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Review

Polyphenol-Loaded Polymeric Matrixes as Potential Biopharmaceuticals against Cancer

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Abstract: Polyphenols have attracted attention for their anti-inflammatory, antidiabetic, and anticancer properties. Due to the antioxidant and anti-inflammatory potential of these molecules, they are also proposed as a potential therapeutic tool to prevent complications of cancer and decrease the secondary effects of conventional chemotherapeutic drugs. Nonetheless, polyphenols such as flavonoids and phenolic acids have low bioavailability, as they are highly metabolized. Thus, administration strategies have been developed to enhance the anticancer properties of polyphenols. Most of these strategies involve different encapsulation techniques, such as nanoencapsulation, nanoemulsion, and the use of other polymeric matrixes. These techniques can increase the activity of these compounds after going through the gastrointestinal process and improve their solubility in an aqueous medium. This review comprises recent studies regarding encapsulation techniques to enhance the bioactivity of polyphenols against cancer and their current state in clinical studies. Overall, micro- and nanoencapsulation techniques with different polymers enhanced the anticancer properties of polyphenols by inhibiting tumor growth, modulating the expression of genes related to metastasis and angiogenesis, decreasing the expression of pro-inflammatory biomarkers.

Keywords: polyphenols; cancer; encapsulation; anticancer; biomaterials; polymers

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1. Introduction

Phenolic compounds, known by the general audience as "polyphenols", are secondary metabolites from plants produced mainly as a defense mechanism against abiotic and biotic factors. These constituents also contribute to pollination by granting color to flowers and plants, attracting pollinators [1]. For their study, polyphenols can be grouped according to their chemical structure, number of phenol rings, and number and distribution of their -OH groups. The most common groups are (1) flavonoids: anthocyanins, chalcones, dihydrochalcones, dihydroflavonols, flavanols, flavanones, flavones, flavonols, isoflavonoids; (2) lignans, (3) non-phenolic compounds, (4) phenolic acids: hydroxybenzoic acids, hydroxycinnamic acids, hydroxyphenylacetic acids, hydroxyphenylpropanoic acids, hydroxyphenylpentanoic acids, (5) stilbenes, and (6) other polyphenols (Figure 1) [2–4]. Polyphenols are of interest in the nutraceutical and pharmaceutical industries because of their antioxidant, anti-inflammatory, and anticancer properties.

Cancer is a group of diseases that begins when abnormal cells grow uncontrollably and can start in nearly all tissues and organs. Cancer is the second leading cause of death worldwide, with around 9.6 million deaths in 2018. According to the International Agency

for Research on Cancer of the World Health Organization, the cancers that caused most deaths in 2020 were lung, colorectum, liver, stomach, breast, esophagus, pancreas, and prostate cancer (Figure 2).

