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Flavonoids and their derivatives as DNA topoisomerase inhibitors with anti-cancer activity in various cell models: Exploring a novel mode of action

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ABSTRACT

Flavonoids, a diverse group of plant-derived secondary metabolites, have garnered significant attention for their potential anti-cancer properties. This review explores the role of flavonoids as inhibitors of DNA topoisomerases, key enzymes essential for DNA replication, transcription, and cell division. The article offers a comprehensive overview of flavonoid classification, biosynthesis, and their widespread natural occurrence. It further delves into the molecular mechanisms through which flavonoids exert their anti-cancer effects, emphasizing their interactions with topoisomerases. The review provides a thorough analysis of both in vitro and *in vivo* studies that highlight the topoisomerase inhibitory activities of various flavonoids and their derivatives. Key findings demonstrate that flavonoids can function as catalytic inhibitors, poisons, or DNA intercalators, affecting both type I and type II topoisomerases. The structure-activity relationships of flavonoids concerning their topoisomerase inhibitory potency are also examined. This review underscores the potential of flavonoids as promising lead compounds for the development of novel topoisomerase inhibitors, which could have important implications for cancer therapy. However, it also acknowledges the need for further research to fully understand the intricate interactions between flavonoids and topoisomerases within the cellular environment.

1. Introduction

Flavonoids are a group of secondary metabolites present in many plants. They are characterized by polyphenolic compounds consisting of two benzene rings (A and B) joined by a three-carbon heterocyclic ring (C), forming the main skeleton [1]. This unique structure undergoes various modifications, enabling flavonoids to engage in many key biochemical interactions occurring in organisms. Flavonoids are well known to have various anti-inflammatory, antioxidant and anticancer properties [2,3]. Their anticancer properties may derive from their ability to interfere with topoisomerase activity. Topoisomerase plays key roles in gene transcription, translation, recombination, and cell proliferation [4]. During replication and transcription, topoisomerase maintains the topology of the DNA, where it splits upstream and downstream of the active sites, producing supercoils. Topoisomerases regulate these supercoils by relaxing the DNA and changing its tertiary structure without affecting the primary structure [5]. Flavonoids can inhibit topoisomerases in several ways. One method is catalytic inhibition, where flavonoids interfere with the catalytic cycle of topoisomerase without stabilizing the cleavable complex [6]. For example, fisetin is a flavonol that acts as a catalytic inhibitor [7]. Alternatively, quercetin, myricetin, and genistein distort the double helix through intercalation, thereby obstructing the binding of topoisomerase to DNA. Furthermore, quercetin and anthocyanins can interact with topoisomerase poisons [8]. Additionally, flavonoids have the ability to generate reactive oxygen species (ROS), which can further inhibit topoisomerase activity [9].

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The potential of flavonoids to inhibit DNA topoisomerase activity makes them desirable candidates as agents for use in cancer therapy. The aim of this study is to evaluate the potential of flavonoids and their derivatives as DNA topoisomerase inhibitors in *in vitro* and *in vivo* models.

2. Study design

The research work included in this review focused on *in vitro* and *in vivo* studies of flavonoids and their derivatives taken from plants. The studies discuss the mechanisms by which flavonoids inhibit DNA topoisomerase activity, excessive cellular proliferation and apoptosis induction *in vitro* and *in vivo*. The review includes data published between 2000 and 2024 obtained from the NCBI-PubMed and Google Scholar databases. The following keywords were selected: flavonoids and their derivatives, DNA topoisomerase I and II, *in vitro*, *in vivo*, flavonoids and their derivatives as DNA topoisomerase inhibitors in different cellular models. Articles published in languages other than English were excluded from the analysis, as were duplicate articles from different databases. Each selected scientific article was analyzed and the following data were selected and tabulated according to *in vitro* or *in vivo* studies: compound/substance, plant, pure/extract, organism/cell line, activity or mechanism of action and reference.

3. Flavonoids as natural polyphenolic compounds

Flavonoids are ubiquitous in the plant kingdom, occurring in a wide variety of fruits, vegetables, and other plant-based foods. They are particularly abundant in berries, citrus fruits, apples, onions, parsley, and legumes. Beverages such as tea, red wine, and certain fruit juices are also rich sources of flavonoids. These compounds are found in various parts of plants, including leaves, flowers, fruits, seeds, stems, and roots. The concentration and types of flavonoids can vary significantly depending on factors such as plant species, growing conditions, ripeness, and post-harvest processing [10]. In plants, flavonoids serve multiple crucial functions. They act as potent UV protectants, shielding sensitive plant tissues from harmful ultraviolet radiation. Many flavonoids contribute to the vibrant colors of flowers and fruits, playing a role in attracting pollinators and seed dispersers. These compounds are also integral to plant defense mechanisms, offering protection against various pathogens and herbivores. Furthermore, flavonoids function as signaling molecules in plant-microbe interactions and have been implicated in the regulation of auxin transport, influencing plant growth and development. Flavonoids are a class of secondary metabolites characterized by a 15-carbon skeleton arranged in two aromatic rings (A and B) connected by a three-carbon bridge, usually in the form of a heterocyclic ring (C) [11]. They are synthesized via the phenylpropanoid metabolic pathway. This process begins with phenylalanine and involves various enzymes, including chalcone synthase and flavonoid 3′-hydroxylase [12]. Flavonoid compounds undergo numerous modifications, such as glycosylation, acylation, and molecular polymerization, which depend on the oxidation state of the heterocyclic ring and the number of hydroxyl or methyl groups on the benzene ring [13]. These modifications significantly alter the chemical properties and biological activities of the original flavonoid compounds, leading to a diverse range of derivatives used in various applications, including nutrition, medicine, and cosmetics [14].

Flavonoids can be classified according to various criteria, reflecting their diverse structural characteristics and natural occurrence. One classification method is based on the oxidation state of the C-ring, resulting in six main subgroups: flavanols (such as catechins), flavanones, flavones, flavonols, anthocyanidins, and isoflavones. Another classification considers the position of the B-ring attachment to the C-ring, where flavonoids have the B-ring attached at C2, isoflavonoids at C3, and neoflavonoids at C4. Additionally, flavonoids can be categorized based on the presence of specific functional groups, including O-glycosides, C-glycosides, methylated flavonoids, prenylated flavonoids, and sulfated flavonoids. Furthermore, flavonoids are often classified according to their natural sources. For instance, citrus fruits are rich in flavonoids like hesperidin and naringenin, while soybeans contain isoflavones such as genistein and daidzein. Tea is a primary source of catechins, including epigallocatechin gallate, and berries are abundant in anthocyanidins like cyanidin and delphinidin. This multifaceted classification system reflects the complexity and diversity of flavonoid structures found in nature, each with potentially unique biological activities. Through these modifications, scientists have been able to divide this large group into nine major subgroups. Flavones are characterized by a double bond between positions 2 and 3 and a ketone in position 4 of the C-ring, lacking a hydroxyl group at position 3, which distinguishes them from flavonols. Common examples include luteolin and apigenin, found in celery, parsley, and many herbs. These compounds have been studied for their anti-inflammatory and anti-cancer properties [11]. Flavonols are similar to flavones but have a hydroxyl group at the 3-position of the C-ring. Quercetin, kaempferol, and myricetin are well-known flavonols, widely distributed in fruits and vegetables, with high concentrations in onions, kale, and berries. Flavonols have been associated with cardiovascular health benefits and potential neuroprotective effects [15]. Flavanones lack the double bond between positions 2 and 3 of the C-ring and are particularly abundant in citrus fruits, with naringenin and hesperetin being common examples. These compounds have been studied for their potential effects on lipid metabolism and cardiovascular health [16]. Flavanonols, also known as dihydroflavonols, have a hydroxyl group at position 3 of the C-ring but lack the double bond between positions 2 and 3. Taxifolin is a well-known example, and these compounds are less common in nature compared to other flavonoid subclasses [17]. Isoflavones have their B-ring attached at position 3 of the C-ring, rather than position 2 as in other flavonoids. They are sometimes called "phytoestrogens" due to their structural similarity to estrogen. Genistein and daidzein, found in soybeans, are well-known isoflavones, extensively studied for their potential effects on hormone-related conditions and bone health [18]. Flavanols, also called catechins, have a hydroxyl group at position 3 of the C-ring and no ketone group at position 4. Epigallocatechin gallate (EGCG) from green tea is a famous example. Flavanols are known for their strong antioxidant properties and potential health benefits, particularly in cardiovascular and metabolic health [19]. Anthocyanidins are the aglycone forms of anthocyanins, responsible for the red, purple, and blue colors in many fruits and flowers. They have a positively charged oxygen atom in the C-ring. Cyanidin, delphinidin, and pelargonidin are common examples, studied for their antioxidant properties and potential benefits in eye health and cognitive function [20]. Chalcones are considered a subclass of flavonoids, although they have an open C-ring. They serve as precursors for other flavonoids in the biosynthetic pathway. Phloretin is an example of a chalcone, and these compounds have been investigated for their potential anti-inflammatory and anticancer properties [21]. Lastly, aurones are less common flavonoids with a benzofuranone structure, contributing to the yellow color in some flowers. While less studied than other flavonoid subclasses, aurones have shown potential antifungal and anticancer activities in preliminary research [22]. These subgroups are presented in Table 1.

These subclasses of flavonoids exhibit diverse biological activities, often related to their specific structural features. Variations in their chemical structures contribute to differences in bioavailability, metabolism, and potential health effects. Ongoing research continues to explore the unique properties and potential applications of each flavonoid subclass.

The potential health benefits of flavonoids for humans have been the subject of extensive research. Their most well-known property is their antioxidant activity, which helps neutralize harmful free radicals in the body. This antioxidant action is thought to contribute to their anti-inflammatory effects, potentially reducing the risk of chronic diseases associated with inflammation. Numerous studies have investigated the

Table 1
Subdivision of flavonoids into seven major subgroups.

Subclass of Flavonoid	Structure	Major compound	Plants (selected examples)	Properties	Ref.
Flavones	$C_{15}H_{10}O_2$	apigenin, luteolin, baicalein, chrysin	*Apium graveolens* (L.), *Capsicum annuum* (L.), *Mentha* (L.), *Matricaria chamomilla* (L.), *Petroselinum crispum* ((Mill.) Mansf.), *Ginkgo biloba* (L.)	anti-inflammatory anti-cancer	[11, 23–26]
Flavonols	$C_{15}H_{10}O_3$	limocitrin, kaempferol, quercetin, isorhamnetin	*Malus domestica* (Borkh.), *Solanum lycopersicum* (L.), *Allium cepa* (L.), *Vitis vinifera* (L.), *Lactuca sativa* (L.)	cardiovascular health benefits potential neuroprotective effects	[15, 27–34]
Flavanols	$C_{15}H_{12}O_2$	hespertin, eriodictyol, naringin, naringenin, likvirtin, pinocembrin, hesperidin	*Pyrus communis* (L.), *Musa* (L.), *Vaccinium corymbosum* (L.), *Malus domestica* (Borkh.)	lipid metabolism, cardiovascular health	[19, 35–39]
Flavanonols	$C_{15}H_{12}O_7$	Taxifolin, aromadedrin	*Allium cepa* (L.) *Eucalyptus sp.*	anti-infl ammatory, anti-oxidant, anti-diabetic	[17,40, 41]
Flavanones	$C_{15}H_{14}O_2$	catechin, epicatechin, gallocatechin 3-gallate, catechin 3-gallat, gallocatechin, epicatechin 3-gallate, epicatechin 3-gallate	*Citrus aurantiifolia* ((Christm.) Swingle), *Citrus paradisi* (Macfad.), *Citrus sinensis* ((L.) Osbeck), *Citrus limon* ((L.) Osbeck), *Citrus reticulata* (Blanco)	strong antioxidant, potential health benefits, particularly in cardiovascular and metabolic health	[16, 42–45]
Isoflavonoids	$C_{15}H_{10}O_2$	genistein, daidzin	*Glycine max* (L.)	hormone-related conditions, bone health	[18,46]
Neoflavonoids	$C_{15}H_{12}O_2$	benzoyl benzenes, dalbergia phenols, dalbergia lactones, dalbergia quinones	-		[47,48]
Anthocyanins	$C_{15}H_{11}O_+$	Delphinidin, petunidin, cyanidin, malvidin, peonidin, pelargonidin	*Ribes nigrum* (L.), *Vitis vinifera* (L.), *Rubus sp.*	benefits in eye health, cognitive function	[20, 49–53]
Aurones	$C_{15}H_{12}O_2$	Sulfuretin, leptosidin, rihydroxyaurone, Isoaurone, isoaurostatin, colchicine, isobenzofuranone,	*Coreopsis tinctoria* (Nutt.), *Leptospermum scoparium* (J.R.Forst. & G.Forst.), *Antirrhinum majus* (L.)	antifungal, anticancer	[22,54]

anticancer properties of various flavonoids, with some showing promising results in inhibiting cancer cell growth and inducing apoptosis in laboratory settings. Flavonoids have also been associated with cardiovascular health benefits, including improved blood pressure regulation and a reduced risk of heart disease. Emerging research suggests neuroprotective effects, with potential implications for cognitive function and neurodegenerative disorders [55,56].

