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RESEARCH PAPER

# Dietary chalcones with chemopreventive and chemotherapeutic potential

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**Abstract** Chalcones are absorbed in the daily diet and appear to be promising cancer chemopreventive agents. Chalcones represent an important group of the polyphenolic family, which includes a large number of naturally occurring molecules. This family possesses an interesting spectrum of biological activities, including antioxidative, antibacterial, anti-inflammatory, anticancer, cytotoxic, and immunosuppressive potential. Compounds of this family have been shown to interfere with each step of carcinogenesis, including initiation, promotion and progression. Moreover, numerous compounds from the family of dietary chalcones appear to show activity against cancer cells, suggesting that these molecules or their derivatives may be considered as potential anticancer drugs. This review will focus primarily on prominent members of the chalcone family with an 1,3-diphenyl-2-propenon core structure. Specifically, the inhibitory effects of these compounds on the different steps of carcinogenesis that reveal interesting chemopreventive and chemotherapeutic potential will be discussed.

**Keywords** Diet · Chalcone derivatives · Chemoprevention · Chemotherapy

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## Introduction

Polyphenols represent one of the most prevalent classes of compounds found in our daily diet [171]. Over the last ten years, increasing attention has been dedicated to chalcones because of their interesting biological activities. Indeed, chalcones constitute an important group of natural compounds that are especially abundant in fruits (e.g., citruses, apples), vegetables (e.g., tomatoes, shallots, bean sprouts, potatoes) and various plants and spices (e.g., licorice),—many of which have been used for centuries in traditional herbal medicine [29]. Chemically, chalcones are open-chain flavonoids bearing two aromatic rings linked by a three-carbon enone moiety (Fig. 1). The majority of the content of chalcones in citrus fruits and various plants is mediated through the formation of 4,2′,4′,6′-tetrahydroxychalcone (also known as naringenin chalcone **(1)**) by chalcone synthase (Fig. 2) [77]. Naringenin chalcone **(1)** also plays an essential role in the flavonoid biosynthetic pathway and contributes significantly to the total amount of plant flavonoids [35]. Although chalcones occur naturally, they could be available in larger amounts through an efficient and simple synthesis. Briefly, synthesis through base-catalyzed Claisen–Schmidt condensation of an aromatic aldehyde and an appropriate ketone in a polar solvent (methanol or ethanol) renders them a readily available nutrition component/supplement in either natural or synthesized form [147] (Fig. 3).

The present paper is primarily concerned with chalcone derivatives found in edible plants, fruits, and vegetables and with their positive effects in cancer chemoprevention and carcinogenesis. Cancer chemoprevention can target each step of carcinogenesis with natural or synthetic substances [160]. Because of unsatisfactory cancer treatment options and adverse side effects caused by currently used

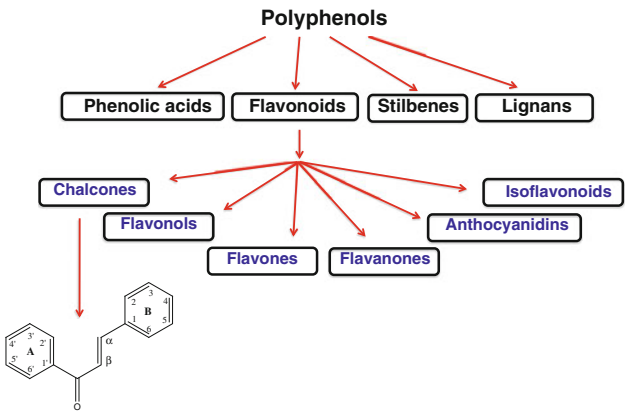


**Fig. 1** Schematic representation of main polyphenol family members. Polyphenols are subdivided into 4 main classes—phenolic acids, flavonoids, stilbenes, and lignans—according to the number of phenol rings they include and the structural elements that bind these rings together [114]. Flavonoids can be further divided into various subclasses of which chalcones, flavonols, flavones, flavanones, anthocyanidins, and isoflavonoids are the most common. The core 1,3-diphenyl-2-propenon chalcone structure is shown

chemotherapeutic compounds, great emphasis has been put on the use of non-toxic dietary substances and botanical products, either alone or in a co-treatment.

Various chalcones completely inhibit different steps of carcinogenesis from the very early stages, including tumor initiation, through promotion, progression, angiogenesis, and invasion, to the very late stages leading to metastasis. They are also strongly implicated in the negative regulation of cell cycle progression and favor cell death mechanisms, predominantly apoptosis, in transformed cells. Moderation of these processes is generally associated with the involvement of chalcones in an elaborate network of inflammatory cell-signaling pathways that largely contribute to tumor promotion.

This review will focus on members of the chalcone class with the 1,3-diphenyl-2-propenon core structure and the inhibitory effect of these compounds on the different steps of carcinogenesis that highlight their interesting chemopreventive and chemotherapeutic potential.

## Inflammation cell-signaling pathways targeted by chalcones

The tight interplay between chronic inflammation and cancer was first established and carefully documented by Virchow in 1863 when he observed leukocytes in neoplastic tissues. Since then, many scientists have provided evidence underlining the strong dependency between these two processes. Natural compounds, including chalcones, have been shown to interact with, abrogate, and abolish inflammatory signaling (see Fig. 4). Moreover, a single compound can target multiple signaling events and contribute to inhibition of the synthesis of inflammatory mediators.

Nuclear factor (NF)-κB is a mediator of inflammatory diseases and cancer and has been shown to induce resistance to various chemotherapeutic agents. This transcription factor is implicated in immunity, anti-apoptosis, proliferation, and activation of more than 550 target genes involved in tumor promotion, angiogenesis, and metastasis. The canonical NF-κB pathway is characterized by a cascade leading to activation of the functional heterodimer p50/p65. After stimulation by tumor necrosis factor (TNF)α, activation of the Iκ kinase (IKK) complex leads to phosphorylation of the inhibitory subunit IκBα followed by subsequent proteasomal degradation. As a result, NF-κB p50/p65 translocates to the nucleus and transcription is activated.

Besides NF-κB signaling, other pathways are strongly linked to inflammation processes, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinases (JNK), and p38 signal transduction pathways. The ERK1/2-mediated signaling pathway is activated by growth factors, cytokines, carcinogens, or viral proteins. Initially, this pathway was thought to be limited exclusively to cell growth and proliferation, but there is growing evidence indicating its involvement in several inflammatory processes [136]. The family of JNK enzymes is implicated in cell proliferation, survival, and apoptosis through the activation of stress and inflammation. Inhibition of JNK-mediated AP-1 activation is a promising approach for inhibition of the inducible expression of inflammatory

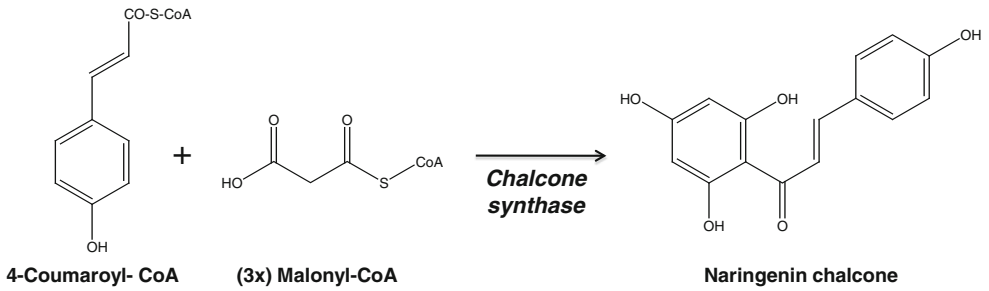


**Fig. 2** Biosynthesis of naringenin chalcone in plants and citruses. The condensation of three molecules of malonyl-CoA and one molecule of 4-coumaroyl-CoA is catalyzed by chalcone synthetase resulting in the formation of naringenin chalcone, which acts as a substrate for further synthesis of flavonoids

