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Therapeutic potential of flavonoids in cancer: ROS-mediated mechanisms

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ABSTRACT

Cancer is a leading cause of morbidity and mortality around the globe. Reactive oxygen species (ROS) play contradicting roles in cancer incidence and progression. Antioxidants have attracted attention as emerging therapeutic agents. Among these are flavonoids, which are natural polyphenols with established anticancer and antioxidant capacities. Increasing evidence shows that flavonoids can inhibit carcinogenesis via suppressing ROS levels. Surprisingly, flavonoids can also trigger excessive oxidative stress, but this can also induce death of malignant cells. In this review, we explore the inherent characteristics that contribute to the antioxidant capacity of flavonoids, and we dissect the scenarios in which they play the contrasting role as pro-oxidants. Furthermore, we elaborate on the pathways that link flavonoid-mediated modulation of ROS to the prevention and treatment of cancer. Special attention is given to the ROS-mediated anticancer functions that (-)-epigallocatechin gallate (EGCG), hesperetin, naringenin, quercetin, luteolin, and apigenin evoke in various cancers. We also delve into the structure-function relations that make flavonoids potent antioxidants. This review provides a detailed perspective that can be utilized in future experiments or trials that aim at utilizing flavonoids or verifying their efficacy for developing new pharmacologic agents. We support the argument that flavonoids are attractive candidates for cancer therapy.

List of Abbreviations: ROS, Reactive oxygen species; EGCG, (-)-epigallocatechin gallate; IUPAC, International Union for Pure and Applied Chemistry; NADPH, Reduced form of nicotinamide adenine dinucleotide phosphate; NOX, NADPH oxidase; COX2, Cyclooxygenase 2; PPARγ, Peroxisome proliferator-activated receptor gamma; NF-κB, Nuclear factor Kappa B; TGFα, Transforming growth factor alpha; EpRE, Electrophile response element; Nrf2, Nuclear factor-E2-related factor; Keap1, Kelch-like-ECH-associated protein 1; Akt, Protein kinase B; H2O2, Hydrogen peroxide; HIF1α, Hypoxia-induced factor-1α; VEGF, Vascular endothelial growth factor; PI3K, Phosphoinositide 3-kinase; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; TNF-α, Tumor necrosis factor alpha; EMT, Epithelial mesenchymal transition; MMP, Matrix metalloproteases; ECM, Extracellular matrix; MAPK, Mitogen-activated protein kinases; ERK, Extracellular signal-regulated kinases; JNK, c-Jun N-terminal kinase; BaP, Benzo(a)pyrene; AP1, Activator protein 1; MDA, Malondialdehyde; ASK1, Apoptosis signal-regulating kinase-1; PKC, Protein kinase C; AMPK, AMP-activated protein kinase; mTOR, Mammalian target of Rapamycin; ATM, Ataxia Telangiectasia Mutant; Stat3, Signal transducer and activator of transcription 3; NSCLC, Non-small cell lung carcinoma; RKIP, Raf kinase inhibitory protein; JAK2, Janus kinase 2; 5-FU, 5-fluorouracil; SGLT, sodium-dependent glucose transporter; CYP450, Cytochrome P450; AHR, Aryl hydrocarbon receptor; HER, Hydroxyethylrutoside; P-gp, P-glycoprotein; MRP, Multidrug resistance associated protein; CDK9, Cyclin dependent kinase-9; CLL, Chronic lymphocytic leukemia; i.v., Intravenous.

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1. Introduction

Cancer remains one of the main diseases that burden healthcare systems worldwide. In fact, over 19 million new cases of cancer were recorded in 2020, with around 10 million deaths globally for the same year [1]. This debilitating loss of human lives urgently calls for concerted efforts to identify and characterize therapies that are more efficacious.

One of the key signaling molecules that play prominent roles in many diseases, including cancer incidence and progression, is reactive oxygen species (ROS) [2–13]. These are highly reactive oxygen-containing molecules that are constantly produced by metabolizing organelles, mainly mitochondria, peroxisomes, and the endoplasmic reticulum [14,15]. With a rather unusual spectrum of actions, ROS appear to elicit both pro-malignant and anti-malignant effects [16]. During normal cellular conditions, small amounts of ROS are produced and kept under a dynamic balance governed by antioxidant effectors [17]. A slight shift of this balance towards oxidative stress activates several signaling pathways that precipitate DNA damage, induce mutagenesis, augment cell proliferation, and exacerbate the Warburg metabolic effect that cancer cells utilize [16]. The mentioned processes favor malignant transformation of cells and enhance tumorigenesis. Counterintuitively, excessive accumulation of ROS precipitates anticancer effects, particularly cell cycle arrest and cell death [16]. The latter occurs via apoptosis, autophagy, and necroptosis [18].

The intricacies of cell signaling in cancer primed the search for therapeutic agents that can target and modulate the function of signaling molecules that can then combat cancer. To this end, regulating ROS levels appears to be a promising therapeutic approach, especially by harnessing the anticancer potential of natural products [19]. Interestingly, several epidemiological studies highlight the inverse correlation between a fruit/vegetable-rich diet and cancer incidence or progression [20,21]. In particular, flavonoids have been recently attracting a lot of attention as potential agents that can be used in ROS-targeted cancer prevention and treatment.

Flavonoids are polyphenolic compounds that have an essential role in protecting plants against ultraviolet energy, microbes, and oxidative stress [22]. As defined by the International Union for Pure and Applied Chemistry (IUPAC), flavonoids in their restricted notion are compounds that follow a C6-C3-C6 carbon backbone. They are arranged as a phenyl

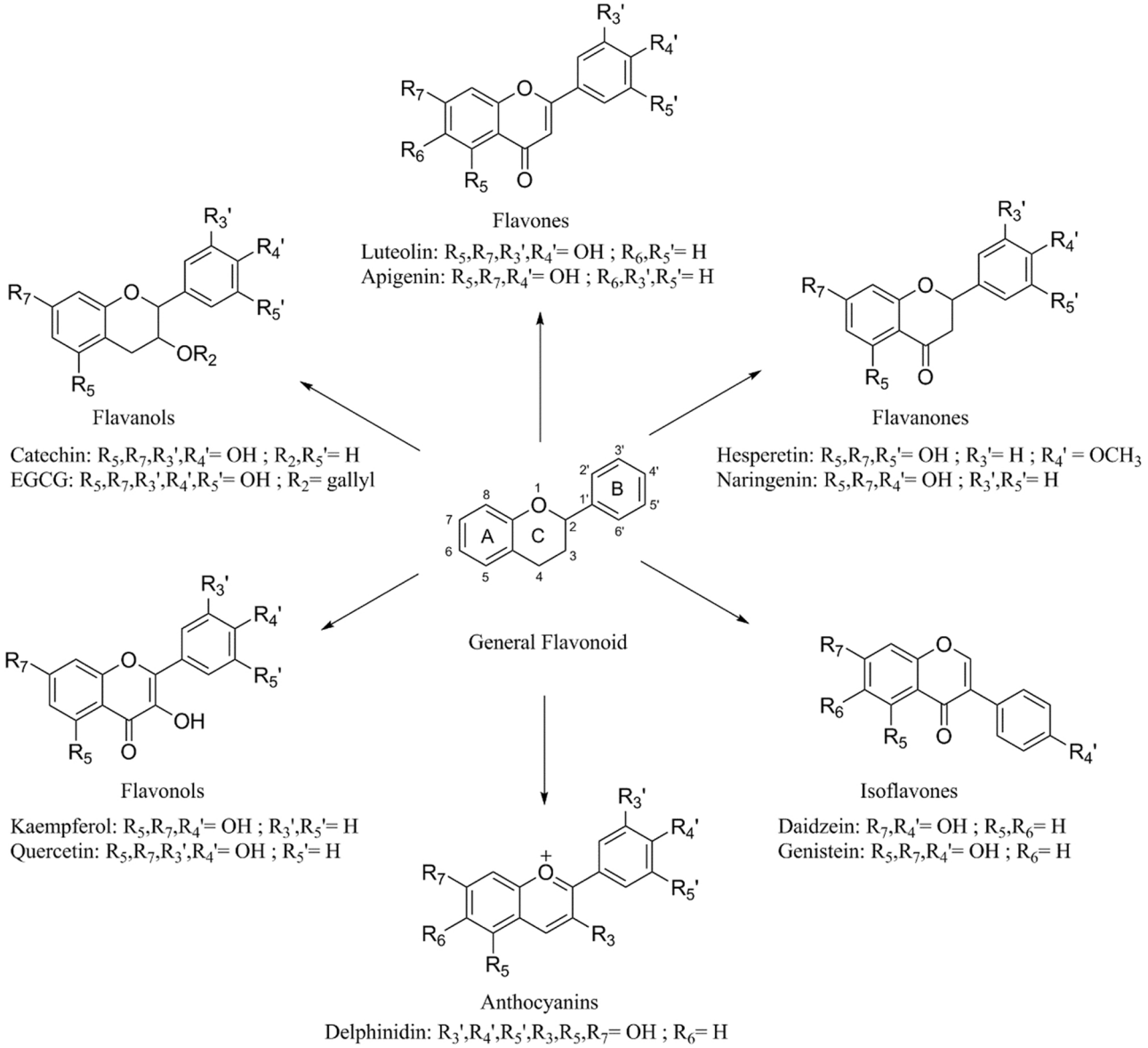


Fig. 1. The general structure of flavonoids along with the representative structure of the main flavonoid subfamilies.

ring (ring A) fused with a pyran ring (ring C), in addition to another phenyl ring (ring B) substituted at position 2 of ring C (Fig. 1) [23]. The number of structurally diverse compounds that belong to the family of flavonoids exceeds 10,000 [24]. These numerous compounds are further classified into subfamilies mainly flavanols, flavanones, flavonols, flavones, and anthocyanins [23] (Fig. 1). Several sources consider isoflavones as a sixth subfamily although they exhibit an exception to the general structure and have their ring B substituted at position 3 of ring C [25]. Flavonoids are ubiquitously found in a plethora of dietary plants and herbs including citrus fruits, oregano, green tea, parsley, cacao, grapes, eggplants, and many others [22] (Table 1). Extensive research started to show the multiple beneficial roles of flavonoids in human health, including anticancer, antihypertensive, or antithrombotic effects [26–28]. Particularly, their anticancer role has been well documented in epidemiological studies and largely attributed to their ability to modulate oxidative stress [19,29]. The aim of this paper is to review and analyze the potential that flavonoids carry as natural therapeutic agents in cancer. We, thereby, highlight their role as antioxidants and explore how the different subfamilies affect tumor incidence and survival by modulating cellular ROS.

2. Flavonoids as antioxidants

ROS are free radicals that function as intracellular messengers but carry the ability to inflict damage on DNA, RNA, and proteins if present in large amounts [37]. In order to mitigate the deleterious effects of these species, cells have developed several repair mechanisms, hence inspiring the potential therapeutic use of antioxidants. Antioxidants are compounds that protect endogenous molecules by attenuating oxidative injury [38]. Owing to their structure, flavonoids can exert an antioxidant effect by acting as reducing agents in several reactions [39]. The underlying mechanisms of flavonoids include scavenging of ROS, inhibiting oxidases responsible for producing the superoxide anion, chelating trace metals, and activating antioxidant enzymes.

