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Molecular Targeted Approaches to Cancer Therapy and Prevention Using Chalcones

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Abstract

There is an emerging paradigm shift in oncology that seeks to emphasize molecularly targeted approaches for cancer prevention and therapy. Chalcones (1,3-diphenyl-2-propen-1-ones), naturally-occurring compounds with widespread distribution in spices, tea, beer, fruits and vegetables, consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α , β -unsaturated carbonyl system. Due to their structural diversity, relative ease of chemical manipulation and reaction of α , β -unsaturated carbonyl moiety with cysteine residues in proteins, some lead chalcones from both natural products and synthesis have been identified in a variety of screening assays for modulating important pathways or molecular targets in cancers. These pathways and targets that are affected by chalcones include MDM2/p53, tubulin, proteasome, NF-kappa B, TRAIL/death receptors and mitochondria mediated apoptotic pathways, cell cycle, STAT3, AP-1, NRF2, AR, ER, PPAR- γ and β -catenin/Wnt. Compared to current cancer targeted therapeutic drugs, chalcones have the advantages of being inexpensive, easily available and less toxic; the ease of synthesis of chalcones from substituted benzaldehydes and acetophenones also makes them an attractive drug scaffold. Therefore, this review is focused on molecular targets of chalcones and their potential implications in cancer prevention and therapy.

Keywords

Chalcones; molecular targets; bioactive dietary compounds; chemoprevention

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

1. INTRODUCTION

Chalcones are widely occurring natural plant products and presented in spices, tea, beer, fruits and vegetables [1–3]. Chalcones belong to the flavonoid family and act as intermediates in the biosynthesis of flavonoids. Chalcones are pharmacologically active and have demonstrated a wide range of biological activities, including anti-oxidative, anti-cancer, anti-mutagenic, anti-microbial, anti-protozoal, anti-histaminic, anti-inflammatory, analgesic and immune-modulator properties [1–3]. More importantly, chalcones have been used in clinics for treatment of gastric ulcers, duodenal ulcers, bronchial asthma, Addison's disease, skin disorders, diabetes, cardiac disease and helicobacter pylori infection [1–3].

Chalcones contain a common 1, 3-diphenyl, propenone template that can be easily modified to alter the biological potential of these molecules. Through the addition of a wide variety of functional groups (aryls, halogens, hydroxyls, carboxylic groups, benzenes, etc.) [4], the biologic activities of chalcones are altered probably due to their interaction with different molecular targets. Even minor structural modification can result in distinct cellular and molecular alterations. The diversity of the chalcone family also lends itself to broad-spectrum biologic applications in oncology, particularly for the development of novel targeted therapies.

Molecular targeted and “biologic” agents in cancer therapy are the result of a rapidly growing understanding of the molecular events which are involved in carcinogenesis, including crucial aberrations in the regulation of apoptosis, cell-cycle control, metastasis and tumor angiogenesis. Currently, small molecule tyrosine-kinase inhibitors and monoclonal antibodies are targeted approaches used to selectively inhibit these key pathways in tumor growth and progression [5]. Indeed, a variety of these agents, have gained widespread use in the clinical treatment of a number of malignancies, such as carcinoma of the colon, breast, ovary, or lung and leukemia [5]. Unlike conventional chemotherapy, targeted agents have a relatively wide therapeutic window and have non-overlapping toxicity profiles [5]. Phytochemicals, like chalcones, have similarly been shown to be relatively nontoxic, and certain chalcone moieties can target key molecular events that may lead to carcinogenesis. Population-based studies in countries with high dietary intake of certain types of chalcones have also shown a correlation with lower incidences of cancer in these areas, which provides support for the further investigation of such natural derivatives for cancer prevention and therapy. Chalcones and their synthetic derivatives thus present a unique opportunity to utilize these well-tolerated, highly modifiable molecules as either chemopreventive drugs or as components in cancer treatment.

2. CHALCONES TARGET THE P53 PATHWAY

The role of p53, the ‘guardian of the genome,’ has been extensively studied over the last 30 years due to its role as an important innate tumor suppressor. In response to DNA damage, oncogene activation, or other cellular stress signals, p53 can mediate a number of varied biologic effects that lead to cell senescence, cell cycle arrest, or apoptosis. Thus, p53 functions to maintain cellular and genomic integrity and prevent proliferation of incipient cancer cells. Loss of p53 function occurs in most human tumors by either mutation of *TP53*

itself or by inactivation of the p53 signal transduction pathway. Mutations in p53 have been identified across a number of different human cancers. In addition, p53 is inactivated by the overexpression of negative regulators, most notably MDM2. The p53 pathway in these tumors can be reactivated by small molecules that inhibit p53/MDM2 interaction, thus preventing p53 proteasomal degradation. Currently, there are at least two compounds of MDM2 inhibitors (JNJ-26854165, Johnson & Johnson and RG7112, F. Hoffmann–La Roche) being tested in phase I clinical trials in patients with hematologic neoplasms and advanced solid tumors [6, 7].

Chalcones were among the first class of compounds that demonstrated activity in modulating the p53/MDM2 interaction. Stoll and colleagues using multidimensional NMR spectroscopy, an ELISA assay that employed a p53 peptide and a gel shift assay, were the first to report that chalcones bound to MDM2 at the p53 transactivation domain and resulted in a release of p53 from both the p53/MDM2 complex as well as the DNA-bound p53/MDM2 complexes [8]. Based on this NMR data, Kumar *et al* [9] hypothesized that the carboxylic acid group of the chalcones could be placed near the base of K51 lysine to form a salt bridge and then break the salt bridge interacting with Glut25 in the p53/MDM2 complex. Therefore, Kumar *et al* [9] designed and synthesized a series of boronic acid chalcone analogues that might form a stronger salt bridge with K51 lysine than the carboxylic acid analogues. They showed that these boronic chalcones were 5–10 fold more toxic to human breast cancer cell lines at low μM range compared to normal breast epithelial cell lines [9]. Modzelewska *et al* [10] from the same group further synthesized a new class of chalcones (bischalcones) that contain a pair of α , β -unsaturated groups. Some of these chalcones were even more potent in preferentially inhibiting the growth of breast cancer cell lines. One bis-chalcone exhibited differential cytotoxicity to an isogenic pair of colon cancer HCT116 cells; p53 $+/+$ cells were more sensitive to the bis-chalcone compared with the p53 $-/-$ cells [10]. Hsu *et al* [11] also reported that the effect of isoliquiritigenin (4, 2',4'-trihydroxychalcone) on the growth of Hep G2 can be attenuated by a dominant negative p53 that blocks p53 transcriptional activity. However, these studies did not specifically investigate the effect of these chalcones on p53/MDM2 interaction. Achanta *et al* [12] reported that 3, 5-bis-(4-boronic acid-benzylidene)-1-methyl-piperidin-4-one (AM114), a bischalcone, selectively inhibited the growth of HCT116 p53 $+/+$ versus p53 $-/-$ cells. The mechanism of action of AM114 was shown to be associated with inhibiting the chymotrypsin-like activity of the 20S proteasome in vitro and then leading to p53 accumulation but not with p53/MDM2 disruption. In another study, Chen *et al* [13] found that trans-4-Iodo, 4'-boranyl-chalcone (TIBC) inhibited MG132, a proteasome inhibitor-caused accumulation of ubiquitinated p53 in human lung cells, suggesting that TIBC may inhibit the interaction of MDM2/p53. Further study by Sasayama *et al* [14] showed that TIBC effectively inhibited the growth of human glioma cell lines irrespective of their p53 status and even decreased the expression of p53 in some glioma cell lines. Using a NMR chemical shift perturbation method for studying lead compounds in ligand-protein interaction, D'Silva L *et al* [15] tested three lead compounds: nutlin-3, a sulfonamide compound (NSC 279287), and a boronic chalcone, with recently reported activity to block the p53-MDM2 interaction. Only nutlin-3 was found to effectively release p53 from the p53/MDM2 complex, whereas NSC279287 and the boronic chalcone either precipitated the

protein or acted as a much weaker MDM2 inhibitor. Cumulatively, these results suggest that inhibition of the MDM2/p53 interaction may not be the primary anticancer mechanism of chalcones.

