Novel Delivery Systems of Polyphenols

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Polyphenols encapsulated in liposomes are known to produce more substantial effects on targeted cells than unencapsulated polyphenols, while having minimal cytotoxicity in healthy cells.

Keywords: polyphenols ; liposomes ; cancer therapy ; chemoprevention ; health

1. Introduction

Polyphenols are a large group of secondary metabolites, consisting of one or more aromatic rings to which one or more hydroxyl groups are attached [1]. They are found in large quantities in various foods, such as fruits, vegetables, coffee, tea, chocolate, and wine, as illustrated in **Figure 1** [2]. Depending on their origin, biological function, and chemical structure, polyphenols can be classified into two different categories: flavonoids and non-flavonoids. The first class comprises flavonols, flavones, flavanones, anthocyanidins, catechins, isoflavones, and chalcones. On the other hand, the second class comprises phenolic acids (such as hydroxybenzoic acid and derivates, along with hydroxycinnamic acids and derivates) and others, including stilbenes, lignans, curcuminoids, and tannins. It is worth mentioning that, among all known polyphenols, 60% belong to the flavonoids group, and 30% include phenolic acids [3].

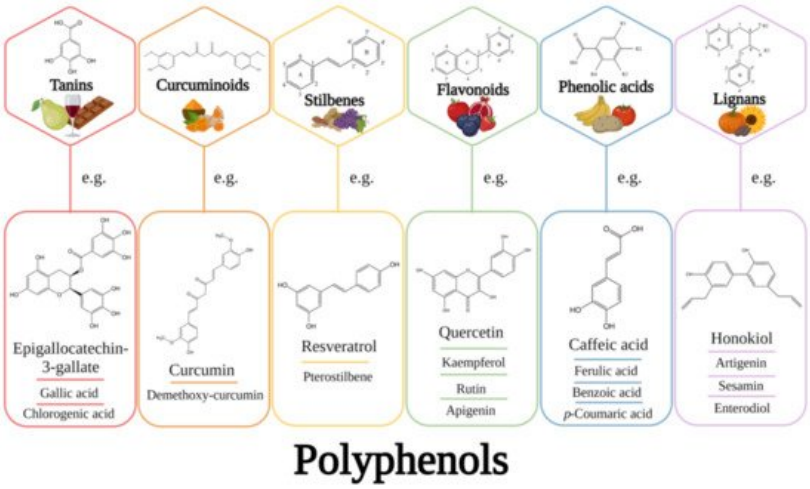

Figure 1. Classification of polyphenols and their biological sources.

2. The Need to Encapsulate Polyphenols in Liposomes

Polyphenols have recently come to the attention of researchers from various fields such as pharmaceuticals, cosmetics, and food, due to their potential for prevention and protection against numerous diseases and their beneficial properties on an individual's health. Many beneficial effects of polyphenols are attributed to their antioxidant, anti-inflammatory, antimicrobial, antimutagenic, anticarcinogenic, and digestion-stimulating properties [4]. Over the years, the effects of polyphenols have been intensively studied in preventing a wide range of conditions, such as diabetes, obesity, cardiovascular disease, neurodegenerative disorders, and cancer [5].

In everyday life, most people pursue a diet rich in polyphenols sourcing from various foods that contain them, such as green vegetables, fruits, soybeans, tea, beer, coffee, or red wine. However, there may be variations in their quantities consumed from one country to another in terms of their consumption. For example, in the United States, Spain, and Australia, estimated consumptions of flavonoids are about 190, 313, and 454 mg/day, respectively [6]. However, because foods contain a variable amount of flavonoids due to their growing environment, storage, processing, or cooking, such data are generally considered approximations of food contents [7].

Because vegetables, fruits, coffee, red wine, and tea are all rich in polyphenols, current research focuses on identifying those responsible for a particular pharmacological or chemopreventive effect, making considerable efforts to elucidate molecular mechanisms of action [8].

Most of the pathological conditions mentioned are related to oxidative stress caused by reactive oxygen and nitrogen species (**Figure 2**). Thus, in particular, polyphenols represent the primary antioxidant agent in fruits, with superior efficacy to vitamin C [9]. It has been determined that the substances with the most substantial antioxidant effect, which can neutralize free radicals by donating an electron or a hydrogen atom, are polyphenols. Therefore, polyphenols inhibit the generation of free radicals while reducing the oxidation rate by inhibiting the formation of active species and free-radical precursors or by deactivating them. Polyphenols usually perform as direct radical eliminators in lipid peroxidation chain reactions (chain breakers). They transfer an electron to the free radical, neutralizing it; after that, they become stable radicals (less reactive), and the chain reactions terminate [10]. In addition to the functions presented above, polyphenols also act as metal chelators. They can cause the chelation of transition metals such as Fe^{2+}, and this process will directly reduce the rate of the Fenton reaction and prevent oxidation caused by highly reactive hydroxyl radicals [11][12]. It is also known that polyphenols can act as co-antioxidants and are part of the regeneration process of essential vitamins [13]. These compounds can induce antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, and catalase that decompose hydroperoxides, hydrogen peroxide, and superoxide anions. In contrast, they can also inhibit the expression of enzymes such as xanthine oxidase [14].