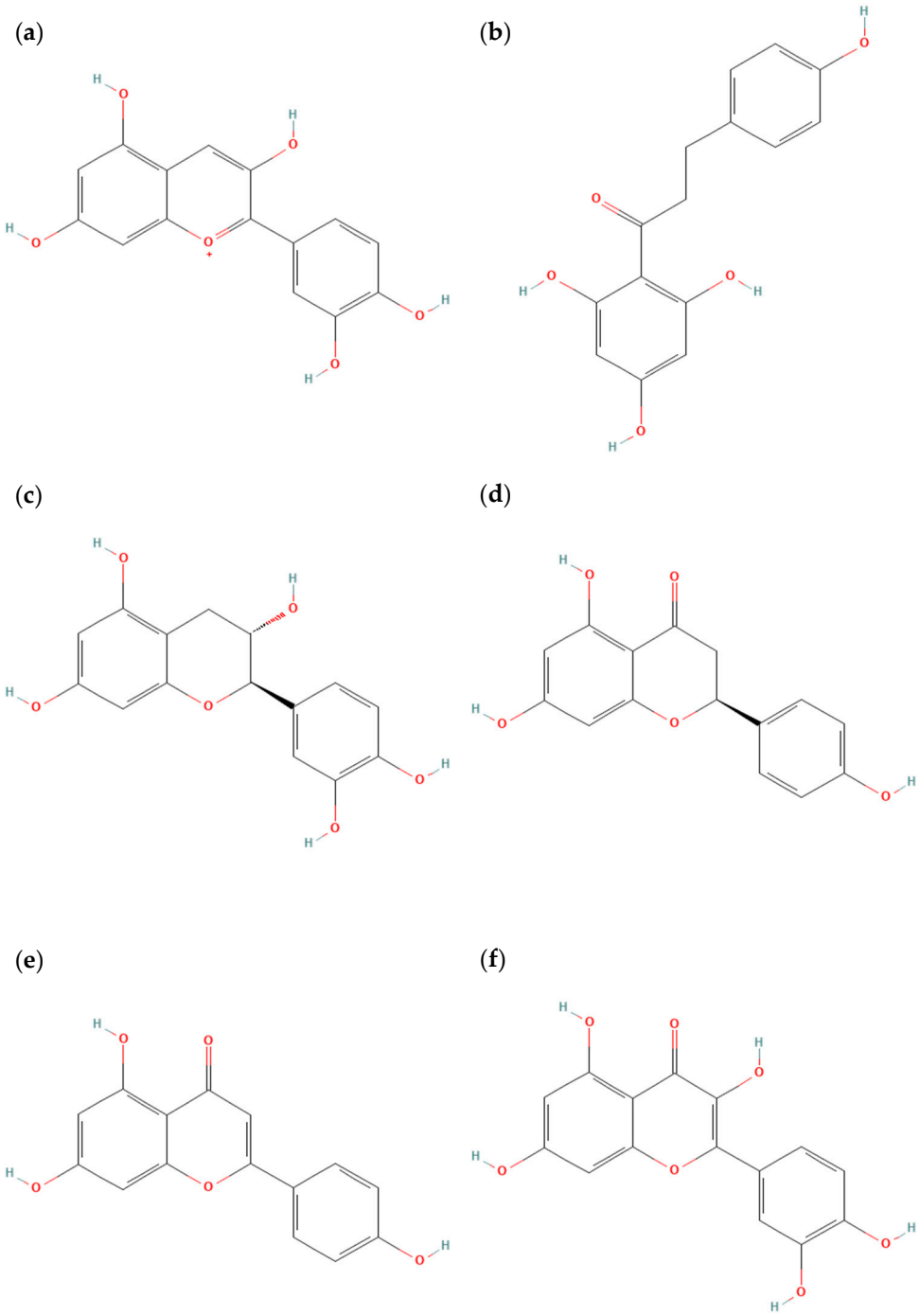

Figure 1. Chemical structures of known polyphenols: (**a**) anthocyanins (cyanidin), (**b**) dihydrochalcones (phloretin), (**c**) flavanols (catechin), (**d**) flavanones (naringenin), (**e**) flavones (apigenin), (**f**) flavonols (quercetin).

Currently, there is evidence that a regular intake of food sources rich in polyphenols can decrease cancer incidence and prevent disease onset. In vitro studies have shown that many polyphenols have antiproliferative activity through several mechanisms of action involved in signaling cascades in the different cancer development stages [6,7]. Furthermore, in vivo studies have also shown that polyphenols can exert an anticancer potential also at this level. Nonetheless, one of the problems dealing with polyphenols

is their low bioavailability because the xenobiotic metabolism highly metabolizes them. In this sense, encapsulation strategies using polymeric matrixes have been developed to increase the bioavailability of polyphenols. This review summarizes recent studies on encapsulation strategies and the available in vivo evidence of their anticancer potential.

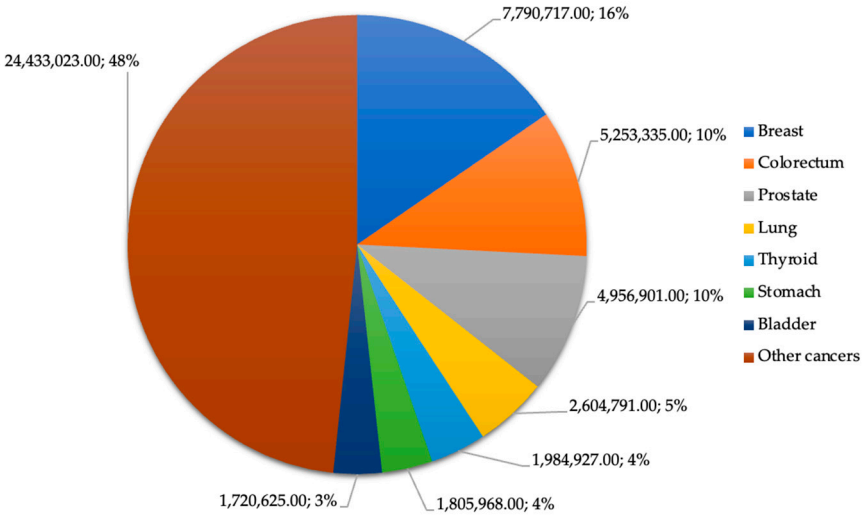

Figure 2. Estimated number of prevalent cases worldwide (5 years) in 2020 for both sexes of all ages. Graphic was made by the authors from data of the International Agency for Cancer Research database [5].

2. Materials and Methods

This work was compiled based on recent literature (2012–2023) from the Scopus, Google Scholar, and Web of Science databases to identify relevant studies on this topic. To identify relevant literature, we combined the keywords polyphenols, flavonoids, phenolic acids, and phenolic compounds with the following keywords: microencapsulation, nanoencapsulation, nanoemulsions, and cancer, anticancer, and antiproliferative. In addition, we decided to include only literature in the English language. Finally, we grouped 91 research papers for this manuscript.

3. Anticancer Properties of Polyphenols

3.1. In Vivo Studies

Different studies in mice and rats showed the potential anticancer properties of polyphenols (Table 1). They can act at different levels, including by apoptosis induction of tumor cells in different ways. In this sense, this type of cell death can be induced by ellagic acid and galangin via increased caspases-3 expression and activity in retinoblastoma tumors and lymphomas [8,9], as well as by an increase in *Bad* and a decrease in *Bcl-2* gene expression by vanillic acid [10]. In addition, it was observed that polyphenols decrease metastasis by inhibiting the migration and invasion of cancer cells; among them, eriodictyol and luteolin showed this effect [11,12]. Furthermore, taxifolin decreased epithelial–mesenchymal transition, an early event of metastasis [13].