In general, most of chalcones demonstrated selectivity against the growth of cancer cells *versus* normal cells. Some chalcones (e.g. Hydroxysafflor yellow AHSYA and imidazole-chalcone) [16–18] have been shown to increase the expression of p53 and selectively inhibited the growth of cancer cells with wild-type p53, whereas other chalcones [e.g. toluenesulfonylamido-chalcone, 4'-(p-toluene sulfonyl amino)-3, 4-dihydroxy chalcone (TSHDC)] was reported to reduce p53 expression [19]. We have demonstrated that flavokawain A, a chalcone from Kava extracts, preferentially inhibited the growth of p53 mutant bladder cancer lines and its effect on cell cycle arrest differed in p53 wild and mutant type bladder cancer cell lines [20]. Flavokawain A induced a G1 arrest in RT4 cells harboring wild-type p53 and G2M arrest in bladder cancer cell lines with mutant p53 [20]. We further have demonstrated that dietary flavokawain A significantly inhibited urothelial tumorigenesis *in vivo* in the UPII-SV40T transgenic model that resembles human urothelial cell carcinoma (UCC) with defects in the p53 and the retinoblastoma (RB) protein pathways [21]. Together, these studies suggest that the diverse chemical structures of chalcones may contribute to their differential effects related to the p53 pathway. Mechanisms of Chalcones' effect on the p53 pathway in cancer cells are summarized as Table 1. There is a potential opportunity to identify those chalcones that re-activate the p53 tumor suppressing pathway through a systematic study of their structure-relationship with mutant p53 cells.

3. CHALCONES TARGET TUBULIN POLYMERIZATION

The use of chalcones as antimetabolic agents was first reported nearly 20 years ago, and represents some of the earliest investigations of chalcones as *therapeutic* agents [23]. Building on the knowledge of colchicine-tubulin structure-activity relationships, chalcone derivatives were modeled as colchicine analogues to achieve a similar reactivity in the tubulin binding site, leading to destabilization of microtubules. Structure activity relationships of a large number of chalcone derivatives were then studied with colchicine and vinblastine (known tubulin-binding antimetabolic agents) as controls. This study paved the way for the multiple studies that have followed looking at the effects of various substitutions on the antimetabolic activity of chalcones that will be reviewed here [24–38] (Table 2).

A number of chalcones that are analogues of combretastatin 4A, such as SD400 and MDL, have demonstrated a similar capacity to bind β -tubulin and thus destabilize microtubule polymers. Ducki *et al* [25, 26] presented a thorough review of alpha-aryl chalcone derivatives, whose structure-activity relationship studies demonstrated both antimetabolic properties (IC₅₀s in the low micromolar range) in K562 leukemia cells with arrest at G2/M phase, as well as antivasular activity (discussed below, see *Angiogenesis*). Boumendjel *et al* [24] similarly synthesized a library of chalcones and identified 3 candidates demonstrating significant antimetabolic activity, again with IC₅₀s in the low micromolar range. As demonstrated by Ducki *et al*, antimetabolic activity appeared to be highly correlated to the degree of methoxylation (25, 26). These candidates were further tested *in vivo* and found to be nontoxic in animal models. Zoldakova *et al* [29] also reported on combretastatin-like

chalcones and identified a candidate demonstrating marked microtubule disruption and cell-cycle arrest in melanoma 512A cells and neural cells. Presumably a similar tubulin-binding mechanism is also at play. Further, this same group of investigators also added a functional platinum complex onto the parent chalcone, rendering further cytotoxic potential by adding DNA adduct effects to the tubulin polymerization effects [35]. Ruan *et al* [36] synthesized a series of resveratrol derivatives with a chalcone moiety and found that these compounds reduced the growth of cancer cell lines through their binding to the tubulin-colchicine binding site, inhibiting tubulin polymerization and inducing G2M arrest during cell cycle progression.

Romagnoli R *et al* [27] reported that the replacement of the double bond of enone system of chalcones with a thiophene moiety enhanced the growth inhibitory and anti-tubulin polymerization effects of the chalcones. Similarly, Mesenzani O *et al* [37] replaced the double bond of antitubulin chalcones with triazoles and tetrazoles. His study suggested that the double bond in the chalcone scaffold may not be essential for the interaction with tubulin, and that these new analogues may have the advantage of being metabolically stable due to the introduction of a chemically inert heterocyclic ring (i.e. triazole or tetrazole). Dyrager C *et al* [38] identified one compound from a series of dihalogenated chalcones and structurally related dienones, which binds to the paclitaxel binding site of tubulin and stabilizes tubulin to the same extent as the docetaxel.

Based on the similarity of the chemical structure of chalcones to combretastatin and their ease of chemical modification, chalcones represent a very attractive starting material for synthesis of novel agents targeting tubulin for treatment of cancers.

4. CHALCONES TARGET PROTEASOMAL ACTIVITY

Chalcones have been shown to exhibit anti-cancer activity based on their ability to affect the proteasome via several different mechanisms. The Ubiquitin-Proteasome System (UPS) plays a major role in the regulation of cancer cell growth and proliferation, being responsible for the majority of protein degradation within the cell [39]. Proteasomal inhibitors, such as bortezomib and carfilzomib have already been used effectively in the clinical setting as targeted therapeutic agents [40]. A novel non-boronic chalcone based derivative has recently been synthesized and characterized by Bazzaro *et al* [41] which targets the catalytic 20s subunit of the proteasome via the interaction of its α , β -unsaturated carbonyl system with the N-terminal threonine residues in the catalytic sites of the proteasome. Significantly, this novel compound exhibited synergistic killing of HPV+ cervical cancer cells when used in combination with the clinically approved proteasome inhibitor Bortezomib. However, chalcone based compound RAMB1 has been shown to inhibit cervical cancer cell growth in a non-20s proteasome dependent manner, by stabilizing p53 levels from preventing its degradation, leading to a compensatory increase in lysosomal protein degradation [42]. This study demonstrated that chalcones can prevent HPV E6 mediated p53 degradation. Importantly, this allows co-treatment with RAMB1 and Chloroquine (a lysosome inhibitor) to synergistically reduce cervical cancer cell viability [42].