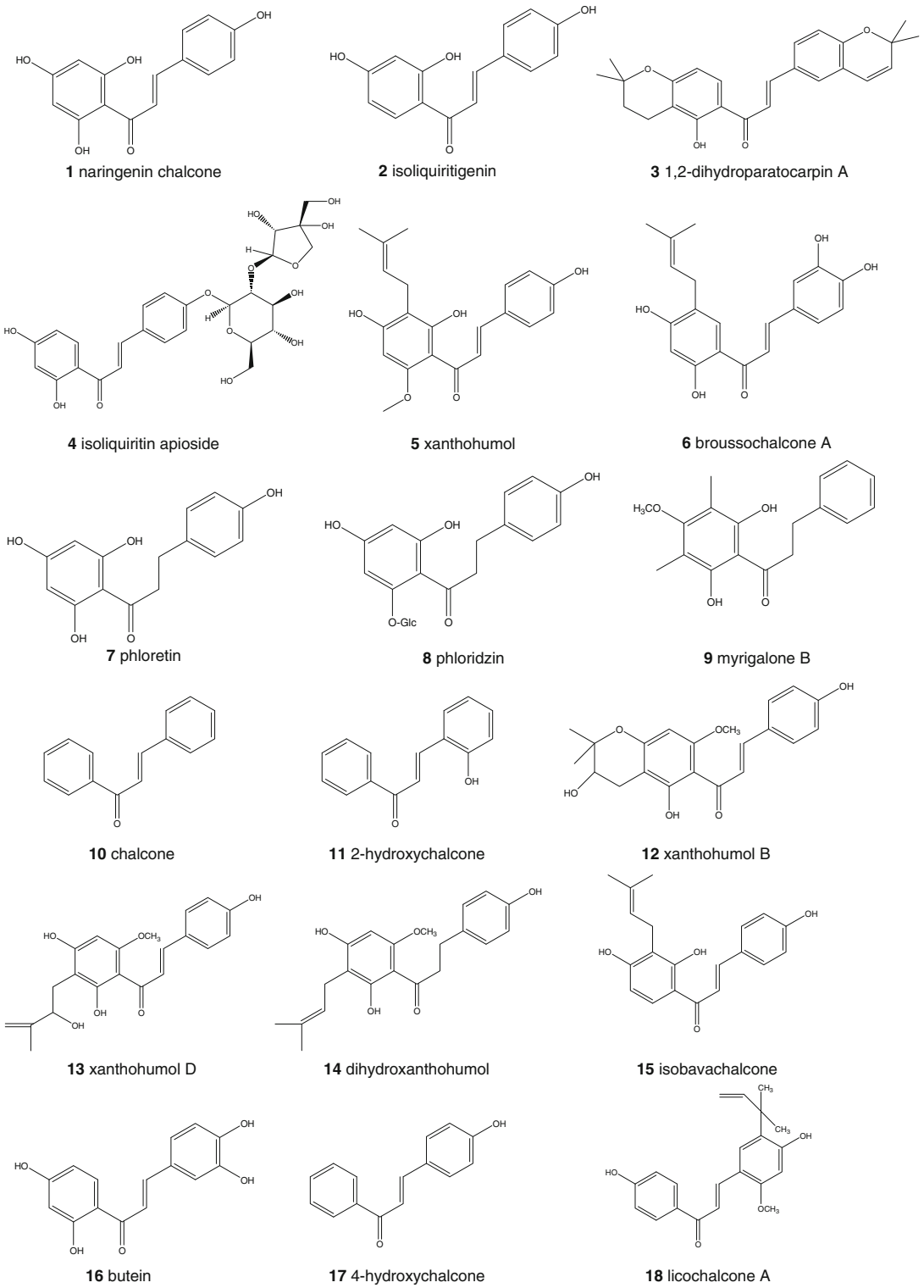


**Fig. 3** Chemical structures of naturally occurring chalcone derivatives

genes in cancer and other pathologies [115]. The p38 mitogen-activated protein kinase (MAPK) pathway is critical for the synthesis and activity of multiple pro-inflammatory cytokines (TNF-α, interleukin (IL)-1, IL-6, IL-8).

Finally, the crosstalk of these pathways with NF-κB cell signaling contributes to induction of key inflammatory enzymes such as cyclooxygenase (COX)-2 and inducible nitric oxide synthase (iNOS) [27].

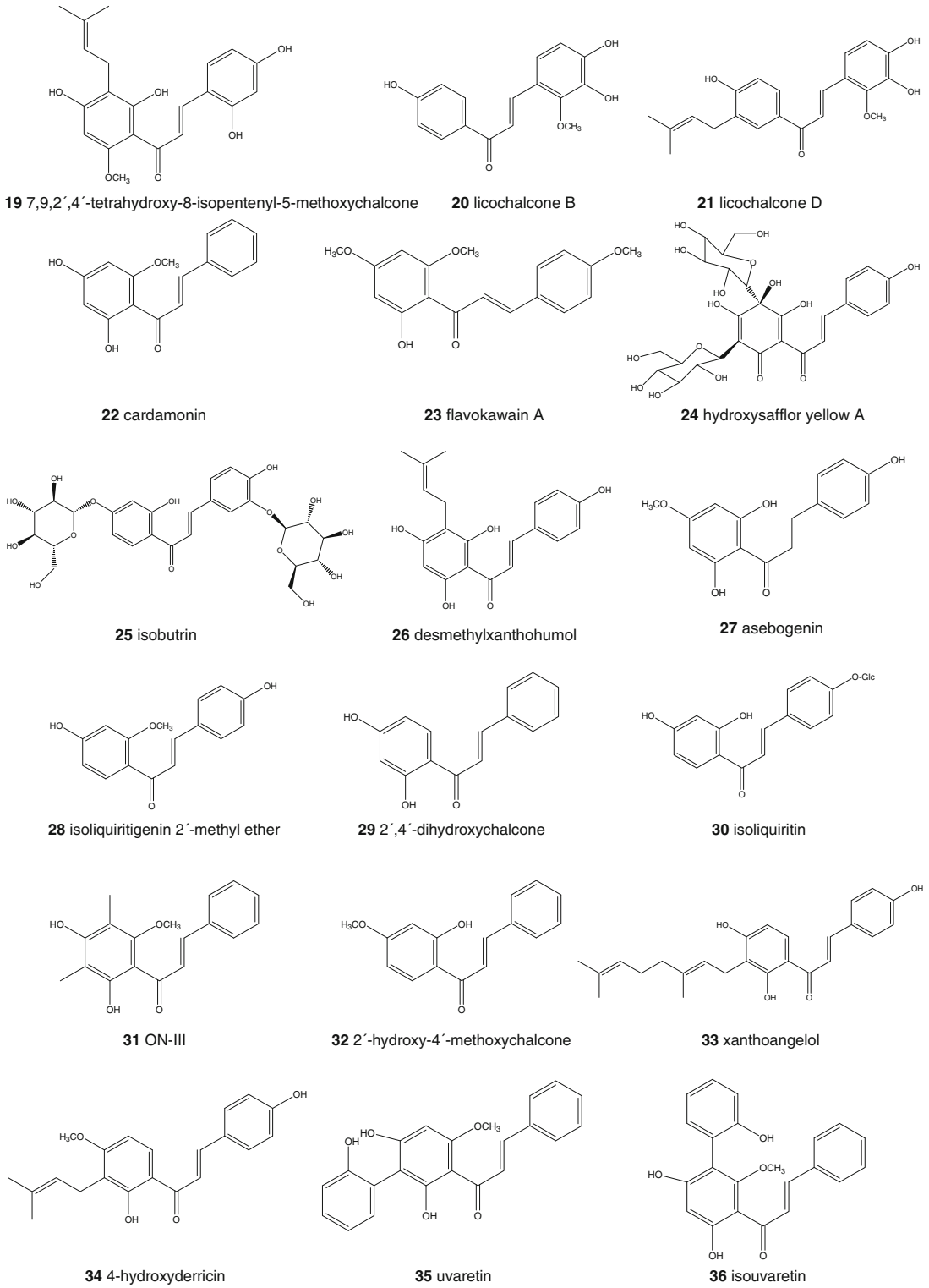


**Fig. 3** continued

It has been reported that chalcone **(10)** provided two distinct cytoprotective mechanisms, depending on the duration of pre-treatment. Initially, chalcone **(10)** abrogated time and dose dependently the activation of signal transducer and activator of transcription (STAT)3 and NF-$\kappa$B in IL-6 and lipopolysaccharide (LPS)-

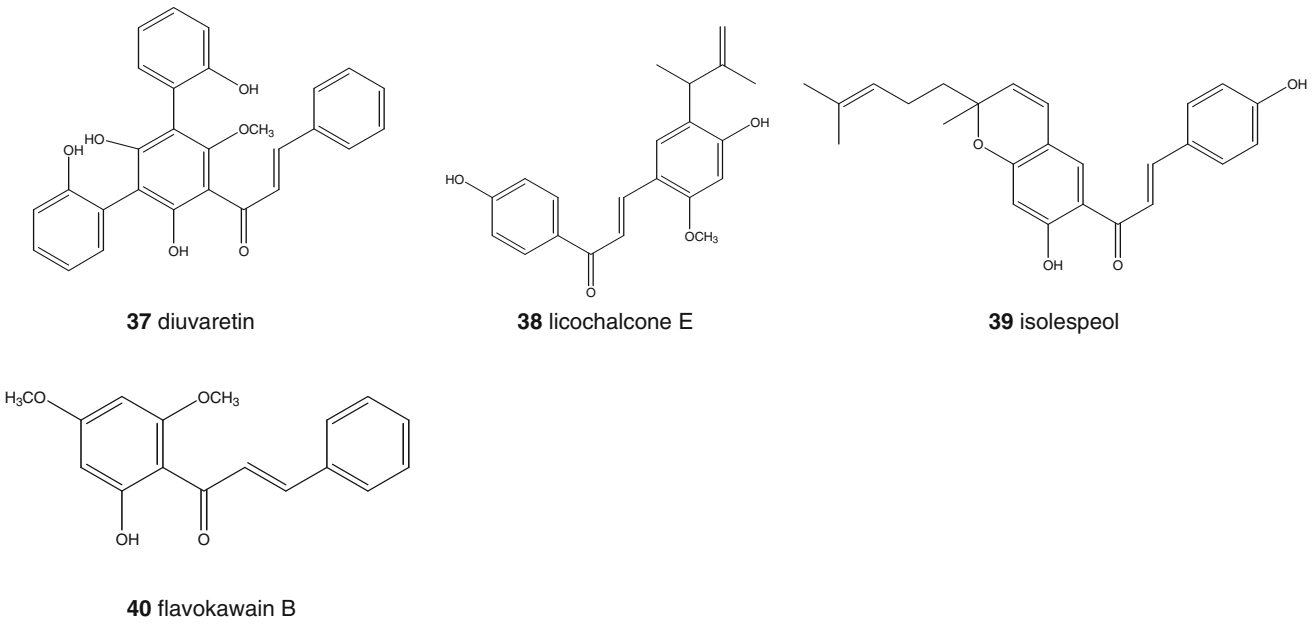


**Fig. 3** continued

stimulated endothelial cells via depletion of intracellular glutathione (GSH) levels. Prolonged chalcone treatment (after 6 h and 12 h), however, rescued the intracellular GSH level, indicating the activation of thiol-related genes. This second cytoprotective mechanism involved the chalcone-mediated accumulation of NFE2-related factor (Nrf)2 in the nucleus, which led to elevated protein levels of thioredoxin reductase and heme oxygenase (HO)-1 [108].

Heme oxygenase-1 plays an important role in inflammatory responses. Its activity catalyzes heme degradation, leading to the production of carbon monoxide (CO) and biliverdin, which is further reduced to bilirubin. Heme oxygenase-1 activity results in cytoprotection against oxidative injury and cellular stresses [5]. As reported, the prenylated chalcone 7,9,2′,4′-tetrahydroxy-8-isopentenyl-5-methoxychalcone **(19)** from *Sophora flavescens* successfully inhibited expression of interferon (INF)-$\gamma$ and tumor necrosis factor alpha (TNF-$\alpha$)-induced chemokines (TARC/CCL17, MDC/CCL22, CTACK/CCL27) via induction of HO-1 [22].