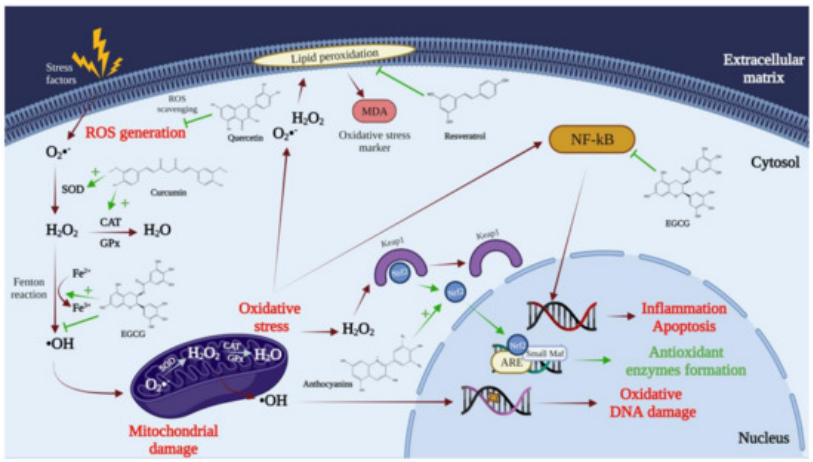

Figure 2. The mechanisms via which polyphenols act on free radicals, reducing oxidative stress. SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; MDA, malondialdehyde; Nrf2, nuclear factor erythroid 2-related factor 2; ARE, antioxidant response elements; Small Maf, musculoaponeurotic fibrosarcoma proteins; Keap1, Kelch-like ECH-associated protein 1; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells.

Through the mechanisms presented above, polyphenols are involved in critical activities that reduce oxidative stress. However, their roles at the cellular level are believed to be much more complicated, requiring further studies to elucidate them. Some polyphenols such as flavonoids are absorbed in the gastrointestinal tract, but their plasma concentration is low (1 µmol/L). The leading cause of this is the rapid metabolism of human tissues [10].

According to research on polyphenols, they have been shown to have the capacity to diminish inflammation by inhibiting edema, suppress the development of tumors, possess proapoptotic and anti-angiogenic properties, modulate the immune system, improve capillary resistance by acting on blood vessel components, protect the cardiovascular system, and limit weight gain [15].

Even though polyphenols have health benefits, the amount of polyphenols that can be administered orally is not enough to reach the concentration needed for systemic therapies to be effective. Characteristics such as low water solubility, poor absorption, and rapid metabolism play a role in decreasing the oral bioavailability of polyphenols [8]. Although there are several definitions of the term bioavailability, the best of these expressions is the part of an ingested compound that can reach the systemic circulation and be distributed to the various targeted tissues where it can exert its biological action [16]. Thus, only a small amount of the molecules administered orally are absorbed due to insufficient gastric residence time, low permeability, or low solubility. The absorption of polyphenols from food is always influenced by their chemical structure (degree of glycosylation or acylation), ability to conjugate with other phenols, molecular size, degree of polymerization, and water solubility. Therefore, the bioavailability of these compounds is low when they are administered orally, due to their poor solubility and rapid metabolism (polyphenols are metabolized extensively in tissues and by the colonic microbiota), as well as their membrane permeability and incompatibility with a process of passive diffusion [17].

Another disadvantage of polyphenols is that they are very unstable and sensitive to environmental factors such as temperature, light, oxygen, acidic pH, and the enzymatic activity in the digestive system. These characteristics can decrease the concentration of polyphenols and even cause a total or partial loss of bioactivity [2]. Thus, in order to have an efficient oral bioavailability, the hydrophilic part of the natural compound (which ensures its dissolution in the gastrointestinal fluids) must be in a balance with the lipophilic part (which has a role in crossing the lipid biomembranes) [18].

Over the years, attempts have been made to remedy these deficiencies by using various drug delivery systems to improve their bioavailability and therapeutic efficacy [8]. Among the approaches that were evaluated, formulation with cyclodextrins [19], simple emulsions, gels, and lipid nanocapsules [20], nanoemulsion [21], or liposomes [22][23] can be listed. Thus, researchers have managed to produce liposomes in which both hydrophilic and lipophilic substances can be incorporated, with high encapsulation efficiency and controlled drug release [24]. An advantage of these compounds is their ability to change the membrane's fluidity, thus achieving easier distribution of plant extracts to the target site. At the same time, the extract has a soluble character, thereby readily determining its location in the structure of liposomes since hydrophilic extracts are encapsulated in the aqueous phase, and amphiphilic and lipophilic compounds are found in the lipid layer of the liposome to reduce a material loss [25][26].

In addition to studies based on polyphenols as therapeutic agents in new therapies and with the development of drug delivery systems, the role of these compounds extends beyond therapeutic agents. They can also be used as primary component modules in drug delivery systems that are innovative. Polyphenols are not only incorporated in drug delivery systems to treat various illnesses, but also frequently employed as fundamental components of novel drug delivery systems due to their significant biological activity. Thus, considering the low toxicity and availability of natural substances, the production of novel drug delivery systems takes advantage of the physical and chemical characteristics of naturally active substances to achieve the design and assembly of drug delivery systems [27].

Polyphenols' intrinsic amphiphilic characteristic is, thus, critical for their use as functional components in novel drug delivery systems. Specifically, the hydroxy groups of polyphenols (as a hydrophilic component) are responsible for this, acting as donors or acceptors of hydrogen bonds, thus playing a role in the interactions between polyphenols and a wide variety of bioactive substances or carriers. In contrast, the aromatic benzene unit of polyphenols (as the hydrophobic component) allows other materials to be hydrophobic, which aids in the development of drug delivery methods [27].

Therefore, due to the chemical structure of polyphenols, they can be combined with a wide variety of materials, such as metals, proteins, polymers, and small molecular compounds through hydrogen bonds, covalent bonds, metal coordination bonding, π–π stacking, and hydrophobic and electrostatic interactions. Polyphenols can not only successfully facilitate drug loading and delivery when combined with other bioactive materials or small molecules, but also safeguard the effective components and nanostructure of drug delivery systems [27].

