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Chapter 2
Flavonoids: Dietary Interveners as Cancer Chemoprotectants

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Abstract

Cancer are cells with altered morphologies and functions that cause an unstoppable growth and proliferation of the same. Therefore, these changes lead to the existence of different types of cancer that reproduce in different organs or tissues in people, with specific genotypes that originate a growing and uncontrollable aggressive mechanisms until they cause programmed cell death. Thus, cancer mortality is growing at an alarming rate despite the drugs currently available. In this context, phytochemicals, specifically flavonoids, which have served as mediators of inflammatory responses, expression of protogenes and inhibit the secretion of adhesion molecules, constitute a promising and effective opportunity that could provide an alternative approach to treat cancers and overcome the challenges faced by current therapies.
Keywords:
Flavonoids; cancer; genes; chemopreventive; proto-oncogenes

Introduction

Cancer cells are those that alter intracellular functions and mechanisms causing uncontrollable growth and proliferation (Ahmed et al., 2019). According to the area and processes that are generated, several types of cancer with different characteristics have been identified. Thus, there is a range of cancer cell genotypes with self-sufficiency in growth, immeasurable replicative potential, assisted ontogenesis, tissue aggression, insensitivity to growth inhibitory signals, and programmed cell death and metastasis (Sun et al., 2023). Thus, cancer mortality is increasing at an alarming rate despite currently available drugs. In this context, phytochemicals, specifically flavonoids, constitute a promising and effective opportunity that could provide an alternative approach to treat cancers and overcome the challenges faced by current therapies (Welborn, 2004).

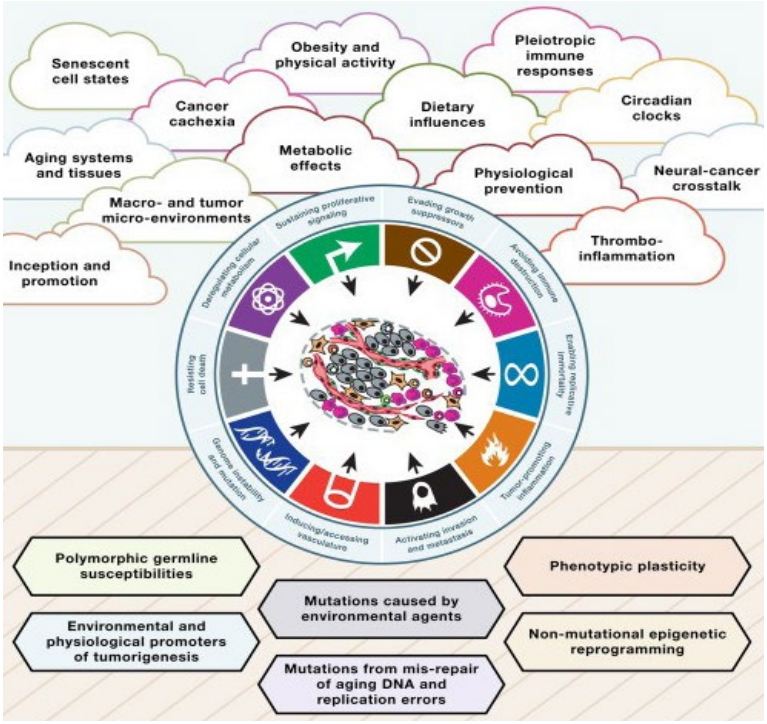
Most research has shown that these compounds reduce the risk of cancer mortality through their anti-inflammatory, antioxidant and anticancer activities (Ahmed et al., 2019). Flavonoids act through different pathways, such as inhibiting several protein kinases like cyclin-dependent kinases (CDK), glycogen synthase kinase 3 (GSK3), dual specificity tyrosine phosphorylation-regulated kinase 1A (DYRK-1A), which are involved in cancer development (Alsawaf et al., 2022; Ponte et al., 2021). They have also shown great potential in the initiation of apoptotic and autophagic cell death and in the inhibition of cancer metastasis by modulating different signaling pathways. These studies suggest that a diet rich in flavonoids is associated with a decreased risk of certain types of cancer, thus arousing interest in using them as chemoprotectants (Zhou et al., 2016). However, human studies remain insufficient and assays are often inconclusive or discordant, so far concerning are the imprecise optimal concentration of flavonoids for cellular function, the poor knowledge of their kinetics and the actual contribution of individual compounds to their effect. This chapter includes an investigation of the pathways of action and cancer chemopreventive effects of flavonoids.

