for lymphoma and its lymphatic targeting offers the additional advantage of avoiding hepatic first-pass metabolism. With this in mind, Elsheikh et al. (2018) developed chylomicrons for oral lymphatic targeting that improved pharmacokinetic parameters in healthy rats (Table 1). In brief, chylomicrons loaded with berberine increased the rate and extent of drug absorption, with concentrations superior to 10 μg/mL being achieved in plasma (Elsheikh et al., 2018). Similar results were obtained with gingerol formulated in proliposomes which inhibited HepG2 cancer cells growth much more potently than the free phenolic compound (Wang et al., 2018a), and with celastrol in another lipid-based carrier tested in rabbits (Freag et al., 2018a).

Curcumin encapsulated in protein NPs exhibited impairment of the viability of MCF-7 cells and an increased oral bioavailability in rats (Liu et al., 2018a). However, μg/mL levels of the drug were maintained for some time by administering curcumin NPs coated with a lipid surfactant to animals (Peng et al., 2018b, 2018c).

Nanoformulations of curcumin, such as Lipocurc® (liposomal, IV), improve the bioavailability and offer potentially better treatment outcomes in cancer patients, but a fast systemic elimination of the drug upon termination of infusion remains problematic (Tsai et al., 2011; Greil et al., 2018; Bolger et al., 2019). Meriva® is a standardized phytosomal mixture of natural curcuminoids with lecithin that greatly increased oral absorption in humans and metabolization to the potent derivative demethoxycurcumin (Cuomo et al., 2011). Indeed, this formulation afforded various relevant effects in clinical studies: decrease of oxidative stress and systemic inflammation in patients with solid tumors receiving chemotherapy (Panahi et al., 2014a, 2014b), attenuation of several adverse effects of chemo- and radio-therapy (Belcaro et al., 2014), increase of response rate of pancreatic cancer patients to gemcitabine (Pastorelli et al., 2018), and partial immunomodulatory effects in leukemia and endometrial carcinoma patients (Golombick et al., 2015; Tuyaerts et al., 2019). In this later study, micromolar concentrations of curcuminoids and metabolites were detected in the plasma of the patients during supplementation (Tuyaerts

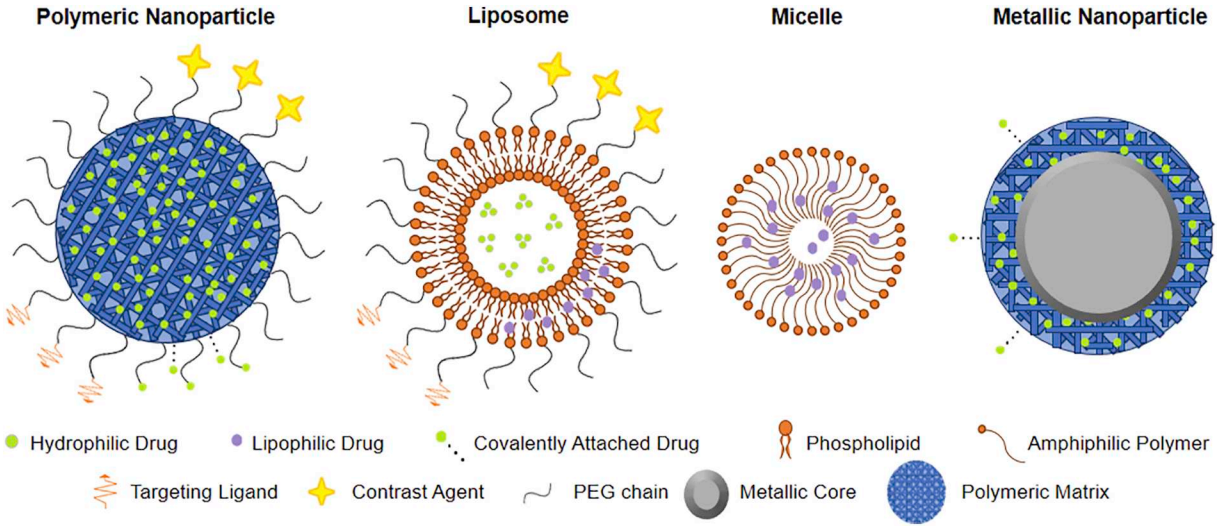

Fig. 2. Schematic representation of common delivery systems developed for anticancer phytochemicals. The phytochemical can be carried by the vehicle in different ways. Surface functionalization possibilities are illustrated in the polymeric nanoparticle and liposome. PEG, polyethylene glycol.

Table 1
Oral delivery systems for improved bioavailability of anticancer phytochemicals demonstrated in animal models.

Phytochemical	Carrier	Pharmacokinetic study	Reference
Berberine	Cremochylomicrons	C_{max}: 10.3 μg/mL *vs* 3.8 μg/mL for the free drug $t_{1/2}$: 4.15 h *vs* 0.57 h for the free drug MRT: 6.3 h *vs* 2.7 h for the free drug AUC: 35 μg·h·mL^{-1} *vs* 13 μg·h·mL^{-1} for the free drug	Elsheikh et al. (2018)
Celastrol	Phytosomes	C_{max}: 0.46 μg/mL *vs* 0.092 μg/mL for the free drug $t_{1/2}$: 10.1 h *vs* 0.96 h for the free drug MRT: 12.7 h *vs* 2.2 h for the free drug AUC: 0.768 μg·h·mL^{-1} *vs* 0.187 μg·h mL^{-1} for the free drug	Freag et al. (2018a)
Curcumin	NPs of rice bran albumin	C_{max}: 0.256 μg/mL *vs* 0.082 μg/mL for the free drug AUC: 1.715 μg·h·mL^{-1} *vs* 0.168 μg·h·mL^{-1} for the free drug	Liu et al. (2018a)
Curcumin	Sophorolipid-coated curcumin NPs	C_{max}: 2.74 μg/mL *vs* 0.47 μg/mL for the free drug AUC: 6.5 μg·h·mL^{-1} *vs* 1.4 μg·h·mL^{-1} for the free drug	Peng et al. (2018b)
Curcumin	Saponin-coated curcumin NPs	C_{max}: 6.91 μg/mL *vs* 0.47 μg/mL for the free drug AUC: 14.1 μg·h·mL^{-1} *vs* 1.4 μg·h·mL^{-1} for the free drug	Peng et al. (2018c)
Genistein	Glyceryl palmitostearate NPs	C_{max}: 1.55 μg/mL *vs* 1.12 μg/mL for the free drug AUC: 6.3 μg·h·mL^{-1} *vs* 3.9 μg·h·mL^{-1} for the free drug	Kim et al. (2017)
Gingerol	Proliposomes	C_{max}: 6.48 μg/mL *vs* 0.87 μg/mL for the free drug $t_{1/2}$: 4.1 h *vs* 1.6 h for the free drug MRT: 3.4 h *vs* 5.7 h for the free drug AUC: 20.1 μg·h·mL^{-1} *vs* 1.2 μg·h·mL^{-1} for the free drug	Wang et al. (2018a)
Quercetin	Lecithin-stabilized polymeric micelles	C_{max}: 1.52 μg/mL *vs* 0.53 μg/mL for the free drug AUC: 0.90 μg·h·mL^{-1} *vs* 0.25 μg·h·mL^{-1} for the free drug	Chang et al. (2018)
Quercetin	Water-in-oil-in-water multiple nanoemulsion	C_{max}: 7.38 μg/mL *vs* 0.34 μg/mL for the free drug AUC: 47.6 μg·h·mL^{-1} *vs* 2.6 μg·h·mL^{-1} for the free drug	Pangeni et al. (2018)
Resveratrol	Proliposomes and NPs of lecithin-chitosan	C_{max}: 0.42 μg/mL *vs* 0.33 μg/mL for the free drug AUC: 1.44 μg·h·mL^{-1} *vs* 0.63 μg·h·mL^{-1} for the free drug	Peng et al. (2018a)

Abbreviations: AUC, area under the concentration–time curve; C_{max}, maximum plasma concentration; MRT, mean residence time; NPs, nanoparticles; $t_{1/2}$, elimination half-life.

et al., 2019).

In a trial of an improved formulation of genistein in pancreatic cancer patients, Löhr et al. (2016) measured maximum plasma concentrations (C_{max}) of 1.1 ± 0.6 μM in 1.5–3 h following a single oral high dose, although the levels decreased to 0.1 μM a few hours after. A favorable pharmacokinetic profile was reported for a genistein immunoconjugate, by infusion, with plasma elimination half-life ($t_{½}$) of 10 h in cynomolgus monkeys and 15 h in leukemia patients (Uckun et al., 1999). Solid lipid particles also prolonged genistein levels in rat plasma in comparison to oral administration of the free drug (Table 1), but upgraded formulations were required to increase absorption and delay clearance of this important isoflavone (Kim et al., 2017).

Regarding quercetin, Pangeni et al. (2018) reported the therapeutic activity of a nanoemulsion co-carrying low doses of the flavonoid and pemetrexed antifolate against A549 tumors in mice. The authors described a substantial increase in intestinal membrane permeability and oral bioavailability of quercetin after a single 40 mg/kg dose. Chang et al. (2018) found that polymeric micelles improved the bioavailability of quercetin not only following oral administration (Table 1), but also after intravenous injection, inhibiting the growth of colon cancer cells *in vivo*, while the placebo unloaded formulation showed no significant effects.

4.2. Delivery systems for improved anticancer efficacy of phytochemicals

In addition to oral administration, innovative delivery systems have also been developed for chemotherapy by IV administration. Table 2 summarizes the outcomes registered while studying these experimental therapies in preclinical cancer models.

4.2.1. Polymeric and inorganic nanoparticles

Previous work showed that encapsulating EGCG in polylactic acid–polyethylene glycol (PLA-PEG) NPs could enhance its chemopreventive proapoptotic and antiangiogenic potential (Siddiqui et al., 2009), so encapsulation of the catechin in chitosan NPs was also tested and the therapeutic efficacy assessed in prostate cancer (Khan et al., 2014) and melanoma models (Siddiqui et al., 2014). Compared with the PLA-PEG nanocarrier designed for systemic delivery, the chitosan NPs were argued better suited for oral administration because of the positive surface charge, mucoadhesive and highly biocompatible properties (Khan et al., 2014). These NPs provided a slow and incomplete release of EGCG in simulated gastric pH, while allowing fast release in simulated intestinal neutral pH fluid, and very relevant anticancer activities were observed *in vitro* and in mouse models (Table 2). NPs of chitosan and poly(aspartic acid) also showed a pH-responsive release of EGCG and, by oral administration, increased the efficacy of the catechin against atherosclerosis in rabbits (Hong et al., 2014), strengthening the concept that adequate nanoformulation can improve drug bioactivity in general.

