



## HOW DO PHENOLIC COMPOUNDS ACT IN THE PREVENTION AND TREATMENT OF CANCER?

### ARTIGO DE REVISÃO

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### ABSTRACT

Cancer is the transformation of healthy cells into tumor cells in a multistage process that can affect any organ of the body. This disease is the second leading cause of death globally. There are now more than 10 million cancer cases per year worldwide, and the most common occurs in the lung, breast, and colon. Several studies demonstrate that lifestyle and eating habits are directly related to tumor cells' appearance, such as high body mass index, low fruit and vegetable intake, lack of physical activity, and tobacco and alcohol use. It is widely believed that diet and nutrients can act as cancer risk-modifiers throughout the process of carcinogenesis, including initiation, promotion, progression, and/or conversion. Different plants have been the source of therapeutic agents. Plant-derived compounds have become indispensable for modern pharmacotherapy, and phenolic compounds are one of the most investigated due to their antitumor activity. Their cellular targets and mechanisms are compiled in the present work. Phenolic compounds are secondary metabolites present in large quantities in medicinal herbs and dietary plants (e.g., fruits, vegetables, and spices). They possess a diverse range of beneficial biological activities, which contribute to their potent effects on inhibiting carcinogenesis. Some benefits include cell proliferation and angiogenesis inhibition and anti-inflammatory, antioxidant, and antimetastatic



activities. Thus, the present review supports the recommendations for consuming foods and drinks rich in phenolic compounds to prevent and possibly treat cancer.

Keywords: Anticancer action, Cancer prevention, Secondary metabolites, Medicinal plants.

## 1. INTRODUCTION

Cancer is a growing health problem worldwide and is the second leading cause of death after heart disease. According to a recent report by the World Health Organization (WHO), from 18 million cancer cases worldwide in 2018, almost 50% resulted in deaths. An estimate suggests that there will be more than 23 million new cases of cancer and more than 13 million cancer-related deaths worldwide by 2030 (INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, 2020). This steady increase in case numbers highlights the urgency of increasing the efforts to promote cancer-prevention initiatives.

Cancer is a generic term to describe a set of diseases marked by an autonomous and rapid expansion of a somatic clone. Carcinogenesis (i.e., cancerous tissue development) is a complex phenomenon, which can be classified into three major steps: initiation, promotion, and progression. Tumor initiation is a quick process related to exposure to carcinogenic agents (how they are distributed into the cells and their interaction with DNA), which results in genotoxic effects. Cancer promotion is a prolonged and reversible stage related to the proliferation of cancerous cells. The last stage is progression, which corresponds to tumor cells' invasion, growth, and metastasis (STEWART and BROWN, 2013). Cancerous cells activate multiple cellular pathways that allow them to modify the microenvironment in its favor and overcome cellular limitations of proliferation, development, and immune surveillance (HANAHAN and WEINBERG, 2011).

The transformation of healthy cells into tumor cells arises from a combination of environmental and genetic factors. However, it is widely known that prolonged use



of tobacco, alcohol abuse, some infectious diseases, poor dietary habits, and a sedentary lifestyle are risk factors (WU *et al.*, 2018).

The association between nutrition and health promotion is a broad and challenging subject. Though there is a sharp increase in adopting healthy habits, driven mainly by social media, poor dietary habits are still considered a significant risk factor for cancer development. Evidence relating nutrition to cancer is shown in several works, including animal, analytical epidemiology, and population behavior studies (MAYNE *et al.*, 2016). Bioactive compounds present in food have affected critical aspects of cell growth, development, and metabolic processes. In addition, food nutrients may act alone or in combination, promoting carcinogenesis inhibition and adequate cellular processes such as apoptosis and differentiation (CHAN *et al.*, 2018).

Medicinal plants are the subject of intense research for their diverse and biologically active secondary metabolites and derivate compounds. Phytochemicals bearing an aromatic ring and one or more hydroxyl groups are called phenolic compounds, to which more than 8,000 compounds have been identified (TUNGMUNNITHUM *et al.*, 2018). When compared to conventional chemotherapy, many of these phytochemicals have yielded promising results in cancer therapy while reducing adverse effects. Therefore, medicinal plants have become an indispensable tool for the pharmaceutical industry and cancer treatment.

This review will discuss the importance of phenolic compounds in cancer treatment and prevention, highlighting their mechanism of action.

## **2. CONVENTIONAL CANCER TREATMENTS**

Conventional cancer treatments involve surgery, radiation therapy, medications, and other interventions to remove, shrink, and stop cancer progression. They are



divided into primary (focuses on removing cancer by surgery, radiotherapy, or chemotherapy), adjuvant (kill any cancer cells that may have remained), and palliative (help attenuate the adverse effects of the previous treatment steps) treatments.

Antitumoral drugs used in chemotherapy are cytotoxic and can be used alone or in combination. The cytotoxic agents rapidly kill dividing cells by binding to mitosis components and/or DNA replication machinery. The second class of drugs targets specific pathways that are essential for cancer survival and spreading. The most common mechanisms of action are alkylating agents, topoisomerase inhibitors, tubulin binding agents, and antimetabolites (SINGH *et al.*, 2016). Alkylating agents are compounds that transfer an alkyl group to a guanine base of DNA, preventing the double helix's strands from correctly binding, causing cross-linking and ruptures. Topoisomerase inhibitors stop DNA replication, RNA transcription, and repair of DNA damage. Tubulin binding agents affect cell mobility and division. These compounds inhibit cell mitosis by binding to tubulin during mitotic spindle formation and prevent the polymerization and depolymerization in the microtubules. The antimetabolites chemotherapy agents act as purine and pyrimidine analogs that affect DNA replication, resulting in cell death.

Although these chemotherapy agents have been used with great success, they induce several adverse effects (HAUNER *et al.*, 2017). The major problem is the lack of discrimination between healthy and cancer cells. Several cells in our body proliferate quickly and have metabolic rates similar to tumor cells. Chemotherapy medications target cells that divide rapidly and have intense metabolisms, such as bone marrow, heart, hair follicle, and digestive tract cells. Consequently, patients under these medications deal with cardiac problems, immunosuppression, chronic inflammation, and hair loss.

The high dosages needed to affect cancer cells aggravate the adverse effects and induce resistance to available drugs, reducing the rate of success (MANSOORI *et*



*al.*, 2017). Therefore, chemotherapy researchers are trending to develop more cancer-specific medications with fewer adverse effects. In this sense, bioactive compounds present in plants are a good source of new compounds with such characteristics. The development of new medicines extracted from natural compounds represents one of the most promising fields of the pharmaceutical industry. There has been an increasing thrust for identifying and isolating natural molecules that exhibit inhibitory properties towards tumor growth and metastasis (CHOUDHARI *et al.*, 2020). These natural products have been vital for the development of multi-agent treatment regimens currently employed in cancer chemotherapy, which are used in the treatment of a variety of malignancies.