3. What Is a Liposome?

Liposomes were first described as swollen phospholipid systems in 1965 at Cambridge University by Bangham and coworkers [28], while testing the institute's new electron microscope by applying negative dye to dry phospholipids [29][30]. The main mechanism for obtaining them is via the self-assembly of surfactants and natural/synthetic lipids in an aqueous solution [31]. From a chemical point of view, liposomes are spherical phospholipid vesicles, nanoscopic or microscopic, composed of one or more concentric lipid bilayers, which encompass an aqueous core (**Figure 3**). They are generally made up of phospholipids and cholesterol, making them readily biodegradable [32]. Thus, the phospholipids used can be natural, such as phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine or obtained by synthesis such as disloyal phosphatidylcholine, destroy phosphatidylcholine, and disloyal phosphatidylethanolamine. After the phospholipid membrane is formed, cholesterol can be incorporated at a high concentration [33].

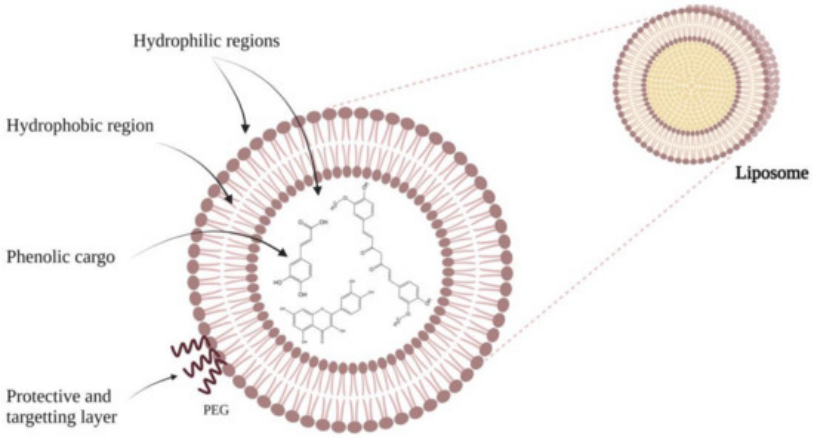

Figure 3. Schematic representation of liposomes.

4. Applications of Liposomes

As outlined above, liposomes are delivery systems that have the ability to encapsulate and release controlled different types of substances, including drugs, nutraceuticals, and even genes, making their use extremely wide [34][35]. Initially, the applications of liposomes were restricted in the medical field, before being later used in cosmetics. However, over time, their popularity has been expanded to other areas, such as delivering vaccines, hormones, enzymes, and vitamins in the body [36]. Liposomes show great flexibility as they can be injected intravenously, intramuscularly, or subcutaneously (liquid suspensions); furthermore, they can be inhaled (aerosol of liposome suspension or lyophilized powder), applied directly to the skin as a suspension, cream, or gel, or even ingested (any of the physical forms) [37].

Considering the benefits offered by liposomes, involving the possibility of large-scale production, the natural ingredients (such as eggs, milk, and soy) involved in manufacturing, biocompatibility, and the ability to transport a wide range of bioactive compounds, they are currently used in many areas, as overviewed in this section [36].

The first popular topic of discussion is drug targeting, allowing to enhance the specificity of a drug that targets the desired cell/tissue. Liposomes can be encapsulated with opsonin and ligands (containing antibodies, apoproteins, hormones). The ligand will specifically recognize the receptor sites and determine the direction of the liposomes to those target sites, where they will accumulate and achieve the anticipated effect. By doing so, liposomes will not be recognized and eliminated by the reticuloendothelial system (liver, spleen, and bone marrow), while the toxicity produced by drugs in untargeted cells/tissues will be minimized [38].

Due to their basic characteristics, namely, the ability to encapsulate various biological substances that can then be delivered to epidermal cells, liposomes are also used in the pharmaceutical and cosmetic fields, e.g., dermatology. Skin hydration is the most critical aspect in skincare. Accordingly, most applications in the field of cosmetics are concerned with this issue of balancing the moisture of the skin. Liposomes can simply hydrate the skin, thus reducing skin dryness, which is the main factor causing skin aging. In addition to this first applicability of liposomes in cosmetics, they can also encapsulate anti-inflammatory agents, immunostimulants, and enhancers of molecular and cellular detoxification, which can produce some therapeutic effects on several skin problems such as dark circles, wrinkles, and age spots [34].

Likewise, due to the rapid development of the food industry in recent years, adding functional compounds to food products has gained more attention. Thus, functional compounds that help to control the flavor, color, texture, or preservative properties of food products have been more widely employed in liposomes. However, these functional compounds are sensitive to environmental factors, processing, and conditions in the gastrointestinal tract, whereas encapsulation could remedy these inconveniences, making liposomes the suitable candidates in such cases [36].

Although there are drawbacks to the degree of encapsulation of polyphenols in liposomes, several studies have reported that both the bioavailability and the efficacy of polyphenols encapsulated in liposomes are improved compared to the free active substance and other transport systems. Various formulations of liposomes showed improved results in terms of the solubility of many polyphenols, for example, resveratrol, quercetin, curcumin, and puerarin [8], as detailed in **Table 1**.

Table 1. Liposomal formulations that have been created for polyphenol-related biological research.