A chitosan-based release system incorporating a core of iron oxide NPs was proposed by Soares et al. (2016) for the possible combination of magnetic hyperthermia and chemotherapy in future interventions. In this line of multifunctional vehicles, chitosan-iron oxide superparamagnetic NPs slowly released phytic acid, by a pseudo-second order model kinetics, impairing HT-29 colon cancer cells viability without noteworthy effect on normal 3T3 fibroblasts cells (Barahuie et al., 2017a). The same type of kinetics was obtained for formononetin release by cyclodextrin-modified single-walled carbon nanotubes that showed cytotoxicity to MCF-7 cells and Hela cells superior to the free isoflavonoid (Liu et al., 2018b), but these formulations were still not evaluated *in vivo*.

For melanoma cells *in vitro*, EGCG becomes considerably growth-inhibitory only at concentrations above 10 μM (Fig. 1), but cytotoxicity is evident at low micromolar levels when encapsulated in NPs (Siddiqui et al., 2014). As observed in many studies (also presented in Table 2), competent carriers can increase the therapeutic efficacy of phytochemicals compared with treatments with the free drug, however, it should be noted that in some works a control group treated with non-loaded carrier is not performed, so that a drug-independent effect of the carrier cannot be discarded in these cases.

PEG has been used to confer nanocarriers a hydrophilic camouflage surface, which can afford several advantages, such as antibiofouling properties, limited phagocytic uptake, and increased solubility in blood, contributing to prolonged circulation of NPs, and potentiates

Table 2
Delivery systems for systemic phytochemicals therapy investigated in preclinical cancer models[a].

Delivery system	Bioactive compound	Cancer models	Main results	Reference
NPs of chitosan	EGCG	*In vivo*: Nude mouse xenograft model of prostate cancer (22Rν1 cells) Nude mouse xenograft model of melanoma (human Mel 928 cells) *In vitro*: Mel 928 cells	*In vivo*: Oral administration of EGCG-loaded NPs delayed the appearance of solid tumors (22Rν1 carcinoma cells) and decreased prostate-specific antigen levels more effectively than free EGCG. EGCG-loaded NPs inhibited the increase in volume of both tumor types, at doses equal or inferior to the free drug, and without noticeable effects in body weight or food and water consumption by animals. Stronger induction of apoptosis (PARP activation, Bax/Bcl-2 ratio and caspase-3, caspase-8 and caspase-9 activation), inhibition of proliferation (Ki-67 and PCNA) and angiogenesis (CD31 and VEGF-positive cells) were also detected in tumor tissues. *In vitro*: Cytotoxicity to Mel 928 cells, including induction of apoptosis (Bax/Bcl-2 ratio, activation of PARP and caspase-9) and cell cycle inhibition increased with nanoencapsulation.	Khan et al. (2014); Siddiqui et al. (2014)
NPs of PLA-PEG copolymer	Resveratrol	*In vivo*: CT26 tumor bearing mouse *In vitro*: CT26 cell line	*In vivo*: IV administration of resveratrol-loaded NPs reduced FDG uptake, tumor volume and improved survival. *In vitro*: Reduced intracellular ROS and promoted death of CT26 colon cancer cells.	Jung et al. (2015)
NPs of PLGA-PEG-targeting ligand conjugated copolymer	EGCG	*In vivo*: Athymic nude mouse xenograft model of prostatic tumor *In vitro*: Prostate cancer LNCaP and PC-3 cell lines	*In vivo*: Targeted and non-targeted NPs enhanced tumor growth inhibition by EGCG and reduced the serum levels of prostate specific antigen. *In vitro*: Uptake of targeted NPs was increased, and anti-proliferative pro-apoptotic activity was higher than that of free EGCG.	Sanna et al. (2017)
NPs of poly-ε-caprolactone, chitosan and decorated with hyaluronic acid	Naringenin	*In vivo*: Urethane-induced lung cancer in albino Wistar rats *In vitro*: Human non-small-cell lung carcinoma (A549) and J774 macrophage cells	*In vivo*: Naringenin-loaded NPs inhibited the growth of tumors and the changes in oxidative stress parameters in tumor tissues, more than with the free counterpart. *In vitro*: Cytotoxicity of NPs to A549 cells returned an IC50 of 5.3 μM, lower than with free naringenin, and much higher than to normal macrophages.	Parashar et al. (2018)
NPs of gold-zein, surface modified with folate-conjugated polydopamine	10-hydroxycamptothecin (as needle-shaped nanocrystals)	*In vivo*: Nude mouse bearing KB cells tumor *In vitro*: KB, Hela and A549 cell lines	*In vivo*: Drug-loaded folate-targeted nanocomplexes showed increased accumulation in blood and tumor, while decreased distribution in the reticuloendothelial system, and greatly inhibited tumor growth, apparently without lesions in other organs. *In vitro*: Cellular internalization of folate nanocomplexes increased in cells expressing folate receptor, and cytotoxicity increased compared to that of the free drug.	Wang et al. (2017)
Micelles of casein (phytosomal phosphatidylcholine envelope)	Resveratrol and *Monascus* yellow pigments	*In vivo*: Mouse model bearing Ehrlich ascites tumor cells *In vitro*: Human breast adenocarcinoma MCF-7 cell line	*In vivo*: Reduction of tumor volume and weight, and growth biomarkers (aromatase, VEGF, NF-kB, cyclin D1), more potent than the free drug combination (IV). *In vitro*: Enhanced cytotoxicity compared to that of the free drugs.	El-Far et al. (2018)

(*continued on next page*)

Table 2 (*continued*)

Delivery system	Bioactive compound	Cancer models	Main results	Reference
Nanoemulsion	Resveratrol, α-tocopherol and coenzyme Q10	*In vivo*: Dimethylbenz[a]anthracene-induced breast cancer model	*In vivo*: Co-loaded self-nanoemulsifying system increased bioavailability of resveratrol and coenzyme Q10. Greater capacity to inhibit tumor growth than the combination of free antioxidants.	Jain et al. (2017)
Nanoemulsion and liposome (including oleic acid, with/without PEGylated lecithin, with/without targeting peptide ligand)	Lycobetaine	*In vivo*: Lewis lung carcinoma (LLC) xenograft model in mouse	*In vivo*: PEGylated liposome afforded the more extended circulation time and accumulation of the drug in LLC tumor, brain, lung and kidney of mice; and the targeting peptide increased accumulation in tumor.	Chen et al. (2018)
		Murine melanoma B16 cells lung metastasis model in mouse	All formulations with the encapsulated drug exhibited a stronger anti-tumor ability compared to the free drug; and PEGylated liposome with targeting peptide was the more potent in inhibiting tumor growth and prolonging survival of LLC-bearing mice, as well as in decreasing Ki-67 and CD31 staining. Survival was also extended in lung metastasis model. Several toxicity parameters in mice indicate the safety of the formulations.	
		In vitro: LLC and human A549 non-small cell lung cancer cell lines	*In vitro*: All formulations improved cellular uptake and pro-apoptotic toxicity of the drug against the cancer cell lines.	
Liposomes	Gambogic acid	*In vivo*: EMT6 breast tumor and B16F10 melanoma bearing mouse models	*In vivo*: Prolonged circulation of the drug in plasma. Enhanced antitumor activity in both tumor models, weight loss lower than 5%, with the higher dose affording notable EMT6 tumor regression with only one IV dose. Reduction of HIF-1α, VEGF-A, STAT3, Bcl-2, NF-κB, Ki-67 and CD31 more effective than with the free drug.	Tang et al. (2018)
		In vitro: EMT6 and B16F10 cell lines	*In vitro*: Cytotoxicity of liposome formulation was similar to that of the free drug.	
Exosomes from bovine milk	Celastrol	*In vivo*: Nude mouse lung cancer cell A549 xenograft model	*In vivo*: Oral administration of celastrol-loaded exosomes inhibited tumor growth with more efficacy than the free drug or the exosomes alone.	Aqil et al. (2016)
		In vitro: H1299 and A549 non-small cell lung carcinoma cell lines	*In vitro*: Exosomal celastrol inhibited the proliferation of A549 and H1299 cells, and inhibited TNFα-induced NF-κB activation.	
Exosomes from bovine milk	Anthocyanidins from bilberry	*In vivo*: Nude mouse lung cancer cell A549 xenograft model	*In vivo*: Oral administration of anthocyanidins-loaded exosomes attenuated volume increase of lung tumors, but free anthocyanidins had no effect.	Munagala et al. (2017)
		In vitro: Lung, breast, pancreatic, prostate, colon and ovarian cancer cell lines	*In vitro*: Milk exosomes have intrinsic anticancer activity, and exosomal formulation of anthocyanidins enhances the antiproliferative activities and inhibits TNFα-induced NF-κB activity in lung (H1299) and breast (MCF7) cancer cells.	

