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Dietary polyphenols for tumor therapy: bioactivities, nano-therapeutic systems and delivery strategies†

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Various dietary polyphenols have demonstrated potent anti-tumor properties and are being evaluated as potential adjuncts in cancer treatment. Although several reviews have offered extensive insights into the anti-tumor activities of dietary polyphenols, they frequently lack a detailed discussion on the design of therapeutic protocols and targeted delivery strategies of these compounds, which impedes the translation of their biological activity into clinical practice. This article aims to deliver a comprehensive review of the anti-tumor properties of dietary polyphenols, while also examining the design and implementation of nanotherapy systems based on these compounds. Additionally, given the challenges of low water solubility and stability of dietary polyphenols, this article outlines the current methodologies for the formulation and delivery of nano-preparations to enhance tumor targeting and therapeutic efficacy. This comprehensive review aspires to deepen our understanding of the operational mechanisms of dietary polyphenols and expand their clinical applications, thereby facilitating the development of polyphenol-based dietary supplements and food additives, and promoting the progress of dietary polyphenol-related nanomedicine.

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1. Introduction

Cancer is a primary cause of death, characterized by abnormal cell division in a small area of the body where cells undergo uncontrolled proliferation, with an imbalance of cellular programmed death and proliferation.[1] According to a report by the World Health Organization (WHO), 19.2 million new cancer cases were reported globally in 2020, along with 9.95 million cancer-related deaths.[2] Although cancer deaths account for about 13% of all deaths worldwide, changing or avoiding key risk factors can prevent more than 30% of cancer deaths.[3] Despite significant advances in cancer treatment, the incidence and mortality rates remain disappointingly high. Recent advancements have demonstrated the feasibility of early-stage cancer eradication through the application of biochemistry, immunotherapy, and contemporary pharmaceuticals. Notably, clinical outcomes for human malignancies such as epithelial ovarian cancer and rectal cancer have exhibited marked improvement, leading to prolonged patient survival. The traditional modalities of cancer treatment have demonstrated high efficacy. However, concerns persist regarding the efficacy, resistance, and toxicity of these treatments for cancer patients, which limit their clinical utility. Therefore, there is an urgent need for more research to develop more effective and less toxic treatments.

Polyphenols and other natural products may serve as ideal alternatives, particularly when utilized in conjunction with other medications, as they may exhibit superior efficacy and safety profiles. Natural dietary polyphenols are plant-derived secondary metabolites that feature hydroxybenzene rings in their chemical structure,[4] ranging from simple flavonoid and phenolic acid structures to more complex colored anthocyanins.[5] These compounds exhibit dynamic therapeutic and health-promoting properties, and extensive research has been conducted on this chemical compound group. Natural dietary polyphenols have the ability to impede the progression of cancer at various stages, thereby maintaining a balance between inhibitory factors and those that induce abnormal cellular changes, ultimately reducing the risk of early cancer development.[6] Simultaneously, polyphenols have the potential to function as potent anticancer agents even in advanced stages of cancer.[7] The natural bioactive compounds often exert their effects by modulating key molecular signal transduction pathways, such as the nuclear factor kappa-B (NF-κB), protein kinase C (PKC) signaling, oxidative stress,[8] and G

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protein-coupled receptor (GPCR) pathways, which have been implicated in the growth and progression of cancer.[9] *In vitro* and *in vivo* studies have demonstrated that polyphenols derived from various dietary sources can significantly contribute to the delay of cancer development and progression.[10] This is achieved through the reduction of cancer cell proliferation, preventing the formation of new blood vessels, causing cells to stop dividing or die, as well as controlling the body's immune response.[11]

Currently, some polyphenols are undergoing clinical trials and have shown promising results in cancer prevention. Polyphenols exhibit limited bioavailability as a result of inherent factors (including their chemical structure, molecular weight, and poor water solubility) and external factors (such as reduced gastrointestinal stability, significant molecular transformations in phase I and II metabolism, and swift elimination from the body).[12,13] Consequently, the limited application of polyphenols in pharmaceuticals and functional foods is greatly hindered by their inefficient delivery system and poor bioavailability.[14] A range of methodologies, including the utilization of nanotechnology, have been employed to improve the solubility and bioavailability of polyphenols.[15] Researchers have also developed dynamic drug delivery systems for specific targets[16] to further improve the bioavailability and absorption of these compounds within the gastrointestinal tract, facilitating their delivery to designated organs. Meanwhile, a variety of approaches have been proposed to investigate the individual and combined anticancer effects as well as chemopreventive properties of polyphenols. Notwithstanding the swift advancements in nanotechnology, the potential clinical applications of dietary polyphenols in oncology appear to be more promising. Nevertheless, there remains a paucity of thorough elucidation regarding the mechanisms of action of dietary polyphenols and the formulation of nanomedicines. It is imperative to furnish a comprehensive overview to expedite the development and clinical evaluation of polyphenol-based dietary adjuvants and targeted therapeutic drugs.

This review presents a categorization of dietary polyphenols and their sources, while investigating their anti-tumor bioactivities, including specific molecular targets, and emphasizes the potential of dietary polyphenols as anti-cancer agents. Additionally, the review emphatically examines the strategies for the development of tumor targeted dietary polyphenol-based nano-therapeutic systems. Moreover, it also discusses potential delivery methods designed to enhance the bioavailability of polyphenols and offers a thorough examination of these approaches.

2. Classification of dietary polyphenols

The production of phenolic substances, a class of intricate bioactive molecules, is mediated by the naturally occurring shikimic acid and acetate pathways.[17] Polyphenols, which literally means "having multiple phenolic groups", are mostly found in the daily human diet.[18] They are secondary metabolites distinguished by the occurrence of multiple aromatic rings and two or more hydroxyl groups. These compounds are prevalent in almost medicinal and edible plant components such as roots, stems, leaves, flowers, fruits, and seeds, which serve as the most abundant dietary sources of phenolic compounds.[19] Furthermore, these bioactive compounds are abundantly present in everyday food sources, rendering them easily accessible and safe for consumption. Phenolic compounds have about 8000 known chemical structures and are divided into five major classes: phenolic acid (including hydroxybenzoic acid and hydroxycinnamic acid), stilbenes, lignans, flavonoids (including flavanols, isoflavones, anthocyanins, flavanones, flavones and flavonols), and tannins (Fig. 1).