Cancer

Cancer is a cellular disease that is produced by the alteration of the regulatory mechanisms of cell division, causing damage to cellular DNA in a chain reaction, and as a consequence, generates an uncontrolled proliferation of cells. Consequently, cells continue to mutate and perpetuate themselves by secreting their own growth and angiogenic factors (Welborn, 2004). Cancer is induced by multifactorial processes (Figure 1) such as tumor promoters, modulating transcription factors (NFκB, AP-1, STAT 3), anti-apoptotic proteins (AKt, BcL2, Bcl-XL), apoptotic proteins (Caspases, PARP), protein kinases (Cyclins and Cyclin-

dependent kinase), adhesion molecules, cyclooxygenases (COX) and growth factor signaling pathways (Swietach et al., 2014; Aggarwal, 2006). Aberrant gene expression leads to a number of important biological process changes in cancer cells, which are called hallmarks and molecular features of cancer, comprising six biological capabilities acquired during the development of human tumors. The hallmarks constitute an organizing principle for understanding the complexity of the disease (Swietach et al., 2014; Hanahan and Weinberg, 2011).

Figure 1. Factors influencing carinogenesis

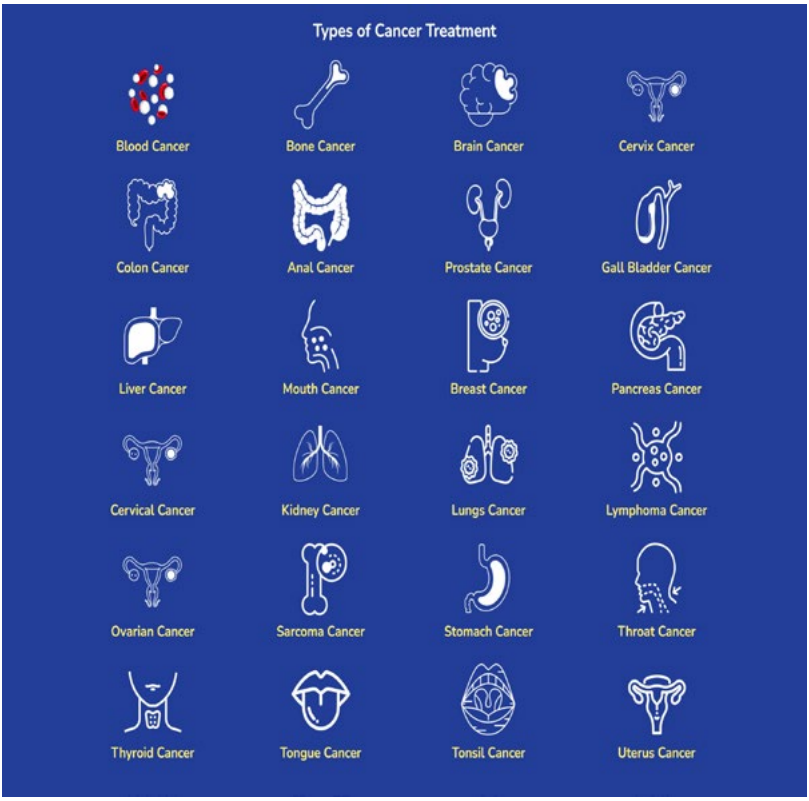


Source: Palacios-Castrillo (2024).