(*continued on next page*)

Table 2 (*continued*)

Delivery system	Bioactive compound	Cancer models	Main results	Reference
Exosomes from bovine milk	Curcumin	*In vivo*: CaSki cervical cancer xenograft model	*In vivo*: Curcumin concentration at different organs increased with exosomal formulation of the drug (oral). Oral administration of curcumin-loaded exosomes inhibited tumor growth with more efficacy than the exosomes alone, while the free drug had no effect. Animals treated with exosomes (with or without curcumin) displayed no signs of toxicity.	Aqil et al. (2017a)
		In vitro: Lung A549 and H1299, cervical Caski and HeLa, and breast MDA-MB-231 and T47D cancer cell lines	*In vitro*: Exosomal curcumin showed antiproliferative activities and inhibited TNFα-induced NF-κB activity in lung and breast cancer cells, more than the free curcumin	
NPs of PLGA-PEG	Wortmannin in combination with cisplatin	*In vivo*: Nude mouse xenograft model of platinum-sensitive A2780 and platinum-resistant A2780cis ovarian cancer cells	*In vivo*: Sub-therapeutic doses of the drugs in NPs delayed the increase in volume of both tumor models, without increasing off-target toxicity, and increased the levels of cisplatin-DNA adducts within the nucleus of cells.	Zhang et al. (2018)
		In vitro: A2780 and A2780cis cell lines	*In vitro*: Encapsulated wortmannin maintained the capacity to inhibit DNA repair, displayed cytotoxicity and strong treatment synergy, and radiosensitized platinum-resistant cells.	
Glyceryl monooleate liquid crystalline NPs	Resveratrol in combination with pemetrexed	*In vivo*: Urethane-induced lung cancer in mice	*In vivo*: IV administration of loaded NPs decreased tumor mass, malignant surface lesions and Ki-67 staining, activated caspase-3 and inhibited angiogenesis (VEGF), more effectively than the free drugs. Survival rates and safety assessment (hepatorenal pathology) were also improved with the encapsulated drugs formulation.	Abdelaziz et al. (2019)
		In vitro: A549 lung cancer cells	*In vitro*: Cellular uptake of carrier and enhanced cytotoxicity of drugs to lung cancer cells.	
Transferrin-functionalised microemulsion	Celastrol in combination with β-elemene	*In vivo*: Mouse xenograft model of A549 lung cancer cells	*In vivo*: Microemulsion performed better than the free drugs (IV) inhibiting tumor growth (mass and Ki-67 marker), inducing apoptosis and improving animal survival. Safety evaluation of circulating markers of hepatorenal injury and liver and spleen tissues pathology pointed no obvious systemic toxicity.	Zhang et al. (2019)
		In vitro: A549 and Lewis lung cancer cells	*In vitro*: Synergistic antiproliferative effect of the drugs and further enhanced with carrier against cells.	

Abbreviations: EGCG, epigallocathechin-gallate; FDG, fluorodeoxyglucose; IV, intravenous; LLC, Lewis lung carcinoma; NPs, nanoparticles; PARP, poly(ADP-ribose) polymerases; PCNA, proliferating cell nuclear antigen; PEG, polyethylene glycol; PGLA, poly(lactide-co-glycolide); PLA, polylactic acid; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription-3; VEGF, vascular endothelial growth factor.

[a] Information is given for a diversity of physical supports, natural compounds and reported therapeutic actions. Adverse toxicity and *in vitro* effects are also referred when studied.

accumulation in tumors (enhanced permeability and retention effect) with lower nonspecific protein adsorption. A different strategy was followed to prolong the action of 10-hydroxycamptothecin, a derivative of camptothecin, in the form of a polyprodrug amphiphile that self-assembles into micelles with the outer shell being superhydrophilic, thus preventing the nanostructure from unwanted nonspecific interaction, which is the main cause of its rapid clearance (Chen et al., 2017).

Nanoparticles of PLA-PEG were used as vehicles for resveratrol (Table 2), and clearly reduced the growth of tumor (derived from CT26 colon cancer cells) in mice and reduced cancer cell number, colony forming capacity, fluorodeoxyglucose uptake and ROS production, while causing apoptosis *in vitro* (Jung et al., 2015). In this amphiphilic system, PEG represented the hydrophilic portion of the copolymer and PLA, the hydrophobic one. PEG was also used to decorate iron oxide NPs loaded with gallic acid (Rosman et al., 2018), and graphene oxide NPs loaded with camptothecin (Deb and Vimala, 2018), showing anticancer activity against different cell lines *in vitro*.

Sanna et al. (2017) explored the functionalization of PEG surface NPs with ligands that bind to the extracellular domain of prostate-specific membrane antigen, a protein overexpressed in prostate cancer epithelial cells, for targeted delivery of EGCG (Table 2). The NPs were prepared from poly(lactide-co-glycolide)-PEG (PLGA-PEG) block copolymer, in blend with poly(caprolactone) (PCL) to ensure rapid precipitation of the hydrophilic PLGA-PEG, and encapsulated EGCG. Binding of two targeting ligands to the protein antigen was investigated by computational docking experiments, while cytotoxicity of EGCG-loaded NPs was studied with hormone-sensitive and hormone-independent prostate carcinoma cells. Cellular internalization of the targeted NPs was clearly superior in a cell line expressing the target protein. Although free catechin at 20 μM concentration showed no significant effects, EGCG-NPs were toxic to the carcinoma cells and disturbed the levels of cell cycle regulatory proteins. In animal experimentation, EGCG-loaded NPs limited the increase in tumor volume more efficiently than the free catechin, and the targeted NPs showed a slightly higher antitumor activity. Delivery systems and NPs based on PLGA are popular platforms because of their potential for rapid clinical approval (Danhier et al., 2012).

Naringenin is another flavonoid entrapped in PCL nanoparticles decorated with hyaluronic acid as the moiety targeting the cluster determinant 44 receptor (CD44) overexpressed in tumor cells (Table 2). The NPs were produced layer-by-layer using the cationic biopolymer chitosan as an intermediate layer, and hyaluronic acid at the surface yielded a negative zeta potential (Parashar et al., 2018). Particles showed good stability, including in conditions of varied pH mimicking gastrointestinal fluids, and hyaluronic acid surface contributed to permeation through excised mucosa of rat small intestine. Other assays with a fluorescent tracer suggest the drug was internalized and the delivered naringenin caused G2/M phase arrest of human non-small-cell lung carcinoma cells, supporting the anti-lung tumor activity observed *in vivo* both with preventive and therapeutic administration (Table 2).

4.2.2. Protein-based nanocarriers

Abraxane (R) is an albumin-bound NP formulation of paclitaxel with exceptional properties because it relies on gp60-mediated transcytosis, already clinically approved (Xie et al., 2016), and proteins are increasingly explored in functional nano-platforms for targeted and controlled drug release at tumor tissues. IV administration of EGCG carried in nanocomplexes with heat treated β-lactoglobulin (and the antioxidant 3-mercapto-1-hexanol) inhibited the growth of A375 human melanoma tumors in mice (Yang et al., 2017).

Wang et al. (2017) fabricated multicomponent nanostructures based on gold NPs and zein (corn protein) for improved delivery of 10-hydroxycamptothecin. The carrier surface was modified with folate-conjugated polydopamine, and the drug was encapsulated in the form of needle-shaped nanocrystals for superior pharmacokinetic and pharmacodynamic properties, such as longer retention time in plasma, cellular internalization, and effective tumor targeting and growth suppression (Table 2). Folate is another targeting moiety in anticancer drug delivery taking advantage of high expression of folate receptors in tumor cells. The hydrophobicity of zein (glutaraldehyde crosslinked shell) was also employed in the preparation of nanocapsules with an oily core for oral co-delivery of resveratrol and exemestane, eliciting higher efficacy in cellular and mouse models of breast cancer than the free drugs (Elzoghby et al., 2017).

More recently, El-Far et al. (2018) loaded casein micelles with a drug cocktail, including resveratrol, and reported good hemocompatibility (low or negligible hemolytic activity) of the system and potential also for breast cancer therapy (Table 2), while genipin-crosslinked caseinate-chitosan NPs increased the stability of encapsulated curcumin, its delivery to cell cytoplasm and the anticancer activity (Razi et al., 2018).

4.2.3. Lipid-based and vesicular delivery systems

Liposomes and nanoemulsions are classic nanoscale formulations using safe excipients, and particularly PEGylated liposomes have a good track of translation into clinic for cancer treatment (Chen et al., 2018; Tang et al., 2018). Resveratrol was combined with other antioxidants in a self-nanoemulsifying drug delivery system apparently well internalized by Caco-2 cells and giving promising results with an *in vivo* prophylactic model of breast cancer induced by 7,12-dimethylbenz[a] anthracene (Jain et al., 2017). This approach was recognized as having a great potential to increase the bioavailability of poorly water-soluble drugs and could be more explored for phytochemicals (Rehman et al., 2017).

Lycobetaine is an alkaloid from *Lycoris radiata* that inhibits topoisomerases I and II and showed cytotoxic action against several carcinoma cell lines and tumor xenografts, but the plasma half-life is very limited (Chen et al., 2018). Encapsulation of lycobetaine in liposomes and nanoemulsions both increased the cytotoxicity of the drug (Table 2), but liposome exhibited a slower release behavior (Chen et al., 2018). In these formulations, oleic acid was used to facilitate lipid solubility of the drug and PEGylated lecithin assessed to enhance the circulation time. Moreover, a targeting peptide ligand expected to function as adjuvant for tumor penetrability was co-administered, and the results endorse PEGylated liposomes for lycobetaine anti-lung cancer therapy. Liposome-encapsulated curcumin also showed cytotoxic action against A549 lung cancer cells *in vitro* (Ibrahim et al., 2018).

Tang et al. (2018) investigated the solvent-assisted active loading into the inner aqueous core of liposomes of the poorly soluble drug gambogic acid, a xanthonoid isolated from the exudate of *Garcinia hanburyi*. The liposome formulation prevented the burst release of the drug and reduced its hemolytic toxicity, and relevant antitumor activities were observed, associated with inhibition of proinflammatory proangiogenic and proliferation markers (Table 2). Phosphatidylcholine liposomes were also applied over silica-coated iron oxide NPs with loaded doxorubicin, and the nanosystem's cytotoxicity was assessed with MCF-7 human breast adrenocarcinoma and U87 glioblastoma cells under magnetic field (Sharifabad et al., 2016).

An innovative carrier for oral delivery of phytochemicals are exosomes, extracellular membrane vesicles secreted by different cells and found in body fluids (and cell culture supernatants). Recently, Farooqi et al. (2018) presented the potential of using exosomes as delivery systems with low toxicity, capable of evading the immune system and thus offering new targeting possibilities for natural compounds. Milk-derived exosomes have been tested as natural nanocarriers for loading of celastrol (Aqil et al., 2016), of a potential synergistic mixture of anthocyanidins (Munagala et al., 2017), and for increased bioavailability and efficacy of curcumin (Aqil et al., 2017a), and very relevant therapeutic actions were described with different cancer models (Table 2). Moreover, significantly enhanced antitumor activity was also

observed with exosomal formulations of paclitaxel and anthocyanidins combined towards A2780 ovarian tumor xenografts (Aqil et al., 2017b).