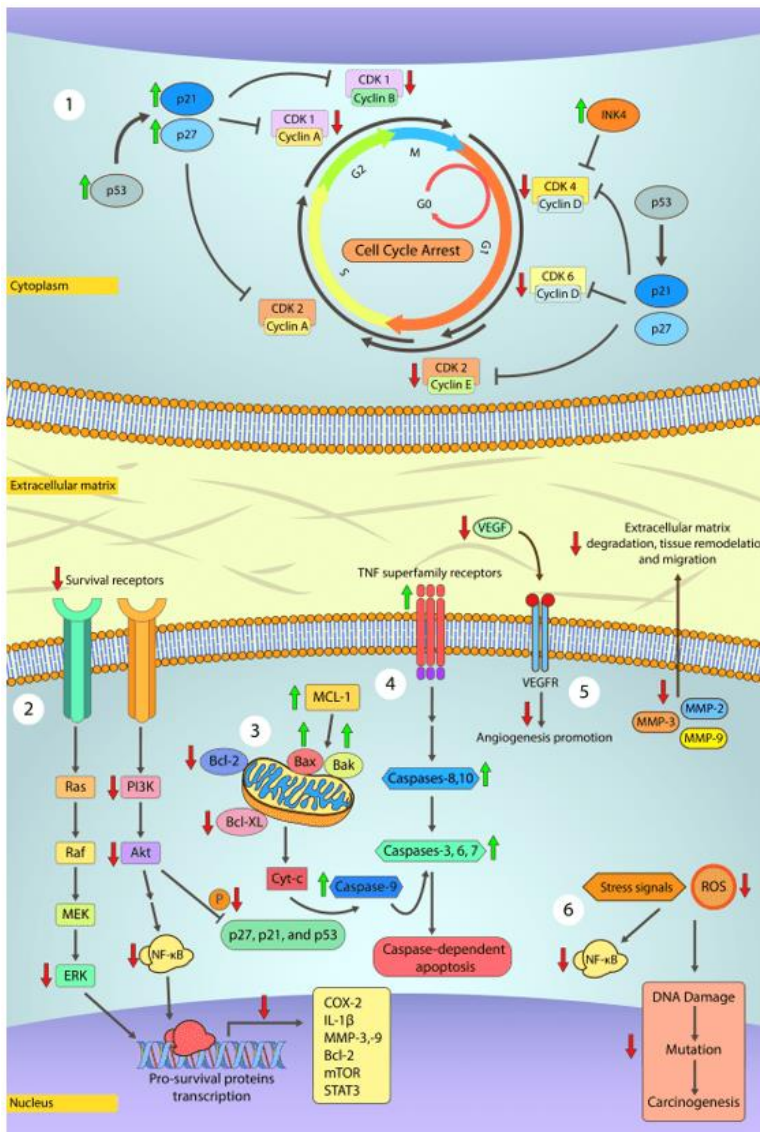
### 3. PHENOLIC COMPOUNDS AND CANCER

Phenolic compounds are secondary metabolites that have an aromatic ring bearing one or more hydroxyl groups. They have been subdivided into phenol carboxylic acids, flavonoids, tannins, coumarins, lignans, quinones, stilbenes, curcuminoids, chalcones, and alkaloids (GAN *et al.*, 2019). Phenolic compounds are especially found in medicinal plants, which account for a significant part of their pharmacological properties. More than 8,000 phenolic compounds have already been reported (COSTEA *et al.*, 2018).

Prior researches have demonstrated that the beneficial effects of dietary phenols include antioxidant, anti-inflammatory, and anticlastogenic activities (VELU *et al.*, 2018). Several studies have tested the ability of crude extracts rich in phenolic compounds or fractions containing a mixture them to inhibit cancer progression and development, both *in vitro* and *in vivo* (KUETE *et al.*, 2016, MULLER *et al.*, 2019; RAHAIEE *et al.*, 2020). Given the great structural diversity of bioactive plant-derived compounds, defining structure-activity relationships is difficult to deduce their underlying molecular mechanisms (KAPINOVA *et al.*, 2018).

However, the anti-carcinogenic effects of phenolic compounds are primarily due to the ability to induce cell cycle arrest, inhibit oncogenic signaling cascades of cell proliferation, angiogenesis, and stimulation of apoptosis (Figure 1). Besides that, phenolic compounds also modulate ROS levels and pro- and anti-inflammatory cascades, promote transcription of tumor suppressor proteins such as p53, and help cell differentiation and correct development (SINGH *et al.*, 2016; CHOUDHARI *et al.*, 2020).

Figure 1. Main steps at which polyphenols may treat cancer.





- 1) Polyphenols may act upon cell cycle progression by interfering with the expression and activity of many proteins in different stages. Polyphenols such as resveratrol, genistein, quercetin, and epigallocatechin-3-gallate induce the upregulation of p53, a tumor suppressor effector. p53 upregulation leads to DNA repair. In case of failure in this step, p53 binds directly to p21 (prevents cells from shifting from G1 to S phase, results in cell accumulation in phases G0/G1), p27 (involved in cell cycle arrest) (Directly binds to Cyclin/CDK complexes - inhibitors) and Bax (p53-dependent apoptosis promoter) genes promoters, resulting in increased expression. Polyphenols may also induce p21 and p27 expression by p53-independent pathways. Both p21 and p27 may arrest the cell cycle in different steps by interfering with Cyclin/CDK complexes formation and reducing the expression of CDK 2, 4, and 6; and cyclins A, D, and E.
- 2) MAPK and PI3K/Akt pathways are both related to cancer cell proliferation, survival, differentiation, and motility. In general, MAPK and PI3K/Akt pathways are constitutively activated in human cancer and lead to the activation of pro-survival genes, namely COX-2, IL-1b, MMP-2,3,9 (cleave of extracellular matrix components, growth factors, and cell adhesion proteins; allow migration, invasion, metastasis, and angiogenesis), Bcl-2 (antiapoptotic protein) and mTOR (regulates protein synthesis, cell growth, and proliferation). Inactivation of Akt pathway prevents the phosphorylation of p27, p21, and p53 proteins, previously described as cell cycle controllers. Prior studies have shown that some polyphenols like Gambogic acid and Epigallocatechin gallate arrest MAPK and PI3K/Akt downstream signaling.
- 3) Apoptosis is a tightly controlled process in most cells and is critically important for life and maintaining homeostasis. Conversely, cancer cells fail to undergo programmed cell death. Polyphenols may promote apoptosis in cancer cells by inducing the release of cytochrome c from mitochondria, activation of caspases-3, -8, and -9 while downregulating Bcl-2, Bcl-XL expression via modulation of NF- $\kappa$ B signaling.
- 4) TRAIL is a death ligand from the TNF superfamily and is implied in transducing



*apoptosis signals in cancer cells without harming normal cells. Alongside TRAIL, other members of this superfamily, e.g., FasL/FasR, TNF- $\alpha$ /TNFR1, and Apo3/DR3, are the best-characterized ligands. Polyphenols may act upon such ligands and increase their sensitivity and transcription via p53 downstream signals. These ligands, upon activation, recruit cytoplasmic adapter proteins that signal and initiate the intrinsic apoptotic pathway by activating caspase-8, which in turn activate caspase-3 to initiate cell degradation. Caspase-8 also promotes the release of cytochrome c in the intrinsic pathway.*

*5) Angiogenesis is a key process characterized by sprouting novel blood vessels that allow cancer cells to grow rapidly and metastasize. VEGF is the main regulator of angiogenesis and is upregulated by NF- $\kappa$ B. Several polyphenols like luteolin and resveratrol have been shown to reduce VEGF expression and secretion.*

*6) At high concentrations, free radicals pose as a risk for cell functionality. Free radicals damage cell structures and biomolecules, especially DNA, which can result in the development of cancer and many other health issues. Due to the intense metabolism in cancer cells, free radicals production occurs at a higher rate. In general, polyphenols are able to scavenge and neutralize free radicals avoiding further damage to neighboring cells.*

*Source: Own authorship (2020).[/caption]*

Resveratrol, a phytoalexin able to trigger anti-proliferative and pro-apoptotic mechanisms, serves as an excellent example of the impacts of administering phenolic compounds to treat diseases. The main actions are modulation of pro-oncogenic miRNAs and tumor suppression; NF $\kappa$ B, PPAR, PGC1 $\alpha$ , NRF1,2, p53 transcription factors, and TGF $\beta$  signaling targeting pathways (WRIGHT *et al.*, 2017; FERRAZ DA COSTA *et al.*, 2018; SUN *et al.*, 2019). In a computational study, resveratrol and some derivatives targeted the  $\alpha$ v $\beta$ 3 integrin receptor, which could result in a blockade of cell proliferation and migration (HO *et al.*, 2018). Subbaramaiah and coworkers showed that the mixture of several dietary polyphenols from Zyflamend®, including resveratrol, EGCG, and curcumin,





suppressed levels of pro-inflammatory mediators (TNF- $\alpha$ , IL-1 $\beta$ , COX-2, phospho-Akt, phospho-p65, NF- $\kappa$ B-binding activity) in the mouse model of obesity-associated mammary gland inflammation (SUBBARAMAIAH *et al.*, 2013). *Acacia hydaspica* R. Parker is known to possess several medicinal properties. Four active polyphenols, namely, 7-O-galloyl catechin, catechin, methyl gallate, and catechin-3-O-gallate, have been linked to inhibit cell growth and survival in prostate cancer (PC-3) and breast cancer (MDA-MB-231) cells. The polyphenols induced apoptosis by targeting various signaling factors such as PI3-K, JAK2, Akt-1, STAT3, MAPK (ERK1/2, pERK1/2), NF $\kappa$ B, Bcl-xL and survivin. Further, those compounds inhibited NF $\kappa$ B pathway activation, which are related to initiation and acceleration of tumorigenesis, suggesting its chemopreventive role (HOFFMANN and BALTIMORE, 2006; AFSAR *et al.*, 2016).