2.1. Scavenging reactive oxygen species

Several structural characteristics of flavonoids allow their antioxidant capabilities. By virtue of the hydroxyl group on ring B and the 2,3-double bond conjugated with the 4-oxo functionality, flavonoids can reduce ROS, such as hydroxyl, peroxyl, and peroxynitrite radicals [39,40]. This occurs via the donation of a hydrogen atom as well as an electron from the flavonoid hydroxyl group [38], a reaction that then produces a relatively stable flavonoid radical [38]. This process is favored thermodynamically due to the lower reduction potential of flavonoids, ranging from 0.23 to 0.75 V, compared to that of free radicals (1.0–2.3 V). Thus, it is postulated that flavonoids carry out their antioxidant function via two one-electron transfer reactions (Fig. 2). First, the highly oxidizing radical is reduced, and a flavonoid radical (o-semiquinone) is formed [41,42]. After that, the flavonoid radical, depending on its structure, has three possible fates: coupling with another oxidizing radical, donation of another hydrogen atom forming a quinone, or dimerization with another flavonoid radical [43] (Fig. 2).

It is noteworthy to mention that the first reaction can occur in the presence of high levels of transient metal ions resulting in a pro-oxidant flavonoid [39]. Therefore, the stability of the flavonoid radical dictates its path whether to propagate or interrupt a chain reaction [44]. Ring B is more electron-rich than ring A making it a selective target for the free radicals [42]. Importantly, the pattern and number of hydroxyl groups influence the radical scavenging ability of flavonoids [40]. However, it may not necessarily be the number of hydroxyl groups that is affecting the antioxidant activity of flavonoids. The highest reaction rates and lowest IC50 values belong to the catechol-containing flavonoids rather than the most hydroxylated compounds [42,43]. Consequently, the 3′− 4′ catechol structure in ring B is a strong indicator of antioxidant ability along with a hydroxyl group on the 3-position of ring C (Table 2) [38].

The catechol moieties form hydrogen bonds with the 3-OH causing planarity of the flavonoid molecule [38,44]. This planarity permits conjugation and electron delocalization aided by the conjugation of the unsaturated double bond on carbons 2 and 3 with the 4-oxo group [38]. The extended conjugation reduces the energy of the flavonoid radical, further stabilizing it. This is supported by the large decrease of ΔHf, defined as the difference in heat of formation between the flavonoid and its corresponding radical, in the presence of the mentioned structural characteristics [43]. On the other hand, loss of hydrogen bonding leads to strain, thus compromising electron delocalization across the flavonoid rings as well as coplanarity. This loss significantly impacts the radical scavenging capacity of flavonoids (Table 2) [38].

In addition to that, glycosylation and methylation strongly suppress the antioxidant activity of flavonoids [38–40]. The added glycosides and methyl groups lead to steric effects that negatively impact electron delocalization of the flavonoid [45]. This also includes changes in planarity, where an increase in the energy of the flavonoid is expected, thus decreasing its stability, and diminishing its antioxidant activity [38]. Similarly, the presence of only one hydroxyl group in ring B decreases flavonoids' ability to reduce free radicals [39]. Moreover, the variation in antioxidant ability between polyhydroxylated and polymethoxylated compounds can be attributed to the different hydrophobic profiles of these flavonoids [38].

With regards to their interaction with ROS, flavonoids display the greatest reactivity with hydroxyl radicals. This may be attributed to the high reactivity of these radicals with aromatic compounds [44]. Indeed, flavonoids are effective scavengers of hydroxyl radicals with rates in the order of 109 M-1 s-1 [42]. In contrast, very low constant rates for the superoxide ion have been reported [44], where recorded rates were in the 104 M-1 s-1 range [42]. Eventually, the charge of the flavonoids seems to counteract its scavenging efficacy. Generally, flavonoids have low pKa values (4−5) and are thus deprotonated at neutral pH [42]. This causes an electrostatic repulsion of the superoxide anion and, subsequently, a two-time decrease in the reaction rate constant for every negative charge in the flavonoid [42]. Based on that, flavonoids seem to be more effective in inhibiting enzymes responsible for production of the superoxide anion rather than the slow inactivation of the anion itself [42].

2.2. Inhibiting superoxide-producing enzymes

The flavonoid hydroxyl group is known to reduce free radicals by donating a hydrogen atom and an electron [38]. This reaction also produces a relatively stable flavonoid radical [38] (Fig. 3A). Moreover, flavonoids' ability to inhibit ROS-producing enzymes such as xanthine oxidase, cyclooxygenase, and NADPH oxidase (NOX) is a major attribute of their antioxidant capacity.

Xanthine oxidase is a significant source of ROS as it generates a superoxide ion while catalyzing the oxidation of xanthine and hypoxanthine to uric acid [46–48]. Flavonoids, due to their characteristic structures, display a competitive and a mixed competitive-noncompetitive inhibition of xanthine oxidase [47]. The hydroxyl groups on positions 5 and 7 in ring A play the most important

Table 1
Flavonoids and their dietary sources.

Flavonoid	Dietary Source	Reference
EGCG	Cocoa, green tea	[30,31]
Hesperidin/ Hesperetin	Oranges, grapefruit, clementine, mandarin	[32]
Naringenin	Citrus fruits, tomatoes, thyme	[33]
Quercetin	Apples, berries, grapes, red onions, broccoli, red wine	[34]
Luteolin	Celery, chili peppers, carrots, lettuce, spinach	[35]
Apigenin	Parsley, chamomile, artichokes, oregano	[36]

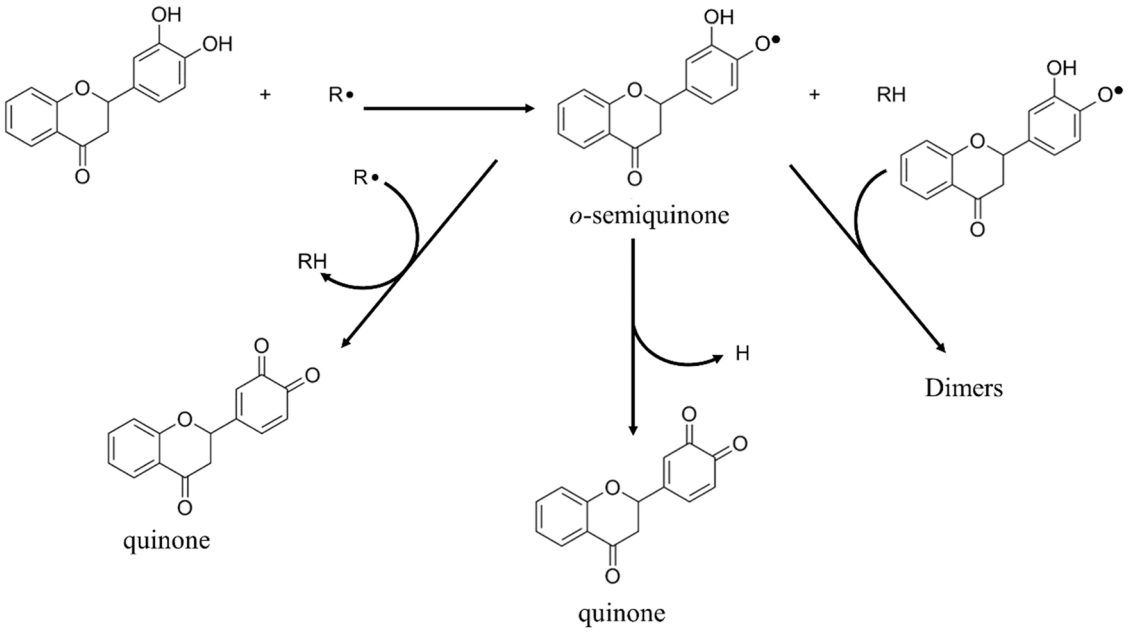
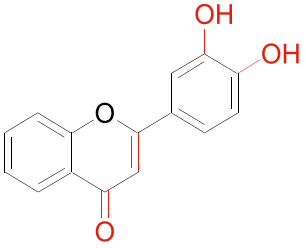
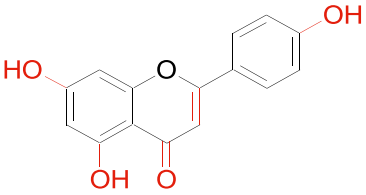
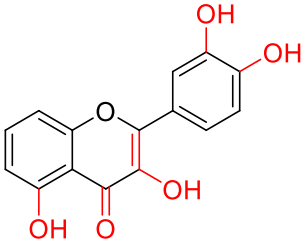


Fig. 2. The mechanism of ROS scavenging by flavonoids. The free radical (R•) is first reduced into R-H while the flavonoid is oxidized into a flavonoid radical. This flavonoid radical then has three possible fates (from left to right); reduce another free radical and form a quinone, donate a hydrogen atom and form a quinone, or pair-up with another flavonoid radical and form a dimer.

Table 2
Structure-activity relationships of flavonoids on their different antioxidant activities.

Antioxidant mechanism	Optimal structural characteristics	Sample structure	Examples
Scavenging ROS	• 3′,4′–Catechol moiety • 2,3–Double-bond • 4–Carbonyl group		Quercetin Luteolin EGCG Apigenin
Inhibiting Superoxide-forming Enzymes	• 5,7–Hydroxyl group • 4′–Hydroxyl group • 2,3–Double bond • 4–Carbonyl group		Quercetin Isorhamnetin Kaempferol Myricetin
Chelating Trace Metals	• 3′,4′–Catechol moiety • 3,5–Hydroxyl group • 2,3–Double-bond • 4–Carbonyl group		Kaempferol Quercetin Taxifolin

