The Role of Phenolic Compounds in the Fight against Cancer – A Review

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Abstract: Cancer is a worldwide scourge; it's the leading cause of death in developed countries and is increasing in developing countries. Mankind has been trying with effort to find better and cheaper treatments with fewer side effects, to reduce the incidence of the disease and its consequent mortality. For many years, phenolic compounds have been intensely studied for their antitumor, proapoptotic and antiangiogenic effects. In recent years, the usage of these compounds has increased considerably.

This manuscript intends to structurally characterize the different phenolic compounds (flavonoids, hydroxycinnamates, hydroxybenzoates, coumarins, xanthones, chalcones, stilbenes, lignins and lignans) and their metabolic pathways as well as review the most important results regarding these compounds and their derivatives in cancer treatment and prevention both in tumor cell lines *in vitro*, in murine models *in vivo* and finally some results regarding human trials.

Keywords: Animal models, anticancer, antitumoral, cell lines, clinical trials, phenolic compounds.

1. INTRODUCTION

Cancer is a worldwide burden that causes millions of deaths each year. In fact, it is the leading cause of death in developed countries, slaughtering 7.6 millions of lives in 2008. The developing countries have begun to register increasing cases of cancer due to cancer-causing behaviors like smoking and unbalanced diets. Of the 7.6 million deaths in 2008, 64% were in developing countries [1]. The economic impact on the prophylaxis and treatment of this disease is monumental, reaching in 2002, over 60 million dollars in the United States alone [2]. The social and cultural implications are harder to calculate but also deserve a profound and adequate reflection as they afflict millions of citizens around the world. Despite the giant leap that anticancer treatments have undergone in the past decades it is still imperative to diminish the mortality and suffering of patients and reduce the costs of treatments. The world needs faster, more efficient and specific treatments for the different types of cancer, and one of the main drawbacks is drug resistance. This resistance may emerge from a variety of reasons, including alteration in the binding site of the target, metabolism and export mechanisms *via* genetic or epigenetic alterations [3]. The quest to find these efficient drugs is everlasting and worldwide research is growing every day.

Since ancient times, plants have been used as remedies to treat different types of illnesses and lesions with satisfying results. Today, more than 60% of anticancer drugs come from natural compounds or are derived from them, making these bioactive molecules become increasingly interesting for drug companies, even as prototypes of final formulations for anticancer drugs [4, 5]. It is known that plant extracts can display interesting anticancer effects on cell lines and murine models, yielding higher effects when compared to pure natural or synthetic compounds. Despite this remarkable effect, it is difficult to assess which compounds are interacting with the cancer cells or if this orchestrated effect is due to synergy between various compounds. Another disadvantage of extracts is the difficulty to obtain enough quantity of plants to produce them, while the natural compounds can, in some cases, be synthesized in a laboratory, reducing the need for intense gathering.

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2. SECONDARY METABOLITES

For 200 years, modern chemistry has managed to describe the functions of plant primary metabolites as being related to basic functions like cell division and growth, respiration, storage and reproduction. These metabolites comprehend phytosterols, acyl lipids, nucleotides, amino acids and organic acids. Secondary metabolites tend to accumulate in plant tissues; they play an important role in the plants adaptation process, acting as antibiotics, antifungals, antivirals, UV absorbing agents to reduce damage to tissues, signal molecules, allelopathic agents, attractants for pollinators and seed-dispersing animals as well as protecting the plant against herbivores. For mankind, these metabolites are also important for providing dyes, fibers, glues, oils, waxes, flavoring agents, perfumes, insecticides, herbicides and are sources of new natural drugs for many diseases [6, 7]. The secondary metabolites are usually classified through their biosynthetic pathways, and are divided into three large families: alkaloids, terpenes and steroids, and phenolic compounds [6]. They are mainly found in storage tissues rather than in vegetative ones, due to their high biologic potency [8].

2.1. Terpenes and Steroids

Terpenes and steroids are known for their lipophilic properties and their biosynthetic origin through the mevalonate and mevalonate-independent pathways. In terms of structure, they are unsaturated cyclic or linear hydrocarbons with varying degrees of oxygenation. They are subdivided according to the number of five carbon units (isoprene) which are the building blocks of these compounds. It is now known that isoprene occurs naturally but is not involved in the formation of these compounds, rather by isomers of isopentenyl pyrophosphate and dimethylallyl pyrophosphate. Terpenes may vary from monoterpenoids (C_{10}) to tertraterpenoids (C_{40}), which are forty carbon molecules. Steroids are modified triterpenoids (C_{30}) and derive from squalene which is transformed into lanosterol. The basic structure of steroids is the well-known cholesterol molecule, with the typicall four fused cycloalkane rings. Substitutions in the functional groups surrounding the nucleus which is formed by the fused rings, confer a high metabolic activity to steroids, allowing them to be used as hormones, drugs and anti-inflammatory medication [7-11].

2.2. Alkaloids

The alkaloids are a diverse group of low molecular weight, nitrogen-containing compounds. They also play a defensive role in

plants, defending them from herbivores and pathogens. As many as 12000 alkaloids have been used as pharmaceuticals, stimulants, narcotics and poisons since the first alkaloid, morphine, was discovered [7]. Not all alkaloids derive from amino acids and, allowing a division into four groups: a) alkaloids derived from amino acids (ornithine, arginine, lysine, histidine, phenylalanine/ tyrosine, tryptophan, anthranilic acid and nicotinic acid); b) purine alkaloids (xanthine and caffeine); c) aminated terpenes (diterpene aconitine, triterpene solanine); e) polyketide alkaloids (consisting of nitrogen introduced into a polyketide carbon skeleton) [12].

2.3. Phenolic Compounds

Phenolic compounds are widely dispersed throughout the plant kingdom representing about 8000 different phenolic structures. As secondary metabolites they also display defensive, growth and development effects. They have at least one aromatic ring with one or more hydroxyl groups attached, being able to range from low molecular weight molecules to large and complex ones. The biosynthesis of phenolic compounds involves the shikimate, phenilpropanoid and flavonoid pathways [7, 13]. Phenolic compounds generally appear as esters and glycosides rather than as free compounds due to the conferred stability of these molecules. This family of compounds is one of the most studied worldwide and innumerous publications report beneficial effects in various aspects of human health and well-being [13-15]. Fig. (**1**) represents the various groups of molecules within the phenolic compounds family, while Table **1** displays their structure as well as the number of carbons and representative compounds.

2.3.1 Hydroxybenzoic Acids

Regarding the Hydroxybenzoic acids group, they are composed of seven carbon molecules with a C6-C1 skeleton and are produced through the shikimate pathway. These compounds are universally distributed in the plant kingdom, being gallic, protocatechuic, vanillic, and syringic acids the four most abundant compounds. Within this group of compounds there is a sub-group, the tannins, which vary greatly from small molecules to large ones. There are two categories of tannins, the hydrolysable and the non-hydrolysable or condensed tannins. The hydrolysable tannins have a central core of polyhydric alcohol such as glucose and hydroxyl groups which can be esterified by gallic acid, while condensed tannins are structurally more complex and are the result of polymerization by some flavonoids [7, 10, 16, 17].

2.3.2. Hydroxycinnammic Acids

The Hydroxycinnamic acids represent a group of compounds that derive from cinnamic acid through the phenilpropanoid pathway. They display a C6-C3 skeleton of *trans*-phenyl-3-propenoic acid with one or more hydroxyl groups attached to the phenyl moiety, some of which may be methylated. The precursors of this group of compounds are the aminoacids L-phenylalanine and L-tyrosine. Hydroxycinammic acids display a defensive and UV protective effect in plant models. The most abundant compounds within this group are *p*-coumaric, caffeic and ferulic acids [7, 10, 18, 19].

2.3.3. Coumarins

Coumarins derive from phenolic acids and display a benzene ring fused to an oxygen heterocycle. The four most common coumarins are coumarin, umbelliferone, esculetin and scopoletin among the 1000 naturally occurring ones in higher plants. Free coumarins can be found in plants, but most of the simple ones are usually glycated. The major quantities of coumarins are found in roots and seeds, but have also been described in all the different organs of plants [20, 21].

2.3.4. Xanthones

These compounds occur mostly in higher plant families, namely in the Gentianaceae, Guttiferae, Polygalaceae, Leguminosae, Lythraceae, Moraceae, Loganiaceae, and Rhamnaceae. Structurally they are comprised of heterocyclic compounds, quite similar to flavonoids, with a C6-C1-C6 skeleton. Xanthones are usually classified in 5 major groups: Simple oxygenated xanthones, xanthone glycosides, prenylated and related xanthones, xanthonolignoids and miscellaneous. Their *in vitro* and *in vivo* antitumor potential has recently been object of a considerable numbert of studies [22].

2.3.5. Chalcones

Chalcones display a C6-C3-C6 skeleton without a heterocyclic C-ring and are intermediates in the formation of all flavonoids. They have an open chain conformation with two aromatic rings joined by a three-carbon α,β- unsaturated carbonyl system. Most chalcones are yellow colored and occur mostly in flowers, but can be found in other plant organs. Some occur as glycosides, although most of them are found as free aglycones. They have been reported to have antioxidant, anti-fungal and anti-cancer properties [21, 23].

2.3.6. Stilbenes

The members of the stilbene family exhibit a C6-C2-C6 structure and derive from the same biosynthetic pathway as flavonoids. Although small, these compounds are widely distributed throughout the plant kingdom. There are over 200 stilbenes and stilbene glycones reported in higher plants. The most important stilbene is resveratrol, which has been extensively studied in recet years due to its antitumor potential [7, 21].
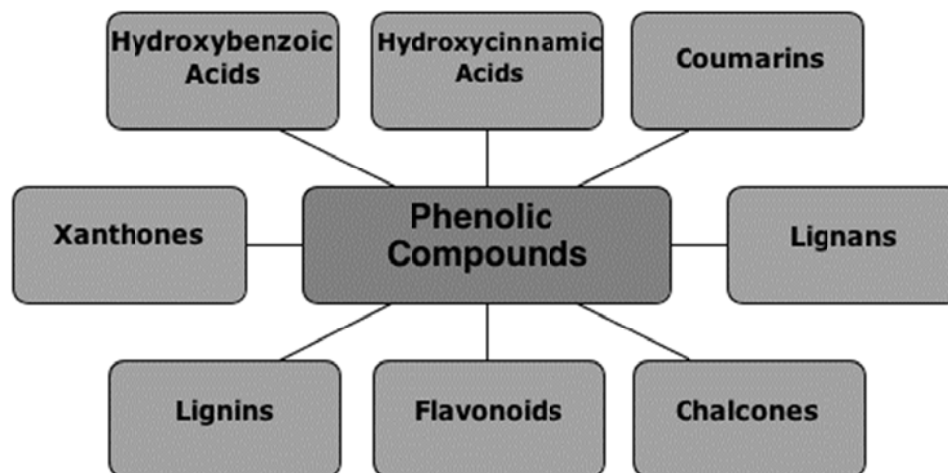

Fig. (1). Molecular groups of the phenolic compounds family.