In some experimental studies, phenolic compounds acted upon angiogenesis, an important landmark for cancer progression and migration. Mojzis and coworkers used the Flavin7, a flavonoid complex supplement, in an *in vitro* testing and reported its antiangiogenic activity in HUVEC-lines (MOJZIS *et al.*, 2008). In another study, conducted by Huang *et al.* (2020) using the cell lineage SK-BR-3 of breast cancer, oregano flavonoids showed the ability to inhibit the growth of mammary tumor cells by suppressing of the VEGF/VEGFR-2, MMP3 and MMP9 signaling pathways (HUANG *et al.*, 2020).

The study from Martino *et al.* (2019) used a polyphenol rich extract from *Annurca* apple (APE) upon breast cancer MDA-MB-231 cell. Researchers treated the cells with APE and analyzed cell cycle progression by flow cytometry. Cellular population in phase G2/M increased significantly in treated cells by a p21-independent process. This is particularly important because p21 behaves like a dual regulator. Depending on the cellular type, p21 may suppress or promote tumor development. APE, like other polyphenols extract, acts upon a multitude of tumor-related pathways. In the same study, APE shown to inhibit ROS/NF- $\kappa$ B anti

apoptotic pathway and activated ROS/JNK pro-apoptotic pathway (MARTINO *et al.*, (2019). More mechanisms of action are described in the table bellow (Table 1).

Table 1. Representative compounds within the different subclasses of phenolic compounds and their respective molecular targets in the human organism.

Subclass	Compounds	Molecular targets
<b>Hydroxybenzoic acids</b>	3,4-Dihydroxybenzoic acid	Apoptosis mediated by Fas/FasL pathway (LIN <i>et al.</i> , 2007).  Upregulation of pro-apoptotic mediators (LIN <i>et al.</i> , 2007).
	Ellagic acid	Stimulate expression of caspases-3 and -9 and Bax (LIU <i>et al.</i> , 2017).  Reduce the expression of pro-inflammatory markers via NF-kB (LIU <i>et al.</i> , 2017).
		Inhibition of metastasis (LIU <i>et al.</i> , 2017).
		Reduce the expression of PI3K, metastasis and invasiveness (WANG <i>et al.</i> , 2019).
<b>Hydroxycinnamic acids</b>	Caffeic acid	Cell cycle arrest at G0/G1 phase and increase in caspases-1, -3 and -8, expression resulting in apoptosis (PELINSON <i>et al.</i> , 2019).
	Sinapic acid	Reduction in MMPs expression preventing metastasis, increase in apoptosis related effectors (Eroğlu <i>et al.</i> , 2018).
<b>Coumarins</b>	Fraxin	Cell cycle arrest (MENEZES and DIEDERICH, 2019; MOHAMED <i>et al.</i> , 2019;
	Auraptene	Activation of caspases-3 and -9 (ELSHEMY and ZAKI, 2017).
	Warfarin	
	Calanolide A	Antiproliferative effect (HAO <i>et al.</i> , 2019; GARG <i>et al.</i> , 2020)
	Novobiocin	Inhibition of NF-kB (YIN and YU, 2018; HASSANEIN <i>et al.</i> , 2020).
<b>Xanthones</b>	Mangostin	Downregulation of Cyclins/CDKs expression (LIU <i>et al.</i> , 2019; NAUMAN <i>et al.</i> , 2020).
	Desoxygartanin	
	Garcinone	
	1,5,8-trihydroxy-3-	Inhibition of angiogenesis and metastasis by



	methoxy xanthone	reducing the expression of VEGF and MMP-2 and -9 (BARUA <i>et al.</i> , 2020; KLEIN-JÚNIOR <i>et al.</i> , 2020). Inhibition of PI3k/Akt and ERK-dependent pathways (BARUA <i>et al.</i> , 2020).
<b>Chalcones</b>	Flavokawain B	Inhibition of CDKs and cell cycle arrest (BORTOLOTTA <i>et al.</i> , 2017).
	Lonchocarpin	Activation of Caspase pathway (BORTOLOTTA <i>et al.</i> , 2017).
	Chalcone-Indole derivatives	Upregulation of pro-apoptotic genes (BORTOLOTTA <i>et al.</i> , 2017).
	Chalcone-imide derivatives	
	Chalcone-quinoline derivatives	
<b>Stilbenoids</b>	Resveratrol	Cell cycle arrest via activation of p21 and p27 (HEO <i>et al.</i> , 2018).  Reducing the expression of the oncogenic microRNA, miR-221 NF-κB (WU and CUI, 2017).
	Piceatannol	Reduce the expression of p38, MAPK and c Myc; and cleavage of caspase-3 (LUCAS <i>et al.</i> , 2018; BANIK <i>et al.</i> , 2020).
<b>Lignans</b>	Sesamin	Increase the expressions of Bax and caspase-3; and inhibition of mTOR leading to autophagy (DEESRISAK <i>et al.</i> , 2020).
	Honokiol	Inducing the release of mitochondrial cytochrome c to cytosol  Regulation of EGFR signaling pathway (XIE <i>et al.</i> , 2016; YANG <i>et al.</i> , 2017)
<b>Lignins</b>	-	
<b>Flavonoids</b>		
<b>Flavones</b>	Apigenin	Cytotoxic effect via direct targeting of mitochondria, leading to increased ROS production and cytochrome c releasing (SALMANI <i>et al.</i> , 2017; WANG and ZHAO, 2017)
	Chrysin	Induction of Endoplasmic reticulum stress, inhibition of PI3k/AKT pathway and apoptosis mediated by activation of ERK1/2 MAPK and p38 MAPK pathways (RYU <i>et al.</i> , 2017).
	Luteolin	Increase in BAX/Bcl-2 ratio and cell cycle arrest at G1/S phase (LU <i>et al.</i> , 2017; ZHANG <i>et al.</i> , 2017).
<b>Flavonols</b>	Quercetin	Apoptosis and cell cycle arrest at phase G2/M induced by reactivation and increased expression of p53 (CHOU <i>et al.</i> , 2010; CLEMENTE-SOTO <i>et al.</i> , 2019)



	Kaempferol	Promotion of cell death via the IRE1-JNK-CHOP pathway (KIM <i>et al.</i> , 2018).
	Chrysofenolol	Increased and sustained ERK1/2 activation resulting in apoptosis (LANG <i>et al.</i> , 2020).
<b>Flavanones</b>	Hesperidin	Cell cycle arrest via downregulation of Cyclin D1 and upregulation of p21 and p53 (KAMARAJ <i>et al.</i> , 2019; AGGARWAL <i>et al.</i> , 2020).
	Eriodictyol	Induction of apoptosis mediated by inhibiting phosphorylation of PI3K, Akt, and NF- $\kappa$ B (LI <i>et al.</i> , 2020).
	Naringin	Increase the potency of chemotherapeutic agents
	Naringenin	Inhibits cell growth via inhibition of PI3K/AKT/mTOR signaling pathway (CHENG <i>et al.</i> , 2020; MEMARIANI <i>et al.</i> , 2020).
<b>Isoflavonoids</b>	Genistein	Cancer cells growth inhibition as a result of inhibiting Akt phosphorylation (GONG <i>et al.</i> , 2003).
	Vestitol	Downregulation of cancer related proteins (NANI <i>et al.</i> , 2018).
	Neovestitol	
	Puerarin	Cancer microenvironment modulation, allowing infiltration and activity of immune cells, and administration of chemotherapeutic agents (XU <i>et al.</i> , 2020).
<b>Anthocyanidins</b>	Malvidin	Induction of G1/S phase cell arrest and apoptosis  Activation of p38 MAPK and suppression of Akt, resulting in growth inhibition and apoptosis (LIN <i>et al.</i> , 2020).
	Cyanidin	Inhibition of NF- $\kappa$ B signaling molecules and activation of the protective pathway, Nrf2 (LEE <i>et al.</i> , 2020).

