Review

Anti-Cancerous Potential of Polyphenol-Loaded Polymeric Nanotherapeutics

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Abstract: Recent evidence has extensively demonstrated the anticancer potential of nutraceuticals, including plant polyphenols. Polymeric nanocarrier systems have played an important role in improving the physicochemical and pharmacological properties of polyphenols, thus ameliorating their therapeutic effectiveness. This article summarizes the benefits and shortcomings of various polymeric systems developed for the delivery of polyphenols in cancer therapy and reveals some ideas for future work.

Keywords: cancer therapeutics; polymeric carriers; nanoparticles; polyphenols; cell lines

1. Introduction

A large number of food ingredients have beneficial effects on human health. In particular, during the last decade, polyphenols and antioxidants have been extensively investigated for their therapeutic effectiveness after their intravenous administration [1].

Polyphenols contain a minimum of one aromatic ring, as well as hydroxyl groups ranging from a minimum of one ring. They are different from each other on the basis of the number of aromatic rings and phenol groups [2] and can be grouped into two main classes: flavonoids and non-flavonoids [3]. The former contains 15 carbon atoms, comprising two aromatic rings connected by a three-carbon link, while the latter contains heterogeneous compounds with phenolic acids having between one and six carbon atoms. Quercetin, kaempferol, apigenin, and myricetin belong to flavonoid class, while resveratrol, vanillin, and ellagitannins are examples of non-flavonoids.

Polyphenols are biologically active compounds, having useful effects against various chronic diseases, including cancer [4]. The biological activities of polyphenols are generally attributed to their antioxidant potential [5]. However, a comprehensive explanation for the biological effects of polyphenols is still uncertain [6]. In addition, their effects are also believed to be modulated via distinct actions on the signaling pathways at a cellular level [7].

Clinical studies on cancer therapy have reported a significant decrease in the therapeutic effectiveness of conventional cytotoxic compounds. The reduced efficacy is not only attributed to their unsuitable physicochemical properties, such as lipophilicity, but also to inappropriate pharmacokinetic
features, including multidrug resistance, poor penetration into tumor microenvironment, and toxicity to non-diseased cells [8–10]. A wide array of research activities has been conducted to decipher these issues by several approaches, including the investigation of alternative anticancer compounds, as well as the development of targeted nanotherapeutics.

2. Polyphenol-Loaded Polymeric Nanotherapeutics for Cancer Treatment

The pathophysiology of cancer involves molecular-level changes in biological processes. Thus, in recent years, approaches have emerged to develop nanodiagnostic and nanotherapeutic modalities, such as lipid nanoparticles, nanohybrids, and polymeric nanoparticles [11–13]. In preclinical and initial clinical trials, these nanocarriers have exhibited excellent performance as drug delivery vehicles [14–16]. Nano-sized drug delivery systems have several promising features, including improved stability, enhanced solubility, and increased surface area to volume ratio. In addition, the surface properties of such carriers can be modified to attain controllable pharmacological and physicochemical features, thereby reducing barriers to effective chemotherapy in cancer [17]. Additionally, an ameliorated therapeutic index and diminished toxicity to healthy cells are also achieved through the nanotherapeutic approach [17]. It is remarkable that active and passive targeting could be used to deliver drugs to specific sites. These properties are significantly important for typical biologically active compounds, such as polyphenols for their translation into useful therapeutic modalities. Regardless of the promising progress in basic cancer biology at the preclinical level, polyphenols have inappropriate pharmacological properties, such as low bioavailability due to inefficient systemic access, and thus require high doses for optimum therapeutic effect [18]. Although in vitro studies have proved the biological effectiveness of polyphenols, these findings could not be achieved in vivo due to their instability in the physiological conditions of temperature, pH, and enzyme system. Their stability and therapeutic effectiveness could be improved by developing polyphenol-loaded nanotherapeutics. Therefore, biologically active polyphenols could be combined with nano-sized carriers to overcome the drawbacks of conventional anticancer therapy and develop a clinically efficacious treatment for cancer.

2.1. Polymer-Based Nanovesicles

Polymeric vesicles are prepared using amphiphilic block copolymers, which contain a lipophilic and a hydrophilic segment. These self-assembled structures have variable shapes and sizes, such as polymersomes [19] and micelles [20]. These vesicular systems have drug delivery capabilities and offer specific benefits.

Polymersomes are bilayered vesicles, composed of high molecular weight amphiphiles. Thus, they allow slow permeability of drugs due to the strong mechanical properties of their membranes [21]. Additionally, the surface of polymersomes is modified by using shell-producing, water-soluble, flexible polymers to reduce polymersomes–macrophages interactions [22]. Moreover, polymeric micelles are composed of a lipophilic core and a hydrophilic shell, into which lipophilic and hydrophilic drugs can be loaded and delivered, respectively [21]. These vesicles exhibit a narrow size distribution, ranging between 20 and 80 nm, and are long-lasting in systemic circulation [23–25], but, due to their poor stability, they undergo premature drug leakage in the bloodstream, resulting in reduced therapeutic efficacy and enhanced undesired effects. Polyphenol-loaded polymersomes and micelles have been synthesized by using natural polymers, such as dextran, chitosan, gelatin, casein, and polyethylene glycols PEG, due to their biodegradable and biocompatible features Tables 1 and 2.