Chalcone derivatives can also affect proteasomal activity by targeting deubiquitinating enzymes without inhibiting the activity of the 20S proteasomal subunit itself. Three recently described chalcones act as inhibitors of deubiquitinating enzymes, depleting free ubiquitin in the cell and causing an accumulation of polyubiquitinated proteins ultimately resulting in p53 stabilization, tumor suppressor upregulation, and oncogene suppression [43]. This provides a promising alternate means of targeting proteasomal activity in a highly effective manner without having to directly target proteasomal subunits.

5. CHALCONES MODULATE CELL CYCLE PROGRESSION

The use of chalcones as antimetabolic agents that can induce G2M arrest in cell cycle progression was first reported almost 20 years ago as described previously [23]. In addition to cell cycle interruption by targeting tubulin and microtubule polymerization, there have been a number of other chalcone targets that also interrupt cell cycle progression and subsequently signal apoptosis [44–47]. The proposed mechanisms of action are varied but centered primarily around their impact on various cyclins and cyclin-dependent kinases (CDKs). Cell cycle arrest and cytotoxicity with these chalcone derivatives is mediated by downregulation of cyclin expression [45, 46], inhibition of topoisomerase II [47], or enhanced expression of p21(CIP1/WAF1), which is a universal inhibitor of cyclin-dependent kinases [46, 47]. All of these pathways eventually trigger apoptotic pathways and subsequent dose-dependent growth inhibition [46–51]. The previously discussed chalcone-based inhibitors of deubiquitinating enzymes similarly resulted in downregulation of cyclin D1 and upregulation of several tumor suppressor genes, most notably p53, resulting once again in G2M arrest [43]. Interestingly, the chalcone known as Cardamonin has been shown by Park *et al* to suppress colon cancer cell proliferation by depleting β -catenin levels in a proteasome-dependent fashion, thereby also suppressing cyclin D1 and c-myc expression [51].

6. MECHANISMS OF CHALCONES INDUCED CELL DEATH

Many chalcones have demonstrated the ability to induce apoptosis through the targeting of the mitochondrial pathway. The specific molecular components targeted by chalcones that affect the mitochondrial pathway are varied, as are their chemical structures. There does not seem to be an overall requisite set of substitutions to render apoptotic effects of chalcones. A number of authors have demonstrated effects of their respective chalcones on the induction of pro-apoptotic proteins Bak [52, 53] and Bax [52–54], and decrease in anti-apoptotic proteins Bcl-2 [11, 52, 53, 55] and Bcl-X [11, 52, 53, 56], resulting in the cumulative response of caspase-9 activation. In line with these observations, two studies reported that apoptotic cell death marked by caspase-9 activation [52, 55, 57] could be inhibited with the pretreatment of cells with a caspase inhibitor [11]. An additional line of indirect evidence regarding mitochondrial uncoupling was described by Navarini *et al* [58], whereby mitochondrial ATP and GSH were reduced in melanoma cells, potentially destabilizing the mitochondrial membrane. Finally, direct effects of chalcone treatment on cell mitochondrial membrane depolarization have been reported in multiple studies, leading to activation of apoptotic pathways [59–63].

In addition, a number of studies have demonstrated that chalcones can induce cancer cell apoptosis through effects on the extrinsic pathway. Tang *et al* [64] demonstrated that the chalcone flavokawain B (FKB) led to upregulation of proapoptotic proteins death-receptor 5 (DR5/TRAILR2), Puma and Bim, while decreasing expression of apoptotic inhibitors XIAP and survivin in androgen receptor negative prostate cancer cells. Further, synergy with TRAIL was demonstrated. This was accompanied by an increase in cytotoxicity *in vitro*, as well as decreased tumor growth *in vivo*. The effects of FKB on cell growth inhibition could additionally be negated with shRNA silencing of Bim expression. Notably, there was minimal toxic effect on normal prostate epithelial cells. Upregulation of death receptors was similarly demonstrated by Yun *et al* [54] who found that Pandaturin A increased both Fas and TRAIL expression leading to increased apoptosis in prostate cancer cells. Similarly, several other investigators noted increased DR5 expression in both leukemia and colon cancer cells, and in once case was able to demonstrate that chalcone-induced death receptor overexpression was able to restore sensitivity to TRAIL-mediated apoptosis in TRAIL-resistant cells [65–68].

Szliszka *et al* [69] also studied a panel of five chalcones in prostate cancer cell lines, finding that all five compounds markedly increased TRAIL-mediated apoptosis and cytotoxicity in cells previously demonstrated to be TRAIL resistant. The same investigators then studied another panel of molecules including 2 chalcones and 3 dihydrochalcones and again demonstrated markedly increased TRAIL-mediated apoptosis in the same resistant prostate cancer cell line [70]. Thus, several independent reports suggest that there is some synergy between chalcones and TRAIL which can overcome aspects of TRAIL resistance in cancer cells [64, 69, 70]. Further, given that the broad spectrum of chalcones structures appears to have similar effects on the death receptor pathway, combined with the clear activity in prostate cancer cell lines and animal models, suggests that chalcones have significant potential as chemopreventive drugs or therapeutic adjuncts in cancer therapy.

Recently, Champelovier *et al* [71] reported that two chalcone derivatives, JAI-51 and MBL-II-58, with minor structural differences induce cell death in glioblastoma cell lines via a significantly different mechanism. JAI-51 induces apoptosis through the activation of caspase-3, -8 and -9, whereas, MBL-II-58 treatment causes autophagic cell death in a ROS, but not caspase and protein synthesis, dependent manner. JAI-51 also selectively inhibited high proliferative cancer cells versus normal human nucleated blood cells and normal human skin fibroblast cells [71]. These results indicated that even minor changes in chalcone structures can lead to significantly different molecular mechanisms for chalcone induced cell death. He *et al* [72] also showed that Chalcone-24 did not activate caspase cascade and induce apoptosis. Instead, Chalcone-24 treatment of lung cancer (A549 and H1299) and bladder cancer (UM-UC-3) cell lines caused a non-apoptotic death, autophagy-mediated and Receptor-Interacting Protein (RIP) 1- and RIP3-dependent necroptosis. Robinson *et al* [73] described that a chalcone derivative 3-(2-methyl-1H-indol-3-yl)-1-(4-pyridinyl)-2-propen-1-one (i.e., MIPP) induced massive accumulation of vacuoles by dysregulation of macropinocytosis in glioblastoma cells leading to a novel caspase-independent cell death, named Methuosis. Mechanisms of chalcones induced cell death are summarized in Figure 1 and Table 3.

7. CHALCONES AND THE NF- κ B PATHWAY

NF- κ B is a critical transcription factor with widespread cellular effects that plays an important role in carcinogenesis, although, the oncogenic factors that result in the constitutive activation of NF- κ B seen in many cancers have yet to be clearly elucidated. Nevertheless, NF- κ B downstream effects are well recognized in cancer, including upregulation of tumor promoting cytokines and survival genes (e.g., Bcl-2), inhibition of apoptosis, and promotion of angiogenic factors, as well as a migratory and invasive phenotype that is associated with tumor progression. Thus, aberrant regulation of NF- κ B is involved in cancer development and progression as well as in drug resistance. Inhibitors of NF- κ B mediate effects potentially leading to antitumor responses or greater sensitivity to the action of antitumor agents. With regard to chalcones as inhibitors, it would appear that structural complexity is not a requisite for NF- κ B inhibitory activities, as reported in structural activity relationship studies [74, 75].