Source: Own authorship (2020).

## 4. ANTICANCER PROPERTIES OF PHENOLIC COMPOUNDS

### 4.1 HYDROXYBENZOIC ACIDS

Hydroxybenzoic acids compose a group of seven carbon molecules with a C6-C1 skeleton, which 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 to large molecules (CROZIER and CLIFFORD, 2006).

Tannins are a group of polymeric phenolic substances known to demonstrate promising antimicrobial activity through the inactivation of adhesins, cell envelope, enzymes, and different transport proteins (KY *et al.*, 2015). These compounds can be divided into two groups, namely hydrolyzable and condensed tannins. Most activities of the proanthocyanidins and hydrolyzable tannins, including antioxidant and free radical scavenging capacity, largely depend on their structure; for example, an increase in anti-radical effects was observed with an increase in the degree of polymerization (SIENIAWSKA, 2015). According to recent reports, the antimicrobial activity of plant extracts rich in gallotannin is attributed to the inactivation of membrane-bound proteins (FENG *et al.*, 2011).

More than 32 species in 112 tested traditional Chinese medicinal plants associated with anticancer contain tannin constituents, such as gallotannins (CAI *et al.*, 2004). It was observed in a study that a gallotannin-rich extract obtained from pods and seeds of *Caesalpinia spinosa* induces loss of mitochondrial membrane potential ( $\psi_m$ ), nuclei fragmentation, and caspase-dependent apoptosis *in vitro* in several tumor cells (CASTAÑEDA *et al.*, 2012). Ellagitannins represent an important class of phytochemicals that are being increasingly investigated for their chemopreventive and anticancer activities (ISMAIL *et al.*, 2016). Proanthocyanidins (GSPs) can be found in many plants, but this powerful compound is most abundant in the bark of the maritime pine and grapes. GSPs have demonstrated many biological properties in studies with grape seeds (AGUIAR *et al.*, 2014), including antioxidant and anticancer effects (GAO *et al.*, 2018).

The extract of the transformed root of *Leonurus sibiricus* was tested upon glioma cells (grades I-III). The extract rich in vanillic acid and gentisic acid, 4-hydroxybenzoic acid, 1,3-dicaffeoylquinic acid, and  $\alpha$ -resorcylic acid were able to impair mitochondrial membrane potential and an increase in ROS production.



Modulation of apoptosis-associated genes also triggered cell death. The extract induced apoptosis by reducing the expression of Bcl-2 and increasing the expression of Bax, p53, and caspases -3, -8, and -9 (SITAREK *et al.*, 2017). Gallic Acid (GA), another phenolic acid well known to possess a wide range of biological activities, have been tested with success upon several cancer cell lines, such as TE-2 (esophageal cancer), MKN-28 (gastric cancer), MDA-MB-231 (breast cancer), CaSki (cervix cancer), and HT-29 and Colo201 (colon cancer). In research conducted by Lee *et al.* (2017), GA induced different effects depending on the cell type. For MCF-7 (breast cancer), GA triggered cell-cycle arrest at phase G2/M but not apoptosis (FARIED *et al.*, 2007). However, for MDA-MB-231 cells, GA induced G1 phase arrest and apoptosis. The main mechanism involved in this action was up-regulation of p21 and p27, followed by downregulation of CDK-4 cyclin D1 and Cyclin E- CDK2 complexes (LEE *et al.*, 2017). In the work of Sánchez-Carranza *et al.* (2017), gallic acid was further tested upon cancer cell lines with high incidence and mortality, namely PC3 (prostate), HeLa, Ca Ski (cervical), Hep3B, and HepG2 (hepatocellular) carcinoma cells. In this study, GA induced cell cycle arrest at phases S and G2/M and increased the expression of PARP, Caspases-3, and -9, which, consequently, increase Bax expression (SÁNCHEZ-CARRANZA *et al.*, 2017). Therefore, several mechanisms of action are observed for different cell lines and forms of administration.

## 4.2 HYDROXYCINNAMIC ACIDS

Hydroxycinnamic Acids (HCAs) are naturally occurring compounds, and their alkyl esters may possess enhanced biological activities (MARTINI *et al.*, 2019). Structurally, hydroxycinnamic acids are hydroxy metabolites of cinnamic acid with a C6–C3 backbone. Subclasses of these acids include caffeic, caftaric, (neo)chlorogenic, cinnamic, coumaric, and ferulic acids (often linked with dietary fibers that form esters with hemicellulose), and curcumin. Dietary sources include apples and grapes (and their juices), blueberries, cereal grains and bran, cherries,



cinnamon (cinnamic acid), coffee, ginger, lettuce, olives, oranges, pears, pineapples, plums, potatoes, prunes, spinach, strawberries, sunflower seeds, turmeric, and select herbs (e.g., basal, marjoram, oregano, rosemary, sage, and thyme) (COSTAIN, 2001; SELMA *et al.*, 2009; MORENO-JIMÉNEZ *et al.*, 2019).

Caffeic acid (3,4-dihydroxycinnamic acid) is a phenolic compound widely distributed in medicinal plants, including fruits, vegetables, wine, coffee, olive oil, and others. Therefore, it is present in human plasma in a diet-dependent concentration (NARDINI *et al.*, 1998; MILES *et al.*, 2005). Based on the antioxidant and antiangiogenic effects of caffeic acid, retinal revascularization of Retinopathy Of Prematurity (ROP) could be a target for the pharmacological application of caffeic acid (KU *et al.*, 2016). Furthermore, caffeic acid has been shown to possess anti-inflammatory and protective effects against nickel-induced oxidative liver damage (NARDINI *et al.*, 2000; PARI and RASATH, 2008). Many studies have indicated that the reactive oxygen species scavenging and anti-inflammatory activities observed in herbs may be attributed to the various natural phenolic components (e.g., chlorogenic acid, caffeic acid, isoquercitrin, and quercetin) that have antioxidant effects (BOSE *et al.*, 2009; DAMASCENO *et al.*, 2017). In this context, these natural compounds' anticancer potential is confirmed since inflammatory processes and reactive species activity are closely associated with the origin and maintenance of various types of cancer (XU *et al.*, 2017).

Curcumin is a trending flavonoid described as chemosensitizing and that possesses a modulating role on signaling pathways involved in apoptosis, cell proliferation, tissue invasion, metastasis, and angiogenesis (MORTEZAEI *et al.*, 2019). The therapeutic benefits of curcumin have been demonstrated in multiple chronic diseases, such as inflammation, arthritis, metabolic syndrome, liver disease, obesity, neurodegenerative diseases, and, above all, in several cancers (GIORDANO and TOMMONARO, 2019). Curcumin anticancer properties arise from downregulating signaling pathways essential to cancer development and progression, which includes NF- $\kappa$ B, STAT3, Activated Protein-1 (AP-1), Epidermal



Growth Response-1 (Egr-1), cyclin D1, the antiapoptotic genes Bcl-2, Bcl-xL, Cyclooxygenase 2 (COX-2), and Matrix Metalloproteinase 9 (MMP-9) (GIORDANO and TOMMONARO, 2019). Despite its poor aqueous solubility and low bioavailability, curcumin has been the subject of many works due to its outstanding holotropic effect, being tested alone and in combination with conventional chemotherapy drugs. In addition, curcumin has been associated with nano-particulate delivery systems, improving monotherapy and yielding significant results to overcome the problems related to dosage and delivery.

An interesting case was the encapsulation of curcumin to a Glycyrrhetic Acid (GA)-modified chitosan-cystamine-poly( $\epsilon$ -caprolactone) copolymer (PCL-SS-CTS-GA) micelle for co-delivery of DOX and curcumin to hepatocellular carcinoma. In this work, curcumin was encapsulated in the form of a pH-sensitive drug (YAN *et al.*, 2016). After internalization, the contact with the acidic pH inside the tumor provokes the carrier to open and release curcumin and doxorubicin. This method resulted in a higher cytotoxicity effect than the individual drugs. More in-depth information about curcumin's nano-particulate delivery systems and its application can be found hereof (BATRA *et al.*, 2019).