In addition, signaling pathways such as PI3K/Akt and MAPK/ERK are related to cell proliferation, which could be downregulated by caffeic acid and caffeic acid phenylpropyl ester in induced colon cancer [14].

On the other hand, inflammation and oxidative stress are two physiological processes which have been linked to cancer [15]; in this context, naringenin had an anticancer effect in the lungs by decreasing the expression of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (a bridge between inflammation and cancer), which decreased the expression of cytokines such as interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF-α); at the same time, this flavanone could increase the antioxidant enzymes and non-enzymatic antioxidants, exerting a cytoprotective function against induced lung cancer [16].

Moreover, taxifolin increased the antioxidant response by the upregulation of the nuclear factor erythroid 2-related factor 2 (Nrf2) and decreased inflammation by downregulation of the NF-κB and Wnt/β-catenin signaling pathways in induced colon cancer [17]; also, Nrf2 upregulation in induced hepatic cancer by vanillic acid was detected [10].

Table 1. Effect of polyphenols supplementation against cancer in rats and mice models.

Compound	Dose	Model	Effect	Reference
Caffeic acid	50 nmol/kg	Mice with human colon cancer xenografts	Inhibition of tumor growth via downregulation of PI3K/Akt and MAPK/ERK signaling	[14]
Caffeic acid phenylpropyl ester	50 nmol/kg	Mice with human colon cancer xenografts	Inhibition of tumor growth via downregulation of PI3K/Akt and MAPK/ERK signaling	[14]
Chlorogenic acid	20–40 mg/kg	Mice with breast cancer xenografts	Decrease in tumor growth and inhibition of metastasis via an increase in CD4+ and CD8+ cells in the spleen	[18]
Ellagic acid	40 mg/kg	Mice with human bladder cancer xenografts	Decrease in tumor growth rate, infiltrative behavior, and tumor-associated angiogenesis.	[19]
	80 mg/kg	Mice with induced lymphoma	Induction of apoptosis via an increase in caspase-3 expression and activity and PKCs activity and a decrease in LDH-A activity and expression in ascites fluid	[8]
Eriodictyol	60 mg/kg	Mice with mammary cancer xenografts	Decrease in tumor growth and progression and in lung metastasis	[11]
Galangin	25–50 mg/kg	Mice with human retinoblastoma xenografts	Decrease in tumor growth via a decrease in Akt signaling pathway and increase in caspase-3 level	[9]
Luteolin	1.2 mg/g	Mice with AOM/DMH-induced colon cancer	Decrease in LDH levels and in iNOS and COX-2 expression in colon tissue	[20]
	100 mg/kg	Mice with human epithelial xenograft	Decrease in migration and invasion	[12]
Naringenin	50 mg/kg	Mice with benzo(a)pyrene induced lung cancer	Downregulation of CYP1A1, PCNA, and NF-κB expression; decrease in lipid peroxidation, TNF-α, IL-6 and IL-1β; increase in antioxidant enzymes activity in lung tissue	[16]
Quercetin	30 mg/kg	Mice with AOM/dextran sodium sulfate-induced colorectal cancer	Decrease in tumor growth and proliferation via a decrease in inflammation and ROS	[21]
	25–50 mg/kg	Rats with DMH-induced colon cancer	Decrease in tumor incidence and multiplicity; downregulation of the Wnt signaling pathway in colon tissue	[22]
Taxifolin	4 μg/kg	Mice with DMH-induced colon cancer	Upregulation of the Nrf2 signaling pathway, downregulation of the NF-κB and Wnt signaling pathways in colon tissue	[17]

Table 1. *Cont.*

Compound	Dose	Model	Effect	Reference
	1 mg/kg	Mice with human lung cancer xenograft	Decrease in tumor size via inhibition of PI3K and TCF4 signaling and by decreasing epithelial–mesenchymal transition	[13]
Vanillic acid	75 mg/kg	Rats with DMH-induced hepatic cancer	Upregulation of the Nrf2 signaling pathway; induction of apoptosis via an increase in *Bad* and *Caspase-3* genes expression and decrease in *Bcl-2* gene expression; decrease in proliferation via a decrease in *Cyclin D1* gene expression in hepatic tissue	[10]

On the other hand, studies on different populations have shown that the intake of polyphenols is associated with a reduced cancer risk (Table 2). In this context, the concentration in the serum of flavonoids such as kaempferol and naringenin was associated with a lower breast cancer risk [23]; similarly, anthocyanidins and flavan-3-ols caused similar effects with synergism with butyl benzyl phthalate [24]. Also, the phenolic acids ferulic acid and caffeic acid reduced the risk to develop prostate cancer [25], and bladder cancer risk showed an inverse association with flavonols and lignans intake [26]. Interestingly, a study demonstrated an association between thyroid cancer risk and the intake of flavonoids and phenolic acid, but only in patients with a BMI $\geq$ 25, which can be attributed to the anti-inflammatory activity of these compounds, as obesity is a low-grade inflammation disease [27]. However, some studies indicated no association between polyphenols consumption and decrease in cancer risk, including colorectal, pancreatic, and epithelial ovarian cancer [28–31]. In contrast, a study in the Iranian population showed a lower colorectal cancer risk associated with polyphenols consumption, indicating variation between populations [32].

