Polyphenol

Subjects: Integrative & Complementary Medicine
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The use of naturally derived drugs in anti-cancer therapies has grown exponentially in recent years. Among natural compounds, polyphenols have shown potential therapeutic applications in treatment due to their protective functions in plants, their use as food additives, and their excellent antioxidant properties, resulting in beneficial effects on human health. Building more efficient cancer therapies with fewer side effects on human health can be achieved by combining natural compounds with conventional drugs, which are typically more aggressive than natural chemicals with polyphenols.

natural health products polyphenols flavonoids oncology

1. Introduction

Cancer is a group of diseases that involve the unusual growth of malignant cells with the potential to invade or metastasize to other parts of the body. Lifestyle has a big influence on the causes of cancer and may lead to habits that are fundamental to the development of lifestyle diseases. In addition, pollution, exposure to dangerous chemicals, radiation, stress, smoking, and alcohol consumption can lead to the development of cancer [1]. However, the initiation and development of cancer is not limited to lifestyle causes, but can result from changes in the human genome.

Over the past few years, preclinical and clinical cancer research has identified various collections of developmentally important genes that remain relatively quiescent in normal tissues [2].

Under normal circumstances, the body's immune system can identify and eliminate cancer cells; however, cancer cells have an "immune escape" mechanism that allows them to evade recognition and attack by the immune system in various ways, allowing them to multiply in the body and prevent elimination [3].

Research to date has made tremendous progress in the prevention, detection, and treatment of cancer, leading to a decline in mortality rates. The use of conventional cancer treatment procedures, such as chemotherapy and radiation therapy, often causes harmful side effects. Therefore, the current goals of cancer research are related to the development of new therapies that are less harmful to the human body. Natural compounds can be very useful in this respect [4][5].

Natural compounds derived from plants or phytochemicals have been used in traditional medicine for centuries. Phytochemicals are chemical compounds that are produced by plants; they are usually involved in the growth of

plants or in the process of protecting them against predators or pathogens [6][7]. Currently, the use of phytochemicals, especially polyphenols, as alternative anticancer drugs is a promising alternative to conventional therapies [5][8]. In addition, the human body develops resistance to the conventional drugs that are involved in cancer therapy [9].

2. Polyphenols

Polyphenols are secondary metabolites that are produced by plants, and they are characterized by the presence of numerous phenolic rings [10]. The main sources of polyphenols are blueberries, grapes, olive oil, cocoa, nuts, peanuts, and other fruits and vegetables that contain up to 200–300 mg of polyphenols per 100 g fresh weight [11]. **Figure 1** shows the classification of the main groups of polyphenols.