The phenolic acids are aromatic carboxylic acids containing hydroxyl derivatives and characterized by the presence of a single phenolic ring in their molecular structure. They can be classified into two types: hydroxybenzoic acid and hydroxycinnamic acid derivatives. Hydroxycinnamic acid derivatives, including caffeic, *p*-coumaric, ferulic, and sinapic acids, exhibit higher abundance in plants compared to benzoic acid derivatives, which include gallic acid, protocatechuic acid, and *p*-hydroxybenzoic acid. Hydroxybenzoic acids, which are derived from benzoic acid, possess a parent structure characterized by a C6–C1 configuration. In contrast, hydroxycinnamic acids, originating from cinnamic acid, are typically present in plants as simple esters of glucose or quinic acid.[20] The distinctive structural characteristics of phenolic acids endow them with notable antioxidant properties, in addition to a range of other health benefits. Stilbenes, a subclass of phenylpropanoid compounds, are defined by a 1,2-diphenylethylene core that consists of two phenolic rings linked by methylene bridges. Although stilbenes are present in relatively low concentrations in plants, they have garnered increasing attention due to their multifaceted effects on both plant diseases and human health.[21] Resveratrol, a representative compound of stilbene, is widely acknowledged for its potential in safeguarding cardiovascular health and mitigating the risk of chronic ailments such as diabetes.[22] Lignans, a group of phytoestrogens derived from two phenylpropane derivatives (C6–C3 monomer), exhibit remarkable structural diversity and are extensively found in the roots, stems, leaves, and seeds of various plant species.[23] They can be found abundantly in fiber-rich plants such as cruciferous vegetables (for instance, broccoli), root vegetables (such as carrots), and alliums (like garlic), as well as grains like oats and barley, and legumes including soybeans. The increasing number of reports on lignans have demonstrated their ability to bind to estrogen receptor (ER), exhibit diverse pharmacological effects, and disrupt cancer-promoting mechanisms.[24]

The most prevalent polyphenols in the human diet are flavonoids. Flavonoids possess a fundamental chemical structure known as a C6–C3–C6 skeleton, which comprises two benzene rings connected by a third heterocyclic ring that incorporates an oxygen pyrrole ring.[25] Currently, approximately 6000 varieties of flavonoids have been identified. Flavonoids exist in

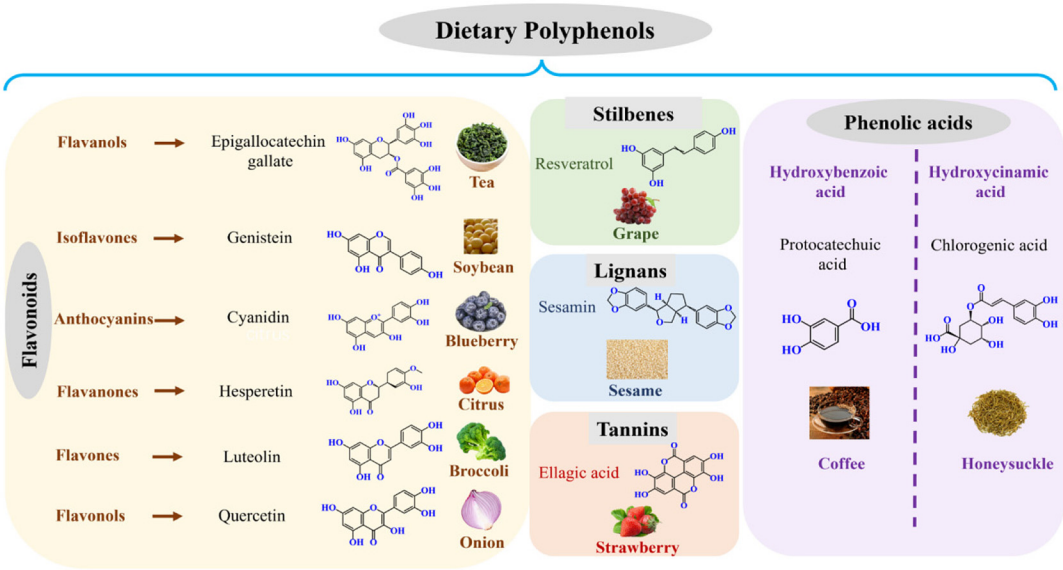

Fig. 1 Classification sources and representative compounds of dietary polyphenols.

various forms including aglycones, glycosides, and methylated derivatives, and can be categorized into six primary subgroups: flavanols, isoflavonoids, anthocyanins, flavonones, flavonols, and flavones.[26] It is noteworthy that flavonoids are widely present in varieties of vegetables, fruits, and plant-based beverages, serving as dietary supplements that contribute to health promotion and disease prevention. Naturally occurring dietary flavonoids predominantly exist in the form of glycosides, including glucosides, galactosides, rhamnosides, arabinosides, and citrinosides. Among them, the predominant flavonoid types identified in plants include flavone *O*/*C*-glycosides and flavonol *O*-glycosides. Flavonoid *O*-glycosides are predominantly present in the 3- or 7-*O*-glycoside configurations, whereas the majority of flavonoid *C*-glycosides are characterized by 6- and 8-*C*-glycosidic structures.[27]

There are three types of tannins including condensed tannins (proanthocyanidins), hydrolyzable tannins (gallo- and ellagitannins) and phlorotannins. Condensed tannins, commonly referred to as proanthocyanidins, are present in the form of flavanol dimers, oligomers, and polymers. These compounds can be categorized into subclasses – namely procyanidins, prodelphinidins and profisetinidins – based on the specific flavanol units they incorporate, which include catechin, gallocatechin, and fisetinidol, respectively. In certain instances, galloylated proanthocyanidins are produced when some flavanol units undergo esterification with gallic acid. These tannins are found in a variety of edible plant sources, including fruits (such as apples, grapes, and plums), legumes (including beans and lentils), nuts (like almonds, hazelnuts, and pecans), grains (such as barley and sorghum), as well as processed food products like fruit juices, cocoa derivatives, wine, and ciders. Additionally, hydrolyzed tannins, which include gallic tannins and ellagitannins, primarily exist as polyesters of gallic or ellagic acid that contain polyol components, typically glucose. Focusing solely on ellagitannins, an extensive array of nearly 1000 distinct hydrolyzable tannin structures has been identified. The prevalence of condensed tannins is higher compared to their less common counterparts. Nonetheless, the aforementioned compounds can be obtained from a variety of sources, such as strawberries, raspberries, pomegranates, mangoes, pecans, walnuts, and wines, particularly those which have been aged in oak barrels. Additionally, phlorotannin is a polymer of oligomers, primarily consisting of phloroglucinol units that are interconnected by biaryl and/or diaryl ether bonds, and is predominantly found in brown algae.[28] The antioxidant properties of these compounds suggest that their consumption may significantly contribute to the reduction of oxidative stress and inflammation, thereby potentially lowering the risk of developing various non-communicable diseases (NCDs) (such as diabetes,[29] cardiovascular disorders,[30] cancers, *etc.*). These chronic conditions are influenced by a multitude of factors, including genetic predispositions, physiological and environmental conditions, as well as lifestyle choices.