4.3. Multifunctional systems

Synergism with classical chemotherapeutics and reduction of the side effects of chemo/radiotherapy are other potential benefits of natural drugs. Theaflavin and EGCG encapsulated in PGLA nanosystems were described to have higher chemosensitization effects than the free compounds by increasing the anticancer activity of cisplatin towards A549 lung carcinoma, HeLa cervical carcinoma and THP-1 leukemia cells, as well as in mice bearing Ehrlich ascites carcinoma cells (Singh et al., 2015). Wortmannin is a fungal furanosteroid metabolite that inhibits phosphoinositide 3-kinase, blocking DNA repair, and its nanoformulation with PGLA increased its stability and potential as a radiosensitizer, which revamped the interest in the compound (Karve et al., 2012). Very recently, Zhang et al. (2018) developed NPs for co-delivery of cisplatin and wortmannin that demonstrated therapeutic efficacy against both platinum–sensitive and platinum–resistant ovarian cancer, superior to the free drugs or single-drug loaded NPs (Table 2). Combined cargoes affording anti-lung tumor activity in mouse models are β-elemene plus celastrol (Zhang et al., 2019) and pemetrexed plus resveratrol (Abdelaziz et al., 2019).

Phytochemicals are also being included in theranostic systems, multifunctional carriers having a diagnostic/imaging agent along with therapeutic drug with the goal of simultaneous delivery and monitoring of target tissues (Conde et al., 2016). In addition to the aforementioned 10-hydroxycamptothecin in NPs of gold-zein complex (Table 2) that could be traced *in vivo*, phytochemicals tested in theranostic delivery systems are polyphenols, such as quercetin (Malekzadeh et al., 2017) or gallic acid (Usman et al., 2017), and the reported anticancer effects are indicated in Table 3. Many systems contain NPs/gadolinium contrast agents for magnetic resonance imaging diagnostic, and very recently a tannic acid-containing system compatible with bimodal imaging was developed (Wang et al., 2018b). Interestingly, Conti et al. (2016) suggested the use of apoferritin as curcumin carrier to specifically target cancer stem cells that have upregulated L-ferritin receptor (Table 3). Recently, Zayed et al. (2019) used fluorescent thiol-capped quantum dots conjugated to albumin NPs for the delivery of resveratrol to target mannose receptor in xenografted breast cancer cells in mice.

Protocatechuic acid is a common metabolite of polyphenols hypothetically mediating the anticancer action of those compounds (Krajka-Kuźniak et al., 2015). The theranostic nanohybrids designed by Usman et al. (2018a, 2018b) enabled a pseudo-second order kinetics of protocatechuic acid release and much more extended at mild acidic pH (Table 3).

Acid-responsive release in the tumor (acidic) microenvironment and for intracellular targeting may give a significant advantage for cancer therapeutic systems. Alginate is a biocompatible polysaccharide able to form structures with different properties under gentle conditions and silica NPs with disulfide-linked alginate were proposed for redox and pH dual stimuli-responsive carriers (Mendes et al., 2003; Yuan et al., 2018). The tendency of alginate to dissolve in alkaline media endorses its use as support of colon-targeted delivery systems (Zhang et al., 2017), but these additional delivery routes will be discussed in the following section.

5. Exploring alternative routes and tissue barriers for improved delivery

Therapeutic carriers become instrumental to explore alternative routes of administration that can reduce drug metabolism or overcome physiological barriers to achieve higher accumulation at cancer sites. Moreover, release systems can be tailored to optimize spatiotemporal distribution and bioactivity profiles of tumor-targeting drugs (Gasselhuber et al., 2010; Silva et al., 2017). These possibilities should be exploited for rational chemopreventive and therapeutic interventions with phytochemicals having low bioavailability and multifactorial concentration-dependent actions (Fig. 1).

The potential of modulated release was demonstrated by Hu et al. (2015), who were able to improve dose efficacy and safety of combined lapatinib and paclitaxel therapy in breast cancer mouse model using a co-delivery system that released the drugs with different kinetics. A thermosensitive pluronic F-127 hydrogel with loaded NPs for peritumoral injection was used in this case and other options are being tested with diverse natural compounds and delivery routes.

5.1. Mucosal delivery of anticancer phytochemicals

Mucosa in gastrointestinal and respiratory tracts as well as in eyes and reproductive organs offer areas with ease of access for drug delivery, enabling systemic absorption and local targeting (Freag et al., 2018b). The main barrier for mucosal drug absorption in general is the hydrophilic mucus layer that covers mucosal tissues, and mucoadhesive formulas are used to increase the residence time by attachment to mucus glycoproteins or mucosal membranes (Ansari et al., 2018).

5.1.1. Buccal delivery

Buccal delivery of celastrol (tripterine) was achieved with a nanocarrier incorporated into mucoadhesive chitosan-hydroxypropyl

Table 3
Theranostic delivery composites incorporating phytochemicals for cancer treatment and tumor imaging.

Phytochemical	Delivery system	Therapeutic effects	Reference
Curcumin	Apoferritin loaded with gadolinium contrast agent	Induced cell death and reduced self-renewal in MDA-MB-231 and TUBO cells, and their derived cancer stem cells-enriched tumor spheres, and inhibition of breast cancer growth *in vivo*	Conti et al. (2016)
Gallic acid	NPs of zinc/aluminum-layered double hydroxide containing gadolinium and gold	Polyphenol and loaded carriers were more toxic to cancer HepG2 cells than to normal 3T3 fibroblasts	Usman et al. (2017)
Protocatechuic acid	NPs of graphene oxide, gadolinium and gold; NPs of magnesium/aluminum-layered double hydroxide containing gadolinium and gold	Polyphenol and loaded carriers were more toxic to cancer HepG2 cells than to normal 3T3 fibroblasts	Usman et al. (2018a,b)
Quercetin	NPs of iron oxide coated with poly(citric acid)-PEG and folic acid	Empty carrier showed no effect, but the quercetin-loaded inhibited the growth of HeLa and MDA-MB-231 cells	Malekzadeh et al. (2017)
Tannic acid	NPs of self-assembled poly(propylene oxide) poloxamer Pluronic F-127 and tannic acid	For tumor imaging, NPs incorporating near-infrared fluorescent dye and Zr-89 accumulated in tumors, and showed good *in vitro* biocompatibility	Wang et al. (2018b)
Resveratrol	Mannose-grafted albumin-QDs, co-delivery of pemetrexed	Internalization and cytotoxicity to breast cancer cells *in vitro*, and *in vivo* tumor growth inhibition, apoptosis promotion and angiogenesis inhibition superior to the free drugs. In addition to serum stability and hemato-compatibility of the system, no immunogenicity was detected in safety animal study.	Zayed et al. (2019)

Abbreviations: NPs, nanoparticles; PEG, polyethylene glycol; QDs, quantum dots.

methylcellulose composite sponges (Freag et al., 2018b). Carrier decoration with protamine improved mucopenetration as screened by *ex vivo* assay with chicken pouch mucosa and increased bioavailability of the drug in rabbits after application in the animal's cheek. Cellulose derivatives were also used to prepare mucoadhesive buccal films able to release resveratrol that permeated through goat buccal mucosa in Franz diffusion apparatus over hours and without inducing noticeable histopathological abnormalities (Ansari et al., 2018). These promising results with chief anticancer phytochemicals ask for further studies in cancer models.

5.1.2. Intranasal brain targeting

Treatment of patients with recurrent malignant glioma with the monoterpene perillyl alcohol by simple inhalation is well tolerated and effective (da Fonseca et al., 2013), and brain targeting with chemotherapeutics intranasal delivery systems is adding encouraging results, e.g. with micelle-encapsulated camptothecin against intracranial glioma model as reviewed by Khan et al. (2017). More recently, kaempferol was delivered to rat brain by nasal administration using a mucoadhesive nanoemulsion compatible with nasal mucosa (Colombo et al., 2018). This flavonoid delivery system was tested *in vitro* against C6 glioma, but awaits *in vivo* therapeutic evaluation. Direct nose-to-brain delivery of resveratrol was illustrated by Trotta et al. (2018) using chitosan-coated fatty microparticles. IV infusion of a low dose of free resveratrol (0.2 mg to healthy rats) resulted in undetectable levels in cerebrospinal fluid, even after 3 h, whereas nasal administration of an equivalent dose of encapsulated resveratrol yielded μg/mL concentrations in less than 1 h. In this case, no resveratrol was detected in rat bloodstream, suggesting that the microparticulate carrier system targets a nose-CNS pathway bypassing the blood-brain barrier.

Alternative delivery routes to the CNS have a great interest, since the blood-brain barrier hinders the access of chemotherapeutics to the brain. In addition to the tight junctions between the brain microvessel endothelial cells and expression of drug efflux transporters (P-glycoprotein and others), a mechanism of lysosomal sequestration and disposal by phagocytic neutrophils was recently suggested to contribute to the active exclusion of drugs, such as doxorubicin, from entering the brain (Noack et al., 2018). Aglycone flavonoids can cross the blood-brain barrier apparently by passive transcellular diffusion as predicted from their lipophilicity (Youdim et al., 2003), and some phytochemicals downregulate or inhibit breast cancer resistance protein (Kaur and Badhan, 2017), hence can be useful to facilitate barrier penetration by drugs in the treatment of brain diseases, including brain cancer. Importantly, NPs have been found to prolong the retention of phytochemicals at different brain regions (Tsai et al., 2011). In an original application of curcumin's optical and therapeutic properties, theranostic NPs capable of transmigration across the blood-brain barrier successfully delivered the drug against glioblastoma multiforme in the brain (Singh et al., 2016).

5.1.3. Colon targeted delivery

Different oral administration colon-targeted delivery systems have been developed for resveratrol interventions and some were tested *in vivo*. Comparing with administration of the free drug, encapsulation in Ca-pectinate beads increased resveratrol capacity to counteract inflammation in ulcerative colitis model in rats and to inhibit sphingosine kinase 1 implicated in progression to colon cancer (Abdin, 2013). In a similar model, icariin (prenylated kaempferol) carried in alginate-chitosan microspheres also showed a protective action, and accumulation of the vehicle in mouse colon was followed using a fluorescent tracer (Wang et al., 2016). The anionic polysaccharides alginate and pectin are often selected as oral vehicles targeting the colon, not only due of their safety and bioadhesive properties, but because they can withstand the stomach and small intestine acid and then dissolve in colon alkaline environment.