NF- κ B activity is negatively regulated primarily by I κ B α , which essentially keeps NF- κ B in an inactive state. I κ B α in turn is regulated by I κ B α kinase β (IKK), which phosphorylates I κ B α in the presence of cellular stress signals and causes the dissociation of the I κ B α /NF- κ B complex, leaving NF- κ B free to translocate to the nucleus and affect gene expression. Inhibition of IKK, therefore, can lead to inhibition of NF- κ B by keeping it locked to I κ B α in an inactive state. This mechanism of NF- κ B regulation is the target of a number of agents, including chalcones. Chalcones contain a highly electrophilic α , β -unsaturated carbonyl moiety that can react with free sulfhydryl groups of thioredoxin and cysteine residues in proteins [76, 77]. Indeed, Pandey *et al* [78] demonstrated that butein (3,4,2',4'-tetrahydroxy chalcone) inhibited NF- κ B and NF- κ B regulated gene expression through its conjugation of cysteine 179 residue of the IKK β and then stabilization of I κ B α protein. Similarly to this result, the following multiple naturally-occurring chalcones were found to prevent the degradation of I κ B α and in turn block NF- κ B activation: brousochalcone A from *Broussonetia papyrifera* Vent., Isoliquiritigenin present in *Glycyrrhiza* and *Dalbergia*, 4-hydroxyonchocarpin obtained from *Psoralea corylifolia*, Cardamonin isolated from *Alpinia rafflesiana*, flavokawain A and B from the kava plant, Xanthoangelol D isolated from *Angelica keiskei*, Xanthohumol present in *hops* (*Humulus lupulus* L.), Hydroxysafflor yellow A (HSYA) from *Carthamus tinctorius* L., panduratin A from *Boesenbergia rotunda stercurensis*, etc. [1, 2, 79–85]. However, Orlikova *et al* [86] reported that 4'-hydroxychalcone inhibited NF- κ B activation via an IKK-independent mechanism, which was suggested to be involved in its mediated inhibition of proteasome function and then stabilization of I κ B α . 4'-Hydroxychalcone has no direct effect on IKK but nevertheless may attenuate its activity indirectly through inhibition of I κ B α . Kim *et al* [87] found that stercurensin, a chalcone isolated from the leaves of *Syzygium samarangense*, could inhibit the NF- κ B activation via preventing the formation of the transforming growth factor- β -activated kinase 1 (TAK1)/ TAK1-binding protein 1 (TAB1) complex.

In addition to conjugated double bonds, chalcones have a completely delocalized π -electron system on both benzene rings, providing chalcones a greater probability of undergoing electron transfer reactions. The B-ring has a flexible ring structure and can easily convert cis-chalcone to trans-chalcone or vice versa. Trimethoxy chalcone at the A-ring with fluoro,

chloro, bromo substitution in on the B-Ring, like 2'-hydroxy-3-bromo-6'-methoxychalcone, 2'-methoxy-3,4-dichlorochalcone, flavokawain A, or flavokawain B, were demonstrated to be better inhibitors of NF- κ B [83, 84, 86]. Reddy *et al* [88] synthesized a series of bichalcones and identified that some significantly blocked the nuclear translocation of NF- κ B p65. The differential effects of chalcones on different components of the NF- κ B pathways are shown in Table 4 and Figure 2.

8. ANDROGEN AND ESROGEN RECEPTOR PATHWAYS

The androgen receptor (AR) is an important mediator of prostate cancer development and progression and consequently a therapeutic opportunity for chalcones therapy. Shirota *et al* [89] isolated five antiandrogenic diels-alder-type Adducts from *Brosimum rubescens* consisting of chalcone derivatives and a prenylcoumarin. Prostate cancer progression is frequently accompanied by mutations in the AR, which render an antagonist-to-agonist conversion. Thus, previously hormone-sensitive cancers become insensitive to androgen ablation therapy, while the AR signal pathway remains active. As a result, ARs can inappropriately activate transcription in androgen-independent prostate cancer cells via mechanisms that are resistant to castration and AR antagonism. Zhou *et al* [90] screened a series of ionone-based chalcones and discovered one pan-antagonist of the AR in a panel of prostate cancer cell lines with various AR mutations. This chalcone represents a novel antiandrogen that is simultaneously effective against multiple AR mutants that confer resistance to anti-androgens currently used in the clinics. Chen *et al* [91] similarly investigated isoliquiritigenin in hormone-resistant prostate cancer cells and demonstrated a downregulation of AR and an AR-related product (prostate specific antigen), which was coupled with cytotoxicity in 2 prostate cancer cell lines with IC₅₀s in the low micromolar range. Kim *et al* [92] identified that chalcones with an o-methoxy group on A ring can inhibit AR nuclear translocation and AR mediated gene expression by increasing the formation of the AR-Hsp90 complex in the cytoplasm.

Anti-estrogen targeted therapies, such as those commonly employed in breast cancer treatment, are mediated though a number of different molecules in the steroid pathway. The use of chalcones to target the estrogen pathway has focused on modulation of either the estrogen receptor (ER) or aromatase activity responsible for conversion of androgens to estrogens. One of the early reports of targeting the estrogen receptor with chalcones was demonstrated by Satomi *et al* [93], who reported that 3'-methyl-3hydroxychalcone, apart from cell cycle arrest effects, blocked the binding of estradiol to type-II estrogen binding sites yielding downstream pathway effects and inhibiting cell proliferation. Similarly, De Vincenzo *et al* [49] investigated a series of both natural and synthetic chalcones in established and primary ovarian cancer cell lines, showing inhibition of estradiol binding to the type-II estrogen receptor and inhibiting cell proliferation.

Anti-estrogen activity mediated by aromatase inhibition with the chalcones butein and isoliquiritigenin (ISL) have been demonstrated in breast cancer models [94, 95]. Both butein and isoliquiritigenin showed inhibitory K(i) values of 0.32 and 3 μ M range, respectively. ISL was further studied *in vivo* in a xenograft model using MCF-7 breast cancer cells transfected with aromatase and showed a significant decrease in tumor growth. These effects

were correlated with a demonstration of decreased mRNA expression of aromatase in the presence of ISL. In contrast to the anti-estrogenic and antiproliferative effects reported by Ye *et al* [95], Maggiolini and colleagues [96] reported the paradoxical action of ISL as an estrogenic agonist of both estrogen receptor isoforms in the same breast cancer cell model. The authors found that at lower concentrations (10 nM to 1 μ M), ISL stimulated the estrogen receptor and downstream transcriptional activity leading to cell proliferation which could be blocked with known anti-estrogens. At higher concentrations (1 to 10 μ M), however, ISL was cytotoxic to both hormone dependent and hormone independent cell lines, suggesting that ISL cytotoxic effect may be independent of the estrogen receptor at these concentrations. These studies highlight the importance of the need for appropriate quantification of chalcone concentrations in dietary supplements in order to derive the specific chemopreventive benefits. Differential effects that are independent of estrogen are also suggested by the work of Rafi *et al* [97]. Licochalcone-A was demonstrated to be a phytoestrogen with paradoxical cytotoxic effect in both breast cancer and leukemia cell lines [97, 98]. The authors attributed the cytotoxicity of this estrogenic compound to the modulation of Bcl-2 in favor of apoptosis. Thus, while chalcones can have estrogenic agonist properties, the balance between hormone dependent cancer cell proliferation *versus* hormone independent cytotoxicity depends on the specificity of these compounds to other cellular targets, like Bcl-2, which can be simultaneously targeted.