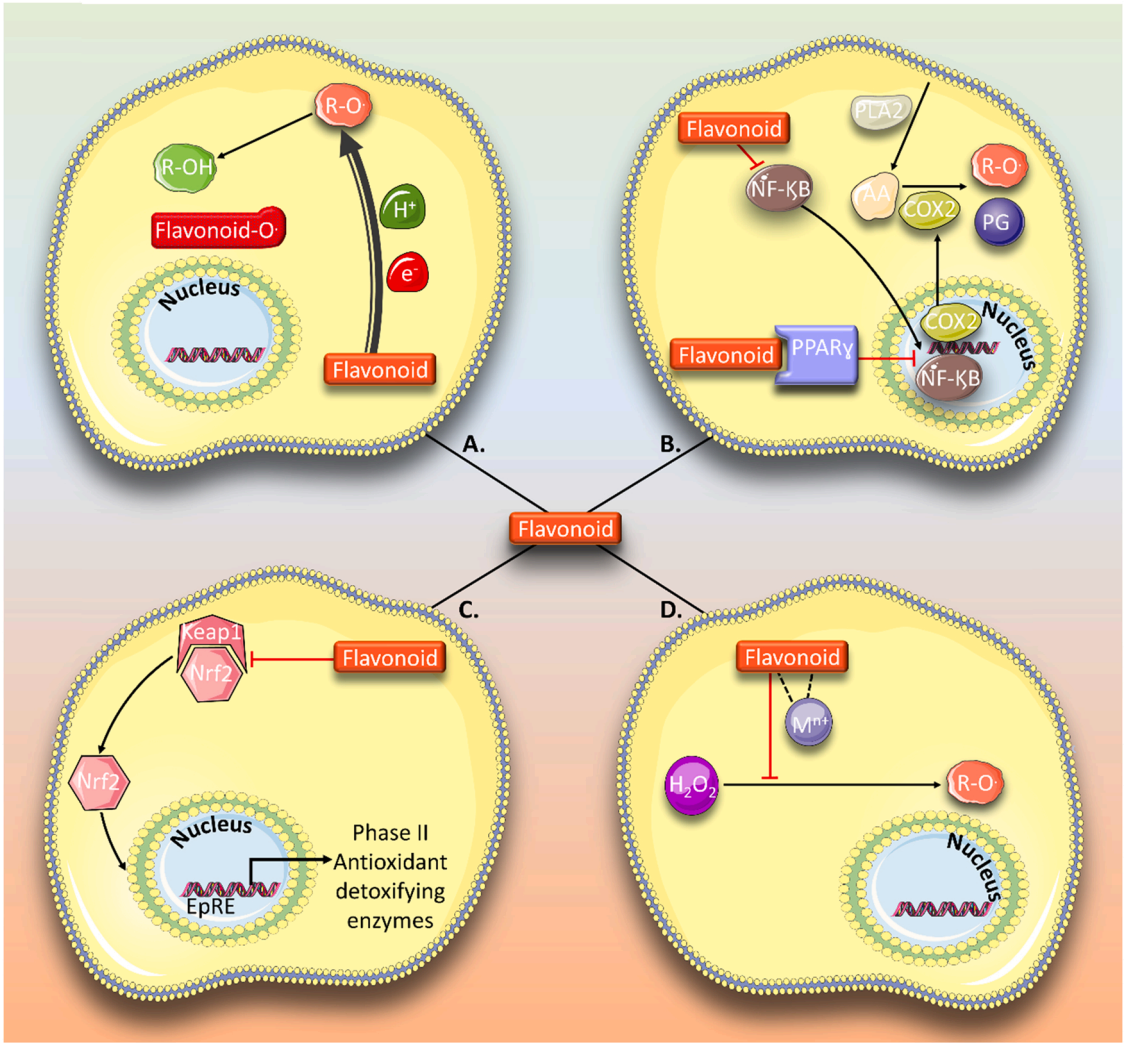


Fig. 3. Summary of some of the functions contributing to flavonoid antioxidant capacities. (A) Flavonoids donate a hydrogen atom and an electron to free radicals (R-O•) thus reducing them. (B) Flavonoids inhibit NF-kB from binding to the nuclear NF-kB response element (NF-kB RE). In addition, flavonoids act as ligands activating PPARγ which, in its turn, inhibits the NF-kB RE. This response element is responsible for the expression of COX-2, which acts on arachidonic acid (AA) to produce prostaglandins (PG) and free radicals (R-O•). Therefore, the double blockage of COX-2 transcription by flavonoids results in decreased oxidative stress. (C) Flavonoids disrupt the binding of Keap1 to Nrf2. This allows the nuclear translocation of Nrf2 and its activation of EpRE, thus enhancing the expression of phase II detoxifying enzymes. (D) Flavonoids chelate trace metals (Mn+) thus preventing their participation in the Fenton reaction with H2O2 to generate free radicals.

role in xanthine oxidase inhibition [46] (Table 2). These moieties interact with the amino acid residues near the active site of the enzyme via hydrogen bonding, an interaction deemed essential for the inhibitory effect [47]. Specifically, hydrogen bonds are formed by the C7-OH with Asn-768, Thr-1010, and Glu-1261, and by the C5-OH with Arg-880 according to structure-based molecular modelling and molecular docking simulations [47,48]. Apparently, π-stacking between ring B and Phe-914 of xanthine oxidase further enhances the active site binding [47,48]. In addition, the 2,3-double bond in ring C impacts flavonoid inhibitory effects (Table 2). This double bond allows for conjugation and coplanarity across the three rings of the flavonoid [46]. It also contributes to the π-π interactions affecting the flavonoid and enzyme interactions [47]. Therefore, it is proposed that a planar flavonoid is central to the xanthine oxidase inhibition since non-planar flavonoids do not exhibit the aforementioned inhibitory effect [46,48].

Glycosylation and methylation of the hydroxyl groups on ring A can result in a markedly decreased xanthine oxidase inhibition [46,48]. The glycoside moiety disrupts the electron cloud among the flavonoid rings causing steric hindrance [47]. Indeed, this prevents the electrostatic interaction of the flavonoid rings with the amino acid residues of the active site [46,47]. In addition, the presence of a C3 hydroxyl group on ring A slightly weakens the inhibitory effect on xanthine oxidase [46,48]. This hydroxyl group stretches into the hydrophobic pocket of the active site destabilizing the flavonoid-enzyme interaction and decreasing the binding affinity [48]. In contrast, substitutions on ring B have practically no effect on the inhibition of xanthine oxidase [46].

Cyclooxygenase 2 (COX2), an inducible isoform of cyclooxygenase, is activated by inflammatory mediators [49]. Its overexpression is associated with cancer, partly due to its augmentation of ROS levels, which in turn contribute to tissue damage [49,50]. Flavonoids inhibit COX2 by suppressing its transcription and modulating its signal transduction [50] (Fig. 3B).

A key anti-inflammatory molecule that suppresses cytokine production is the peroxisome proliferator activated factor gamma (PPARγ) [51]. Contextually, flavonoids with certain functional groups can bind and activate PPARγ [50]. Structurally, hydroxylation of the carbons 5 and 7 in ring A, as well as the 4′ position in ring B, has been shown to be crucial for this purpose [52]. Moreover, the 2,3-double bond is also implicated in flavonoids' ability to activate PPARγ (Table 2) [50]. It is worth noting that the number of hydroxyl groups is of less importance than their pattern. This is confirmed by the fact that 3′, 4′, and 5′ hydroxylated B rings do not significantly affect the transcriptional action of

COX2 [53]. Additionally, the presence of a 3′ hydroxyl group in ring B leads to a decreased PPARγ activation [50].

Flavonoids can also suppress COX-2 expression by modulating activities of key regulators. For instance, an interplay between flavonoids and nuclear factor kappa B (NF-κB) appears to suppress COX2 expression [50]. By blocking the lipopolysaccharide-induced activation of the NF-κB, flavonoids inhibit the activity of COX2 promoter leading to decreased COX2 mRNA and protein levels [50]. This may be due to the fact that flavonoids can substantially reduce the DNA binding capacity of NF-κB [54]. In addition, flavonoids can inhibit COX2 transcription by suppressing another important modulator, namely transforming growth factor alpha (TGFα), which is known to drive COX2 promoter by activating certain protein-tyrosine kinases [50]. It is speculated that a resorcin moiety on certain flavonoids is the main determinant of the inhibition of the promoter activity. However, the presence of a glucuronide on the 3-position of ring C effectively nullifies the inhibitory effect on COX2 [50].

Another key player in ROS production is the enzyme NOX. Indeed, NOX rids cells of pathogens via ROS production in a process known as oxidative burst [55]. This was thought to be exclusive to phagocytes; however, a family of NOX enzymes has been found in various tissues [55]. In the context of their antioxidant role, flavonoids are able to inhibit NOX activity. The presence of a 4′-OH on ring B along with a saturated 2,3-bond in ring C establishes an inhibitory effect on NOX (Table 2) [56]. This inhibitory effect is further potentiated by a vicinal hydroxy methoxy pattern. Disruption of the assembly of the multiprotein complex needed for full enzymatic activity appears to be the underlying mechanism [56]. In contrast to the other antioxidant roles of flavonoids, the presence of a catechol moiety on ring B diminishes the ability to inhibit NOX [56].

2.3. Chelating trace metals

Flavonoids possess the ability to chelate trace metals involved in ROS-producing reactions. Iron stimulates the production of the hydroxyl radical via the Fenton reaction (Fig. 3D) [38,57]. Moreover, iron and copper may promote lipid radical formation via lipid peroxidation [58]. Iron cations exist as both ferrous (Fe2 +) and ferric (Fe3 +) forms that are important for the initiation of lipid peroxidation [58]. In a 2:1 stoichiometric ratio, flavonoids with a hydroxyl moiety on C3 along with the carbonyl group on C4 can bind iron [57]. Moreover, the presence of a catechol group on ring B (3′ and 4′ positions), a hydroxyl group on C5 in ring A, and a 2,3-double bond enhance iron chelation (Table 2) [58,59]. In such flavonoids, there are three possible chelation sites: the 3′−4′ catechol moiety, the 3-hydroxyl and 4-carbonyl groups, and the 5-hydroxyl and 4-carbonyl groups (Fig. 4) [58,59]. Chelation is thought to be preferred at the 5-hydroxyl and 4-carbonyl sites as it forms a six-membered ring conveying greater stability [58,59]. This is supported by computational analysis showing a 10 kcal/mol energy decrease in such a complex compared to five-membered ring complexes formed at other sites (Fig. 4) [59]. The complexes formed upon flavonoid-iron interaction are found to be a deprotonated flavonoid with the ferrous ion and a doubly deprotonated flavonoid with the ferric form. However, it should be noted that flavonoids preferentially chelate the ferrous cation [58].

On the other hand, flavonoids reduce copper ions much more readily than iron ions [58]. This is based on the difference in standard reduction potential of the couples with Cu^{2+}/Cu at + 0.15 V and Fe^{3+}/Fe at + 0.77 V [58]. Indeed, lower reduction potential leads to a more thermodynamically preferred reaction. Nonetheless, the number of hydroxyl groups on the flavonoid is the main determinant of the chelating capacity [58]. Interestingly, some flavonoids display an increased number of electrons donated in the reactions compared to the number of hydroxyl groups present. Oxidative polymerization is thought to be the reason behind this observation [58]. Although it has been suggested that flavonoids shift to a pro-oxidative role in the presence of metals, flavonoids are shown to chelate metal ions and intercept the formation of ROS in the majority of cases [39,58].

2.4. Activating antioxidant enzymes

One of the key mechanisms by which flavonoids exert their antioxidant effects is, not unexpectedly, through activation of antioxidant enzymes. The electrophile response element (EpRE) is a regulatory sequence of genes encoding phase II detoxifying enzymes such as, UDP-glucuronyltransferase, glutathione-S-transferase, and quinone reductase [40]. These enzymes facilitate glucuronidation of endogenous and exogeneous compounds, detoxification of radicals, and prevention of quinine redox cycling, respectively [60]. Under normal conditions, nuclear factor-E2-related factor (Nrf2) is associated with the chaperone

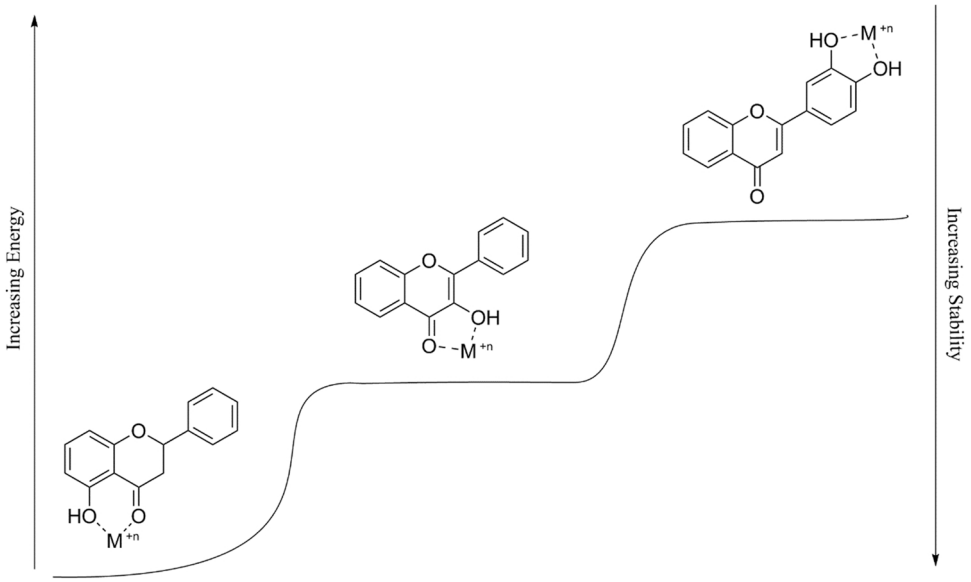


Fig. 4. Energy and stability of metal-flavonoid complexes. There are three possible binding sites of a metal cation (M+n) to a metal-chelating flavonoid. The energy-stability graph depicts that the preferred binding site is the one that generates a six-membered ring with lowest energy and greatest stability compared to the other binding sites that form five-membered rings.