Cancer is derived from two classes of genes (oncogenes and tumor suppressor genes), the former are derived from mutated versions of genes called proto-oncogenes, which control cell proliferation, survival and spread (Kontomanolis et al., 2020). They are also described as phenotypically dominant and are not associated with inherited cancer syndromes, whereby their activation is responsible for uncontrolled cell division, enhancing survival and spread. On the other hand, tumor suppressor genes (TSGs) have the function of inhibiting cell proliferation and survival, i.e., they are involved in the control of cell cycle progression and apoptosis. Also, TSGs are phenotypically recessive and are

responsible for inherited cancer syndromes (Honoki et al., 2024; Hanahan and Weinberg, 2011). When the cell has mutations in its DNA, it may have altered specific genes that predispose the cells to more aggressive cancers (Kontomanolis et al., 2020; Swietach et al., 2014). At present, the organs and tissues of the human body are prone to generating cancer (Figure 2), which can be formed due to both genetic and external factors (lack of nutritional care, stress, sedentary lifestyles).

Figure 2. Cancer developed in different organs of the human body.



Source:

Relationship between flavonoids and cancer

Foods of plant origin contain bioactive compounds that have beneficial health effects. These dietary agents suppress inflammatory processes that allow transformation, hyperproliferation and initiation of carcinogenesis (Concettina et al., 2016). Flavonoids are one of the major components of the human diet,

with an average intake of 1 g/day. The compounds can be obtained from foods of plant origin, primarily for their antioxidant, anti-inflammatory, antiviral, antineoplastic and anticarcinogenic properties (Suhail et al., 2024).

In the structures of flavonoids, there is a relationship of C-ring substitution that distinguishes the different classes of flavonoids. Typically, these compounds are hydroxylated at the 3, 5, 7, 3', 4' and/or 5' positions, and may be additionally methylated, acetylated, prenylated or sulfated. In their natural sources they are found as free aglycones, glycosylated or acylated derivatives and in the form of oligomeric or polymeric structures (proanthocyanidins), the latter being constituted by the union of a variable number of flavan-3-ol units. Most flavonoids are in the form of *O*-glycosides or, less frequently, as C-glycosides, except for the flavanols (Huang, Cai and Zhang, 2010; Ahmed et al., 2019). Glycosyls can be attached to hydroxyl groups 3, 7 or 4', and directly linked to C-6 or C-8 carbons (Dias et al., 2021). Sugars can be esterified with aliphatic or aromatic acids (Suhail et al., 2024; Kopustinskiene et al., 2020). The differences in the substitutions in their structures (the substituent functional group, number, distribution and orientation in space) determine the molecular mechanism of action, electron delocalization, molecule rearrangement, reactive oxygen species (ROS) scavenging capacity, ability to generate intra- or inter-molecular hydrogen bonds, metal ion chelation, steric effects and electronic properties, which confer different properties depending on their structure (Yadav et al. 2023; Osman et al., 2015).

For example, the presence of hydroxyl groups at carbon 3 (3-OH), flavonols and flavan-3-ols have planar structure, whereas flavones and dihydroflavones are slightly folded. The structural planarity generates conjugation and electron dislocation, which acts by increasing the stability of the flavonoid phenoxyl radical. Removal of the 3-OH group eliminates planarity and conjugation, decreasing the desired antioxidant properties. Likewise, glycosylation at the 3-OH group also decreases this property compared to its aglycones due to steric effect (Drețcanu et al., 2022).

The bioavailability and effectiveness of flavonoids depend on their structure and their aforementioned substituents (Kopustinskiene et al., 2020). It is for this reason that the consumption of these compounds is proposed as a good option for the containment of various diseases caused by oxidative damage, such as cancer (Huang et al., 2022). Likewise, they have been given importance in cancer chemoprevention as preventive dietary interventions; as they can act on all three pathways in the carcinogenesis process (Table 1) (Suhail et al., 2024; Zhou et al., 2016). In this sense, these compounds facilitate the donation of hydrogens or electrons from the hydroxyl groups that make possible the neutralization of free radicals (Dias et al., 2021).

Table 1. Flavonoids with anticancer activity.