3. Tumor suppressive activity of dietary polyphenols

In their dietary form, most polyphenols exist as glycosylates or free glycans and undergo biotransformation predominantly within the gastrointestinal tract, liver, and gut microbiota. Dietary polyphenols have garnered considerable attention from researchers owing to their remarkable anti-inflammatory, anticancer, and immunomodulatory properties.[31] Polyphenols play an important role in cancer chemoprevention. Multiple research studies have demonstrated that the daily consumption of specific polyphenols is closely linked to the prevention

of various types of cancers.[32] The intrinsic anticancer properties of dietary polyphenols maybe attributed to their direct regulation of diverse signaling pathways or their indirect modulation of epigenetic regulation, inflammation, and gut microbiota. Dietary polyphenols exert their chemoprophylaxis through a variety of molecular mechanisms that act on the apoptosis signaling pathway of cancer cells. The anticancer properties of dietary polyphenols primarily manifest in their ability to inhibit various aspects of tumor development, including proliferation, growth, invasion, metastasis, and angiogenesis. Additionally, dietary polyphenols regulate programmed cell death processes such as apoptosis and pyroptosis, suppress chemoresistance, enhance the immune response against cancer cells, and modulate the tumor immune microenvironment (TIME).

3.1. Intrinsic anti-tumor bioactivity of dietary polyphenols

Previous studies have demonstrated that various dietary polyphenols, including resveratrol,[33] curcumin,[34] quercetin,[35] tea polyphenols such as catechin,[36] epicatechin,[37] and epigallocatechin gallate (EGCG) from tea and cocoa derivatives[38,39] and compounds like oleuropein and hydroxytyrosol[40] found in olive oil,[41] exhibited significant anti-tumor properties, which are being explored for their potential in cancer therapy development.[10] Dietary polyphenols have been shown to inhibit the proliferation[42,43] and metastasis of cancer cells, and induce apoptosis, and suppress angiogenesis[44] through multiple mechanisms.[45,46] They exerted their inhibitory effects by modulating various signaling pathways associated with tumor progression, including phosphatidylinositol 3-kinase/phosphorylation of protein kinase B (PI3K/AKT),[47] mammalian target of rapamycin (mTOR),[48] signal transducer and activator of transcription (STAT),[49] tumor protein 53 (p53),[50] and NF-κB.[51] Furthermore, dietary polyphenols play a role in regulating the anti-tumor immune response by promoting the activation of tumor-associated macrophages[52] and cytotoxic T cells, as well as natural killer cells.[53] Evidence suggested that these polyphenols can influence the expression of immune checkpoints such as PD-L1/PD-1, thereby enhancing anti-tumor immune responses and improving the efficacy of immune checkpoint therapies.[54] Additionally, recent studies also suggested that dietary polyphenols may impact tumor progression through the modulation of gut microbiota and their metabolites.[55] A comprehensive overview of the bioactivities of dietary polyphenols against cancer is provided in the ESI,† with the anti-tumor effects and mechanisms of action of various polyphenols summarized in Table S1.† And Fig. 2 visually illustrates the tumor-suppressive effects of dietary polyphenols. Consequently, the potent anti-tumor biological activities of dietary polyphenols are significant for drug development and dietary adjunct therapies.

3.2. Sensitize tumor chemotherapy

Polyphenol compounds in diet can be used in combination with approved clinical anti-cancer drugs to enhance cancer treatment efficacy.[56] Currently, many cancer chemotherapy drugs often cause patients to experience nausea, vomiting, and other toxic side effects, damaging the patient's body, and the development of drug resistance in multiple drugs has resulted in more cases of cancer treatment failure.[57] Consequently, it is crucial for overcoming tumor drug resistance by deepening our understanding of the underlying mechanisms of drug resistance arising from cellular heterogeneity within tumors, and improving drug sensitivity through alternative strategies.

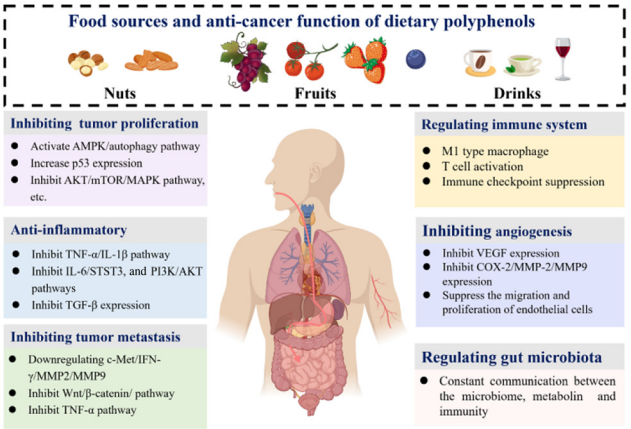

Fig. 2 Inhibitory effect of dietary polyphenols on tumors.

Numerous studies have demonstrated that polyphenols can enhance the efficacy of chemotherapy drugs, allowing for anti-tumor activity at lower doses and mitigating the toxic effects on organisms.[58] This phenomenon is largely ascribed to the metabolic modulation exerted by polyphenols, which enhances pharmacokinetic profiles, thereby resulting in a significant reduction in drug side effects and body resistance.[59] Curcumin has been shown to synergistically enhance the anti-tumor effects of chemotherapy drugs by providing protection to the body.[60] Arellano-Rodríguez *et al.* demonstrated that curcumin effectively reduces tumor volume by upregulating prostate apoptosis response protein 4 (PAR4) in tumor cells, sensitizing them to cisplatin.[61] Additionally, Paciello *et al.* revealed that curcumin can enhance the chemotherapy effects of drugs by modulating drug resistance factors such as nuclear factor, erythroid 2 (NFE2) like bZIP transcription factor (Nrf) 2, NF-κB, and STAT3 in tumors, while also mitigating cisplatin-induced cochlear toxicity through regulation of the Nrf-1/HO-1 and P53 pathways.[62] Lu *et al.* have also demonstrated that curcumin can mitigate oxaliplatin-induced liver damage and reduce oxidative stress by activating Nrf-1, as well as increasing the expression of HO-1.[63] Another study has also indicated that the combination of curcumin and cisplatin enhances their anti-tumor activity in breast cancer, significantly reducing the drug's kidney toxicity while suppressing tumor growth *in vivo*.[64] Simultaneously, curcumin has been observed to augment the sensitivity of cisplatin and reverse tumor resistance in various other cancer types.[65–67] In addition to its synergistic effect with cisplatin therapy, curcumin has also been shown to enhance the tumor suppressor activity of other