Flavonoids may interact with other nutrients in various ways. They can reduce glucose absorption by suppressing carbohydrate-hydrolyzing enzymes, such as alpha-amylase and alpha-glucosidase, and the glucose transporter in the intestinal lining. Fat intake enhances the bioavailability of flavonoids and their intestinal absorption by increasing the secretion of bile salts, which promotes the incorporation of flavonoids into micelles. Conversely, protein intake may decrease the bioavailability of flavonoids, affecting both their antioxidant efficacy and protein digestibility. Additionally, the gut microbiome plays a crucial role in the absorption and metabolism of flavonoids [57–61].

4. Molecular mechanisms of flavonoid anticancer activity

Flavonoids have garnered significant attention in cancer research due to their potent anticancer properties. These naturally-occurring substances have demonstrated the ability to alleviate cancer symptoms through multiple mechanisms, offering a multi-faceted approach to cancer prevention and treatment [62,63]. The anticancer effects of flavonoids are particularly noteworthy due to their ability to target various hallmarks of cancer simultaneously, making them promising candidates for both chemoprevention and as adjuncts to conventional cancer therapies [64]. One of the most striking features of flavonoids is their dual role in cellular homeostasis. Under normal physiological conditions, flavonoids function as potent antioxidants, protecting cells from oxidative stress and maintaining cellular redox balance [65]. However, in cancer cells, these same compounds can act as pro-oxidants, selectively inducing oxidative stress and triggering apoptotic pathways [66]. This dichotomy in their action underlies many of their anticancer effects and contributes to their selective toxicity towards cancer cells [62,63]. The anticancer activities of flavonoids encompass a wide range of cellular processes. They have been shown to inhibit cell proliferation, a fundamental characteristic of cancer cells, by interfering with various signaling pathways involved in cell growth and division. Flavonoids can also induce cell cycle arrest, typically at the G2/M or G1/S checkpoints, preventing cancer cells from completing their replication cycle. Moreover, these compounds are potent inducers of apoptosis, the programmed cell death pathway often dysregulated in cancer cells [62,63]. In addition to their direct effects on cancer cell survival and proliferation, flavonoids exhibit significant anti-metastatic properties. They can inhibit the invasion and migration of cancer cells, crucial steps in the metastatic cascade. This is achieved through various mechanisms, including the modulation of matrix metalloproteinases (MMPs) [67] and the inhibition of angiogenesis, the formation of new blood vessels essential for tumor growth and spread [68]. Flavonoids exert their anticancer effects through modulation of various signaling pathways that are crucial for cancer cell survival, proliferation, and metastasis. This modulation involves complex interactions with multiple cellular targets, including transcription factors, protein kinases, and other signaling molecules. Of particular importance is the ability of flavonoids to modulate inflammatory pathways, which play a crucial role in cancer development and progression [69]. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a pivotal transcription factor involved in inflammation, cell survival, and cancer progression. Flavonoids have been shown to inhibit NF-κB activation through various mechanisms, thereby reducing pro-inflammatory signaling and creating a less favorable environment for tumor growth and progression [70]. For instance, quercetin suppresses NF-κB activation by inhibiting IκB kinase (IKK) activity, thereby preventing the phosphorylation and degradation of IκB, the inhibitory protein that sequesters NF-κB in the cytoplasm [71]. Epigallocatechin-3-gallate (EGCG) from green tea inhibits NF-κB activation by suppressing the degradation of IκBα and blocking the nuclear translocation of the p65 subunit of NF-κB [72]. Similarly, apigenin has been shown to inhibit NF-κB activation in various cancer cell lines, leading to decreased expression of anti-apoptotic genes and increased sensitivity to chemotherapy [73]. In addition to NF-κB, flavonoids modulate other transcription factors. EGCG and quercetin have been reported to inhibit the activity of activator protein-1 (AP-1), another transcription factor involved in cell proliferation and survival [74]. Some flavonoids, such as genistein, have been shown to activate the tumor suppressor p53, leading to cell cycle arrest and apoptosis [75]. Flavonoids also interact

with various protein kinases, many of which are crucial for cancer cell signaling. Many flavonoids, including quercetin and luteolin, inhibit the activity of receptor tyrosine kinases such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR). This inhibition leads to decreased cell proliferation and angiogenesis [76]. Flavonoids also modulate the mitogen-activated protein kinase (MAPK) pathways, including ERK, JNK, and p38. For example, EGCG has been shown to inhibit the ERK1/2 pathway in various cancer cell lines, leading to decreased cell proliferation [77]. The phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which is frequently dysregulated in cancer, is another target of flavonoids. Compounds such as quercetin and kaempferol have been shown to inhibit this pathway, leading to decreased cell survival and increased apoptosis [78].

Flavonoids modulate the expression and activity of various cell cycle regulators. Many flavonoids, including apigenin and luteolin, inhibit the activity of cyclin-dependent kinases (CDKs), leading to cell cycle arrest [79,80]. Flavonoids such as EGCG and quercetin have been shown to downregulate the expression of cyclin D1, a key regulator of G1/S phase transition [81,82]. In terms of apoptosis-related pathways, flavonoids have been shown to modulate both the intrinsic and extrinsic apoptotic pathways. Many flavonoids, including quercetin and EGCG, upregulate pro-apoptotic proteins (e.g., Bax, Bad) and downregulate anti-apoptotic proteins (e.g., Bcl-2, Bcl-xL) [83]. Some flavonoids, such as apigenin, have been shown to sensitize cancer cells to death receptor-mediated apoptosis by upregulating the expression of death receptors [84]. Emerging evidence suggests that flavonoids can also modulate epigenetic mechanisms. Some flavonoids, including EGCG and genistein, have been shown to inhibit DNA methyltransferases, leading to reactivation of silenced tumor suppressor genes [85]. Certain flavonoids, such as curcumin, can modulate histone acetyltransferases and deacetylases, affecting gene expression patterns in cancer cells [86].

The multifaceted nature of the anticancer activities of flavonoids, coupled with their generally low toxicity and wide availability in the human diet, makes them particularly attractive subjects for cancer research. As we delve deeper into the specific mechanisms underlying their anticancer effects, we gain not only a better understanding of cancer biology but also insights into potential new strategies for cancer prevention and treatment.

5. DNA topoisomerases in cell division and cancer

Topoisomerases are essential enzymes that play a crucial role in DNA metabolism by altering the topological state of DNA. These enzymes are critical for DNA recombination, transcription, replication, and chromosome segregation [87,88]. Topoisomerases resolve topological problems arising during various cellular processes, particularly during replication and transcription where DNA strand separation leads to supercoil formation. They regulate supercoils by relaxing DNA and altering its tertiary structure without affecting its primary structure [89]. Topoisomerases can relax negative supercoils, relax supercoils of both types, or introduce supercoils into DNA, depending on the specific enzyme. For instance, bacterial DNA gyrase introduces negative supercoils, while reverse gyrase introduces positive supercoils [90]. Topoisomerases are classified into two main types: Type I and Type II. Type I topoisomerases are further subdivided into type IA and type IB. Type IA includes bacterial topoisomerase I, topoisomerase III α/β, and reverse gyrase, while type IB comprises eukaryotic topoisomerase I and mitochondrial topoisomerase. Type II topoisomerases are divided into two subclasses: type IIA and type IIB. Type IIA topoisomerases include eukaryotic topoisomerase II α/β, bacterial DNA gyrase, and topoisomerase IV. Type IIB topoisomerases include topoisomerase VI, which is found in archaea and some higher plants [91,92]. These enzymes differ in their mechanisms of action and cellular functions. Type I topoisomerases cleave one strand of DNA, while type II topoisomerases cleave both strands. This classification reflects the diverse roles of topoisomerases in maintaining genomic stability and facilitating various DNA-dependent processes.(Fig. 1)

Topoisomerases perform two primary functions: relaxation of superhelical DNA and decatenation of intertwined DNA molecules. These enzymes alter DNA topology by creating transient breaks in the DNA backbone, allowing strand passage, and then resealing the breaks. Type I topoisomerases relax supercoils by cleaving one DNA strand, rotating it around the intact strand, and then religating the break. Type II topoisomerases, on the other hand, cleave both DNA strands, pass another double-stranded DNA segment through the break, and then reseal it, enabling both relaxation and decatenation [93,94]. Recent studies have revealed that topoisomerase activity is significantly enhanced on chromatin substrates compared to naked DNA. For instance, topoisomerase II demonstrates remarkably high processivity on buckled chromatin fibers, capable of relaxing over 12,000 supercoils before dissociating. This enhanced activity is attributed to the intrinsic DNA crossings present within nucleosomes, which provide abundant substrate sites for topoisomerase II. The relaxation rate of topoisomerase II varies depending on the topological state of chromatin - it is faster on buckled, more compact chromatin and slower on less compact chromatin in the pre-buckled regime. These findings highlight how the structural properties of chromatin modulate topoisomerase activity to maintain appropriate levels of DNA supercoiling in different genomic contexts [95]. Topoisomerase I (TOP1) relaxes both positive and negative supercoils during DNA replication, recombination, and transcription. The enzyme consists of four domains: the N-terminal domain, the core domain, the linker domain, and the C-terminal domain, which contains the active site tyrosine residue [96]. During transcription, TOP1 is recruited to and activated by the phosphorylated C-terminal domain of RNA polymerase II, allowing it to relax supercoils generated ahead of and behind the transcription complex. TOP1 plays a critical role in preventing the accumulation of R-loops, which are stable RNA-DNA hybrids that can form during transcription and lead to genomic instability if not properly resolved. Recent research has uncovered a novel non-enzymatic function of TOP1 in regulating global transcription levels. This function depends on a conserved secondary DNA-binding surface on TOP1, distinct from its catalytic site, which acts to downregulate RNA synthesis [97]. A loss-of-function mutation (R548Q in mice) on this surface leads to hypertranscription in mouse embryonic stem cells, highlighting TOP1's complex role in fine-tuning transcriptional output [98]. During DNA replication, TOP1 relieves torsional stress ahead of the replication fork, facilitating fork progression. Additionally, TOP1 has been implicated in the repair of ribonucleotides mistakenly incorporated into DNA, further emphasizing its multifaceted role in preserving genomic integrity [99].

Topoisomerase II (TOP2) exists in two isoforms, α and β, which are

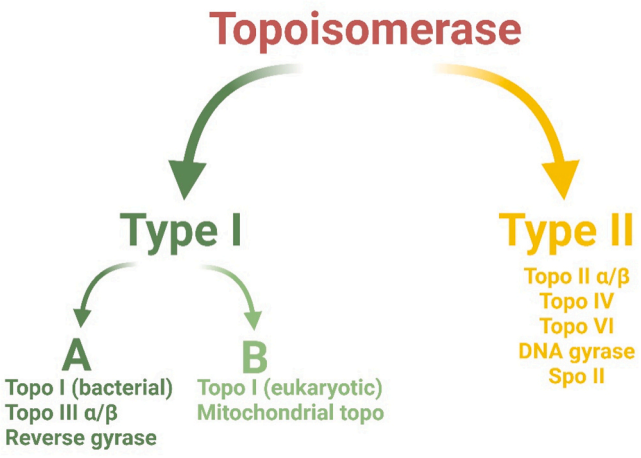

Fig. 1. Classification of topoisomerase.

encoded by separate genes. Both isoforms are large homodimeric enzymes, with each monomer consisting of three domains: an N-terminal ATPase domain, a central DNA-binding and cleavage domain, and a C-terminal domain crucial for nuclear localization and regulation [100]. TOP2α is predominantly expressed in proliferating cells and is essential for chromosome segregation during mitosis. It plays a critical role in decatenating sister chromatids, allowing for proper chromosome separation during cell division. TOP2α also shows a preference for relaxing positive supercoils, doing so about 10-fold faster than negative supercoils, an ability linked to elements in its C-terminal domain [101]. In contrast, TOP2β is expressed more uniformly across cell types and has distinct functions in transcription regulation and chromatin organization. Recent studies have revealed that TOP2β is recruited to loop anchors to alleviate positive supercoils induced by cohesin-derived DNA extrusion, a process crucial for the formation and maintenance of topologically associated domains (TADs) [102]. TOP2β also plays a significant role in transcriptional regulation, particularly for immediate early genes (IEGs). It generates transient DNA double-strand breaks at IEG promoters upon transcriptional activation, a process regulated by ERK2-mediated phosphorylation [103]. Interestingly, while TOP2α is indispensable for cell survival due to its role in chromosome segregation, TOP2β is not essential for cell viability but is crucial for proper neural development and function. The distinct roles of these isoforms highlight the versatility of TOP2 enzymes in maintaining genomic stability and regulating gene expression [104].