Flavonoids	**Type of cancer**	**Reference**
Artemisinin	Breast cancer, Liver, and pancreatic	Efferth 2017
EGCG, Epigallocatechin	Breast, skin, lung, prostate and bladder	Iqbal et al. 2017
Doxorubicin, rutin and quercetin	Breast cancer, and lung	Jaradat et al. 2016
Psoralidin	Prostate and stomach	Pahari et al. 2016
Luteolin	Colorectal cancer, Glioblastoma	Rocchetti et al. 2023; Osman et al. 2015
Crocetin	Lung and Hippocampal	Bakshi et al., 2009
Procyanidins	Colon	Cheah et al. 2014
Apigenin	Prostate, lung, osteosarcoma &prostate	Yadav et al. 2023
Curcumin	Melanoma	Chacko and Jacob 2022
Cardamonin	Breast	Arzi et al. 2022
Baicalein	Breast	Sun et al. 2023
Hesperidin	Breast	Ávila-Gálvez et al., 2019
Daidzein	Prostate	Ponte et al. 2021
Genistein	Prostate, Bladder, Colon and Rectal, Non-small Cell Lung	Ponte et al. 2021; Pintova et al., 2019 ; Citrin et al., 2016; Messing et al., 2012
Cyanidin	Oral	Ponte et al. 2021

Source: own elaboration

Another of its benefits is to inhibit certain mediators that are activated under inflammatory conditions, as well as other mediators of inflammatory processes such as proinflammatory cytokines (i.e. NF-κB), chemokines, iNOS expression or activity, inhibit gene expression and secretion of TNF-α, IL-1β or IL-6 and adhesion molecules (Suhail et al., 2024; Khan et al., 2021). It should be emphasized that each flavonoid has its own mechanisms and effects for different situations in the stages of carcinogenesis. Furthermore, it has been observed that the effect of flavonoids shows different dose-dependent behavior in each cell type (Huang et al., 2022).

Flavonoids act at early stages of tumor initiation or by intervening in tumor proliferation pathways, in which they have been shown to inhibit the enzymatic

activity of phase 1 enzymes, whose metabolic products can activate various procarcinogens, such as cytochrome P450 isoenzymes (CYPA1 and CYP1A2) (Huang et al., 2022; Selvakumar et al., 2020; Huang, Cai and Zhang, 2010). Thus, they help to decrease the occurrence of tumors in this initiation phase by modifying GSH levels and modulating the activity of cytochrome P450 enzymes, GPx, SOD and catalase, which are responsible for metabolically activating many compounds that can interact with cellular neutrophils and trigger carcinogenesis (Hasin et al., 2024; Alsawaf et al., 2022).

During phase 2, flavonoids also induce enzymes that promote the modulation of gene expression of detoxifying enzymes detoxification and elimination of carcinogens from glucuronidation, sulfation, acetylation or methylation reactions (Gardeazabal et al., 2019; Concettina et al., 2016). Also, it has been described that they can modulate PI3K/AKT signal transduction pathways, MAPKs (ERKs, JNKs, p38 MAPKs), PKCs, AP-1 and NF-kB for the regulation of cell survival, cell proliferation and programmed cell death (Yahfoufi et al., 2018). Thus, some authors have shown that flavonoids are able to inhibit the enzyme xanthine oxidase (Rahaman et al., 2022) and COX (Kopustinskiene et al., 2020). Los flavonoides son eficaces en la inhibición de la xantina oxidasa, la COX o LOX55 (de Luna, et al., 2023; Zhou et al., 2016). On the other hand, different types of cancer are related to hyper-activation of cyclin-dependent kinases (CDK), due to mutations or repressions in the coding genes of these cyclins. Several studies found that flavopiridol was able to induce cell cycle disruption in G1 or G2/M by inhibiting CDK (Arzi et al., 2022; Ponte et al., 2021). Esterification with acetyl or malonyl groups at the 6' sugar position of certain isoflavones (genistein and diadzein), is thought to be key to their anti-inflammatory activity (Pintova et al., 2019; Citrin et al., 2016; Messing et al., 2012). tudies in breast cancer suggest that some flavonoids act in inhibiting the enzyme DNA dimethyltransferase, i.e., cause inactivation of tumor suppressors (Yahfoufi et al., 2018; Paluszczak y col, 2010). Therefore, these have attracted attention for their potential effects on cancer prevention. Specific studies of the chemopreventive activities of flavonoids are shown in Table 2.