### **4.3 COUMARINS**

Coumarins are a group of secondary metabolites characterized by a 2H-chromen-2-one-(1,2-benzopyrone, or 2H-1-benzopyran-2-one)-oxa-heterocycle, produced by many medicinal plants. This oxa-heterocyclic ring structure allows easy binding to several proteins, making coumarins and their derivatives great candidates for new drugs research (KAUR *et al.*, 2015). It is known that coumarins are able to establish strong interactions with many protein sites such as hydrophobic and  $\pi$ - $\pi$  stacking interactions with aromatic amino acids; binding to positively charged amino acids via cation- $\pi$  interactions; hydrogen bonds; and dipole-dipole interactions (REN *et al.*, 2018). Being the most studied pharmacological properties





of coumarins are antiviral, antimutagenic, antioxidant, anti-inflammatory, and anticancer (STEFANACHI *et al.*, 2018).

Coumarins and its derivatives are involved in different pathways in cancer, such as kinase inhibition, cell cycle arrest, angiogenesis inhibition, Heat Shock Protein (HSP90) inhibition, telomerase inhibition, antimitotic activity, carbonic anhydrase inhibition, monocarboxylate transporters inhibition, aromatase inhibition and sulfatase inhibition (GEISLER *et al.*, 2011; SAIDU *et al.*, 2012; LIN *et al.*, 2014; THAKUR *et al.*, 2015).

Current research focuses in modifying coumarins structure to yield compounds with enhanced anticancer properties. For example, coumarins substituted in position 4, originated strong antiproliferative compounds against breast carcinoma, A-549 human lung cancer, SKBr-3, MCF-7, HepG2, PLC/PRF5, and Huh7 (MORSY *et al.*, 2015; AN *et al.*, 2018; ZHANG *et al.*, 2021). In addition, coumarins may be hybridized with azoles, furoxans, imines, chalcones and dimerized. The hybridization process with other pharmacophores may improve affinity and activity, reducing adverse effects and overcoming drug resistance. This process may be viewed in details in a review produced by Zhang and Xu (2019).

#### 4.4 XANTHONES

Xanthones are secondary metabolites commonly occurring in a few higher plant families. Their high taxonomic value and their pharmacological properties, such as monoamine oxidase inhibition, anti-inflammatory, *in vitro* toxicity, and *in vivo* antitumor activity, have provoked great scientific interest (RUAN *et al.*, 2017). Chemically, xanthones (9H-xanthen-9-ones) are heterocyclic compounds with the dibenzo- $\gamma$ -pyrone framework. The xanthone nucleus is numbered according to a biosynthetic convention with carbons 1–4 being assigned to acetate-derived ring A and carbons 5–8 to the shikimate-derived ring B (FERNANDES *et al.*, 2019).



Xanthenes, similarly to coumarins, are considered privileged structures, which means that their structure allows the binding to several biological targets. Thus, these molecules have been modified and combined to other drugs to improve therapy success while reducing severe adverse effects. In literature, natural xanthenes, its synthetic or chemically modified compounds have provided good results in cancer therapy.

Gambogic acid is a natural xanthone found in *Garcinia maingayi* and *Garcinia morella* trees resin. The mechanisms involved in Gambogic acid anticancer are described in several reports being the ability of altering oncogenic genes expression, activation of apoptosis cascades, inhibition of telomerase activity, and cell cycle arrest, the most described properties. Ovarian cancer is a serious condition affecting many women around the world, causing more than 125,000 deaths, and a sharp increase in the number of cases. Conventional radiotherapy and chemotherapy used to treat many types of cancers, though effective, are less selective, highly wearing and followed by severe adverse effects. Evidence from previous works have shown that Gambogic acid is a highly selective anticancer agent that acts by inhibiting NF- $\kappa$ B, MAPK/ERK, and PI3K/AKT signaling pathways, and have been used by Tang et al. (2017) to treat ovarian cancer. Gambogic acid arrested the cell cycle of SKOV3 cells at phase G2/M and induced apoptosis mediated by caspases-3 and -9 activation. Also, gambogic acid inhibited the binding of p65 to DNA further reducing SKOV3 cells proliferation.

Mangiferin is another natural xanthone with a wide spectrum of anticancer properties, acting upon many cancer cell lines (IMRAN *et al.*, 2017). Mangiferin has been shown to suppress cyclin B1 and Akt phosphorylation, resulting in cell arrest at phase G2/M in SGC-7901 cells (DU *et al.*, 2018). In another work, mangiferin reduced the expression of Matrix Metalloproteinases (MMP) -2 and -9 in ovarian cancer cells (ZENG *et al.*, 2020). The high expression of MMPs observed in many cancer types, contributes to increase cancer invasiveness, metastasis and angiogenesis.



The relationship between form and biological activity is an ever-increasing research field. In special, chirality is considered one of the hottest topics in drug design, research and development. The study of enantiomers biological properties aids in the search for molecules with increased activity and with the capacity to overcome cancer resistance and evasion. Recently xanthonones derivatives and its modified forms are extensively studied regarding enantio-selectivity (CALCATERRA and D'ACQUARICA, 2018).

Xanthonolignoids consists a group of xanthonones bound to a phenylpropane core by a dioxane ring with pharmacological potential in cancer treatment. Synthetic kielcorins, a subclass of xanthonolignoids, have been evaluated *in vitro* upon MCF-7 (breast cancer), TK-10 (renal cancer), and UACC-62 (melanoma cell) cell lines (SOUSA *et al.*, 2002). It was observed that the growth inhibitory effect was dose-dependent and dependent of isomerism. Another interesting case is of psorospermin, isolated from the bark and roots of the African plant *Psorospermum febrifugum*. Psorospermin contain two stereogenic centers with four possible stereoisomers, all of which have antitumor activity and topoisomerase-II-dependent DNA alkylation. However, the (R,R)-isomer of psorospermin had a better performance (HEALD *et al.*, 2005). Further information regarding chiral modifications and derivatives of xanthonones may be found here (FERNANDES *et al.*, 2019).

## 4.5 CHALCONES

Chalcones are open-chain flavonoids with a common skeleton of 1,3-diphenylprop-2-en-1-one. Both naturally occurring and synthetic chalcones show an array of biological activities, including anti-bacterial, anti-viral, antioxidant, anti-inflammatory, immunosuppressive and anticancer activities (BUKHARI *et al.*, 2013; VENTURELLI *et al.*, 2016; GAONKAR and VIGNESH, 2017). Because of the simplicity of their chemical structures and their vast variety of actions, compounds



with chalcone-based structures are currently receiving a great deal of attention (ELKHALIFA *et al.*, 2019).

Several studies have demonstrated that chalcones can induce cancer cell apoptosis through effects on the extrinsic pathway (JANDIAL *et al.*, 2014). Tang and collaborators (2010) demonstrated that the chalcone flavokawain B (FKB) led to the up-regulation of DR5/TRAILR2 (death receptor 5/TRAIL receptor 2). This was accompanied by an increase in cytotoxicity *in vitro*, as well as decreased tumor growth *in vivo*. Notably, there was a minimal toxic effect on normal prostate epithelial cells (TANG *et al.*, 2010).

Lonchocarpin is a natural chalcone found in *Pongamia pinnata* (L.) Pierre, which have been shown to induce apoptosis in CEM leukaemic cell line (EL-GAMAL *et al.*, 2017), and more recently in lung cancer cells (CHEN *et al.*, 2017). Lonchocarpin was evaluated upon H292 cells and analyzed by 3D-QSAR to understand the mechanism underlying its apoptotic behavior. Data obtained indicates that lonchocarpin reduces the expression of Bcl-2 and upregulation of Bax, leading to activation of caspase-3. Further, lonchocarpin was shown to bind to BH3-binding groove of antiapoptotic proteins, contributing to caspase-3 activation and triggering apoptosis (CHEN *et al.*, 2017).