chemotherapy agents. Tian *et al.* utilized curcumin to inhibit lin-28 homolog B (Lin28B) expression in hepatocellular carcinoma, thereby increasing cell sensitivity to paclitaxel.[68] Furthermore, curcumin has been found to improve the inhibitory effect of doxorubicin (DOX) on drug-resistant breast cancer cells and reverse the resistance of tumor cells to DOX.[69] Clinical trials in patients undergoing 5-fluorouracil (5-FU)/oxaliplatin chemotherapy have also demonstrated the safety and tolerability of curcumin as a daily oral dietary supplement, further ensuring its suitability for subsequent clinical studies.[70] Resveratrol, another polyphenol with cancer-fighting properties, has been demonstrated to exhibit synergistic effects with drugs.[71] Research has indicated that the initial administration of resveratrol, in conjunction with platinum-based chemotherapeutic drugs, can increase the apoptotic sensitivity of ovarian cancer cells and mitigate the development of chemotherapy resistance. Additionally, this combination has been shown to inhibit tumor cell metastasis and enhance the overall effectiveness of chemotherapy.[72] Dun *et al.* also validated that the combination of resveratrol and 5-FU significantly enhances tumor cell apoptosis, activates caspase-3 and P53 protein levels, effectively increases the Bax/Bcl-2 ratio, and markedly inhibits the proliferation of skin cancer cells.[73] In addition to inhibiting tumor progression, resveratrol has also been found to mitigate tissue damage induced by chemotherapy drugs. Resveratrol can alleviate symptoms such as myocarditis caused by penicillin during tumor chemotherapy, as well as nephrotoxicity induced by arsenic trioxide, and reduce the adverse effects of drugs, indicating its promising preclinical application prospects.[74]

The combination of tea polyphenols and chemotherapy drugs represents a novel treatment approach. The synergistic effects of tea polyphenols with bleomycin,[75] cisplatin, 5-FU,[76] paclitaxel and other drugs have been shown to significantly inhibit the proliferation and growth of tumor cells while enhancing their inhibitory activity. Furthermore, compared to monotherapy, the modulation of tea polyphenols on tumor proliferation and drug resistance gene expression can significantly suppress tumor drug resistance and enhance the efficacy of drug treatment.[59] Additionally, other dietary polyphenols such as gallic acid,[77] tannic acid[78] and genistein[79] polyphenols have been demonstrated to exert a synergistic effect with chemotherapy drugs, improving tumor resistance while enhancing the therapeutic effects of drugs. They also provide a certain degree of tissue protection and mitigate the toxic side effects caused by drugs.

4. Polyphenol-based nano-therapeutic systems

The presence of hydroxyl groups in polyphenols imparts distinctive physical and chemical characteristics, enabling the formation of nanoparticles or polymers in conjunction with various metals,[80] proteins,[81] and polymers[82] to improve therapeutic efficacy in cancer treatment. Owing to their distinctive structure and covalent/non-covalent interactions with ligands,[83] polyphenols exhibit enhanced antioxidant activity[84] as well as magnetic[85] and photothermal properties,[86] rendering them highly promising in the development of tumor-targeted therapy nanoplatforms.[87,88]

4.1. Metal–polyphenol networks

Catechol moieties and galloyl groups, rich in polyphenols, can effectively form complexes with metal ions to construct metal–polyphenol complexes, which have become the most widely used strategy for polyphenol-based treatment systems.[58] Dietary polyphenols possess the ability to chelate iron ions and are employed in the treatment of iron overload in tumors. The interaction between tannic acid and iron ions is extensively utilized in the development of therapeutic systems for tumor treatment. Nanostructures derived from this complex, in conjunction with docetaxel, disrupt microtubule architecture and inhibit the activity of glutathione peroxidase 4 (GPX4). This disruption results in a significant increase in the production of reactive oxygen species, which plays a critical role in inducing both cellular apoptosis and ferroptosis.[89] As shown in Fig. 3A, to achieve drug accumulation and targeted delivery, the iron tannate complex enables drug encapsulation and retention in the acidic matrix of the tumor microenvironment for enhanced chemotaxis.[90]

In addition to ferroptosis, photothermal therapy also plays a crucial role in the polyphenol-based treatment system. Tannic acid and the complex assembly of Fe^{3+}/Mn^{2+} exhibit excellent photothermal effects, which can lead to the inhibition of the PD-1/PD-L1 pathway and synergize with ferroptosis to induce a potent anti-tumor immune response and promote tumor apoptosis.[91] To enhance drug retention in the acidic tumor microenvironment for improved accumulation and targeted delivery, Sun *et al.* fabricated nanofibers chelated with gallic acid, aspirin, iron(II), and polyvinylpyrrolidone. These nanostructures possess unique dimensions and structures that effectively prolong tumor enrichment time.[92] In addition to the synergistic effect with photothermal therapy, Liang *et al.* incorporated the photosensitized agent chlorin e6 (Ce6) into an EGCG-based metal polyphenol network with CD44 targeting in order to enhance ferroptosis in tumor cells through photodynamic therapy.[93] Simultaneously, metal polyphenol drug delivery networks have demonstrated the ability to mitigate the systemic toxicity of anti-tumor drugs. EGCG-induced inhibition of carbonyl reductase 1 (CBR1) protein expression can decrease the conversion of DOX to doxorubicinol (DOXOL), thereby enhancing tumor-specific toxicity and reducing the adverse effects of DOX.[94] Catechin and magnesium (Mg)(II) nanocomposite particles have been utilized for the targeted delivery of small interfering RNA (siRNA) to tumors. Beyond the inherent anticancer properties of catechin–Mg(II) granules, siRNA-loaded nanocomplexes demonstrated a pronounced inhibitory effect on the PI3K/AKT signaling pathway, which significantly impeded tumor progression in clinically relevant animal models of bladder cancer.[95] Additionally, metal polyphenol nanoparticles for drug delivery