Table 2. Studies of the association between polyphenols intake and cancer risk.

Compound(s)	Cancer Type	Population	Subjects (Age)	Effect	Reference
Flavonols and lignans	Bladder	477,312 European subjects	35–70 years	Inverse association between flavonols and lignans intake and bladder cancer risk	[26]
Flavonols, isorhamnetin, kaempferol, flavanones and naringenin	Breast	877 Chinese women with breast cancer, 792 control subjects	25–70 years	The concentration of the flavonoids in the serum was associated with a lower breast cancer risk	[23]
Anthocyanidins and flavan-3-ols	Breast	233 Mexican women with breast cancer, 221 control subjects	>18 (mean 53) years	Higher intake of flavonoids reduced the risk of breast cancer, synergistically working with butyl benzyl phthalate	[24]
Flavonols, flavones, flavanones, flavan-3-ols, and anthocyanins	Colorectal	51,528 US male health professionals and 121,701 US female nurses	Men: 40–75 years Women: 30–55 years	No decrease in colorectal cancer was detected	[28]
Flavonoids	Colorectal	521,448 European subjects (with exceptions)	35–70 years	No association between flavonoids intake and colorectal cancer was found	[29]

Table 2. *Cont.*

Compound(s)	Cancer Type	Population	Subjects (Age)	Effect	Reference
Phenolic acids, hydroxycinnamic acids, flavonols, and stilbenes	Colorectal and colorectal adenoma	129 Iranian subjects with colorectal cancer, 130 with colorectal adenoma, and 240 controls	30–79 years	Higher intake of phenolic acids, hydroxycinnamic acids, and flavonols was associated with a decrease in colorectal cancer risk. Higher intake of stilbenes was associated with a lower colorectal adenoma risk.	[32]
Polyphenols	Epithelial ovarian cancer	309,129 European women	35–70 years	No association between polyphenols intake and endothelial ovarian cancer was found	[30]
Naringenin, peonidin, and catechin	General	14,029 US subjects	>18	Inverse association between flavonoids intake and cancer mortality	[33]
Flavonoids and lignans	Pancreatic	477,309 European subjects	25–70 years	No association between flavonoids and lignans intake and pancreatic cancer was found	[31]
Caffeic acid and ferulic acid	Prostate	118 Italian prostate cancer subjects, 22 controls	Mean age: 69.13 years	High intake of phenolic acids may be associated with a decrease in prostate cancer risk	[25]
Polyphenols and phenolic acids	Thyroid	476,108 European subjects	35–70 years	Inverse association between polyphenols and phenolic acids intake and thyroid cancer risk in patients with BMI $\geq$ 25	[27]

3.2. Clinical Studies

The effect of polyphenols supplementation has been studied on various cancers, including bladder, colorectal, oral, and prostate cancer (Table 3). For example, the compound curcumin has been studied for both oral cancer and familial adenomatous polyps (a condition that leads to colorectal cancer); in this sense, curcumin decreased interleukin content in the saliva and induced the attraction of T cells to the tumor microenvironment [34]. In contrast, no effect was observed on the mean size and number of polyps in the lower intestinal tract [35]. On the other hand, studies indicated no beneficial effect of epigallocatechin gallate against colorectal and prostate cancer [36,37]; in contrast, cranberry fruit powder rich in phenolic compounds was able to reduce the serum level of prostate-specific antigen in patients after prostate cancer removal, serving as a prophylactic agent against the recurrence of this disorder [38]. Furthermore, a ginger extract with 5% of gingerols decreased the proliferation of crypts in patients with a high risk of colorectal cancer [39].

Table 3. Clinical studies of polyphenols against different types of cancer.

Cancer	Compound	Dose	Subjects	Effect	Reference
Bladder	Genistein	300 or 600 mg	59 subjects with urothelial bladder cancer	Inhibition of bladder cancer growth by inhibiting the phosphorylation of the epidermal growth factor receptor	[40]
Colorectal	Ginger (*Zingiber officinale*) extract with 5% of gingerols	2 g	21 healthy subjects with a high risk of colorectal cancer	Decrease in the proliferation of crypts	[39]
	Epigallocatechin gallate	780 mg	32 subjects with rectal aberrant crypt foci	No difference in the number of the rectal aberrant crypt foci	[37]

Table 3. *Cont.*

Cancer	Compound	Dose	Subjects	Effect	Reference
Familial adenomatous polyposis	Curcumin	3000 mg	44 subjects with familial adenomatous polyposis	No difference in the mean number or size of polyps	[35]
Oral	*Curcuma longa* phenolic extract	100 or 200 mg	12 oral cancer patients 13 normal subjects	Decrease in IL-1β, IL-6, and IL-8 content in the saliva. Increased gene expression related to differentiation and T cell recruitment to the tumor microenvironment.	[34]
Prostate	Cranberry fruit powder	1500 mg	62 subjects with prostate cancer	Decrease in serum prostate-specific antigen	[38]
	Epigallocatechin gallate	600 mg	43 subjects with a prior negative biopsy, but suspicious	No difference in fatty acid synthase or antigen Ki-76	[36]

These studies indicate a possible beneficial effect of different kinds of polyphenols against various cancers; however, their limitations should be considered, including a small sample size and the acute administration of polyphenols in some studies. Thus, more solid and robust clinical studies are necessary, considering the high variety of polyphenols and types of cancer, as well as other strategies to improve polyphenols bioaccessibility and bioavailability.