Kelch-like-ECH-associated protein 1 (Keap1) preventing the former from nuclear translocation [60,61]. However, flavonoids disrupt this interaction promoting Nrf2 translocation, thus leading to EpRE activation (Fig. 3C) [40,60,61]. By the same mechanism, flavonoids also induce metallothioneins that are protective against metal toxicity [61]. Other antioxidant enzymes activated by flavonoids include glutathione peroxidase and glutathione reductase, with the latter being activated by a protein kinase B (Akt)-dependent cascade [40]. As such, flavonoids promote the formation of water from hydrogen peroxide (H2O2) and regenerate reduced glutathione for further use.

3. Flavonoids in Cancer

Carcinogenesis can be described in terms of three prominent phases that encompass several processes and hallmarks. The three phases are initiation, promotion, and progression [62]. Flavonoids have the potential to interrupt the process of carcinogenesis at its different phases through variable mechanisms [22]. A majority of these mechanisms is related to the oxidative state of the cell as well as flavonoids' ability to modulate levels of ROS.

Initiation of carcinogenesis is defined as the accumulation of several irreversible mutations that affect the genome [63]. ROS can mediate these alterations by promoting DNA instability and damaging genetic material [2]. Loss of function mutations that affect the expression of tumor suppressor genes and gain of function mutations that promote protooncogenes are highly implicated in cancer initiation [63]. For instance, ROS-mediated hypermethylation, and consequently silencing, of tumor suppressor genes has been shown to induce tumorigenesis [64]. Flavonoids are known to alleviate oxidative stress-induced mutagenesis and hinder the process of malignant transformation [22]. Furthermore, flavonoids mitigate the epigenetic modifications induced by ROS.

In carcinogenesis, promotion refers to the reversible process of change in expression rather than molecular changes in the DNA itself [63]. A major transcription factor implicated in tumor survival is NF-κB [14]. By diminishing ROS levels, flavonoids can suppress NF-κB's pro-survival effects and in turn, decelerate tumorigenesis.

Flavonoids also elicit ROS-related effects that attenuate the progression phase of tumorigenesis, an irreversible phase that involves the late manifestations of malignant growth and transformation, such as angiogenesis, invasiveness, migration, and lack of cell death [14]. Indeed, ROS are implicated in signaling pathways that involve all these mechanisms. For instance, ROS potentiate the actions of hypoxia-induced factor-1α (HIF1α) and its downstream effector, vascular endothelial growth factor (VEGF), a potent driver of angiogenesis in solid tumors [18,65]. It is the ROS-induced inhibition of prolyl hydroxylases, enzymes that hydroxylate and thus destroy HIF1α, that underlies the increased accumulation of HIF1α [14].

While flavonoids' antioxidant capacity endows them with the ability to favorably modulate the aforementioned processes, caution is warranted when discussing the role of antioxidants as anticancer agents. That is because increasing evidence suggests that antioxidants may indeed promote carcinogenesis under certain conditions [66]. Compelling findings generated from mouse studies suggest that antioxidants can facilitate the progression of lung cancer [67] and promote the metastasis of melanoma in mice models [68,69]. Therefore, antioxidants, including flavonoids, should not be considered tumor-preventing agents in absolute terms and across all contexts. Rather, they should be utilized only in the context in which they have undergone rigorous in vitro and in vivo testing and proven to be of tangible benefit.

Surprisingly, flavonoids have been shown to elicit pro-oxidative

Table 3
The anticancer role of flavonoids achieved through their antioxidant effects.

Flavonoid	Cell type	Mechanism	Result	Reference
EGCG (Flavanol)	Hepatocytes, lymphocytes and colonocytes	↓DNA damage	Prevent mutagenesis	[70,71]
	–	Detoxify 2-hydroxyamino-3-methylimidazo[4,5-*f*] quinoline	Prevent mutagenesis	[72]
	Breast cancer cells	↓NOX1	Inhibit anchorage independent growth and invasion	[73]
	Lung cancer cells	↓NF-κB, ↓TNF-α	Induce apoptosis and inhibit proliferation	[74,75]
	Nasopharyngeal cancer cells	↓NF-κB, ↓Twist1	Inhibit metastasis, self-renewal capacity and EMT	[76]
	Fibrosarcoma	↓NF-κB, ↓Bcl2, ↑Bax	Induce apoptosis	[77]
		↓ERK1/2, ↓MMP-2, ↓MMP-9	Inhibit metastasis	[78,79]
Hesperidin (Flavanone)	Hematopoietic cells	↓DNA damage	Prevent mutagenesis	[80]
	Lung cancer cells	↓DNA damage	Prevent mutagenesis	[81]
		↑Antioxidant capacity	Inhibit proliferation	[82]
		↓MMPs	Inhibit metastasis	[81]
	Liver cancer cells	↓NF-κB, ↓AP1, ↓MMP-9	Inhibit metastasis	[83,84]
	Larynx, cervical, and breast cancer cells	–	Induce cell death	[85]
Hesperetin (Flavanone)	Lung cancer cells	↓MDA-DNA complexes	Prevent mutagenesis	[86]
		↓NF-κB, ↓TNF-α	Inhibit proliferation	[86]
Naringenin (Flavanone)	Hepatocytes	↓DNA damage	Prevent mutagenesis	[87]
	Gastric cells	↓DNA damage	Prevent mutagenesis	[88]
	Lung cancer cells	↓MDA-DNA complexes	Prevent mutagenesis	[89]
	Osteosarcoma	–	Inhibit progression and recurrence	[90]`
Quercetin (Flavonol)	Dalton's lymphoma cells	↓PKC	Induce apoptosis	[91]
	Liver cancer cells	↓Cyclin A, ↓CHK1	Inhibit proliferation	[92]
	Breast cancer cells	↓Nrf2	Induce apoptosis	[93]
	–	↓ATM	Radio-sensitization of tumors	[94]
Luteolin (Flavone)	Bladder cancer cells	↓mTOR	Induce apoptosis and inhibit proliferation	[95]
	Colorectal cancer cells	↑JNK, ↑MAPK	Induce apoptosis	[96]
	Lung cancer cells	↓Mitochondrial membrane potential	Induce apoptosis	[97]
	Squamous carcinoma cells	↓Src, ↓Stat3, ↓S100A7	Inhibit metastasis	[98]
Apigenin (Flavone)	B-cell lymphoma cells	↑p53, ↓Stat3	Induce autophagy	[99]
	Skin cancer cells	↓MAPK, ↓AP1, ↓MMP-1	Inhibit incidence and metastasis	[100]

effects in certain scenarios. The cytocidal effect that several flavonoids possess when used in certain cancers is primarily attributed to their ability to evoke excessive oxidative stress [19,70]. As previously discussed, excessive ROS accumulation by flavonoids can activate apoptotic, autophagic, and necroptotic pathways leading to reduction in tumor size [18].

A myriad of these potential mechanisms has been well-established. ROS-mediated anticancer effects of individual flavonoid molecules along with their mechanisms of action are dissected and analyzed below (and summarized in Tables 3 and 4).

Table 4
The anticancer role of flavonoids achieved through their pro-oxidant effects.

Flavonoid	Cell type	Mechanism	Result	Reference
EGCG (Flavanol)	Pancreatic cancer cells	↑JNK	Induce apoptosis and inhibit proliferation	[101]
	Glial cancer cells	↑JNK	Induce apoptosis	[102]
	Lung cancer cells	↑DNA damage	Induce apoptosis	[103]
	Prostate cancer cells	↑ Mitochondrial depolarization	Induce apoptosis	[104]
	Malignant B cells	↓Mitochondrial membrane potential, ↑ cytochrome c, ↑Smac/DIABLO, ↑AIF, ↑caspase-3 & −9	Induce apoptosis	[105]
Hesperidin (Flavanone)	Cervical cancer cells	↑Mitochondrial stress	Induce apoptosis and inhibit proliferation	[106]
Hesperetin (Flavanone)	Colorectal cancer cells	↓Bcl2, ↑Bax	Induce apoptosis	[107]
	Gastric cancer cells	↓Bcl2, ↑Bax	Induce apoptosis	[108]
	Breast cancer cells	↑ASK1, ↑JNK, ↑Bax, ↑caspase9	Induce apoptosis	[109]
Naringenin (Flavanone)	Placental choriocarcinoma cells	↑ERK1/2	Induce apoptosis	[110]
	Pancreatic cancer cells	↑ASK1	Induce apoptosis	[111]
	Epidermoid carcinoma cells	↑DNA fragmentation ↑mitochondrial depolarization, caspase-3	Induce apoptosis and inhibit proliferation	[112]
	Breast cancer cells	↓MMP-9 & −2	Potentiate the action of tamoxifen; Inhibit proliferation, inhibit migration, induce apoptosis	[113]
		↓PI3K/AKT	Potentiate the action of tamoxifen; Inhibit proliferation	[114]
	Prostate cancer cells	↓ERK1/2 ↑PI3K/AKT	Potentiate the action of paclitaxel; induce apoptosis	[115]
Quercetin (Flavonol)	Colorectal cancer cells (HT29)	↑caspase-3, ↑cytochrome c, ↓Pakt, ↓cyclin D1, ↑COX2	Inhibit survival and induce apoptosis	[116]
	Colorectal cancer cells (HCT116)	↑Sestrin 2, ↑AMPK, ↑mTOR	Induce apoptosis	[117]
	Colorectal cancer cells (SW620)	↑p53, ↑p21 ↑Bax, ↑cytochrome c, ↑caspase-3 & −9, ↑Apaf 1	Inhibit proliferation and induce apoptosis	[118]
	Prostate cancer cells	↑DNA damage, ↓CDK2, ↓ cyclin E & D, ↓Bcl-2, ↑Bax, ↑caspase-3, −8 & −9, ↓mitochondrial membrane potential	Inhibit cell cycle and induce apoptosis	[119]
		↓hnRNPA1, ↑GRP78, ↑CHOP	Sensitization of prostate cancer cells to paclitaxel	[120]
	Gastric cancer cells	↓Mitochondrial membrane potential, ↑Bad, ↑Bax, ↑Bid, ↓Bcl-2, ↓Bcl-x, ↑JUNB proto-oncogene, ↓VEGFB, ↓CDK10, ↓KDELCE	Induce apoptosis	[121]
	Breast cancer cells	–	Induce apoptosis	[122]
Luteolin (Flavone)	NSCLC	↓Bcl-2, ↑caspase-3, -8, & -9, ↑p38 MAPK	Radio-sensitization of tumors; induce apoptosis	[123]
	Pancreatic cancer cells	↓Nrf2, ↑RKIP, ↓Snail	Induce apoptosis	[124]
	Glial cancer cells	↑PERK, ↑eIF2α, ↑ATF4, ↑CHOP ↑cleaved-caspase 12	Induce apoptosis	[125]
	Cervical cancer cells	–	Induce apoptosis	[126]
	Liver cancer cells	↓Mitochondrial membrane potential, ↑mitochondrial swelling ↑cytochrome c, ↑caspase-3	Induce apoptosis	[127]
	Cholangiocarcinoma cells	↓Nrf2, ↓γ-glutamylcysteine ligase, ↓heme oxygenase-1 proteins, ↑mitochondrial depolarization, ↑cytochrome c, ↓Bcl-2, ↓Bcl-xl, ↑caspase-3 & −9	Induce apoptosis	[128]
Apigenin (Flavone)	Bladder cancer cells	↓Mitochondrial membrane potential, ↑p53, ↑p21, ↑p27, ↓cyclin A1, B, E & D, ↓Cdc25C, ↑Bax, ↑Bad, ↑Bak, ↓Bcl-2, ↓Bcl-xl, ↓Mcl-1, ↑cytochrome c, ↑caspase-3, −7 &−9, ↑PARP	Induce apoptosis	[129]
	Prostate cancer cells	↑p53, ↓NF-κB/p65, ↓p21/WAF-1, ↓Bcl-xl, ↓Bcl-2, ↑Bax	Induce apoptosis	[130]
	Lung cancer cells	↑DNA damage ↓Bid, ↓Bcl-2, ↓procaspase-8; ↑Bax, ↑caspase-3, ↑AIF, ↑cytochrome c, ↑GRP78, ↑GADD153, ↓mitochondrial membrane potential	Induce apoptosis	[131]
		–	Induce apoptosis	[132]
	Liver cancer cells	↓Mitochondrial membrane potential, ↓Bcl-2 ↑caspase 3 ↑poly (ADP-ribose) polymerase.	Potentiate the action of 5-FU; induce apoptosis	[133]
		↑Mitochondrial membrane potential, ↑mitochondrial swelling, ↑cytochrome c, ↑caspase-3	Induce apoptosis	[134]
	Papillary thyroid cancer cells	↑DNA damage, ↑beclin-1, ↓p62 ↑formation of acidic vesicular organelles (AVOs), ↓Cdc25	Induce autophagy	[135]
	Ovarian cancer cells	↑Mitochondrial depolarization, ↑caspase-3, ↑Bax, and ↓Bcl-2	Potentiate the action of paclitaxel; induce apoptosis	[136]
	Cervical cancer cells	↑caspase-2	Potentiate the action of paclitaxel; induce apoptosis	[137]