Polyphenol	Production Method	% (*w*/*w*) Polyphenol/ Lipids	Encapsulation Efficiency	Biological Effects	Ref.
Curcumin	Lyophilization (Freeze-drying)	10–25	45% ± 0.2%	In vivo: antiangiogenic activity and tumor growth inhibition	[39] [40]
		15	73.7% ± 1.6%	Enhanced stability	[41]
	Evaporation method with some modification				
	Thin-film hydration	N/S	87.8% ± 4.3%	Slower release and better accumulation	[42]
	Ethanol injection	N/S	46.6% ± 1.0%	More stable during storage	[43]
Resveratrol	Lyophilization (Freeze-drying)	20	N/S	Prostate cancer incidence was minimized, and bioavailability was enhanced	[44]
	Thin-film hydration	10	>90%	The toxicity of free resveratrol was considerably lowered	[45]
	Film hydration	N/S	78.14% ± 8.04%	Enhanced delivery	[46]

Polyphenol	Production Method	% (*w*/*w*) Polyphenol/ Lipids	Encapsulation Efficiency	Biological Effects	Ref.
Quercetin	Film hydration and lyophilization procedure	30	N/S	Enhanced solubility, bioavailability, and antitumor activity in vivo	[23]
	Film hydration and sonication	N/S	87.1% ± 2.7%	Maintained higher plasma quercetin concentrations	[47]
	Emulsification/evaporation	10	69.42–85.72%	Inhibited growth of glioma cancer cells	[48]
Silymarin	Film hydration	20	92.56% ± 0.93%	Better oral bioavailability	[49]
	Reverse evaporation technique	10	69.22% ± 0.6%	Higher bioavailability	[50]
	Supercritical fluid technology	N/S	91.4%	Enhanced oral bioavailability	[51]
Dehydro-silymarin	Film hydration and freeze-drying	25	81.59% ± 0.24%	Better oral bioavailability	[52]
Epigallocatechin-3-gallate (EGCG)	Film hydration and sonication/extrusion	20	84.6% ± 3.8%	Protection against deterioration Even at lower doses, there was an increase in carcinoma cell death	[53]
	Film hydration	10	80% ± 3%	Enhanced targeted delivery and controlled release	[54]
	Reverse-phase evaporation method	N/S	85.79% ± 1.65%	Modulated the proliferation of tumor cells	[55]

Polyphenol	Production Method	% (*w*/*w*) Polyphenol/ Lipids	Encapsulation Efficiency	Biological Effects	Ref.
Fisetin	Film hydration and extrusion	18	58%	Enhanced bioavailability and antitumor activity	[22]
	Probe sonication	7–15	N/S	Better antiangiogenic and anticancer activities	[56]
Honokiol	Film hydration and sonication	20	95.43% ± 2.76%	Strong anticancer effect on breast cancer	[57]
				Enhanced cytotoxicity and cellular uptake	
Anthocyanins	Film hydration	N/S	90.1% ± 2.3%	Enhanced bioavailability and promoted accumulation in tumor	[58]
		N/S	43%	Enhanced antioxidant activity	[59]
		4.5–9		Enhanced chemical stability and bioavailability	[60]
	Hydration and ultrasound combined				
	Improved supercritical carbon dioxide (SC-CO_2)	20	50.6%	Enhanced stability and bioavailability	[61]

According to **Table 1**, the encapsulation ratio varies, even in the case of the same encapsulated polyphenol, and it can be concluded that the encapsulation rate is dependent on the structure of the polyphenol, the lipid composition of the liposome, and its formulation [8].

The liposome–polyphenol complex has another crucial benefit, which is its increased chemical stability, thereby maintaining long-term efficacy [8] or inducing effects that cannot be achieved otherwise by administering free polyphenols [53]. At the same time, the active polyphenols can be injected into nonorganic solvents due to the improved solubility of the substance in the liposomes, which decreases the systemic toxicity and increases the maximum dose tolerated by the body, thus enabling administration of a higher amount of polyphenols in vivo [8].

Studies on the use of polyphenols encapsulated in liposomes performed in vitro/in vivo have revealed that they have similar or better efficacy than free polyphenols [39][56]. Therefore, starting from this idea, several researchers have encapsulated different polyphenols in liposomes to observe the effects and benefits of each, a topic that is discussed in the next section (**Figure 4**).

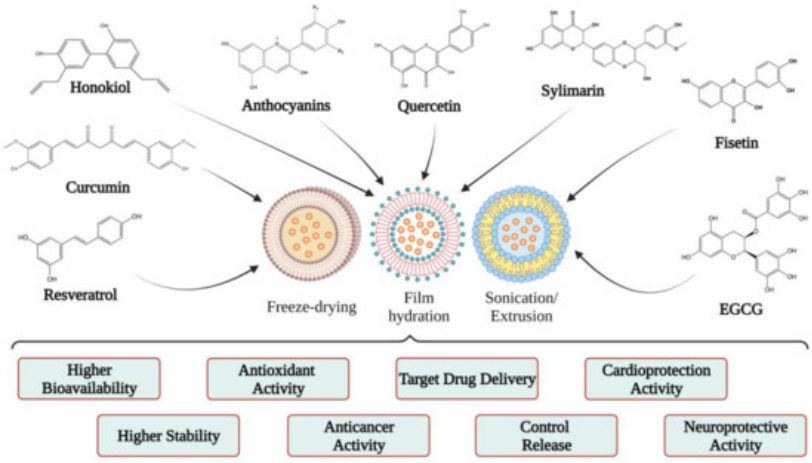

Figure 4. Examples of liposomal forms developed for polyphenol biological studies.

5. Polyphenols Encapsulated into Liposomes and Their Potential Health Benefits

5.1. Quercetin

Quercetin (QC) is a flavonoid plant coming from the word “quercetum” (oak forest), which is part of the Fagaceae family and genus *Quercus*. The literature on QC has highlighted several important characteristics such as its antioxidant, anticarcinogenic, antiviral, anti-obesity, anti-inflammatory, and antihypertensive activities [62]. Due to its antioxidant character, quercetin can eliminate free radicals [63]. This property originates from a large number of conjugated hydroxyl and orbital groups through which QC can donate electrons and hydrogen or eliminate H_2O_2 and superoxide anions.