Licochalcone A **(18)** strongly inhibited NF-$\kappa$B nuclear localization along with the subsequent DNA binding and transcriptional activities induced by TNF-$\alpha$. Mechanistic studies with licochalcone A **(18)** uncovered the underlying mechanism; the repression was not due to impairment of receptor-interacting protein (RIP) or IKK-$\beta$ recruitment to tumor necrosis factor receptor (TNFR)1 but rather arose from inhibition of IKK activation and subsequent I$\kappa$B degradation. The authors suggested that cysteine 179 of the IKK complex is essential for licochalcone A-induced IKK inhibition [39]. Interestingly, Furusawa et al. [41] demonstrated that if NF-$\kappa$B was induced by LPS, the effect of licochalcone A **(18)** appeared further downstream at the level of p65. Licochalcone A **(18)** strongly inhibited phosphorylation of p65 at serine 276 leading to abrogation of its interaction with p300 and subsequent reduction in NF-$\kappa$B transactivation. Later on, a similar mechanism leading to inhibition of LPS-induced NF-$\kappa$B activation was also confirmed for licochalcone B **(20)** and licochalcone D **(21)** together with reduced LPS-induced production of nitric oxide (NO), TNF-$\alpha$, and monocyte chemoattractant protein (MCP)-1 [40].

A similar mechanism was observed for cardamonin **(22)**, a natural product from *Artemisia absinthium*. NF-$\kappa$B activation and related iNOS production in LPS-stimulated cells were inhibited by a direct effect on the capacity of the transcription factor to bind DNA [50]. Interestingly, Israf et al. [60] reported inhibition of COX-2 and iNOS expression by cardamonin **(22)** via dose-dependent suppression of I$\kappa$B$\alpha$ phosphorylation and degradation in LPS-induced RAW 264.7 macrophages, clearly describing a cell-type-specific effect of this compound. A similar effect on the NF-$\kappa$B pathway was reported for broussochalcone A **(6)** by Cheng et al. [19].

Additionally, inhibition of NF-$\kappa$B activity by downregulation of the IKK complex has been reported for flavokavain A **(23)**, which is isolated from *Piper methysticum*. p38-regulated/activated kinase (PRAK) and MAPK-activated protein kinase (MAPKAP-K)-3 were also suppressed, as demonstrated by a group from Scotland and Luxembourg [36].

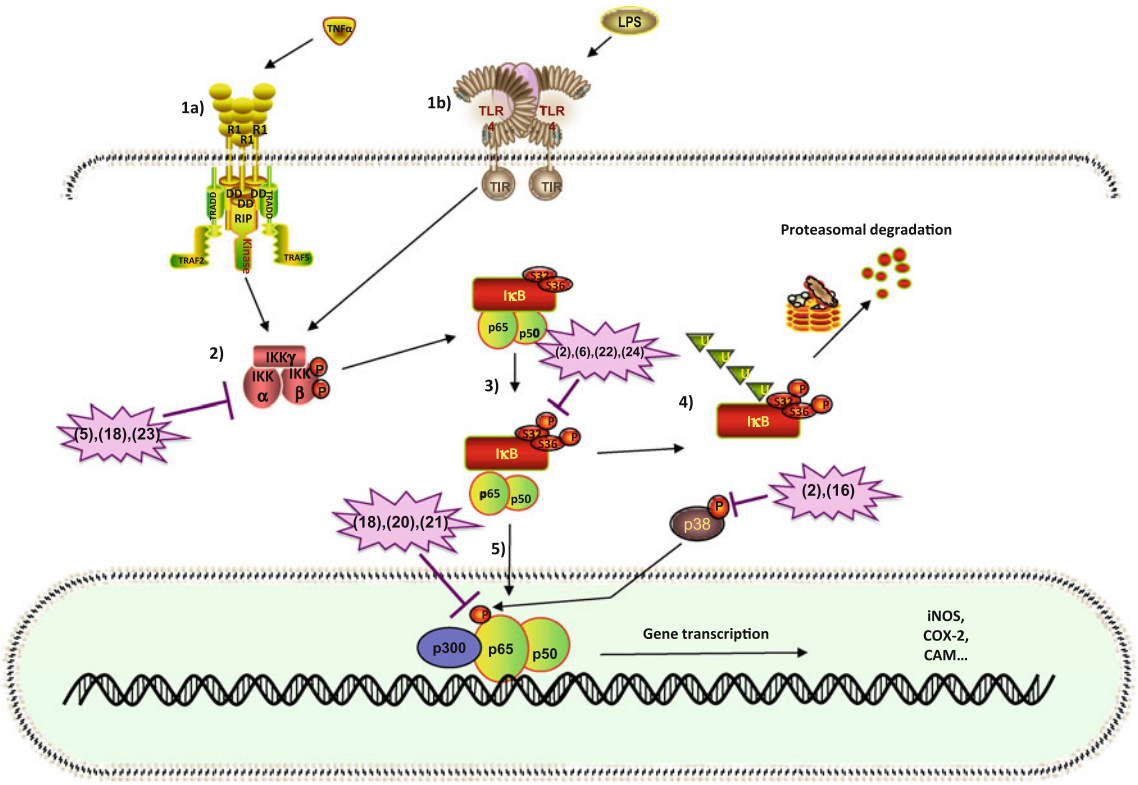


**Fig. 4** Involvement of naturally occurring chalcone derivatives in the NF-κB inflammation pathway. **1a** TNFα and/or **1b** LPS ligands interact with corresponding receptors, recruiting several signaling proteins to form a primary signaling complex. **2** Transmission of signal resulting in IKK activation. **3** IKK subsequently phosphorylates serines 32 and 36 of the IκB inhibitor, **4** which in turn creates binding sites for ubiquitination and shifts IκB to proteasomal degradation. **5** NF-κB subunits are released from the inhibitor complex and translocated to the nucleus where they bind DNA and activate transcription of several genes. Chalcone derivatives block the NF-κB pathway at different steps: inhibition of IKK activity (chalcones **5**, **18**, **23**), suppression of IκBα phosphorylation (chalcones **2**, **6**, **22**, **24**), direct inhibition of p65 binding to DNA (chalcones **18**, **20**, **21**) or reduction in p38 phosphorylation (chalcones **2**, **16**). *Arrows* represent induction/activation and *blunt-ended lines* represent repression/inactivation. *Abbreviations*: *TNFα* tumor necrosis factor alpha, *LPS* lipopolysaccharide, *IκB* inhibitor of kappa B, *IKK* IκB kinase, *NF-κB* nuclear factor kappa B. This figure was generated with ScienceSlides software

Modification of IKK and p65 cysteine residues after xanthohumol **(5)** treatment of leukemia cells was described by Harikumar et al. [48] Xanthohumol **(5)** downregulated both constitutive and inducible NF-κB activities. Furthermore, direct inhibition of IKK activation was related to xanthohumol-mediated alteration of the cysteine 179 residue, whereas direct binding inhibition of p65 to DNA could be linked to modification of a p65 cysteine residue. Cho et al. [21] demonstrated that in INF-γ-stimulated RAW 264.7 macrophages, xanthohumol **(5)** inhibited binding activity of STAT-1α and interferon regulatory factor (IRF)-1.

Hydroxy safflor yellow A **(24)**, the main active monomer of *Carthamus tinctorius*, significantly inhibited phosphorylation of IκBα and subsequent p65 transactivation by preventing its translocation to the nucleus. The transcriptional level of pro-inflammatory cytokines TNF-α, IL-1α, and IL-6 was reduced, while mRNA expression of anti-inflammatory cytokine IL-10 was potentiated [18].

Naringenin chalcone **(1)**, abundant in tomato skin, inhibited in a dose-dependent manner the production of pro-inflammatory mediators such as TNF-α, MCP-1, and NO in LPS-stimulated macrophages [53].

Kim et al. [70] reported that the anti-inflammatory properties of isoliquiritigenin **(2)** are mediated by down-regulation of iNOS, COX-2, TNF-α, and IL-6. These proteins were downregulated by inhibition of NF-κB via suppression of IKK, ERK1/2 and reduction in p38 phosphorylation. Inhibition of NF-κB activation by blocking the phosphorylation and subsequent degradation of IκBα has also been reported independently by Kumar et al. and Kwon et al. [81, 84]. Isoliquiritigenin **(2)** potentiated HO-1 expression through the ERK1/2 pathway in RAW 267.4 cells, thus effectively inhibiting macrophage-derived inflammation [93]. In prostate cancer cells, isoliquiritigenin **(2)** inhibited cancer cell invasion and migration by abrogating JNK/AP-1 signaling [83].