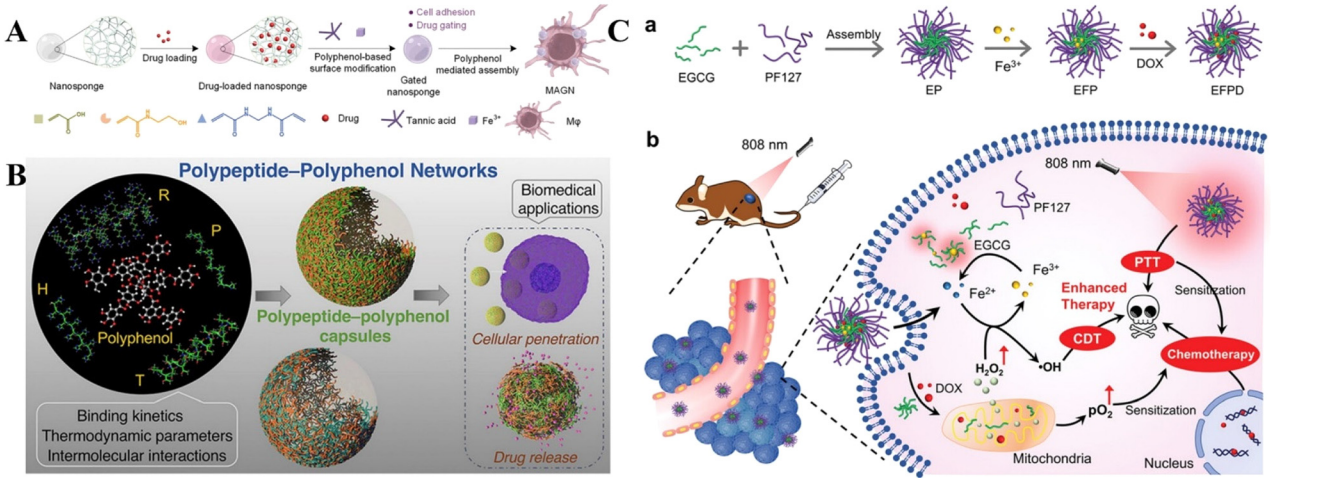

Fig. 3 Modification of surfaces and the assembly of dietary polyphenols within nanoparticles (A).[90] Strategies for supramolecular assembly and drug delivery involving polyphenols and peptides (B).[98] Construction and implementation of the polyphenol-based nanotherapy system (C).[99] Strategy and process of the self-assembly of EGCG and polymer to construct nanoparticles and drug delivery (a). Schematic diagram of the operational mechanism of photothermal therapy and chemotherapy (b).

also exhibited remarkable retention capabilities and improved accumulation in tumors. In contrast to traditional tumor targeting methods, the targeted modulation of macrophages through metal polyphenol networks is also utilized for regulating the tumor immune microenvironment. Han *et al.* fabricated manganese–polyphenol nanonetworks by combining tannic acid with manganese ions and encapsulating CpG-oligodeoxynucleotides.[96] The nanoparticle can effectively enter macrophages and promote their M1-type polarization to enhance tumor immunity. This research also expands the potential applications of metal polyphenol nanoplatforms and enhances the inhibitory effect on malignant tumors. In addition to metal ions, complex particles of polyphenol–cisplatin have been developed to improve tumor therapy. Pegylated gallic acid complex with Pt(II) in functionalized drugs can form stable nanoparticles for controlled drug loading and release in the tumor microenvironment.[97]

4.2. Polyphenol–polymer nanocomplexes

The utilization of polyphenol-based supramolecular assembly in biomaterials has driven the advancement of nanomedicine by reducing reliance on complex chemicals.[82] Additionally, self-assembly of dietary polyphenols and polymers is employed for tumor targeting and drug delivery.[100] As shown in Fig. 3B, Han *et al.* conducted a detailed study on the polyphenol–polypeptide network using molecular docking and binding kinetics techniques, demonstrating the interaction between different types of peptides, amino acids, and polyphenols utilized in nanoparticle construction.[98] The designed polyarginine–tannic acid nanocapsule exhibited high cell permeability and drug delivery efficiency, leading to increased mortality of tumor cells. To enhance the tumor tissue penetration and accumulation efficiency of nanocarriers, polyphenol–polymer self-assembled nanoparticles were utilized for improved tumor targeting. Tannic acid can self-assemble with polyethylene–polypropylene glycol (F-127) through hydrogen bonding and hydrophobic forces, facilitating the loading of DOX. These self-assembled particles possess low toxicity and pH sensitivity, enabling highly effective cancer treatment.[101] In order to integrate multiple therapeutic modalities, Shi *et al.* co-assembled EGCG, F-127 and iron(III) ions with DOX for the concurrent execution of chemotherapy, photothermal therapy and ferroptosis, resulting in enhanced tumor ablation while minimizing drug toxicity (Fig. 3C).[99]

Utilizing the strong affinity of polyphenols for bioactive molecules, Liang *et al.* developed EGCG-poly(ethylene glycol) (PEG) nano-micellar complexes for the targeted delivery of DOX to tumor. The synthesis of EGCG-PEG is achieved through an aldehyde-mediated reaction, which results in a complex shell that effectively encapsulates DOX. The intermolecular interactions between EGCG and DOX facilitate a significant loading of DOX, thereby ensuring its stability within the core of the complex. This structural arrangement, characterized by the interactions among EGCG, PEG, and DOX, imparts remarkable stability and high drug loading efficiency to the nano-micelles, ultimately enhancing tumor targeting and improving the anti-cancer efficacy of DOX.[102] In addition to the interaction with PEG, EGCG is employed in conjunction with hyaluronic acid to function as a drug delivery system. The covalent attachment of sulfhydryl-modified hyaluronic acid to EGCG is facilitated through a nucleophilic addition reaction, leading to the self-assembly of nano-micellar complexes. This assembly is driven by non-covalent interactions between EGCG and sorafenib. When compared to free sorafenib, the resultant complex exhibits improved biocompatibility and enhanced tumor-targeting properties, which significantly extend the intravenous circulation time of the drug and increase its therapeutic efficacy against leukemia stem cells, while simul-

taneously mitigating toxic side effects.[103] These studies have established a robust groundwork for the development of a universal polyphenol-based nanomedicine platform and treatment system, paving the way for a new research direction in polyphenol-based cancer targeted therapies.

4.3. Polyphenol coated nanomaterials

Due to the distinctive nanostructures and biological interactions associated with nanomaterials, significant advancement has been achieved in the development of tumor treatment systems utilizing these materials.[104] Metal nanoparticles, mesoporous silica nanoparticles, and Metal Organic Frameworks (MOFs) have demonstrated significant tumor-inhibitory properties. Nevertheless, the application of these individual nanomaterials frequently presents challenges related to biotoxicity and limited cyclic stability, which can hinder their therapeutic efficacy. Currently, polyphenols are being employed as surface coatings for nanomaterials to enhance their tumor-targeting capabilities and biocompatibility.