4. Polymeric Matrixes to Encapsulate Polyphenols

Polyphenolic compounds are secondary metabolites found more frequently in fruits and plants; several beneficial health effects have been attributed to them, and there is also the possibility of using them as adjuvants or biopharmaceuticals to treat chronic degenerative diseases such as cancer. However, due to the low solubility and low bioavailability that they present, in recent years, different alternatives have been sought to increase both their solubility in an aqueous medium and their bioavailability, as well as to increase their protection in the medium in which they are dissolved, since the majority of these compounds are susceptible to changes caused by light, temperature, pH, etc. [41]. That is why different alternatives have been proposed to encapsulate them by various techniques such as spray drying, nanoemulsion, coacervation, films, and others, which help these compounds enhance their activity in some cases. In Table 4, we can observe some of the advantages and disadvantages of encapsulated vs. non-encapsulated phenolic compounds, emphasizing that different amounts of these compounds may encapsulated using the different techniques, due to their chemical and/or physicochemical nature. For this reason, most researchers try not to use encapsulation methods that can damage or deteriorate the phenolic compounds [42–46].

Furthermore, the variety of functional groups in these compounds means that they may establish different covalent or non-covalent interactions and coordinate with diverse metals (See Figure 3).

Chitosan, being a natural cationic polysaccharide, shows high biocompatibility, low toxicity and biodegradability. Cyclodextrins are among the most widely used oligomers of natural origin for the encapsulation of active ingredients of natural origin and have been modeled for the encapsulation of different synthetic and natural active compounds, such as polyphenolic compounds [47]. Due to the polycationic characteristics that these matrices usually have, they usually contain groups that are capable of ionizing to establish an electrostatic interaction with free -OH groups (hydrogen bonds) or can produce esterification reactions with carbonyl groups to generate covalent bonds, as well as coordinate with different metals; so, a high content of these groups (-OH) in polyphenolic compounds could help these compounds to encapsulate in a greater proportion [47–52].

Table 4. Comparison of the advantages and disadvantages of encapsulated and non-encapsulated phenolic compounds.

Encapsulated	Non-Encapsulated
• Increased solubility in aqueous medium • Higher content of bioavailable phenolic compounds after the gastrointestinal process • Increased activity of encapsulated compounds after the gastrointestinal process • Low content of compounds within the capsule, depending on the size and chemical characteristics of the particle and the compounds.	Ionization and/or loss of phenolic compounds throughout the gastrointestinal process Low solubility in aqueous medium, high solubility in organic media frequently unfit for human consumption. Decreased activity of polyphenolic compounds after the gastrointestinal process