5.1.4. Lung and vaginal delivery

Lung cancer can benefit from local drug therapy if specific non-toxic formula is feasible to obtain. PGLA-coated magnetic NPs with quercetin showed cytotoxicity against human lung cancer cells, but not against lung epithelial cells, and positive 7-days safety studies were carried out with healthy mice (Verma et al., 2013). Kabary et al. (2018) developed and tested inhalable lipid-based composites carrying rapamycin and berberine. Lung carcinoma was induced with urethane in mice, but insufflation with the spray-dried carrier reduced tumor growth as indicated by Ki-67, caspase-3 and angiogenesis markers. Similarly, a combination therapy with low-dose etoposide and berberine using albumin NPs was proposed for deep lung deposition and with differential release patterns of the two drugs (Elgohary et al., 2018).

Localized therapy is also obviously interesting for cancers of the female reproductive tract and is being increasingly pursued with advances in biomaterials and new *in vivo* models. Camptothecin-loaded PLGA NPs lavaged into the vagina prophylactically prevented the development of an adenovirus-induced vaginal cancer in mice and paclitaxel-loaded mucus-penetrating particles reduced growth of cervicovaginal tumors and animal mortality (Neves et al., 2015). Curcumin and resveratrol liposomal formulations for vaginal delivery are under development (Berginc et al., 2014; Jøraholmen et al., 2015), and their anticancer efficacy is still not demonstrated.

5.2. Peritumoral and dermal delivery for bioactivity optimization

5.2.1. Phytochemical-eluting peritumoral implants

Implantable carriers and peritumoral application are attractive therapeutic approaches for maintaining effective local drug concentrations for extended time periods with eased dosing schedules, and potentially attenuating systemic adverse effects. PLA carriers encapsulating anthocyanins with chemopreventive properties were subcutaneously implanted in rats and provided a sustained release of the polyphenols for 28 days (Desai et al., 2010).

Drug administration by intravesical instillation can reduce recurrence of bladder cancer and delivery of 10-hydroxycamptothecin loaded in a thiol-responsive nanogel improved drug biodistribution and antitumor efficacy in rats (Guo et al., 2017). It is worth noting that nanogel delivery increased penetration of the compound (fluorescence monitoring) into the full-thickness wall of bladder, favoring the therapeutic action of the alkaloid.

A cancer delivery system administered intravenously needs to overcome several physiological barriers, and usually a five-step cascade is considered, namely, blood circulation, tumor accumulation, (tumor deep) penetration, cellular internalization and (intracellular) drug release. Diffusional hurdles augment in stroma-rich solid tumors, such as pancreatic cancer, where abundant intercellular stromata hinder chemo- and immune-therapeutic agents reaching cancer cells. However, an original strategy for camptothecin derivative SN-38 delivery was described, turning stroma barrier into an advantage. Yasunaga et al. (2013) developed an immunoconjugate targeting tumor stromal collagen IV with a drug linker sensitive to the acidic pH of the tumor microenvironment, allowing a highly localized concentration in tumor with the antibody-drug conjugates extravasated from leaky tumor vessels and bound to the stroma. The immunoconjugate was able to release drug in physiological conditions outside the cells and was effective treating hypovascular and stroma-rich pancreatic cancer. The success of the strategy can be rationalized as using the stroma extracellular matrix as a scaffold for accumulation of phytochemical vehicle and pH-controlled release of the drug that can then diffuse towards the cancer cells.

5.2.2. Dermal and transdermal delivery

Diffusional limitations can be explored in drug dermal and transdermal delivery to control the rate of drug input over a prolonged time. A variety of gel, emulsions, liposomal and NP systems, microneedles,

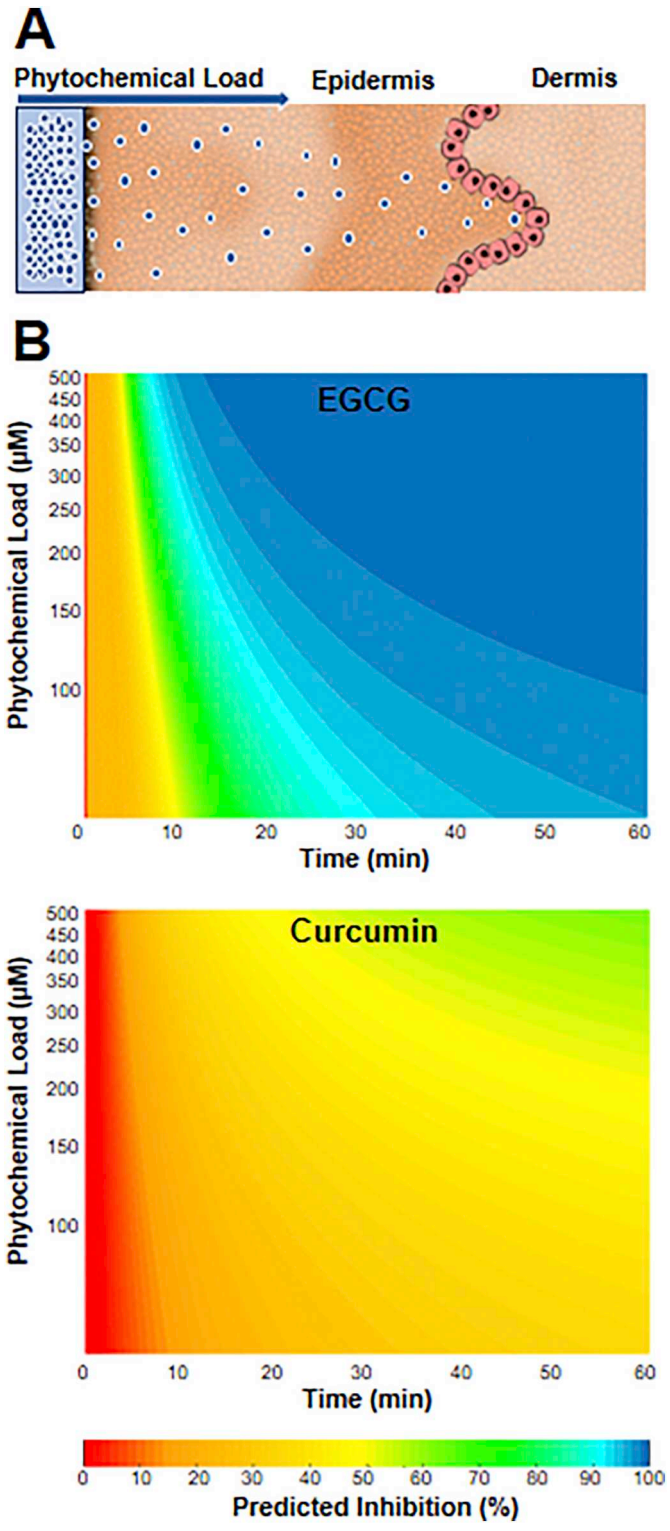

Fig. 3. Simulation of anti-melanoma bioactivity of epigallocatechin-3-gallate (EGCG) and curcumin delivered by skin patch-releasing systems with different phytochemical loads. (A) Schematic representation of drug diffusion through the skin layers and eventually reaching the melanocytes at the epidermis-dermis border. (B) Prediction of the time evolution of anti-melanoma bioactivity at the epidermis-dermis border, considering skin patch-releasing systems with different drug loads. Details regarding the simulation method can be found in Silva et al., 2017. These simulated data indicate that a lower load of EGCG enables a significant inhibitory capacity (green and blue colors) faster than with curcumin. (For interpretation of color references in this figure legend, the reader is referred to the web version of the article.)

iontophoresis, and other techniques are employed to cross the permeability barrier of the skin, enhancing drug penetration into and through the skin. Transdermal delivery shares some advantages with other alternative routes mentioned earlier, but requires efficient drug penetration to reach systemic circulation, while delivery of different therapeutic agents into the skin is pursued to target local skin cancers (Liu et al., 2018c).

Recently, gelatin-oleic acid NPs were able to release sesamol that permeated through mice skin and the system showed activity against MCF-7 breast cancer cells *in vitro* (ElMasry et al., 2018). Iontophoresis was combined to deliver liposome-loaded curcumin and signal transducer and activator of transcription-3 siRNA in excised porcine skin (Jose et al., 2017). This system exhibited higher activities against the growth of human epidermoid cancer cells than the free drugs, suggesting an innovative option for treatment of skin cancer.

For melanoma, EGCG showed significant pharmacological actions by reducing proliferation, migration/invasion potential and metastasis to distant tissues (Silva et al., 2017), and curcumin's anti-melanoma activity *in vitro* and *in vivo* was enhanced by nanodelivery (Muddineti et al., 2017), urging the development of skin delivery systems for these compounds.

The goal of targeted delivery of anticancer agents is always to achieve specific delivery to target tissues or cells in order to maximize their therapeutic effectiveness, while minimizing the problematic side effects. Phytochemicals are not free of adverse effects (Rengasamy et al., 2019), and for example, EGCG showed cytotoxic effects in dermal fibroblasts at 200 μM concentration (Silva et al., 2017). In addition to the general targeting strategies for selective delivery of drugs, e.g. stimuli-responsive carriers, the stratified organization of skin may provide an opportunity for drug spatial targeting. Simulation methods available to predict drug percutaneous absorption, combined with concentration-effect curves (Fig. 1), can be used to estimate concentration and bioactivity profiles through skin layers, and this approach may help to design controlled release systems that potentially optimize drug concentration at the target layer (Fig. 3).