According to existing data, QC has shown anticancer effects on several mechanisms. For example, it has been shown that QC caused cell-cycle arrest in the G2/M phase by activating the p53 tumor suppressor protein, thereby inhibiting the activity of cyclin dependent kinase 2 (CDK2), cyclin A, and cyclin B [64]. In addition, this flavonoid can suppress the synthesis and expression of heat-shock protein and block the signal transduction pathways by inhibiting protein tyrosine kinase and downregulating oncogene expression (c-myc, ki-ras) [65]. Regarding the action of quercetin in angiogenesis, it has been shown that it affects the VEGFR-2 mediated pathway, causing under-expression of the AKT (protein kinase B) regulatory factor, thus inhibiting blood vessel growth and restricting tumor growth in prostate and breast cancer [66]. Quercetin can also determinate apoptosis in tumor cells by stimulating proapoptotic proteins such as BAX and caspases (3, 6, 7, 8, and 9). Furthermore, QC can stop the expression of antiapoptotic proteins such as Bcl-2 and terminate cancer metastasis. In order to form metastases, epithelial-to-mesenchymal transition (EMT), a process that involves downregulation of epithelial-type proteins (e.g., E-cadherin), and stimulation of expression of mesenchymal markers, including N-cadherin and Vimentin, must occur. Thus, in this case, quercetin can decrease the occurrence of EMT by overexpressing E-cadherin and under-expressing N-cadherin and Vimentin [66].

The most recent investigation reported that QC could inhibit the growth of different types of cancer cells, including colorectal, prostate, liver, pancreatic, breast, kidney, lung, and ovarian, via modulation of various cellular processes (**Figure 5**). In addition, QC can exhibit selective cytotoxic activity toward cancer cells without producing adverse effects on normal cells [67]. On the other hand, QC has slight aqueous solubility and bioavailability and is rapidly metabolized, and these disadvantages can diminish its effectiveness in treating diseases [68].

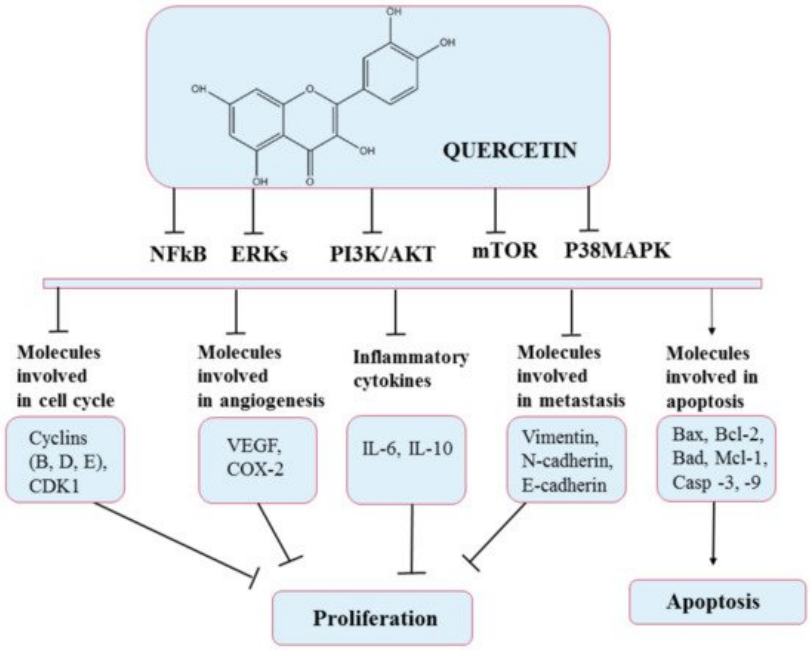

Figure 5. Chemical structure of quercetin and mechanism of action of quercetin through different molecular targets resulting in apoptosis or stopping proliferation.

5.2. Curcumin

Curcumin is a natural yellow polyphenolic compound extracted from turmeric roots (*Curcuma longa*). It is a multifunctional compound that has been widely used in traditional medicine due to its various therapeutic activities in anti-inflammation, antioxidation, antiproliferation, and anti-angiogenesis [69]. Curcumin acts on several pathways, producing growth suppression and angiogenesis, as illustrated in **Figure 6**.

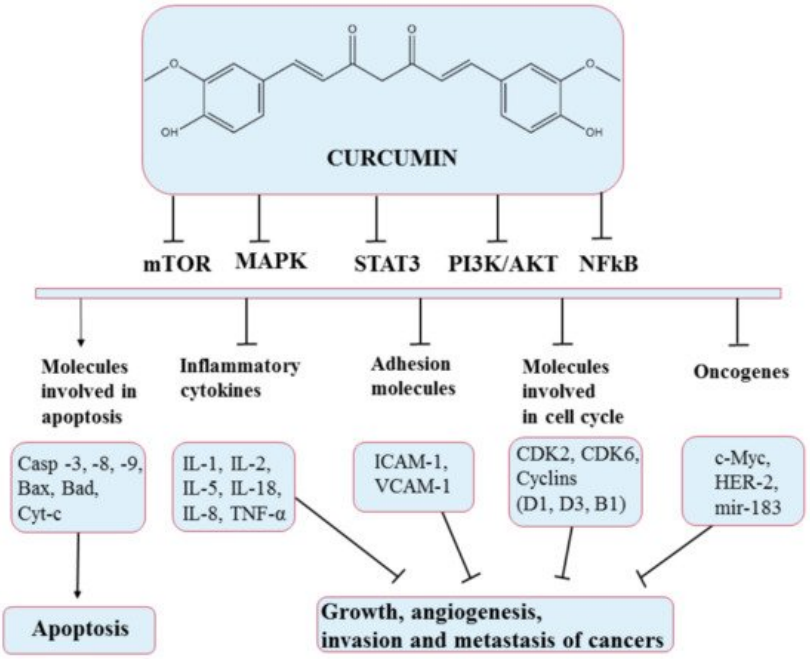

Figure 6. Chemical structure of curcumin and mechanism of action of curcumin through different molecular targets, resulting in apoptosis or growth suppression, angiogenesis, invasion, and metastasis of cancers.