We present the summary results of mechanisms of chalcones' action on androgen receptor and estrogen receptor pathways in Table 5 and Figure 3.

9. CHALCONES TARGET MULTIDRUG RESISTANCE TRANSPORTERS

A number of authors have investigated the ability of chalcones to mediate drug resistance to conventional chemotherapeutics by modulating multidrug efflux transporters (MDRs) known to be important components in cellular accumulation of drugs. The majority of studies have studied the ability of chalcones to inhibit two well-characterized members of the ABC transporter family, P-glycoprotein (P-gp or ABCB1) and BCRP (breast cancer resistance protein/ABCG2). Indeed, many cancers have been shown to overexpress MDR transport proteins, and expression of MDR proteins has been associated with poor prognosis in a number of cancers.

In the late 1990's, Bois and colleagues explored the ability of chalcones to bind recombinant P-gp, found that certain moieties including a trihydroxy-4-iodochalcone and a 4'-octyloxy-trihydroxychalcone demonstrated the highest affinities for P-gp [99, 100]. These moieties also bound the ATP-binding region, increasing the likelihood that these compounds would inhibit P-gp transport function, though this was not specifically tested in their series. Other authors have looked at the ability of their chalcone derivatives to modulate increased drug accumulation via effects on P-gp. Ivanova *et al* [101] demonstrated a 100-fold increase in drug accumulation via inhibition of P-gp in lymphoma cells, most effective in a chalcone with a π -chloro group on Ring B, with IC₅₀ concentrations in the low-micromolar range. Similarly, Liu *et al* [102] demonstrated that chalcones with basic moieties on Ring A increased drug accumulation in breast cancer cells by inhibition of P-gp using the calcein assay. However, these same basic chalcone molecules were ineffective in modulation

BCRP-mediated drug efflux of mitoxantrone. Non-basic Ring A moieties, by contrast, were highly effective in inhibiting BCRP and increasing mitoxantrone uptake, up to 300%. These findings are in agreement with Han *et al* [103], who also found that non-basic chalcones, specifically dimethoxy- or dihydroxyl- substitutions on Ring A, increased both drug uptake of mitoxantrone and cytotoxicity by 2 to 5-fold in breast cancer cells. Qian *et al* [104] further corroborated such findings, similarly utilizing a dihydroxy-substituted dimethylchalcone and showing a 3.9-fold increase in cytotoxicity in combination with doxorubicin in a drug resistant cell line. They further demonstrated an *in vivo* increase in chemosensitivity to doxorubicin showing decreased tumor weights in a xenograft model using the same drug-resistant cell line [104]. Finally, Boumendjel *et al* [105] looked at their compound, JAI-51, noted to be structurally similar to that of Liu *et al*, and found a similar restoration of chemosensitivity to both daunorubicin and mitoxantrone in paired sensitive and resistant cell lines, indication that their chalcone inhibited both P-gp and BCRP. Further, their compound did not show any differential cytotoxicity in cell lines overexpressing either P-gp or BCRP compared to parental controls, implying that JAI-51 was not a substrate for these pumps. Unique to this study was the additional investigation of tubulin binding, which showed that in addition to efflux drug pump inhibition, JAI-51 also destabilized microtubules by binding in the colchicine-tubulin site. Antitumor activity was substantiated in an *in vivo* glioblastoma model. Since one of the limiting phenomena for the use of common microtubule destabilizers like paclitaxel or vinblastine is drug resistance mediated by P-gp or BCRP, these compounds may be active agents in taxane-resistant cancers [105]. De Vincenzo *et al* [49] by contrast, looked for activity of their 3-methyl-2-butenyl Ring A substituted chalcones against P-gp, but did not find significant inhibition. Gu *et al* [106] synthesized a series of bifendate-chalcone hybrids without stimulation on the P-gp ATPase activity and found that these chalcone hybrids are more potent than known P-gp inhibitors bifendate and verapamil. Thus, varying substitutions can clearly affect the utility of chalcones to bind and inhibit P-glycoprotein or BCRP, and the ideal chalcone would address both efflux pathways. The results described above are summarized in Table 6.

Other drug resistance pathways or modulators, such as inhibition of glutathione S-transferase P1-1 (GSTP1-1) are less well studied, but Wang *et al* [107] has reported that carboxylic acid Ring A substitutions confer inhibition of the enzyme. The authors speculate that these compounds might conjugate with glutathione through Michael addition to act like suicide inhibitors of GSTP1-1. In a screening assay, trans-chalcones were found to activate the kelch-like ECH-associated protein 1 (Keap1)-nuclear factor erythroid 2-related factor 2 (NRF2) pathway suggesting their usefulness for detoxifying oxidative/electrophilic stress [108].

10. CHALCONES TARGET THE TUMOR VASCULATURE

Both targeting tumor neovascularization and existing tumor blood vessels using chalcones have been reported. With regard to targeting neovascularization, a number of authors have investigated chalcone derivatives' efficacy in targeting endothelial cell invasion, migration and tube formation using *in vitro* assays [109–113]. Both Chang *et al* [114] and Albini *et al* [109] reported on the inhibition of NF κ B and Akt pathways after chalcone exposure which was associated with subsequent endothelial cell apoptosis. This was accompanied by

decreased endothelial migration, invasion, and formation of tube-like structures. Madan *et al* [115] similarly noted inhibition of NF κ B in endothelial cells after chalcone exposure, noting that relatively high concentrations of their hydroxychalcone (up to 60 μ M) were nontoxic to cells. Given that NF κ B is a key transcriptional factor for cellular adhesion molecules (CAMs), the authors also investigated the expression of CAMs in endothelial cells and found that chalcone treatment decreased levels of various CAMs including VCAM and ICAM [116]. Since cellular adhesion molecules are important proangiogenic mediators of endothelial cell interaction and adherence in the tumor extracellular matrix, this data suggests that certain chalcones may induce antiangiogenic effects through multiple mechanisms, both intracellular and extracellular. Zhu and colleagues [117] demonstrated inhibition of VEGF-R2 (KDR) signaling as well as upstream Akt activation. This was correlated with decreased endothelial growth as well as VEGF-stimulated tumor growth in two xenograft models, due in part to decreased vessel density. In a structure-based virtual screening, Rizvi *et al* [118] identified a series of quinolyl-thienyl chalcones as potent VEGFR-2 kinase inhibitors with IC₅₀ of 73.41 nM for the lead compound. Interestingly, several authors have reported that the effect of chalcones on endothelial cells, including decreased proliferation and apoptosis, seem to occur at very low concentrations when compared to those needed to reach IC₅₀ levels in tumor cells. Nam and colleagues found their compound, 2-chloro-2',5'-dihydroxychalcone, to have an IC₅₀ value up to 66-fold more potent in HUVEC cells compared to tumor cells [112]. Similarly, Pilatova *et al* [113] found that in concentrations non-toxic to tumor cells, their compound inhibited VEGF-induced migration of HUVECs, and decreased MMP-9 and VEGF secretion. Thus, these findings would suggest that given the proper chemical modifications, certain chalcones appear to selectively and potently target endothelial cells, but can also have cytotoxic effects on tumor cells in high enough concentrations. Further, several xenograft models have confirmed the activity of chalcones in significantly slowing tumor growth, indicating that these compounds likely effect both tumor cells as well as tumor endothelium. Thus, chalcones may offer a viable strategy to target multiple cells within the tumor compartment. The mechanisms of chalcones' action are listed in Table 7.