Gelatin–dextran micelles loaded with tea polyphenols were studied for their effect on breast cancer using MCF-7 cells and it was found that the encapsulated polyphenols had an enhanced efficacy compared with their free form [26]. Later on, this carrier was loaded with curcumin for the treatment of HeLa cancer cells. The results revealed an improvement in the pharmacokinetic and therapeutic properties of the encapsulated curcumin, compared with its control [27]. In addition, polyvinyl pyrrolidone–PEG conjugates were used to develop polymersomes loaded with Cotinus
coggygria flavonoids for the treatment of glioblastoma [28]. Moreover, curcumin delivery systems were prepared by using protein-type polymers, such as gelatin, casein, and keratin [29–33]. In addition to their biocompatibility, these materials supported curcumin's efficacy on cancerous cells of the lung and cervix [29,30]. Curcumin-loaded chitosan–stearic acid conjugates exhibited an improvement in the curcumin efficiency against colon cancer [34]. Curcumin polymersomes and micelles have been prepared with an aim of enhancing their anticancer activity. Owing to its stealth properties and biocompatible nature, PEG is extensively used in the fabrication of nanoparticulate systems. In vitro testing of PEG–polyanhydride esters and PEG–polylactic acid vehicles for curcumin and doxorubicin showed their synergism in HeLa and MCF-7 cancer cells. The polymer conjugates were prepared by a solvent evaporation technique [35,36]. The solvent evaporation-induced synthesis of curcumin-loaded micelles of polycaprolactone and PEG was aimed at the treatment of various cancers, such as breast [37] and ovarian [38] cancer cells in vitro, and colon [39], breast [40], and lung [41] in xenograft mouse models. The anticancer efficacy of these polycaprolactone–PEG–curcumin nanomicelles against lung and brain tumors was further enhanced through their modification by using different fatty acids, such as oleic acid, linoleic acid, and palmitic acid [42,43]. In some other studies, 1,2-distearyl-sn-glycero-3-phosphoethanolamine-N-[methoxypolyethylene glycol-2000] was employed for the synthesis of curcumin micelles to treat colon and ovarian cancers in vitro and in vivo, showing synergism with doxorubicin [44,45] and paclitaxel [46]. These in vitro and in vivo studies depict the promising characteristics of the polymeric polymersomes and micelles for delivering various polyphenols, including curcumin.
### Table 1. Polyphenol-loaded polymersomes for the treatment of cancer.

| No. | Components of Nanoparticles | Method of Preparation | Polyphenol + Synergistic Agent | Type of Cancer In Vitro Model/In Vivo Model Promisingly Treated with the Fabricated Nanotherapeutic Formulation | References |
|-----|----------------------------|-----------------------|-------------------------------|-------------------------------------------------------------------------------------------------|------------|
| 1   | Polyvinyl pyrrolidone-PEG  | Emulsion evaporation  | Plant polyphenols              | Glioblastoma DBTRG-05MG                                                                 | [28]       |
| 2   | Keratin                    | Solvent evaporation   | Curcumin                      | Cervical cancer HeLa                                                                            | [29]       |
| 3   | Gelatin                    | Solvent evaporation   | Curcumin                      | Lung cancer H1299                                                                              | [30]       |
| 4   | PEG-Oleic acid             | Thin layer evaporation| Curcumin                      | Brain cancer U87MG                                                                              | [42]       |

PEG: polyethylene glycol.

### Table 2. Polyphenol-loaded polymeric micelles for the treatment of cancer.

| No. | Components of Nanoparticles | Method of Preparation | Polyphenol + Synergistic Agent | Type of Cancer In Vitro Model/In Vivo Model Promisingly Treated with the Fabricated Nanotherapeutic Formulation | References |
|-----|----------------------------|-----------------------|-------------------------------|-------------------------------------------------------------------------------------------------|------------|
| 1   | Gelatin–Dextran            | Self-assembly-Genipin-Crosslinking | Plant polyphenols              | Breast cancer MCF-7                                                                             | [26]       |
| 2   | Gelatin–Dextran            | Self-assembly-Genipin-Crosslinking | Curcumin                      | Cervical cancer HeLa Healthy mice                                                              | [27]       |
| 3   | Casein                     | Self-assembly          | Curcumin                      | Cervical cancer HeLa                                                                            | [32]       |
| 4   | Zein–PEG                   | Self-assembly          | Curcumin                      | Ovarian cancer NCI Healthy mice                                                                 | [33]       |
| 5   | Chitosan–Stearic acid      | Self-assembly          | Curcumin                      | Colon cancer Primary Xenograft mice                                                             | [34]       |
| 6   | PEG–Polyanhydride esters   | Solvent evaporation    | Curcumin                      | Cervical cancer HeLa                                                                            | [35]       |
| 7   | PEG–Polylactic acid        | Solvent evaporation    | Curcumin + Doxorubicin        | Breast cancer MCF-7 Xenograft mice                                                              | [36]       |
| 8   | PEG–Polycaprolactone       | Thin-layer evaporation | Curcumin                      | Breast cancer MDA-MB-436                                                                         | [37]       |
| 9   | PEG–Polycaprolactone       | Thin-layer evaporation | Curcumin                      | Breast cancer 4T1–4T1 Xenograft mice                                                            | [40]       |
| 10  | PEG–Polycaprolactone       | Self-assembly          | Curcumin                      | Cervical cancer HeLa Healthy mice                                                               | [39]       |
| 11  | PEG–Polycaprolactone       | Thin-layer evaporation | Curcumin                      | Colon HT-29                                                                                     | [39]       |
| 12  | PEG–Polycaprolactone       | Thin-layer evaporation | Curcumin + Doxorubicin        | Lung cancer LL/L2 Xenograft mice                                                                | [41]       |
| 13  | PEG–Polycaprolactone       | Thin-layer evaporation | Curcumin                      | Cervical cancer HeLa Healthy mice                                                               | [42]       |
| 14  | Linoleic acid–PEG–Polycaprolactone | Self-assembly                  | Curcumin                      | Lung A549                                                                                       | [43]       |
| 15  | Linoleic acid–PEG–Polycaprolactone | Self-assembly                  | Curcumin                      | Cervical cancer HeLa                                                                            | [32]       |
| 16  | PEG–Palmitic acid          | Self-assembly          | Curcumin                      | Ovarian cancer SK-OV-3TR                                                                          | [45]       |
| 17  | PEG2000–DSPE               | Thin-layer evaporation   | Curcumin + Paclitaxel         | Ovarian cancer NCI SK-OV-3TR Xeno graft mice                                                     | [46]       |
| 18  | PEG2000–DSPE               | Thin-layer evaporation   | Curcumin + Paclitaxel         | Colon cancer HCT-116 Xeno graft mice                                                             | [44]       |
| 19  | PEG2000–DSPE               | Thin-layer evaporation   | Curcumin + Doxorubicin        | Cervical cancer HeLa Healthy mice                                                               | [47]       |
| 20  | PEG–Doxorubicin            | Self-assembly          | Curcumin + Doxorubicin        | Cervical cancer HeLa Healthy mice                                                               | [47]       |
| 21  | PEG–Doxorubicin            | Self-assembly          | Curcumin + Doxorubicin        | Hepatic HepG2                                                                                   | [47]       |
| 22  | Poloxamers F127 F68        | Thin-layer evaporation   | Curcumin                      | Cervical cancer HeLa                                                                            | [48]       |
| 23  | Poloxamers-PEG–Succinate   | Solvent evaporation    | Curcumin                      | Ovarian cancer NCI                                                                              | [49]       |
| 24  | Poloxamers F127            | Thin-layer evaporation  | Resveratrol, Curcumin + Doxorubicin | Ovarian cancer SK0-3 Healthy mice                                                              | [50]       |
| 25  | Poloxamers F127            | Thin-layer evaporation  | Resveratrol, Quercetin + Doxorubicin | Ovarian cancer SK0-3 Healthy mice                                                              | [51]       |
| 26  | Apolipoprotein-E3          | recombinant DNA        | Resveratrol                    | Glioblastoma A-172                                                                               | [52]       |
| 27  | Polycaprolactone–PEG–Succinate | Thin-layer evaporation                  | Resveratrol                    | Breast cancer MCF-7                                                                             | [52]       |
| 28  | Casein                     | Self-assembly          | Epigallocatechin gallate       | Colon cancer HT-29                                                                              | [53]       |
| 29  | Polyactic acid–PEG         | Thin-layer evaporation  | Epigallocatechin gallate       | Pancreatic cancer MiaPaca-2                                                                     | [54]       |

