Anticancer Properties of Polyphenols

Subjects: Food Science & Technology

Contributor: Manuel Adrian Picos-Salas , Melissa García-Carrasco , José Basilio Heredia , Luis Angel Cabanillas-Bojórquez , Nayely Leyva-López , Erick Paul Gutiérrez-Grijalva

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.

polyphenols cancer encapsulation anticancer

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][3][4]. Polyphenols are of interest in the nutraceutical and pharmaceutical industries because of their antioxidant, anti-inflammatory, and anticancer properties.

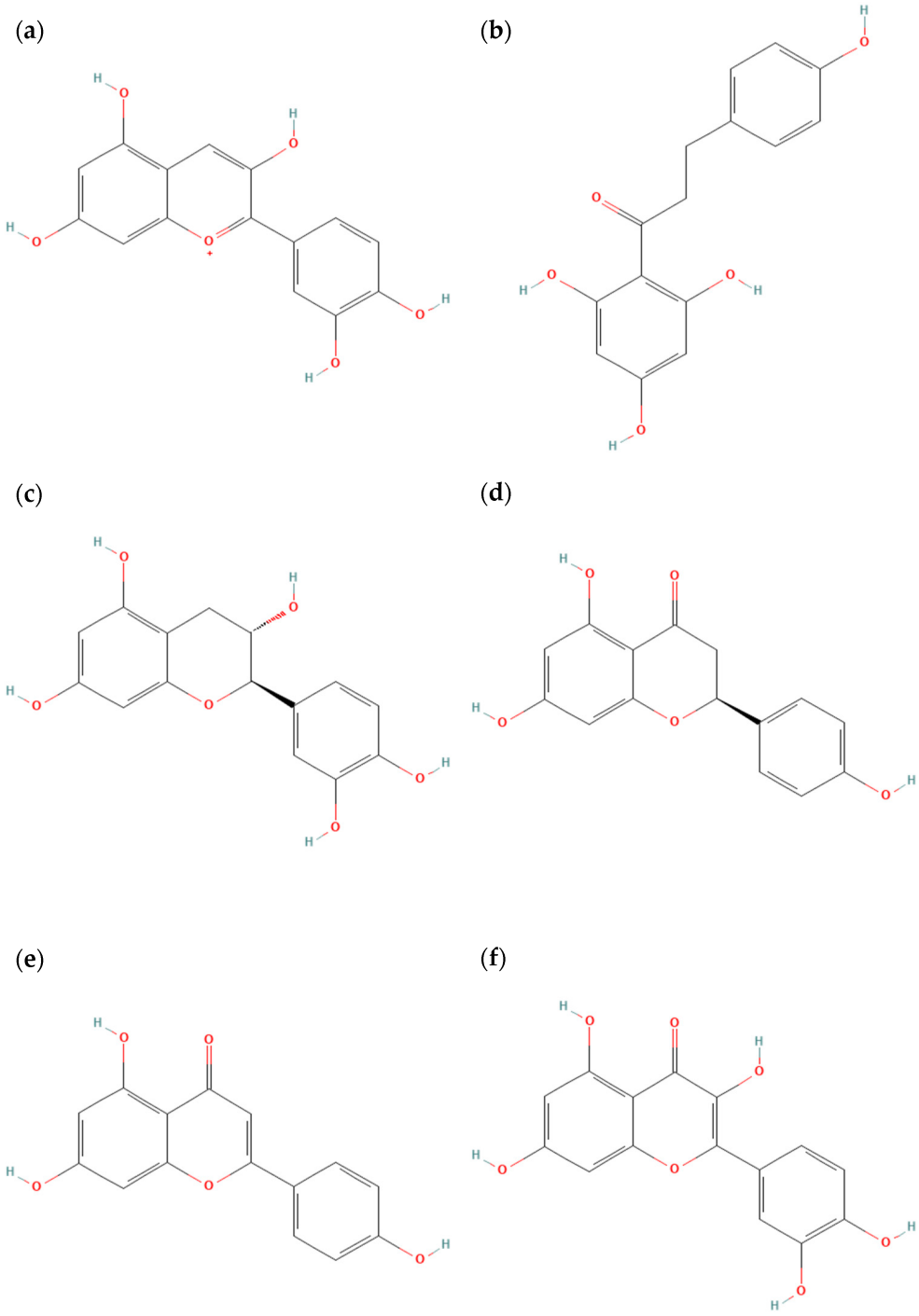

Figure 1. Chemical structures of known polyphenols: (**a**) anthocyanins (cyanidin), (**b**) dihydrochalcones (phloretin), (**c**) flavanols (catechin), (**d**) flavanones (naringenin), (**e**) flavones (apigenin), (**f**) flavonols (quercetin).

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**).