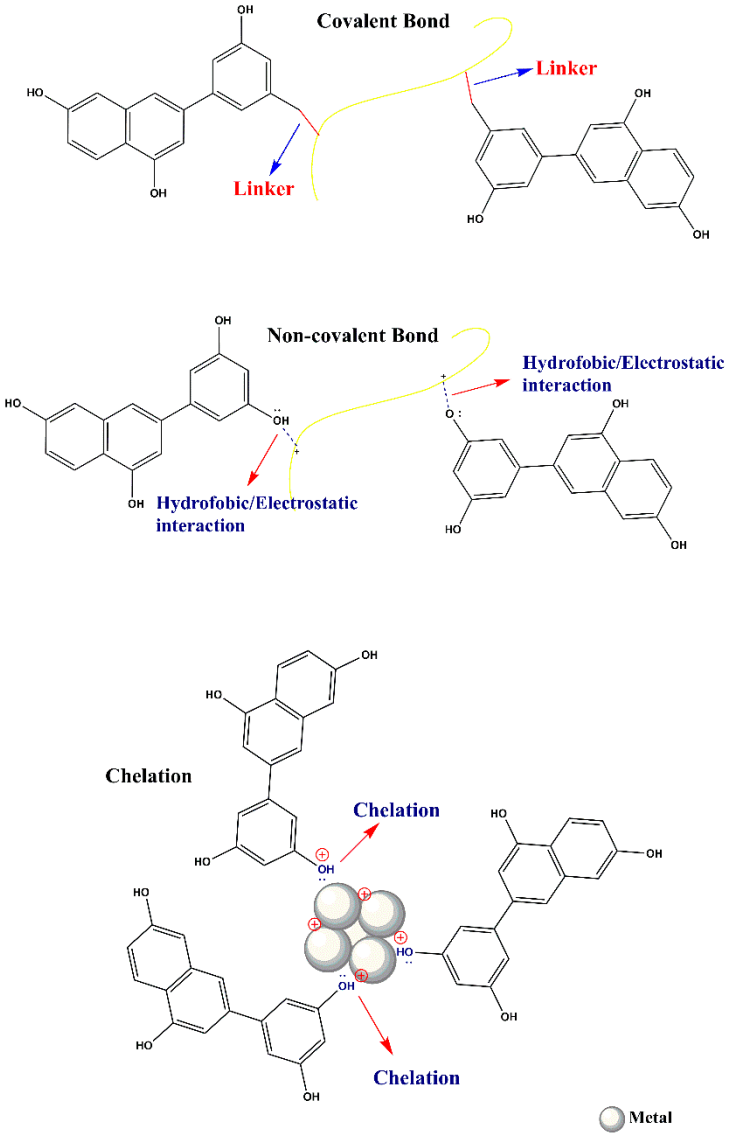

Figure 3. Types of interactions of polyphenols with different polymers.

For this reason, the formulation of capsules with synthetic polymers and biopolymers with polycationic characteristics such as chitosan, albumin, whey protein, poly(d,l-lactide-co-glycolide (PGLA), among others, is normally used [53–55]. The following Table 5 provides a summary of some of the polymers used for the encapsulation of phenolic compounds on the nanometric scale (1–1000 nm).

Table 5. Summary of polymers used for the encapsulation of phenolic compounds on the nanometric scale.

Wall Materials	Interaction	Technique of Encapsulation	Phenolic Compound	Application	Reference
Chitosan–PEGMA Chitosan	Hydrogen bond	Desolvation method Nanoemulsion	*Lippia graveolens* (ethanolic extract) *Posidonia oceanica* extract	- Inhibitory activity against neuroblastoma cell migration.	[43,56]
Chitosan–poly (d,l-lactide-co-glycolide)	Hydrogen bond	Double emulsion solvent evaporation	Cranberry powder extracts	Cytotoxicity of colon cancer cells (HT-29)	[57]
β-Cyclodextrin	Hydrogen bond	Coacervation Desolvation method	Curcumin Resveratrol and Oxyresveratrol	Transdermal delivery (melanoma treatment) Antiproliferative effect in prostate cancer cells	[58]
Carboxymethyl cellulose–lactoferrin	Hydrogen bond	Desolvation method	Hidroxypropyl-beta-cyclodetrin–Polyphenol honokiol	Inhibition of tumor growth in in vivo studies (EAT)	[59]
α-tocopherol and polystyrene block–polyethylene glycol	Covalent and chelation	Flash nanoprecipitation	Tannic acid, Paclitaxel	Against OVCA-432 ovarian cancer cells	[60,61]
In(III) and Cu(III)	Covalent		Catechol 3,4-dihydroxycinnamic	Contrast Agent	[62]
Albumin	Hydrogen bond	Desolvation method	Piceatannol	Down-regulation of p65 and HIF-1 (proteins associated with different types of cancer)	[63]
Casein	Hydrogen bond	Desolvation method Coacervation (Spray drying)	Quercetin and Curcumin Resveratrol	Against MCF-7 breast cancer cells Increased bioavailability of resveratrol in plasma	[64,65]
Whey protein	Hydrogen bond	pH-cycling treatment	Apigenin	Against colorectal cancer cells HTC-116 and HT-29	[61]
Poly-(lactide-co-glycolide) acid (PLGA)	Hydrogen bond	Nanoprecipitation Emulsion (O/W)	Sonoran desert propolis *Callistemon citrinus* Phenolics and berberine Polydatin	Antiproliferative activity Antiproliferative effect in breast cancer cells (MCF-7, MCF-10A, and MDA-MB 231) Decreasing lipid peroxidation activity in hamster induced with oral cancer	[66–68]
$^{PGF}CaCO_3$-PEG	Chelation	-	Gallic acid	Suppressed 4T1 tumor growth	[69]
Retinoic acids and hyaluronic acid	Hydrogen bond	Dialysis	Curcumin	Present sensibility to GSH and promote the liberation of curcumin in esophageal cancer cells (ECA-109)	[70]
Soluplus	Hydrogen bond	Desolvation method	*Posidonia oceanica* Extract	Inhibitory activity against neuroblastoma cell migration	[56]
Whey protein–maltodextrin/Arabic gum	Hydrogen bond	Coacervation	Grape seed extract	Combination of the different polymers improved microencapsulation	[71]
Poly(ε-caprolactam)–hyaluronic acid	Hydrogen bond	Nanoprecipitation	Naringenin	Antiproliferation of lung cancer cells	[72]

For microencapsulation (1–1000 μM), biopolymers such as maltodextrin, gum arabic, B-cyclodextrin, modified chitosan (water soluble), sodium alginate, whey protein, among others, are commonly used. The techniques used to prepare these microcapsules vary and include spay drying, lyophilization, extrusion, freeze–drying, emulsion, etc. Unlike nanoencapsulation, non-covalent interactions predominate in microencapsulation (hydrogen bonds, electrostatics, etc.) [73–77]. In the following Table 6 some examples of microencapsulation are shown.

Table 6. Summary of some examples of polyphenol microencapsulation.