## 4.6 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 (CROZIER and CLIFFORD, 2006; FAUSTINO *et al.*, 2018).

Combretastatins are natural cis-stilbenes that are isolated from the bark of the African willow tree (*Combretum caffrum*). The most prominent representative of this group of compounds, combretastatin A-4 (3'-hydroxy-3,4,4',5-tetramethoxy-cis-



stilbene; CA-4) exerts high antimitotic and antiangiogenic activities. Presently, phase III clinical trials are underway to test the anticancer effects of a phosphate prodrug of CA-4 (CA-4P, also known as fosbretabulin; trade name Zybrestat). CA-4P is used alone or in combination with traditional chemotherapeutic agents or with radiotherapy (SIEMANN *et al.*, 2009; NAINWAL *et al.*, 2019).

Resveratrol (RSV) is probably one of the most well-known polyphenols, found in a relatively small number of plants (31 genera), and in small quantities. RSV is a member of the stilbene family, which is characterized by two benzene rings linked via isopropyl moiety separated by a double bond (KASIOTIS *et al.*, 2013). If the plant is attacked by pathogens or there is a high incidence of UV, RSV biosynthesis is increased. The historical paper of Pezzuto's research team about the anticancer properties of resveratrol paved the way to the discovery of a wide array of therapeutical mechanisms. Said work reported that RSV acted upon all stages of cancer development - initiation, promotion and progression - and mediated anti-inflammatory response (JANG *et al.*, 1997). Other works disclose many other beneficial properties such as antioxidant, improving circulatory health, antidiabetic and neuroprotector (ELSHAER *et al.*, 2018).

Despite the poor bioavailability and water solubility, RSV is a promising chemopreventive and chemotherapeutic agent. Many researches have shown the action of RSV in modulating several apoptosis related proteins such as the upregulation of PARP, Caspases, BAX, BID, BAK; and downregulation and/or degradation of antiapoptotic proteins, MCL-1, Bcl-XL, and Bcl-2, in several cancer cell lines (SINGH *et al.*, 2017). The cell cycle progression is further controlled by a series of signaling cascades that regulates DNA replication, division and proliferation of cells. The checkpoints G1, S and G2/M regulate DNA replication and cell fate, and are controlled by p53 as well as positive regulators (cyclin dependent kinases and cyclins) and negative regulators (p21<sup>WAF1/CIP1</sup>, p27<sup>KIP1</sup>). Resveratrol is implicated in the tumor suppressor p53 activation, leading to cell cycle arrest and apoptosis (SINGH *et al.*, 2017). Administration of resveratrol at



concentrations of 12.5 - 200  $\mu\text{mol/L}$  for 48 h resulted in significant inhibition of colorectal cancer stem cell HCT 116 proliferation (YANG *et al.*, 2015). Results shown an increased proportion of cells arrested in G0/G1 phase. Furthermore, RSV act as a chemo sensitization agent by increasing cisplatin cytotoxicity in CIS-resistant HCT-116 CRC cells (OSMAN *et al.*, 2015), and to promote a reduction of NF- $\kappa$ B activation and translocation, mediated by a suppression of I $\kappa$ B $\alpha$  phosphorylation and degradation (WRIGHT *et al.*, 2017). For more information regarding RSV anticancer mechanisms of action see here (ELSHAER *et al.*, 2018; RAUF *et al.*, 2018; VERVANDIER-FASSEUR and LATRUFFE, 2019).

#### 4.7 LIGNANS

Lignans are naturally occurring plant phenols that are derived biosynthetically from phenylpropanoids, are commonly referred to as dimers, with complex skeletons and characteristic chemical functions, but some are trimers or tetramers. The widely distributed lignans are important components of food and medicine that are derived from plants, and they have been target compounds for organic synthesis and biological-function research because of many types of bonding of the C6–C3 units, and oxidation of the structures (SUGAHARA *et al.*, 2008; GROSSO *et al.*, 2017).

Different types of lignans have considerable attention because of their pharmacological features such as the Platelet-Activating Factor (PAF) antagonistic, estrogenic, antifungal, antihypertensive, sedative, antioxidant and antitumor activities (SILVA and ALCORN, 2019). Enterolactone (EL) is a bioactive phenolic metabolite known as a mammalian lignan derived from dietary lignans, has been reported to reduce risk, decrease mortality rate and improve overall survival particularly in breast, prostate, colon, gastric and lung cancer (MALI *et al.*, 2019). Plants with high lignan contents have been used as folk medicine in China, Japan, and the Eastern World since ca. 1,000 years. Nowadays, their extensive use in traditional medicine makes lignans an important family of lead compounds for the



development of new therapeutic agents based on structural modifications (GORDALIZA *et al.*, 2004).

The famous tumor therapy drug podophyllotoxin (cyclo lignanolide) was first identified in *Podophyllum peltatum*, which Native Americans used to treat warts, and also found in a traditional medicinal plant *Podophyllum emodi var. chinense* (EFFERTH *et al.*, 2007). Sesamin, a lignan in sesame seeds (*Sesamum indicum*), possesses potent anticancer properties. The anticancer effects of sesamin have been mainly attributed to its anti-proliferative, pro-apoptotic, anti-inflammatory, antimetastatic, anti- and pro-angiogenic, and pro-autophagocytic activities (MAJDALAWIEH *et al.*, 2017).

Jun and collaborators demonstrated that aschatin, fargesin, liriorelinol B dimethyl ether and magnolin decreased mRNA expression and osteolytic factor PTHrP secretion in MDA-MB-231 cells (JUN *et al.*, 2014).

## 4.8 LIGNINS

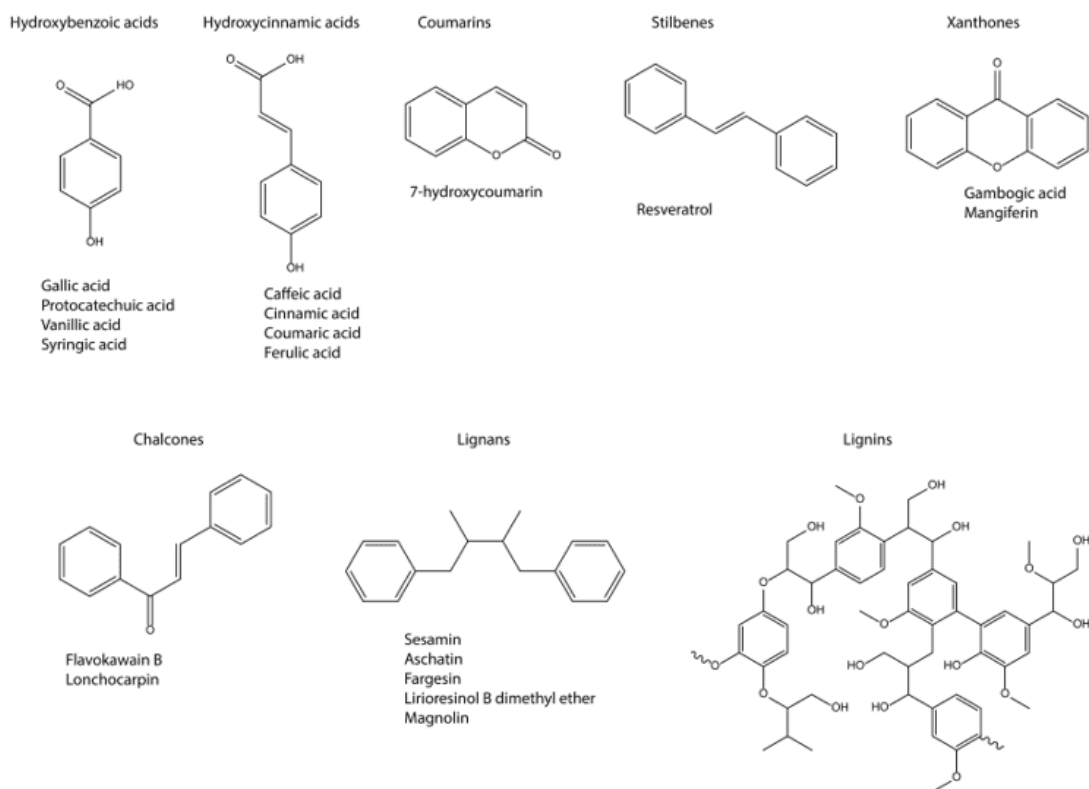
Lignin is an important organic polymer which is abundant in cell walls of some specific cells (LIU *et al.*, 2018), it is a complex of aromatic polymers that consist of monomeric subunits, i.e., p-hydroxyphenyl, guaiacyl, and syringyl units (BOERJAN *et al.*, 2003; ROGERS *et al.*, 2004). Along with cellulose and hemicellulose, lignin is the main component of secondary cell walls (ZHONG *et al.*, 2011). It has many biological functions such as water transport, mechanical support and resistance to various stresses (LIU *et al.*, 2018). The proper lignin deposition in specialized cell types is essential for the appropriate plant development (YOON *et al.*, 2015).