5.3. Honokiol

Honokiol is a lignan found in several species of the genus *Magnolia*, which is distributed worldwide [70][71]. Honokiol is obtained by purification of the bark and seed cones of the magnolia tree [72]. It is known that extracts from *Magnolia* bark are used as traditional herbal medicines in Korea, China and Japan, and other countries [73]. Many lignans with anticancer potential act by shrinking the tumor, decreasing the expression of estrogen, insulin growth factor, vascular endothelial growth factor, and matrix metalloproteinases enzymes, and enhancing caspase 3 [74].

This polyphenol produces effects on many molecular targets that modulate the expression of genes controlling the different hallmarks of cancer [75]. Mechanisms of action include retarding the cell cycle (via effects on cyclins D and B) [76],

inducing apoptosis (by upregulating the expression of proteins that control apoptosis such as Bcl-xL, Bcl-2), inhibiting angiogenesis (via regulation of hypoxia-inducible factor 1-alpha (HIF1α) and VEGF gene expression) [77][78], and interdicting invasion and metastasis [79]. Some of these pathways and molecules implicated are illustrated in **Figure 7**. Honokiol has also been shown to produce promising results in the case of chemoresistance. It shows chemosensitization effects when combined with well-known chemotherapeutics [75].

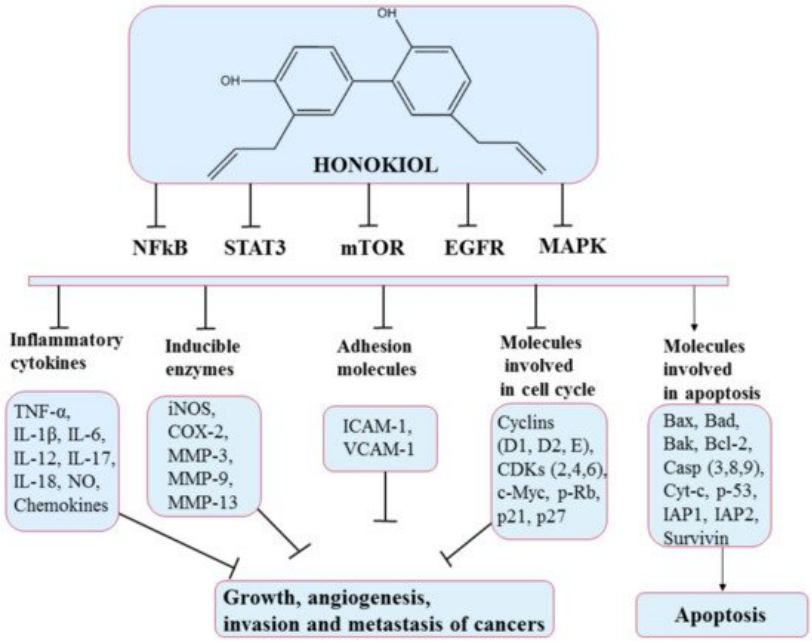

Figure 7. Chemical structure of honokiol and mechanism of action of honokiol through different molecular targets that suppress growth, angiogenesis, and invasion of cancers (adapted from Arora et al., 2012).

5.4. Resveratrol

Resveratrol is a stilbenoid natural polyphenol, isolated for the first time in 1939 from *Veratrum grandiflorum* [80]. Since its first certification, resveratrol has been identified in various plants such as plums, pistachios, berries, and peanuts. However, the most abundant source is represented by fresh grape skin, where it occurs in concentrations as high as 50–100 mg/g [81][82]. In recent years, due to its beneficial effects on health, resveratrol has received the attention of researchers [83]. It is found in two isomeric forms, *cis* and *trans*, but the predominant isomer is *trans*, which has the most potent therapeutic effects due to its conformation [82][84]. In addition, it is also obtained via chemical or biotechnological synthesis from yeast *Saccharomyces cerevisiae* for industrial applications [85].

Resveratrol is sensitive to light, pH, and high temperatures due to its unstable hydroxyls and C=C double bond. In this regard, many studies have aimed to increase its stability in an effort to expand its use [86]. The *trans* form of resveratrol is stable under acidic conditions at room or body temperature, but resveratrol degrades rapidly when the pH is alkaline. Therefore, by lowering the temperature and pH and by limiting the exposure to light and oxygen, the stability of this isomer can be improved [87].

Similar to the other polyphenols, resveratrol has a low bioavailability due to poor absorption and rapid metabolism of glucuronidated and sulfated compounds, followed by their excretion [88]. Hence, the poor bioavailability of this compound is a major problem in amplifying its effects in humans and, as such, so many approaches have been attempted to increase its bioavailability [89]. The effectiveness of resveratrol depends mainly on a combination of factors such as dosage, method of administration, the origin of the targeted tumor, and other substances present in the diet that may interfere with this polyphenol [83]. Thus, to improve the bioavailability, it is necessary to carry out studies on the delivery routes, the formulations and modulation of resveratrol metabolism, and possible interactions of resveratrol with other food components. On the other hand, another possible approach to its bioavailability is creating novel resveratrol-based derivatives [90].