Topoisomerase III (TOP3) is a type IA topoisomerase, with TOP3A being the primary isoform involved in DNA replication and genome stability. TOP3A plays a critical role in resolving complex DNA structures during replication, particularly at sites of transcription-replication conflicts (TRCs) [105]. Recent studies have shown that TOP3A forms cleavage complexes (TOP3Accs) with single-strand breaks in DNA, where a TOP3A molecule is covalently bound to the 5′ end of the break. These TOP3A-DNA protein crosslinks (TOP3A-DPCs) arise from abortive catalytic cycles and must be removed to prevent DNA damage and genomic instability. TOP3Accs are primarily formed during S-phase, and their repair involves multiple pathways, including the SPRTN-TDP2 pathway during S-phase and the ATM-MRE11-CtIP pathway in G2 phase. TOP3A is particularly crucial for sensing and resolving TRCs in the 5′-regions of transcribed and replicated genes. As part of the TRR (TOP3A-RMI1-RMI2) complex, TOP3A associates with the Plk1-interacting checkpoint helicase (PICH) to produce extremely high-density positive supercoils. This process drives decatenation by TOP2α, providing the first evidence for topoisomerase-induced stable domains of positive supercoils in eukaryotic cells. The TRR complex is essential for the dissolution of double Holliday junctions during homologous recombination, preventing crossover formation and maintaining genome stability [106]. Recent genome-wide binding studies using CUT&Tag methods have revealed that TOP3A binding signals are suppressed by inhibition of DNA replication and are concentrated within promoters and the first 20 kb regions of the 5′-end of genes, further emphasizing its role in managing TRCs. These findings highlight the multifaceted roles of TOP3A and the TRR complex in maintaining genomic integrity during DNA replication and recombination [107]. Topoisomerase activity is tightly regulated through various mechanisms, including post-translational modifications and protein-protein interactions. A key regulatory mechanism involves phosphorylation by kinases such as ERK2. Recent research has uncovered an important regulatory axis between ERK2 and topoisomerase II, particularly TOP2B, in the activation of immediate early genes (IEGs). ERK2 phosphorylates the C-terminal domain of TOP2B, modulating its activity to favor transcriptional activation. While both ERK1 and ERK2 enhance TOP2B's catalytic rate for relaxing positive DNA supercoils, ERK2 uniquely delays TOP2B catalysis of negative DNA supercoiling [108]. This differential regulation is crucial for maintaining appropriate levels of DNA supercoiling during gene activation. Topoisomerases also interact with various other proteins, forming functional complexes. For instance, TOP3A interacts with RMI1 and RMI2 to form the TRR complex, which is essential for dissolving double Holliday junctions during homologous recombination [109].

Topoisomerases have emerged as important targets for cancer therapy due to their crucial roles in DNA replication and cell division. Topoisomerase inhibitors are classified based on their mechanism of action: catalytic inhibitors, which prevent the enzyme from carrying out its catalytic functions, and topoisomerase poisons, which stabilize the covalent enzyme-DNA complex, leading to persistent DNA strand breaks. The structural features of effective topoisomerase inhibitors are critical for their potency and specificity. Key features include extended planar aromatic systems that facilitate DNA intercalation, hydrogen bond donors and acceptors that enhance the stability of the drug-enzyme-DNA complex, polycyclic ring systems that provide structural rigidity and proper spatial orientation of functional groups, flexible linkers between rigid aromatic moieties allowing adaptability to the topoisomerase-DNA binding pocket, cationic centers that improve interaction with the negatively-charged DNA phosphate backbone, balanced lipophilicity for cellular penetration and interaction with hydrophobic pockets of topoisomerases, structural mimicry of DNA bases or nucleotides for precise fitting into the active site, and electron-rich aromatic systems that engage in π-π stacking interactions with DNA base pairs and aromatic amino acid residues in the enzyme. Recent advances in topoisomerase research have significantly expanded our understanding of these enzymes' roles beyond their classical functions in managing DNA topology. New insights into their involvement in transcription regulation, chromatin organization, and the resolution of transcription-replication conflicts have emerged. The discovery of non-enzymatic functions, such as TOP1's role in global transcription regulation, highlights the multifaceted nature of these enzymes [110–112].

6. Mechanisms of flavonoid-mediated topoisomerase inhibition

Flavonoids can inhibit topoisomerases through several mechanisms presented in Fig. 2 and described below. One type of topoisomerase inhibition by flavonoids is catalytic inhibition

involves flavonoids interfering with the catalytic cycle of topoisomerases without stabilizing the cleavable complex. For example, fisetin, a flavonol, acts as a catalytic inhibitor of both topoisomerase I and II in human colon carcinoma cells [113,114]. Poison/interfacial inhibition occurs when flavonoids stabilize the covalent DNA-enzyme cleavage complex, preventing religation of the cleaved DNA strands, which can lead to DNA strand breaks and apoptosis. Quercetin and myricetin act as topoisomerase II poisons in human leukemia cells, inducing cleavable complex formation. Genistein, an isoflavone, induces topoisomerase IIβ-mediated DNA sequence rearrangements, which may have implications in infant leukemia [115–117]. Some flavonoids can interfere with the activity of known topoisomerase poisons. For instance, quercetin enhanced the inhibitory effect of the topoisomerase I poison 10-hydroxycamptothecin (HCPT) on catalytic activity in vitro and synergistically induced DNA damage and apoptosis with HCPT in MCF7 breast cancer cells. Conversely, anthocyanins from blackberries suppressed irinotecan-induced topoisomerase I cleavable complex formation and DNA strand breaks in the colon of Wistar rats [118,119]. DNA intercalation is another mechanism by which flavonoids with planar structures can inhibit topoisomerases. By inserting between base pairs and distorting the double helix, flavonoids like quercetin, myricetin, and fisetin can interfere with topoisomerase binding and activity [120,121]. Lastly, the pro-oxidant properties of some flavonoids can contribute to their topoisomerase inhibitory effects. Flavonoids can generate reactive oxygen species (ROS) through autoxidation or redox cycling, causing oxidative DNA damage and poisoning of topoisomerases. The pro-oxidant activity of myricetin may play a role in its topoisomerase II poisoning effects in human leukemia cells [116,122].

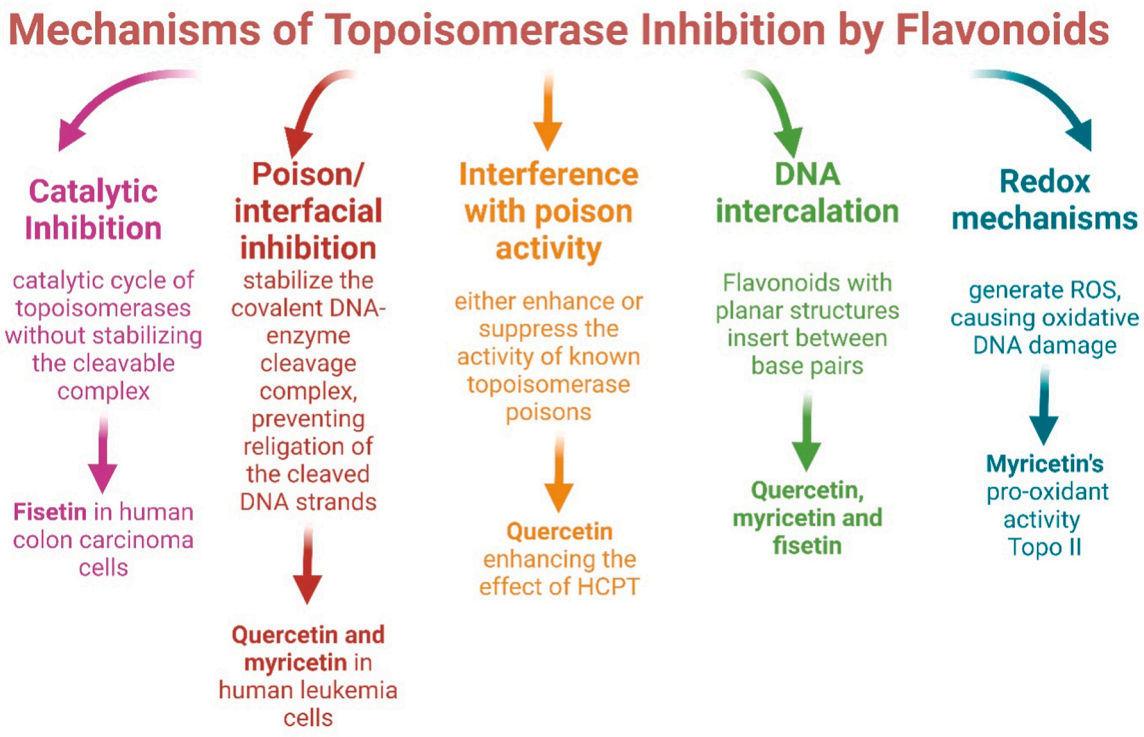

Fig. 2. Mechanisms of topoisomerase inhibition by flavonoids.

7. *In vitro* and *in vivo* studies of flavonoids as topoisomerase inhibitors

Flavonoids and their derivatives have emerged as potent inhibitors of DNA topoisomerases, exhibiting a wide range of effects on both type I and type II enzymes. This table summarizes in vitro and *in vivo* studies investigating the topoisomerase-inhibitory activities of various flavonoid compounds (Table 2).

The data reveal that flavonoids such as quercetin, kaempferol, myricetin, and their glycosides consistently demonstrate inhibitory effects on both topoisomerase I and II [134,141]. Notably, epigallocatechin gallate (EGCG), a major component of green tea, shows significant inhibition of both topoisomerase I and II, with specificity towards different isoforms [125,127,159].

Interestingly, the mechanism of inhibition varies among flavonoids. Some, like genistein, act as topoisomerase II poisons by stabilizing the covalent DNA-enzyme complex [126,160]. Others, such as myricetin and daidzein, function as catalytic inhibitors [147]. Certain flavonoids, including luteolin and apigenin, exhibit dual mechanisms, acting as both poisons and catalytic inhibitors depending on their concentration [147, 160].

The structural features of flavonoids appear to play a crucial role in their topoisomerase-inhibitory activity. For instance, the presence of hydroxyl groups at specific positions (e.g., 3′ and 4′ on the B-ring) often correlates with increased inhibitory potency [127]. Additionally, glycosylation patterns can significantly influence the activity and specificity of these compounds [141].

It is noteworthy that many of these studies utilize pure compounds or standardized extracts, allowing for a more precise understanding of structure-activity relationships [123,124,131]. However, some investigations also explore the effects of complex plant extracts, highlighting the potential synergistic effects of multiple flavonoids in natural sources [143,148,161]. This compilation of studies underscores the potential of flavonoids as lead compounds for the development of novel topoisomerase inhibitors, which could have significant implications in cancer therapy and other fields where modulation of DNA topology is crucial [135–137].

8. Conclusions and future directions

The extensive research reviewed in this article underscores the significant potential of flavonoids as DNA topoisomerase inhibitors and their promise in cancer therapy. The complexity and versatility of these compounds are evident in the diverse mechanisms by which flavonoids interact with topoisomerases, including catalytic inhibition, poisoning, and DNA intercalation. The structure-activity relationships elucidated in various studies offer valuable insights for the rational design of more potent and selective topoisomerase inhibitors based on flavonoid scaffolds. However, this review also identifies several challenges and opportunities for future research. A deeper understanding of the bioavailability and metabolism of flavonoids *in vivo* is crucial for developing effective dosing strategies and predicting potential drug-drug interactions. While many flavonoids exhibit promising activity against topoisomerases, improving their selectivity for cancer cells over normal cells remains a critical goal. Future research should focus on developing flavonoid derivatives with enhanced tumor-targeting capabilities. The potential synergistic effects of flavonoids with conventional chemotherapeutic agents merit further investigation, as such combinations could result in more effective treatment regimens with reduced side effects. Additionally, the potential for cancer cells to develop resistance to flavonoid-based topoisomerase inhibitors should be explored, and strategies to overcome such resistance should be developed. While numerous in vitro and pre-clinical studies have shown promising results, more robust clinical trials are needed to establish the efficacy and safety of flavonoids as topoisomerase inhibitors in human patients. Advances in structural biology and computational chemistry present opportunities for structure-based drug design approaches, aiming to develop novel flavonoid derivatives with optimized topoisomerase inhibitory properties. Continued exploration of natural sources of flavonoids, particularly from under-explored plant species, may lead to the discovery of new compounds with unique topoisomerase inhibition profiles. Another exciting area for future research is the potential

Table 2
In vitro, *In vivo* studies on inhibition of topoisomerase activity after treatment with flavonoid compounds.