Note: PEG2000–DSPE—1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxypolyethylene glycol-2000].
Favorable disposition of curcumin and doxorubicin was achieved when these drugs were combined in PEG micelles for cervical and hepatic cancer [47]. Few studies have documented a profound toxicity of curcumin-loaded poloxamer nanocarriers towards HeLa [48] and ovarian cancer cells [49]. In addition, poloxamer nanoformulations containing resveratrol and doxorubicin exhibited a synergistic effect on ovarian cancer in mice [50]. A resveratrol–quercetin combination exhibited the same effect in ovarian tumors [51]. Moreover, resveratrol was encapsulated into PEG–polycaprolactone conjugate, and the resulting micelles were surface-modified with apolipoprotein and used for the treatment of glioblastoma [51] and breast cancer [52]. Lastly, some other studies reported epigallocatechin gallate delivery in colon cancer from PEG–polylactic acid [53] and in pancreas cancer from casein micelles [54]. The micelles of various polymers, such as PEG and polycaprolactone, showed an improved anticancer efficacy of the loaded polyphenols, such as quercetin, resveratrol, and curcumin.

2.2. Polymer-Based Nanoparticles

High stability, uniform particle size, excellent drug loading efficiency, and controlled release of drug are important characteristics of polymeric nanoparticles [55], which are spherical or irregular shaped, colloidal systems loaded with drugs [56]. A wide range of biocompatible, natural, and synthetic polymers have been utilized as polymeric nanoparticles to deliver anticancer drugs [57,58]. Table 3 illustrates the representative examples of polymers used as nanoparticles for the delivery of polyphenols. Due to their biocompatible and biodegradable features, chitosan and polylactic-co-glycolic acid PLGA have been extensively studied for polyphenol delivery [59]. To prevent the uptake of nanoparticles by macrophages, the surface functionalization of nanoparticles can be modified by using polyethylene glycol PEG and its derivatives [60]. The selection of the procedure for the fabrication of polymeric nanoparticles depends on various factors, such as the properties of the employed polymer, drug, and the desired end product to achieve the desired, controllable physicochemical and pharmacological performance in vitro and in vivo. Table 4 also depicts some extensively employed approaches, such as emulsion solvent removal, polymer interaction, and radical polymerization.

Compared with free polyphenols, polyphenol extracts loaded into chitosan, PLGA–polycaprolactone nanoparticles exhibited boosted apoptosis induction and cell internalization, resulting in the enhanced antiproliferative activity in various cell line studies [61–63].