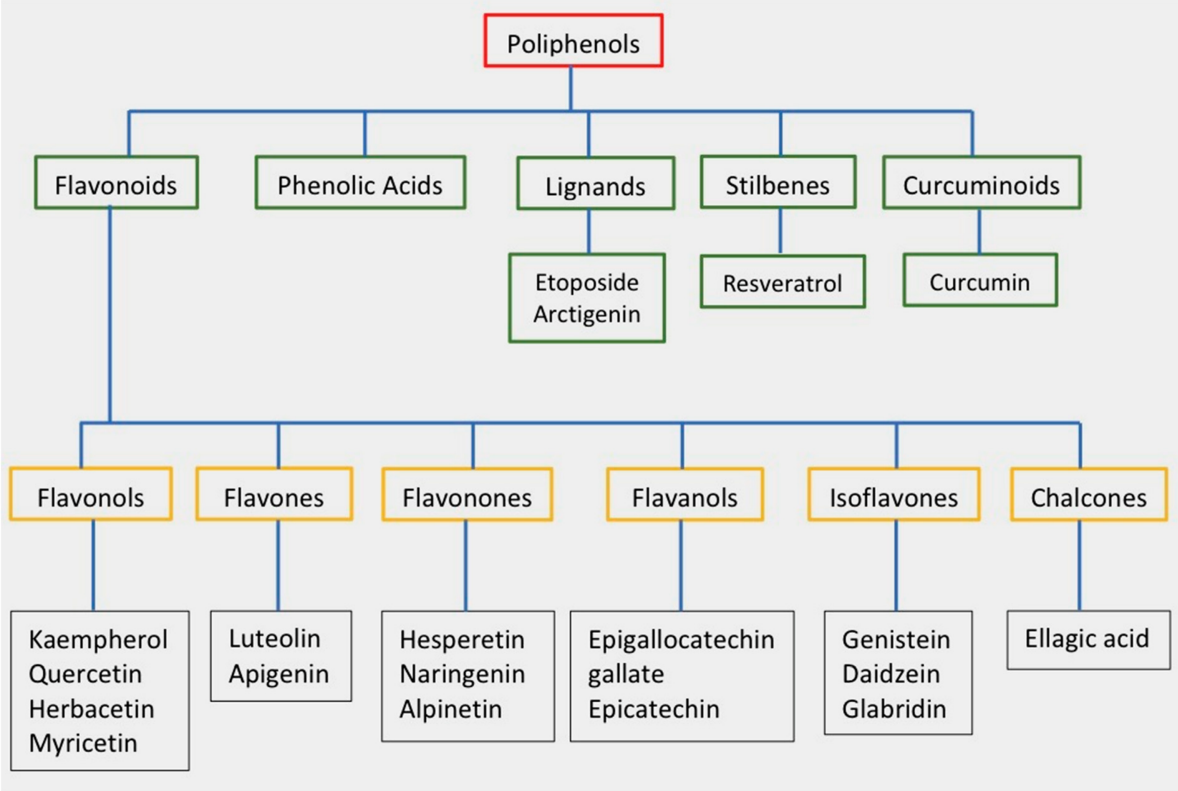

Figure 1. Classification of polyphenols and flavonoids. Examples of each subgroup with antitumor activity are listed.

Polyphenols can be extracted by simple and ecological techniques, including ultrasonically assisted extraction. T After extraction, polyphenols retain most of their properties. This characteristic facilitates research into the use of these compounds as potential anticancer drugs [12][13].

2.1. Flavonoids

The most important group of polyphenols the family. Flavonoids consist of over 6000 molecules that have been identified and isolated. Flavonoids are found in abundance in colorful vegetables and fruits such as blueberries, apples, grapes, oranges, strawberries, plums, and in some common foods and drinks, including dark chocolate, nuts, red wine, tea, soybeans and soybean derivatives, spinach [14].

2.2. Phenolic Acids

Another subgroup of polyphenols that can be found in several plants, especially in dried fruit, is phenolic acids. These compounds are characterized by the presence of a phenolic ring and have the function of an organic carboxylic acid [15].

Phenolic acid (p-coumaric acid) has shown medicinal properties that make it a likely candidate for the treatment of cancer.

P-coumaric acid (or 4-hydroxycinnamic acid) is an organic compound that is derived from cinnamic acid, which can be found in many different edible plants (tomatoes, carrots, garlic, mushrooms, white beans, and other plants). Moreover, p-coumaric acid that is contained in pollen is a component of honey [16].

In the last decade, several studies have been published that confirm the antitumor activity of p-coumaric acid in breast and gastric cancer cells [17][18][19].

2.3. Lignans

Lignans are diphenolic compounds found in a wide variety of plants, including broccoli, beans, soybeans, rye, sesame seeds, pumpkin seeds, linseed, and some berries in very small amounts [20]. Lignans are one of the two main groups of phytoestrogens that are known for their own good antioxidant properties [21]. Numerous lignans can be considered possible anticancer drugs. Among them are etoposide, arctigenin, and magnolol, the main lignans that are studied in medicine. In addition, etoposide is a commercial lignan, belonging to the podophyllotoxin subfamily, that is used to treat various types of cancer such as lung cancer and breast cancer [22][23]. However, etoposide chemotherapy has several side effects, including low blood cell counts, vomiting, diarrhea, fever, loss of appetite, and alopecia.

Arctigenin Some plants produce arctigenin, especially in the seeds of the greater burdock (*Arctium lappa*). Current studies have shown that arctigenin inhibits the growth of various cancer cells, including cells in the stomach, lung, liver, and colon, as well as leukocytes [24]. At the same time, the addition of arctigenin enhances the action of caspase-3, a protein that plays a key role in the death of cancer cells. Huang et al. showed that the treatment of OVCAR3 and SKOV3 ovarian cancers with arctygenin causes apoptosis of neoplastic cells in vitro [25].