6. Current perspectives and challenges

Despite the advancements in prevention, diagnosis and treatment, cancer remains one of the major causes associated with decreased life expectancy, morbidity and mortality. Continued research of novel strategies in different fronts is therefore needed, and novel approaches utilizing phytochemicals and natural compounds are expanding. As summarized in Table 4, human trials with green tea catechin- and anthocyanidin-rich oral preparations have provided relevant results against carcinogenesis-initiating events, such as DNA damage, lipid oxidation, inflammation, and proliferation. Currently available results are more compelling against smoking-associated cancer risk, colorectal, esophageal, hepatic and oral cancer, assuming long-term (at least 6 weeks) interventions are followed (Hakim et al., 2008; Kresty et al., 2016; Luo et al., 2006; Mallery et al., 2008; Shin et al., 2018; Thomasset et al., 2009; Wang et al., 2014). The trials consistently indicate absence or low toxicity of natural compounds even in high doses that increase the levels of such compounds in plasma and target tissues (NCT00666562; NCT00233935; Thomasset et al., 2009). However, trials failed to exhibit preventive effect against prostate, cervical and ovarian carcinogenesis (Garcia et al., 2014; Kumar et al., 2015; Linden et al., 2003; Nguyen et al., 2012; Trudel et al., 2013; Zhang et al., 2016a). Several of these ineffective interventions had shorter duration, less than 6 months (Garcia et al., 2014; Nguyen et al., 2012; Zhang et al., 2016a).

Plant-derived agents and pharmacophores represent a meaningful part of the drugs used in cancer treatment for a long time (Newman and Cragg, 2016). Meanwhile, the clinical approval of alternative delivery approaches, namely liposome-encapsulated forms of doxorubicin first, then of irinotecan (Onivyde) among other drugs (Tang et al., 2018), and

Table 4
Clinical studies of catechin- and anthocyanin-rich preparations (oral) targeting premalignant injury or chemoprevention[a].

Phytochemical formulation	Condition	Main results	References
Green tea	Endogenous nitrosation induced by amine-rich diet	Nitrosation was significantly decreased by a week supplementation with moderate amounts of green tea (2 g – 4 cups per day). However, high amounts (4 g – 8 cups per day) increased endogenous nitrosation.	Vermeer et al. (1999)
Green tea polyphenol capsules	High risk of liver cancer due to exposure to hepatitis B and aflatoxin	Urine excretion of DNA damage biomarker (8-OHdG) decreased after 3 months of treatment, but not after 1 month.	Luo et al. (2006)
Green tea	Heavy smoking within GSTM1 and/or hOGG1 genotypes	Urine levels of 8-OHdG decreased in GSTM1-positive smokers regardless of their hOGG1 genotype by moderate consumption of green tea.	Hakim et al. (2008)
Green tea polyphenols	High consumption of fumonisin b1	Decrease in urinary levels of the fumosin, sphinganine (Sa), sphingosine (So) and Sa/So ratio in groups treated with the extract.	Xue et al. (2015)
Green tea or Polyphenon E	Smokers with chronic obstructive pulmonary disease	Phase II – Completed (178 participants): Increases in urinary levels of 8-OHdG in both green tea and Polyphenon E groups after 6 months, while there was a decrease in the placebo group. Inversely, levels of the oxidative lipid marker 8-iso-PGF2α decreased in treatment groups, and increased in the placebo group.	NCT00363805
Polyphenon E	Nonmetastatic bladder cancer	Phase II – Completed: Dose-dependent accumulation of EGCG in non-malignant bladder tissue: placebo: 0.00 ng/mL; 800 mg/day: 0.50 ng/mL; 1200 mg/day: 1.72 ng/mL	NCT00666562
Green tea, Black tea, Placebo tea	Smoking-related oxidative stress	Phase II – Completed (176 participants): A 35% decrease in 8-OHdG levels after 6 months 4 cups/day of green tea in females and a 26% decrease in 8-iso-PGF2α in females after 6 months of drinking the same quantity of black tea. No significant changes were observed in males.	NCT02719860, Hakim et al. (2017)
Green tea extract	Endoscopic removal of colorectal adenomas	Group supplemented with 0.9 g/day for 12 months of green tea extract (n = 71) had 0.56 risk ratio when compared with the control group (n = 72). Less cases of relapsed adenoma in the extract-treated group.	NCT02321969, Shin et al. (2018)
Fish oil and Green tea extract	Prostatic intraepithelial neoplasia	Green tea extract afforded EGCG plasma concentrations of 30.71 ± 14.19 ng/mL (48.96 ± 14.19 ng/mL in combination with fish oil), but no significant differences in FAS or Ki-67 levels, compared to placebo (12–20 weeks).	NCT00253643, Zhang et al. (2016a)
Polyphenon E	Prostatic intraepithelial neoplasia and atypical small acinar proliferation	Phase II – Completed: Increase in EGCG plasma concentrations, but no differences in the number of prostate cancer cases in treated group (400 mg/day for a year, n = 49) compared to the placebo group (n = 48).	NCT00596011, Kumar et al. (2015)
Polyphenon E	Human papillomavirus and low-grade cervical intraepithelial neoplasia	Phase II – Completed: Group treated with 800 mg/day for 4 months (n = 50) showed no toxicities and no clearance/resolution of human papillomavirus or cervical intraepithelial neoplasia, compared to placebo group (n = 48).	NCT00303823, Garcia et al. (2014)
Green tea	Remission of advanced stage ovarian cancer	Phase II – Completed (16 patients): Recurrence rate not satisfactory after 18 months (500 mL/day), hence trial was terminated.	NCT00721890, Trudel et al. (2013)
Green tea extract	High breast density, menopausal women	Phase II – Completed: Comparing with placebo group (n = 537), decaffeinated green tea extract (843 mg/day of EGCG for 12 months) did not significantly change mammographic density, but there was a statistically significant decrease on percent mammographic density in younger women (50–55 years).	NCT00917735, Samavat et al. (2017)
Polyphenon E	Barrett's esophagus	Phase I – Completed (44 participants): Escalating dose 400, 800 and 1200 mg/day did not reached the maximum tolerated dose, and increased EGCG levels in the esophagus: 0.79 pmol/g (placebo), 6.06 pmol/g (400 mg), 35.67 pmol/g (800 mg) and 34.95 (1200 mg).	NCT00233935, Joe et al. (2015)
Polyphenon E ointment	Actinic keratosis	Phase II – Terminated: No significant differences from the daily application of ointment with a concentration of 5.5–8.5% of EGCG for 12 weeks (51 participants).	NCT00005097, Linden et al. (2003)
Polyphenon E	Prostate cancer men scheduled to prostatectomy	Phase I – Completed: After treatment during 3–6 weeks (800 mg EGCG/day), tea catechins were present in plasma, but levels in the prostatectomy tissue were low to undetectable. Changes in systemic and tissue biomarkers were not statistically significant compared to placebo.	NCT00459407, Nguyen et al. (2012)
Anthocyanin-rich bilberry extract (Mirtocyan)	Colorectal cancer patients scheduled to resection of primary tumor or liver metastases	Escalating doses of the extract, for 7 days before resection surgery, showed no adverse effects. At day seven there was a dose-dependent increase in anthocyanin concentrations in both plasma and urine. Accumulation in colorectal tumor tissue versus adjacent normal tissue, most prominent anthocyanin approx. 94 ng/g versus 39 ng/g, respectively. Anthocyanins or metabolites were not detected in liver. Decrease in proliferation (7%, Ki-67) in tumors from all patients and the lowest dose reduced insulin-like growth factor levels.	Thomasset et al. (2009)

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Table 4 (*continued*)

Phytochemical formulation	Condition	Main results	References
Bioadhesive black raspberry gel	Oral intraepithelial neoplasia	41% of participants treated with a 10% (w/w) black raspberry gel showed a decrease in lesion grade, 23% an increase in lesion grade and 35% remained stable. No gel-associated toxicity was found. There was significant reduction of loss of heterozygosity indices at the tumor suppressor gene-associated loci. Modulation of inflammation and apoptosis-related genes after application of gel four times daily for 6 weeks.	Shumway et al. (2008), Mallery et al. (2008)
Lyophilized black raspberries	Barrett's esophagus	Intervention with 45 g per day for 6 months increased detoxification in epithelium (increase in GST-pi) and decreased urinary lipid peroxidation maker. A fraction of the patients (15%) exhibited low grade toxicities (epigastric pain, diarrhea, and constipation), but were able to continue the trial upon a reduction in dosage.	Kresty et al. (2016)
Black raspberries suppositories (and powder)	Familial adenomatous polyposis (rectal polyps)	Treatment with suppositories (9 months) decreased the burden of rectal polyps, along with reduction of cellular proliferation and modulation of signaling pathways and DNA methylation in tissues. Addition of oral black raspberry powder to the treatment yielded no additional benefit. 3/14 patients were nonresponders.	Wang et al. (2014)

Abbreviations: 8-iso-PGF2α, 8-iso-prostaglandin F2α; 8-OHdG, 8-hydroxydeoxyguanosine; EGCG, epigallocathechin-gallate; FAS, fatty acid synthase; GST, glutathione S-transferase; GSTM1, glutathione S-transferase mu 1; hOGG1, 8-oxoguanine DNA N-glycosylase 1.

[a] Trial publications and/or at clinicaltrials.gov (with results in March of 2019) were collected.

also paclitaxel NPs (Newman and Cragg, 2016), is stimulating further development of the field with special interest for phytochemicals.

6.1. Taking advantage of carrier systems

An ideal drug delivery system maintains the drug within a desired therapeutic range after a single dose, and/or target the drug to a specific region while simultaneously lowering the systemic levels of the drug. Many different systems and strategies have been evaluated for drug targeting to tumors over the years. Most often, systems include liposomes, polymers, micelles, NPs and antibodies, and strategies of drug targeting to cancer cells, drug targeting to endothelial cells or triggered drug delivery. Significant progress has been made in this area of research both at the preclinical and clinical levels, and a number of (primarily passively tumor-targeted) nanomedicine formulations have been approved for clinical use (Newman and Cragg, 2016; Tang et al., 2018).

The recent developments of drug delivery systems for cancer therapy have been dominated by the use of nanomaterials. The large surface area of nanocarriers enable high drug loading efficiency and surface functionalization diversity for improved targeting and delivery to cancer cells. Nonspecific interactions with blood cells, serum proteins and tissue components after *in vivo* administration is a possible drawback of some systems, potentially aggravated in the case of nanomaterials with high surface exposition, and important toxic effects were previously reported in animal models (Miao et al., 2013; Xu et al., 2015). Better biocompatibility has been pursued by surface functionalization with hydrophilic nontoxic molecules, such as PEG, polysaccharides or serum albumin (Fan et al., 2016; Fernandes et al., 2017; Miao et al., 2013). Surface modification with PEG can enhance hemocompatibility, *in vivo* stability and circulation time, and it was described to substantially reduce the toxicity of graphene oxide nanosheets injected IV to mice (Miao et al., 2013). PEGylation of phytochemicals delivery systems has been tested *in vivo* (Tables 2 and 3), and other available options for surface functionalization may enable further validation of improved safety, blood circulation and biocompatibility after systemic administration.