Table 2. Flavonoids and their anticarcinogenic activities.

Flavonoids	**Mechanism of action for biological activity**	**Reference**
Apigenin	It has shown to increase anticancer activity via JAK-STAT and Wnt/Catenin signalling pathway	Ozbey et al. 2019
Luteolin	It induces autophagy and initiates apoptosis in MCF-7, ANA-1 and ACS gastric cells via akt, JNK and p38 signalling cascade.	Liao et al., 2018

Flavonoids	Mechanism of action for biological activity	Reference
Tangeritin	It cases cell cycle arrest via Cyp1A1 and Cyp1B1 mediated metabolism as seen in MCF-7 and MDA-MB-468 breast cancer cell lines.	Surichan et al. 2018
Quercetin	It decreases cancer mortality via cell cycle inhibition and initiation of apoptosis.	Hirpara et al. 2009
kaempferol	Help in initiation of apoptosis and induction of autophagy via increase in expression of miR-340 micro RNA in (Colon) HCT-116, HCT15, SW480 and A549 human lung cancer cell lines.	Han et al. 2018
Myricetin	Inhibits metastasis via inhibition of cell migration as seen in prostate cancer.	Ye et al. 2018; Kumar et al. 2023
Hesperetin	Initiated apoptosis in H522 lung cancer cells	Elango et al. 2018
Naringenin	Decreased cancer metastasis via voltage gated sodium channels and initiated both early and late apoptosis in prostate cancer	Gumushan Aktas and Akgun 2018
Taxifolin	Decreased carcinogenesis through mTOR/PTEN axis and CYP1B1 mediated cancer	Haque et al. 2018
Epigallocatechingallate (EGCG)	Increased chemoprevention and apoptosis through Abl/Bcrmediated p38-JAK2/STAT3/Akt and MAPK/JNK pathways in chronic myeloid leukemia and Glioblastoma cancer cells respectively	Grube et al. 2018
EGCG, catechin	Decreased cancer growth through programmed cell death	Xiao et al. 2019
Cyanidin	Decreased angiogenesis in MCF-7 cells through STAT3/VEGF signalling pathway	Ma and Ning 2019
Delphinidin	Increased initiation of apoptosis and induction of autophagy in HER2 positive MDA-MB-453 cancer cells	Chen et al. 2018
Genistein	Increased apoptosis and decreased cellular proliferation in human laryngeal Mcl-1 and EP3 expressing melanoma cancer cells respectively	Ma et al. 2018
Isoliquiritigenin	Reduce the incidence of colitis-associated colorectal cance. Increase the abundance of Bacteroidetes, Butyricicoccus, Clostridium, Lachnospiraceae, Rikenellaceae and Ruminococcus; reduce the abundance of Enterococcus, Escherichia, Firmicutes and Helicobacteraceae	Wang et al., 2016
Epigallocatechin gallate	Suppress the growth of colorectal cancer. Increase the abundance of Bifidobacterium and Lactobacillus	Wang et al., 2017
Baicalin	Repress the growth of colorectal cancer and block gut inflammation. Produce the bioactive metabolite, baicalein, by gut microbiota Exhibit cytotoxicity toward gastric cancer cells. Attenuate the virulence of Helicobacter pylori	Chen et al., 2018

Flavonoids	Mechanism of action for biological activity	Reference
Rutin	Block colonic carcinogénesis. Reduce the fecal concentration of lithocholic acid and hyodeoxycholic acid	Han et al., 2009
Flavonoid glycosides (apigenin, kaempferol, luteolin, quercetin)	Exert antiproliferative effects on colorectal cancer cells. Increase the growth of beneficial bacteria including Bifidobacterium and Bacteroides; enhance the concentration of SCFAs	Eid et al., 2013
Protocatechuic acid	Prevent esophageal carcinogénesis. Lower the expression of inflammation markers (sEH, COX-2 and iNOS	Peiffer et al., 2014