Curcumin is a pharmacologically active polyphenol with low water solubility. Therefore, many studies have been conducted to prepare its effective formulations. In this context, an important effort is the development of curcumin-loaded nanoparticles. Therapeutic studies involving various cancer cell lines, including cervical and prostate cells, osteoclasts, and melanocytes [64–68], revealed that these nanoparticles exhibited controlled release of curcumin, resulting in effective passive targeting. It is noteworthy that both free curcumin and curcumin-loaded nanoparticles have the same mechanism of action. In addition, curcumin-loaded nanoparticles have been synthesized by a free radical polymerization method using polyethylene glycol acrylate, N-isopropylacrylamide, and N-vinyl-2-pyrrolidone for the treatment of pancreatic cancer. These nanoparticles showed insignificant toxicity in mouse [69]. Another study reported the synthesis of curcumin-loaded nanoparticles by an emulsion polymerization method using chitosan and butyl-cyanoacrylate together for the treatment of hepatic cancer [69]. In addition, free curcumin and curcumin nanoparticles were compared in various cell lines, such as colon, prostate, and ovarian. The nanoparticles of curcumin induced cellular uptake and the apoptosis boosting resulting in the ameliorated anticancer activity than its free form [70–72]. PLGA nanoparticles containing PEG were fabricated to improve curcumin efficacy against prostate and colon cancer [73–75], while curcumin–silk fibroin nanoparticles have been shown to have a potential role in human hepatocellular carcinoma Hep3B, human neuroblastoma Kelly cells, and human bone marrow-derived mesenchymal stem cells hBMSCs [76]. Moreover, curcumin was encapsulated into pH-responsive nanogels to enhance its efficacy against colon cancer [75]. To
achieve a synergistic effect, curcumin nanoparticles containing conventional anticancer drugs, such as doxorubicin [77] and 5-fluorouracil [78], have been employed for breast cancer treatment. For the treatment of ovarian cancer, a useful association between curcumin- and cisplatin-loaded nanoparticles has been noted [79]. Furthermore, curcumin combined with gemcitabine in nanoparticles, prepared by free radical polymerization using \(N\)-isopropylacrylamide, \(N\)-vinyl-2-pyrrolidone, and acrylic acid, exhibited a synergistic anticancer effect in animal models [80]. Thus, compared to that of free curcumin, curcumin nanoparticles induce cellular uptake, and the apoptosis boosting leads to increased anticancer activity in various cell lines, such as colon, prostate, and ovarian.

Using natural polymers, such as gelatin [81] and a PLGA–PEG combination [82], as well as synthetic polymers, including chitosan–casein–PEG derivatives [82], the synthesis of epigallocatechin gallate nanoparticles with improved stability and in vitro activity against various organs, such as prostate, alimentary canal, breast, and stomach [81–84], was achieved. Furthermore, epigallocatechin gallate nanoparticles containing doxorubicin were prepared which exhibited a synergistic anticancer effect against Ehrlich ascites cancer [85]. In vivo studies in xenograft mice have also proved the effective stability and activity of epigallocatechin gallate nanoparticles against stomach, prostate, and melanocyte carcinoma [86–88]. In addition, epigallocatechin gallate combined with cisplatin in a nanoparticulate formulation was developed as a new synergistic therapy for some invasive cancers [89,90].

Some studies reported the nanoencapsulation of resveratrol into bovine serum albumin [91], gelatin [92], PLGA [93], and PLGA–PEG derivatives [94], revealing an increase in resveratrol activity against cancer of various organs, such as prostate, ovaries, breasts, and lungs [91–94]. Resveratrol-loaded PLGA–PEG nanoparticles were surface-modified using transferrin for active targeting of glioma cancer cells in vivo [95].

Quercetin and 5-fluorouracil were co-encapsulated into chitosan, and the resulting nanoparticles showed a synergistic effect against pancreatic cells in vitro [96]. Another synergistic study described the promising potential of quercetin–tamoxifen loaded into PLGA nanoparticles for the treatment of breast cancer in model mice [97]. Lastly, a four-component system was formulated using poly-butyl cyanoacrylate, \(\alpha\)-tocopherol, and PEG for the delivery of hyaluronic acid into liver cancerous cells in vitro [98]. The preparation of nanoparticles loaded with epigallocatechin gallate, resveratrol, quercetin, and 5-fluorouracil with improved stability and in vitro activity against various organs, such as stomach, prostate, ovaries, alimentary canal, and breast, can be achieved using various natural polymers, such as gelatin, PEG, and PLGA, alone and in combination with synthetic polymers, such as chitosan and casein.
### Table 3. Polyphenol-loaded polymeric nanoparticles for the treatment of cancer in vitro.