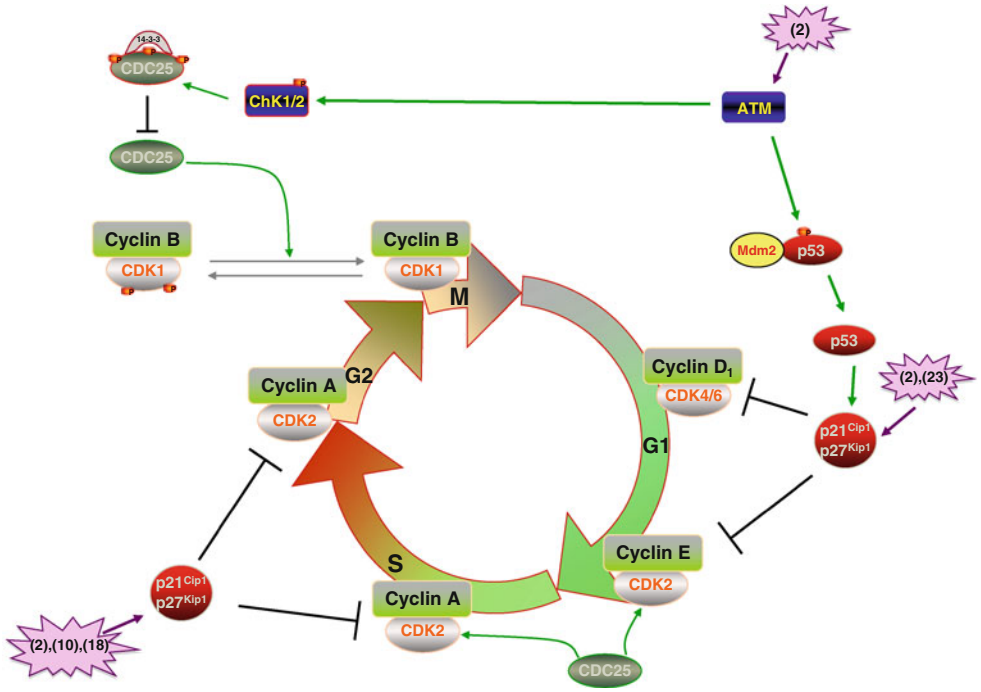


**Fig. 5** Involvement of naturally occurring chalcone derivatives in regulation of the cell cycle. Chalcone derivatives may induce ATM (chalcone **2**), which in turn phosphorylates p53, thus decreasing p53/MDM2 interaction. However, ATM augmentation subsequently leads to phosphorylation of Chk1 and Chk2 and reduces the level of Cdc25c resulting in G2/M arrest. By activating inhibitors of Cdks (p21 and p27), chalcone derivatives may participate in cell cycle arrest in either G1 or G2/M phase (chalcones **2**, **10**, **18**, **23**). *Arrows* represent induction/activation and *blunt-ended lines* represent repression/inactivation. *Abbreviations*: *Cdk* cyclin-dependent kinase, *ATM* ataxia telangiectasia mutated, *Chk* checkpoint homolog serine/threonine-protein kinase, *Cdc25c* cell division cycle 25 homolog C. This figure was generated with ScienceSlides software

Butein **(16)** has been shown to act as an anti-inflammatory agent useful in the treatment of intestinal inflammation. In TNF-α-stimulated HT-29 colon adenocarcinoma cells, butein **(16)** inhibited p38 phosphorylation and osteopontin-mediated IκBα phosphorylation [92]. Moreover, Pandey et al. [138] investigated the mechanism by which butein **(16)** attenuates IκBα phosphorylation. They reported that IKK is inactivated directly via the cysteine 179 residue. A co-isolated constituent from *Butea monospera* extract, isobutrin **(25)**, also displayed potent inhibitory activity toward IKK complex activity [149].

Similar effects on various inflammatory pathways and HO-1 activation have been published for a variety of synthetic chalcone derivatives with structures optimized for improved functionality [5, 94, 96, 140, 141].

## Chalcones as inhibitors of the cell cycles

As mentioned previously, the antiproliferative activity of chalcone derivatives is tightly linked with cell cycle arrest and initiation of the cellular apoptotic machinery. Cyclins and cyclin-dependent kinases (Cdks) are two key regulatory factors and are crucial components of cell cycle progression. Alterations to the expression or post-transcriptional modifications of these compounds lead to deregulation of cell cycle functions. Involvement of diverse chalcone derivatives in these processes has been described (see Fig. 5).

Chalcone **(10)** alone showed potential to interact with cell cycle progression. The simultaneous enhancement of p21 and p27 expression and reduction of cyclin B1, cyclin A, and Cdc2 levels leads to G2/M phase arrest in both human MCF-7 and MDA-MB-231 breast cancer cell lines as well as in human T24 and HT-1376 bladder cancer cell lines [57, 158].

Isoliquiritigenin **(2)** was shown to reduce cyclin D1, cyclin E, and Cdk4 levels, which together with increased p27 levels contributed to downregulation of the cyclin D1–Cdk4 complex and induced early G1 arrest in human DU145 and rat MLL prostate cancer cells. In addition, phosphorylation of cell division cycle (Cdc)2 was enhanced concurrent with reduction of Cdc25c levels, leading to inactivation of Cdc2–cyclin B1 complexes and subsequent late G2/M phase arrest [97]. Similarly, perturbation of the cell cycle at the G2/M phase by induction of universal inhibitors of Cdks, such as p21 (CIP1/WAF1) and p27, was observed in leukemia CCRF-CEM cells [195], human cervical cancer HeLa cells [139], uterine leiomyoma cells [68], human hepatoma Hep G2 cells [54], human

lung cancer A549 cells [59], and human prostate cancer LNCaP cells [65].

Licochalcone A **(18)** led to G2/M arrest by similar mechanisms via induction of p21 and p27, attenuation of Cdks 2, 4, and 6, and downregulation of cyclin D1 in androgen-independent PC-3 prostate cancer cells [38, 188].

Flavokavain A **(23)**, the major component of the traditional kava tea consumed predominately by men in Fiji, Vanautu and Western Samoa, produced cell cycle arrest by different mechanisms in cells expressing wild-type p53 versus cells expressing mutated p53. In p53 wild-type RT4 cells, flavokavain A **(23)** mediated arrest in G1 phase by accumulation of Cdk2 kinase inhibitors p21 and p27. In p53 mutated cell lines, however, flavokavain A **(23)** prevented the G2/M transition via persistent activation of Cdk1 kinase activity and increased levels of cyclin B1, which counteracted the decreased level of Cdc25C. The Cdk1-inhibitory kinases Myt1 and Wee1 were suppressed, allowing Cdk1 to remain dephosphorylated [167].

A promising strategy leading to disruption of aberrant cell cycle progression of defective cells is attenuation or abrogation of MDM2/p53 complex formation. The oncoprotein MDM2 inhibits the tumor suppressor protein p53, which is considered a genome integrity checkpoint. Inactivated p53 has been shown to be expressed in many human tumors. Stoll et al. [162] reported that chalcone derivatives might antagonize the interaction between MDM2 and p53 by binding to a subsite of the p53-binding cleft of human MDM2, thereby releasing p53 from the complex and restoring its transcriptional activity. The stability of p53 can be further enhanced by activation of ataxia telangiectasia mutated (ATM), which phosphorylates p53 at serine 15, thus decreasing p53/MDM2 interaction. Studies performed by Hsu et al. [58] in human cervical carcinoma HeLa cells revealed that isoliquiritigenin-mediated cell cycle blockade in G2/M phase is associated with extended activation of ATM accompanied by phosphorylation of Chk2 and Cdc25c and subsequent p53 phosphorylation. The p53-dependent inhibition of the cell cycle in G1 phase has been described [55]. Similar patterns have been reported for butein **(16)**, where the growth of hepatoma cancer cells was inhibited via ATM augmentation, followed by Chk1 and Chk2 phosphorylation and Cdc25c level reduction leading to G2/M phase arrest [120].

Synthetic chalcones were shown to disrupt the p53-MDM2 binding, resulting in elevated p53 activity that explained previously observed anticancer properties [14].

The ability of chalcones to interact with tubulin, leading to alterations in the microtubule network, indicates another mechanism that results in cell cycle blockade. In several cases, the cytotoxicity-mediated inhibition of cell growth by chalcones correlates with their capability to bind to tubulin and thereby abrogate microtubule polymerization [86]. Although there are few known inhibitors of tubulin assembly among naturally occurring chalcones, a large library of chalcone analogues was synthesized. Many showed convincing antimitotic properties as microtubule-depolymerizing agents with $IC_{50}$ values of sub-μM and low μM concentrations (see Table 1) [10, 31, 69, 87].

## Chalcones as inducers of cell death mechanisms

The induction of apoptosis is a hallmark of cancer treatment. A large spectrum of chalcone derivatives with pro-apoptotic properties have been found in various edible or medicinal plants. Induction of apoptosis in gastric cancer cells has been reported for 2′,4′-dihydroxychalcone **(29)** isolated from *Herba oxytropis* [110] and for uvaretin **(35)**, isouvaretin **(36),** and diuvaretin **(37)** from *Uvaria acuminata* in leukemia cells [125]. Similarly, 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (ON-III) **(31)** extracted from buds of traditional Chinese medicinal herb *Cleistocalyx operculatus***,** which are used for a preparation of herbal tea in Vietnam, triggered apoptosis in breast and leukemia cancer cells [101, 181]. Licochalcone E **(38)** isolated from *Glycyrrhiza inflata* induced apoptosis in endothelial cells [17].

An important apoptotic cell death mechanism is activated via the TNF superfamily members, particularly tumor necrosis factor–related apoptosis-inducing ligand (TRAIL). TRAIL selectively induces programmed cell death via interaction with death receptors TRAIL-R1 (DR4) or/and TRAIL-R2 (DR5) in various cancer cells without a harmful effect on normal tissue. However, reduced expression of these receptors or elevated expression of antiapoptotic proteins leads to TRAIL resistance [169, 189]. The involvement of specific chalcones in apoptotic cell death is summarized in Fig. 6.

Szliszka et al. [166] showed that chalcone **(10)** and four of its natural analogues, licochalcone A **(18)**, isobavachalcone **(15)**, xanthohumol **(5),** and butein **(16)**, strongly enhanced the apoptosis-inducing potential of TRAIL and thus sensitized TRAIL-resistant LNCaP prostate cancer cells.