Table 1. Classification through number of carbons and basic structure of molecules within the phenolic compounds family.

Number of Carbons	Classification	Example	Basic Structure
7	Hydroxybenzoic acids	Gallic acid	
9	Hydroxycinnamic acids	*p*-coumaric acid	
9	Coumarins	Esculetin	
13	Xanthones	Mangiferin	
14	Stilbenes	Resveratrol	
15	Flavonoids	Naringenin	

2.3.7. Lignins

Lignin is a polymer with many branches, composed of three simple alcohols known as monolignols. There are three major groups of lignins: lignins of softwoods (gymnosperms), lignins of hardwoods (angiosperms) and lignins of grasses (non-woody or herbaceous plants). It is the third most abundant polymer in nature, topping 300 billion metric tons on Earth. In plant tissues, lignin is bonded to other polymers like cellulose and hemicellulose. Antioxidant, anti-hypertensive and anticancer properties have been described in lignins, lignin derivatives and in complexes formed with them [24-27].

2.3.8. Lignans

Lignans are the result of the union of two cinnamic acid residues or their biogenic relatives. They are distributed throughout the plant kingdom in many vascular plant families, being present in all their organs. These compounds are also known for their beneficial effects, namely anticancer, antioxidant, hepatoprotective and antiviral [28, 29].

2.3.9. Flavonoids

The flavonoids are the most numerous group of molecules within the phenolic compounds and are widespread through the plant kingdom. They are polyphenolic compounds that derive from chalcones and display an arrangement of three aromatic rings (A, B and C) with fifteen carbons and a C6-C3-C6 skeleton which can have innumerous substituents. The A ring is a benzene, condensed with a six-member ring (C), which carries a phenyl benzene in position 2 (ring B) as a substituent. Ring C can be a heterocyclic pyran (Table **2**). Flavonoids have a mixed biosynthesis, and are products of both the shikimate and acetate pathways. They accumulate mainly in the epidermis of leaves and skin of fruits, and are involved in UV protection, pigmentation, disease resistance and stimulation of nitrogen fixing. Sugars, in the form of glycosides are normally joined with flavonoids and while they increase water solubility along with hydroxyl groups, other substituents like methyl groups and isopentenyl units increase their lipophilic properties. The main subclasses of flavonoids are flavonols,

Table 2. Representation of the basic structures of the flavonoid subclass.

Classification	Examples	Basic Structure
Flavonol	Quercetin Kaempferol Myricetin	
Flavone	Apigenin Chrysin	
Flavanol	Catechin	
Isoflavone	Genistein	
Flavanone	Hesperidin	
Anthocyanin	Pelargonidin Cyanidin	

flavones, flavanols or flavan-3-ols, isoflavones, flavanones and anthocyanidins [7, 10, 30-32]. Table **2** represents the basic structure and some examples of all these subclasses.

2.3.9.1. Flavonols

Flavonols are considered, not without debate, the most widespread flavonoids throughout the plant kingdom, and considered, along with flavones, the major subclass of flavonoids. The most abundant compounds within the flavonols are myricetin, quercetin and kaempferol that tend to occur as *O*-glycosides. Conjugation usually occurs at the third carbon of the C-ring, although conjugations have also been found at positions 5, 7, 4', 3' and 5'. It is estimated that in Western countries the daily intake of flavonols is between 20 to 50 mg, and although these compounds are found in many fruits and vegetables, considerable quantity differences may be found between the same species, due to seasonal changes, varietal and edaphoclimatic variations. The benefits of flavonols consumption are related to protection against athero-sclerosis, osteoporosis, diabetes mellitus and certain cancers [7, 32, 33].

2.3.9.2. Flavones

The flavones are structurally related to flavonols and are also considered a major subclass within the flavonoids; they occur usually as 7-*O*-glycosides, although other substitutions can be found. These compounds derive directly from flavanones, by abstraction of two hydrogen atoms and introduction of a double bond between carbons 2 and 3. Flavones seem to have protective and communication roles in plants, protecting against UV radiation and interacting with microbes, insects and other plants. The most common compounds within the flavones are apigenin, chrysin and luteolin. The main benefits to human health from flavones are antioxidant, anticarcinogenic, antiviral, anti-inflammatory and antiatherosclerotic [7, 34].

2.3.9.3. Flavanols

The flavanols or flavan-3-ols are the most complex subclass of flavonoids; they encompass simple molecules like catechin and large polymeric proanthocyanidins. This subclass of flavonoids, unlike the others is not planar due to a saturated C3 element in the heterocyclic C-ring. In plant systems, the flavanols act against harmful intruders like microbes, insects and herbivores; they also have the ability to chelate metals and to confer resistance to high lead levels. In food, flavanols are responsible for astringency, bitterness, sourness, salivary viscosity, aroma and color formation. The average daily consumption of flavanols in the United States was 57.7 mg/person in between 2004 and 2005. Once inside the body, these compounds have shown antioxidant, anticarcinogen, antiviral and neuroprotective effects [7, 35].

2.3.9.4. Isoflavones

The isoflavones, also known as phytoestrogen compounds due to their phytoestrogenic activity, differ from other subclasses within the flavonoids class by having the B-ring attached to the C3 carbon rather than the C2. Isoflavones are only found in leguminous plants, being soybeans the highest producer. The main representatives of the isoflavones are genistein and daidzein along with their respective acetyl, malonyl and aglycone forms. Isoflavones have been reported to have antitumor activity along with antioxidant and antiviral potential, although some data is controversial [7, 36-38].

2.3.9.5. Flavanones

The flavanones are usually considered a minor subclass within the flavonoids due to their limited occurrence, mainly in fruits and especially in citrus. They are characterized by the absence of a double bond and a chiral center in the C ring. Chalcones are usually incorporated into this subclass due to being similar to flavanones; the main difference is the open C ring in chalcones, and the possibility of conversion of flavanones into chalcones in alkaline media and vice-versa in acidic environments. Examples of

flavanones are hesperidin (orange juice) and naringine (grapefruit) and due to the high levels of hesperidin in orange juice, it has a sour taste, while naringine is sweeter. Flavanones have also been reported to have anticancer properties and effective in preventing cardiovascular diseases [7, 39-41].

2.3.9.6. Anthocyanidins

Anthocyanidins, also known as condensed tannins are present throughout the plant kingdom, especially in their glycated forms; the anthocyanins are found in fruits and flowers in a higher quantity, but also in leaves, stems and roots. These molecules are responsible for conferring red, blue and purple colors in plants as well protecting them from excessive light and attracting pollinators. The most abundant anthocyanidins are pelargonidin, cyaniding, delphinidin and peonidin. Conjugation with other molecules can take place in positions 3, 5, 7, 3' and 5', creating bigger molecules. In terms of human health, anthocyanins have been reported to have anti-inflammatory potential, DNA protection and regulator of immune responses [7, 42-45].

3. CANCER MECHANISMS

Cancer may have various endogenous causes (e.g. inherited mutations, hormones, and immune conditions) which are inevitable, but also exogenous ones, like tobacco consumption, diet related, radiation, and infectious organisms. The close link between cancer and oxidative stress, arising from various sources, gives way to some debate within the scientific community due to the role of prooxidants. While some scientists point them as potentially carcinogenic, others disagree and appoint out their bennefficial mitigating effect on certain types of cancer [46]. Despite this controversy, prooxidants are known to be involved in carcinogenesis. According to Anand *et al*. [47], whom reviewed the literature and stated that "cancer is a preventable disease that requires major lifestyle changes", only 5 to 10% of cancers were caused by genetic defects and the remaining 90 to 95% were due to environment and lifestyle. This could be a promising premise, but, attending to the current number of smokers worldwide, the nutritional imbalanced diets of developed and developing countries and the wrong behaviors regarding Sun exposure, the cases of cancer are estimated to grow. In fact, considering that by 2050, 27 million new cancer cases and 17.5 million deaths are estimated to occur [48] it is imperative to understand cancer mechanisms in order to intervene with the right methodologies.

Meng *et al*. [49] reviewed the major theories that lead to cancer, available since the beginning of the century, and divided them into 8 categories:

- Cancer caused by viruses
- Chromosomal abnormalities
- Somatic mutations
- Accumulated multiple mutations
- Immunological surveillances
- Nonhealing wounds
- Nonmutagenic mechanisms
- Tissue organization field theories

Regarding cancer caused by viruses, when Francis Peyton Rous claimed in 1911 that cancer could be induced by a virus, the scientific community discredited his work, and only 50 years later was hiswork recognized with a Nobel Prize of Physiology or Medicine. Today, it is widely known that viruses like Epstein-Barr, Hepatitis B, Human T-cell lymphototropic type 1, Papillomavirus, Hepatitis C, Kaposi's sarcoma-associated herpesvirus and Merkel cell polyomavirus can induce carcinogenesis. Although some oncogenic viruses are common among humans, not all infections lead to cancer. The biggest setback in this field is the multitude of

mechanisms used by each virus to induce cancer, but the scientific community is also using them to counter-attack [50-52].

In terms of chromosomal abnormalities, many tumors have the same genesis, either by nonrandom deletion or aberration of specific parts of chromosomes. In 2000 more than 600 recurrent balanced chromosome rearrangements had been identified [53, 54].

It is known that changes in the immune system, hormonal status, gene expression, and signaling between tissues have a key role in terms of probability and timing of cancer progression, but somatic mutation is the only process that determines progression of tissues at all ages, explaining the variation in age of cancer incidence. The somatic mutation theory premises are: 1) cancer is derived from a single somatic cell that has accumulated multiple DNA mutations; 2) the default state of cell proliferation in metazoa is quiescence; 3) cancer is a disease in cell proliferation caused by mutations in genes that control proliferation and the cell cycle. The sporadic cancers that derive from somatic mutation represent 95% of all cancers, and are some of the most researched throughout the world. It is now generally accepted that most tumors don't perpetuate themselves with only one mutation; many mutated chromosomes have been found in tumors and the rate and complexity of the mutations dictate the speed and danger of each type of cancer [55-57].