3.1. Flavanols

3.1.1. (-)-epigallocatechin gallate (EGCG)

EGCG is one of the extensively studied flavonoids due to its characterization as the main constituent of green tea, a herb that is associated with several health benefits [30]. Indeed, green tea elicits protective capacity against cardiovascular diseases, cancer, obesity, neurodegenerative disorders, diabetes, and several other pathologies [138]. The anti-malignant effect of EGCG is due to its ability to inhibit initiation, promotion, and progression of cancer [71,139].

The notion that EGCG inhibits tumor initiation is supported by evidence showing that it attenuates ROS-mediated DNA damage in premalignant cells [140]. These effects have also been reported in vivo in models utilizing several types of cells, such as hepatocytes, lymphocytes, and colonocytes [70,71]. The antimutagenic activity of EGCG lies in its ability to donate electrons and thus inactivate electrophilic carcinogens such as 2-hydroxyamino-3-methylimidazo[4,5-*f*]quinoline, a mutagen present in cooked meat [72].

EGCG also exerts anti-promotion and anti-progression effects in several cancer types. For instance, EGCG protects against 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)-induced malignant transformation of breast cancer cells [73]. PhIP, a carcinogen that is also present in cooked meat, is known to induce several cellular processes that are considered hallmarks of cancer [141]. These include the anchorage independent growth, invasion, reduced need for growth factors, and migration. The stated PhIP-induced processes are intimately linked to the activation of the NOX1/ROS axis in premalignant and malignant cells [73]. Interestingly, treatment of these cells with EGCG significantly reduced NOX1/ROS signaling and halted the tumorigenic processes [73].

A battery of EGCG anticancer mechanisms appear to be due to its ability to diminish ROS-mediated NF-κB activation, a potent driver of several signaling molecules implicated in cancer-related phenotypes [139,142]. Indeed, tumor necrosis factor alpha (TNF-α), a major contributor to the promotion and progression of different cancers [143], is suppressed by EGCG [74,75]. Additionally, EGCG's attenuation of NF-κB suppresses nasopharyngeal cancer [76] by inhibiting metastasis, reducing self-renewal capacity, and preventing epithelial-mesenchymal transition (EMT). Moreover, in fibrosarcoma for example, the antioxidant capacity of EGCG underlies this flavonoid's ability to evoke apoptosis by inactivating NF-κB, which in turn suppresses the anti-apoptotic protein, Bcl2 (Fig. 5) [77]. In addition, EGCG can suppress invasion and metastasis by inhibiting matrix metalloproteases 2 and 9 (MMP-2 and MMP-9) expression [78,79,144] (Fig. 5). EGCG-induced downregulation of MMPs is mediated by suppressing phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) [78]. Given that ROS inhibit MAPK phosphatases, which negatively regulate MAPK [145], we speculate that decreasing ROS levels and subsequent ERK1/2 phosphorylation inhibition contribute, at least partly, to the antioxidant effects of EGCG in preventing and treating fibrosarcoma.

Interestingly, several studies have reported that the anticancer effects of EGCG are mediated by pro-oxidant functions rather than antioxidant ones. As previously mentioned, flavonoids mitigate free radical production via the Fenton reaction by binding iron. However, EGCG deviates from this property by exhibiting a pro-oxidative effect manifested by driving the Fenton reaction forward and generating more radicals [146]. Indeed, EGCG exhibits a high reducing power on Fe^{3+} thus promoting the reaction and producing more free radicals [146]. Moreover, EGCG-dependent ROS production underlies the compound's pro-apoptotic effects in several cancer types. For instance, in pancreatic cancer cells, EGCG induces cell cycle arrest and promotes apoptosis [147] by provoking mitochondrial damage, ROS level elevation, and c-Jun N-terminal kinase (JNK) activation [101]. Similarly, in glioma cells, EGCG-induced apoptosis is mediated by ROS production and subsequent JNK phosphorylation [102]. Likewise, EGCG exhibits pro-apoptotic effects in lung cancer cells both in vitro and in vivo via increasing ROS levels and subsequent DNA damage [103]. Interestingly, these deleterious effects were not observed in normal organs of EGCG-perfused mice indicating a selective role of the drug towards

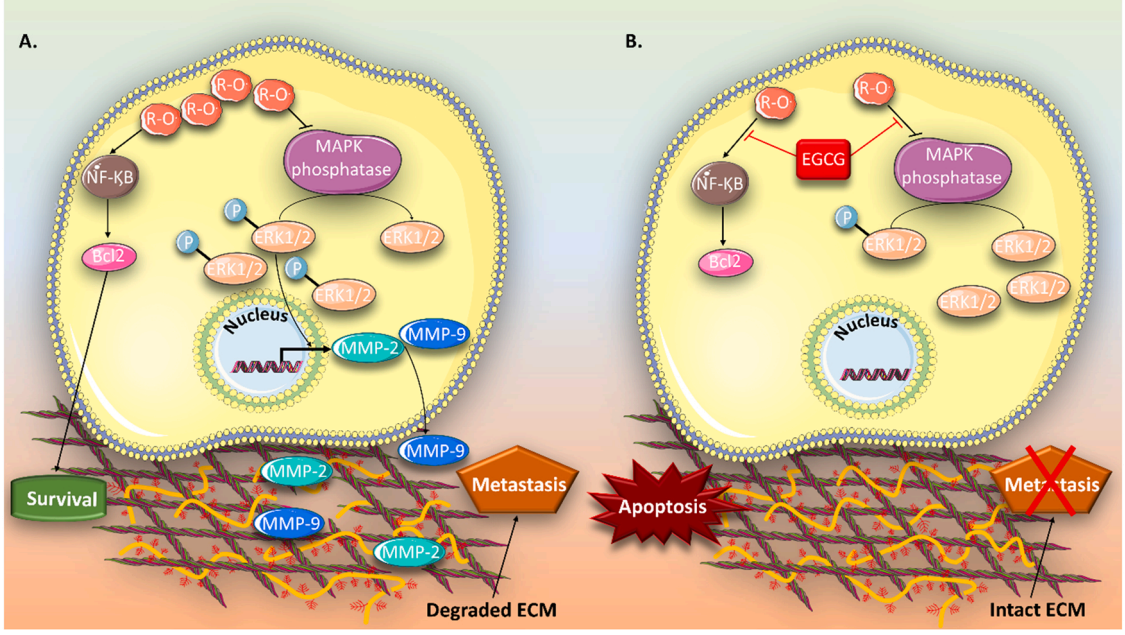


Fig. 5. Comparison between untreated and EGCG treated fibrosarcoma cells: (a) In the untreated cells, the elevated ROS levels activate NF-κB which in its turn activates the antiapoptotic protein Bcl-2 promoting cell survival. In parallel, ROS suppresses the action of MAPK phosphatase leading to the accumulation of ERK1/2 proteins in their phosphorylated active state. Subsequently, ERK1/2 enhance the expression of MMP-2 and MMP-9, which in their turn degrade the ECM and promote metastasis of the malignant cells; (b) The treatment of fibrosarcoma with EGCG alleviates oxidative stress. This prevents the activation of the NF-κB/Bcl-2 pathway and causes apoptosis of the cells. Furthermore, the lack of ROS lifts the inhibition off MAPK phosphatases, which in their turn deactivate ERK1/2. This blocks the expression of MMPs, preserves the ECM and hinders metastasis.

malignant cells [103]. Similarly, oxidative stress-dependent apoptosis is well-documented in prostate cancer cells [104] and malignant B lymphocytes [105], but the underlying mechanisms are yet to be explored.

3.2. Flavanones

3.2.1. Hesperidin/ Hesperetin

Hesperidin and its aglycone, hesperetin, are famous flavanones that are abundant in citrus fruits, mainly sweet oranges, mandarin, and clementine [32]. The two compounds do not only differ by their structure, but also by their absorption profiles. While hesperetin is directly absorbed by the enterocytes of the small intestine, hesperidin must be metabolized by the colon microbiota before being absorbed by the enterocytes [148]. This means that the former is more rapidly absorbed than the latter. Interestingly, hesperetin's bioavailability and distribution in biological systems can be further enhanced using polymeric nanoparticles [149]. This then makes hesperetin a promising therapeutic molecule.

Many of the anticancer effects of hesperidin are owed to its ability to abrogate ROS generation or suppress oxidative stress-induced genome instability and DNA damage induced by nicotine in lung cells (Fig. 6) [80,81]. It is well-known that mutagenic effects of carcinogens like nicotine are pivotal for initiating carcinogenesis and acquiring new malignant characteristics [63]. Therefore, hesperidin's role in blocking the genotoxicity of these molecules hinders carcinogenesis. In addition, hesperidin was also shown to inhibit carcinogen-induced proliferation of malignant cells. For instance, in lung cancer cells, hesperidin inhibited ROS-mediated benzo(a)pyrene (BaP)-induced proliferation by promoting the cells' antioxidant capacity (Fig. 6) [82]. Furthermore, hesperidin reduces acetaldehyde-induced invasive potential of hepatocellular carcinoma. This is achieved by blocking the activities of two ROS-activated transcription factors, NF-κB and activator protein 1 (AP1) [83]. Therefore, hesperidin, through its antioxidant effect, attenuates the actions of NF-κB and AP1 and subsequently diminishes the pro-invasive actions of MMP-9 [83]. These results are mirrored in liver cancer induced by 12-O-tetradecanoylphorbol-13-acetate [84]. Interestingly, the ROS-scavenging effects of hesperidin are sometimes associated with suppression of MMP-mediated invasiveness [81] (Fig. 6). Likewise, hesperidin exhibits prominent antioxidant-related cytocidal effects in several carcinomas, namely larynx, cervix, and breast [85]. However, the implicated mechanisms behind these effects are yet to be elucidated.