Lignin fibers ingested adsorb carcinogen substances in the gut and reduce its resident time in the colon to the exposure time of carcinogen, and consequently the chances of developing cancerous polyps. Lignin is also known to possess ROS scavenging properties thus present an additional mode for preventing the

development of cancer (LU *et al.*, 1998). It is known that lignin has antioxidant properties, so oxidative stress can be controlled (QAZI *et al.*, 2017). Addition of a P-gp modulator with the anticancer agent reduced the resistance to the drug and the binding of a ligand specifically directed the formulation to cancer cells and, therefore, the safety of normal cells can be restored (SIDDIQUI *et al.*, 2018).

The structure of the non-flavonoid compounds may be checked on the following figure 2 (Figure 2).

Figure 2. Non-flavonoid compounds classes and some representative compounds



Source: Own authorship (2020).





## 4.9 FLAVONOIDS

Flavonoids have been strongly linked with beneficial effects in many human, animal, and *in vitro* studies (MONDAL and RAHAMAN, 2020). Chemically, most flavonoids are based on a fundamental structure that has a skeleton formed by 15 carbon atoms, consisting of two benzene rings (A and B), connected through a chain, three carbons between them, and oxygen as a heteroatom (Figure 3) (SIMÕES *et al.*, 2007).

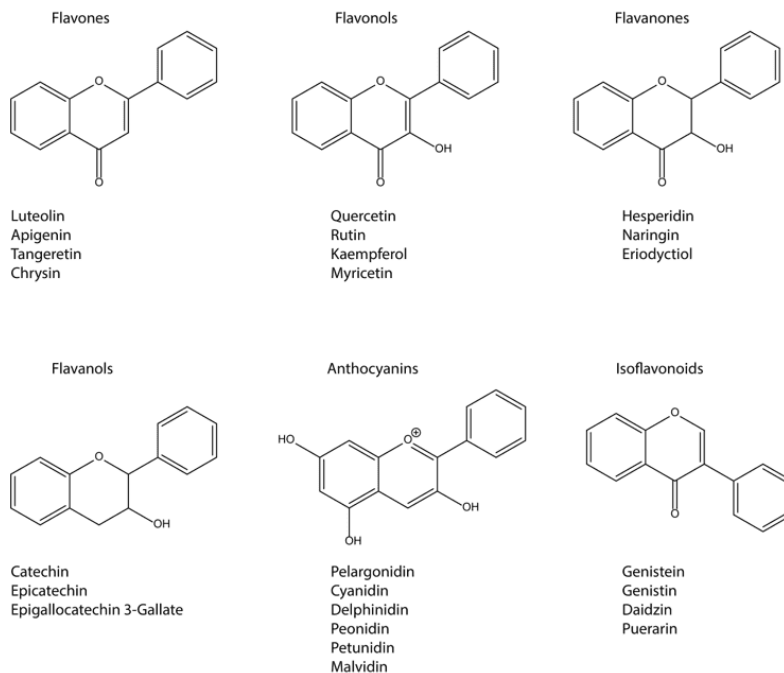
As described by Huang *et al.* (2013), according to the saturation level and opening of the central pyran ring, they are categorized mainly into flavones (basic structure, B ring binds to the 2 position), flavonols (having a hydroxyl group at the 3 position), flavanones (dihydroflavones) and flavanonols (dihydroflavonols; 2–3 bond is saturated), flavanols (flavan-3-ols and flavan-3,4-diols; C-ring is 1-pyran), anthocyanins (anthocyanidins; C-ring is 1-pyran, and 1–2 and 3–4 bonds are unsaturated), isoflavonoids (mainly isoflavones; B ring binds to the 3 position), neoflavonoids (B ring binds to the 4-position), and biflavonoids (dimer of flavones, flavonols, and flavanones) (HUANG *et al.* 2013).

Flavonoids have been linked to reducing the risk of major chronic diseases including cancer because they have powerful antioxidant activities *in vitro*, being able to scavenge a wide range of reactive species. One class of compounds currently under investigation in cancer prevention are flavonoids, a large group of molecules with similar structures (CLERE *et al.*, 2011; MAGGIONI *et al.*, 2015). Several flavonoids have diverse bioactivities, for example, apigenin could inhibit cell adhesion and invasion; reduce the formation of diol epoxide 2, mitochondrial proton F0F1-ATPase/ATP synthase, prostaglandin synthesis, and IL-6 and 8 (interleukin) production; block the expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin; and induce cell differentiation and interferon-gamma gene expression (LINDENMEYER *et al.*, 2001; NOEL *et al.*, 2006). Furthermore, genistein, luteolin, quercetin,

Epigallocatechin, Epigallocatechin Gallate (EGCG), and silymarin as well as apigenin show antiangiogenic and antimutagenic properties (JOHNSON, 2007).

In addition, apigenin, genistein, quercetin, EGCG, and silymarin could suppress the activation of NF- $\kappa$ B and AP1 and block signal transduction pathways (SURH, 2003; LINDENMEYER *et al.*, 2001; NOEL *et al.*, 2006; JOHNSON, 2007). Silymarin also prevented the induction of apoptosis and suppressed protein kinases and MAPKs (KIM *et al.*, 2019). Soy isoflavone genistein was an angiogenesis inhibitor that could inhibit the growth of new blood vessels and showed antitumor and antiangiogenic activity in mouse models of melanoma and breast cancer (FARINA *et al.*, 2006). Moreover, some isoflavones (e.g., genistein and daidzein) were phytoestrogens and could mimic the biological activity of estrogens and modulate steroid hormone metabolism. Therefore, they might play an important role in Breast Cancer (BC) prevention (MENSE *et al.*, 2008; FAN *et al.*, 2019).

Figure 3. Flavonoid compounds structure



Source: Own authorship (2020).



### 4.9.1 FLAVONOLS

Flavonols are considered 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 (FERREIRA *et al.*, 2013). Quercetin is a flavonoid widely distributed in onions, apples, red wine, tea, lemon, tomato, honey, broccoli, kale and beans (NGUYEN *et al.*, 2017).

An antioxidant potent flavan-3-ol, EGCG, protects DNA damage and initiates repair mechanisms in various cancer models (LU *et al.*, 2013). EGCG is the most abundant catechin in green tea and is a traditional antioxidative free radical scavenger (YIN *et al.*, 2008). The flavanols or flavan-3-ols are the most complex subclass of flavonoids; they encompass simple molecules like catechin and polymeric proanthocyanidins. This subclass of flavonoids, unlike the others, is not planar due to a saturated C3 element in the heterocyclic C-ring (FERREIRA *et al.*, 2013).

Catechins (tea polyphenols) namely, (-)-Epicatechingallate (ECG), (-)-Epigallocatechin Gallate (EGCG), (-)-Epicatechin (EC) and (-)-Epigallocatechin (EGC) are strong phytochemicals isolated from *Camellia sinensis*. Catechins have demonstrated great potential in different clinical and human trials (MAITI *et al.*, 2017). They have strong anti-breast cancer properties by upregulating the expression of anti-oxidases such as Superoxide Dismutase (SOD), catalase and Glutathione peroxidase (GHS-px) (XIANG *et al.*, 2016).