Cardamomin **(22)**, a chalcone isolated from *Catimbium speciosum*, which is used as herbal tea or in essential oils, enhanced TRAIL-induced apoptosis in TRAIL-resistant cells. The underlying mechanism includes increased expression of death receptor (DR)4 and DR5 and reduced Bcl-xL levels following cardamomin treatment of human colorectal adenocarcinoma DLD1 cells [134]. Butein **(16)** alone has been shown to induce apoptosis in human leukemia HL-60 cells via positive modulation of caspase-3 activity associated with downregulation of Bcl-2 expression and upregulation of Bax expression [72]. Subtoxic

**Table 1** Semi-synthetic and synthetic chalcone derivatives as antiproliferative agents

| Chalcone derivative | Parent natural product (if available) | Targeted cellular processes | References |
|---|---|---|---|
| 15 dihydroartemisinin derivatives | Artemisinin (*Artemisia annua*) | Cell viability<br>Cell proliferation apoptosis | [179] |
| 21 derivatives polyoxygenated on the A ring | Tangeretin (Citrus) | Cell proliferation | [145] |
| Boronic acid CA-4 analogues:cis-6, trans-6 | Combretastatin A4 (*Combretum caffrum*) | Cell proliferation<br>Inhibition of tubulin assembly | [79] |
| 4 analogues | Combretastatin A4 (*Combretum caffrum*) | Cell proliferation<br>Inhibition of tubulin assembly angiogenesis | [78] |
| 97 combretastatin-like chalcones | Combretastatin A4 (*Combretum caffrum*) | Cell viability<br>Cell cycle<br>Inhibition of tubulin assembly | [31] |
| 65 derivatives with basis functionalities | | Cell proliferation | [107] |
| 19 methoxylated derivatives | | Cell proliferation<br>Cell viability inflammation | [8] |
| 12 $\beta$-chlorovinyl derivatives | | Cell proliferation inflammation | [7] |
| 17 piperidinylchalcones derivatives | | Cell proliferation<br>Cell cycle | [106] |
| RVC-588<br>(4,4′-dihydroxychalcone) | | Cell viability<br>Cell proliferation<br>Cell death | [156] |
| 2′,4′,6′-tris(methoxymethoxy) chalcone | | Cell proliferation | [95] |
| 4′-(p-toluenesulfonylamido)-4-hydroxychalcone | | Cell proliferation | [91] |
| JAI-51 | | Cell proliferation<br>Cell cycle<br>Inhibition of tubulin assembly | [10] |
| MDL-27048 | | Cell proliferation<br>Cell cycle<br>Inhibition of tubulin assembly | [69] |
| 644 chalcone derivatives | | Cell proliferation<br>Cell cycle<br>Inhibition of tubulin assembly | [87] |

concentrations of butein **(16)** in combination with TRAIL increased expression of DR5 and boosted caspase-3 activity, allowing apoptosis in TRAIL-resistant U937 cells [71]. Similarly, subtoxic combinations of isoliquiritigenin **(2)** and TRAIL rapidly induced apoptosis in colon cancer HT29 cells by influencing the interaction between TRAIL and its receptor [186]. In prostate and gastric cancer cells and human cervical carcinoma HeLa cells, isoliquiritigenin **(2)** disrupted the mitochondrial membrane potential, resulting in mitochondrial apoptotic pathway activation [58, 64, 111].

A novel approach to the induction of apoptosis is the use of 'mitocans', therapeutic and preventive drugs that preferentially target mitochondria and possess anticancer activity [146]. Xanthohumol **(5)** corresponds well to this definition; it is able to inhibit complexes I-III of the respiratory chain, which subsequently leads to excessive superoxide anion radical ($O_2^{-\cdot}$) production in the mitochondria. This compound also produces a breakdown of the mitochondrial membrane potential followed by cytochrome c release as an initial, irreversible step of apoptosis induction. Thus, mitochondria serve as novel cellular targets for naturally occurring anticancer drugs [163]. In addition, apoptosis induction through ROS generation by xanthoangelol **(33)**, a major constituent of *Angelica keiskei*, was described by Motani et al. in neuroblastoma [121]. Another component of this plant, isobavachalcone **(15)**, induced apoptosis in neuroblastoma by downregulation of

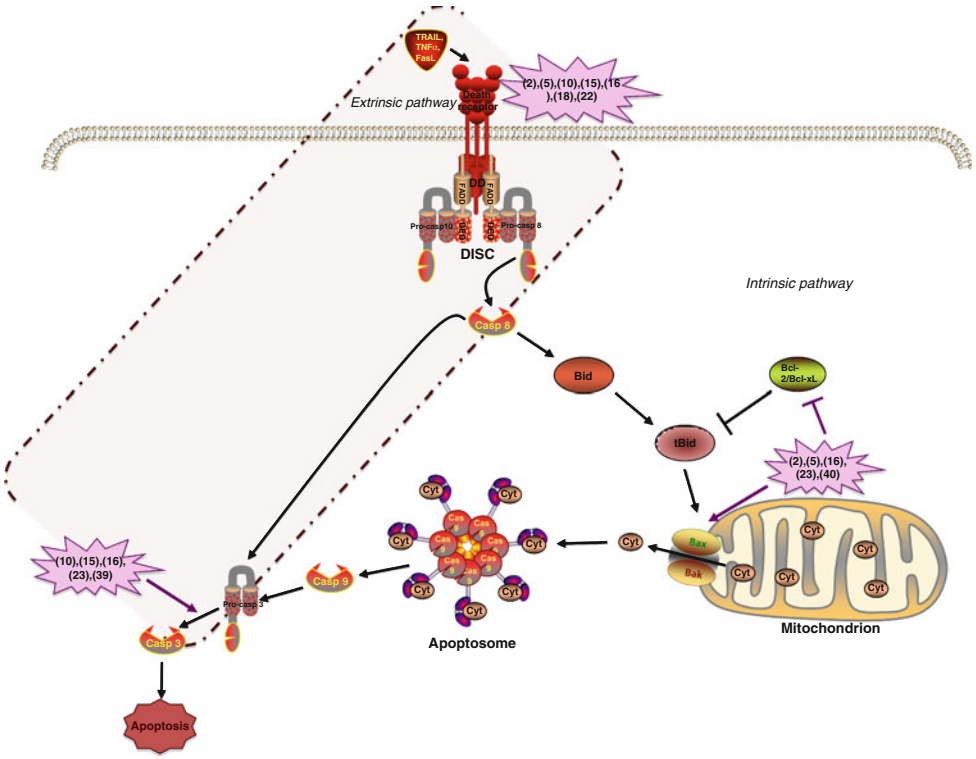


**Fig. 6** Involvement of naturally occurring chalcone derivatives in apoptotic cell death. Chalcones potentiate the extrinsic apoptotic pathway: chalcones enhance the apoptosis-inducing potential of TRAIL partially by increased expression of death receptors DR4 and DR5 (chalcones **2**, **5**, **10**, **15**, **16**, **18**, **22**). Chalcones are implicated in the intrinsic apoptotic pathway: chalcones target mitochondria either by disruption of the mitochondrial membrane potential (chalcones **2**, **5**) or by downregulation of anti-apoptotic proteins like Bcl-xL, Bcl-2, and upregulation of Bax and Bak (chalcones **16**, **23**, **40**). Chalcones induce apoptosis via positive modulation of caspase-3 activity (chalcones **10**, **15**, **16**, **23**, **39**). *Arrows* represent induction/activation and *blunt-ended lines* represent repression/inactivation. *Abbreviations*: *TNFα* tumor necrosis factor alpha, *TRAIL* TNF-related apoptosis-inducing ligand, *FasL* Fas ligand, *FADD* Fas-associated death domain, *DD* death domain, *DED* death effector domain, *DISC* death-inducing silencing complex, *Casp* caspase, *Bid* Bcl-2 interacting domain, *Cyt* cytochrome C. This figure was generated with Science-Slides software

pro-caspase 3 and 9 followed by upregulation of cleaved caspase 3 and 9 and Bax induction, similar to the effects of chalcone **(10)** in human bladder cancer cells [128, 158]. Moreover, no cytotoxicity was observed against non-transformed cells [128]. A similar mechanism was described for isolespeol **(39)**, isolated from the traditional starch crop *Artocarpus communis* cultivated in tropical and subtropical regions [33], in human liposarcoma SW-872 cells [187, 188].

Zi et al. showed evidence that flavokavain A **(23)**, traditionally consumed by South Pacific Islanders in kava tea extract, induced apoptosis in bladder cancer cells partially through both the Bax-dependent, mitochondrial pathway, and the downregulation of anti-apoptotic proteins like Bcl-xL, x-linked inhibitor of apoptosis protein (XIAP), and survivin. Flavokavain A **(23)** activated caspase 9, caspase 3, and poly (ADP-ribose) polymerase (PARP) cleavage. Furthermore, loss of mitochondrial membrane potential was followed by a release of cytochrome c that was linked to an increased Bax/Bcl-xL ratio [194]. The related chalcone flavokavain B **(40)**, which is used in food and traditional Chinese medicine, exhibits potently caspase- and mitochondria-dependent apoptotic activity accompanied by cytochrome c release and translocation of Bak to the mitochondria. Induction of GADD153, which regulates the expression of several Bcl-2 family members and enhances ROS production by depletion of glutathione, has also been observed. In connection with this effect, flavokavain B **(40)** reduced the expression of prosurvival Bcl-2, amplified the expression of proapoptotic Bim, and triggered intracellular ROS generation in human colon cancer cells [82]. Similarly, Tang et al. [168] showed that flavokavain B **(40)** caused upregulation of Bim and Puma pro-apoptotic proteins and downregulation of XIAP and survivin anti-apoptotic proteins in androgen-negative prostate cancer cells.

Apoptosis is the most frequently observed mechanism of chalcone-mediated cell death, but it is definitely not the only mechanism. In addition to apoptosis, licochalcone A **(18)** also induced autophagy-related cell death in LNCaP prostate cancer cells. Suppression of Bcl-2 expression and downregulation of the mammalian target of rapamycin

(mTOR) pathway led to the formation of autophagic vacuoles and acidic vesicular organelles, the classical characteristics of autophagy [184].

## Effect of chalcones on tumor initiation

The initiation stage of carcinogenesis is closely related to phase I and II carcinogen metabolism and to elevated production of reactive oxygen species (ROS) and reactive nitrogen species (RNS).

Phase I xenobiotic metabolism represents enzymatic activation that allows processing of pro-carcinogens into carcinogens. However, these metabolites are frequently further transformed by phase II detoxifying enzymes that deactivate harmful radicals and electrophiles. Anti-initiation properties are therefore linked to the inhibition of phase I enzymes (cytochrome (CYP) P450, 1A1, 1A2, 1B1) and/or the induction of phase II enzymes (NAD(P)H, quinone reductase (QR), gluthatione *S*-transferase (GST)) [44].