Similar to hesperidin, hesperetin also possesses anticancer potential derived from its antioxidant effects. In lung cancer cells, hesperetin prevents the release of lipid peroxidation products, such as malondialdehyde (MDA), subsequent to BaP-induced ROS production. This inhibits the interaction of MDA with DNA and nullifies the resulting

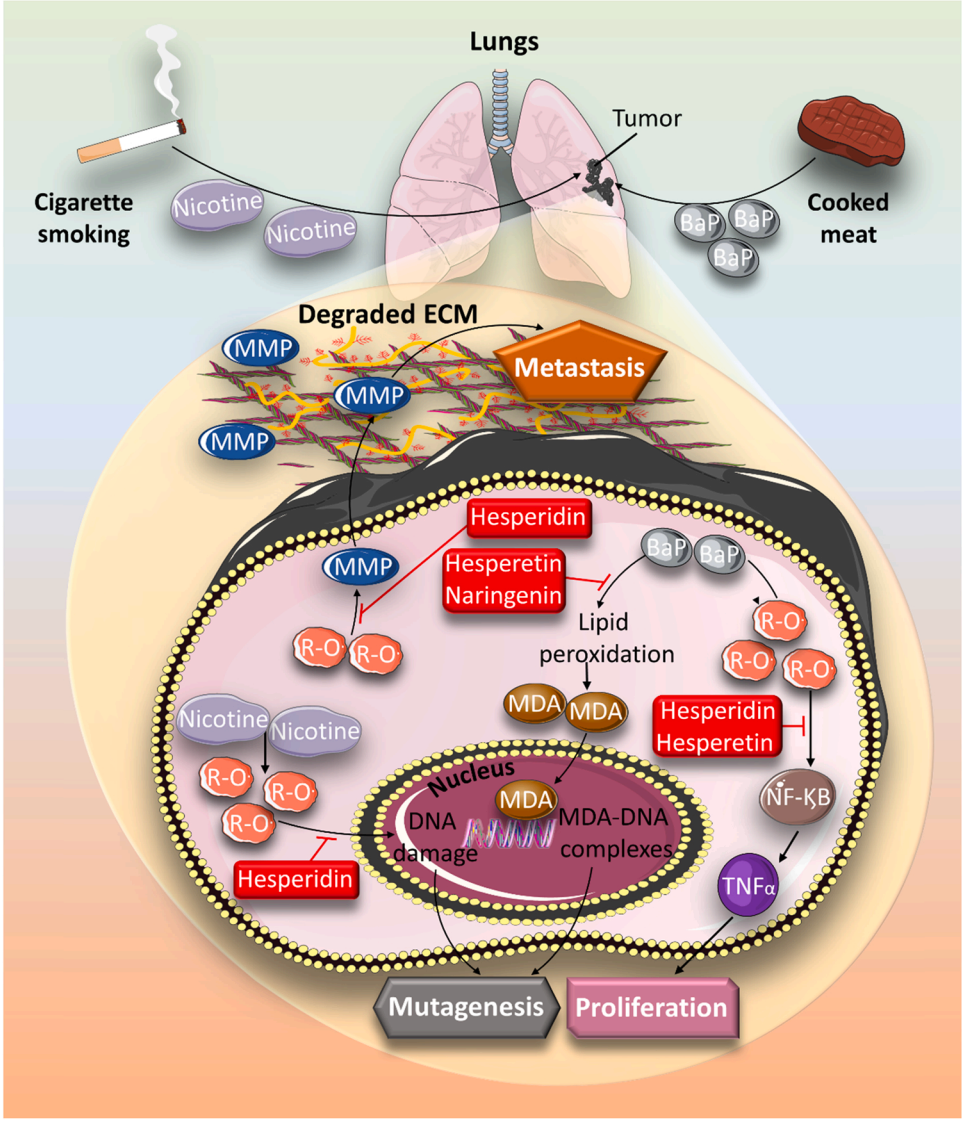


Fig. 6. The different functions of hesperidin, hesperetin, and naringenin in blocking BaP- and nicotine-induced lung carcinogenesis. BaP, a carcinogen present in cooked meat, promotes oxidative stress in lung cancer cells. This leads to activation of the NF-κB/TNF-α axis, which in its turn precipitates pro-proliferative effects. However, hesperidin and hesperetin have the capacity to prevent the ROS-mediated activation of NF-κB and the resulting proliferation of lung cancer cells. Moreover, BaP exposure is capable of inducing lipid peroxidation and production of MDA. The latter is known to form complexes with DNA leading to genotoxicity. Interestingly, both hesperetin and naringenin can prevent the BaP-induced lipid peroxidation and thus prevent mutagenesis. A similar result is also achieved by hesperidin against the nicotine-induced DNA damage. Finally, hesperidin can alleviate the ROS-mediated promotion of MMPs activity, therefore, hindering metastasis.

deleterious events (Fig. 6) [86]. Besides offsetting mutagenesis, hesperetin is also capable of halting BaP-induced proliferation of these cells. Hesperetin's antiproliferative effects are mediated by the inhibition of BaP/ROS/NF-κB pathway and the subsequent alleviation of expression of the pro-proliferative transcription factor, TNF-α (Fig. 6) [86,143].

In a similar fashion to EGCG, both hesperidin and hesperetin play pro-oxidative roles in certain types of cancer. Indeed, hesperidin suppresses the antioxidant activity of glutathione transferase [150], while hesperetin blocks the action of catalase, superoxide dismutase, and glutathione peroxidase [107]. These characteristics partly explain the rise of ROS seen upon treatment of certain cancer cell types with these flavanones. In this context, it has been shown that hesperidin induces a substantial rise in ROS levels in human cervical cancer cells. This oxidative stress promotes mitochondrial damage and leads to cell cycle arrest and increased apoptosis in the malignant cells [106]. In parallel, hesperetin treatment of colon adenocarcinoma cells promotes accumulation of ROS, which in turn elicits pro-apoptotic effects mediated by Bax activation and Bcl2 suppression [107]. Similarly, hesperetin induces oxidative stress in gastric cancer cells and shifts the balance towards the pro-apoptotic protein Bax [108]. Furthermore, hesperetin promotes Bax/ caspase 9-mediated apoptosis in breast cancer cells via ROS-induced activation of apoptosis signal-regulating kinase-1 (ASK1)/ JNK signaling [109].

3.2.2. Naringenin

Naringenin is a flavanone with promising anticancer effects owed to its ability to suppress cellular oxidative stress. It is abundant in citrus fruits, especially grapefruit and garden thyme [32,33]. By suppressing oxidative stress, naringenin protects against hepatocarcinogenesis induced by N-nitrosodiethylamine [87]. Similarly, naringenin hinders the development of N-methyl-N′-nitro-N-nitrosoguanidine-promoted gastric carcinoma, also via its antioxidant capacity [88]. Moreover, naringenin suppresses the formation of MDA-DNA complexes generated in BaP-evoked lung carcinogenesis (Fig. 6) [89]. Furthermore, it impedes the progression of osteosarcoma by preventing ROS accumulation [90]. Besides, naringenin's antioxidant role prolongs cancer-free remission of patients with surgically removed osteosarcomas [90].

Conversely, ample evidence demonstrates that naringenin can act as an anti-cancer molecule through its pro-oxidative potential. This is attributed to the compound's inhibitory actions on the antioxidant enzyme glutathione reductase [150]. Naringenin-triggered oxidative stress produces cytotoxic effects in several cancer cell types. For instance, in placental choriocarcinoma, naringenin induces oxidative stress and subsequent apoptosis by ROS-dependent activation of ERK 1/2 [110]. On the other hand, naringenin activates the ROS/ASK1 signaling pathway leading to apoptosis of pancreatic cancer cells [111]. Furthermore, it induces oxidative stress-dependent cell-cycle block and apoptosis in epidermoid carcinoma cells [112]. It is noteworthy to mention that naringenin has the potential of being used as an adjuvant therapy for cancer treatment and an add-on therapy with other chemotherapeutic drugs. In fact, naringenin, via elevation of ROS levels, potentiates tamoxifen's action in breast cancer cells [113], as well as paclitaxel inhibition of prostate cancer progression [115]. This means that combination of naringenin with other chemotherapeutic drugs allows for lower doses to be used, thereby minimizing the likelihood of dose-dependent adverse effects [114].

3.3. Flavonols

3.3.1. Quercetin

This flavonol is present in high amounts in certain vegetables, such as kale, onions, and broccoli, and beverages namely tea infusions and red wine [34]. Unlike other flavonoids, data about the causal relationship between quercetin's anticancer effects and its antioxidant activity are limited. One of the studies highlighting this correlation was conducted in mice with Dalton's lymphoma, where quercetin appeared to induce apoptosis of malignant cells and reduce tumor size by alleviating oxidative stress and attenuating protein kinase C (PKC) signaling [91]. Similarly, quercetin's antiproliferative effects in liver cancer cell line HepG2 is attributed to its antioxidant effect and the subsequent down-regulation of cyclin A and check-point kinase 1 (CHK1) [92].

In contrast, quercetin elicits pro-oxidative effects in a vast number of cancers owing to its multifaceted activities. First, quercetin, itself, can undergo redox reactions in the cell and be transformed into a radical (Quercetin-O•) thus increasing ROS accumulation [151]. Second, the compound is known to deplete glutathione and to inhibit thioredoxin reductase, two important defenders against oxidative stress [152,153]. Interestingly, the differential anticancer effects of quercetin in different colorectal cancer (CRC) cell lines have been attributed to COX2 activation [116]. In this context, quercetin appears to be more potent in inducing oxidative stress-mediated apoptosis of HT29 compared to HCT15 cells, two CRC cell lines. This discrepancy is due to the overexpression of COX2 and subsequent dramatic elevation of ROS in HT29 but not HCT15 cells [116]. Importantly, this cytotoxicity is dependent on ROS-mediated activation of Sestrin 2/ AMP-activated protein kinase (AMPK)/ mammalian target of Rapamycin (mTOR) signaling pathway [117]. In addition, quercetin elicits ROS-mediated apoptosis in another colon cancer cell line, SW620, [118] as well as in prostate and gastric cancer cells [119,121].

Quercetin's antitumor effects in breast cancer are not as clear-cut. In fact, one study showed that treatment of MCF-7, a breast cancer cell line, with quercetin and vitamin C alleviates oxidative stress and diminishes Nrf2 activity, which in turn promotes apoptosis [93]. Alternatively, quercetin-provoked apoptosis in MCF-7 cells has been attributed to quercetin-induced accumulation of ROS in these cells [122]. In this context, it was pointed that quercetin displays biphasic effects depending on the concentration used and the treatment duration [154]. Indeed, a closer look at these contradictory studies reveals that, although similar concentrations were used, the duration of quercetin supplementation in one study was limited to 6 h [93], while it was extended to 48 h in the other one [122].