Molecular docking studies have confirmed that PI3K and mTOR signaling pathways are targets of Epigallocatechin Gallate (EGCG) as it strongly binds to the active site of PI3K kinase domain revealing ATP-competitive activity in MDA-MB-231 breast cancer cell line (OLIVEIRA *et al.*, 2016). EGCG also inhibits downstream Phosphatidylinositol 3-Kinase (PI3K)/Akt activation along with EGFR



signaling, down-regulates Fatty Acid Synthase (FAS) leading to growth inhibition and caspase-mediated cell death of MCF-7 BC (PAN *et al.*, 2007). Besides, EGCG has shown an affinity to bind to target proteins like 67-kDa laminin receptor, 70 kDa Zeta-associated protein (Zap-70), Phosphoinositide 3 Kinase (PI3K), Ras-GTPase Activating Protein (GAP), vimentin and Bcl-xL and Bcl-2 to inhibit BC cells development (LI *et al.*, 2014).

Tea catechin arrest cell cycle at G2/M phase by activating several signaling cascades, regulate cyclin A expression, phosphorylate JNK/SAPK, cyclin B1 and Cdk proteins and induces apoptosis by activating the expression caspase-3, 8, 9 enzymes (ALSHATWI, 2010; BUDISAN *et al.*, 2017).

Catechin Gallate (CG) induces apoptosis in BC cells by down-regulating the expression of Bcl-2, Bcl-XI followed by the suppression of PI3K, NF $\kappa$ B and JAK/STAT signaling cascades (AFSAR *et al.*, 2016). A clinical trial showed that EGCG (400 mg for 2–8 weeks) has displayed promising results in human breast cancer cells by down-regulating HGF and VEGF and reducing the of MMP-2 and MMP- 9 enzymes (MAITI *et al.*, 2017).

Quercetin has shown strong anti-BC cell effects by regulating miRNA expression. Quercetin has increased the expression of pro-apoptotic-Bax (Bcl-2 associated X) and caspase-3 and decreases the expression of oncogenic-EGFR in MDA-MB-231 and MCF-7 cells by upregulating the expression of miR-146a. Quercetin upregulates the miR-146a expression, inhibits cancer development through Bax and caspase-3 activation and inhibits invasion through down-regulating EGFR expression. Furthermore, quercetin has significantly increased miR-146a expression in xenograft cells and reduced tumor volume in mice (TAO *et al.*, 2015). Based on these experimental studies, quercetin could be a promising anti-breast cancer agent and more detailed studies are needed (IQBAL *et al.*, 2018).



### 4.9.2 FLAVONES

The flavones are structurally related to flavonols and are considered a major subclass within the flavonoids; they occur usually as 7-O-glycosides, although other substitutions can be found. The most common compounds within the flavones are apigenin, chrysin and luteolin (FERREIRA *et al.*, 2013). Apigenin, a flavone widely found in many medicinal plants including *Lycopodium clavatum* L. (club moss) and some vegetables such as *Petroselinum crispum* L. (parsley) and *Apium graveolens* L. (celery), has been reported to have a beneficial effect against UV-B induced DNA damage and inflammatory diseases (SALMANI *et al.*, 2017).

Apigenin reduces the risk of ovarian cancers as demonstrated by a population study conducted in ovarian cancer patients (GEORGE *et al.*, 2017). Apigenin was also reported to modulate DNA damage by inhibiting casein kinase 2, a regulator of cell proliferation, the mediator of the DNA damage response and NF- $\kappa$ B activation in malignant glioma cells (KROONEN *et al.*, 2012).

Luteolin, a flavone found in *Salvia tomentosa* Mill. (Balsamic sage) and many other plants protect SSBs induced by oxidative stress in PC12 rat pheochromocytoma cells (SILVA *et al.*, 2008). Luteolin activates intrinsic apoptotic pathways by inducing DNA damage and p53 in many cancer cells (GEORGE *et al.*, 2017).

Chrysin reduces the disturbances of redox status, named superoxide dismutase, catalase, glutathione peroxidase and GSH in liver, kidney and brain tissues of rats treated with D-galactose (ANAND *et al.*, 2012). In another study, chrysin protects free-radical-mediated oxidative stress induced by N $\omega$ -nitro-L-arginine methyl ester in Wistar male rats (GEORGE *et al.*, 2017).

### 4.9.3 FLAVANONES

The flavanones are usually considered a minor subclass within the flavonoids due to their limited occurrence, mainly in fruits and especially in citrus (REF). Examples



of flavanones are hesperidin (orange juice) and naringin (grapefruit) and due to the high levels of hesperidin in orange juice, it has a sour taste, while naringine is sweeter (FERREIRA *et al.*, 2013). Dietary polyphenols like ellagic acid, genistein, emodin and guggulsterone have also been proved involved with the regulation of cell cycle and apoptosis in various cancer cells (LAPENNA and GIORDANO, 2009). Naringenin, present in orange peel, was found to have the potential to induce DNA damage and apoptosis in HaCaT immortalized keratinocytes and in various other cancer cells (EL-MAHDY *et al.*, 2008). Flavanones have been reported as a potent anticancer agent, this potentially protective effect has been related to the various properties of these compounds, which include anti-oxidative and anti-inflammatory activities (MURTI and MISHRA, 2014; STEVENS *et al.*, 2019).

#### **4.9.4 ISOFLAVONES**

Soy isoflavones, also called isoflavonoids, represent a class of chemical compounds known as phytoestrogens, linked or not to sugar molecules, and comprise aglycone: genistein (5,7,4-trihydroxyisoflavone), glycitein (7,4-dihydroxy-6-methoxyisoflavone) and daidzein (7,4-dihydroxyisoflavone). These isoflavonoids can act both as agonists, antagonists, or as modulators of selective estrogen receptors (BARNES *et al.*, 1994). Isoflavones have one of the highest rates of absorption compared to other flavonoid classes (SELMA *et al.*, 2009). Isoflavones have antiestrogenic as well as estrogenic effects on breast cancer cells in culture, in animal models, and clinical trials (ZIAEI and HALABY, 2017).

*In vitro* studies have demonstrated a weak proliferative effect of isoflavones on breast cancer cells or even blockage of these effects, which are promoted by estradiol in these cells (PITKIN, 2012). A large cohort study with over 11,000 patients revealed that consumption of soy food may be beneficial in ER-negative post-menopausal women, and then, found that soy consumption correlated with reduced incidence and mortality of breast cancer (CHI *et al.*, 2013).



In a study of Basu and collaborators (BASU and MAIER, 2018) the analogs of isoflavones, lignans and resveratrol can modulate the expressions of cell cycle regulators, as a consequence of inhibition of the cell cycle and proliferation of breast carcinomas (BASU and MAIER, 2018).

#### **4.9.5 ANTHOCYANIDINS**

Anthocyanidins, also known as condensed tannins are present throughout the plant kingdom, especially in their glycosylated forms; the anthocyanins are found in fruits and flowers in a higher quantity, but also leaves, stems and roots. The most abundant anthocyanidins are pelargonidin, cyanidin, delphinidin and peonidin. Conjugation with other molecules can take place in positions 3, 5, 7, 3' and 5', creating bigger molecules (FERREIRA *et al.*, 2013).

The anthocyanins and anthocyanidins have gathered the attention of the scientific community owing to their anti-inflammatory, antioxidant, and cancer-inhibitory properties. Studies have been demonstrated that anthocyanins and anthocyanidins inhibit the pro-inflammatory NF- $\kappa$ B pathway and suppress abnormal epithelial cell proliferation (SOUSA MORAES *et al.*, 2019).

### **5. CONCLUSION**

Currently, several studies emphasized, the evaluation of specific points of tumor metabolism. Immunological aspects and induction of apoptosis are being analyzed. Moreover, cell proliferation is not the only event to be fought to treat cancer, but the tumor's ability to nourish itself, invade adjacent tissues and create new blood vessels are major obstacles for traditional therapies. Hereupon, increasing studies for new chemical treatments and alternative and/ or adjuvant therapies have been observed. The relationship between cells and components of the extracellular matrix are fundamental in the occurrence of the tumor, both for invasion and for angiogenesis mechanisms. Polyphenols have antioxidant, antitumor and anti-



inflammatory properties and the consumption of plants rich in polyphenols brings health benefits, giving them a potent preventive and protective action, and strong curative potential, which has been scientifically explored in recent decades. In this way, the present review work supports the recommendations for the consumption of foods and drinks rich in phenolic compounds to the prevention and treatment of cancer.

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