Lee et al. investigated the effect of arctigenin (ATG) on doxorubicin-induced cell death (DOX) using human breast cancer cells MDA-MB-231. The results showed that DOX-induced cell death was enhanced by concurrent treatment with ATG/DOX in a concentration-dependent manner and that this was associated with increased DOX

uptake and the suppression of multidrug-resistance-associated protein 1 (MRP1) gene expression in MDA-MB cells-231 [26].

2.4. Resveratrol

Resveratrol is a natural polyphenol from the stilbene family. Resveratrol is produced by several plants (grapes, almonds, beans, blueberries, raspberries, mulberries, peanuts, etc.) in response to infections and injuries, or as a defense against various attacks by pathogens such as fungi and bacteria [27]. In addition, red wine contains significant amounts of resveratrol.

In 1997, Jang et al. were the first investigators to report the inhibition of skin cancer development in mice with resveratrol [28]. Since then, many studies have suggested that resveratrol is able to prevent or delay the onset of cancer [29][30][31].

In fact, studies have shown that resveratrol is active in vitro against many human cancers, including cancers of the breast, skin, ovary, stomach, prostate, colon, liver, pancreas, and cervix, as well as thyroid cancer cells, lymphoid carcinoma cells, and myeloid carcinoma cells [32].

Resveratrol has been shown to be beneficial at various stages of neoplastic disease (tumor initiation, promotion, and progression). For example, resveratrol protects DNA against reactive oxygen species (ROS) and traps the hydroxyls, superoxides, and free radicals produced in cells (events that are usually associated with tumor initiation) [33].

In addition, human clinical trials with resveratrol have been conducted with satisfactory results [34][35][36].

2.5. Curcuminoids

Curcuminoids are natural polyphenols that contain two phenolic units linked by a linear diarylheptanoid. Among them, curcumin is one of the best known and researched structures, with high potential as a drug. Nevertheless, the poor solubility of curcumin in water of acidic and physiological pH requires a variety of alternatives to avoid losing the efficacy of curcumin as a drug [37].

Curcumin has been used in anticancer therapies for various types of cancer: lung, cervical, prostate, breast, bone, and liver [38]. Nevertheless, the administration of free curcumin has some drawbacks, including poor water solubility, instability under water conditions, and low bioavailability [39].

Many different clinical trials have been conducted on the use of curcumin as an anticancer drug. Recently, various research groups have reported that the combination of curcumin with gemcitabine-based chemotherapy is safe and that its use is possible in pancreatic cancer patients [40][41][42].

Overall, gemcitabine adjuvant therapy with curcumin phytosome complex is not only safe, but it also effectively translates into a good first-line response rate for advanced pancreatic cancer.

Table 1 shows the most important studies on the molecular mechanisms of anticancer activity of the main polyphenols and flavonoids.

Table 1. Mechanisms of anticancer activity of selected polyphenols and flavonoids.

Flavonoids	Cancer Model	Mechanisms	Ref
Apigenin	Hepatocellular carcinoma doxorubicin-resistant cell BEL-7402/ADM Nude mice	Sensitizes drug-resistant cells to doxorubic through suppressing miR-520b/ATG7 axis.	[43]
	Breast cancer T47D, MDA-MB-231	Induction of protective autophagy and apoptosis.	[44]
	Colorectal cancer HCT116	Autophagy inhibitor significantly enhanced the apoptosis.	[45]
	Hepatocellular carcinoma Hepg2	Increases levels of Caspase-3, PARP cleavage, and Bax/Bcl-2 ratios.	[46]
	Non-small cell lung cancer EGFR-TKIs-resistant NCI-H1975 (Apigenin + Gefitinib)	Inhibits the AMPK pathway and autophagy flux, leading to enhanced apoptotic cell death. Inhibits multiple oncogenic drivers such as c-Myc, HIF-1α, and EGFR, and reduces Gluts and MCT1 protein expression. Downregulates Cyclin D1, CDK4, E-cadherin, MMP2, and MMP9, and induces G0/G1 cell cycle arrest and cell metastasis.	[47]
	Colorectal cancer cisplatin-resistant cell HT-29	Induces autophagic cell death and inhibits the growth of cells by targeting the m-TOR/PI3K/AKT signaling pathway. Autophagy inhibits the occurrence of MDR.	[48]
Baicalein	Breast cancer (MDA-MB-468), prostate cancer (PC3),	The investigated compounds cause intracellular copper mobilization and ROS production, resulting in cancer cell death.	[49]
	Prostate cancer PC-3, DU145 Breast cancer MDA-MB-231	Activation of AMPK and ULK1 and downregulation of mRNA level of mTOR/Raptor induces autophagic cell death. Upregulates the expression of Beclin1, Atg5, Atg7, ULK1, and LC3B-II. Induction of autophagic cell death.	[50]