Despite the extremely low bioavailability of this polyphenol, recent studies found strong evidence that resveratrol can prevent or delay the onset of cancer, heart disease, ischemic and chemically induced damage, diabetes, pathological inflammation, and viral infections [83]. In particular, resveratrol has shown anticancer effects by altering glycolysis and molecules involved in the cell cycle (resveratrol upregulates p53 protein, thereby downregulating the expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [91] and suppressing cancer cell growth (stops cell cycle at G1 and G1/S phases by inducing the expression of CDK inhibitors and proliferation. Resveratrol causes a high

production of nitric oxide synthases (NOS), thus inhibiting cell proliferation [92], inducing apoptosis (through the intrinsic pathway via the activation of caspase 3 and caspase 9, the determined release of cytochrome c, upregulation of Bax expression, and downregulation of Bcl-2 expression [91]) promoting antitumor immune responses, and preventing cancer cell adhesion, migration (also reduced by resveratrol through the EGFR/PI3K signaling pathway [93]), and invasion by modulating active molecules and gene expression through various signaling pathways (**Figure 8**). In addition, different doses of resveratrol may induce different effects, which can sometimes be opposite [94]. Therefore, it is crucial to identify the most effective dose and administration route. Likewise, it has been documented that resveratrol induces cell death in tumor tissues with relatively no effect on normal tissues in the vicinity of the tumor [95]. Mukherjee et al. (2010) reported that lower doses of resveratrol could result in health benefits, while higher doses affect tumor cells via proapoptotic effects [96]. Thus, future studies based on this polyphenol are needed to fully decipher its effects.

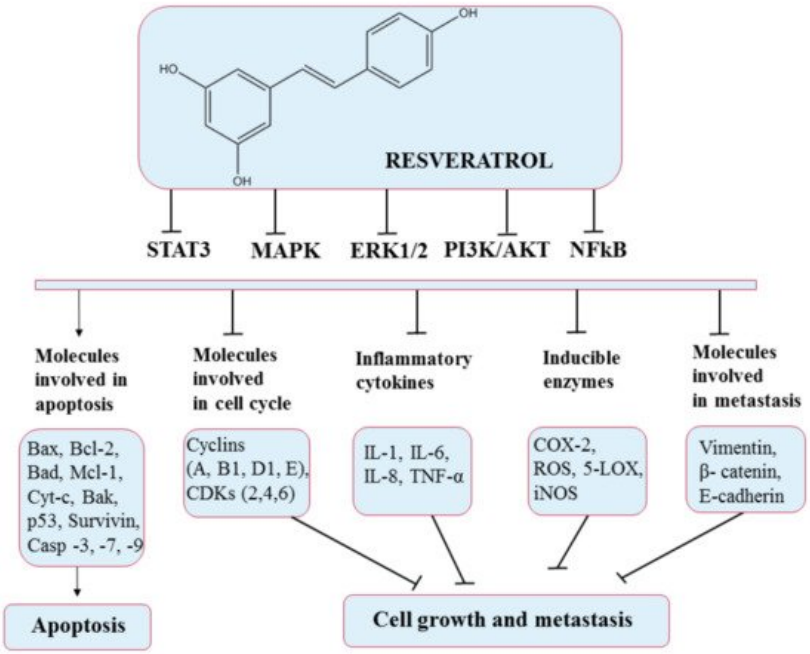

Figure 8. Chemical structure of resveratrol and its mechanism of action through different molecular targets that result in apoptosis or growth suppression and metastasis of cancers.

5.5. Anthocyanins

Considering their great health benefits, this section focuses on anthocyanins. Anthocyanins are pigments that are responsible for the various colors (blue, red, purple) of fruits, flowers, and vegetables. They can be stacked in vegetative tissues, where they fulfill the role of protection against biotic and abiotic factors. In nature, anthocyanins are found in the form of glycosides, which have one or more sugars bound to the aglycone nucleus. The chemical structure is C6–C3–C6, with two benzene rings (A and B) and a heterocyclic C ring. Due to this structure, anthocyanins have been shown to have strong antioxidant, anticancer, anti-inflammatory, and cardioprotective activities, as well as effects related to vision improvement [97][98].

The most frequent anthocyanin aglycones found in plants are delphinidin, cyanidin, petunidin, peonidin, pelargonidin, and malvidin. Nevertheless, these compounds are found in plants at different levels. Cyanidin has the largest proportion in plant tissues (50%), followed by pelargonidin, peonidin, and delphinidin, each representing a percentage of 12%; finally, petunidin and malvidin each make up a percentage of 7%. The unique properties of anthocyanins and anthocyanidins may have an impact on their anticancer effectiveness, antioxidant activities, and bioavailability [99].

Like other classes of polyphenols, anthocyanins can cause anti-inflammatory and antitumor effects on several types of cancer cell lines such as breast, liver, colon, prostate, ovarian, and skin cancers. These anticancer effects appear to be linked to cancer cell growth suppression via increased oxidative stress biomarkers and induction of apoptosis via the mitochondrial route [100]. As a consequence, they seem to be attractive therapeutic options.

Anthocyanins work as antioxidants by scavenging free radicals and lowering lipid peroxidation and ROS levels. Numerous studies have also reported that anthocyanins can mediate oxidative stress in many signaling pathways such as PI3K/Akt/mTOR and Ras/ERK/MAPK, targeting their component molecules. In addition, anthocyanin-rich formulations have been found to suppress H_2O_2 and TNF-α-induced VEGF expression, as well as promote caspase pathways, thereby exerting anticarcinogenic and antiangiogenic effects. They also exhibit anti-inflammatory activities by significantly reducing

cyclooxygenase-2 (COX-2), inflammatory interleukins (ILs), inducible nitric oxide synthase iNOS, and NF-κB. Furthermore, anthocyanins can stimulate the apoptosis of cancer cells by activating cell death receptors such as BAX and Bcl-2 and caspases 3, 7, and 8 [101]. Additionally, anthocyanin extracts were reported to mediate cell metastasis by inhibiting matrix metallopeptidase 2 (MMP-2) and matrix metallopeptidase 9 (MMP-9) through the PI3K signaling pathway [99]. All these pathways and the molecules involved are presented in **Figure 9**.