		IN VITRO			
Compound Substance	**Plant**	**Pure/extract**	**Cell line/organism**	**Function/Effect**	**Ref.**
(7-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-(6-O-acetyl-hex−2-ene-α-D-erythro pyranosyl)genistein)	-	synthetic compound	DU 145	inhibit topoisomerase II activity	[123]
4'-hydroxychalcones	-	synthetic compound	Jurkat cells transformed from TIB−152	inhibition of topoisomerase I	[124]
Epigallocatechin−3-gallate (EGCG)	-	synthetic compound	HCT 116, VACO 241, SW 480	interacts with and inhibits topoisomerase I	[125]
Genistein	-	synthetic compound	BT, C3ABR, L3, AT1ABR	inhibits topoisomerase II by stabilizing the covalent DNA cleavage complex	[126]
EGCG	*Camellia sinensis* (L.) Kuntze)	isolated from commercial oolong tea (>98 % pure)	COLO 201, HeLa, A549, Vero, calf thymus gland, wheat germ	inhibits topoisomerases I and II, with the 3 and 3′ positions being important for this inhibitory activity. Furthermore, EGCG shows selective inhibition against topoisomerases I from different sources	[127]
Isoliquiritigenin	-	synthetic compound	Normal brain cells, U87	a reversible inhibitory effect on TOP I activity,	[128]
Quercetin	-	synthetic compound	*Escherichia coli* strain BL21(DE3)	inhibits supercoiling activity of bacterial gyrase and in duces DNA cleavage	[129]
Kaempferol derivatives	*Lens culinaris* (Medik.)	isolated from aerial parts	HL−60	They reduce DNA damage induced by etoposide, a topoisomerase II inhibitor, in peripheral blood mononuclear cells but do not affect DNA damage in HL−60 cancer cells	[130]
N-Benzyl derivatives of 6-aminoflavone	-	synthetic compound	MCF−7, A−549	topoisomerase II inhibitor	[131]
Kaempferol 3-O-beta-D-(6"-E-p-coumaroyl)-glucopyranoside (tiliroside)	*Potentilla argentea* L.	isolated from aerial parts	MCF−7	Human topoisomerase I and II inhibitor	[132]
Quercetin diacylglycoside analogues	-	synthetic compounds	*Escherichia coli* -gyraze, *Staphylococcus aureus* -topoisomerase IV	inhibit topoisomerase IV enzymes	[133]
Quercetin	-	synthetic compound	K562	moderate levels of topo II-DNA complexes but not topo I-DNA complexes	[134]
Fisetin	-	synthetic compound	K562	not induce topo I- or topo II-DNA complexes, but acted as a catalytic inhibitor of both enzymes.	[134]
Myricetin	-	synthetic compound	K562	do not induce topo I- or topo II-DNA complexes, but act as a catalytic inhibitor of both enzymes	[134]
Apigenin	-	synthetic compound	K562	moderate levels of topo II-DNA complexes but not topo I-DNA complexes	[134]
4-Hydroxyderricin	*Angelica keiskei* (Miq.) Koidz.)	isolated from roots	HL60, CRL1579, A549, AZ521	inhibit topoisomerase II activity	[135]
Nevadensin	-	synthetic compound	HT29	inhibitor of DNA topoisomerase I	[136]
Biflavonoid 2",3"-diidroochnaflavone	*Luxemburgia nobilis* (Eichler)	isolated from leaves	K562, murine Ehrlich carcinoma	inhibit both topoisomerase I and II activities in relaxation and decatenation assays	[137]
Luteolin	-	synthetic compound	HL−60, HP 100	induces apoptosis via topo II-mediated DNA cleavage	[138]
Silybin	-	synthetic compound	EPI cells, FIB cells, hepatocellular carcinoma HepG2 cell line	weak topoisomerase I inhibitor	[139]
Limocitrin 3-*O*-rutinoside	*Evodia officinalis* (Dode.)	isolated from fruits	HT−29, MCF−7, HepG2	inhibitory effects on DNA topoisomerases I and II (70 and 96 %)	[140]
Flavonol glycosides including kaempferol 3-O-(5-*O*-acetyl-α-D-apiofuranosyl)−7-*O*-α-L-rhamnopyranoside, kaempferol 3-*O*-α-L-arabinopyranosyl−7-*O*-α-L-rhamnopyranoside, kaempferol 3-*O*-[α-L-rhamnopyranosyl(1→2)-β-D-glucopyranosyl]−7-O-α-L-rhamnopyranoside, and kaempferol 3-*O*-[α-L-rhamnopyranosyl(1→2)-β-D-galactopyranosyl]−7-*O*-α-L-rhamnopyranoside	*Vicia faba* (L.), *Lotus edulis* (L.)	isolated from aerial parts	MCF7, HeLa, HepG2	inhibition of topoisomerase I and II	[141]
A naringenin isomer (5,7,3′-trihydroxyflavanone)	*Ardisia compressa* (Kunth)	isolated from leaves	HT−29 (ATCC HTB−38),	anti-topo II activity	[142]

(*continued on next page*)

Table 2 (*continued*)

		IN VITRO			
Compound Substance	**Plant**	**Pure/extract**	**Cell line/organism**	**Function/Effect**	**Ref.**
			C2BBe1 (clone of Caco−2 (ATCC HTB−37))		
34 polyphenolic compounds, primarily flavonoid glycones and aglycones luteolin, gossypetin, 5,7-dihydroxyflavone, 3,4-dihydroxyflavone, 5,7,3,4-tetrametho xyflavone, 5,6,7,3,4,5-hexamethoxyflavone, apigenin, naringenin, hesperitin, genistein, prunetin, 7,3,4-trihydroxyisoflavone, tamarixetin, rhamnetin, luteolin−4-O-glucoside, luteolin−7-O-glucoside, orientin, quercetin dihydrate, morin, daidzein, resveratrol, phloretin, phloridzin dihydrate, myricetin, diosmin, rutin, kaempferol, (+) catechin, (−)-epicatechin, piceatannol, silibinin, fisetin, quercitrin, (−)-epigallocatechin gallate, (−)-epicatechin gallate	-	synthetic compounds	pGEM®−9Zf(−) DNA plasmid	topo I poisons and DNA intercalators	[120]
Embelin, gallic acid, norbergenin, chlorogenic acid, bergenin, procyanidin, ardisianone, EGCG dimer, flavone, quercetin glycoside, ardisenone, myricetin derivative, myricitrin, rutin, ardisiaquinone, quercitrin, kaempferol derivative, kaempferol, Isorhamnetin	*Ardisia compressa* (Kunth)	isolated from leaves	HepG2	topo II catalytic inhibition	[143]
Cocoa-derived flavanols, including epicatechin, catechin, and procyanidins	*Theobroma cacao* (L.)	cocoa extract	HL−60, Raji cells	inhibition of topoisomerase II	[144]
7"-O-methyl-agathisflavone	*Ouratea hexasperm* ((A. St.-Hil.) Baill.)	isolated from leaves	K562, Ehrlich carcinoma cells	inhibit human DNA topoisomerase I and II	[145]
Amentoflavone	*Ouratea semiserrata* ((Mart. & Nees) Engl.)	isolated from leaves	K562, Ehrlich carcinoma cells	inhibit human DNA topoisomerase I	[145]
Eighteen flavonoids	*Bidens pilosa* L.	isolated from the whole plant	DLD−1	inhibitor of DNA topoisomerase I	[146]
Luteolin, quercetin, genistein, apigenin	-	synthetic compounds	Chinese hamster V79 cells	topoisomerase II poisons through DNA intercalation	[147]
Myricetin, daidzein, fisetin	-	synthetic compounds	Chinese hamster V79 cells	catalytic inhibitors of topoisomerase II	[147]
Flavonoid fraction	*Malus* sp.	isolated from peels	HepG2, WI−38	inhibited human DNA topoisomerases I and II	[148]
Isoflavones, flavanonols, chalcones, isoflavonolignan, isoflavoquinone	*Amburana cearensis* (Allemão) A.C.Sm.)	synthetic compounds	pHOT1 plasmid DNA	isoflavones odoratin, calycosin and dilmin induced significant production of linear DNA, acting as topoisomerase II poisons. Other compounds acted as catalytic inhibitors of topoisomerase II.	[149]
Chalcones (synthetic)	-	synthetic compound	HT−1376, HeLa, MCF−7	inhibitory activity against human topoisomerase IIα	[150]
Chrysosplenetin	*Artemisia annua* (L.)	isolated from whole plant	MCF−7	Topoisomerase I and II inhibition	[151]
Narigenine-cipro-floxacin	-	synthetic compound	*Bacillus subtilis* ATCC6633, *Staphylococcus aureus* ATCC25923, *Escherichia coli* ATCC35218, *Candida albicans* ATCC90873	inhibition of both the DNA gyrase and efflux pump	[152]
Flavopiridol	-	synthetic compound	HCT116 and its p53-null variant	effects of topoisomerase I poisons	[153]
Myricitrin	*Capsicum lanceolatum* (Greenm. C.V.Morton & Standl.)	isolated from leaves	MCF7, HT−29, 786–0, PC−3, HL−60	inhibitory effect on DNA-Topoisomerase Type IIa	[154]
Baicalein	*Oroxylum indicum* ((L.) Kurz)	isolated from stem-bark	*Escherichia. coli* BL21 (DE3)pLysS	inhibits DNA topoisomerases I and II	[155]
Luteolin	*Vitex negundo* (L.)	isolated from leaves	normal human T-cell blasts, *Leischmania donovani* AG83	inhibits DNA topoisomerases I and II and induces apoptosis	[156]
Quercetin	*Fagopyrum esculentum* (Moench)	buckwheat	normal human T-cell blasts, *Leischmania donovani* AG83	inhibits DNA topoisomerases I and II and induces apoptosis	[157]

(*continued on next page*)

Table 2 (*continued*)

		IN VITRO			
Compound Substance	**Plant**	**Pure/extract**	**Cell line/organism**	**Function/Effect**	**Ref.**
Genistein	-	synthetic compounds	J82, SCaBER, TCCSUP	Inhibits topoisomerase I	[157]
Tea flavanols (catechin, epicatechin, epigallocatechin, epigallocatechin gallate)	-	synthetic compounds	Chinese hamster ovary fibroblast AA8 cells,	Inhibits topoisomerase II activity	[158]
		IN VIVO			
Myricitrin	*Capsicum lanceolatum* ((Greenm.) C.V. Morton & Standl.)	isolated from leaves	*Drosophila melanogaster*	inhibitory effect on DNA-Topoisomerase Type IIa	[154]
Baicalein	*Oroxylum indicum* ((L.) Kurz)	isolated from stem-bark	*Leischmania.donovani* AG83	inhibits DNA topoisomerases I and II	[155]
Luteolin	*Vitex negundo* (L.)	isolated from leaves	Male golden hamsters, *Leischmania.donovani* AG83	inhibits DNA topoisomerases I and II and induces apoptosis	[156]
Quercetin	*Fagopyrum esculentum* (Moench)	buckwheat	Male golden hamsters, *Leischmania donovani* AG83	inhibits DNA topoisomerases I and II and induces apoptosis	[156]
Genistein	-	synthetic compounds	10-week-old female SCID nude mice	Inhibits topoisomerase I	[157]

epigenetic effects of flavonoids, especially in relation to their anti-cancer properties.

In summary, flavonoids represent a promising class of compounds in the ongoing search for effective and well-tolerated anticancer agents. Their ability to inhibit topoisomerases through multiple mechanisms, coupled with their generally low toxicity, positions them as valuable leads in drug discovery efforts. As our understanding of the complex interactions between flavonoids and topoisomerases deepens, so too does the potential for developing novel flavonoid-based therapies that could significantly impact future cancer treatment strategies. The diverse anti-cancer activities of flavonoids, combined with their widespread availability in nature, make them an exciting and potentially fruitful area of investigation in the search for new and improved cancer treatments.