A greater variety can be seen in the cell targeting strategies employed in phytochemicals delivery systems, from hyaluronic acid and folate to more specific targeting moieties (Section 4.2). A novel perspective was just introduced by Elgohary et al. (2018) aimed at directing etoposide plus berberine nanocomposites to cancer cells expressing sialo-glycan structures implicated in tumor progression and immune evasion (Taniguchi and Karin, 2018; Xing et al., 2018).

A deeper understanding of the influence of chemical and physical properties of the drug carriers has the potential to enhance the anticancer action of phytochemicals. In addition to being critical for physicochemical stability, polydispersity and redox properties, studies indicate the morphological characteristics of delivery systems will affect biological responses (Peng et al., 2018d; Zhang et al., 2016b). Nanoparticles are more likely to form stable dispersions and size, shape and surface chemistry determine protein binding affinities, interaction with membranes, cellular internalization and impact on intracellular processes. Differential bioactivity of phytochemicals at subcellular locations and targets are also being disclosed (Abdullah and Ravanan, 2018; Lagoa et al., 2011) with possible advantage for devising new delivery methods.

The present review reveals that a variety of delivery systems and strategies are being explored to enhance the bioavailability, distribution, targeting, cellular uptake and action of anticancer phytochemicals. Liposomes, lipid, polysaccharide and protein NPs, polymer conjugates, micelles, nanoemulsions and gels were demonstrated to improve the chemotherapeutic efficacy of EGCG, curcumin, resveratrol, celastrol, camptothecins, and other plant-derived drugs in various cancer models.

The bioavailability limitations related to stability, absorption and metabolism of compounds can be overcome with lipid-based and other vehicles (Elsheikh et al., 2018; Jung et al., 2015; Lambert and Elias, 2010), thus improving pharmacokinetics of phytochemicals with interest for prophylaxis and therapeutics of cancer (Tables 1, 4 and 5). Tables 5 and 6 present clinical trials registered at clinicaltrials.gov assessing the effectiveness of formulations for the delivery of phytochemicals in cancer therapy. The formulations of curcumin, resveratrol, black raspberry and genistein have shown good tolerability and beneficial outcomes (i.e., partial tumor marker responses and decreased lesion incidence); however, acceptable antitumor effect has not been established yet (Table 5). The liposomal preparation of curcumin for infusion has suppressed pancreatic tumor growth in a mouse xenograft model (Bolger et al., 2019) and immunomodulatory effects have also been observed in humans with oral phytosomal curcumin (Table 5). Other formulations of these polyphenolic phytochemicals are being investigated in humans and results are waited (NCT01294072).

In addition to oral administration, delivery systems can adjust phytochemicals pharmacokinetics in intravenous therapy, as demonstrated with PLGA–casein NPs entrapping EGCG in the shell and paclitaxel in the core, so that the catechin release in rat bloodstream was much more prolonged and preceded the delayed paclitaxel peak

Table 5
Clinical trials of phytochemical delivery formulations in cancer patients[a].

Phytochemical	Delivery system	Cancer type	Description and/or Main results	References
Curcumin	Phytosome lecithin-based (Meriva® curcuminoids)	Leukemia	Decreased absolute lymphocyte count in a subset of lymphocytic leukemia patients accompanied by an increase in CD4 and CD8 T-lymphocytes and Natural Killer cells.	Golombick et al. (2015)
	Nanodispersion	Advanced cancers	Phase I – Completed: No results were available.	NCT01201694
	Plant exosomes	Colon cancer	Phase I – Active, not recruiting: No results were available.	NCT01294072
	Phytosome lecithin-based (Curcuphyt®/Meriva®)	Endometrial carcinoma	Phase II – Completed: Seven patients orally consumed 2 g/day of curcumin phytosome exhibited downregulation of Major Histocompatibility Complex expression on leucocytes, upregulation of CD96 levels on CD16- cells, reduction of monocyte frequency and decreased inducible costimulator (ICOS) expression by CD8+ T cells. There was no difference in inflammatory biomarkers, frequency of other immune cell types, T cell activation or cyclooxygenase-2 expression. Questionnaires pointed improvement in quality of life, although not statistically significant.	NCT02017353, Tuyaerts et al. (2019)
	Liposomes (Lipocurc®)	Advanced cancers	Phase I/II – Active, not recruiting: Dose escalation studies resulted in no drug-limiting toxicity up to intravenous infusion rates of 300 mg/m^2 over 6 h, where 1/6 patients developed hemolysis and 3 showed hemoglobin decreases. Plasma curcumin concentrations were stable during infusion, but followed by a rapid decline. As evaluated by RECIST, no anti-tumor activity was observed, but 2 patients exhibited significant tumor marker responses and some clinical benefit.	NCT02138955, Greil et al. (2018)
	Micelles	Prostate cancer	Phase II – Active, not recruiting: Sixty four patients received treatment with 120 mg/day of the curcumin formulation or placebo for 3 days before and during radiotherapy. Although the formulation was well tolerated there were no significant differences in the occurrence of radiation-induced proctitis or cystitis.	NCT02724618, Saadipoor et al. (2018)
Resveratrol	Micronized trans-resveratrol	Polycystic ovary syndrome (cancer risk)	Phase (not applicable) – Unknown status: Thirty four patients were randomly assigned to resveratrol treatment (1500 mg/day orally) or placebo. Resveratrol decreased total testosterone, dehydroepiandrosterone sulfate and fasting insulin levels, and increased insulin sensitivity index.	NCT01720459, Banaszewska et al. (2016)
			Phase IV – Unknown status: Combination with simvastatin versus simvastatin monotherapy. No results were available	NCT02766803
Polyphenols (anthocyanins and others)	Bioadhesive black raspberry gel	Oral intraepithelial neoplasia	Phase I/II – Completed: Application of 10% (w/w) gel reduced lesion size and histological grade, and caused loss of heterozygosity, whereas the placebo group exhibited an increase in lesion size.	NCT01192204, Mallery et al. (2014)

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Table 5 (*continued*)

Phytochemical	Delivery system	Cancer type	Description and/or Main results	References
Genistein	B43-genistein immunoconjugate	Leukemia	Phase I – Unknown status: Patients with previous chemotherapeutic failure were treated with intravenous infusions of 0.1–0.32 mg/kg/day dose levels either for ten consecutive days or for three consecutive days for 3 weeks (9 infusions). The tested doses were well-tolerated, though some cases of drug-related fever. Pharmacokinetic analysis indicated a plasma half-life of 20 ± 5 h, mean residence time of 24 ± 5 h and a systemic clearance rate of 20 ± 3 ml/h/kg. In 14 patients, one presented durable complete remission and two had transient responses.	NCT00004858, Uckun et al. (1999)
	Crystalline form (AXP107-11®)	Pancreatic adenocarcinoma	Phase I/II – Unknown status: Sixteen patients received varying doses (400–1600 mg/day) in an initial phase and then in combination with gemcitabine chemotherapy. No drug-limiting toxicity was reached, although 14 patients experienced at least one toxic event (thrombocytopenia and neutropenia). Pharmacokinetic test suggest a five-fold improved oral bioavailability. Survival at 6 months was 44% and 19% at 1 year.	NCT01182246, Löhr et al. (2016)
	Nanosuspension (BIO 300®)	Non-small-cell lung carcinoma	Phase I/II – Recruiting: Mitigation of pneumonitis and pulmonary fibrosis induced by standard radiotherapy and chemotherapy (paclitaxel and carboplatin). No results were available.	NCT02567799
	Genistein combined polysaccharide	Prostate cancer	Phase (not applicable) – Completed: Oral treatment with genistein-rich extract, 5 g/day (450 mg/day of genistein and 450 mg/day of other aglycone isoflavones). Patients after radio/chemotherapy and afterwards treated with the extract showed no reduction in PSA levels, but 8 out of 13 patients in the active surveillance group showed 3% to 61 % decreases in PSA after 6 months intervention.	NCT00269555, deVere White et al. (2004)
			Phase II/III – Completed: No results were available.	NCT00584532

Abbreviations: PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria In Solid Tumors guideline.

[a] Search was carried at clinicaltrials.gov (March of 2019) and withdrawn studies were excluded.

Table 6
Clinical trials of camptothecins delivery formulations completed at an advanced clinical phase[a].

Phytochemical	Delivery system	Cancer type (drug combination)	ClinicalTrials.gov identifier
Irinotecan	Liposomes[b]	Metastatic pancreatic cancer (with 5-fluorouracil and leucovorin)	NCT01494506[b]
	Liposomes	Colorectal cancer (with floxuridine)	NCT00361842
	Liposomes	Pancreatic neoplasms	NCT00813163
	Liposomes of SN-38 (irinotecan metabolite)	Colorectal cancer	NCT00311610
	Eluting beads (drug release microspheres)	Liver cancer from colorectal cancer	NCT02015754; NCT00844233
	PEG-irinotecan	Colorectal cancer (with cetuximab)	NCT00856375; NCT00598975
Lurtotecan	Liposomes	Small cell lung cancer	NCT00046787
		Head and neck cancer	NCT00022594
		Ovarian neoplasms	NCT00046800
		Ovarian/tubal/peritoneal cancer	NCT00010179
Camptothecin	Cyclodextrin-based nanoparticles	Ovarian/tubal/peritoneal cancer	NCT01652079
		Advanced solid tumors	NCT00333502
		Stomach, gastroesophageal, or esophageal cancer	NCT01612546
		Non-small cell lung cancer	NCT01380769
	Poly-L-glutamate conjugate	Colorectal cancer (with 5-fluorouracil and leucovorin)	NCT00291785
		Ovarian cancer	NCT00291837
	Aminocamptothecin coloidal dispersion	Kidney cancer	NCT00003551
Rubitecan	Liposomes	Non-small-cell lung cancer	NCT00250068
		Endometrial cancer	NCT00249990

[a] Search was carried at clinicaltrials.gov (March of 2019) and phase I trials were excluded.
[b] Phase III trial. Liposomal formulation Onivyde® is approved for clinical use.

concentration (Narayanan et al., 2014). Enhanced therapeutic efficacy has been associated to greater stability of the bioactive drug encapsulated in a vehicle (Razi et al., 2018). Li et al. (2018) reported that curcumin loaded in polysaccharide NPs had higher stability under different decomposing conditions and increased toxicity against B16F10 melanoma cells than free curcumin.