Targeting existing tumor vasculature, as opposed to the neovasculature discussed above, has also been reported using chalcone derivatives. By and large, a significant proportion of the compounds which produce this effect are combretastatin analogues. Combretastatins, such as CA-4P, have been extensively studied and are currently in advanced stages of investigation in cancer clinical trials. Although it was first recognized that combretastatins functioned by anti-tubulin and antimetabolic mechanisms, like colchicine they were also found to have significant effects in tumor blood vessels. The classic histopathologic finding of combretastatins is a central tumor necrosis, which ensues as a result of disruption of the tumor vessels which feed the tumor. This has not yet been fully investigated with chalcone-based combretastatin analogues, though similar properties, affecting both the cell cycle as well as tumor vessels have been demonstrated [25, 26, 110].

11. OTHER MOLECULAR CANCER TARGETS ARE MODULATED BY CHALCONES

Signal-transducer-and-activator-of-transcription 3 (STAT3) is a latent cytoplasmic transcription factor that plays pivotal roles in malignant transformation, cell growth, tumorigenesis, inflammation and angiogenesis by increasing the expression of various genes such as MMP2, MMP9, Bcl-xL, Bcl-2, cyclin D1, Mcl-1 and VEGF. STAT3 is therefore considered as a suitable anti-cancer drug target. Funakoshi-Tago *et al* [119] have shown that Licochalcone A potently induce apoptosis of TEL-Jak2-transformed cells by inhibiting the phosphorylation and nuclear localization of STAT3 in human leukemia cells. Pandey *et al* [120] demonstrated that Butein inhibited both constitutive and inducible STAT 3 activation by induction of a protein tyrosine phosphatase SHP-1 in multiple myeloma (MM) cells. Cardamonin also exhibited an *in vivo* anti-inflammatory activity in lipopolysaccharide (LPS)-challenged peritoneal macrophages of ICR mice by suppressing IFN- γ induction and STATs-1, 2, 3 and 4 activation [121].

Human epidermal growth factor receptor kinases, such as EGFR, ErbB-2, and ErbB-3, have demonstrated their clinical values as cancer drug targets. Li *et al* [122] reported that ON-III (2', 4'-dihydroxy-6'-methoxy-3', 5'-dimethylchalcone) inhibits ErbB-2 tyrosine kinase phosphorylation and its mediated activation of AKT and MAPK, leading to induction of Bim expression and apoptosis in ErbB-2 overexpressing human breast cancer cells. Yang *et al* [68] have shown that Butein inhibits EGF-stimulated auto phosphotyrosine level and tyrosine-specific protein kinase activities of EGF receptor and p60c-src *in vitro* in Human hepatoma cells (HepG2) cells. Molecular modeling suggested that butein may be docked into the ATP binding pocket of EGFR. Jung *et al* [123] also showed that Isoliquiritigenin inhibited cell proliferation of human (DU145) and rat (MatLyLu) prostate cancer cells via inhibition of ErbB3 signaling and PI3K/Akt pathway.

The wingless-type (Wnt) pathway plays a central role in embryonic development and aberrant activation of the Wnt pathway contributes to the progression of several major human cancers [124]. Therefore, chalcones with Wnt inhibitor activity have major therapeutic potential. Cho *et al* [125] demonstrated that cardamonin the Wnt/beta-catenin signaling pathway through promoting the degradation of intracellular beta-catenin in HEK293 reporter cells and human normal melanocytes.

Agents that target the mammalian target of rapamycin (mTOR) signaling pathway are of significant clinical translational values. Sun *et al* [126] reported that the WJ9708011 (a methoxychalcone derivative) inhibited the mTOR pathway and protein synthesis *via* an Akt- and AMPK-independent fashion. Similarly, naturally-occurring chalcones, including licochalcone-A, isoliquiritigenin, cardamonin and xanthohumol were also shown to modulate the mTOR activity under different experimental conditions [127, 128]. Other important molecular targets, including c-Myc, Nrf2, mutant BRAF and aurora kinases are found to be modulated by chalcones (see Table 8).

12. SUMMARY AND PERSPECTIVES

Chalcones play a central role in the flavonoid synthesis pathway and is ubiquitously present in many kinds of natural products, including many dietary products like spices, tea, beer, fruits and vegetables. In different screening assays, chalcones have been able to target multiple cellular molecules, such as MDM2/p53, tubulin, proteasome, NF-kappa B, TRAIL/death receptors and mitochondria mediated apoptotic pathways, cell cycle, STAT3, AP-1, NRF2, AR, ER, PPAR- γ , β -catenin/Wnt and others (Figure 4). However, it remains unclear whether these concentrations of chalcones that were used *in vitro* can also be reached in *in vivo* conditions. Further experiments are necessary to examine the pharmacologically reachable concentrations of these chalcones. Nevertheless, chalcones are easy to chemically modify and synthesis to generate compounds with a wide variety of structural diversities. This property of chalcones makes chalcones to be very attractive as one of basic building blocks for synthesis of molecularly targeting agents. In the coming era of molecularly targeted therapy and personalized medicine, both naturally-occurring and synthetic chalcones may be very useful tools for studying basic mechanisms of cancer treatment, prevention and for developing novel agents for targeted cancer therapies.

Chalcones offer a very large repository of bioactive compounds with diverse molecular targets. Chalcones with even minor structural changes can result in targeting distinct cellular processes [71, 72, 110, 111]. The chemical structures of chalcones appear to play a critical role in determining their molecular targets. Some chalcones can have multiple targets and then affect various steps of carcinogenesis from tumor initiation to metastasis. Limited pilot clinical trials also have reported that some chalcones are well tolerated and non-toxic to humans and have reasonable pharmacokinetic properties [133]. Therefore, some lead chalcones are in the process of further characterization and optimization for investigative clinical trials for treatment of cancer, viral and cardiovascular disorders, and some have been in human use as cosmetic formulation ingredients and food additives [134–136]. These chalcones, either as nutraceuticals or as novel therapeutic agents, would provide a promising approach to cancer chemoprevention.