Immunological surveillance was first hypothesized by Burnet and Thomas [58, 59], back in 1959, postulating that the immune system can recognize and destroy nascent transformed cells. After being abandoned, this theory regained prominence in 1990, when the usage of animal models confirmed a cancer immunoediting mechanism. There are three essential phases: 1) elimination; 2) equilibrium and 3) escape. Initially, nascent transformed cells are eliminated by immune effector cells as part of an innate response. In the equilibrium stage, the elimination of the transformed cells sculpts the immune system inducing tumor variants decreasing immunogenicity and becoming resistant to effector cells. Finally in the escape phase, tumor-derived factors induce several escapes from immune attack, therefore promoting the tumor growth [60, 61].

The theory that cancer could be related with wound healing started with Alexander Haddow and, short after, Harold Dvorak, whom described cancer as a nonhealing wound. Today, it is known that wound healing shares common features with tumor genesis; in fact, both tissue regeneration and tumorigenesis involve cell proliferation, survival and migration, which are controlled by growth factors and cytokines as well as inflammatory and angiogenic signals. Understanding the similarities between wounds and the development of cancer as well as the wrong healing patters may help understand the uncontrolled growth of tumors [62-64].

The nonmutagenic mechanisms of carcinogenesis are based on the fact that the development of a tumor might not be due to mutations or aberrations in the DNA, but to mitogens and cytotoxic carcinogens. Regarding mitogens, these can cause increased cell replication without displaying any cytotoxicity by interacting directly with cell receptors. A result of this uncontrolled replication is pleiotropic responses like enzyme induction, cytomegaly and peroxisome proliferation. On the other hand, cytotoxic carcinogens induce histopathological lesions, necrosis and the release of specific enzymes into the serum. Cell proliferation resulting of cytotoxic compounds replaces the cells that are damaged after this aggression, and may stimulate growth of spontaneously occurring preoplastic cells. This increased cell division may also induce genetic damage by increasing the number of genetic errors due to rapid cell division and reduced time for accurate DNA repair [65, 66].

Finally, the organization field theory is based on the hypothesis that carcinogenesis is a problem of tissue organization and that proliferation is the default state of all cells. The underlying mechanism of this theory states that carcinogens disrupt the normal interactions between cells in the stroma and parenchyma of a given organ. This disruption would reduce the cell's understanding of its positional and historical background. The alteration of the stroma-epithelium would result in a hyperplastic state. The last step in this hypothesis would be the modification of the tissue pattern that could result in dyplasia or even in metaplasia [67, 68].

All cancer theories have limitations and fail to explain thoroughly certain types of cancer as well as the underlying mechanisms behind them. While some research groups look deeper into the genesis of a tumor, others venture into how natural or synthetic compounds can destroy the tumor.

4. FIGHTING CANCER WITH PHENOLIC COMPOUNDS

In 2003, when the complete human genome was sequenced, many scientists throughout the world considered it a landmark for the future treatment of genetic and non-genetic diseases [69]. Although many advances have been made, natural compounds did not lose their influence, in fact, between 1981 and 2006, 47.1% of the 155 clinically approved anti-cancer drugs, were unmodified natural products or their semi-synthetic derivatives or even synthesized molecules based on natural models.

Some of the biggest contributions in terms of pure molecules come from the secondary metabolites of plants, namely polyphenols, and have had important roles both "*in vitro*" and "*in vivo*":

4.1. Hydroxybenzoic Acids

The most studied compounds in this group are gallic, ellagic and ferulic acids (Table **3**). In terms of "*in vitro*" chemotherapeutic assays, in 2007, Madlener *et al.* [70] used gallic acid in leukemic cell lines and reported an inhibition of ribonucleotide reductase (enzyme that catalyzes the formation of deoxyribonucleotides from ribonucleotides) activity in tumor cells, resulting in a halt to tumor growth. Early and late apoptosis was dependent on the concentration of gallic acid. In another study regarding leukemia, gallic acid induced apoptosis by inhibiting BCR/ABL kinase (an oncogene), NF-kB (protein complex that is responsible for DNA transcription) and COX-2 (enzyme involved in cancer expression by promoting cell division and inhibiting apoptosis) [71]. This acid also proved to be effective against glioma cell lines in a dose dependent manner. Moreover it had a selective cytotoxicity to the glioma cells when compared to sane brain cells and decreased cell viability, proliferation and reduced angiogenesis [72]. Gallic acid also had remarkable effects on lung cancer cell lines by inducing apoptosis and activating caspases (apoptotic enzymes). In murine models, gallic acid seemed to reduce the rate of tumor gowth [73]. Regarding ellagic acid, a study carried out in 2011, used this compound against murine colon cancer and reported some interesting results; the mice were inoculated with 1,2-dimethyl hydrazine (carcinogenic inducing compound) for 15 weeks and then treated with ellagic acid for the following 15. This hydroxybenzoic acid prevented the activation of PI3K/Akt pathway (associated with colon carcinogenesis) which down regulated Bcl-2 proteins (apoptosis regulator proteins), increased Bax levels (pro-apoptotic protein) and activated caspase-3. Finally, this cascade of events resulted in elevation of cytochrome c and consequent apoptosis of the cancer cells [74]. Ellagic acid also seems to be promising for local chemotherapy. Kim *et al.* [75] used a chitosan/ellagic acid composite implanted subcutaneously in rats with glioma and reported angiogenesis suppressing capabilities as well as apoptosis in an ellagic acid concentration-dependent manner.

Ferulic acid seems to have some type of chemopreventive effect when administered orally, both in skin and mammary murine cancers by preventing the formation of these tumors. Although the mechanisms of this effect are not fully understood, the results are promising [76, 77].

Table 3.   Hydroxybenzoic acids and related compounds with reported antitumor activity.

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Gallic acid	Leukemia	*In vitro* human cell lines	Ribonucleotide reductase inhibition Apoptosis	[70]
	Glioma	*In vitro* human *In vitro* murine cell lines	Cell viability, proliferation and angiogenesis decrease	[72]
	Lung carcinoma	*In vitro* human cell lines *In vivo* murine models	Apoptosis and DNA damage Activation of caspases Tumor inhibition *in vivo*	[73]
Ellagic acid	Colon carcinoma	*In vivo* murine models	Prevention of Pl3k/Akt activation Bax expression and caspases-3 activation leading to apoptosis	[74]
	Glioma	*In vivo* murine models	Angiogenesis suppressing Apoptosis	[75]
Ferulic acid	Skin carcinoma	*In vivo* murine models	Prevention of tumor formation	[76]
	Mammary carcinoma	*In vivo* murine models	Prevention of tumor formation	[77]
Cuphiin D1 (tannin)	Leukemia Epidermoid carcinoma Hepatocellular carcinoma Prostate carcinoma Cervical carcinoma Murine sarcoma-180	*In vitro* human cell lines *In vitro* murine cell lines	Apoptotic properties Tumor inhibition	[80] [78]
Oenothein B (tannin)	Mammary carcinoma Fibrosarcoma Leukemia Epidermoid carcinoma Hepatocellular carcinoma Prostate carcinoma Cervical carcinoma Murine sarcoma-180	*In vivo* murine models *In vitro* human cell lines *In vitro* murine cell lines	Macrophages activation Tumor inhibition	[79] [78]
Cuphiin D2	Mammary carcinoma Fibrosarcoma Leukemia Epidermoid carcinoma Hepatocellular carcinoma Prostate carcinoma Cervical carcinoma Murine sarcoma-180	*In vivo* murine models *In vitro* human cell lines *In vitro* murine cell lines	Macrophages activation Tumor inhibition	[78]
Woodfordin C	Mammary carcinoma Fibrosarcoma Leukemia Epidermoid carcinoma Hepatocellular carcinoma Prostate carcinoma Cervical carcinoma Murine sarcoma-180	*In vivo* murine models *In vitro* human cell lines *In vitro* murine cell lines	Macrophages activation Tumor inhibition	[78]

Tannins, a sub-class of hydroxybenzoic acids also manifest some antitumoral activity. Cuphiin D1, an hydrolysable tannin proved to have some apoptotic properties against leukemia cell lines [78], another tannin, oenothein B, proved to be effective against mammary carcinoma and fibrosarcoma in murine models by activating macrophages [79]. Wang *et al*. [80] carried out a study with four tannis extracted from *Cuphea hyssopifolia*. They tested cuphiin D1, cuphiin D2, oenothein B and woodfordin C against human oral epidermoid carcinoma, human promyelocytic leukemia, human hepatocellular carcinoma, human prostate carcinoma, human cervical carcinoma and mouse sarcoma cell lines. Surprisingly, all the tested tannins inhibited the growth of the tumors and revealed lower cytotoxicity than Adriamycin (a commercially available antibiotic used in certain types of cancer) in a normal cell line. Moreover, these tannins also inhibited the viability of sarcoma tumor cell lines as well as *in vivo* mice models.

4.2. Hydroxycinnamic Acids

One of the most important compounds within the hydroxycinammic acids is caffeic acid which displays some anticancer activities (Table **4**). Chen *et al*. [81] used its derivative, caffeic acid phenethyl ester (CAPE) in human leukemic cell lines and reported an arrest on the tumor growth. At the time, the authors didn't understand the mechanisms leading to the activity. Two decades afterwards, Kuo *et al*. [82] used the same caffeic acid derivative on human glioma cell lines, and described an inhibition of growth of the cells by decreasing the hyperphosphorylation of the protein retinoblastoma, that when in this state is incapable of suppressing tumors. Furthermore, they found that CAPE up-regulates cyclin dependent kinase inhibitors p16, p21 and p27. After this preliminary assay, murine xenografts were attempted and proved that CAPE decreased the size of tumors in a dose dependent manner by reducing the number of mitotic cells and proliferating cell nuclear antigen positive cells. Other authors have also proved the excellent results of CAPE against glioma cell lines, by inactivating DNA and arresting the cell cycle of the tumor cells [83, 84]. Cinnamic acid also displays an antitumor activity, namely against colon adenocarcinoma by antiproliferative methods like enzyme induction and modulation of the cAMP signaling pathway [85]. Cinnamic acid derivatives, drupanin and baccharin, inhibits the growth of HeLa-60 cell lines by inducing apoptosis [86]. Panobinostat, is an anticancer drug that derives from the hydroxycinnamic acid group and acts by inhibiting histone deacetylase, which intervenes in carcinogenic pathways [87, 88]. Despite already being commercialized, hepatic clinical studies are still being carried out to access its efficacy [89].