Source: own elaboration

Another mechanism responsible for the antineoplastic effect is at the level of apoptosis, whose deregulation plays an important role in oncogenesis. Flavonoids have been shown to induce apoptosis in some neoplastic cell lines, while excluding healthy cells from this effect. Therefore, finding inhibitors or modulators of CDK activity represents a new challenge in cancer treatment. Cell apoptosis is another effect in which flavonoids could be involved, in which they have been shown to induce apoptosis only in cancer cells by altering the expression of heat shock proteins (HSP; Khan et al., 2021), with the decrease of ROS (de Luna et al., 2023) and with the modification of molecular signaling pathways (Zhou et al., 2016).

On the other hand, flavonoids can act as pro-oxidants derived from their high reactivity of their metabolisms and depending on the cell treated, as well as the dose and time of exposure, leading to cell apoptosis, so that it can avoid and prevent the development of tumors (Khan et al., 2021; Zhou et al., 2016). It is important to keep in mind that the chemoprotective activity of flavonoids may be effective for one type of cancer cell and show no effect on another type of tissue. Studies in this regard should take into account the trade-off between the cytotoxic effect of flavonoids against tumor cells and the cytoprotective effect on healthy cells. In addition, it has been observed that the effect of flavonoids shows a different dose-dependent behavior in each type of cell (de Luna, et al., 2023; Selvakumar et al., 2020; Huang, Cai and Zhang, 2010).

Conclusion

Numerous studies suggest that a diet rich in flavonoids may reduce the incidence of certain types of cancer. The attributed effects of flavonoids on cancer cells are many related to their antioxidant and anti-inflammatory properties; however, the multiple mechanisms involved include modulation of molecular events and signaling pathways associated with cell survival, proliferation, differentiation, migration, angiogenesis, hormonal activities, detoxification enzymes and immune responses.

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Flavonoides: Intervenciones dietéticas como quimioprotectores contra el cancer

Flavonoides: Intervenientes dietéticos como quimioprotetores do câncer

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Resumen

El cáncer son células con morfologías y funciones alteradas que provoca un crecimiento y proliferación imparable de las mismas. Por lo anterior, estos cambios conllevar a que existan diferentes tipos de cáncer que se reproducen en diferentes órganos o tejidos en las personas, con genotipos específicos que originan un creciente e incontrolable de mecanismos agresivos hasta ocasionar muerte celular programada. Así, la mortalidad por cáncer crece a un ritmo alarmante a pesar de los fármacos disponibles en la actualidad. En este contexto, los fitoquímicos, concretamente los flavonoides, que han servido como mediadores de respuestas inflamatorios, la expresión de protogenes e inhibir la secreción de moléculas de adhesión, por lo que constituyen una oportunidad prometedora y eficaz que podría proporcionar un enfoque alternativo para tratar los cánceres y superar los retos a los que se enfrentan las terapias actuales.
Palabras clave: flavonoids; cancer; genes; quimiopreventivo; proto-oncogenes.

Resumo

O câncer são células com morfologias e funções alteradas que causam um crescimento e uma proliferação imparáveis das mesmas. Portanto, essas alterações levam à existência de diferentes tipos de câncer que se reproduzem em diferentes órgãos ou tecidos das pessoas, com genótipos específicos que originam mecanismos agressivos crescentes e incontroláveis até causarem a morte celular programada. Assim, a mortalidade por câncer está crescendo em um ritmo alarmante, apesar dos medicamentos disponíveis atualmente. Nesse contexto, os fitoquímicos, especificamente os flavonoides, que têm atuado como mediadores de respostas inflamatórias, expressão de protogenes e inibem a secreção de moléculas de adesão, constituem uma oportunidade promissora e eficaz que poderia fornecer uma abordagem alternativa para tratar cânceres e superar os desafios enfrentados pelas terapias atuais.
Palavras-chave: Flavonoides; câncer; genes; quimiopreventivo; proto-oncogenes.