| No. | Components of Nanoparticles | Method of Preparation | Polyphenol + Synergistic Agent | Type of Cancer | In Vitro Model | In Vivo Model | Promisingly Treated with the Fabricated Nanotherapeutic Formulation | References |
|-----|-----------------------------|-----------------------|-------------------------------|----------------|---------------|---------------|---------------------------------------------------------------|------------|
| 1   | Polylactic-co-glycolic acid PLGA–PEG | Emulsion solvent evaporation | Pomgranate polyphenols | Breast cancer | MCF-7, Hs578T | None | | [61] |
| 2   | Chitosan | Ionic gelation | Tea polyphenols | Hepatic cancer | Hep G2 | None | | [62] |
| 3   | Polycaprolactone | EXP | Plant polyphenols | Gastric cancer | MKN28 | None | | [63] |
| 4   | Alginate-Chitosan–Poloxamers F127 | Ionic gelation | Curcumin | Cervical cancer | HeLa | None | | [64] |
| 5   | Fibrinogen | CaCl₂ Crosslinking | Curcumin | Prostate cancer | PC3 | None | | [65] |
| 6   | PLGA | Emulsion solvent evaporation | Curcumin | Breast cancer | MCF-7 | None | | [65] |
| 7   | PLGA | Emulsion solvent evaporation | Curcumin | Osteosarcoma | U2OS | None | | [66] |
| 8   | Chitin | Emulsion solvent evaporation | Curcumin | Melanoma | A375 | None | | [67] |
| 9   | Peptide | Ionic gelation | Curcumin | Medulloblastoma | DAOY | None | | [68] |
| 10  | N-Isopropylacrylamide-N-vinyl-2-pyrrolidone-Polyethylene glycol acrylate | Self-assembly | Curcumin | Pancreatic cancer | Capan-1, MiaPaCa2, PL-5, PL-8, Su86.86, BxPC-3, PANC-1, E3LZ10.7 | Healthy mice | None | | [69] |
| 11  | PLGA–PEG | Nanoprecipitation | Curcumin | Colon cancer | HT-29 Healthy mice | None | | [70] |
| 12  | PLGA | Nanoprecipitation | Curcumin | Ovarian cancer | A2780, A2780CP | None | | [71] |
| 13  | Cellulose | Nanoprecipitation | Curcumin | Prostate cancer | C4-2, PC-3, LNCaP, DU-145 | None | | [72] |
| 14  | PLGA | Nanoprecipitation | Curcumin | Prostate cancer | DU-145, PC-3 Xenograft mice | None | | [73] |
| 15  | Human serum albumin | Emulsion solvent evaporation | Curcumin | Colon cancer | HCT116, HCT116 Xenograft mice | None | | [74] |
| 16  | Human serum albumin | Emulsion solvent evaporation | Curcumin | Pancreatic cancer | MiaPaCa2 | None | | [74] |
| 17  | Gelatin–Polyacryl-amidoglycolic acid | Emulsion polymerization | Curcumin | Colon cancer | HCT-116 | None | | [75] |
| 18  | Silk fibroin | Physical adsorption and coprecipitation | Curcumin | Human hepatocellular carcinoma | Hep3B, human neuroblastoma Kelly cells, Human bone marrow-derived mesenchymal stem cells hBMSCs | None | | [76] |
| 19  | Chitosan–Polybutyl cyanoacrylate | Emulsion polymerization | Curcumin + Doxorubicin | Breast cancer | MCF-7 | None | | [77] |
| 20  | PLGA | Emulsion solvent evaporation | Curcumin + 5-fluorouracil | Breast cancer | MCF-7 | None | | [78] |
| 21  | PLGA | Nanoprecipitation | Curcumin + Cisplatin | Ovarian cancer | A2780CP | None | | [79] |
| 22  | PLGA | Nanoprecipitation | Curcumin + Cisplatin | Breast cancer | MDA-MB-231 | None | | [79] |
| 23  | N-Isopropylacrylamide-N-vinyl-2-pyrrolidone-Acrylic acid | Radical polymerization | Curcumin + Gemcitabine | Pancreatic cancer | Pa03C Xenograft mice | None | | [80] |
Table 4. Polyphenol-loaded polymeric nanoparticles for the treatment of cancer in vitro.

| No. | Components of Nanoparticles | Method of Preparation | Polyphenol + Synergistic Agent | Type of Cancer In Vitro Model | In Vivo Model | Promisingly Treated with the Fabricated Nanotherapeutic Formulation | References |
|-----|-----------------------------|----------------------|-------------------------------|-------------------------------|--------------|-------------------------------------------------------------------|------------|
| 1   | Gelatin–Polyelectrolyte    | Layer-by-layer       | Epigallocatechin gallate      | Breast cancer MBA-MD-231      | [81]         |                                                                   |            |
| 2   | PLGA–PEG                   | Nanoprecipitation    | Epigallocatechin gallate      | Prostate cancer LNCaP         | [82]         |                                                                   |            |
| 3   | Casein-phospho-peptide-Chitosan | Geripin-Crosslinking | Epigallocatechin gallate      | Hepatic cancer HepG2          | [83]         |                                                                   |            |
| 4   | Casein-phospho-peptide-Chitosan | Geripin-Crosslinking | Epigallocatechin gallate      | Gastric cancer BGC823         | [83]         |                                                                   |            |
| 5   | Casein-phospho-peptide-Chitosan | Geripin-Crosslinking | Epigallocatechin gallate      | Colon cancer Caco-2           | [84]         |                                                                   |            |
| 6   | Hyaluronic acid            | Self-assembly        | Epigallocatechin gallate +    | Cancer of the external auditory canal | [85]       |                                                                   |            |
| 8   | Chitosan                   | Ionic gelation       | Epigallocatechin gallate      | Prostate cancer ZR-1 Xenograft mice | [87]       |                                                                   |            |
| 7   | Chitosan                   | Ionic gelation       | Epigallocatechin gallate      | Melanoma Me928 Me928 Xenograft mice | [88]       |                                                                   |            |
| 9   | Chitosan–Gelatin–PEG      | Ionic gelation       | Epigallocatechin gallate      | Gastric cancer Luc MKN45 Xenograft mice | [88]       |                                                                   |            |
| 10  | PLGA                       | Nanoprecipitation    | Epigallocatechin gallate + Cisplatin | Lung cancer A549               | [89]       |                                                                   |            |
| 11  | PLGA                       | Nanoprecipitation    | Epigallocatechin gallate + Cisplatin | Cervical cancer HeLa           | [89]       |                                                                   |            |
| 12  | PLGA                       | Nanoprecipitation    | Theaflavin                    | Leukemia THP-1                 | [89]       |                                                                   |            |
| 13  | PLGA                       | Solvent evaporation  | Epigallocatechin gallate + Cisplatin | Lung cancer A549 Ehrlich ascites carcinoma Xenograft mice | [90]       |                                                                   |            |
| 14  | PLGA                       | Solvent evaporation  | Epigallocatechin gallate      | Cervical cancer HeLa           | [90]       |                                                                   |            |
| 15  | PLGA                       | Solvent evaporation  | Theaflavin                    | Leukemia THP-1                 | [90]       |                                                                   |            |
| 16  | PLGA                       | Solvent evaporation  | Theaflavin                    | Cancer of the external auditory canal | [90]       |                                                                   |            |
| 17  | PLGA–PEG                   | Nanoprecipitation    | Resveratrol                   | Prostate cancer DU-145, LNCaP | [91]       |                                                                   |            |
| 18  | Bovine serum albumin       | Nanoprecipitation    | Resveratrol                   | Lung cancer NCI-H460           | [92]       |                                                                   |            |
| 19  | Bovine serum albumin       | Nanoprecipitation    | Resveratrol                   | Ovarian cancer SKOV3           | [93]       |                                                                   |            |
| 20  | PLGA                       | Emulsion method      | Resveratrol                   | Breast cancer MCF-7            | [94]       |                                                                   |            |
| 21  | Maleimide–PEG–Polyactic acid | Self-assembly       | Resveratrol                   | Glioblastoma CT26, U87 CT26 Xenograft mice | [95]       |                                                                   |            |
| 22  | Chitosan                   | Ionic gelation       | Quercetin + 5-fluorouracil    | Pancreas cancer MiaPaCa2       | [96]       |                                                                   |            |
| 23  | PLGA                       | Emulsion solvent evaporation | Quercetin + Tamoxifen        | Breast cancer MCF-7 Xenograft mice | [97]       |                                                                   |            |
| 24  | PLGA                       | Emulsion solvent evaporation | Quercetin + Tamoxifen        | Colon cancer Caco2            | [97]       |                                                                   |            |
| 25  | Hyaluronic acid–Polybutyl cyanoacrylate–a-Tocopheryl–PEG–Succinate    | Radical polymerization | Morin hydrate                 | Lung cancer A549 S180 Xenograft mice | [98]       |                                                                   |            |
| 26  | Hyaluronic acid–Polybutyl cyanoacrylate–a-Tocopheryl–PEG–Succinate    | Radical polymerization | Morin hydrate                 | Hepatic cancer LO2             | [98]       |                                                                   |            |
2.3. Polymer-Based Conjugates