4.3. Coumarins

Coumarins represent a group of compounds that have been described as having antitumoral activity to a certain extent. Within this group, compounds such as coumarin, 4-hydroxycoumarin, 7-hydroxycoumarin, psoralidin, warfarin, dicoumarol, daphetin and aesculetin, as well as complexes with other compounds, have been studied for anticancer properties (Table **5**). In terms of *in vitro* studies, coumarin and its derivatives, along with 7-hydroxycoumarin, had activity against human pancreatic [90] and lung [91] cancer cell lines. Jung *et al*. [92] synthesized 4-hydroxycoumarin derivatives and tested them against various human cancer cell lines (lung, ovarian, melanoma, brain and colon), postulating that three of these derivatives had satisfactory anticancer effects against the cell lines and one of them had excellent results. Psoralidin is known to have an antitumor effect by inducing TRAIL-mediated apoptosis in cervical cancer. TRAIL is an apoptosis-inducing ligand of the TNF superfamily [93]. Daphetin seemed to exhibit anticancer results against renal carcinoma cells by activating p38 and inhibiting S phase of the cell cycle, but did not promote apoptosis [94]. Dicoumarol, another compound from the coumarin family doesn't seem to inhibit cancer cell lines, but in turn enhances the activity of anticancer drugs like cisplatin [95] and doxorubicin [96]. Aesculetin has also demonstrated apoptotic activity against cervical cancer cell lines [97]. Complexes between coumarins and other molecules are also prone to inhibit cancer cell lines *in vitro.* Thati *et al*. [98],

demonstrated that a complex between copper-coumarin-dioxyacetic acetate-phenathroline ([Cu(cdoa)(phen)2]) against kidney adenocarcinoma and hepatocellular carcinoma displayed satisfactory antiproliferative effect, especially for the liver cancer cell lines. Not many *in vivo* studies have been reported regarding coumarins, although the *in vitro* studies have opened the opportunity for this. Lake [99] reviewed coumarin metabolism, toxicity and carcinogenicity in rodents and humans and postulated that although this compound could induce cancer in rodents it was safe to be consumed by humans due to an excretion metabolic pathway present in humans that is a minor one in rodents, generating toxicity to them. Moreover, he reviewed the anticancer *in vivo* studies and reported that coumarin inhibited forestomach and mammary cancer in mice as well as spontaneous tumors in transgenic mice. Finally, he also reviewed the clinical trials that this compound was involved in, and concluded that the side effects were mild and hepatotoxicity was reverted after the treatment with coumarin was terminated. Marshall *et al*. [100], reported that coumarin had a stationary effect in 12 of 45 patients with metastic renal cell carcinoma, while Nolte *et al*. [101] reported that the combined treatment of coumarin and cimetidine (histamine H_2 receptor antagonist) had no effect on 17 patients with advanced malignant melanoma. Recently, a study published on clinicaltrials.gov reported that the combined treatment of the coumarin warfarin with vatalanib, could help patients with advanced solid tumors. While the kinase inhibitor vatalanib stopped

Table 4. Hydroxycinnamic acids and related compounds with reported antitumor activity.

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Caffeic acid phenethyl ester	Leukemia	*In vitro* human cell lines	Oncogene suppression and tumor inhibition	[81]
	Glioma	*In vitro* murine cell lines *In vivo* murine xenografts	Hyperphosphorylation decrease of retinoblastoma Up-regulation of kinase inhibitors p21, p27 and p16	[82]
	Glioma	*In vitro* murine cell lines	p38 MAPK mediation of CAPE-induced p53-dependent apoptosis	[83]
Cinnamic acid	Glioma	*In vitro* murine cell lines *In vivo* murine xenografts	Inhibition of motility Induction of tumor suppressor RhoB Metastasis inhibition	[84]
	Colon adenocarcinoma	*In vitro* human cell lines	Enzyme induction Modulation of cAMP signaling pathway	[85]
Cinnamic acid derivatives	Cervical carcinoma	*In vitro* human cell lines	Apoptosis	[86]

Table 5. Coumarins and related compounds with reported antitumor activity.

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Coumarin derivatives	Pancreatic cancer	*In vitro* human cell lines	Cytotoxicity to cancer cells	[90]
Courmarin 7-hydroxycoumarin	Lung carcinoma	*In vitro* human cell lines	Inhibition of cell proliferation Apoptosis induction	[91]
4-hydroxycoumarin derivatives	Lung carcinoma Ovarian carcinoma Melanoma Brain carcinoma Colon carcinoma	*In vitro* human cell lines	Cytotoxicity to cancer cells	[92]
Psoralidin	Cervical carcinoma	*In vitro* human cell lines	TRAIL mediated apoptosis	[93]
Daphetin	Renal carcinoma	*In vitro* human cell lines	Activation o p38 Cell cycle arrest	[94]
Dicoumarol	Bladder carcinoma Prostate carcinoma	*In vitro* human cell lines	Enhancement of anticancer drugs	[95] [96]
Aesculetin	Cervical carcinoma	*In vitro* human cell lines	ROS mediated apoptosis	[97]
Copper-coumarin-dioxyacetic acetate-phenathroline complex	Kidney adenocarcinoma Hepatocellular adenocarcinoma	*In vitro* human cell lines	Antiproliferative effect	[98]
Coumarin	Renal carcinoma	Epidemiological studies	Enhancement of anticancer drug	[100]
Warfarin	Solid tumors	Epidemiological studies	Side effect of anticancer drug reduction	[102]

the tumor growth by inhibiting angiogenesis, warfarin prevented the formation of blood clots [102].

4.4. Xanthones

Xanthones are a small group of compounds that have also proven interesting as natural anticancer molecules. The most notorious origin of xanthones is the fruit of the purple magosteen (*Garcinia mangostana*), yielding a number of xanthones, especially α-, β- and γ-mangostin which are also the most studied compounds of this group (Table **6**). These three compounds have been described as *in vitro* chemopreventive and chemotherapeutic agents against, colon carcinoma [103-105], leukemia [106], melanoma [107], neck carcinoma [108], glioblastoma [109] and others [110]. Ho *et al.* [111] investigated the *in vitro* activity of 6 xanthones against 14 cell lines, and postulated that garcinone E was the best compound among the studied by inducing apoptosis in hepatoma, gastric and lung cancer cells proving to be more potent than commercial anticancer drugs. Other xanthones have also been investigated to a lesser extent against cholangiocarcinoma. These compounds, isomorellin, isomorellinol, forbesione and gambogic acid inhibited growth of those cancer cells in a dose dependent manner, being isomorellinol the most potent compound [112]. Although this group of polyphenols seems to have promising molecules with regard to *in vitro* assays, virtually no record of *in vivo* or clinical trials is reported against cancer. This might be due to a poor understanding of the mechanism of action of xanthones, which should be investigated thoroughly [113].

4.5. Chalcones

Chalcones are a family of polyphenols with a wide spectrum of biological activities, namely antioxidant, antibacterial, anti-inflammatory, immunosuppressive and anticancer. Phloretin, a very bioactive chalcone has been tested against human melanoma cell lines, and displayed apoptotic effect against the cancer cells [114] (Table **7**). This same compound was found to potentiate the effect of paclitaxel, an anticancer commercial drug that inhibits cell mitosis [115]. Arbutin also displayed a remarkable effect against melanoma cell lines by down regulating cancer genes [116]. Szliszka *et al.* [117] tested 2 chalcones (chalcone and 2',6'dihydroxy-4'-methoxychalcone) and 3 dihydrochalcones (2',6'-dihydroxy-4'4-dimethoxydihydrochalcone, 2',6'-dihydroxy-4'-methoxydihydro-chalcone, and phloretin) against human prostate cancer cells and discovered that all the compounds induced TRAIL mediated apoptosis against the cell lines. Synthetic chalcones have also been the target of many studies. Although they are synthesized in laboratorial conditions and not isolated from plants, their effect on various cell lines has also been satisfactory [118-121]. In 2011, Orlikova *et al*. [122] published a review regarding the chemo-preventive and chemotherapeutic potential of dietary chalcones, where all the studies surrounding the effects of chalcones against cancer (*in vitro* and *in vivo*) were compiled. The authors concluded that some chalcones could intervene in a beneficial way in several steps of carcinogenesis and could be included in anticancer therapies. Moreover, the chalcones should be extensively studied in order to identify and characterize the naturally occurring ones while laboratorial synthesis to potentiate their effects should also be encouraged.

4.6. Stilbenes

This small group of compounds, although comprised of hundreds of compounds, one of them stands high above the others, resveratrol. This compound, mainly found in grapes has been described as a chemopreventive and chemotherapeutic agent (Table **8**). The first record of its chemopreventive activity dates back to 1997 [123]. Since then, resveratrol and its analogues have undergone assays for virtually all human cancers. It has been screened *in vitro* against kidney and breast cancer [124], leukemia [125] and many others. In murine models, resveratrol also exhibits good anticancer effects and is also described as a sensitizer for anticancer drugs [126]. Resveratrol has taken part in various epidemiological studies, namely for gastro intestinal tumors [127], colorectal cancer [128],

Table 6.   Xanthones with reported antitumor activity.

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
α-Mangostin β-Mangostin γ-Mangostin	Colon carcinoma Leukemia Melanoma Neck carcinoma Glioblastoma	*In vitro* human cell lines	Apoptosis Cell cycle arrest	[103] [104] [105] [106] [107] [108] [109]
Garcinone E	Hepatocellular carcinoma Lung carcinoma Gastric carcinoma	*In vitro* human cell lines	Apoptosis Cell cycle arrest	[111]
Isomorellin Isomorellinol Forbesione Gambogic acid	Cholangiocarcinoma	*In vitro* human cell lines	Apoptosis Cell cycle arrest	[112]

Table 7.   Chalcones with reported antitumor activity.

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Phloretin	Melanoma	*In vitro* human cell lines	Apoptosis	[114]
	Hepatoma	*In vitro* human cell lines	Enhancement of anticancer drug	[115]
Arbutin	Melanoma	*In vitro* human cell lines	Down regulation of cancer genes	[116]
Chalcone 2',6'dihydroxy-4'-methoxychalcone 2',6'-dihydroxy-4'4-dimethoxydihydrochalcone 2',6'-dihydroxy-4'-methoxydihydrochalcone Phloretin	Prostate carcinoma	*In vitro* human cell lines	TRAIL mediated apoptosis	[117]

Table 8. Stilbenes with reported antitumor activity.