Metal nanomaterials, particularly those based on gold, have been recognized as effective agents for photothermal therapy in tumor treatment, exhibiting favorable photothermal properties and significant tumoricidal effects. To enhance the biocompatibility of gold nanomaterials, Leng *et al.* implemented a modification of the tannin–iron network structure on the surface of gold nanorods, subsequently coupling mercaptofolate to augment both the biocompatibility and tumor-targeting capabilities of these nanomaterials. The enhanced targeting of the composite material is anticipated to increase the photothermal treatment efficacy of gold nanorods and to facilitate the Fenton reaction resulting from the degradation of tannin–iron within the tumor microenvironment, thereby promoting chemokinetic therapy.[105] Furthermore, Pd/Pt/Au trimetallic nanoparticles with multi-enzyme activity designed by Hou *et al.* were also coated with a tannin–iron network to enhance biocompatibility, facilitate tumor targeting, and enable responsiveness to the tumor microenvironment.[106]

The porosity and elevated specific surface area of mesoporous silica confer significant drug loading capabilities; however, the controlled release of drugs at tumor sites presents challenges. Li *et al.* performed EGCG coating on the surface of mesoporous silica following the adsorption of DOX. This strategy was designed to enhance the stability of the nanomaterial and to establish binding sites for subsequent modifications with aptamers. The degradation of EGCG within the tumor microenvironment promotes the release of the drug from the mesoporous silica. Importantly, the use of the EGCG coating not only allows for the attachment of additional targeted recognition molecules, but also supports the controlled release of the drug from the nanosystem.[107]

Utilizing the interactions between polyphenols and proteins, Yang *et al.* engineered tannin–glucose oxidase (GOx)-coated porphyrin MOF nanomaterials, which were further modified with homologous tumor cell membranes. This novel strategy led to the development of highly targeted nanosystems designed for intravenous administration in murine tumor models. Within the tumor microenvironment, the cascade reaction initiated by these nanosystems is capable of generating a synergistic therapeutic effect, thereby effectively hindering the progression of solid tumors.[108] The aforementioned research suggests that the application of biocompatible polyphenol coatings represents a viable approach to enhance the targeting capabilities of nanomaterials and facilitate the controlled release of pharmaceuticals.

5. Polyphenol delivery strategies for tumor therapy

The utilization of polyphenols has been constrained due to their limited oral bioavailability, which can be overcome by encapsulating them into nano-formulations, thereby enhancing their anticancer activity. The creation of nanosystems to improve the physicochemical stability of dietary polyphenols can be done using novel techniques made possible by nanotechnology.[109] Fig. 4 illustrates conventional delivery systems for dietary polyphenols.

5.1. Polymeric nanomaterial delivery

The self-assembled architecture of amphiphilic polymers in an aqueous environment, commonly referred to as a micelle, is characterized by a hydrophobic core surrounded by a hydrophilic shell. In addition to simple physical adsorption, polyphenols can also utilize non-covalent interactions with the polymer's core structure (such as hydrogen bonding and hydrophobic interactions) to enhance the loading efficiency of these carriers.[110] Polymer nanomaterials are extensively utilized in cancer therapy and as biomolecular nanocarriers due to their distinctive properties, including adjustable size, shape, surface chemistry, and biocompatibility.[111,112] These

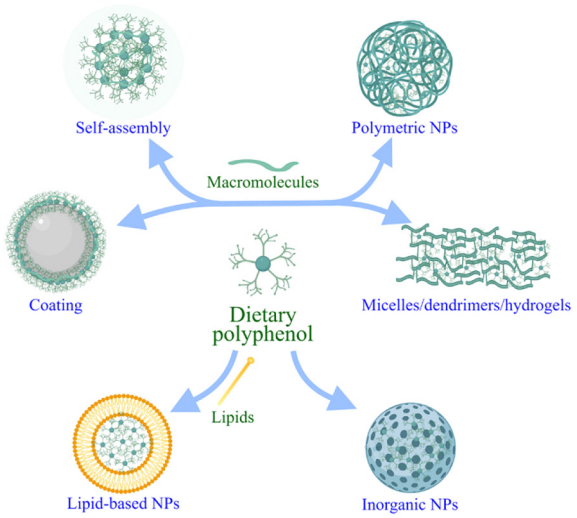

Fig. 4 Schematic diagram of dietary polyphenol nano-delivery systems, including assembly types and delivery carriers.

materials can be tailored to encapsulate and release therapeutic agents into tumor cells, primarily in the form of polymer nanoparticles, nanocapsules, nanospheres, polymer micelles and dendrimers, thus leading to improved therapeutic outcomes.[113]

Polymer nanoparticles are defined as submicron-sized entities that are formed from either synthetic or natural polymers, with diameters generally falling within the range of 1 to 1000 nanometers.[114] Mahdian *et al.* encapsulated curcumin in chitosan nanocapsules within a gelatin hydrogel and applied it to CT26 colon cancer cells, resulting in a decrease in cell viability.[115] Research has shown that curcumin, when encapsulated within sodium alginate-based polymer micelles that create colloidally stable micelles of approximately 200 nm in size, exhibits significant *in vitro* cytotoxic effects against MC38-carcinoembryonic antigen (CEA) mouse colon cancer cell lines. Furthermore, it has been observed to possess *in vivo* antitumor efficacy in two distinct mouse tumor models, specifically the MC38-CEA colon cancer and 4T1 breast cancer models.[116] Zeynalzadeh *et al.* investigated the anticancer properties of curcumin in polyamido–curcumin dendrimer complexes, finding that the compound can enhance the growth inhibitory effect of curcumin on MG-6 and HT-29 cell lines.[117] Alfei *et al.* have developed a dendritic nanodevice incorporating gallic acid as an innovative approach to address cytotoxic resistance in human neuroblastoma. The principal findings indicated that the pro-oxidative effects of gallic acid on the dendritic polymer system resulted in an elevation of ROS production in neuroblastoma cells, even at minimal concentrations. This approach may potentially enhance tumor sensitivity to anti-tumor medications *in vivo*, thereby reducing the cytotoxic dosage and systemic toxicity of drugs.[118] Honokiol, a lignan predominantly sourced from the traditional Chinese medicinal plant *Magnolia officinalis*, exhibits notable anticancer properties. Due to its brief half-life in the bloodstream, the co-administration of honokiol with nanocarriers enhances the efficacy of its therapeutic effects.[119] Tang *et al.* synthesized an 80 nm spherical EGCG-functionalized chitin (CE) polymer. The tumor growth inhibition rate of CE-honokiol NPs (40 mg kg^{-1}) was found to be 83.55% ($p < 0.05$), significantly higher than that of honokiol (40 mg kg^{-1}) (30.15%). The drug delivery system demonstrated excellent tumor selectivity and growth inhibition both *in vitro* and *in vivo*, establishing its effectiveness as a delivery system for liver cancer drugs.[120] He *et al.* synthesized and prepared a gamma-cyclodextrin metal–organic framework (CD-MOF) to encapsulate honokiol, resulting in honokiol-loaded CD-MOF (honokiol@CD-MOF) with improved apparent solubility and enhanced dissolution rate. This can significantly increase the uptake and transport of drugs in intestinal epithelial cells, thereby improving the oral absorption and bioavailability of honokiol.[121]