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ABBREVIATIONS

ABCB1	P-glycoprotein
AM114	3, 5-bis-(4-boronic acid-benzylidene)-1-methyl-piperidin-4-one
AP-1	the activator protein 1
AR	androgen receptor
ATP	Adenosine triphosphate
BCRP or ABCG2	breast cancer resistance protein

CDKs	cyclin-dependent kinases
DR5/TRAILR2	death-receptor 5/ TNF-related apoptosis-inducing ligand receptor 2
ER	estrogen receptor
ELISA	The enzyme-linked immunosorbent assay
FKB	flavokawain B
GSH	Glutathione
HSYA	Hydroxysafflor yellow A (HSYA)
ICAM-1	Intercellular Adhesion Molecule 1
ISL	isoliquiritigenin
IKK	I κ B α kinase β
Keap1	kelch-like ECH-associated protein 1
LPS	lipopolysaccharide
MDRs	multidrug efflux transporters
MDM2	Mouse double minute 2 homolog
MM	multiple myeloma
NF-κB	nuclear factor-kappa B
NRF2	nuclear factor erythroid 2-related factor 2
RIP	Receptor-Interacting Protein
NMR	Nuclear magnetic resonance
NRF2	nuclear factor erythroid 2 [NF-E2]-related factor 2
P-gp	P-glycoprotein
PPAR-γ	peroxisome proliferator-activated receptor- γ
RB	retinoblastoma
SIRT1	sirtuin-1
STAT3	Signal transducer and activator of transcription 3
TAB1	TAK1-binding protein 1
TAK1	the formation of the transforming growth factor- β -activated kinase 1 (α)/
TIBC	trans-4-Iodo, 4'-boranyl-chalcone
TRAIL	TNF-related apoptosis-inducing ligand
TSHDC	toluenesulfonylamido-chalcone, 4'-(p-toluene sulfonyl amino)-3, 4-dihydroxy chalcone
UCC	urothelial cell carcinoma

UPS	Ubiquitin-Proteasome System
VCAM-1	Vascular cell adhesion protein 1
VEGF-R2	vascular endothelial growth factor receptor 2

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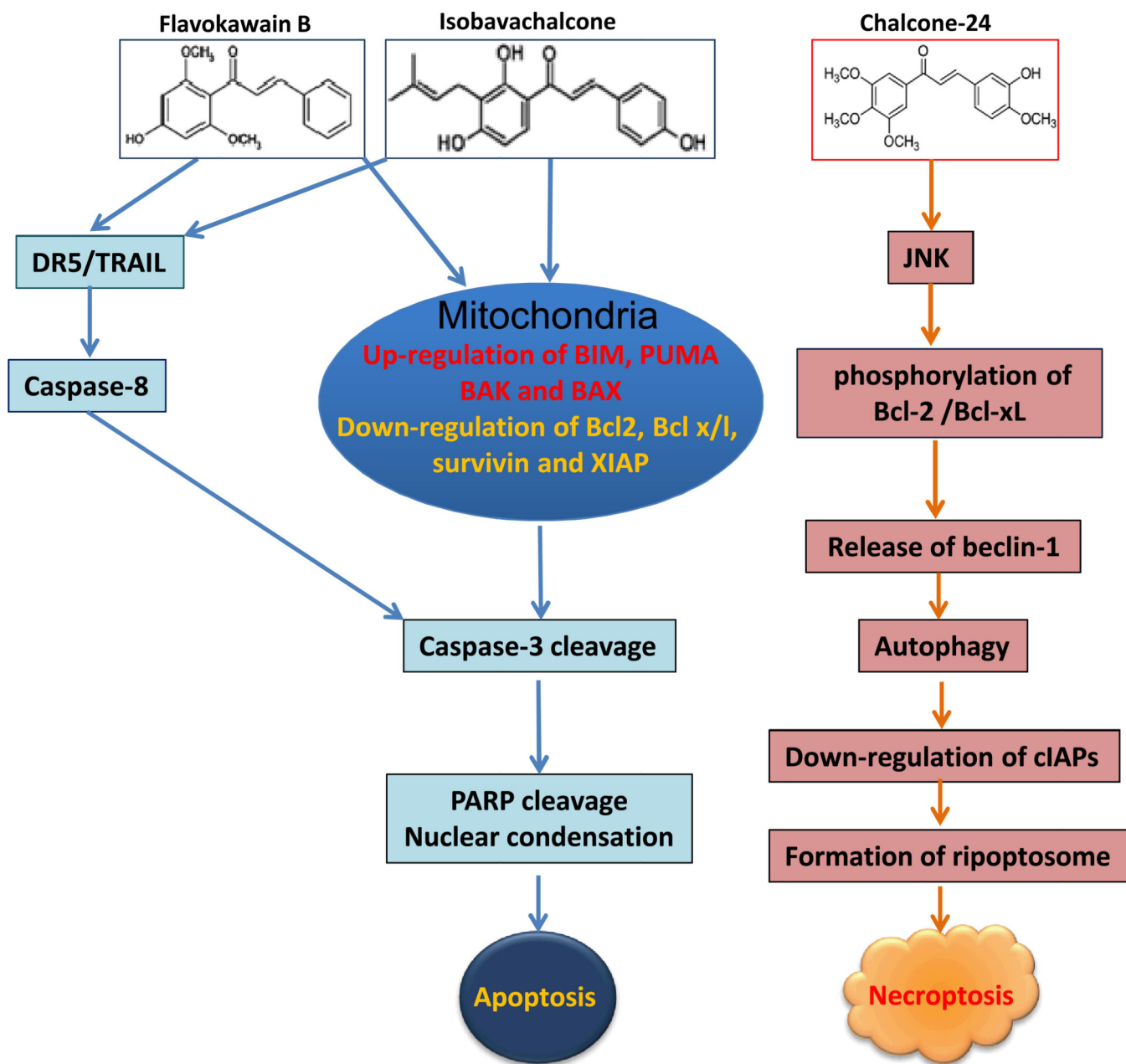


Fig. (1). Chalcones with minor structural changes result in distinct processes of cell death. Flavokawain B and Isobavachalcone induce apoptosis by activation of both mitochondria and death receptor mediated pathways. Chalcone-24 induces autophagic cell death via activation of the JNK pathway and down-regulation of cIAPs.