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Resveratrol	Leukemia Mammary carcinoma Skin carcinoma	*In vitro* human cell lines *In vivo* murine xenografts	Cell differentiation induction Inhibition of preneoplastic lesions Tumorigenesis inhibition	[123]
	Breast carcinoma Kidney carcinoma	*In vitro* human cell lines *In vivo* murine xenografts	Promotion of Argonaute2 expression	[124]
Resveratrol	Leukemia	*In vitro* human cell lines	Apoptosis Cell cycle arrest	[125]
	Neuroblastoma Glioma Pancreatic carcinoma Breast carcinoma Prostate carcinoma Leukemia Renal carcinoma	*In vitro* human cell lines	Sensitizer of anticancer drugs	[126]
	Gastrointestinal carcinomas	Epidemiological studies	*Ongoing*	[127]
	Colorectal carcinoma	Epidemiological studies	*Undisclosed results*	[128]
	Healthy individuals	Epidemiological studies	Lower doses of resveratrol (1.0, 2.5 and 5.0 g) are detectable in human plasma	[129]
Sophrastilbene α-viniferin ε-viniferin Rhaponticin	Squamous cell carcinoma Submandibular glad carcinoma Leukemia	*In vitro* human cell lines	Toxicity against cancer cells Activation of caspases	[135]
3,4,5-trimethoxy-4V-bromo-*cis*-stilbene	Lung carcinoma	*In vitro* human cell lines	DNA fragmentation Apoptosis	[136]
3,5-dihydroxy-4'-acetoxy-*trans*-stilbene	Prostate carcinoma Melanoma	*In vitro* human cell lines *In vivo* murine xenografts	Limited potential *in vivo*	[137]

as a preventive measure against cancer [129]. Due to the multitude of results of the various types of assays, resveratrol has been a target of many anticancer reviews [130-132]. Pterostilbene and piceatannol, which belong to the stilbene group, have also been described as chemopreventive and chemotherapeutic agents both *in vitro* and *in vivo* [133, 134]. Other stilbenes have also been investigated less extensively, but have also shown some type of anticancer effects, such as the compounds like sophrastilbene, α-viniferin, ε-viniferin, rhaponticin [135], 3,4,5-trimethoxy-4'bromo-*cis*-stilbene [136] and 3,5-dihydroxy-4'-acetoxy-*trans*-stilbene [137], although very limited feedback was reported in murine xenografts.

4.7. Lignins

Lignins are possibly the least studied polyphenols group in terms of chemoprotective and chemotherapeutic potential. To the authors knowledge only one study was conducted to investigate the chemopreventive effect of Kraft lignins (Table **9**). In that study, lignins resulting from chemical treatment of wood and paper were tested for adsorption to N-nitrosamines in healthy human and murine cell lines in order to prevent tumorigenesis arising from nitrosamines. Košiková *et al.* [138] reported that the good binding of the lignins revealed protective effects of the cell's DNA.

4.8. Lignans

Mammalian lignans are the result of metabolisation of dietary lignans and both display beneficial effects on human health. Mammalian lignans were discovered in human urine around 1980, and by 1998, various experiments had been conducted using lignans as beneficial compounds. Among these investigations, the role of two dietary lignans (secoisolariciresinol and matairesinol) had been tested both *in vitro* and *in vivo* against breast, colon and skin cancer, and while the *in vitro* assays showed good inhibition concentrations, the *in vivo* results were, at the time, still scanty [139] (Table **9**). Since then, other dietary lignans have been

studied for their chemopreventive and chemotherapeutic effects. Syringaresinol has been tested *in vitro* against leukemia and displayed cell cycle arrest at G1 phase mediated by cyclin-dependent kinases, followed by apoptosis demonstrated by morphological changes in a dose and time dependent manner, making this polyphenol a good candidate as a chemotherapeutic agent [140]. Another lignan, hydroxymatairesinol, has been tested in murine models with induced prostate cancer. The mice fed with hydoxymatairesinol displayed smaller tumors as well as a halt in tumor growth and in some cases regression [141]. One of the most studied lignans is podophyllotoxin for its beneficial effect against cancer. It is used as a starting compound to synthetize two commercial anticancer drugs, etoposide and teniposide [142]. The *in vivo* application of this polyphenol has resulted in tumor regression in murine models, although tumor regrowth would take place after treatment. Other limitations such as poor solubility in water and tumor resistance have inspired clinicians and scientists to develop water soluble compounds to overcome its solubility [143], and to join podophyllotoxin with other molecules like fatty acids to overcome tumor resistance and improve pharmacological efficacy [144]. In terms of epidemiological studies, podophyllotoxin is used in anticancer preparations along with other chemicals [145-148]. Landete [149] reviewed the lignans, from their sources, dietary intake, metabolism, metabolization to mammalian lignans, health implications and future prospects. The author covered the effects on colon, breast, prostate and intestinal cancer, which seem to be the most effective targets of this polyphenol. In terms of future perspectives, the author advised investigation to uncover the mechanisms of action at a molecular level as well as a closer look into nutrigenomics and nutrigenetics.

4.9. Flavonoids

4.9.1. Flavonols

The most active flavonols against cancer are quercetin and kaempferol (Table **10**). They have been extensively studied against

Table 9.   **Lignins and lignans with reported antitumor activity.**

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Kraft lignins	Sane human skin cells Quasidiploid hamster cells	*In vitro* human cell lines *In vitro* murine cell lines	Adsorption to nitrosamines DNA protective effect	[138]
(-)Syringaresinol	Leukemia	*In vitro* human cell lines	Cell cycle arrest Apoptosis	[140]
7-Hydroxymatairesinol	Prostate carcinoma	*In vivo* murine models	Cell proliferation reduction Tumor reduction	[141]
Podophyllotoxin and polyethylene glycol	Leukemia Lung carcinoma	*In vitro* human cell lines *In vivo* murine models	Better tumor inhibition compared to podophyllotoxin alone	[143]
Podophyllotoxin and fatty acids analogs	Solid tumors Leukemia	*In vitro* human cell lines	Cytotoxicity towards cancer cells Low cytotoxicity towards sane cells	[144]

Table 10.   **Flavonols with reported antitumor activity.**

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Quercetin	Leukemia Raji Burkitt lymphoma	*In vitro* human cell lines	Morphological changes Condensation of nuclear chromatin Nuclear fragmentation Apoptosis	[150]
	Gastric adenocarcinoma Hepatocellular carcinoma Lung adenocarcinoma	*In vitro* human cell lines	Inhibition of tyrosine kinase and of important steps of angiogenesis like proliferation, migration, and tube formation of human microvascular dermal endothelial cells in human	[151]
	Various cancers	Epidemiological studies	Decrease in α-fetoprotein	[157]
	Prostate cancer	*In vitro* human cell lines	Inhibition of oncogenes and genes controlling the cell cycle	[152]
Quercetin and quercetin-5',8-disulfonate	Colon cancer Breast cancer	*In vitro* human cell lines	Cell cycle arrest	[153]
QC12 (3'-(N-carboxymethyl)carbamoyl-3-4'-5-7-tetrahydroxyflavone)	Various cancers	Epidemiological studies	Quercetin bioavailability between 20 and 25% in plasma	[158]
Quercetin copper(II) complex	Lung adenocarcinoma	*In vitro* human cell lines	Cytotoxic for the cancer cell lines DNA binding Apoptosis and growth inhibition	[155]
Quercetin in polyethylene glycol 4000 lipossomes	Lewis lung cancer Colon adenocarcinoma Hepatoma	*In vivo* murine models	Apoptosis Growth inhibition	[156]
Kaempferol	Hepatocarcinoma	*In vitro* human cell lines	Cell viability reduction	[159]
	Pancreatic carcinoma	*In vitro* human cell lines	Growth enzymes inhibition Apoptosis	[160]
Kaempferol+TRAIL	Colon cancer Prostate cancer	*In vitro* human cell lines	Caspase dependent apoptosis	[161]
Kaempferol	Osteosarcoma	*In vitro* human cell lines *In vivo* murine models	Cell viability reduction Ca^{2+} increase Alteration of protein expression Apoptosis	[162]

various murine and human cell lines with remarkable effects. Back in 1994, quercetin proved to be effective against chronic myeloid leukemia, Molt-4 acute lymphocytic leukemia, Raji Burkitt lymphoma in terms of morphological changes, condensation of nuclear chromatin, nuclear fragmentation and induced apoptosis in a time and concentration dependent manner [150]. Since then, quercetin has been investigated in various human cell lines. Tan *et al*. [151] reported an inhibition of tyrosine kinase and of important steps in angiogenesis like proliferation, migration, and tube formation of human microvascular dermal endothelial cells in human gastric adenocarcinoma, hepatocellular carcinoma and lung adenocarcinoma. Severe and moderately aggressive human prostate cancer cell lines were also inhibited by quercetin through inhibition of specific oncogenes and genes that control the cell cycle [152]. Quercetin is known to be metabolized during the human digestion

and also has a very poor solubility. These drawbacks have led research groups to attempt to derive this compound, create complexes with metals or to encapsulate it in lipossomes. Derivatives like quercetin-5',8-disulfonate, proved to have anticancer properties in colon and breast cancer cell lines, by arresting the cell cycle, surpassing quercetin itself [153]. Tan *et al*. [154, 155] have combined quercetin with both copper and zinc and reported that these complexes were cytotoxic for the cancer cell lines and by binding to the DNA induced apoptosis and growth inhibition. Finally, Yuan *et al*. [156] proposed encapsulation of quercetin in polyethylene glycol 4000 lipossomes to overcome its poor solubility. The methodology involved intravenous (i.v.) injecting with subsequent accumulation in the tumor cells. *In vivo* assays with mice suffering from Lewis lung cancer, colon adenocarcinoma and hepatoma were performed. Apoptosis and

growth inhibition was detected for all tumors, thus eliminating a considerable drawback in the application of quercetin for cancer treatment. In terms of epidemiological studies involving quercetin, the first one was conducted in 1996, this Phase I clinical trial involved 51 patients with various terminal cancers. They were administered i.v. escalating doses of quercetin with a maximum of 1700 mg/m^2 for three weeks. Nephrotoxicity was detected at the maximum concentration and a recommended concentration was fixed at 1400 mg/m^2 for future type II trials. In one patient CA-125 (biomarker for ovarian cancer) was significantly reduced, and all the patients suffering from hepatocellular carcinoma revealed a reduction of α-fetoprotein, which is usually high in these types of cancer. Although this was an interesting finding, no regression in the tumor was detected in radiological assays [157]. In 2001, Mulholland *et al*. [158], confronted with the usage of DMSO (Dimethyl sulfoxide), which is known to cause hemolysis, to overcome the staggering low solubility of quercetin in water, synthesized a quercetin derivative, QC12 (3'-(N-carboxymethyl) carbamoyl-3-4'-5-7-tetrahydroxyflavone). The authors administered 400mg of this compound to six terminal state cancer patients through either oral or i.v.. At this concentration, the authors found no evidence of toxicity towards the patients and, although i.v. administered QC12 had a bioavailability 20~25% of quercetin, the orally administered one was not found in the plasma. They postulated that other derivatives should be researched in order to potentiate bioavailability of quercetin.