Wall Materials	Interaction	Technique of Encapsulation	Phenolic Compound	Application	References
Maltodextrin/modified chitosan/pectin	Hydrogen bond	Spay drying	*Punica granatum* peels extract	The cytotoxicity was improved when the extract was encapsulated in AGS (human gastric adenocarcinoma) and A549 (human lung carcinoma) cell lines	[78]
Whey protein	Hydrogen bond	Emulsion	Grape Phenolic	After digestion, the activity of the polyphenols was stabilized	[79]
Maltodextrin	Hydrogen bond	Spray drying	Grape phenolics	After digestion, the activity and the bioaccessibility of the polyphenols increased	[79]
Sodium alginate	Hydrogen bond	Extrusion	*Bifidobacterium bifidum* and *Lactobacillus gasseri* in combination with quercetin	Combining probiotics and quercetin resulted in a more effective protection and prevented hepatomegaly. Mechanistically, the results suggested that microencapsulated probiotics in combination with quercetin could exert the inhibition of the canonical Wnt/β-catenin signaling pathway in the colon	[80]

5. Studies with Polyphenol-Loaded Polymeric Matrixes with Anticancer Properties

We aimed to analyze information on the evidence of the pharmaceutical potential of polyphenols in polymeric matrixes. This section aims to summarize the recent information on in vivo studies using nano- or microparticles loaded with purified polyphenols (alone or in combination). So far, our literature research found few reports that we will mention. Encapsulation of polyphenols is being studied to increase the effectiveness of anti-cancer drugs. For instance, in a melanoma skin cancer mice model, treatment with nanoparticles containing co-encapsulated curcumin and chrysin in poly lactic-co-glycolic acid (PLGA) at the two concentrations of 15 mg/kg each and 30 mg/kg each showed better inhibition of tumor growth than treatment with the single encapsulated compounds. In addition, the treatment with the co-encapsulated polyphenols also decreased the expression of the MMP-9, MMP-2, and TERT genes, which are involved in metastasis and angiogenesis [81].

Hesperedin-conjugated gold nanoparticles in Wistar albino rats with diethylnitrosamine-induced hepatocarcinogenesis decreased the expression of the pro-inflammatory biomarkers TNF-α and NF-κB in the treated animals, which are involved in cancer proliferation. Moreover, the treatment with encapsulated hesperedin also decreased the levels of the proliferative marker proliferating cell nuclear antigen [82].

Baohuoside I (50 mg/kg) micelles mixed with lecithin and Solutol HS 15 in nude mice showed antitumor activity against non-small cell lung cancer by inhibiting tumor growth. The authors mentioned that the combination of bahuaoside I and Solutol could improve the cytotoxicity against this type of cancer cells due to the drug's reduced efflux by inhibition of glycoprotein P.

Chitosane–sodium alginate microencapsulated quercetin (15 mg/100 g diet) with *Bifidobacterium bifidum* and *Lactobacillus gasseri* (10^7 CFU/100 g diet each) supplemented to C57BL/6J mice (ApcMin/+ mice model for gut cancer) significantly reduced the number of aberrant crypt foci by 45–57% and the number of adenomas by 60–80%. Moreover, after 73 days, the treatment modulated the regulation of the Wnt/β-catenin signaling pathway (polyp formation and colorectal cancer development). Therefore, it was hypothesized that the action against colorectal cancer of the co-encapsulation was partially mediated by the anti-inflammatory properties of quercetin and by the suppression of colonic mucosa cellular proliferation by the probiotics' effect [80].

A study by Khan et al. [83] on a naringenin- (D2) loaded PLGA–doxorubicin nanoparticles treatment in Sprague-Dawley rats showed improved naringenin bioavailability and its distribution mainly in the liver. Furthermore, the author showed that the nanoencapsulated particles had antitumor properties in nude female mice with ectopic MCF-7-induced tumors, as the treatment decreased the tumor size from 2220 mm^3 in the control animals to 75.78 mm^3 in the treated animals.

Das et al. [84] formulated nanoparticles with apigenin and poly(lactic-co-glycolide) and administered them to Sprague Dawley rats with skin cancer induced by UVB irradiation and the carcinogen BaP. Oral and topical nanoencapsulated apigenin delayed the tumor onset and tumor multiplicity. The study also showed that the treatment decreased the damage in the epidermis and dermis, which could be related to the delayed tumor formation. Further analysis showed that apigenin administration reduced the expression levels of PCNA, upregulated the expression of apaf-1, caspase 9, and modulated the bax/bcl-2 ratio.

A study by Siddiqui et al. [85] evaluated the anticancer properties of epigallocatechin-3-gallate-encapsulated chitosan nanoparticles administered orally, five times a week, in athymic male nude mice implanted with Mel 928 cells (human melanoma cell xenograft model). It was reported that the nanoencapsulated flavanol inhibited the growth of melanoma tumors in the treated mice, without toxicity. Furthermore, one of the possible mechanisms of action by which this happened might involve the observed increased levels of pro-apoptotic Bax and the decreased anti-apoptotic Bcl-2 levels. Also, it was observed that the treatment modulated cyclin-dependent kinases such as CDK 4 and CDK 6 and decreased the expression levels of Ki-67 and PCNA, involved in tumor progression and cell proliferation.