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Tomasz Śliwiński: Writing – review & editing. **Tomasz Kowalczyk:** Writing – original draft, Visualization, Supervision, Conceptualization. **Natasza Wiertek-Płoszaj:** Resources, Data curation. **Laurent Picot:** Writing – review & editing, Investigation. **Malwina Dudzic:** Resources, Data curation. **Anna Merecz-Sadowska:** Writing – review & editing, Writing – original draft, Investigation. **Joanna Sikora:** Writing – review & editing. **Przemysław Sitarek:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

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References

[1] A.N. Panche, A.D. Diwan, S.R. Chandra, Flavonoids: an overview, J. Nutr. Sci. 5 (2016) e47, https://doi.org/10.1017/jns.2016.41.
[2] G. Di Carlo, N. Mascolo, A.A. Izzo, F. Capasso, Flavonoids: old and new aspects of a class of natural therapeutic drugs, Life Sci 65 (4) (1999) 337–353, https://doi.org/10.1016/S0024–3205(99)00120–4.
[3] S. Kumar, A.K. Pandey, Chemistry and biological activities of flavonoids: an overview, ScientificWorldJournal 2013 (2013) 162750, https://doi.org/10.1155/2013/162750.
[4] Y. Pommier, Drugging topoisomerases: lessons and challenges, ACS Chem. Biol. 8 (1) (2013) 82–95, https://doi.org/10.1021/cb300648v.
[5] L. Scotti, F.J. Bezerra Mendonca, F.F. Ribeiro, J.F. Tavares, M.S. da Silva, J. M. Barbosa Filho, M.T. Scotti, Natural product inhibitors of topoisomerases: review and docking study, Curr. Protein Pept. Sci. 19 (3) (2018) 275–291, https://doi.org/10.2174/1389203718666170111114442.
[6] C.A. Austin, K.L. Marsh, Eukaryotic DNA topoisomerase II beta, Bioessays 20 (3) (1998) 215–226, https://doi.org/10.1002/(SICI)1521–1878 (199803)20:3<215::AID-BIES5>3.0.CO;2-Q.
[7] M. López-Lázaro, E. Willmore, C.A. Austin, The dietary flavonoids myricetin and fisetin act as dual inhibitors of DNA topoisomerases I and II in cells, Mutat. Res. Genet. Toxicol. Environ. Mutagen. 696 (1–2) (2010) 41–47, https://doi.org/10.1016/j.mrgentox.2009.12.010.
[8] A.W.K. Yeung, N. Choudhary, D. Tewari, A. ElDemerdash, O.K. Horbanczuk, N. Das, V. Pirgozliev, M. Lucarini, A. Durazzo, E.B. Souto, A. Santini, H. P. Devkota, M.S. Uddin, J. Echeverría, D. Wang, R.-Y. Gan, M. Brnčić, R.E. Kalfin, N.T. Tzvetkov, A. Jóźwik, M. Solka, N. Strzałkowska, J.O. Horbańczuk, A. G. Atanasov, Quercetin: total-scale literature landscape analysis of a valuable nutraceutical with numerous potential applications in the promotion of human and animal health – a review, Animal Sci. Papers Rep. 39 (3) (2021) 199–212.
[9] H.R. Lu, H. Zhu, M. Huang, Y. Chen, Y.J. Cai, Z.H. Miao, J.S. Zhang, J. Ding, Reactive oxygen species elicit apoptosis by concurrently disrupting topoisomerase II and DNA-dependent protein kinase, Mol. Pharmacol. 68 (4) (2005) 983–994, https://doi.org/10.1124/mol.105.011544.
[10] S. Kumar, A.K. Pandey, Chemistry and biological activities of flavonoids: an overview, Scientific World J. 2013 (2013) 162750, https://doi.org/10.1155/2013/162750.

[11] A.N. Panche, A.D. Diwan, S.R. Chandra, Flavonoids: an overview, J. Nutr. Sci. 5 (2016) e47, https://doi.org/10.1017/jns.2016.41.
[12] M.L.F. Ferreyra, S.P. Rius, P. Casati, Flavonoids: biosynthesis, biological functions, and biotechnological applications, Front. Plant Sci. 3 (2012) 222, https://doi.org/10.3389/fpls.2012.00222.
[13] S. Chen, X. Wang, Y. Cheng, H. Gao, X. Chen, A review of classification, biosynthesis, biological activities and potential applications of flavonoids, Molecules 28 (13) (2023) 4982, https://doi.org/10.3390/molecules28134982.
[14] W.B. Zhuang, Y.H. Li, X.C. Shu, Y.T. Pu, X.J. Wang, T. Wang, Z. Wang, The Classification, molecular structure and biological biosynthesis of flavonoids, and their roles in biotic and abiotic stresses, Molecules 28 (8) (2023) 3599, https://doi.org/10.3390/molecules28083599.
[15] P.C. Hollman, M.B. Katan, Absorption, metabolism and health effects of dietary flavonoids in man, Biomed. Pharmacother. 51 (8) (1997) 305–310, https://doi.org/10.1016/s0753–3322(97)88045–6.
[16] E. Tripoli, M.La Guardia, S. Giammanco, D.Di Majo, M. Giammanco, Citrus flavonoids: molecular structure, biological activity and nutritional properties: a review, Food Chem. 104 (2) (2007) 466–479, https://doi.org/10.1016/j.foodchem.2006.11.054.
[17] F. Ververidis, E. Trantas, C. Douglas, G. Vollmer, G. Kretzschmar, N. Panopoulos, Biotechnology of flavonoids and other phenylpropanoid-derived natural products. Part I: chemical diversity, impacts on plant biology and human health, Biotechnol. J. 2 (10) (2007) 1214–1234, https://doi.org/10.1002/biot.200700084.
[18] D.C. Vitale, C. Piazza, B. Melilli, F. Drago, S. Salomone, Isoflavones: estrogenic activity, biological effect and bioavailability, Eur. J. Drug Metab. Pharmacokinet. 38 (1) (2013) 15–25, https://doi.org/10.1007/s13318–012 -0112-y.
[19] J.V. Higdon, B. Frei, Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions, Crit. Rev. Food Sci. Nutr. 43 (1) (2003) 89–143, https://doi.org/10.1080/10408690390826464.
[20] H.E. Khoo, A. Azlan, S.T. Tang, S.M. Lim, Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits, Food Nutr. Res. 61 (1) (2017) 1361779, https://doi.org/10.1080/16546628.2017.1361779.
[21] B. Orlikova, D. Tasdemir, F. Golais, M. Dicato, M. Diederich, Dietary chalcones with chemopreventive and chemotherapeutic potential, Genes Nutr 6 (2) (2011) 125–147, https://doi.org/10.1007/s12263–011-0210–5.
[22] C. Zwergel, F. Gaascht, S. Valente, M. Diederich, D. Bagrel, G. Kirsch, Aurones: interesting natural and synthetic compounds with emerging biological potential, Nat. Prod. Commun. 7 (3) (2012) 389–394, https://doi.org/10.1177/1934578x1200700322.
[23] S.V. Luca, I. Macovei, A. Bujor, A. Miron, K. Skalicka-Woźniak, A.C. Aprotosoaie, A. Trifan, Bioactivity of dietary polyphenols: the role of metabolites, Crit. Rev. Food Sci. Nutr. 60 (4) (2020) 626–659, https://doi.org/10.1080/10408398.2018.1546669.
[24] H. Meyer, A. Bolarinwa, G. Wolfram, J. Linseisen, Bioavailability of apigenin from apiin-rich parsley in humans, Ann. Nutr. Metab. 50 (2) (2006) 167–172, https://doi.org/10.1159/000090736.
[25] G.L. Hostetler, R.A. Ralston, S.J. Schwartz, Flavones: food sources, bioavailability, metabolism, and bioactivity, Adv. Nutr. 8 (3) (2017) 423–435, https://doi.org/10.3945/an.116.012948.
[26] B.Y. Khoo, S.L. Chua, P. Balaram, Apoptotic effects of chrysin in human cancer cell lines, Int. J. Mol. Sci. 11 (2010) 2188–2199, https://doi.org/10.3390/ijms11052188.
[27] A.V. González-de-Peredo, M. Vázquez-Espinosa, E. Espada-Bellido, C. Carrera, M. Ferreiro-González, G.F. Barbero, M. Palma, Flavonol composition and antioxidant activity of onions (Allium cepa L.) based on the development of new analytical ultrasound-assisted extraction methods, Antioxidants 10 (2021) 273, https://doi.org/10.3390/antiox10020273.
[28] S. Sekhon-Loodu, A. Catalli, M. Kulka, Y. Wang, F. Shahidi, H.V. Rupasinghe, Apple flavonols and n-3 polyunsaturated fatty acid–rich fish oil lowers blood C-reactive protein in rats with hypercholesterolemia and acute inflammation, Nutr. Res. 34 (2014) 535–543, https://doi.org/10.1016/j.nutres.2014.05.002.
[29] R. Flamini, F. Mattivi, R.M. De, P. Arapitsas, L. Bavaresco, Advanced knowledge of three important classes of grape phenolics: anthocyanins, stilbenes and flavonols, Int. J. Mol. Sci. 14 (2013) 19651–19669, https://doi.org/10.3390/ijms141019651.
[30] M. Fiol, S. Adermann, S. Neugart, S. Rohn, C. Mügge, M. Schreiner, A. Krumbein, L.W. Kroh, Highly glycosylated and acylated flavonols isolated from kale (Brassica oleracea var. sabellica)—structure–antioxidant activity relationship, Food Res. Int. 47 (2012) 80–89, https://doi.org/10.1016/j.foodres.2012.01.014.
[31] A.R. Proteggente, A.S. Pannala, G. Paganga, L.V. Buren, E. Wagner, S. Wiseman, P. Frans, C. Dacombe, C.A. Rice-Evans, The antioxidant activity of regularly consumed fruit and vegetables reflects their phenolic and vitamin C composition, Free Radic. Res. 36 (2002) 217–233, https://doi.org/10.1080/10715760290006484.
[32] A.J. Stewart, S. Bozonnet, W. Mullen, G.I. Jenkins, M.E. Lean, A. Crozier, Occurrence of flavonols in tomatoes and tomato-based products, J. Agric. Food Chem. 48 (2000) 2663–2669, https://doi.org/10.1007/s00394–009-0011–4.
[33] P.S. Larmo, B. Yang, S.A. Hurme, J.A. Alin, H.P. Kallio, E.K. Salminen, R. L. Tahvonen, Effect of a low dose of sea buckthorn berries on circulating concentrations of cholesterol, triacylglycerols, and flavonols in healthy adults, Eur. J. Nutr. 48 (2009) 277–282, https://doi.org/10.1021/jf000070p.
[34] P.S. Colombo, G. Flamini, M.S. Christodoulou, G. Rodondi, S. Vitalini, D. Passarella, G. Fico, Farinose alpine Primula species: phytochemical and morphological investigations, Phytochemistry 98 (2014) 151–159, https://doi.org/10.1016/j.phytochem.2013.11.018.
[35] M.A. Awad, F.H. Hadi, Effect of aqueous extract of green tea on gene expression of CYP17, CYP11A, LH beta subunit and LHr genes in males Wistar rats exposed to oxidative stress by streptozotocin, J. Madenat Alelem Univ. Coll. 11 (2019) 6–15.
[36] J. Pico, K. Xu, M. Guo, Z. Mohamedshah, M.G. Ferruzzi, M.M. Martinez, Manufacturing the ultimate green banana flour: impact of drying and extrusion on phenolic profile and starch bioaccessibility, Food Chem. 297 (2019) 124990, https://doi.org/10.1016/j.foodchem.2019.124990.
[37] D. Pal, P. Verma, Flavonoids: a powerful and abundant source of antioxidants, Int. J. Pharm. Pharm. Sci. 5 (2013) 95–98.
[38] T. Zhang, X. Wei, Z. Miao, H. Hassan, Y. Song, M. Fan, Screening for antioxidant and antibacterial activities of phenolics from Golden Delicious apple pomace, Chem. Cent. J. 10 (2016) 47, https://doi.org/10.1186%2Fs13065–016-0195–7.
[39] E. Tripoli, M.La Guardia, S. Giammanco, D.Di Majo, M. Giammanco, Citrus flavonoids: molecular structure, biological activity and nutritional properties: a review, Food Chem 104 (2007) 466–479, https://doi.org/10.1016/j.foodchem.2006.11.054.
[40] F. Ververidis, E. Trantas, C. Douglas, G. Vollmer, G. Kretzschmar, N. Panopoulos, Biotechnology of flavonoids and other phenylpropanoid-derived natural products. Part I: chemical diversity, impacts on plant biology and human health, Biotechnol. J. 2 (2007) 1214–1234, https://doi.org/10.1002/biot.200700184.
[41] J.W. Lee, N.H. Kim, J.Y. Kim, J.H. Park, S.Y. Shin, Y.S. Kwon, H.J. Lee, S.S. Kim, W. Chun, Aromadendrin inhibits lipopolysaccharide-induced nuclear translocation of NF-κB and phosphorylation of JNK in RAW 264.7 macrophage cells, Biomol. Ther. 21 (2013) 216–221, https://doi.org/10.1002/biot.200700184.
[42] M.A. Alam, N. Subhan, M.M. Rahman, S.J. Uddin, H.M. Reza, S.D. Sarker, Effect of citrus flavonoids, naringin and naringenin, on metabolic syndrome and their mechanisms of action, Adv. Nutr. 5 (2014) 404–417, https://doi.org/10.3945%2Fan.113.005603.
[43] S. Patra, R. Nayak, S. Patro, B. Pradhan, B. Sahu, C. Behera, S.K. Bhutia, M. Jena, Chemical diversity of dietary phytochemicals and their mode of chemoprevention, Biotechnol. Rep. 30 (2021) e00633, https://doi.org/10.1016/j.btre.2021.e00633.
[44] J.J. Peterson, G.R. Beecher, S.A. Bhagwat, J.T. Dwyer, S.E. Gebhardt, D. B. Haytowitz, J.M. Holden, Flavanones in grapefruit, lemons, and limes: a compilation and review of the data from the analytical literature, J. Food Compos. Anal. 19 (2006) S74–S80, https://doi.org/10.1016/j.jfca.2005.12.009.
[45] J.J. Peterson, J.T. Dwyer, G.R. Beecher, S.A. Bhagwat, S.E. Gebhardt, D. B. Haytowitz, J.M. Holden, Flavanones in oranges, tangerines (mandarins), tangors, and tangelos: a compilation and review of the data from the analytical literature, J. Food Compos. Anal. 19 (2006) S66–S73, https://doi.org/10.1016/j.jfca.2005.12.006.
[46] S. Chu, J. Wang, Y. Zhu, S. Liu, X. Zhou, H. Zhang, C. Wang, W. Yang, Z. Tian, H. Cheng, et al., An R2R3-type MYB transcription factor, GmMYB29, regulates isoflavone biosynthesis in soybean, PLoS Genet. 13 (2017) e1006770, https://doi.org/10.1007/s11103–015-0349–3.
[47] K. Mori-Yasumoto, Y. Hashimoto, Y. Agatsuma, H. Fuchino, K. Yasumoto, O. Shirota, M. Satake, S. Sekita, Leishmanicidal phenolic compounds derived from Dalbergia cultrata, Nat. Prod. Res. 35 (2021) 4907–4915, https://doi.org/10.1080/14786419.2020.1744140.
[48] X. Yin, A. Huang, S. Zhang, R. Liu, F. Ma, Identification of three Dalbergia species based on differences in extractive components, Molecules 23 (2018) 2163, https://doi.org/10.3390%2Fmolecules23092163.
[49] S. Chaves-Silva, A.L.Dos Santos, A. Chalfun-Júnior, J. Zhao, L.E. Peres, V. A. Benedito, Understanding the genetic regulation of anthocyanin biosynthesis in plants–tools for breeding purple varieties of fruits and vegetables, Phytochemistry 153 (2018) 11–27, https://doi.org/10.1016/j.phytochem.2018.05.013.
[50] J. Fang, Classification of fruits based on anthocyanin types and relevance to their health effects, Nutrition 31 (2015) 1301–1306, https://doi.org/10.1016/j.nut.2015.04.015.
[51] A.N. Kim, K.Y. Lee, E.J. Jeong, S.W. Cha, B.G. Kim, W.L. Kerr, S.G. Choi, Effect of vacuum–grinding on the stability of anthocyanins, ascorbic acid, and oxidative enzyme activity of strawberry, LWT 136 (2021) 110304, https://doi.org/10.1016/j.lwt.2020.110304.
[52] R. Veberic, A. Slatnar, J. Bizjak, F. Stampar, M. Mikulic-Petkovsek, Anthocyanin composition of different wild and cultivated berry species, LWT Food Sci. Technol. 60 (2015) 509–517, https://doi.org/10.1016/j.lwt.2014.08.033.
[53] A. Badhani, S. Rawat, I.D. Bhatt, R.S. Rawal, Variation in chemical constituents and antioxidant activity in Yellow Himalayan (Rubus ellipticus Smith) and Hill Raspberry (Rubus niveus Thunb, J. Food Biochem. 39 (2015) 663–672, https://doi.org/10.1111/jfbc.12172.
[54] A. Alsayari, A.B. Muhsinah, M.Z. Hassan, M.J. Ahsan, J.A. Alshehri, N. Begum, Aurone: a biologically attractive scaffold as anticancer agent, Eur. J. Med. Chem. 166 (2019) 417–431, https://doi.org/10.1016/j.ejmech.2019.01.078.
[55] S.H. Thilakarathna, H.P.V. Rupasinghe, Flavonoid bioavailability and attempts for bioavailability enhancement, Nutrients 5 (2013) 3367–3387, https://doi.org/10.3390%2Fnu5093367.
[56] A. Kozłowska, D. Szostak-Węgierek, Flavonoids-food sources and health benefits, Roczniki Państwowego Zakładu Higieny 65 (2014) 79–85.
[57] D.M. Kopustinskiene, V. Jakstas, A. Savickas, J. Bernatoniene, Flavonoids as anticancer agents, Nutrients 12 (2020) 457, https://doi.org/10.3390/nu12020457.