Kaempferol has also been studied for potential anticancer properties. In terms of human cell lines, kaempferol proved to be effective against hepatocarcinoma. This type of tumor is known to create hypoxia to surrounding cells, therefore promoting its own growth and making it resistant to chemotherapy. Kaempferol proved to reduce tumor cell viability even under hypoxic conditions [159]. In two types of human pancreatic cell lines, kaempferol proved to be better than 5-FU (fluorouracil, an anticancer drug) by inhibiting growth enzymes and promoting apoptosis in a concentration dependent manner [160]. Kaempferol can also be joined with anticancer agents, like TRAIL; in a study published in 2008, Yoshida *et al*. [161] reported that the combined effect of these two compounds induced considerable caspase dependent apoptosis rates in colon and prostate cancer cell lines, whilst the individual compounds were very poor in apoptosis induction. As a control assay they tested kaempferol+TRAIL in normal peripheral blood mononuclear cells with low toxicity to these sane cells. Human osteosarcoma cell lines have also been inhibited by kaempferol, namely by loss of cell viability, increase in cytoplasmic Ca^{2+}, alteration of certain protein expression and apoptosis. *In vivo* studies have also been trialed and a reduction in osteosarcoma tumor growth was detected [162].

4.9.2. Flavones

The major representative molecule within the flavones is chrysin. It has demonstrated good results in various types of cancers (Table **11**). It induced caspase 3 mediated apoptosis and enhanced Akt phosphorylation by inhibiting Pi3k (enzyme responsible for cell growth) in human leukemic cell lines [163]. Like kaempferol, chrysin can also be joined with TRAIL to enhance anticancer effects. In 2011, Li *et al*. [164] used human nasopharyngeal carcinoma, colorectal cancer, cervix carcinoma and hepatoma cell lines to test the synergy of these compounds. Although there was no observed effect for the isolated compounds, the treatment with the mixture of both enhanced apoptosis in four cell lines. In an attempt to understand the mechanisms behind this synergy, the authors pre-treated the cells with chrysin before adding TRAIL which resulted in weak results, implying that cell death was enhanced by chrysin but induced by TRAIL.

In terms of murine models, chrysin has yielded good results against diethylnitrosamine (DEN) induced heptocarcinogenesis; 250 mg/kg (body weight) of chrysin was administered to the mice and changes in enzymes and protein expression were detected, as well as a reduction in number and size of nodules formed, pointing

Table 11.   Flavones with reported antitumor activity.

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Chrysin	Leukemia	*In vitro* human cell lines	Caspase 3 mediated apoptosis	[163]
Chrysin + TRAIL	Nasopharyngeal carcinoma Colorectal cancer, Cervix carcinoma Hepatoma	*In vitro* human cell lines	Enhancement of apoptosis	[164]
Chrysin	Hepatocarcinogenesis	*In vivo* murine models	Changes in enzymes and protein expression Reduction in number and size of nodules	[165]
	Hepatocellular carcinoma	*In vivo* murine models	Attenuated biochemical and histological changes Reduction of α-fetoproteins and embriogenic antigen	[166]
Flavopiridol	60 different cell lines	*In vitro* human cell lines *In vitro* murine cell lines *In vivo* murine models	Cytotoxicity against tumor cell lines Tumor inhibition	[167]
Flavone core structure	Colon adenocarcinoma	*In vitro* human cell lines	Reduction of cell proliferation Induction of apoptosis	[168]
Pectolinarin, Linariin, Isolinariin A, Isolinariin B, Paracetylpectolinarin, Pectolinarigenin, Pectolinarigenin-7-*O*-β-Glucoside, Antirrhide and Antirrhinoside	Large lung cell carcinoma Hepatocellular carcinoma Renal adenocarcinoma Amelanotic carcinoma Colorectal adenocarcinoma	*In vitro* human cell lines	Reduction of cell proliferation	[169]
Chrysing long chain derivatives	Liver carcinoma	*In vitro* human cell lines	Antiproliferative activity	[170]
Flavone acetic acid	Leukemia	*In vivo* murine models	Tumor supression	[171]
	Various human carcinomas	Epidemiological studies	No reported benefitial effects	[174]
P276-00	Various human carcinomas	*In vitro* human cell lines *In vivo* murine models	Antiproliferative potential	[177]
P276-00	Breast carcinoma	Epidemiological studies	*Ongoing*	[178]

out a hepatoprotective and chemopreventive activity of this flavonol [165]. The same effect was reported in another study involving chrysin and murine models, where hepatocellular carcinoma was induced by N-nitrosodiethylamine in mice which were then treated with chrysin, resulting in attenuated biochemical and histological changes when compared to the control group. Moreover, chrysin reduced the levels of α-fetoproteins and embriogenic antigen (tumor markers). Finally, the most remarkable effect was a restoration of cell architecture of liver tissue, confirming a chemotherapeutic effect [166].

Flavopiridol, another effective flavonol has also been used both *in vitro* and in *vivo* against various cancers. Drees *et al*. [167] tested this compound *in vitro* against 60 different cancer cell lines. For a control assay they used sane bone marrow cell lines which only displayed sings of toxicity for concentrations above 100 ng/ml. Flavopiridol displayed cytotoxicity at concentrations as low as 0.1 ng/ml, especially in prostate and melanoma xenografts. Moreover, 14 of the 23 tumor cell types were inhibited in a greater manner than the control bone marrow cells. The *in vivo* assays were only performed in prostate cancer, which was the most affected under *in vitro* assays. In this case, flavopiridol was administered in the maximum tolerated dose (19 mg/kg) to have significant activity and after the administration the tumor regrew, implying that treatment should be longer than 2 weeks.

The core structure of flavones (2-phenyl-4*H*-benzopyran-4-one), a flavone, also indicated some antitumor activity against human colon adenocarcinoma by reducing cell proliferation and induction of apoptosis in a greater manner than campothecin (alkaloid based anticancer drug) [168].

In 2005, Tundis *et al*. [169] isolated all the flavones and respective derivatives from the plant *Linaria reflexa*, including pectolinarin, linariin, isolinariin A, isolinariin B, paracetylpectolinarin, pectolinarigenin, pectolinarigenin-7-*O*-β-glucoside, antirrhide and antirrhinoside, screening them against large lung cell carcinoma, hepatocellular carcinoma, renal adenocarcinoma, amelanotic carcinoma, colorectal adenocarcinoma and sane human fetal lung tissue as a control. All the compounds displayed interesting results against colorectal carcinoma and large lung cell carcinoma; pectolinarin was also effective against amelanotic melanoma. Pectolinarigenin and its derivatives were active against amelanotic melanoma and large lung cell carcinoma. The less sensitive cell line was renal adenocarcinoma.

In order to overcome the limitations of natural compounds in terms of bioavailability and cytotoxic effects, many research groups have started synthesizing compounds based on natural ones but removing structural limitations. Lv *et al*. [170] synthesized long chain derivatives of chrysin and tested them against human liver cancer. Among them, the compounds that had a higher activity were hexadecyl 2-(5-hydroxy-4-oxo-2-phenyl-4*H*-chromen-7-yloxy)acetate and N-hexadecyl 2-(5-hydroxy-4-oxo-2-phenyl-4*H*-chromen-7-yloxy)acetamide displaying antiproliferative activity comparable to arlotinib (anticancer drug). Furthermore, they used docking simulations to determine the binding mode of these compounds and determined that both these compounds bonded quite well with the epidermal growth factor receptor (EGFR) postulating that they could be interesting chemotherapeutic agents.

To this date, not many flavones have been subject to epidemiological studies, except flavone acetic acid. In the mid 80's, dozens of flavones from Lyonnaise Industrielle Pharmaceutique were subjected to preliminary screening against murine leukemia. Among all the compounds tested, flavone acetic acid had the greatest activity and continued to a phase I murine study that through pharmacokinetics confirmed that a quick hydrolysis of this compound was responsible for tumor suppression. In addition, no myelosupression or major toxicity was detected. When the clinical trials escalated to human subjects, there was no antitumor activity,

but this limitation was not due to poor penetration. Further studies confirmed that the mechanisms of action in murine and human species were different, leading to its poor activity in humans, and inspiring research groups to pursue the underlying mechanisms of this promising drug in the human body [171-176].

Recently, a flavone derivative has been tested against various cell lines and xenografts; this compound, P276-00 has yielded excellent results, with an antiproliferative potential of 30-fold higher than cisplatin (a chemotherapeutic drug) and 26-fold higher tumor sensitivity. This compound has been tested against cisplatin resistant tumors of central nervous system, melanoma, prostate and renal cancers, among others. Due to the outstanding results of this molecule, in 2011, a clinical trial was started to determine the effects of P276-00 administered in escalating doses with two anticancer drugs (Gemcitabine and Carboplatin) in subjects with metastic breast cancer [177, 178].

4.9.3. Flavanols

Most of the compounds in this group derive from the catechin backbone being the most abundant compounds found in green tea. Despite the widely accepted benefits of these compounds for cancer treatment, reports of the beneficial effects of isolated compounds are not that abundant. With regard to catechin, it is known to prevent metastasis of melanoma in murine models (Table **12**). This compound inhibits tumor formation and increases the life span of the animals. *In vitro* tests uncovered that catechin also inhibits the migration of melanoma cells across the collagen matrix of a Boyden chamber [179]. A catechin derivative, catechin hydrate, was effective in inhibiting by 50%, the growth of human cervical cancer cell lines *in vitro*, by increasing caspase-3, -8 and -9 and by inducing apoptosis [180]. Despite the scarce studies on the isolated effects of catechin, there is a considerable amount of publications regarding conjugations of this compound with a variety of other molecules. In 2004, Farivar-Mohseni *et al*. [181] used the known ability of catechin to inhibit cyclooxygenase (prostanoid producing enzyme) and conjugated it with NS-398 (also a prostanoid inhibiting enzyme) and tested their synergistic capacity against various bladder and prostate cancer cell lines. For both cancer types, the synergy was evident, resulting in a reduction in cell growth and apoptosis in a more severe manner than with the isolated compounds. Catechin has also been joined with inositol hexaphosphate (a carbohydrate) against pancreatic cancer cell lines. This conjugate increased apoptosis and inhibited cell growth in a greater manner that the isolated compounds [182]. Vittorio *et al*. [183] used dextran, a branched glucan in conjunction with catechin against pancreatic ductal adenocarcinoma. The cancer line was killed after being exposed to this conjugate. Moreover, dextran-catechin was less toxic to normal pancreatic cells than catechin alone. Anticancer clinical trials using catechin as an anticancer or cancer preventive drug are extensive, although in some cases, there is no way of knowing if the drug is strictly composed by catechin or if derivatives like epigallocatechin, epigallocatechin-3-gallate and other are also present. A great number of these trials intend to assess the preventive effects of catechin against unspecific cancers [184], and on specific types of cancer, like cervical and esophageal [185,186]. Finalized studies using catechin as an experimental drug have studied bladder and prostate cancer [187-189]. An ongoing study, with a primary due date scheduled for January 2013 is studying the effect of catechin in colorectal cancer [190].