Calcium phosphate-nanoencapsulated resveratrol was tested in a Swiss albino mouse model of skin cancer using 0.5 and 1 μg of nanoresveratrol; 30 min after treatment, the animals received topical 7,12-dimethylbenz[a]anthracene (DMBA)-initiated/12-O-tetradecanoylphorbol-13-acetate (TPA) to promote two-stage skin cancer. The calcium phosphate had a nanoencapsulation efficiency of 85% [86]. Moreover, edema in mice decreased using 10 μg of resveratrol alone, but this effect was observed with 0.5 μg of nanoencapsulated nanoresveratrol, which was attributed to the better stability of nanoencapsulated resveratrol and higher antioxidant and its anti-inflammatory activity; this also resulted in lower incidence and burden of the skin tumors. In both cases, calcium phosphate-nanoencapsulated resveratrol showed better results than non-encapsulated resveratrol.

In Table 7, we show a summarized revision of cases in which the anticancer properties of encapsulated polyphenols were evaluated using in vivo models.

In general, polyphenol delivery with polymers enhanced their anticancer properties by inducing cell cycle arrest, inducing apoptosis, enhancing antioxidant defense enzyme activity (such as superoxide dismutase activity), inhibiting cell proliferation, metastasis, and angiogenesis [87].

There are some studies that delt with polymer-loaded and -encapsulated polyphenols that evaluated their anticancer potential in vivo. However, preclinical and clinical studies are scarce. Further research on the pharmaceutical properties of these molecules should be carried out. Clinical studies are needed to evaluate their potential as pharmaceutical agents for the treatment or coadjuvant treatment of cancer.

Table 7. In vivo studies on the anticancer properties of encapsulated polyphenols.

Wall Agent	Encapsulated Polyphenol	Treatment	Result	References
Chitosan, nanoencapsulation	Quercetin	C57BL6 mice used to examine anti-tumor activity. Tumors were induced in immunocompromised mice, using human xenografts obtained with A549 and MDA-MB-468 cells. Chitosan–quercetin nanoencapsulation increased superoxide dismutase activity in treated mice.	Tumor regression (62.86% and 49.96% volume reduction for A549 and MDA-MB-468 cells, respectively) was observed after treatment with chitosan-nanoencapsulated quercetin, as a better anticancer agent than quercetin alone.	[87]
Whey protein isolate, nanoencapsulation	Apigenin	Male and female C57BL/6J mice were administered nanoencapsulated apigenin at 50 mg/kg	Chitosan nanoencapsulation of apigenin improved the latter's bioavailability with respect to free apigenin. Nanoencapsulation improved the absorption of apigenin	[61]
Poly(lactide-co-glycolide) and levan	Curcumin	The nanoformulation consisted of 10 mg of curcumin, 50 mg of poly(lactide-co-glycolide), and 80 mg of levan. Intraperitoneal administration of the formulation for 17 days	The nanoformulation of poly(lactide-co-glycolide) and levan with curcumin enhanced curcumin accumulation at the tumor site. The treatment also inhibited NF-kB.	[88]
Liposomes	Plumbagin and genistein (10:1 ratio)	Xenografted tumors by subcutaneous injection of PC3 or LNCaP prostate cancer cells in female athymic nude mice. Liposomes (1.5 mg genistein/kg and 15 mg plumbagin/kg bodyweight) were administered intravenously for 18 days.	Treatment with genistein and plumbagin-loaded liposomes decreased by nearly 80% the tumor growth.	[89]
Dextran–deoxycholic acid amphiphilic polymer	Silybin (co-encapsulated with paclitaxel)	Subcutaneous inoculation of A549 cells in BALB/c nude mice. The nanoencapsulated paclitaxel and silybin (7 mg/kg and 10 mg/kg bodyweight, respectively) were administered through the tail vein.	Co-encapsulated paclitaxel/silybin enhanced blood circulation from 1 to 5 h.Tthe improved blood circulation also enhanced the tumor accumulation of the compounds and caused tumor growth suppression	[90]
Epigallocatechin-3-gallate–iron nanoparticles with doxorubicin	Epigallocatechin-3-gallate	Intravenous injection in 4T1 tumor-bearing BALB/c mice with epigallocatechin-3-gallate–iron nanoparticles with doxorubicin.	Treatment decreased tumor volume and caused necrosis in tumors, which was associated with tumor growth inhibition.	[91]

6. Conclusions

Studies have shown that the encapsulation of polyphenols can lead to several pharmaceutical advantages, such as increased bioavailability and distribution to tissues and organs of polyphenols, decreased side effects of the currently used chemotherapy agents, prevention of drug cellular efflux (thus, increasing drug bioavailability), and can modulate the expression levels of biomarkers related to cell proliferation, tumor growth, and progression. With the biopharmaceutical perspective in mind, further studies should focus on evaluating the anticancer mechanisms of polyphenols loaded in macro and nano polymeric matrixes. So far, few studies have focused on this subject. However, given the increasing prevalence and economic burden of cancer worldwide, more attention should be given to the potential of polyphenols as chemotherapeutic agents or as coadjuvants of the currently used chemotherapy agents.

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