Quercetin has the potential to be a useful neoadjuvant therapy for cancer treatment. For instance, it can contribute to the radiosensitization of tumors by inhibiting Ataxia Telangiectasia Mutant protein (ATM) [94]. This protein is activated by oxidative stress and is highly implicated in the resistance of malignant cells to radiation. Therefore, owing to its antioxidant capacity, quercetin suppresses ATM and renders the cancer cells more prone to death by radiation [94]. Besides, quercetin has the potential to be a useful add-on therapy with other chemotherapeutic drugs. It potentiates the action of paclitaxel on prostate cancer cells by promoting ROS accumulation [120]. However, quercetin use in cancer treatment may be hampered by its low bioavailability, which can be greatly improved by delivering the drug using liposomal formulations [155].

3.4. Flavones

3.4.1. Luteolin

Luteolin is abundant in certain vegetables and herbs such as bell peppers, parsley, celery, and carrots [35]. This agent displays prominent anticancer effects mediated by attenuation of oxidative stress. In bladder cancer cell line T24, luteolin induces a drop in ROS levels and a subsequent inactivation of mTOR signaling resulting in cell cycle arrest and apoptosis [95]. Additionally, luteolin induces apoptosis in CRC cells by ameliorating ROS levels as well as by activating JNK and MAPK. However, the exact pathways remain to be elucidated [96]. In lung carcinoma, luteolin elicits pro-apoptotic effects by virtue of its antioxidant capacity [97]. Moreover, luteolin abolishes the invasive and metastatic capacity of squamous cell carcinoma through inhibiting Src activity and subsequently suppressing signal transducer and activator of transcription 3 (Stat3)/S100A7 pro-metastatic pathway [98]. Given that ROS activates Src [2], it is tempting to speculate that luteolin-mediated

inhibition of Src is ascribed to its antioxidant activity.

Luteolin, like the other flavonoids, displays a pro-oxidative capacity in some types of cancers and under certain conditions. For instance, ROS-mediated autophagy is observed after treatment of non-small cell lung carcinoma (NSCLC) with luteoloside, a glycoside of luteolin. The underlying mechanism appears to be an oxidative stress-dependent activation of phosphoinositide 3-kinase (PI3K) and subsequent induction of the Akt/ mTOR/ p70S6K pathway [156]. In addition, luteolin sensitizes NSCLC to radiotherapy-induced cell death via increasing ROS production [123]. Other pro-oxidant mechanisms underlying the anticancer property of luteolin have been identified. Pancreatic cancer cells maintain a slightly elevated level of ROS, which can be utilized by these cells as previously mentioned. However, this level is kept under control by Nrf2 in order to avoid an excessive deleterious increase [124] (Fig. 7A). In contrast to other flavonoids, luteolin inhibits Nrf2, which can then result in an uncontrolled accumulation of ROS, thus activating the pro-apoptotic Raf kinase inhibitory protein (RKIP) and inhibiting the pro-survival protein Snail [124] (Fig. 7B). In addition, luteolin can induce ROS-mediated apoptosis in glioblastoma [125], cervical cancer [126], hepatic cancer [127] and cholangiocarcinoma [128]. The mechanisms governing this property remain unclear. It is important to mention that the prooxidative effects of luteolin appear to be selective towards malignant cells and spare normal cells [127].

3.4.2. *Apigenin*

This flavone is abundant in celery, parsley, and chamomile infusions [36]. Apigenin shows a significant anticancer potential owing to its antioxidant capacity. Indeed, experiments on Kaposi sarcoma virus-related B-cell lymphoma clearly demonstrate that apigenin, through alleviating oxidative stress and inducing p53, can trigger autophagy [99]. ROS reduction leads to STAT3 inhibition, which is likely one of the main stimuli leading to autophagy induction [99]. Apigenin's antioxidant activity accounts also for its anticancer effect in skin carcinogenesis. In this context, apigenin-induced decrease in ROS modulates the activation of MAPK and AP1 in keratinocytes culminating in repression of MMP-1 [100], one of many enzymes known to promote skin cancers [157].

Apigenin also exerts prooxidative functions in certain cancer cell types. These effects can be attributed, in part, to glutathione depletion and inhibition of the antioxidant enzyme superoxide dismutase [129, 133]. Moreover, apigetrin, a more stable glycoside of apigenin, shows potency in inhibiting the progression of cell cycle and inducing apoptosis in gastric cancer cells [158]. Both effects are mediated by elevated ROS levels, which result in cleavage of caspase 8, activation of the pro-apoptotic Bax, and suppression of Janus kinase 2 (JAK2)/ Stat3 signaling [158] (Fig. 8). In addition, apigenin-induced ROS accumulation is implicated in promoting apoptosis of bladder cancer [129], prostate cancer [130], lung cancer [131,132], and hepatic cancer [134]. Furthermore, apigenin can cause autophagy of papillary thyroid cancer cells through oxidative stress-dependent DNA damage [135].

It is important to mention that apigenin may act as a potential add-on therapy with commonly used chemotherapeutic drugs. For instance, synergistic effects are observed when paclitaxel and apigenin are used together in ovarian and cervical cancers. These effects are attributed to apigenin's enhancement of ROS accumulation [136,137]. Similarly, the prooxidative properties of apigenin augment the cytotoxic action of 5-fluorouracil (5-FU) in hepatocellular carcinoma [133].

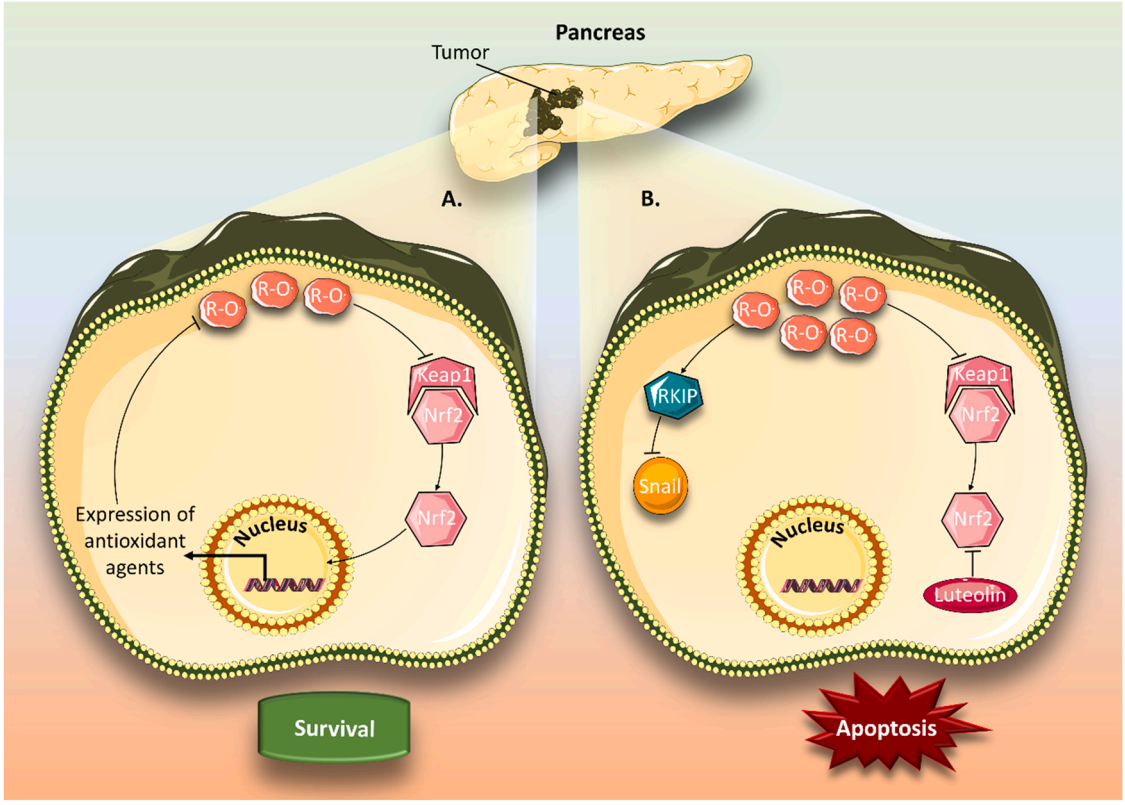


Fig. 7. Comparison between pancreatic cancer cells untreated and treated with luteolin: (a) In untreated pancreatic cancer cells, ROS levels are slightly elevated. This prevents Keap1 from binding to Nrf-2. The free Nrf-2, in its turn, acts as a transcription factor that increases the expression of antioxidant enzymes. These enzymes keep ROS levels under control and prevent excessive elevation, as part of a negative feedback loop; (b) When pancreatic cancer cells are treated with luteolin, Nrf-2is inhibited, and the feedback loop is disrupted. This elicits an uncontrolled increase in ROS levels. The incited oxidative stress activates RKIP, which blocks the pro-survival protein Snail. The end result is apoptosis of the luteolin-treated malignant cells.

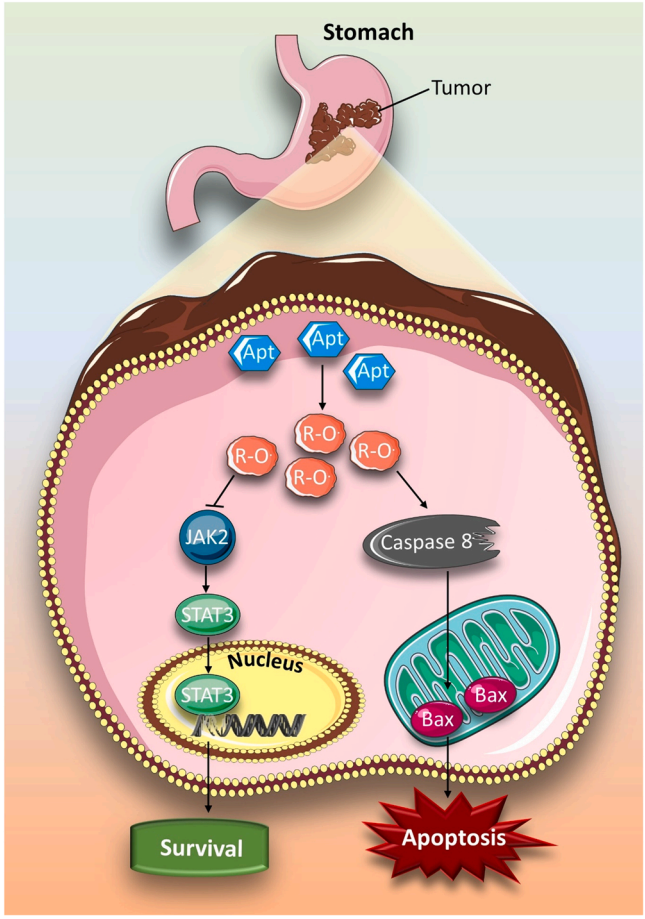


Fig. 8. The anticancer role of apigetrin in gastric cancer cells. Treatment of gastric cancer cells with apigetrin (Apt) promotes oxidative stress. The accumulated ROS promote the cleavage of caspase 8, thus activating it. Activated caspase 8 enhances the activation of the pro-apoptotic protein Bax. ROS also inhibit the JAK2/ Stat3 pro-survival pathway. ROS-mediated effects culminate in inducing apoptotic death.