Inhibition of this very early step of carcinogenesis is tightly associated with the well-described antioxidant properties of natural compounds. Production of scavenging ROS (superoxide-, hydroxyl radical, hydrogen peroxide, hypochlorous acid) and NO leads to prevention of oxidative damage to DNA, which would otherwise result in oxidative stress-induced genotoxicity. Overproduction of ROS following the induction of oxidative stress contributes significantly to tumor initiation, and a long-term elevation of ROS levels also plays a role in tumor promotion [80]. Similarly, the involvement of RNS cannot be exclusively assigned to either the initiation or the promotion steps of carcinogenesis [133].

It has been shown that chalcones possessing predominantly hydroxyl and prenyl substituents exhibit important antioxidant properties, specifically the induction of quinone reductase activity [45]. Isoliquiritigenin **(2)** with three hydroxyl groups acts as a monofunctional inducer of phase II enzymes, including GST and QR by triggering the antioxidant response element (ARE) in the promoter region of the QR gene [20, 24]. Cuendet et al. [25] demonstrated the ability of isoliquiritigenin to induce QR activity in colon and GST activity in rat liver tissue. Furthermore, among 9 isolates identified from *Glycyrrhiza glabra*, isoliquiritigenin **(2)** is one of the three most potent antioxidant compounds exhibiting peroxynitrite scavenging activity. It has been demonstrated that this compound inhibits nitric oxide (NO) production [20]. Similarly, 1,2-dihydroparatocarpin A **(3)**, a prenylated chalcone isolated from extracts of roots or stolons of licorice, mediated effective antioxidant protection against peroxynitrite and nitric oxide [20, 185].

Additionally, isoliquiritin apioside **(4),** a phytochemical isolated from the 'Rlicca' fraction of *Glycyrrhiza glabra*, reduced oxidative stress–induced genotoxicity by inhibiting hydrogen peroxide and 4-nitroquinoline-1-oxide (4-NQO) in human peripheral blood lymphocytes [67].

The prenylated chalcone xanthohumol **(5)**, isolated from beer, strongly inhibited CYP1A activity with an $IC_{50}$ in the nM range and almost completely inhibited this activity at low μM concentrations [42, 51]. Furthermore, a low μM concentration was sufficient to double the specific QR activity, which contributes to detoxification by reduction in reactive quinones to less-reactive hydroquinones [42]. Interestingly, xanthohumol **(5)** also possessed potent hydroxyl- and peroxyl radical scavenging activities that were 8.9- and 2.9-fold higher, respectively, than the reference compound Trolox. In addition, lipopolysaccharide (LPS)-induced inducible nitric oxide synthase (iNOS) expression and the resulting increase in NO production in RAW 264.7 murine macrophages were decreased in a dose-dependent manner by xanthohumol **(5)** [44].

Another prenylated antioxidative chalcone, broussochalcone A **(6)** isolated from *Broussonetia papyrifera vent*, inhibited NO production in LPS-stimulated RAW 264.7 cells in a dose-dependent manner that was independent from a direct effect on iNOS enzyme activity. From a mechanistic point of view, this compound seems to suppress the NF-$\kappa$B pathway resulting in a decreased level of iNOS expression. Broussochalcone A **(6)** also exhibited free-radical scavenging activity, including superoxide- and hydroxyl-radical inhibition, which may contribute to its antilipid peroxidation activity in rat brain homogenates [19].

Several studies indicate that dihydrochalcones exhibit particularly potent antioxidant properties [23, 118, 151].

Phloretin **(7)** and its glucoside phloridzin **(8)**, two naturally occurring dihydrochalcones isolated from apples, displayed strong scavenging potential against peroxynitrite [151]. Moreover, phloridzin **(8)** possesses a remarkable antioxidant activity against superoxide radical, hydrogen peroxide, and hypochlorous acid [23].

Mathiesen et al. [118] reported that myrigalone B **(9)** from the plant *Myrica gale* is an interesting scavenger of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and an inhibitor of lipid peroxidation in isolated hepatocytes treated with tert-butyl hyperoxide.

Interestingly, neohesperidin dihydrochalcone, a hemisynthetic compound used as an intense sweetener and permitted for a commercial use as a food additive in Europe, is produced by the hydrogenation of neohesperidin, which is abundant in citrus fruits. Like phloridzin **(8)**, neohesperidin dihydrochalcone exhibits scavenging activities for various ROS with a preference for non-radical ROS including hydrogen peroxide and hypochlorous acid [23].

Finally, Makita et al. [113] demonstrated that the dietary flavonoids chalcone **(10)** and 2-hydroxychalcone **(11)** have an inhibitory effect on 4-NQO-induced oral carcinogenesis.

## Effects of chalcones on tumor promotion

The second phase of carcinogenesis, tumor promotion, is tightly linked to the initiation phase. Generation and activation of endogenous tumor promoters (prostaglandins (PGs), 17$\beta$-estradiol (E2)) leads to altered gene expression, affects chromatin structure and disturbs signal transduction pathways. Therefore, inhibition of COX-1 and COX-2, which catalyze the formation of PGs, plays an important role in the prevention of tumor promotion [165].

Hormones such as 17$\beta$-estradiol represent another class of endogenous tumor promoters that stimulate cell growth via interaction with estrogen receptors. This interaction leads to increased risk for breast and uterine cancer [150]. Thus, reduction of endogenous estrogen levels is a promising strategy to decrease and prevent tumor promotion [43].

Chronic inflammation also generates elevated levels of NO and contributes to tumor promotion. Xanthohumol **(5)** has been shown to successfully inhibit iNOS production and both COX-1 and COX -2 activities [42, 43]. The activity of chalcones against inflammatory processes was demonstrated by Zhao et al. [192], who showed potent inhibition of LPS-induced NO production without any cytotoxicity, paralleled by iNOS expression, by xanthohumol **(5)**, xanthohumol B **(12)**, xanthohumol D **(13)**, dihydroxanthohumol **(14)**, and a novel chalcone oxidation product of xanthohumol **(5)**, all isolated from *Humulus lupulus*. Surprisingly, the suppression of NO production mediated by dihydroxanthohumol, which lacks a double bond between the $\alpha$ and $\beta$ positions, showed much weaker patterns of inhibition than the other 4 chalcones. Altogether, suppression of LPS-induced iNOS protein expression apparently mediates the inhibition of COX-1 and COX-2 by xanthohumol **(5)** [43]. Furthermore, the antiestrogen potential of xanthohumol **(5)** was confirmed by efficient inhibition of both human recombinant aromatase and estrogen-mediated induction of alkaline phosphatase (ALP) in Ishikawa human endometrial adenocarcinoma cells. Xanthohumol **(5)** alone does not possess any intrinsic pro-estrogenic potential [43, 44].

Various chalcone derivatives may positively affect the suppression of tumor promotion initiated by 7,12-dimethylbenz[alpha]anthracene (DMBA) and mediated by 12-O-tetradecanoylphorbol-13-acetate (TPA). Isobavachalcone **(15)**, isolated from *Angelica keiskei,* significantly inhibited in vivo TPA-induced skin tumor promotion in mice [1]. Similar results were obtained with isoliquiritigenin **(2)**, a phenolic constituent of licorice [20]. This compound inhibited TPA-independent tumor promotion in mice treated with DMBA and suppressed TPA-stimulated production of PGE2 in intact epidermal cells. However, it seems that isoliquiritigenin **(2)** exerts its antitumor-promoting effect through the lipoxygenase (LOX) inhibition in non-epidermal cells because it failed to inhibit 12-LOX and COX in an epidermal subcellular fraction [177]. Ye et al. [182] recently demonstrated that isoliquiritigenin **(2)** inhibits the CYP19 enzyme (aromatase), which catalyzes rate-limiting step of the conversion of androgens, such as testosterone and androstenedione to estrogens.

Similarly, the plant tetrahydroxychalcone butein **(16)** is a potent aromatase inhibitor that facilitates downregulation of estrogen synthesis, thereby producing protective effects against the initiation and promotion of breast cancer [173].

Interestingly, a combination of naringenin chalcone **(1)**, the main active component of tomato skin, and 4-hydroxychalcone **(17)** effectively inhibited aromatase and 17$\beta$-hydroxysteroid dehydrogenase in a low μM range [88].

Licochalcone A **(18)**, another phytochemical isolated from licorice, belongs to a family of promising compounds with potent antitumor activity. In vitro experiments confirmed that licochalcone A suppressed the generation of NO and PGE2 and inhibited the expression of iNOS and COX-2 induced by LPS in RAW 264.7 cells [85].

Within the polyphenol family, prenylated flavonoids are leading molecules for the prevention of tumor promotion due to their unique structure and promising aromatase inhibitory properties. Semisynthetic chalcone analogues of the naturally occurring prenylated flavonoid abyssinone II from *Broussonetia papyrifera* were tested for their potential to inhibit CYP19. Surprisingly, only one compound showed inhibition potential and it was less potent than racemic abyssinone II. The successful derivative featured two hydroxyl groups on the A ring and one methoxy group accompanied by a 3-methylbutyl-2-enyl substituent on B ring [112].

## Effect of chalcones on tumor progression

Uncontrolled cell proliferation, alterations in terminal cell differentiation, and impairment of apoptosis are key characteristics of tumor cell progression. In this section, we will focus only on the antiproliferative and toxicity-induced effects of natural compounds as the involvement of chalcone derivatives on cell cycle and cell death mechanisms we discussed separately.

Severe side effects, such as nephrotoxicity, hepatotoxicity, ototoxicity, or neurotoxicity, are triggered by currently used chemotherapeutic agents. These adverse impacts on health shift the attention to search for novel drugs among natural compounds with promising bioactivity that lacks such side effects. Thus, combination of naturally occurring compounds with commercially used chemotherapy agents is a promising strategy leading to

reduction in treatment dosage, reduction in side effects, enhancement of drug efficacy, and reduced drug resistance. Furthermore, identification of compounds with selective cytotoxicity to transformed cells would improve tumor treatment.