Instead of a single polyphenol encapsulation and delivery strategy, a combination delivery strategy of chemical sensitizers and cytostatic polyphenols has been also designed. Shitole *et al.* reported chemotherapeutic drugs docetaxel (DTX) and quercetin encapsulated in chemically modified polymer nanocapsules for targeting prostate cancer. The nanocapsule, measuring 120 to 140 nanometers in size and featuring a negatively charged surface, encapsulates two drugs. The capsule exhibited potent cytotoxicity by enhancing caspase 3 activity, while also demonstrating selective accumulation within cancer cells, effectively inhibiting tumor growth and differentiation.[122] Jurczyk *et al.* developed poly(lactide)-*co*-PEG nanomicelles coated with docetaxel and resveratrol, and assessed their encapsulation and release efficiency. Results have demonstrated that the combination of dual drug delivery exhibits more pronounced tumor cytotoxicity compared to single drug delivery, providing a valuable reference for the selection and combination of tumor-targeting drugs.[123] Similarly, PEG-based nano-micelles can also be prepared by self-assembly encapsulation of DOX and salvianolic acid A. The mPEG-Poly (ε-caprolactone) (PCL)-encapsulated small nanocolloid particles demonstrate high drug loading and controlled release, as well as biodegradability, thereby preserving the anti-tumor efficacy of the drug while ensuring good organ and tissue safety.[124]

Furthermore, a diverse range of polymer nanocarriers have been developed for the transportation of dietary polyphenols. Lazer *et al.* synthesized hesperetin with folate-modified chitosan as a polymeric molecule to form nanoparticles, which effectively improved water solubility and targeted tumors. The unique size of the nanoparticles enables them to penetrate tumor blood vessels, leading to significant enhancement in tumor inhibition and induction of apoptosis.[125] Ligands of luteinizing hormone-releasing hormone can be conjugated to polylactic acid glycolate for targeted therapy of prostate cancer, based on the specific protein expression profile on the tumor surface. Polyethylene glycol can serve as a spacer to link the targeted molecules and therapeutics, docetaxel and quercetin, in order to formulate nanocapsules. This approach has the potential to significantly enhance drug uptake by tumor cells and increase cytotoxicity, demonstrating notable advantages of combination therapy.[122]

5.2. Lipid-based delivery

Currently, a range of lipid-based nanomaterials have been used to treat cancer and other diseases.[126] It is a rational approach to enhance bioavailability by incorporating drugs into lipid nanoparticles.[127] Due to their biodegradability, biocompatibility, and targeting capabilities, lipid-based nanoparticles have been utilized in various drug delivery routes including oral, transdermal, ocular, and intravenous administration.[128]

The predominant technologies utilized for the encapsulation of polyphenols using lipid nanomaterials include liposomes,[129] noisome,[130] nanostructured lipid carriers (NLC),[131] solid lipid nanoparticles (SLN),[132] and lipid nanoemulsion.[133] These materials have gained significant traction in oncological therapies, primarily due to their biocompatibility and favorable tolerance within the human body.[134] Additionally, these lipid-based systems can be engineered to exhibit specific targeting capabilities, facilitating the selective delivery of thera-

peutic agents to cancer cells while reducing potential adverse effects on healthy tissues.[135]

Recent investigations have focused on the utilization of liposomes as delivery systems for the encapsulation of drugs and bioactive molecules in the context of cancer therapy. These nanosystems are capable of encapsulating anti-cancer agents within their lipid bilayer or aqueous core, thereby offering several advantages, such as protection against degradation, improved stability, and extended circulation time within the organism. Consequently, liposomes hold promise for augmenting the bioavailability of polyphenols in cancer treatment. In a study conducted by Elkhoury *et al.*, curcumin was encapsulated in chitosan-coated nano-liposomes derived from salmon lecithin, which demonstrated a significant inhibition of tumor growth in MCF-7 breast cancer cells. The findings indicated that the anticancer efficacy of the encapsulated compound surpassed that of free curcumin at a concentration of 5 μM, thereby suggesting that liposomal formulations may enhance the effectiveness of chemotherapy.[129]

NLCs are lipid-based nanoparticle systems that consist of either solid or liquid lipids encased within a surfactant-stabilized core, which enables the encapsulation of hydrophobic pharmaceutical compounds.[136] NLCs have attracted considerable interest for their prospective applications in oncological therapies, attributed to their enhanced drug loading capacity, improved stability of the drug, and ability to facilitate controlled drug release.[137] Gadag *et al.* formulated resveratrol NLC and utilized microneedle arrays for localized drug delivery to breast tissue, with the objective of augmenting the effectiveness of breast cancer treatment.[131] Huguet-Casquero *et al.* utilized NLC for the encapsulation of oleuropein, and this compound was shown to enhance and sustain its protective effects against oxidative stress in lung cancer and cystic fibrosis cells.[138] Schemes to improve the targeting of liposome nanoparticles have also been developed. By using lipids, cholesterol and 1,2-distearoyl-*sn-glycero*-3-phosphoethanolamine-*N*-[maleimide (polyethylene glycol)-2000] (DSPE-PEG2000-Mal), curcumin and resveratrol can be encapsulated to form nanoparticle drug particles. SP_{94}, a short peptide with specific binding to liver cancer cells, can be surface-modified on nanoparticles, allowing the constructed nanoparticles to accumulate in tumors and enhance cell uptake through the enhanced permeability and retention (EPR) effect and SP_{94}-mediated targeting. The liposome nanoparticles demonstrate a high capacity for drug loading and stability, which allows for controlled drug release and presents opportunities for the development of alternative drug delivery systems.[139]