Camptothecin derivatives irinotecan and topotecan in free forms have been used for therapy of colorectal, small-cell lung and ovarian carcinomas in humans, and an irinotecan liposomal formulation in combination with 5-fluorouracil and leucovorin has been approved for treatment of metastatic pancreatic cancer refractory to gemcitabine-based therapy (Wang-Gillam et al., 2019). Many other delivery systems for camptothecins are under development, and the formulations reaching advanced trials in humans are mostly liposome- and polymer-based (Table 6). Major safety concerns on liposomal irinotecan formulations are neutropenia, diarrhea, vomiting and fatigue (Wang-Gillam et al., 2019), and new camptothecins formulations are being investigated for reduction of toxicity and improvement of efficacy in a wider range of clinical applications, including second-line therapy of refractory ovarian cancer (NCT00291837). Moreover, various formulations of camptothecins are finding therapeutic use in drug combinations, e.g. irinotecan with antimetabolites (Table 6). Actually, several recent studies have confirmed the clinical efficacy of irinotecan in combination with 5-fluorouracil (Kang et al., 2018; Vogl et al., 2019; Wang-Gillam et al., 2019). It is expected that ongoing research would confirm various advantages of camptothecin formulations (e.g., better toxicity profile and efficacy against resistant tumors) and these approaches can be applied to other phytochemicals.

6.2. Searching for novel therapeutic approaches

Although data indicates carrier systems can provide higher concentrations in plasma, only a few studies investigated the distribution of the phytochemical or their eventual metabolites in organs and in tumor tissues to support the concept of preferential delivery (Aqil et al., 2017a; Chen et al., 2018; Wang et al., 2017).

Anticancer efficacy of phytochemicals delivery systems has been tested against a considerable variety of cancer models, mainly xenografted tumors, and several chemically induced tumors (Table 2). Further studies for treatment of metastasis could be very relevant, particularly with specific phyto-antioxidants able to modulate ROS production that promotes metastatic phenotypes (Chen et al., 2018; Kaur et al., 2018; Sznarkowska et al., 2017). These studies require animal models able to mimic clinical conditions for which new therapeutic options are necessary.

There is also a need for chemo-sensitizers to disable resistance to therapies, for example resistance to 5-fluorouracil. In other way, anticancer phytochemicals may enable a reduction of chemotherapy dose and off-target effects, whilst maintaining treatments efficacy. There are innovative examples of using delivery systems to potentiate efficacious combinations of phytochemicals with classic chemotherapeutics (Elgohary et al., 2018; Kabary et al., 2018; Narayanan et al., 2014). More systematic and mechanistic studies are useful to identify optimal drug synergism (Baran et al., 2014; Mahbub et al., 2015), and intensification of research on combination regimes with other therapies in clinical use could facilitate translation of phytochemicals formulations.

Even though at an early stage of development, integration of imaging and other theranostics techniques with delivery systems brings new possibilities for therapeutic protocols and for the investigation of phytochemicals biological actions, including tracking of carriers in the body. As with carbon nanotubes referred in Section 4, graphene oxide-based carriers still await further exploitation for phytochemicals delivery, encouraged by pioneering works with simple polyphenols (Table 3) and the increased cytotoxicity afforded to chlorogenic acid against different malignant cells, but not normal fibroblasts (Barahuie et al., 2017b), and similarly with gallic acid/cadmium sulfide to kidney cells (Peng et al., 2018d). Progress in fabrication of these nanomaterials and gold and iron oxide NPs, compatibles with near-infrared light-responsive systems or multimodal imaging, will deserve attention for phytochemical-based therapies.

Advances have been achieved on administration of resveratrol as a prototypical phytochemical via buccal, nasal, colonic and vaginal delivery systems, urging the development of new vehicles and thorough evaluation of preventive/therapeutic efficacy. In particular, nasal and dermal administration are gaining significant acceptance due to its non-invasiveness, avoidance of first-pass liver metabolism, and direct targeting possibilities. Dermal and transdermal delivery provide controlled drug release with a wide scope of applications for local or systemic deliveries, and simulation tools to design delivery systems may assist future *in vivo* assessments.

A fundamental challenge remaining is to disentangle the role of the possible mechanisms of action participating in the anticancer activity of phytochemicals delivered at tumor regions. Enhanced ROS production

and antioxidant systems that prevent intracellular oxidative damage are associated to rapid proliferation of tumor cells and resistance to treatments (Mahbub et al., 2015; Sznarkowska et al., 2017). Disturbance of antioxidant systems are therefore a plausible anticancer strategy, but with the exception of some studies for NF-κB, the ability of target-delivered phytochemicals to regulate major Nrf2 and glutathione systems in tumors has not been described.

Whereas the antioxidant actions of polyphenols are accepted to play a role in prevention during the early stages of the carcinogenesis process, the predicted redox modulatory actions running with antitumor effects remain cloudy. As discussed in Section 3, several *in vitro* studies with compounds in free form highlight the prooxidant antiproliferative activities, but show antioxidant actions when loaded into delivery systems (Parashar et al., 2018; Pool et al., 2018). Connected to the anti/pro-oxidant action, awareness of the anti-inflammatory potential of phytochemicals in delivery systems was confirmed *in vivo* for gambogic acid, resveratrol and *Monascus* yellow pigments (Table 2).

Noteworthy, novel treatment modalities are emerging based on the immunomodulatory action of phytochemicals (Hou et al., 2018; Liu et al., 2018d; Lu et al., 2016; Xing et al., 2018; Rengasamy et al., 2019). Regarding immune-based therapies, the trastuzumab conjugate with cytotoxic emtansine, a derivative of maytansine from *Maytenus serrate*, is an important targeted therapy for HER2-overexpressing tumors, and latest advances in cancer immunobiology highlight the critical role of the tumor immune microenvironment for cancer progression and response to treatments (Taniguchi and Karin, 2018; Xing et al., 2018). Lu et al. (2016) combined curcumin micelles with a peptide vaccine for increased therapeutic efficacy in a melanoma model due to the changes in immune cells populations at spleen and tumor tissue that generated a more immune-responsive tumor microenvironment. Fraxinellone inhibited the expression of the PD-L1 immune checkpoint (Xing et al., 2018) and, when delivered by a nanoemulsion system, accumulated at tumor, enhanced changes in immune cells subsets and improved the therapeutic effect of a tumor-specific peptide vaccine in mouse (Hou et al., 2018). Very recently, a combination of mitoxantrone and celastrol nanodelivered at melanoma microenvironment stimulated antitumor immunity, induced tumor dormancy and sustained immune surveillance (Liu et al., 2018d). The open possibility of synergistic combinations of natural compounds and immunotherapies clearly deserves further research for their great potential towards new and improved cancer treatments.

7. Conclusions

A great diversity of systems devised for the delivery of promising phytochemicals is under investigation as shown in Fig. 4 that summarizes the data discussed in this work. The critical analysis of the experimental evidences here reviewed give support for the following conclusions and suggestions for future work:

- Oral lipid-containing formulations are able to improve the pharmacokinetics of chemopreventive and therapeutic phytochemicals, and further efforts are necessary to characterize the drug distribution and accumulation at tumor sites;
- The most recommended systems to proceed for clinical evaluation are those with curcumin, resveratrol, EGCG, camptothecins and celastrol delivered by polymer/biopolymer NPs, liposomes or other lipid-based carriers, especially regarding treatment of melanoma, lung and breast cancer (Fig. 4);
- Encouraging results with dermal, buccal, nasal, vaginal, pulmonary and colon-targeted delivery ask for further development of biopolymer films and particles, lipid carriers, or other rationally designed systems for these applications;
- New or improved targeting moieties, protein-based carriers and immunoconjugates of phytochemicals have a high potential to provide novel targeted therapies;
- Further research is necessary to understand the anticancer activity of some phytochemicals, specifically the identification of subcellular targets, and the clarification of antioxidant *vs* prooxidant effects and immunomodulatory actions. This could enable the successful combination of phytochemicals with conventional chemo- or immunotherapies.

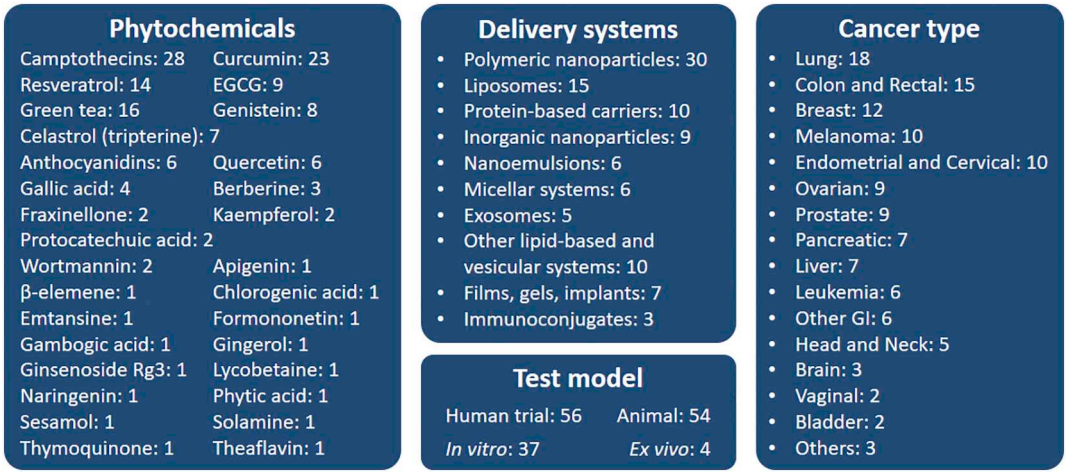

Fig. 4. Number of delivery system types, phytochemicals and cancer models employed in the studies covered by the present review. Most of studies were published in the last three years. EGCG, epigallocatechin-gallate; GI, gastrointestinal.

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Conflict of interest disclosures

The authors declare no conflict of interest.

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