Flavonoids	Cancer Model	Mechanisms	Ref
Quercetin	Breast cancer MCF-7, MDA-MB-231	Induces apoptosis and autophagy by inhibiting the PI3K/AKT pathway.	[51]
	Non-small cell lung cancer A549, H1299	Induces the loss of mitochondrial membrane potential and the release of cyto-c and apoptosis inducing factor into the cytoplasm. Induces autophagy and activates autophagy flux.	[52]
	Human glioblastoma U87 and U251 cell lines	Maturation of microtubule-associated protein 1A/1B-LC3B indicated the activation of autophagy potentially through the PI3K/Akt/mTOR pathway, and inhibition of autophagy by 3-methyladenine decreased the apoptotic cell ratio.	[53]
	Glioblastoma multiforme T98G (quercetin + temozolomide) Anaplastic astrocytoma MOGGCCM (quercetin + temozolomide)	Activates ER stress, increases the level of caspase 12 expression, and changes the shape of nuclei. Inhibition of HSP expression results in severe apoptosis and no obvious signs of autophagy, which decreases mitochondrial membrane potential, and increases level of cyto-c in the cytoplasm and the activation of caspase 3 and caspase 9.	[54]
	Glioblastoma U251, U87	T-AUCB induces overexpression of Atg7 and regulates autophagy-related gene expression.	[55]
	Glioblastoma multiforme T98G (quercetin + sorafenib)	In T98G cells, sorafenib mainly initiated autophagy, resulting in an increased number of autophagic cells with quercetin.	[56]
	Glioblastoma U373MG	Activates JNK signal, increases the expression and translocation of p53 to the mitochondria, and causes the release of cyto-c into the cytoplasm.	[57]
	Melanoma (B16-F10)	Inhibits Akt/PI3 K and MEK-ERK signaling while augmenting UVB-induced nuclear translocation of NF-κb.	[58]
Galangin	Laryngeal carcinoma TU212, HEP-2	Modulates apoptosis through caspase-3, caspase-9, and PARP cleavage activation and bcl-2 downregulation. Regulates apoptosis and autophagy by p38 and AKT/NF-κB/mTOR pathways.	[59]
Epigallocatechin gallate	Non-small cell lung cancer A549 (gefitinib-resistant cell)/	Inhibits autophagy induced by gefitinib and promotes cell death.	[60]
	Colorectal cancer	The combined effect of epigallocatechin Gallate and	[61]

Flavonoids	Cancer Model	Mechanisms	Ref
	HCT-116	quercetin caused cell cycle arrest at the G1 phase.	
Chalcone	Breast cancer Epirubicin-resistant cell MCF-7/ADR	Induction of autophagy and G2/M checkpoint block and downregulation of ABCG2 expression, but no induction of apoptosis. Induces autophagic cell death through inhibition of miR-25 and upregulation of ULK1 expression.	[62]
	Breast cancer MCF-7 cells	Licochalcone A inhibits PI3K/Akt/mTOR activation and promotes autophagy and apoptosis in MCF-7 cells	[63]
	Malignant melanoma	Cell-cycle arrest at the G2/M phase was associated with modulation of expression or phosphorylation of specific cell cycle-associated proteins (cyclin B1, p21, and ChK1) and tubulins.	[64]
	Human uterine sarcoma	Induces A375 cells to differentiate and lose their pluripotency by inhibiting the expression of Notch1, β-catenin, and Oct-3/4 and targeting members of the key signals PI3K/Akt and MEK-ERK pathways.	[65]
	Ovarian cancer OVCAR5 and ES-2	Isoliquiritigenin induced G2/M phase arrest. Furthermore, the expression of cleaved PARP, cleaved caspase-3, Bax/Bcl-2 ratio, LC3B-II, and Beclin-1 levels were increased in Western blot analysis.	[66]
	Human breast cancer	Cell-cycle arrest at G2/M phase and induced apoptosis and autophagy in human breast cancer cells. Interruption of the PI3K/AKT/mTOR/p70S6K/ULK signaling pathway.	[67]

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