[58] S. Scholz, G. Williamson, Interactions affecting the bioavailability of dietary polyphenols in vivo, Int. J. Vitam. Nutr. Res. 77 (2007) 224–235, https://doi.org/10.1024/0300–9831.77 .3.224.
[59] L. Jakobek, Interactions of polyphenols with carbohydrates, lipids and proteins, Food Chem 175 (2015) 556–567, https://doi.org/10.1016/j.foodchem.2014.12.013.
[60] G.B. Gonzales, G. Smagghe, C. Grootaert, M. Zotti, K. Raes, J.Van Camp, Flavonoid interactions during digestion, absorption, distribution and metabolism: a sequential structure-activity/property relationship-based approach in the study of bioavailability and bioactivity, Drug Metab. Rev. 47 (2015) 175–190, https://doi.org/10.3109/03602532.2014.1003649.
[61] M. Swieca, U. Gawlik-Dziki, D. Dziki, B. Baraniak, J. Czyż, The influence of protein-flavonoid interactions on protein digestibility in vitro and the antioxidant quality of breads enriched with onion skin, Food Chem 141 (2013) 451–458, https://doi.org/10.1016/j.foodchem.2013.03.048.
[62] D.M. Kopustinskiene, V. Jakstas, A. Savickas, J. Bernatoniene, Flavonoids as anticancer agents, Nutrients 12 (2020) 457, https://doi.org/10.3390%2Fnu12020457.
[63] R. Pei, X. Liu, B. Bolling, Flavonoids and gut health, Curr. Opin. Biotechnol. 61 (2020) 153–159, https://doi.org/10.1016/j.copbio.2019.12.018.
[64] A. Abusaliya, S.E. Ha, P.B. Bhosale, H.H. Kim, M.Y. Park, P. Vetrivel, G.S. Kim, Glycosidic flavonoids and their potential applications in cancer research: a review, Springer (2021), https://doi.org/10.1007/s13273–021 -00178-x.
[65] T.-y Wang, Q. Li, K.-s Bi, Bioactive flavonoids in medicinal plants: structure, activity and biological fate, Asian J. Pharm. Sci. 13 (2018) 12–23, https://doi.org/10.3390/ph16091229.
[66] V.C. George, G. Dellaire, H.P.V. Rupasinghe, Plant flavonoids in cancer chemoprevention: role in genome stability, J. Nutr. Biochem. 45 (2017) 1–14, https://doi.org/10.3390/metabo13040481.
[67] Y.C. Lin, P.H. Tsai, C.Y. Lin, C.H. Cheng, T.H. Lin, K.P. Lee, K.Y. Huang, S. H. Chen, J.J. Hwang, C.C. Kandaswami, M.T. Lee, Impact of flavonoids on matrix metalloproteinase secretion and invadopodia formation in highly invasive A431-III cancer cells, PLoS One 8 (2013) e71903, https://doi.org/10.1371/journal.pone.0071903.
[68] M.H. Kim, Flavonoids inhibit VEGF/bFGF-induced angiogenesis in vitro by inhibiting the matrix-degrading proteases, J. Cell Biochem. 89 (2003) 529–538, https://doi.org/10.1002/jcb.10543.
[69] M.L. Mansuri, P. Parihar, I. Solanki, M.S. Parihar, Flavonoids in modulation of cell survival signalling pathways, Genes Nutr 9 (2014) 400, https://doi.org/10.1007/s12263–014 -0400-z.
[70] R. Zhong, L. Miao, H. Zhang, L. Tan, Y. Zhao, Y. Tu, M. Angel Prieto, J. Simal-Gandara, L. Chen, C. He, H. Cao, Anti-inflammatory activity of flavonols via inhibiting MAPK and NF-κB signaling pathways in RAW264.7 macrophages, Curr. Res. Food Sci. 5 (2022) 1176–1184, https://doi.org/10.1016/j.crfs.2022.07.007.
[71] P.A. Ruiz, A. Braune, G. Hölzlwimmer, L. Quintanilla-Fend, D. Haller, Quercetin inhibits TNF-induced NF-kappaB transcription factor recruitment to proinflammatory gene promoters in murine intestinal epithelial cells, J. Nutr. 137 (2007) 1208–1215, https://doi.org/10.1093/jn/137.5.1208.
[72] S.P. Lakshmi, A.T. Reddy, L.D. Kodidhela, N.C. Varadacharyulu, The tea catechin epigallocatechin gallate inhibits NF-κB-mediated transcriptional activation by covalent modification, Arch. Biochem. Biophys. 695 (2020) 108620, https://doi.org/10.1016/j.abb.2020.108620.
[73] X. Yan, M. Qi, P. Li, Y. Zhan, H. Shao, Apigenin in cancer therapy: anti-cancer effects and mechanisms of action, Cell Biosci 7 (2017) 50, https://doi.org/10.1186/s13578–017 -0179-x.
[74] Q.P. Dou, Molecular mechanisms of green tea polyphenols, Nutr. Cancer 61 (2009) 827–835, https://doi.org/10.1080/01635580903285049.
[75] Z. Zhang, C.Z. Wang, G.J. Du, L.W. Qi, T. Calway, T.C. He, W. Du, C.S. Yuan, Genistein induces G2/M cell cycle arrest and apoptosis via ATM/p53-dependent pathway in human colon cancer cells, Int. J. Oncol. 43 (2013) 289–296, https://doi.org/10.3892/ijo.2013.1946.
[76] Y.T. Huang, J.J. Hwang, P.P. Lee, F.C. Ke, J.H. Huang, C.J. Huang, C. Kandaswami, E. Middleton Jr., M.T. Lee, Effects of luteolin and quercetin, inhibitors of tyrosine kinase, on cell growth and metastasis-associated properties in A431 cells overexpressing epidermal growth factor receptor, Br. J. Pharmacol. 128 (1999) 999–1010, https://doi.org/10.1038/sj.bjp.0702879.
[77] R. Wei, J. Wirkus, Z. Yang, J. Machuca, Y. Esparza, G.G. Mackenzie, EGCG sensitizes chemotherapeutic-induced cytotoxicity by targeting the ERK pathway in multiple cancer cell lines, Arch. Biochem. Biophys. 692 (2020) 108546, https://doi.org/10.1016/j.abb.2020.108546.
[78] T.A. Zughaibi, M. Suhail, M. Tarique, S. Tabrez, Targeting PI3K/Akt/mTOR pathway by different flavonoids: a cancer chemopreventive approach, Int. J. Mol. Sci. 22 (2021) 12455, https://doi.org/10.3390/ijms222212455.
[79] D. Jiang, D. Li, W. Wu, Inhibitory effects and mechanisms of luteolin on proliferation and migration of vascular smooth muscle cells, Nutrients 5 (2013) 1648–1659, https://doi.org/10.3390/nu5051648.
[80] A.H. Rahmani, M.A. Alsahli, A. Almatroudi, M.A. Almogbel, A.A. Khan, S. Anwar, S.A. Almatroodi, The potential role of apigenin in cancer prevention and treatment, Molecules 27 (2022) 6051, https://doi.org/10.3390/molecules27186051.
[81] P. Asgharian, A.P. Tazekand, K. Hosseini, H. Forouhandeh, T. Ghasemnejad, M. Ranjbar, M. Hasan, M. Kumar, S.M. Beirami, V. Tarhriz, S.R. Soofiyani, L. Kozhamzharova, J. Sharifi-Rad, D. Calina, W.C. Cho, Potential mechanisms of quercetin in cancer prevention: focus on cellular and molecular targets, Cancer Cell Int. 22 (2022) 257, https://doi.org/10.1186/s12935–022 -02677-w.
[82] B.N. Singh, S. Shankar, R.K. Srivastava, Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications, Biochem. Pharmacol. 82 (2011) 1807–1821, https://doi.org/10.1016/j.bcp.2011.07.093.
[83] S. Cheng, N. Gao, Z. Zhang, G. Chen, A. Budhraja, Z. Ke, Y.O. Son, X. Wang, J. Luo, X. Shi, Quercetin induces tumor-selective apoptosis through downregulation of Mcl-1 and activation of Bax, Clin. Cancer Res. 16 (2010) 5679–5691, https://doi.org/10.1158/1078–0432.
[84] X. Yan, M. Qi, P. Li, Y. Zhan, H. Shao, Apigenin in cancer therapy: anti-cancer effects and mechanisms of action, Cell Biosci 7 (2017) 50, https://doi.org/10.1186/s13578–017 -0179-x.
[85] S.M. Henning, P. Wang, C.L. Carpenter, D. Heber, Epigenetic effects of green tea polyphenols in cancer, Epigenomics 5 (2013) 729–741, https://doi.org/10.2217/epi.13.57.
[86] F.U. Hassan, M.S. Rehman, M.S. Khan, M.A. Ali, A. Javed, A. Nawaz, C. Yang, Curcumin as an alternative epigenetic modulator: mechanism of action and potential effects, Front. Genet. 10 (2019) 514, https://doi.org/10.3389/fgene.2019.00514.
[87] F. Cortés, N. Pastor, S. Mateos, I. Domínguez, Roles of DNA topoisomerases in chromosome segregation and mitosis, Mutat. Res. 543 (2003) 59–66, https://doi.org/10.1016/s1383–5742(02)00070–4.
[88] S.J. McKie, K.C. Neuman, A. Maxwell, DNA topoisomerases: advances in understanding of cellular roles and multi-protein complexes via structure-function analysis, Bioessays 43 (2021) e2000286, https://doi.org/10.1002/bies.202000286.
[89] Y. Pommier, A. Nussenzweig, S. Takeda, C. Austin, Human topoisomerases and their roles in genome stability and organization, Nat. Rev. Mol. Cell Biol. 23 (2022) 407–427, https://doi.org/10.1038/s41580–022-00452–3.
[90] S.M. Vos, E.M. Tretter, B.H. Schmidt, J.M. Berger, All tangled up: how cells direct, manage and exploit topoisomerase function, Nat. Rev. Mol. Cell Biol. 12 (2011) 827–841, https://doi.org/10.1038/nrm3228.
[91] G. Capranico, J. Marinello, G. Chillemi, Type I DNA Topoisomerases, J. Med. Chem. 60 (2017) 2169–2192, https://doi.org/10.1021/acs.jmedchem.6b00966.
[92] D.A. Sutormin, A.K. Galivondzhyan, A.V. Polkhovskiy, S.O. Kamalyan, K. V. Severinov, S.A. Dubiley, Diversity and functions of type II topoisomerases, Acta Naturae 13 (2021) 59–75, https://doi.org/10.32607/actanaturae.11058.
[93] T. Dasgupta, S. Ferdous, Y.C. Tse-Dinh, Mechanism of type IA topoisomerases, Molecules 25 (2020) 4769, https://doi.org/10.3390/molecules25204769.
[94] A.K. McClendon, N. Osheroff, DNA topoisomerase II, genotoxicity, and cancer, Mutat. Res. 623 (2007) 83–97, https://doi.org/10.1016/j.mrfmmm.2007.06.009.
[95] J. Lee, M. Wu, J.T. Inman, G. Singh, S.H. Park, J.H. Lee, R.M. Fulbright, Y. Hong, J. Jeong, J.M. Berger, M.D. Wang, Chromatinization modulates topoisomerase II processivity, Nat. Commun. 14 (2023) 6844, https://doi.org/10.1038/s41467–023-42600-z.
[96] B.C. Soren, J.B. Dasari, A. Ottaviani, F. Iacovelli, P. Fiorani, Topoisomerase IB: a relaxing enzyme for stressed DNA, Cancer Drug Resist 3 (2020) 18–25, https://doi.org/10.20517/cdr.2019.106.
[97] Y. Pommier, Y. Sun, S.N. Huang, J.L. Nitiss, Roles of eukaryotic topoisomerases in transcription, replication and genomic stability, Nat. Rev. Mol. Cell Biol. 17 (2016) 703–721, https://doi.org/10.1038/nrm.2016.111.
[98] M.S. Lau, Z. Hu, X. Zhao, Y.S. Tan, J. Liu, H. Huang, C.J. Yeo, H.F. Leong, O. V. Grinchuk, J.K. Chan, J. Yan, W.W. Tee, Transcriptional repression by a secondary DNA binding surface of DNA topoisomerase I safeguards against hypertranscription, Nat. Commun. 14 (2023) 6464, https://doi.org/10.1038/s41467–023-42078–9.
[99] J.S. Williams, A.R. Clausen, S.A. Lujan, L. Marjavaara, A.B. Clark, P.M. Burgers, A. Chabes, T.A. Kunkel, Evidence that processing of ribonucleotides in DNA by topoisomerase 1 is leading-strand specific, Nat. Struct. Mol. Biol. 22 (2015) 291–297, https://doi.org/10.1038/nsmb.2989.
[100] Z. Skok, M. Durcik, Z. Zajec, D.G. Skledar, K. Bozovičar, A. Pišlar, T. Tomašič, A. Zega, L.P. Mašič, D. Kikelj, N. Zidar, J. Ilaš, ATP-competitive inhibitors of human DNA topoisomerase IIα with improved antiproliferative activity based on N-phenylpyrrolamide scaffold, Eur. J. Med. Chem. 249 (2023) 115116, https://doi.org/10.1016/j.ejmech.2023.115116.
[101] T.N. Soliman, D. Keifenheim, P.J. Parker, D.J. Clarke, Cell cycle responses to Topoisomerase II inhibition: molecular mechanisms and clinical implications, J. Cell Biol. 222 (2023) e202209125, https://doi.org/10.1083/jcb.202209125.
[102] L. Uusküla-Reimand, M.D. Wilson, Untangling the roles of TOP2A and TOP2B in transcription and cancer, Sci. Adv. 8 (2022) eadd4920, https://doi.org/10.1126/sciadv.add4920.
[103] M. Amoiridis, J. Verigos, K. Meaburn, W.H. Gittens, T. Ye, M.J. Neale, E. Soutoglou, Inhibition of topoisomerase 2 catalytic activity impacts the integrity of heterochromatin and repetitive DNA and leads to interlinks between clustered repeats, Nat. Commun. 15 (2024) 5727, https://doi.org/10.1038/s41467–024-49816–7.
[104] J.L. Nitiss, DNA topoisomerase II and its growing repertoire of biological functions, Nat. Rev. Cancer. 9 (2009) 327–337, https://doi.org/10.1038/nrc2608.
[105] A.H. Bizard, I.D. Hickson, The many lives of type IA topoisomerases, J. Biol. Chem. 295 (2020) 7138–7153, https://doi.org/10.1074/jbc.REV120.008286.
[106] L.K. Saha, S. Saha, X. Yang, S.N. Huang, Y. Sun, U. Jo, Y. Pommier, Replication-associated formation and repair of human topoisomerase IIIα cleavage complexes, Nat. Commun. 14 (2023) 1925, https://doi.org/10.1038/s41467–023-37498–6.
[107] H. Zhang, Y. Sun, S. Saha, L.K. Saha, L.S. Pongor, A. Dhall, Y. Pommier, Genome-wide Mapping of Topoisomerase Binding Sites Suggests Topoisomerase 3α (TOP3A) as a Reader of Transcription-Replication Conflicts (TRC), bioRxiv [Preprint]. (2024). https://doi.org/10.1101/2024.06.17.599352.