Licochalcone A **(18)** was studied as a candidate for overcoming cisplatin-induced toxicity. Licochalcone A **(18)** reduced the size of solid tumors and induced neither nephrotoxicity/hepatotoxicity nor oxidative stress. The suppression of proliferation was moderated through reduction in DNA synthesis in CT-26 murine colon carcinoma cells. Oral administration of licochalcone A prior to cisplatin treatment inhibited cisplatin-induced kidney and liver damage as indicated by alterations in the serum NO and tissue lipid peroxidation levels. Licochalcone A **(18)** was also able to replenish GSH levels [90].

A similar study of isoliquiritigenin **(2)** confirmed its role in reducing chemotherapy-induced kidney and liver toxicity [89]. It was recently reported that isoliquiritigenin **(2)** selectively inhibited the proliferation of C4-2 and LNCaP prostate cancer cells, while a similar dosage range did not affect the viability of normal IEC-6 epithelial cells [191]. Isoliquiritigenin **(2)** has also been shown to significantly reduce viability and proliferation in a dose-dependent manner in uterine leiomyoma cells, human lung cancer cells, and CCRF-CEM leukemia cells. These effects were related to induction of apoptosis and increased cell cycle arrest [59, 68, 195]. Interestingly, isoliquiritigenin **(2)** downregulates proliferation in HL-60 cells and mediates their monocytic differentiation [100].

Li et al. [102] carried out a detailed phytochemical investigation into Brazilian red *Propolis*, considered a healthy food in various parts of the world, which led to the isolation of four hydroxychalcone derivatives among more than 40 compounds. Three out of four chalcones possessed a conjugated double bound and showed accentuated cytotoxicity to murine colon 26-L5 carcinoma, murine B16-BL6 melanoma, murine Lewis lung carcinoma (LLC), human lung adenocarcinoma A549, human cervix adenocarcinoma HeLa, and human HT-1080 fibrosarcoma cell lines. However, reduction to the single-bond characteristic of hydrochalcones impaired the cytotoxic activity. The authors also stressed the importance of a methoxy substituent at the C-2′ position of the A ring and the absence of substituents on the B ring as a structure that preferentially potentiates cytotoxic properties.

Similar observations were published by De Vincenzo et al. [26] who determined the effects of 15 natural and synthetic chalcones on ovarian cancer cell proliferation. The presence of an $\alpha$-$\beta$ double bond potentiated the antiproliferative properties of the chalcone scaffold.

Butein **(16)** and a number of other hydroxy- and dihydroxychalcones were tested for their cytotoxic effect on human colon adenocarcinoma cell proliferation. Butein **(16)** proved to be the most active compound for growth inhibition [183].

A batch of prenylated flavonoids, including the chalcones xanthohumol **(5)** and desmethylxanthohumol **(26)** isolated from *Humulus lupulus*, has shown in vitro effective inhibition of the proliferation of prostate cancer cells. Xanthohumol **(5)** appeared to be the most potent compound, whereas the antiproliferative activity of desmethylxanthohumol **(26)** was weaker [28]. Furthermore, xanthohumol **(5)** inhibited the activity of human DNA polymerase $\alpha$, the only initiator of de novo DNA synthesis among the eukaryotic polymerases [44].

Likewise, dihydrochalcone asebogenin **(27)**, which is found in several plants, including *Piper aduncum*, and used as a condiment and for cocoa flavoring, downregulated the proliferation of murine B cells [180].

The primary antiproliferative mechanisms related to growth inhibition in different cancer cell lines are apoptosis induction and blocking of cell cycle progression. These mechanisms have been reported for naturally occurring flavonoids including chalcone **(10)** (1,3-diphenyl-2-propenon) [57, 158], isoliquiritigenin **(2)** [55, 56], and isoliquiritigenin 2′-methyl ether **(28)** isolated from *Caesalpinia sappan* [98], butein **(16)** [120, 137], and 2′,4′-dihydroxychalcone **(29)** from *Herba oxytropis* [110, 187].

In addition, a huge array of hemisynthetic or synthetic chalcone analogues has been created to identify the most efficient structure for the inhibition of proliferation (see Table 1) [9, 91, 95, 145, 148, 156, 179].

## Inhibition of invasion

Invasion leads to the localized destruction of normal tissue and is linked to the highest mortality in patients with cancer either directly or via metastasis. The first step, local invasiveness, requires escape of the cancer cells from the epithelium of origin (primary tumor) and their migration as separate individuals, known as the epithelial–mesenchymal transition (EMT). The major role in blocking this process is played by the transmembrane glycoprotein E-cadherin. E-cadherin is implicated in cell–cell adhesion by binding epithelial cells together through adherent junctions. Furthermore, E-cadherin forms a complex with catenins, cytoplasmic proteins that link E-cadherin to the actin cytoskeleton. E-cadherin/catenin-mediated intercellular adhesion is essential for the anti-invasive properties of these proteins. Upregulation of the functions of the E-cadherin–catenin invasion-suppressor complex by natural compounds may serve as a target for anti-invasive therapy [143, 172]. Certain plant molecules have been reported to interfere with targets involved in invasion [11, 12, 142].

Plant polyphenolic compounds seem to be promising anti-invasive agents. Xanthohumol **(5)** and other prenylated

chalcones exhibit particularly interesting activities [13]. The inhibitory effect of xanthohumol **(5)** has been shown to be mediated through positive functional regulation of the E-cadherin–catenin invasion-suppressor complex [172].

Parmar et al. [143] screened 100 alkaloid and polyphenolic compounds for their anti-invasive potential. The authors used highly invasive human MCF-7/6 mammary carcinoma cells, which are known for their ability to invade a normal tissue segment within 1 week. These cells were placed in contact with fragments of normal embryonic chick heart. Anti-invasive effects were observed for chalcones presenting a prenyl group. This effect was partially mediated by selective cytotoxicity to MCF-7/6 cells, whereas normal heart tissue was not affected.

Furthermore, a series of studies with prenylated and *O*-allylated chalcones revealed the importance of methoxy groups at the C-2 and C-5 positions and the presence of a bromide atom at the C-3 position of the B ring of the prenylated derivatives. Among the *O*-allylated chalcones, replacement of the B-phenyl ring with a furan-2-yl group was found to exhibit the strongest anti-invasive properties [122, 144].

Isoliquiritigenin **(2)** has been shown to inhibit basal and epidermal growth factor (EGF)-induced cell migration in a dose-dependent manner. This compound also affects the invasion and adhesion of prostate cancer cells. Interestingly, isoliquiritigenin decreased both basal and EGF-induced activator protein (AP)-1 binding activity and phosphorylation of Jun N-terminal kinase (JNK), c-Jun, and Akt. A subsequent downregulation of protein and mRNA levels of several adhesion molecules (ICAM, VCAM), growth factors (VEGF), and metalloproteinases (MMP)-9 was observed [83].

Because of the loss of cell–cell adhesion mediated by E-cadherin repression and an increase in cell mobility, growing evidence indicates the importance of epithelial–mesenchymal transition (EMT) in cancer invasion. Recently, butein **(16)** has been implicated in the inhibition of cell invasion by bladder cancer cells. The underlying mechanisms include downregulation of the ERK1/2 and NF-$\kappa$B signaling pathways associated with reversal of EMT [190]. Furthermore, Pandey et al. [138] described the inhibitory impact of butein on cytokine-induced cellular invasion as a result of the repression of NF-$\kappa$B-regulated gene products COX-2 and MMP-9.

## Inhibition of angiogenesis

Inhibition of angiogenesis became one of the target strategies of cancer therapy because tumor-induced development of new capillary blood vessels is essential for tumor development, invasion, and metastasis. Angiogenesis and its inhibition are closely linked to endothelial cells, which produce the required factors for microtumor expansion including matrix metalloproteinases (MMPs) and serine proteases. The activity of these proteins allows endothelial cells to initiate capillary sprouting [61]. However, inflammatory cells, which infiltrate the tumor, become an additional target for angiogenetic therapy and the prevention of vascularization. The progressive alteration within the microenvironment including elevated levels of growth factors, chemokines, and proteolytic enzymes contributes greatly to the onset of angiogenesis [3].

Angiogenesis is regulated through multiple signaling pathways (NF-$\kappa$B, PI3-K/Akt, ERK1/2, hypoxia-inducible factor (HIF)-1$\alpha$), and various mechanisms that lead to modulation of cytokine profiles or alterations in the extracellular microenvironment by MMPs. Some important angiogenic factors are phosphorylation of VEGFR-2 in human umbilical vein endothelial cells (HUVECs) and production of basic or acidic fibroblast growth factors (FGF) and vascular endothelial growth factor (VEGF) in tumors [2].

Many lines of evidence indicate the prominent role of plant polyphenols, including members of the chalcone family, in the fight against pathological angiogenesis (see Table 2) [6, 16, 32, 34, 37, 46, 49, 103–105, 116, 129–132, 154, 157, 159, 164]. Hydroxy safflor yellow A **(24)**, a pigment from the flower petals of *Carthamus tinctorius*, inhibits blood vessel growth of transplanted gastric adenocarcinoma. Xi et al. [176] described downregulation of VEGF and bFGF mRNA expression as the underlying mechanism of inhibition of tumor angiogenesis by this compound.

Isoliquiritin **(30)**, a chalcone isolated from extract of licorice root, was identified as a main compound responsible for an anti-angiogenic effect dependent upon antitube formation [76]. Another licorice-derived flavonoid, isoliquiritigenin **(2)**, negatively affects the aberrant expression of matrix metalloproteinases, which are associated with activated endothelial and tumor cell invasion, through inhibition of the JNK- or p38 MAPK pathways. Furthermore, isoliquiritigenin **(2)** treatment has been shown to inhibit PMA-induced migration and tube formation [66].

Albini et al. [4] reported that xanthohumol **(5)** interferes with the molecular mechanisms of cell migration, invasion, and survival and affects several different pathways that result in potent suppression of angiogenesis. Moreover, oral administration of xanthohumol **(5)** inhibited angiogenesis in a dose-dependent manner in vivo due to the strong reduction in vessel formation, the final morphogenesis phase of angiogenesis. Interestingly, higher doses up to 200 μM produced no adverse health effects, suggesting negligible or no toxicity. From a mechanistic point of view, xanthohumol **(5)** has been shown to inhibit the NF-$\kappa$B and Akt pathways.