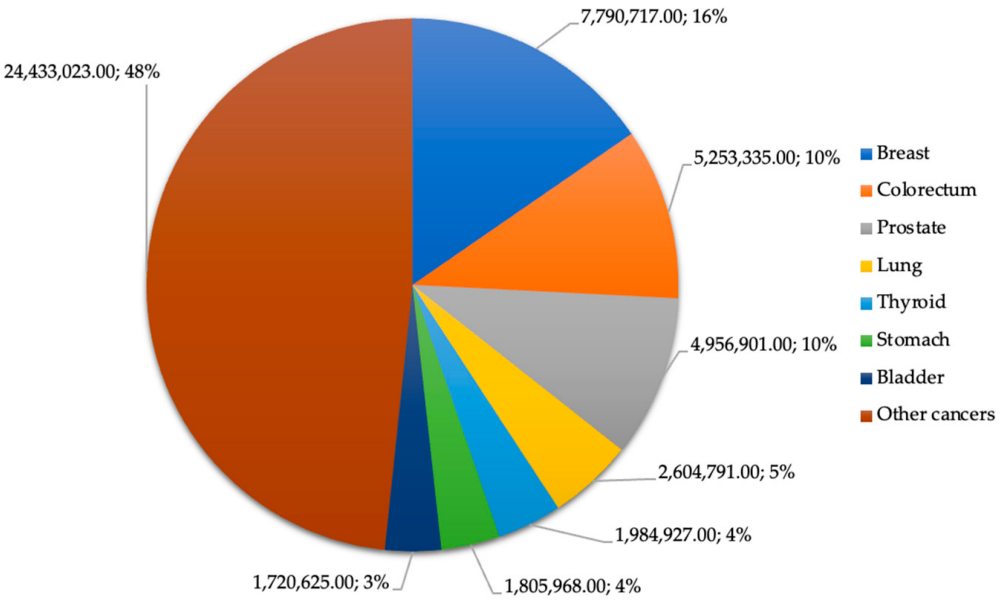

Figure 2. Estimated number of prevalent cases worldwide (5 years) in 2020 for both sexes of all ages.

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 [5][6]. 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.

2. Anticancer Properties of Polyphenols

2.1. 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 [7][8], as well as by an increase in *Bad* and a decrease in *Bcl-2* gene expression by vanillic acid [9]. 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 [10][11]. Furthermore, taxifolin decreased epithelial–mesenchymal transition, an early event of metastasis [12].

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 [13].

On the other hand, inflammation and oxidative stress are two physiological processes which have been linked to cancer [14]; 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 [15]. 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 [16]; also, Nrf2 upregulation in induced hepatic cancer by vanillic acid was detected [9].

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	[13]
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	[13]
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	[17]
Ellagic acid	40 mg/kg	Mice with human bladder cancer xenografts	Decrease in tumor growth rate, infiltrative behavior, and tumor-associated angiogenesis.	[18]
	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	[7]
Eriodictyol	60 mg/kg	Mice with mammary cancer xenografts	Decrease in tumor growth and progression and in lung metastasis	[10]
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	[8]
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	[19]
	100 mg/kg	Mice with human epithelial xenograft	Decrease in migration and invasion	[11]

Compound	Dose	Model	Effect	Reference
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	[15]
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	[20]
	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	[21]
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	[16]
	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	[12]
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	[9]

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similar effects with synergism with butyl benzyl phthalate [23]. Also, the phenolic acids ferulic acid and caffeic acid reduced the risk to develop prostate cancer [24], and bladder cancer risk showed an inverse association with flavonols and lignans intake [25]. 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 ≥ 25, which can be attributed to the anti-inflammatory activity of these compounds, as obesity is a low-grade inflammation disease [26]. However, some studies indicated no association between polyphenols consumption and decrease in cancer risk, including colorectal, pancreatic, and epithelial ovarian cancer [27][28][29][30]. In contrast, a study in the Iranian population showed a lower colorectal cancer risk associated with polyphenols consumption, indicating variation between populations [31].

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	[25]

Compound(s)	Cancer Type	Population	Subjects (Age)	Effect	Reference
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	[22]
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	[23]
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	[27]
Flavonoids	Colorectal	521,448 European subjects (with exceptions)	35–70 years	No association between flavonoids intake and colorectal cancer was found	[28]
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.	[31]
Polyphenols	Epithelial ovarian cancer	309,129 European women	35–70 years	No association between polyphenols intake and endothelial ovarian cancer was found	[29]
Naringenin, peonidin, and catechin	General	14,029 US subjects	>18	Inverse association between flavonoids intake and cancer mortality	[32]
Flavonoids and lignans	Pancreatic	477,309 European subjects	25–70 years	No association between flavonoids and lignans intake and pancreatic cancer was found	[30]

Compound(s)	Cancer Type	Population	Subjects (Age)	Effect	Reference
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	[24]
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 ≥ 25	[26] [33]

ctal, oral, ancer and ecreased contrast, no effect was observed on the mean size and number of polyps in the lower intestinal tract [34]. On the other hand, studies indicated no beneficial effect of epigallocatechin gallate against colorectal and prostate cancer [35][36]; 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 [37]. Furthermore, a ginger extract with 5% of gingerols decreased the proliferation of crypts in patients with a high risk of colorectal cancer [38].

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	[39]
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	[38]
	Epigallocatechin gallate	780 mg	32 subjects with rectal aberrant crypt foci	No difference in the number of the rectal aberrant crypt foci	[36]
Familial adenomatous polyposis	Curcumin	3000 mg	44 subjects with familial adenomatous polyposis	No difference in the mean number or size of polyps	[34]
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	[33]

Cancer	Compound	Dose	Subjects	Effect	Reference
				recruitment to the tumor microenvironment.	
Prostate	Cranberry fruit powder	1500 mg	62 subjects with prostate cancer	Decrease in serum prostate-specific antigen	[37]
	Epigallocatechin gallate	600 mg	43 subjects with a prior negative biopsy, but suspicious	No difference in fatty acid synthase or antigen Ki-76	[35]

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.

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