[108] H. Bunch, D. Kim, M. Naganuma, R. Nakagawa, A. Cong, J. Jeong, H. Ehara, H. Vu, J.H. Chang, M.J. Schellenberg, S.I. Sekine, ERK2-topoisomerase II regulatory axis is important for gene activation in immediate early genes, Nat. Commun. 14 (2023) 8341, https://doi.org/10.1038/s41467–023 -44089-y.
[109] G.M. Harami, J. Pálinkás, Y. Seol, Z.J. Kovács, M. Gyimesi, H. Harami-Papp, K. C. Neuman, M. Kovács, The topoisomerase IIIalpha-RMI1-RMI2 complex orients human Bloom's syndrome helicase for efficient disruption of D-loops, Nat. Commun. 13 (2022) 654, https://doi.org/10.1038/s41467–022-28208–9.
[110] N.K. Sharma, A. Bahot, G. Sekar, M. Bansode, K. Khunteta, P.V. Sonar, A. Hebale, V. Salokhe, B.K. Sinha, Understanding cancer's defense against topoisomerase-active drugs: a comprehensive review, Cancers 16 (2024) 680, https://doi.org/10.3390/cancers16040680.
[111] M.A. Bjornsti, S.H. Kaufmann, Topoisomerases and cancer chemotherapy: recent advances and unanswered questions, F1000 Faculty Rev-1704, F1000Res. 8 (2019), https://doi.org/10.12688/f1000research.20201.1.
[112] V.M. Matias-Barrios, X. Dong, The implication of topoisomerase ii inhibitors in synthetic lethality for cancer therapy, Pharmaceuticals 16 (2023) 94, https://doi.org/10.3390/ph16010094.
[113] G.L. Beretta, L. Gatti, P. Perego, N. Zaffaroni, Camptothecin resistance in cancer: insights into the molecular mechanisms of a DNA-damaging drug, Curr. Med. Chem. 20 (2013) 1541–1565, https://doi.org/10.2174/0929867311320120006.
[114] M. López-Lázaro, E. Willmore, C.A. Austin, The dietary flavonoids myricetin and fisetin act as dual inhibitors of DNA topoisomerases I and II in cells, Mutat. Res. Genet. Toxicol. Environ. Mutagen. 696 (2010) 41–47, https://doi.org/10.1016/j.mrgentox.2009.12.010.
[115] Y. Pommier, E. Leo, H. Zhang, C. Marchand, DNA topoisomerases and their poisoning by anticancer and antibacterial drugs, Chem. Biol. 17 (2010) 421–433, https://doi.org/10.1016/j.chembiol.2010.04.012.
[116] O.J. Bandele, S.J. Clawson, N. Osheroff, Dietary polyphenols as topoisomerase II poisons: B ring and C ring substituents determine the mechanism of enzyme-mediated DNA cleavage enhancement, Chem. Res. Toxicol. 21 (2008) 1253–1260, https://doi.org/10.1021/tx8000785.
[117] A.M. Azarova, R.K. Lin, Y.C. Tsai, L.F. Liu, C.P. Lin, Y.L. Lyu, Genistein induces topoisomerase IIβ- and proteasome-mediated DNA sequence rearrangements: implications in infant leukemia, Biochem. Biophys. Res. Commun. 399 (2010) 66–71, https://doi.org/10.1016/j.bbrc.2010.07.043.
[118] Q. Tang, F. Ji, J. Wang, L. Guo, Y. Li, Y. Bao, Quercetin exerts synergetic anti-cancer activity with 10-hydroxy camptothecin, Eur. J. Pharm. Sci. 109 (2017) 223–232, https://doi.org10.1016/j.ejps.2017.08.013.
[119] M. Esselen, S.W. Barth, S. Winkler, S. Baechler, K. Briviba, B. Watzl, D. Marko, Anthocyanins suppress the cleavable complex formation by irinotecan and diminish its DNA-strand-breaking activity in the colon of Wistar rats, Carcinogenesis 34 (2013) 835–840, https://doi.org/10.1093/carcin/bgs398.
[120] M.R. Webb, S.E. Ebeler, Comparative analysis of topoisomerase IB inhibition and DNA intercalation by flavonoids and similar compounds: structural determinates of activity, Biochem. J. 384 (2004) 527–541, https://doi.org/10.1042/bj20040474.
[121] R.D. Snyder, P.J. Gillies, P. Wilmore, Inhibitory effects of various flavonoids on the α and β isoforms of DNA topoisomerase II, Nutr. Cancer 48 (2004) 101–111.
[122] G. Galati, P.J. O'Brien, Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties, Free Radic. Biol. Med. 37 (2004) 287–303, https://doi.org/10.1016/j.freeradbiomed.2004.04.034.
[123] A. Gogler-Pigłowska, A. Rusin, D. Bochenek, Z. Krawczyk, Aneugenic effects of the genistein glycosidic derivative substituted at C7 with the unsaturated disaccharide, Cell Biol. Toxicol. 28 (2012) 331–342, https://doi.org/10.1007/s10565–012-9227–9.
[124] H.I. Gul, M. Cizmecioglu, S. Zencir, M. Gul, P. Canturk, M. Atalay, Z. Topcu, Cytotoxic activity of 4′-hydroxychalcone derivatives against Jurkat cells and their effects on mammalian DNA topoisomerase I, J. Enzyme Inhib. Med. Chem. 24 (2009) 804–807, https://doi.org/10.1080/14756360802399126.
[125] S.J. Berger, S. Gupta, C.A. Belfi, D.M. Gosky, H. Mukhtar, Green tea constituent (-)-epigallocatechin-3-gallate inhibits topoisomerase I activity in human colon carcinoma cells, Biochem. Biophys. Res. Commun. 288 (1) (2001) 101–105, https://doi.org/10.1006/bbrc.2001.5736.
[126] R. Ye, A. Bodero, B.B. Zhou, K.K. Khanna, M.F. Lavin, S.P. Lees-Miller, The plant isoflavonoid genistein activates p53 and Chk2 in an ATM-dependent manner, J. Biol. Chem. 276 (2001) 4828–4833, https://doi.org/10.1074/jbc.m004894200.
[127] K. Suzuki, S. Yahara, F. Hashimoto, M. Uyeda, Inhibitory activities of (-)-epigallocatechin-3-O-gallate against topoisomerases I and II, Biol. Pharm. Bull. 24 (2001) 1088–1090.
[128] S. Zhao, H. Chang, P. Ma, G. Gao, C. Jin, X. Zhao, W. Zhou, B. Jin, Inhibitory effect of DNA topoisomerase inhibitor isoliquiritigenin on the growth of glioma cells, Int. J. Clin. Exp. Pathol. 8 (2015) 12577–12582.
[129] A. Plaper, M. Golob, I. Hafner, M. Oblak, T. Solmajer, R. Jerala, Characterization of quercetin binding site on DNA gyrase, Biochem. Biophys. Res. Commun. 306 (2003) 530–536, https://doi.org/10.1016/s0006-291x(03)01006–4.
[130] M. Kluska, M. Juszczak, J. Żuchowski, A. Stochmal, K. Woźniak, Kaempferol and its glycoside derivatives as modulators of etoposide activity in HL-60 cells, Int. J. Mol. Sci. 22 (2021) 3520, https://doi.org/10.3390/ijms22073520.
[131] N.M. Thorat, A.P. Sarkate, D.K. Lokwani, S.V. Tiwari, R. Azad, S.R. Thopate, N-Benzylation of 6-aminoflavone by reductive amination and efficient access to some novel anticancer agents via topoisomerase II inhibition, Mol. Divers. (2020), https://doi.org/10.1007/s11030–020-10079–1.
[132] M. Tomczyk, D. Drozdowska, A. Bielawska, K. Bielawski, J. Gudej, Human DNA topoisomerase inhibitors from *Potentilla argentea* and their cytotoxic effect against MCF-7, Pharmazie 63 (2008) 389–393.
[133] A.M.L. Hossion, Y. Zamami, R.K. Kandahary, T. Tsuchiya, W. Ogawa, A. Iwado, K. Sasaki, Quercetin diacylglycoside analogues showing dual inhibition of DNA gyrase and topoisomerase IV as novel antibacterial agents, J. Med. Chem. 54 (2011) 3686–3703, https://doi.org/10.1021/jm200010x.
[134] M. López-Lázaro, E. Willmore, C.A. Austin, The dietary flavonoids myricetin and fisetin act as dual inhibitors of DNA topoisomerases I and II in cells, Mutat. Res. Genet. Toxicol. Environ. Mutagen. 696 (2010) 41–47, https://doi.org/10.1016/j.mrgentox.2009.12.010.
[135] T. Akihisa, T. Kikuchi, H. Nagai, K. Ishii, K. Tabata, T. Suzuki, 4-Hydroxyderricin from Angelica keiskei roots induces caspase-dependent apoptotic cell death in HL60 human leukemia cells, J. Oleo Sci. 60 (2011) 71–77, https://doi.org/10.5650/jos.60.71.
[136] L. Müller, L.R.F. Schütte, D. Bücksteeg, J. Alfke, T. Uebel, M. Esselen, Topoisomerase poisoning by the flavonoid nevadensin triggers DNA damage and apoptosis in human colon carcinoma HT29 cells, Arch Toxicol. 95 (2021) 3787–3802, https://doi.org/10.1007/s00204–021-03162–5.
[137] M.C. Oliveira, M.G. de Carvalho, N.F. Grynberg, P.S. Brioso, A biflavonoid from Luxemburgia nobilis as inhibitor of DNA topoisomerases, Planta Med. 71 (2005) 561–563, https://doi.org/10.1055/s-2005–864159.
[138] N. Yamashita, S. Kawanishi, Distinct mechanisms of DNA damage in apoptosis induced by quercetin and luteolin, Free Radic. Res. 33 (2000) 623–633, https://doi.org/10.1080/10715760000301141.
[139] P. Thongphasuk, W. Stremmel, W. Chamulitrat, 2,3-Dehydrosilybin is a better DNA topoisomerase I inhibitor than its parental silybin, Chemotherapy 55 (2009) 42–48, https://doi.org/10.1159/000175466.
[140] M.L. Xu, G. Li, D.C. Moon, C.S. Lee, M.H. Woo, E.S. Lee, et al., Cytotoxicity and DNA topoisomerase inhibitory activity of constituents isolated from the fruits of Evodia officinalis, Arch. Pharm. Res. 29 (2006) 541–547, https://doi.org/10.1007/bf02969262.
[141] M. Tselepi, E. Papachristou, A. Emmanouilidi, A. Angelis, N. Aligiannis, A. L. Skaltsounis, et al., Catalytic inhibition of eukaryotic topoisomerases I and II by flavonol glycosides extracted from Vicia faba and Lotus edulis, J. Nat. Prod. 74 (2011) 2362–2370, https://doi.org/10.1021/np200292u.
[142] E.Gonzalez de Mejia, S. Chandra, M.V. Ramirez-Mares, W. Wang, Catalytic inhibition of human DNA topoisomerase by phenolic compounds in Ardisia compressa extracts and their effect on human colon cancer cells, Food Chem. Toxicol. 44 (2006) 1191–1203, https://doi.org/10.1016/j.fct.2006.01.015.
[143] A.M. Newell, G.G. Yousef, M.A. Lila, M.V. Ramirez-Mares, E.G. de Mejia, Comparative in vitro bioactivities of tea extracts from six species of Ardisia and their effect on growth inhibition of HepG2 cells, J. Ethnopharmacol. 130 (2010) 536–544, https://doi.org/10.1016/j.jep.2010.05.051.
[144] L. Lanoue, K.K. Green, C. Kwik-Uribe, C.L. Keen, Dietary factors and the risk for acute infant leukemia: evaluating the effects of cocoa-derived flavanols on DNA topoisomerase activity, Exp. Biol. Med. 235 (2010) 77–89, https://doi.org/10.1258/ebm.2009.009184.
[145] N.F. Grynberg, M.G. de Carvalho, J.R. Velandia, M.C. Oliveira, I.C. Moreira, R. Braz-Filho, A. Echevarria, DNA topoisomerase inhibitors: biflavonoids from Ouratea species, Braz. J. Med. Biol. Res. 35 (2002) 819–822, https://doi.org/10.1590/s0100-879x2002000700009.
[146] G. Zeng, Y. Wang, M. Zhu, J. Yi, J. Ma, B. Yang, W. Sun, F. Dai, J. Yin, G. Zeng, Inhibition of DNA Topoisomerase I by flavonoids and polyacetylenes isolated from bidens pilosa L, Molecules 29 (2024) 3547, https://doi.org/10.3390/molecules29153547.
[147] R.D. Snyder, P.J. Gillies, Evaluation of the clastogenic, DNA intercalative, and topoisomerase II-interactive properties of bioflavonoids in Chinese hamster V79 cells, Environ. Mol. Mutagen. 40 (2002) 266–276, https://doi.org/10.1002/em.10121.
[148] M.S. Zheng, N.K. Hwang, J.R. Kim, C.S. Lee, C.S. Seo, J.K. Son, Flavonoid-enriched apple fraction AF4 induces cell cycle arrest, DNA topoisomerase II inhibition, and apoptosis in human liver cancer HepG2 cells, Nutr. Cancer 66 (2014) 1237–1246, https://doi.org/10.1080/01635581.2014.951733.
[149] G.P. de Oliveira, T.M.G. da Silva, C.A. Camara, A.L.B.D. Santana, M.S.A. Moreira, T.M.S. Silva, Isolation and structure elucidation of flavonoids from Amburana cearensis resin and identification of human DNA topoisomerase II-α inhibitors, Phytochem. Lett. 22 (2017) 61–70, https://doi.org/10.1016/j.phytol.2017.09.006.
[150] K. Sangpheak, M. Mueller, N. Darai, P. Wolschann, C. Suwattanasophon, R. Ruga, et al., Computational screening of chalcones acting against topoisomerase IIα and their cytotoxicity towards cancer cell lines, J. Enzyme Inhib. Med. Chem. 34 (2019) 134–143, https://doi.org/10.1080/14756366.2018.1507029.
[151] D. Şöhretoğlu, B. Barut, S. Sari, A. Özel, R. Arroo, In vitro and in silico assessment of DNA interaction, topoisomerase I and II inhibition properties of chrysosplenetin, Int. J. Biol. Macromol. 144 (2020) 736–743, https://doi.org/j.ijbiomac.2020.07.049.
[152] Z.P. Xiao, X.D. Wang, P.F. Wang, Y. Zhou, J.W. Zhang, L. Zhang, J. Zhou, S. S. Zhou, H. Ouyang, X.Y. Lin, M. Mustapa, A. Reyinbaike, H.L. Zhu, Design, synthesis, and evaluation of novel fluoroquinolone-flavonoid hybrids as potent antibiotics against drug-resistant microorganisms, Eur. J. Med. Chem. 80 (2014) 92–100, https://doi.org/10.1016/j.ejmech.2014.04.037.
[153] G. Ambrosini, S.L. Seelman, L.X. Qin, G.K. Schwartz, The cyclin-dependent kinase inhibitor flavopiridol potentiates the effects of topoisomerase I poisons by suppressing Rad51 expression in a p53-dependent manner, Cancer Res 68 (2008) 2312–2320, https://doi.org/10.1158/0008–5472.can-07–2395.