Epigallocatechin-3-gallate (EGCG) is known for being the most abundant flavanol in tea and for a wide range of health benefits. It has been tested against human eosinophilic leukemia cell lines and suppressed cell proliferation in a dose dependent manner. At a low concentration of 40 μM the tumor cells underwent differentiation into mature eosinophil-like cells [191]. This compound also exhibited a considerable apoptotic effect against mouse hepatoma cell lines by cleaving procaspase-12 and increase in phosphorylation of ElF2α (subunit of ElF2 protein, responsible for an important

Table 12.   Flavanols with reported antitumor activity.

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Catechin	Melanoma	*In vitro* human cell lines *In vivo* murine models	Metastasis prevention	[179]
Catechin hydrate	Cervical carcinoma	*In vitro* human cell lines	Inhibition of 50% of cell growth	[180]
Catechin+NS-398	Bladder carcinoma Prostate carcinoma	*In vitro* human cell lines	Cell growth reduction Apoptosis	[181]
Catechin+Inositol hexaphosphate	Pancreatic carcinoma	*In vitro* human cell lines	Cell growth reduction Apoptosis	[182]
Catechin+dextran	Pancreatic ductal adenocarcinoma	*In vitro* human cell lines	Apoptosis	[183]
Catechin	Unspecific solid tumors	Epidemiological studies	Green tea may have ingredients that may prevent cancer	[184]
	Cervical carcinoma	Epidemiological studies	*Undisclosed results*	[185]
	Esophageal carcinoma	Epidemiological studies	*Ongoing*	[186]
	Bladder carcinoma	Epidemiological studies	Green tea may have ingredients that slow the growth of certain cancers	[187]
	Prostate carcinoma	Epidemiological studies	*Undisclosed results*	[188]
		Epidemiological studies	Green tea contains ingredients that may prevent or slow the growth of this cancer	[189]
	Colorectal carcinoma	Epidemiological studies	*Ongoing*	[190]
Epigallocatechin-3-gallate	Leukemia	*In vitro* human cell lines	Proliferation suppression Cell diferentiation	[191]
Epigallocatechin-3-gallate	Hepatoma	*In vitro* murine cell lines	Apoptosis Phosphorylation of ElF2α	[192]
	Melanoma	*In vitro* human cell lines	Downregulation of inflamasommes Mechanism of action	[193]
(-) Epigallocatechin-3-gallate monoesters	Colorectal carcinoma	*In vitro* human cell lines	Inhibition of cell proliferation Apoptosis induction Reduction in hydrogen peroxide production	[194]
Epigallocatechin-3-gallate	Metachronous adenomas of the colorectum	Epidemiological studies	*Ongoing*	[196]
	Breast carcinoma	Epidemiological studies	*Ongoing*	[197]
	Lung carcinoma	Epidemiological studies	*Ongoing*	[198]

regulator of translation initiation) [192]. Ellis *et al*. [193] uncovered the underlying EGCG-induced melanoma inhibition mechanism by using EGCG against melanoma cancer cell lines. According to these authors, the downregulation of inflamasommes (multiprotein oligomer) decreases the secretion of IL-1β (a cytokine) which in turn decreases the activity of NF-kB that finally reduces cell growth. (-) Epigallocatechin-3-gallate monoesters (EGCG-C4, EGCG-C8 and EGCG-C16) were synthesized by Matsumura *et al*. [194] in order to overcome the poor stability of EGCG. *In vitro* studies pointed out a better stability for EGCG-C16 by inhibiting cell proliferation, inducing apoptosis and less production of hydrogen peroxide against colorectal carcinoma. Likewise, in murine models this compound was the most potent in tumor reduction. The undeniable contribution of EGCG has been gathered and reviewed by Singh *et al*. [195] describing that EGCG could fight cancer through various mechanisms, namely an antioxidant potential, induction of apoptosis and cell cycle arrest, effect against phase I and II enzymes, modulation of intracellular signaling cascades, inhibition of epigenetic modifications, inhibition of dihydrofolate reductase and telomerase, inhibition of angiogenesis, modification of miRNA expression and other miscellaneous mechanisms. The chemopreventive and anticancer effects of epigallocatechin-3-gallate have also been assessed through clinical trials, against metachronous adenomas of the colorectum, breast and small cell lung cancer [196-198].

4.9.4. Isoflavones

Genistein and daizedin are the major compounds of the isoflavones and have been described as having antitumor activity and sensitizing effects (Table **13**). Genistein, the most common

compound in soy has been tested against prostate cancer cell lines, and resulted in inhibition of cell proliferation in a dose dependent manner as well as upregulation of glutathione peroxidase and downregulation of apoptosis inhibitors and DNA topoisomerase [199]. Murine models have also been used to assess the effects of genistein. Wang *et al*. [200] attempted to describe the effects to lifetime exposure of different doses of genistein (0, 25 and 250 mm/kg body weight) in rats. These concentrations were given to rats for 11 months, after which they were injected with N-methylnitrosourea to induce prostate cancer. The rats which had consumed the higher dosage of genistein had less prostate and other tumor incidence when compared to the control ones. Another remarkable effect of genistein is the capacity to sensitize tumors for other anticancer medication like gemcitabine and cisplatin, namely against pancreatic, ovarian and cervical cancers. In addition, it also potentiated the effects of TRAIL [201-205]. In 2008, Banerjee *et al*. [206], reviewed the *in vitro* targets of genistein in apoptosis, cell cycle arrest and transcription factors as well as the effects of angiogenesis, metastasis and sensitizing effects, based on previous studies. Two more reviews were published regarding the effect of genistein on cancer, revising the *in vitro*, *in vivo* and clinical trials in which this compound has been involved. Both indicate that despite the remarkable effect of this compound on *in vitro* and *in vivo* assays, clinical trials have failed to come up with standardized methods to test this compound, making it difficult to draw satisfactory conclusions and urging researchers to rethink and design common clinical trials for this natural compound [207, 208]. The clinical trials against cancer using genistein studied both the joint activity of genistein with other drugs (gemcitabine and

Table 13.   Isoflavones with reported antitumor activity.

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Genistein	Prostate carcinoma	*In vitro* human cell lines	Proliferation inhibition Downregulation of apoptosis inhibitor	[199]
		In vivo murine models	Less incidence of prostate cancer and other carcinomas	[200]
Genistein + Gemcitabine	Pancreatic carcinoma	*In vitro* human cell lines *In vivo* murine models	Growth inhibition Apoptosis	[206]
			Downregulation of NF-kB	[202]
Genistein + Cisplatin	Ovarian carcinoma	*In vitro* human cell lines	Inhibition of survivin	[203]
	Cervical carcinoma	*In vitro* human cell lines	Inhibition of NF-kB Inhibition of Akt/mTOR pathways	[204]
Genistein + TRAIL	Glioma	*In vitro* human cell lines	Facilitation of TRAIL-mediated apoptosis	[205]
Genistein + Gemcitabine	Breast carcinoma	Epidemiological studies	*Undisclosed results*	[209]
Genistein	Bladder carcinoma	Epidemiological studies	*Undisclosed results*	[210]
	Breast carcinoma	Epidemiological studies	*Undisclosed results*	[211]
Genistein + Gemcitabine Genistein + erlotinib	Pancreatic carcinoma	Epidemiological studies	*Undisclosed results*	[213]
Genistein	Prostate carcinoma	Epidemiological studies	*Undisclosed results*	[214]
Genistein + Quercetin		Epidemiological studies	*Ongoing*	[215]
Genistein	Bladder carcinoma	Epidemiological studies	*Ongoing*	[216]
Genistein + Gemcitabine	Lung carcinoma	Epidemiological studies	*Ongoing*	[217]
Genistein + Interleukin-2	Melanoma Kidney carcinoma	Epidemiological studies	*Ongoing*	[218]
Daidzein	Breast carcinoma	*In vitro* human cell lines	Cell proliferation inhibition G1 and G2 phases arrest	[219]
	Prostate carcinoma	*In vitro* human cell lines	Angiogenesis inhibition	[220]
Daidzein	Colon carcinoma	*In vitro* human cell lines	Caspase-3 activity increase Cell growth inhibition	[221]
	Breast carcinoma	*In vivo* murine models	Tumor inhibition Apoptosis	[222]
	Mammary carcinoma	*In vivo* murine models	Reduction in tumor multiplicity, incidence, burden and latency	[223]

erlotinib) and the pharmacokinetics of this drug, along with the traditional trials against bladder, breast and pancreatic cancer [209-213]. Currently, on-going clinical trials are studying genistein against prostate, bladder, lung and kidney cancers, as well as melanoma [214-218].

Daidzein has also been studied against cancer, but to a shorter extent when compared to genistein. It has shown *in vitro* activity against breast cancer by inhibiting proliferation in G1 and G2 phases and increase in caspase-9 activity [219]. Similar activity was detected both for prostate and colon cancer, this last one being one of the most common cancers in the world, with poor response too chemotherapeutic agents [220, 221]. Mammary human xenografts have also been sensitive do daidzein,with tumor inhibition and apoptosis described [222]. The preventive capacity of this compound was assessed by Constatinou *et al.* [223] by joining it with tamoxifen and administrating it to mice with induced mammary tumors. The authors concluded that this mixture reduced tumor multiplicity by 76%, incidence by 35%, tumor burden and latency by 95% and 62%, respectively. These favorable results haven't been translated into extensive clinical trials.