An important class of the emerging systems for the treatment of cancer is polymer-based conjugates, which consist of a drug molecule and a hydrophilic polymeric macromolecule covalently bonded to each other. In recent years, tremendous research has been conducted to explore new and functional therapeutic conjugates. Like nanoparticles, polymeric conjugates are also high molecular weight systems that affect a drug’s pharmacokinetics, toxicity, and efficacy [99].

Polymer–drug conjugate—a water-soluble system is composed of a drug-associating unit, another unit for linking an active targeting molecule, such as monoclonal antibody, and a portion for linking either by the conjugation of polyphenol monomers with macromolecules or the polymerization of monomer units of polyphenols. High molecular weight antioxidants can be prepared by three different approaches, namely, enzymatic catalysis, condensation, and radical grafting [101].

Enzymatic catalysis refers to the catalyst-mediated chemical reaction between non-toxic reagents in milder reaction conditions of pH, temperature, and pressure, resulting in the synthesis of distinct structures having controlled chemical properties [102]. In general, a peroxidase or a tyrosinase is used as the catalyst in a coupling reaction.

In condensation reactions, the functional groups of an antioxidant molecule and a polymeric chain react with each other, producing well-defined products with specific mechanical and physical features. As a result of these reactions, the mechanical properties of the product are similar to those of the parent materials. Esterification and acetylation are two important examples of condensation reactions. Generally, these reactions take place in several steps.

Lastly, the radical grafting approach involves free radical coupling between the polyphenol unit and the polymeric moiety in the presence of mild reaction conditions [103], resulting in the synthesis of a characteristic product that retains chemical features of the parent polyphenols.

Polyphenol-loaded polymeric conjugates for the treatment of cancer are summarized in Table 5. For the treatment of pancreatic cancer, a curcumin–gemcitabine combination was loaded with PEG conjugates through a condensation reaction in the presence of carbodiimide [104]. Also, PEG conjugates containing just curcumin have also been prepared for prostate [105] and glioma cancer [106]. Through the same conjugation technique, synergistic cytotoxicity was achieved with resveratrol–biculatamide–PEG conjugates in breast and cervical cancer cells [107] and quercetin–paclitaxel–carboxymethyl chitosan conjugates in hepatic cancer cells [108]. Another study reported the synthesis of curcumin–dithiopropionic acid copolymer, followed by conjugation with PEG [109]. PEG hydrogels containing triphosgene–curcumin conjugates showed an increased effect against proliferation in breast cancer cells [110].