5.3. Delivery systems of inorganic nanomaterials

The high load capacity and versatility of inorganic nanomaterials provide a reliable platform for the design of drug delivery systems.[140] Classic gold,[141] silicon dioxide[142] and other nanoparticles both demonstrate high stability and biosecurity. The low toxicity and biocompatibility of gold nanoparticles are widely acknowledged, and the significant advantages of gold-based nanomaterials in tumor therapy and adjuvant drug delivery research have been well recognized. Loading dietary polyphenols onto gold nanoparticles can offer targeted treatment for tumors. Hsing *et al.* conjugated *n*-butylidenephthalide with pegylated gold nanoparticles to fabricate nanoparticle-based drugs. Through the investigation of the cell uptake efficiency and mode of nanomedicine, it was found that the nanoparticles can regulate the cell cycle of brain cancer cells, induce cell apoptosis, and show low toxicity in normal tissues and organs.[143] Based on the inherent pro-apoptotic properties of gold nanoparticles, the combination of dietary polyphenols and these nanoparticles can improve the therapeutic effect. Resveratrol and gold nanoparticles can be conjugated, and nanoparticles with stable properties can be formed after being coated with *Acacia*. The formation of resveratrol crowns on the surface of gold nanoparticles can increase the uptake and utilization of resveratrol cells and enhance the overall anti-tumor activity.[144]

Due to the pore structure of mesoporous silica, it can simply load resveratrol and promote the amorphization of resveratrol. In the special environment of the tumor, the particle can effectively release resveratrol and reduce the viability of tumor cells.[145] The modified mesoporous silica exhibited a greater reduction in functional diversity during the loading and release of dietary polyphenols. Ionita *et al.* investigated the dissolution rate of polyphenols using various mesoporous silica and examined the impact of modifying multiple groups on resveratrol loading efficiency and release efficiency. The findings indicated that all types of functionalized mesoporous silica were able to enhance the dissolution rate of polyphenols and effectively support resveratrol.[146] Mesoporous silica modified with transferrin-cathepsin B cleavable peptide can provide targeted recognition and controlled drug release in specific environments. After being loaded with resveratrol, the inhibition rate of the granule on tumor cells exceeded 80%, showing good application value.[147] Furthermore, ZIF-based nanoparticles have been utilized for the delivery of dietary polyphenols. The biocompatibility and pH sensitivity of tannic acid modified ZIF-8 nanomaterials create favorable conditions for the controlled release and administration of polyphenols. This nanomedicine system demonstrates efficacy in inhibiting the proliferation and invasion of tumor cells, thereby presenting a promising strategy for the development of targeted tumor delivery and treatment systems.[148]

6. Challenges and future prospects

The efficacy of dietary polyphenols in the prevention and treatment of tumors has been well-documented; however, significant obstacles remain regarding their practical application in clinical settings. A considerable number of studies investigating the anti-tumor effects of dietary polyphenols primarily employ *in vitro* methodologies, which frequently lack corresponding *in vivo* treatment data and clinical trial evidence. Furthermore, dietary polyphenols are vulnerable to various environmental factors, including pH, temperature, and light,

which can negatively impact their stability and therapeutic efficacy. The intricate nature of dietary polyphenols, characterized by multiple active groups and diverse regulatory pathways, further complicates the elucidation of their mechanisms of tumor inhibition. While this complexity may offer potential therapeutic advantages across different tumor types, it also results in inconsistencies between *in vivo* and *in vitro* findings, thereby hindering clinical translation. Additionally, the absence of specificity in *in vivo* targeting presents challenges for patient treatment, highlighting the necessity for a more comprehensive understanding of the metabolic processes and mechanisms associated with dietary polyphenols in tumor therapy to enhance their clinical applicability.

The solubility and targeting of dietary polyphenols are crucial considerations in their bioactivity. The insoluble nature of multi-functional polyphenols limits their effectiveness, while their environmental stability and availability post-ingestion are compromised. Targeted delivery systems have been devised to enhance the water solubility, stability in the digestive and circulatory systems, and tumor-targeting capabilities of dietary polyphenols. However, there remains a dearth of discourse on the safety and metabolic pathways of these intricate multi-type nanocarriers, necessitating thorough investigation and resolution before clinical implementation. Despite the distance from practical application, advancements in nanotechnology hold promise for expediting the development of secure and dependable dietary polyphenol therapies. This progress may facilitate the integration of polyphenols as food additives or dietary supplements in functional or specialized medical foods, offering a wider array of options for consumers and healthcare providers. The combination of dietary polyphenols with approved therapeutic agents is believed to enhance the clinical efficacy against tumors and refine treatment protocols.

7. Conclusions

Polyphenolic compounds have demonstrated considerable promise in the realm of cancer pharmacotherapy, exhibiting notable anti-tumor properties. These compounds, which are prevalent in various natural dietary sources, offer a convenient and biologically safe option for consumption. Organizations such as the WHO and numerous cancer research associations recommend increased intake of fruits and vegetables rich in polyphenols to inhibit tumor progression. The integration of dietary polyphenols as adjuncts to conventional cancer treatments has the potential to significantly enhance therapeutic outcomes with minimal effort, presenting a synergistic approach to cancer therapy. This review presents a comprehensive examination of the diverse categories and sources of dietary polyphenols, explores their mechanisms of action in tumor suppression, and highlights their significant contribution to the development of nano-therapeutic systems. Furthermore, it discusses methodologies for the development of nanosystems aimed at improving the solubility, stability, and targeted delivery of dietary polyphenols, thereby enhancing their bioavailability and anti-tumor efficacy within the organism. The article also outlines the functions of common dietary polyphenols to assist researchers in selecting appropriate compounds for anti-tumor investigations, while minimizing potential adverse effects through an understanding of their active pathways. The incorporation of delivery system design is particularly beneficial for clinical researchers focused on developing nanomedicines characterized by low toxicity and high targeting capabilities, which can amplify the synergistic effects of dietary polyphenols in standard treatment regimens, enhance the overall tumor treatment efficacy, and mitigate adverse reactions. Furthermore, the nano-encapsulation strategy offers valuable insights into the formulation of functional foods that contain stable dietary polyphenols.

Author contributions

Minglu Wang: writing – original draft; conceptualization; and validation. Ying Wang: writing – review and editing. Hongyan Zhang: writing – review and editing; funding acquisition; project administration; and investigation.

Data availability

No primary research results, software or codes have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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