4.9.5. Flavanones

The anticancer potential of flavanones hasn't been studied to the same extent as the other flavonoids, although some activity has been reported, especially on hesperidin and 2'-OH flavanone (Table **14**). Itiogawa *et al.* [224] carried out a screening of 10 flavanones (Sophoraflavanone-B, Senegalensein, Amorilin, Euchrestaflavanone-A, Lupinifolin, Lupinifolinol, Paratocarpin-I,

Erythrisenegalone, Citflavanone and Yukovanol) against human Raji cells infected with Epstein-Barr virus (EBV). This virus is associated with a high risk of various cancers. All the flavanones exhibited inhibitory effect against the infected cells without showing toxicity towards the normal cells. Furthermore, in murine models, only lupinfolin showed tumor inhibition against the induced tumors. Another screening involving Raji cells infected with EBV and flavanones (Munduleaflavanone A, Prostratol F and 40-*O*-Geranylnaringenin among others) resulted in inhibition of infected cells proliferation in a dose dependent manner [225]. Hesperidin, one of the most studied flavanones has been described as an *in vitro* inhibitor of human nasopharyongeal carcinoma epithelial cells and mammary carcinoma cell lines by arresting cell growth, inducing apoptosis and expressing caspase-3 [226, 227]. Shen *et al.* [228], carried out *in vitro* and *in vivo* studies with 8 flavanones (2'-OH flavanone; 4'-OH flavanone; 6-OH flavanone; 7-OH flavanone; Naringenin; Nargin and Toxifolin) against various cell lines of human colon adenocarcinoma. The *in vitro* study pointed out excellent inhibition constants for 2'OH flavanone and apoptosis *via* caspase-3 and very little toxicity towards sane cells. Murine models were used to induce colon adenocarcinoma, and after tumor growth, flavanones were administered. 2'-OH Flavanone was once again the compound with the highest inhibition rates by triggering apoptosis and increasing p21. A very similar study was carried out by Hsiao *et al.* [229] in 2007, where various flavanones were screened against human lung adenocarcinoma, Lewis lung adenocarcinoma, murine lung adenocarcinoma, human gastric epithelial adenocarcinoma and human hepatocellular

adenocarcinoma. Once again the 2'-OH flavanone was the best inhibitor of all the cancer cell lines by arresting the cell cycle and promoting the reduction of cyclin B, D and Cdc2 (proteins that control progression of cells through the cell cycle). The authors then tested this compound in nude mice with Lewis lung tumors. After 8 and 17 days, the mice treated with the flavanone displayed smaller tumors than the control group.

The authors are unaware of any finished or ongoing anticancer clinical trials using flavanones as drugs, this may be due to the little reports of *in vitro* and murine assays regarding this group of flavonoids. Although, as stated above there are some interesting results regarding hesperidin and 2'-OH flavanone; more studies regarding these compounds should be carried out.

4.9.6. Anthocyanidins

Various compounds of this family have also been thoroughly studied for anticancer properties (Table **15**). Many of them have exerted chemotherapeutic properties both *in vitro* and *in vivo*.

Table 14. Flavanones with reported antitumor activity.

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Sophoraflavanone-B Senegalensein Amorilin Euchrestaflavanone-A Lupinifolin Lupinifolinol Paratocarpin-I Erythrisenegalone Citflavanone Yukovanol	Human Raji cell line	*In vitro* human cell lines *In vivo* murine models	EBV inhibitory effect	[224]
Munduleaflavanone A Prostratol F 40-*O*-Geranylnaringenin	Human Raji cell line	*In vitro* human cell lines	EBV inhibitory effect	[225]
Hesperidin	Nasopharyngeal carcinoma	*In vitro* human cell lines	Cell division inhibition Apoptosis	[226]
	Mammary carcinoma	*In vitro* human cell lines	Acumulation of p53 Expression of caspase-3 Cell proliferation inhibition	[227]
2'-OH flavanone 4'-OH flavanone 6-OH flavanone 7-OH flavanone Naringenin Nargin Toxifolin	Colon carcinoma	*In vitro* human cell lines *In vivo* murine models	Caspase-3 induction Apoptosis Tumor growth inhibition	[228]
2'-OH flavanone 4'-OH flavanone 6-OH flavanone Naringin Naringenin	Lung carcinoma Murine lung carcinoma Gastric carcinoma Hepatocellular carcinoma	*In vitro* human cell lines *In vivo* murine models	Cell cycle arrest Reduction of cyclin B, D and Cdc2 Tumor reduction	[229]
Peonidine-3-glucoside	Lung carcinoma	*In vitro* human cell lines	Mobility and invasion reduction Metalloproteinases reduction	[236]
Cyanidin-3-glucoside	Murine skin carcinoma Human lung carcinoma	*In vitro* human cell lines *In vivo* murine models	Inhibition of cell proliferation Tumor size reduction Metastasis inhibition	[237]

Table 15. Anthocyanidins with reported antitumor activity.

Compound	Type of Tumor	Type of Assay	Result Summary	Reference
Delphinidin	Prostate carcinoma	*In vitro* human cell lines *In vivo* murine models	Cell growth inhibition Caspase mediated apoptosis Tumor size reduction	[230]
Delphinidin-3-sabubioside	Leukemia	*In vitro* human cell lines	Caspase -3, -8 and 9 activation Apoptosis	[231]
Cyanidin-3-rutinoside Cyanidin-3-glucoside	Lung carcinoma	*In vitro* human cell lines	Dose dependent inhibitory effect	[232]
Glibenclamide	Gastric carcinoma	*In vitro* human cell lines	Cell viability reduction Apoptosis	[233]
Cyanidin-3-*O*-glucoside	Gastric carcinoma	*In vitro* human cell lines	Reduction of cell proliferation Morphological changes	[234]
Delphinidin Cyanidin	Colorectal carcinoma	*In vitro* human cell lines	Generation of ROS Inhibition of glutathione reductase	[235]
Peonidine-3-glucoside	Lung carcinoma	*In vitro* human cell lines	Mobility and invasion reduction Metalloproteinases reduction	[236]
Cyanidin-3-glucoside	Murine skin carcinoma Human lung carcinoma	*In vitro* human cell lines *In vivo* murine models	Inhibition of cell proliferation Tumor size reduction Metastasis inhibition	[237]

Delphinidin demonstrated a caspase mediated inhibition of cell proliferation and apoptosis against prostate cancer cell lines [230] while its derivative, delphidin-3-sambubioside demonstrated a ROS (Reactive Oxygen Species) mediated apoptotic effect against leukemia cell lines as well as activation of caspase -3, -8 and -9. [231]. Lyanin-3-rutinoside and cyaniding-3-glucoside exhibited a migration and invasion inhibition on lung carcinoma cell lines [232]. Glibenclamide was able to reduce cell viability while inducing apoptosis by ROS dependent JNK enzymes against *in vitro* human carcinoma [233]. Sun *et al.* [234] isolated cyaniding-3-*O*-glucoside from *Myrica rubra* and tested it against 3 types of gastric carcinoma cell lines, resulting in reduction of cell proliferation, typical apoptosis morphological changes in dose dependent manners. Two studies published in 2010 proved the anticancer effect of delphinidin, cyaniding and peonidin-3-glucoside against colorectal and lung carcinoma with satisfactory results [235, 236]. Ding *et al.* [237] in the first anticancer *in vivo* experiment with anthocyanidins used cyanidine-3-glucoside against human lung adenocarcinoma, displaying satisfactory results for the preliminary assays, with inhibition of cell proliferation and complete blockage of cell growth for 40 µM. The authors, inspired by the good results, later induced skin tumors in mice, using 12-O'-tetradecanolyphorbol-13-acetate and subsequently treated them with cyaniding-3-glucoside which proved to reduce tumor size and inhibition of metastasis. Hafeez *et al.* [230] also conducted assays on murine models implanted with prostate cancer cells, which later developed into tumors. Delphinidin decreased the tumor size and reduced the expression of NF-kB/65 nuclear translocation and NF-kB DNA binding activity. Despite few results regarding anthocyanidins as chemotherapeutic compounds, the effectiveness is quite remarkable and further *in vivo* studies should be carried out. To this date, the authors are unaware of any clinical trials regarding anthocyanidins, possibly due to few results from *in vivo* experiments.

5. CONCLUSION

Mankind has come a long way in the fight against cancer. The improvement of many therapies allied to the development of new drugs and treatments have assured in some cases the treatment or cure for certain cancers and a longer life span of patients. Yet, the long battle is far from over, especially due to incorrect food habits from the populations, along with an increase in smoking and pollution. Cancer cases are expected to increase in the near future, posing a threat for people across the globe as well as for governments who will have to waste astronomical funds for treatments if effective ones are not uncovered.

In some cancer cases, synthetic drugs or surgery can eradicate the threat, but highly metastasizing and drug resistant strains keep escaping treatments. The toxicity of synthetic compounds is also difficult to overcome, eliminating promising drugs from eventual administration. Natural compounds, isolated from plants or synthesized in a laboratory can be administered to patients, usually without the side effects and toxicity of synthetic preparations. These compounds can even be added to chemical preparations to increase their effect or to display a sensitizing action. Some natural compounds have been administered with success and are case studies for further applications. One of the main problems with natural compounds is the high cost and delay of compound separation and isolation even before the biological activity being assessed [238], resulting in the waste of considerable amounts of money in compounds that will not have any activity. When the compound is finally isolated the first step to determine its anticancer properties is a screen against cell lines. This type of assay is not free of disadvantages; in fact, some authors report that cell cultures maintained in the same conditions may be altered over time, resulting in "thousands of misleading studies and potentially erroneous papers published" [239]. This phenomenon is transversal to all types of cell cultures, including the cancer cell lines.

The main preliminary study before anticancer compounds are trialed in humans, are murine models. Several considerations should be assessed before conclusions are drawn, namely on the species selected for the study, type of tumors, correct definition of the endpoints and an appropriate statistical evaluation of tumor growth [240]. These steps should not be overlooked in order to provide consistent data regarding the biological activity against specific tumors in further human trials. If a compound has proven satisfactory results in animal models it can then be tested on humans. Although this is the final step in terms of trials for a compound to be readily available for the public it is also the most complicated step. The fact that the trials are carried out in humans requires extra caution in ethics and a well-designed procedure (doses, duration of treatment, concentration, placebos) to eliminate variables that would interfere in the real outcome of the treatment, moreover, it can be difficult to gather specific patients that suffer from the same type of cancer to have enough statistical significance. With all these drawbacks and pitfalls in anticancer treatment is there any hope against cancer? In terms of classic treatments with synthetic compounds, the evolution of technology will bring better and more effective therapeutics, so yes there should be hope. The awareness of the scientific community about the limitations and improvement areas in cancer therapy will surely overcome today's limitations in the near future. Regarding natural compounds, namely phenolic compounds, and considering that only 20% of the world's plants have been investigated [241] it is legitimate to think that many more compounds will be discovered, and in those compounds, many anticancer molecules could be found. Hope can also come from other matrixes, like mushrooms, microbes and marine organisms which are now targets of intense research for chemopreventive and chemotherapeutic anticancer molecules [242, 243].

Attending to the expected growing cases of cancer cases, research around this topic is also expected to increase, both on the mechanisms of cancer development and consequent methods to treat it. Funding for cancer research should be taken seriously, in order to reduce costs of treatments, patient suffering and mortality statistics. Mankind has come a long way in cancer therapy, but the road ahead is still full of challenges and opportunities.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest regarding this manuscript.

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