Compared with the free forms of the tested polyphenols, the anticancer activity of PEG–catechin amides against breast cancer was synergistically increased in the presence of bortezomib [111]. Therapeutic synergism was also observed when hyaluronic acid–epigallocatechin gallate amides containing granzyme B were tested against colon cancer [112]. The therapeutic analysis of catechin–dextran conjugates showed the increased efficacy of catechin in pancreatic cancer cells [113] and in a neuroblastoma model animal [114]. Other studies showed an increase in the anticancer activity of quercetin-loaded polyacrylic acid conjugates towards cervical cancer [115] and gallic acid-loaded gelatin conjugates towards cervical cancer [116]. All these conjugates were prepared by a free radical approach. For the treatment of hepatic, pancreatic, prostate, glioma, and breast cancer, curcumin, resveratrol, and quercetin in combination with standard anticancer agents, such as paclitaxel, gemcitabine, or bortezomib, have been successfully loaded to polymeric conjugates.
| No. | Components of Nanoparticles | Method of Preparation | Polyphenol + Synergistic Agent | Type of Cancer | In Vitro Model Promisingly Treated with the Fabricated Nanotherapeutic Formulation | References |
|-----|-----------------------------|-----------------------|-------------------------------|---------------|---------------------------------------------------------------------------------|------------|
| 1   | PEG                         | Condensation method   | Curcumin                      | Glioma C6     |                                                                                   | [106]      |
| 2   | PEG                         | Condensation method   | Curcumin                      | Prostate cancer PC-3 |                                                                                   | [105]      |
| 3   | PEG                         | Condensation method   | Curcumin + Gemcitabine        | Pancreatic cancer MiaPaCa2, PANC-1, BxPC-3, AsPC-1 |                                                                                   | [104]      |
| 4   | PEG                         | Condensation method   | Resveratrol + Bicalutamide    | Cervical cancer HeLa |                                                                                   | [107]      |
| 5   | PEG                         | Condensation method   | Resveratrol + Bicalutamide    | Breast cancer MCF-7 |                                                                                   | [107]      |
| 6   | Carboxymethyl chitosan      | Condensation method   | Quercetin + Paclitaxel        | Hepatic cancer HepG2 HepG2 | Xenograft mice                                                                 | [108]      |
| 7   | PEG                         | Condensation method   | Curcumin                      | Cervical cancer HeLa, Breast cancer EMT6 EMT6 | Xenograft mice                                                                 | [109]      |
| 8   | PEG–Desaminotyrosyl-tyrosine ethyl ester | Condensation method | Curcumin                      | Breast cancer MDA-MB-231 |                                                                                   | [110]      |
| 9   | PEG                         | Condensation method   | Catechin + Bortezomib         | Breast cancer MDA-MB-231 |                                                                                   | [111]      |
| 10  | Hyaluronic acid–Polyethyleneimine | Condensation method | Epigallocatechin gallate + Granzyme B | Colon cancer HCT-116 |                                                                                   | [112]      |
| 11  | Dextran                     | Free radical grafting | Catechin                      | Pancreatic cancer MiaPaca-2, PL45 | Neuroblastoma IMR-32, Neuroblastoma IMR-32 | [113]      |
| 12  | Dextran                     | Free radical grafting | Catechin                      | IMR-32-CisRes, BE2-C | Xenograft mice                                                                 | [114]      |
| 13  | Dextran                     | Enzyme laccase catalysis | Catechin                      | Neuroblastoma IMR-32 |                                                                                   | [114]      |
| 14  | Polymethacrylic acid        | Free radical grafting | Quercetin                      | Cervical cancer HeLa |                                                                                   | [115]      |
| 15  | Gelatin                     | Free radical grafting | Gallic acid                    | Prostate cancer DU-145, PC-3 |                                                                                   | [116]      |
| 16  | Gelatin                     | Free radical grafting | Gallic acid                    | Renal cancer A498 |                                                                                   | [116]      |

Table 5. Polyphenol-loaded polymeric conjugates for the treatment of cancer.
2.4. Carbon-Based Nanostructures and Nanohybrids

A class of nano-sized materials, known as carbon nanostructures, is extensively being investigated for its therapeutic applications [117]. The representative examples of this interesting group of compounds are graphene and carbon nanotubes because of their good permeability, cheap availability, excellent physicochemical features, and large surface area for the likely interaction with bioactive compounds [118,119].

Graphene is a bidimensional honeycomb-like structure, consisting of a layer of six $sp^2$ carbon atoms [120]. These bodies undergo cell internalization through endocytosis or active processes [121]. Graphene oxide, an oxidative product of graphene, is an efficient drug delivery vehicle, because it contains numerous functionalities, such as carboxylic and hydroxyl groups Figure 1 [122].

![Figure 1](image)

**Figure 1.** A schematic representation showing the ameliorated effect of functionalization on the cytocompatibility of graphene and carbon nanotubes.

Carbon nanotubes are obtained by the condensation of benzene rings having a composition of $sp^2$ carbons, prepared as tube-like structures with a single layer single-walled carbon nanotubes or multiple layers multiple-walled carbon nanotubes [123]. Carbon nanotubes have a strong affinity with different proteins and undergo spiraling movement, thus they are efficiently uptaken by cells, revealing their promising membrane permeability [124].

Graphene oxide and carbon nanotubes are suitable drug delivery vehicles due to their quick physiological distribution, accumulation in various organs, including liver, lungs, kidney, and stomach, and excretion through bile and urine [125–127]. In addition, graphene oxide is a biocompatible and cytotoxic substance [128,129]. However, carbon nanotubes could be toxic and produce inflammation, necrosis, fibrosis, and granuloma due to their reducing potential: this feature of carbon nanotubes may hinder their use in drug delivery [129].

These toxicity problems can be eliminated by combining these materials with biocompatible, water-soluble compounds, especially polymers, generating carbon nanohybrids [130].

Numerous studies have reported the successful application of graphene oxide and carbon nanotubes in drug delivery for cancer therapy [131]; however, only a few studies describe their role in the delivery of polyphenols. For instance, a promising modality describes the polyphenol-induced reduction of graphene oxide, resulting in the bond formation between polyphenols and graphene oxide [132]. In this regard, tea polyphenol extract nanohybrids exhibited an improved antiproliferative action in colon cancer cells [133]. Similarly, the proliferation was profoundly inhibited by resveratrol nanohybrids in ovarian cancer cells [134].

On the other hand, pristine carbon nanotubes have been used in some studies for the delivery of polyphenols [135]. Owing to their toxic features, carbon nanotubes have been made
biologically compatible by coating with suitable polymers, including gelatin Table 6. In this context, multiple-walled carbon nanotubes were combined with polycaprolactone, resulting in the formation of nanohybrids. These nanohybrids loaded with tea polyphenol exhibited a promising therapeutic effect towards hepatic and lung cancer [136].