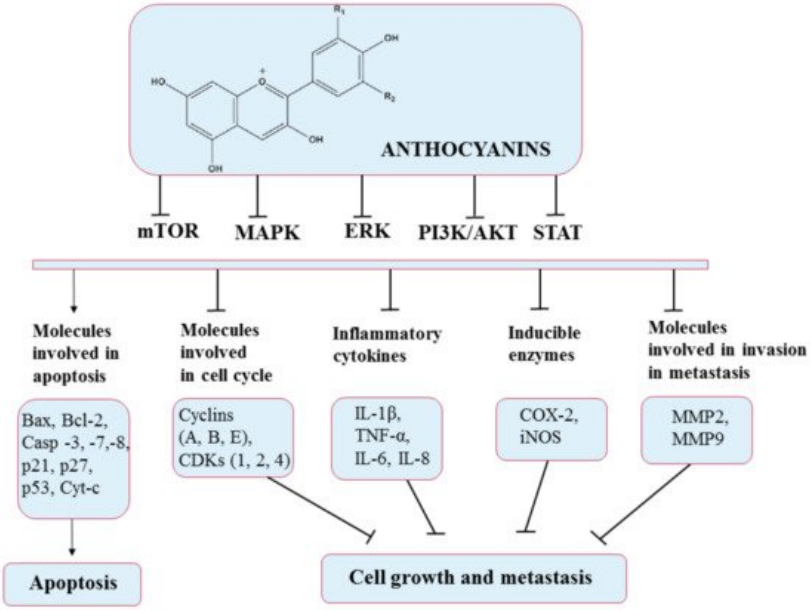

Figure 9. Chemical structure of anthocyanins and their mechanism of action through different molecular targets that result in apoptosis or suppressing growth and metastasis of cancers.

5.6. Epigallocatechin-3-Gallate (EGCG)

Tea is one of the most widely consumed beverages worldwide. Green tea (*Camellia sinensis*), which is made from unfermented leaves, has been demonstrated to have the highest concentration of effective antioxidants [102]. In this type of tea are found four flavanol derivatives epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG) [103]. The main polyphenolic component and the most abundant and physiologically active catechin found in green tea is epigallocatechin-3-gallate (EGCG), which is an ester of epigallocatechin and gallic acid [104][105]. EGCG is a flavone-3-ol type polyphenol, which has in its chemical structure eight free hydroxyl groups, an arrangement that makes it bioactive with versatile biological functions. In addition, aside from some tannin compounds, EGCG has the strongest free-radical-scavenging capacity among common phenolic compounds [106].

This compound has been intensively studied in recent years; research has shown its beneficial effects through its antioxidant, antibacterial, anticancer, antidiabetic, and antiangiogenic properties [105]. The chemopreventive effect of EGCG has a solid basis in studies conducted both in vivo and in vitro in a number of cancers: breast, duodenum, prostate, colon, skin, lung, cervical, and liver [103][107]. Thus, EGCG interferes with various mechanisms such as cell proliferation and differentiation, apoptosis, angiogenesis, and metastasis, with inhibitory effects on several processes in diverse types of cancer such as initiation, promotion, and progression. For example, EGCG has been shown to induce apoptosis in breast cancer by activating apoptosis-related proteins, such as caspase 3 and 9, and in cholangiocarcinoma by inducing apoptotic molecular signals, such as Bax and cytochrome c [104]. Furthermore, EGCG inhibits invasion and epithelial–mesenchymal transition through modulation of MMP-2, MMP-9, and Vimentin [108]. In addition, EGCG has been shown to stop cell division in a variety of cell lines at different stages of the cell cycle [107]. The anticancer effects of EGCG occur via several signal transmission pathways such as MAPK and PI3K/AKT, as presented in **Figure 10** [109].

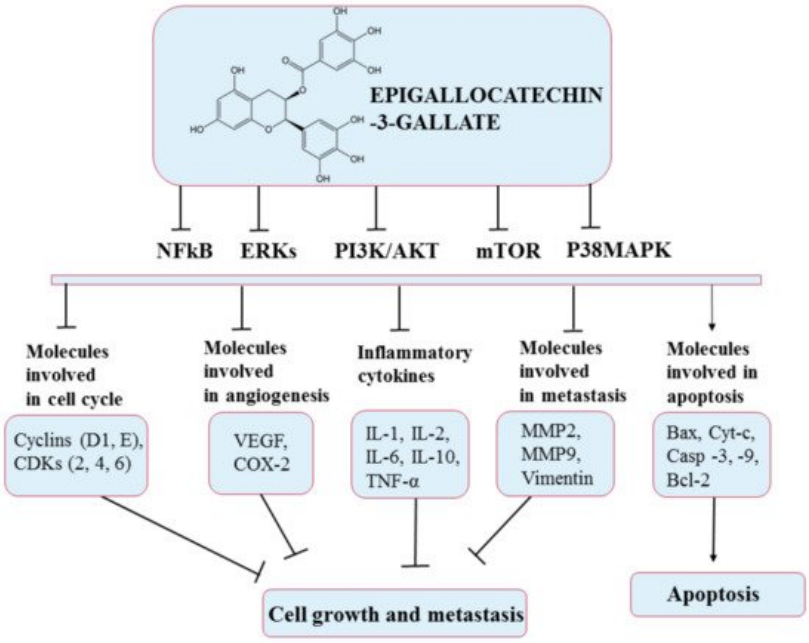

Figure 10. Chemical structure of epigallocatechin-3-gallate and its mechanism of action through different molecular targets that result in apoptosis or growth suppression and metastasis of cancers.

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