[154] R.T. Perdomo, C.P. Defende, P.D.S. Mirowski, T.V. Freire, S.S. Weber, W. S. Garcez, F.R. Garcez, Myricitrin from Combretum lanceolatum exhibits inhibitory effect on DNA-topoisomerase type IIα and protective effect against in vivo doxorubicin-induced mutagenicity, J. Med. Food 23 (2020) 1177–1185, https://doi.org/10.1089/jmf.2020.0033.

[155] B.B. Das, N. Sen, A. Roy, S.B. Dasgupta, A. Ganguly, B.C. Mohanta, H.K. Majumder, Differential induction of Leishmania donovani bi-subunit topoisomerase I–DNA cleavage complex by selected flavones and camptothecin: activity of flavones against camptothecin-resistant topoisomerase I, Nucleic Acids Res. 34 (2006) 1121–1132, https://doi.org/10.1093/nar/gkj502.

[156] B. Mittra, A. Saha, A.R. Chowdhury, C. Pal, S. Mandal, S. Mukhopadhyay, H. K. Majumder, Luteolin, an abundant dietary component is a potent anti-leishmanial agent that acts by inducing topoisomerase II-mediated kinetoplast DNA cleavage leading to apoptosis, Mol. Med. 6 (2000) 527–541.

[157] Y. Wang, H. Wang, W. Zhang, Genistein sensitizes bladder cancer cells to HCPT treatment in vitro and in vivo via ATM/NF-kB/IKK pathway-induced apoptosis, PLoS ONE 8 (2013) e50175, https://doi.org/10.1371/journal.pone.0050175.

[158] K. Neukam, N. Pastor, F. Cortés, Tea flavanols inhibit cell growth and DNA topoisomerase II activity and induce endoreduplication in cultured Chinese hamster cells, Mutat. Res. 654 (2008) 8–12, https://doi.org/10.1016/j.mrgentox.2008.03.013.

[159] C.A. Austin, S. Patel, K. Ono, H. Nakane, L.M. Fisher, Site-specific DNA cleavage by mammalian DNA topoisomerase II induced by novel flavone and catechin derivatives, Biochem. J. 282 (1992) 883–889, https://doi.org/10.1042/bj2820883.

[160] W. Bocian, R. Kawęcki, E. Bednarek, J. Sitkowski, A. Ulkowska, L. Kozerski, Interaction of flavonoid topoisomerase I and II inhibitors with DNA oligomers, New J. Chem. 30 (2006) 467–472, https://doi.org/10.1039/B517245B.

[161] C. Spanou, G. Bourou, A. Dervishi, N. Aligiannis, A. Angelis, D. Komiotis, D. Kouretas, Antioxidant and chemopreventive properties of polyphenolic compounds derived from Greek legume plant extracts, J. Agric. Food Chem. 56 (2008) 6967–6976, https://doi.org/10.1021/jf800842p.