4. Bioavailability, safety, toxicity, and use in human patients

One of the most concerning issues that arise when considering the incorporation of flavonoids as therapeutic drugs is their bioavailability and absorption after oral ingestion. The dominant form of flavonoids found in food is the glycosylated form. In the intestine, flavonoids are generally absorbed via two mechanisms [159]. The first involves an initial step of hydrolysis by a brush border enzyme called lactase phlorizin hydrolase (LPH). This leads to the transformation of flavonoids into their aglycone forms which can readily diffuse into intestinal epithelial cells due to their lipophilic properties [159]. The second mechanism starts with the transport of the hydrophilic glycoside form through membrane transporters such as the sodium-dependent glucose transporter (SGLT1). In this scenario, the hydrolysis step into the aglycone form occurs inside the epithelial cells through the action of cytosolic b-glucosidase (CBG) [159]. Regardless of the mechanism through which they are obtained, the aglycones then undergo selected modifications such as methylation, sulfation, or glucuronidation [160]. Some of the resulting compounds make it into the bloodstream, while others leak back into the intestinal lumen, further lowering the bioavailability of flavonoids. Even the molecules that pass into the bloodstream enter the hepatic circulation, undergo further metabolism, and can be excreted with bile [159]. Therefore, the low bioavailability of flavonoids has been one of the main obstacles impeding their official introduction into the world of pharmacotherapeutics despite their promising effects elucidated through in vivo and in vitro experiments. In fact, the feasibility of using absorption enhancers or pharmaceutical technologies to increase the bioavailability of flavonoids are being actively assessed. Modalities such as lipid-based nanoparticles, cyclodextrin-inclusion complexes, phospholipid complexes, nano-emulsions, and others are being considered [161].

Despite the numerous beneficial effects of flavonoids, their excessive intake poses serious threats to health. As with most drugs, flavonoids are absorbed and metabolized by Phase II enzymes, which carry out different glucuronidation, sulfation, and methylation reactions [162, 163]. Moreover, gut microbiota plays a role in flavonoid metabolism by cleaving the pyrone ring C, dehydroxylating, and reducing flavonoids [162,163]. Despite the different absorption routes, flavonoids reach low micromolar concentrations at best. For instance, catechin levels in plasma plateau at 1.0–3.0 μM upon ingestion of five cups of tea [162, 163]. Finally, flavonoid metabolites are excreted either in the urine or in bile [162].

The toxicity associated with flavonoids arises from their abilities to act as prooxidants, modulate cytochrome P450 (CYP450) enzyme activity, interfere with thyroid hormone production, and interact with nuclear estrogen receptors (ER) and aryl hydrocarbon receptor (AHR) among others [164–166]. In this context, flavonoid-drug interactions are observed with increased plasma concentrations of cyclosporine, felodipine, and nimodipine when taken concurrently with naringin [167]. In addition, flavonoids, in the presence of high concentrations of transient metals, can act as prooxidants leading to ROS formation that damages DNA and oxidizes lipids [165]. Indeed, EGCG was shown to promote rat colon carcinogenesis as it induces H_2O_2 production and ultimately DNA oxidation [165].

Flavonoids modulate the CYP450 enzymes resulting in an induction or inhibition of enzyme activity. Notably, the induction of the CYP1 family of microsomal enzymes is implicated in the activation of procarcinogens [60,165]. Chrysin, quercetin, and naringenin have been shown to increase CYP1A1 activity and were, thus, associated with lung carcinogenesis as well as colorectal carcinoma [60,168]. Moreover, quercetin was shown to increase the expression of CYP1A1 by binding to AHR [60,165]. On the other hand, inhibition of certain CYP1 enzymes promotes the accumulation of certain drugs and increases the risk of toxicity. For instance, the bronchodilator theophylline, which is metabolized by CYP1A2, accumulates in the presence of the enzyme inhibitors daidzein and naringin [60]. Naringin also inhibits CYP3A4 impairing the metabolism of calcium channel blockers, statins, and cyclosporine [60,165]. Moreover, quercetin and its metabolites are both high affinity substrates of serum albumin and competitive inhibitors of CYP2C9 [169]. Warfarin, an anticoagulant drug, is mostly bound to albumin and metabolized by CYP2C9 [170]. Therefore, quercetin, especially at high concentrations, increases the concentration of free unbound warfarin prompting warfarin toxicity in patients [169]. It is worth mentioning that flavonoids are capable of releasing warfarin from serum albumin in greater amounts when compared to non-steroidal anti-inflammatory drugs (NSAIDs) and loop diuretics [170].

Some flavonoids have been shown to be teratogenic and detrimental to development in laboratory studies. Amphibian embryos were dead 24 and 48 h following exposure to high concentrations of naringenin (16 and 25 mg/L), whereas those treated with lower concentrations suffered developmental behavioral and physical defects [166]. This experimental teratogenicity of flavonoids was further corroborated with the ovarian dysfunction and reduced fertility accompanying the use of genistein in mice [164]. Furthermore, the prolonged use of hydroxyethylrutoside (HER), a flavonoid derivative used clinically in pregnant vascular diseases, is associated with coloboma, a congenital ocular abnormality [171]. In addition, some flavonoids, such as genistein and quercetin, act as topoisomerase-II inhibitors leading to fetal DNA lesions at the MLL gene [163]. This accounts for the increased risk of infant acute myeloid leukemia with excessive maternal intake [163]. These findings necessitate more research studies to thoroughly tackle other flavonoid effects

on human adults and neonates.

Flavonoids' toxicity can also be attributed to their modulatory effect on DNA, thyroid hormone production, and estrogen receptors. Quercetin has been shown to cause deleterious effects on DNA strands in the Ames test [163]. In addition, quercetin, genistein, kaempferol, and naringenin have been shown to reduce iodide absorption and inhibit thyroxine as well as thyroid peroxidase synthesis. This inhibition blocks the negative feedback system resulting in increased levels of thyroid stimulating hormone and thyroid hyperplasia [163]. Besides, flavonoids such as apigenin, genistein, and kaempferol have been reported to stimulate estrogen receptors [165]. Indeed, increased intake of these compounds negatively affects male reproductive health and increases the risk for breast and genital tract tumors in humans [165]. Moreover, EGCG has been documented to induce anemia, growth retardation, and hepatic injury in animal studies due to its pyrogallol and gallic acid moieties [165]. Further, the commercial dosage form of catechin has been revealed to provoke hemolytic anemia and/or thrombocytopenia in humans [165].

Although flavonoids demonstrate variable toxicity profiles, they remain rather safe chemicals. In fact, the aforementioned adverse effects rarely occur by diet alone [163]. This is reinforced by studies showing no adverse effects with daily flavonoid consumption up to 68 mg [162, 163]. However, supplementation by pills or other formulations can greatly increase flavonoid concentrations in the body and increase their toxicity risk [163].

Alongside, flavonoids can also be utilized to reduce multidrug resistance especially in cancers. Overexpression of ATP binding cassette transporters such as P-glycoprotein (P-gp) and multidrug resistance associated protein (MRP1/2) is one of the main causes for multidrug resistance [165,167]. These transporters cause the efflux of a variety of substrates, especially anticancer agents, out of cells [167]. Flavonoids, such as biochanin A, EGCG, and quercetin, were shown to inhibit P-gp mediated efflux of doxorubicin, thus increasing its cytotoxicity [165, 167]. It should be noted, however, that quercetin stimulates P-gp efflux at low concentrations but inhibits it at higher concentrations [167]. Furthermore, some flavonoids are capable of inhibiting MRP1 at concentrations less than 10 μM [167]. However, the inhibition of MRP2 causes conjugated hyperbilirubinemia in a similar manner to Dubin-Johnson syndrome [167]. Conversely, some flavonoids, especially luteolin, were found to elicit a synergistic effect on imatinib cytotoxicity in K562 chronic myeloid leukemia cells, even when combined in half doses[172].

Nevertheless, literature on flavonoids use in human cancer is still scarce. Interestingly, one drug that has advanced to phase II trials is flavopiridol, a flavonoid derived cyclin dependent kinase-9 (CDK9) inhibitor, which triggers apoptosis in chronic lymphocytic leukemia patients (CLL) [165]. Multiple phase II studies have been carried out, with most of them showing promising results in CLL patients. Patients with refractory and genetically high risk CLL were treated with a 30 mg/m^2 30-minute intravenous bolus (IVB) of flavopiridol followed by a 30 mg/m^2 4-hour continuous intravenous infusion (CIVI) for dose 1, which was then incremented to 30 mg/m^2 IVB and 50 mg/m^2 CIVI for dose 2 and all subsequent treatments [173]. 53% of the enrolled patients responded to therapy with one complete remission [173]. Diarrhea was the main adverse effect reported, as expected by phase I trials [165,173]. It was also proposed that conjugated hyperbilirubinemia can be observed as a result of MRP2 inhibition by flavopiridol [167]. Flavopiridol was also administered in a phase II trial for relapsed mantle cell lymphoma. The drug maintained the stability of the disease with few partial responses [174]. However, other phase II clinical trials pertaining to metastatic renal cancer and advanced gastric carcinoma were disappointing with no significant results [175,176]. Based on that, flavopiridol exhibits an anti-cancer potential that should be further explored in various combinations with other chemotherapeutic drugs and dosage scheduling. Despite inconsistent trial results, we speculate that flavonoids are capable of becoming part of cancer therapeutic regimens in the future. Whether added as adjuvants to previously known and proven treatments or on their own, the potential flavonoids possess can prove essential in treating cancer patients and improving their prognoses.

5. Concluding remarks

Flavonoids, albeit to variable degrees, have a well-established antioxidant role that confers many of their health protective functions. However, their anticancer activities are associated with differential effects on ROS level depending on cancer type, cell line, oxidative state of the cell, amount of flavonoid used, and duration of exposure (Table 3 and 4). It is well established that ROS are pivotal players in cancer cells. They interact with pathways underlying DNA damage, inflammation, proliferation, cell death, angiogenesis, and metastasis. Therefore, by controlling ROS levels, flavonoids are capable of hindering the initiation, promotion, and progression of cancer via several mechanisms, of which we tried to unravel the most significant.

Besides being potently effective against a wide variety of cancers in vitro and in vivo, flavonoids are recognized as attractive candidates for cancer therapy research given the fact that they are naturally derived compounds. This means that they can be relatively easily extracted from plants which constitute our daily diet. Nevertheless, these results merit to be properly extrapolated to humans to assess the efficacy and safety and to explore their potential clinical utility in cancer treatment.

CRediT authorship contribution statement

Ali H. Eid: Conceptualization, Writing – review & editing, Resources, Formal analysis, Supervision, Project administration, Funding acquisition. **Hasan Slika:** Writing – original draft, Data curation. **Hadi Mansour:** Writing – origina draft, Data curation. **Nadine Wehbe:** Writing – original draft. **Suzanne A. Nasser:** Writing – original draft. **Tarek Ghaddar:** Writing – original draft, Data curation, Resources. **Rabah Iratni:** Writing – review & editing, Formal analysis. **Gheyath Nasrallah:** Writing – review & editing, Formal analysis. **Abdullah Shaito:** Writing – review & editing, Formal analysis. **Firas Kobeissy:** Writing – review & editing, Formal analysis. Investigation: N/A.

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NA.

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Authors' Contributions

A.H.E. conceived of the manuscript. H.S., H.M., N.W., S.A.N., R.I, H. Y., T.G., F.K., and A.H.E contributed to the writing, editing, and drawing. A.H.E made the final edits.

Conflict of interest statement

The authors declare that they have no competing interests.

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