Functional nanohybrids Table 6 have also been prepared by developing covalent bonds between the polyphenol and the polymer through a radical reaction. In this regard, catechin–gelatin conjugate [137,138] and quercetin–methacrylic acid conjugate [139,140] were used as the coating material for multi-walled carbon nanotubes. The obtained nanotherapeutics were found to have enhanced anticancer activity in HeLa cancer cells, compared with the free flavonoids [137,139]. It is remarkable that a synergistic anticancer effect can be achieved by using these flavonoid nanohybrids and radiotherapy together towards neuroblastoma [140] and prostate cancer treatment [138]. All these studies demonstrated that carbon nanotubes and graphene oxide could be successfully utilized for the delivery of the polyphenols, including quercetin and catechins, for the effective treatment of cancer, including hepatic, prostate, and lung cancer.

Table 6. Polyphenol-loaded carbon-based nanohybrids for the treatment of cancer.

| No. | Components of Nanoparticles | Method of Preparation | Polyphenol + Synergistic Agent | Type of Cancer In Vitro Model/In Vivo Model Promisingly Treated with the Fabricated Nanotherapeutic Formulation | References |
|-----|-----------------------------|-----------------------|-----------------------------|--------------------------------------------------------------------|------------|
| 1   | Graphene oxide              | Reduction method      | Tea polyphenols             | Colon cancer HT29, SW48                                             | [133]      |
| 2   | Graphene oxide              | Reduction method      | Resveratrol                 | Ovarian cancer A2780                                               | [134]      |
| 3   | Polycapro-lactone–MWNT      | Electrospinning       | Tea polyphenols             | Lung cancer A549                                                    | [136]      |
| 4   | Polycapro-lactone–MWNT      | Electrospinning       | Tea polyphenols             | Hepatic HepG2                                                       | [136]      |
| 5   | Gelatin–MWNT                | Coating               | Catechin + Radiotherapy     | Prostate cancer DY-145, PC-3, LNCap                                 | [138]      |
| 6   | Gelatin–MWNT                | Coating               | Catechin                    | Cervical cancer HeLa                                               | [139]      |
| 7   | Polymeth-acrylic acid–MWNT  | Radical coupling      | Quercetin                   | Cervical cancer HeLa                                               | [137]      |
| 8   | Polymeth-acrylic acid–MWNT  | Radical coupling      | Quercetin + Cisplatin       | Neuroblastoma IMR-32                                               | [140]      |

Note: MWNT—Multiple-walled carbon nanotubes.

2.5. Magnetic Nanoparticles Manipulation of Nanoparticles Using Magnetic Field

The nanoparticles modulated by a magnetic field, termed magnetic nanoparticles, are extensively studied drug delivery vehicles for the treatment of inflammation, cancer, and other chronic diseases [141,142]. In addition to remote actuation, an alternate magnetic field with high radiofrequency can be applied for the heating of nanoparticles Figure 2 to augment the microenvironment temperature and enhance the probability of synergism.

In recent years, several studies Table 7 have reported the application of magnetic nanoparticle as a vehicle for the delivery of polyphenols for the treatment of tumors. It has been reported that curcumin conjugates possess profound cytotoxicity in Caco-2 cells, glioma [143], and breast cells [144]. Another study described the improved pharmacokinetics and cytotoxicity of curcumin–poloxamer nanoparticles, compared with curcumin alone [145]. Furthermore, magnetic nanoparticles coated with catechin–dextran conjugate exhibited an excellent anticancer activity towards pancreatic cancer [146]. A similar therapeutic outcome was observed when colon cancer cells were treated with epigallocatechin gallate–dextran conjugate [147]. The in vitro treatment of SMMC-7721 tumor cells with quercetin-loaded nickel nanoparticles exhibited synergism between the therapeutic effect and the permeability-enhancing effect of quercetin and nickel nanoparticles, respectively [148]. The nanocarriers for the delivery of polyphenols are studied in vivo to a limited extent, likely due to the fact that these nanoparticles, like any nano-sized drug delivery system, circulate for a short time in the blood as well as exhibit non-specific features. A representative study [147] reporting in vivo
experiments on green tea-coated magnetic nanocrystals described their promising transport and uptake properties, suggesting their potential use in therapeutics and multimodal imaging.

![Concept Figure](image)

**Figure 2.** A concept figure showing drug release from magnetic nanoparticles under the effect of alternating magnetic field.

| No. | Components of Nanoparticles | Method of Preparation | Polyphenol + Synergistic Agent | Type of Cancer In Vitro Model/In Vivo Model | References |
|-----|-----------------------------|-----------------------|-----------------------------|----------------------------------------|------------|
| 1   | Hyaluronic acid-Iron         | Layer-by-layer        | Curcumin                    | Colon cancer Caco-2                     | [143]      |
| 2   | Polyvinyl pyrrolidone-Iron   | Layer-by-layer        | Curcumin                    | Glioma C6                              | [143]      |
| 3   | Iron–Poloxamers F127         | Nanopre-cipitation    | Curcumin                    | Pancreatic cancer HPAF-II, Pan-c-1/Xenograft mice | [145]      |
| 4   | Iron–Dextran                 | Solution method       | Catechin                    | Pancreatic cancer MIA Paca2             | [146]      |
| 5   | Nickel                      | Electro-chemical deposition | Quercetin                | Hepatic cancer SMMC-7721                | [148]      |

**3. Conclusions**

In spite of extensive research struggles, the limitations to achieving effective cancer therapy are still unresolved. Similarly, natural products, including polyphenols, have been known for their anticancer effects for a long time, but their clinical use is still a dream. The above discussion reveals that the exclusive use of polyphenols as cancer therapy is inadequate for translation into therapeutic protocol; rather, due to the substantial synergism observed in study models, polyphenols can be suggested in combination with standard therapeutic modalities. Moreover, it is encouraging that a wide range of safe and effective polymeric nanoparticulate systems are available for the delivery of multiple compounds. Thus, polyphenols could be recommended for clinical use in the future.

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