**Table 2** Plant polyphenols with anti-angiogenic properties

| Polyphenolic compound | Molecular target | References |
|---|---|---|
| Red wine polyphenols | VEGF, pro-MMP-2, (MT1)-MMP | [130, 132] |
| Green tea polyphenols | VEGF, MMP-2, MMP-9 | [116] |
| Epigallocatechin-3-gallate | VEGF | [16] |
| Delphinidin | VEGF | [131] |
| Cyanidin | | |
| Methylophiopogonanone B | VEGF | [49] |
| Luteolin | VEGF | [6] |
| Wogonin | VEGF | [104, 105] |
| Genistein | VEGF, bFGF, uPA, PDGF-A, TF, MMP-2, MMP-9 | [34, 46, 154, 164] |
| Apigenin | HIF-1, VEGF | [32] |
| Chrysin | HIF-1, VEGF | [37, 103] |
| Silibinin | MMP-2 | [159] |
| Flavonoids (acacetin, apigenin, chrysin, genistein, kaempferol, morin, naringin, naringenin, rutin) | VEGF | [157] |

*Cleistocalyx operculatus*, a plant used in traditional Chinese medicine, contains 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (ON-III) **(31)**. This compound is known to reversibly inhibit the phosphorylation of VEGFR tyrosine kinase. Additionally, 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone abrogates VEGFR-mediated signal transduction via suppression of MAPK and Akt activation [78, 126, 135, 152, 174, 193]. Because hydroxylated chalcones are frequent in nature, 2′-hydroxy-4′-methoxychalcone **(32)** was investigated [99]. Previously, the inhibition of PGE2 production by this chalcone was reported to result from downregulation of COX-2. COX-2 promotes neovascularization through enhanced prostaglandin production and elevated release of angiogenic growth factors [175]. Furthermore, COX-2 has been detected in the angiogenic vasculature of tumors and suppression of angiogenesis by COX inhibitors has been observed [52, 117, 170]. 2′-hydroxy-4′-methoxychalcone **(32)** was able to suppress vascular formation and inhibit excessive angiogenesis in a bFGF-enhancing matrigel plug assay [99].

Several studies have reported that synthetic or semisynthetic chalcone analogues exhibit anti-angiogenic potential against HUVEC tube formation, development of sprouts during an aortic ring assay, or inhibition of endothelial cell growth in vitro. These compounds include boronic acid chalcone [78], chalcone analogues related to curcumin [174], various chalcone derivatives with a substituted backbone [126, 152], and chalcone carboxylic acid [135].

## Inhibition of metastasis

Metastasis, or the ability of cancer cells to infiltrate the normal tissue surrounding a tumor and to travel to another non-adjacent organ and create new tumors, is linked with poor prognosis. The antimetastatic properties of natural compounds are therefore closely related to their anti-angiogenetic and anti-invasive features [73, 190].

Two main components of the roots of *Angelica keiskei*, xanthoangelol **(33)** and 4-hydroxyderricin **(34)**, have been identified as potent antimetastatic chalcone derivatives [74, 75]. These compounds inhibited tumor growth and lung metastasis in Lewis lung carcinoma (LLC)-bearing mice, which led to increased survival time of carcinectomized mice. Xanthoangelol **(33)** also suppressed liver metastasis and the growth of metastasized tumor cells from intrasplenically implanted LLC. The mechanism of these antimetastatic activities has been shown to involve both inhibition of tumor-induced neovascularization and, more significantly, inhibition of DNA synthesis in LLC cells.

Yamazaki et al. showed that isoliquiritigenin **(2)** induced a significant reduction in metastatic nodules in the lung in a renal mouse cell carcinoma model. Furthermore, this treatment did not cause leukocytopenia, a common feature of a large panel of chemotherapeutic drugs. These results indicate a promising use of isoliquiritigenin **(2)** as a protective agent against chemotherapy-induced leukocytopenia.

Although the mechanisms of isoliquiritigenin **(2)** activity were not completely elucidated, the authors suggested that suppression of pulmonary metastasis may result from a combination of isoliquiritigenin-promoted activation of macrophages, lymphocytes, and direct cytotoxicity [178].

Butein **(16)**, the biologically active component of *Rhus verniciflua*, which is used as a food additive in Korea, showed in vitro disruption of the clonogenic growth of small numbers of primary breast cancer cells seeded into fibroblast co-cultures. These results suggest that butein **(16)** may suppress the growth of breast cancer micro-metastases [153].

As metastasis is a chemokine-guided multistep process based on the dissemination of cancer cells from the primary tumor into specific organs, the control and/or inhibition of specific chemokines provides promising targets. Particular chemokines may promote metastasis by acting directly on tumor cell migration and invasion. CXC chemokine receptor 4 (CXCR4) and its only known ligand, CXC chemokine ligand 12 (CXCL12), are involved in chemotactic regulation of breast cancer metastasis by expressing non-random patterns in all target organs [123, 124].

Müller et al. [123] reported that neutralization of the interaction between CXCL12 and CXCR4 in vivo significantly impairs metastasis of breast cancer cells to regional lymph nodes and to the lung. These results triggered a search for small neutralizing molecules that are able to inhibit CXCL12. Hachet-Haas et al. [47] identified several synthetic chalcone derivatives that reduced binding of CXCL12 to CXCR4. In particular, the structure of 3-chloro-2′-methoxy-3′-hydroxychalcone fits perfectly within the hydrophobic pocket of CXCL12, producing a high-affinity interaction that can disrupt the interaction with CXCR4.

## Structure–activity relationship

Several studies have focused on the discovery of a structure–activity relationship in order to better predict the bioactivity of newly identified chalcone derivatives.

Chalcones that exhibit anti-inflammatory properties generally feature an $\alpha$-$\beta$ unsaturated bond. This allows the molecule to act as a Michael acceptor for nucleophilic species including glutathione (GSH) or cysteine residues on proteins such as IKK-beta [119]. Generally, these target modifications lead to a major decrease or loss of anti-inflammatory activities [62].

Several studies have shown that antiproliferative effects on cancer cells are associated with the presence of one or more hydroxyl substituents on the chalcone scaffold. Hydroxyl derivatives of chalcone have more potent anti-proliferation properties than other chalcone derivatives [15, 26, 109]. Furthermore, the presence of 2′-hydroxy group in a chalcone molecule has been shown to be crucial for the enhancement of the anti-inflammatory properties of these molecules. This potent effect was explained by an increase in the electrophilic properties of an $\alpha$-$\beta$ unsaturated ketone by hydrogen bonding between the 2′-hydroxy group and the ketone moiety (also referred to as the keto, carbonyl, or enone moiety). Moreover, electron-donating groups on the A ring could stabilize the GSH adduct by reducing the acidity of the alpha hydrogen [63, 108].

Modification of chalcone structures by substitution with a prenyl side chain also affects their biological activities. Prenylation as protein post-translational modification results in higher protein lipophilicity and targets the modified protein to cell membrane. Therefore, it is assumed that prenylation of chalcone molecules might influence their solubility, cellular uptake, and subcellular localization [44].

Compounds with various glycosidic substitutions on the aromatic rings exhibited attenuated ability to suppress proliferation relative to the corresponding aglycones. A possible explanation is that the reduced lipophilicity caused by the sugar moiety complicates cellular uptake of the compound by passive diffusion through the cell membrane [70, 127].

The ability of chalcone derivatives to interact with the different steps of carcinogenesis has been shown to require specific structural features.

The structural basis for radical scavenging activity seems to be the formation of energetically favored intramolecular hydrogen bonds. Compounds that can adopt conformations in which the A ring and the carbonyl group are orthogonal are more successful radical scavengers [118].

The inhibitory activity of chalcones on NO production is believed to be linked to the presence of an $\alpha$–$\beta$ double bond. Molecules with a single bond exhibited a weaker effect on NO production than corresponding molecules with an unsaturated bond [192].

Similar mechanisms are valid for the potential of chalcones to inhibit the NF-$\kappa$B pathway. The reduction in the alkene into a single bond completely attenuates their inhibition potential [161].

The primary structural feature responsible for microtubule depolymerization activity was hypothesized by comparison with the structure of colchicine. Colchicine inhibits microtubule polymerization by binding to tubulin. The chalcone possessing 3,4,5-trimethoxyphenyl groups on the A ring and an $\alpha$-methyl group within the enone moiety fits better into the colchicine-binding site of tubulin than other chalcone derivatives. Thus, alpha-methyl chalcones are believed to exhibit greater cytotoxic activity than unsubstituted analogues [30].

A study of induction of HO-1 by methoxychalcones revealed that an increasing number of methoxy groups on the aromatic rings at the 3, 4, 5 and 3′, 4′, 5′ positions correlated with progressive induction of HO-1, while methoxy substituents at the 2, 4, 6 positions or alone at the 4 and 4′ position were ineffective [155].

## Conclusion

Nature offers a large reservoir of bioactive compounds. The use of these compounds in the treatment of various diseases, including cancer, might complement or even substitute for current medical therapeutic strategies.

Whereas some molecules apparently act via a single mechanism and thus target one particular cellular process, many chalcones apparently act as multifunctional compounds. Xanthohumol **(5)** and isoliquiritigenin **(2)** are representatives of this second category. These chalcones are involved in various steps of carcinogenesis from tumor initiation to metastasis formation and do not appear to be specifically targeted. Despite the fact that their mechanisms seem to be nonspecific, they might nevertheless selectively target one distinct regulatory protein that modulates many downstream signaling pathways and thus initiate a cascade of cellular events that lead to the described spectrum of effects. Obviously, structural requirements play an essential role and are correlated to the observed bioactivity. Therefore, the identification and precise characterization of naturally occurring chalcones, whether as nutraceuticals or as novel therapeutic agents, is a promising approach to fight illnesses such as cancer. Although chalcone derivatives are common in nature, the fast and simple synthesis or chemical modification of chalcones allows rapid generation of large numbers of novel compounds that may be useful for both chemoprevention and inhibition of carcinogenesis.

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