Chalcones

The NF- κ B pathway

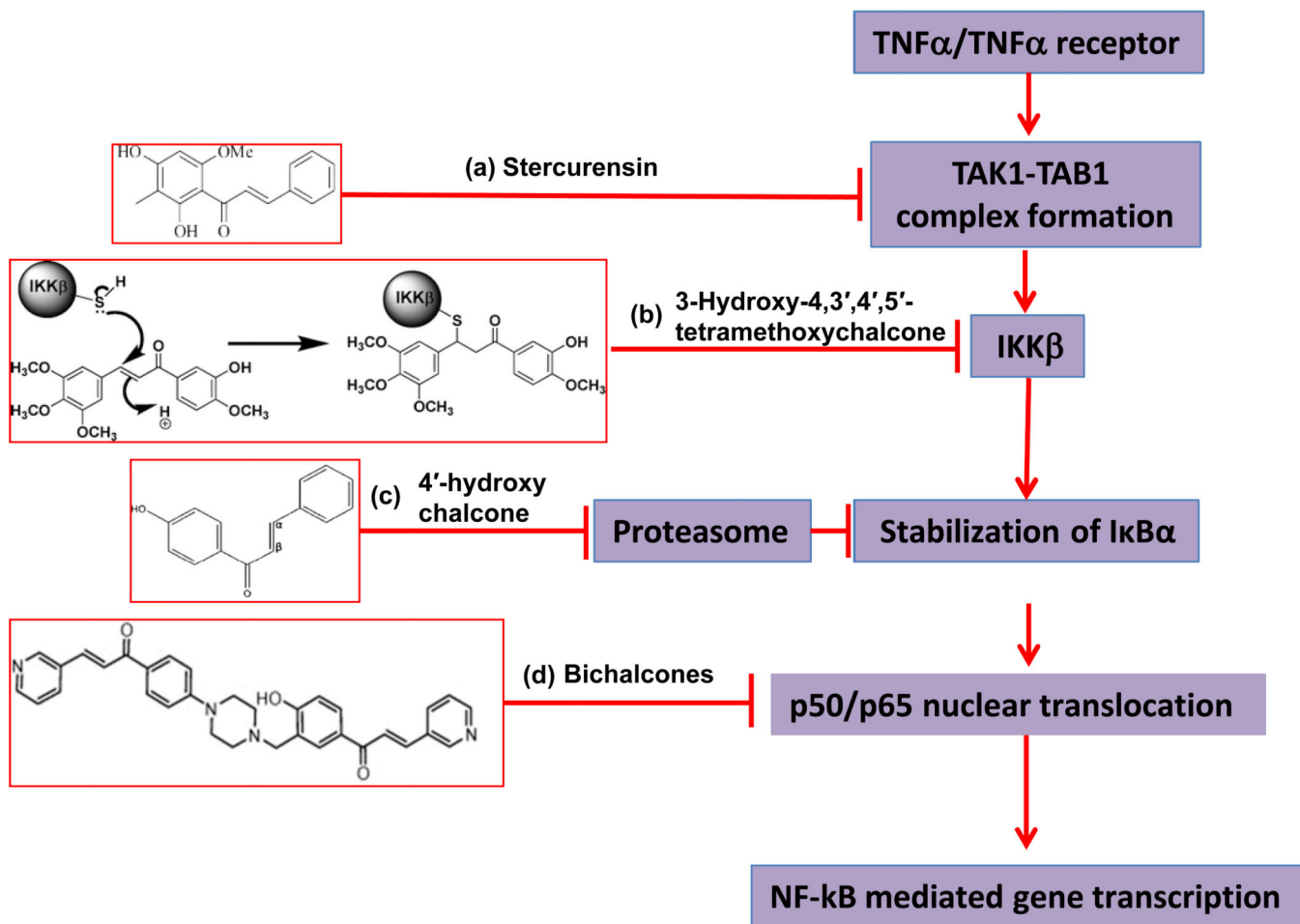


Fig. (2). Different structural types of chalcones primarily target different components of canonical NF- κ B pathway. (a) Stercurensin inhibits the formation of TAK1/TAK1 complex; (b) 3-Hydroxy-4,3',4',5'-Tetramethoxychalcone conjugates the lysine residuals of IKK β and block IKK β activity; (c) 4'-hydroxy chalcone inhibits the proteasomal activity and stabilize I κ B α ; (d) Bichalcones inhibits NF- κ B subunits p50/p65 nuclear translocation

Chalcones and chalcone analogs

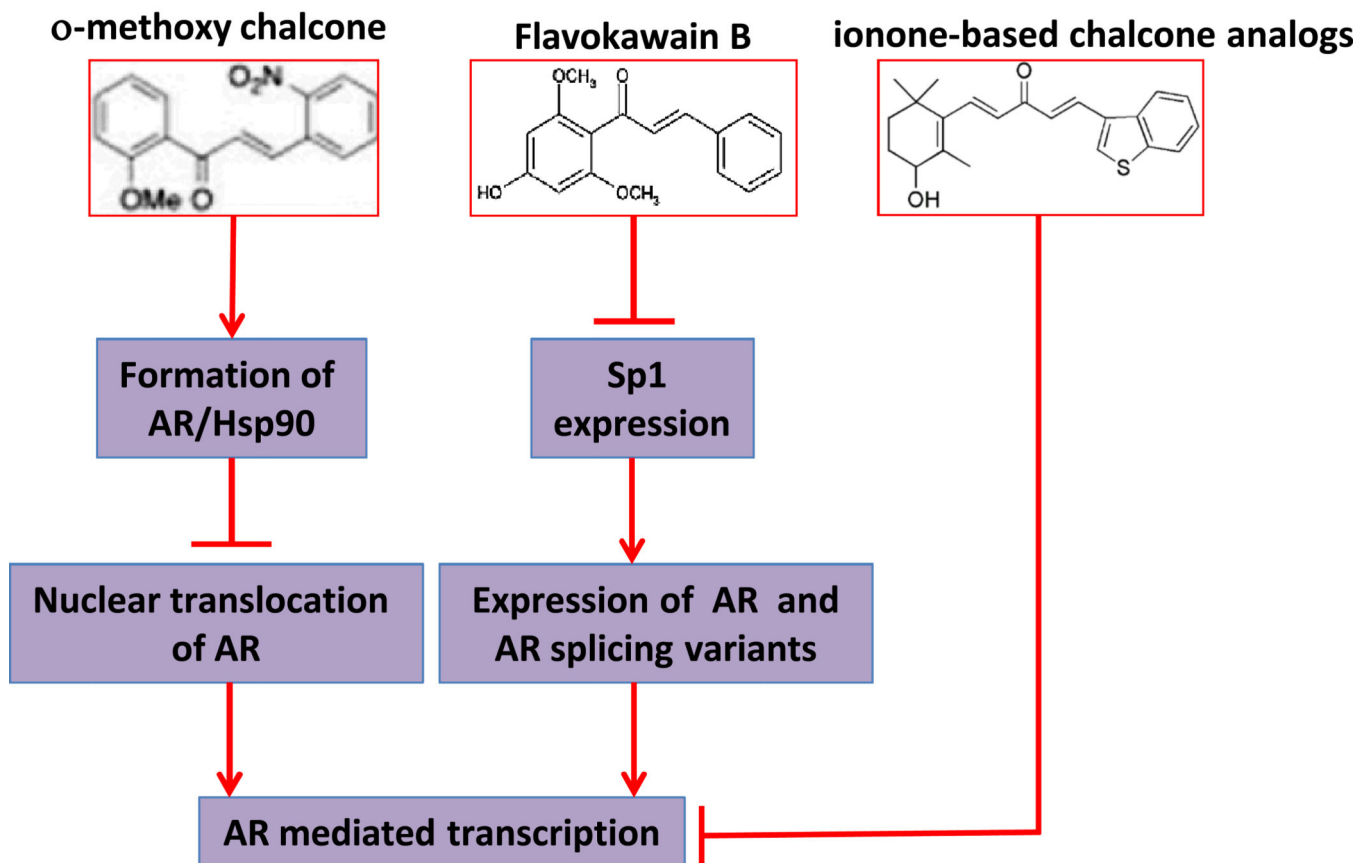


Fig. (3). The simplified mechanisms of chalcones and their analogs' action on androgen receptor signaling. o-Methoxy chalcones increase the formation of the AR/Hsp90 complex and block the nuclear translocation of AR. Flavokawain B down-regulates the expression of Sp1 and inhibits the Sp1 transcriptional regulated expression of AR and AR splicing variants. Ionone-based chalcone analogs inhibit both wild-type and mutant types of ARs mediated gene transcription.

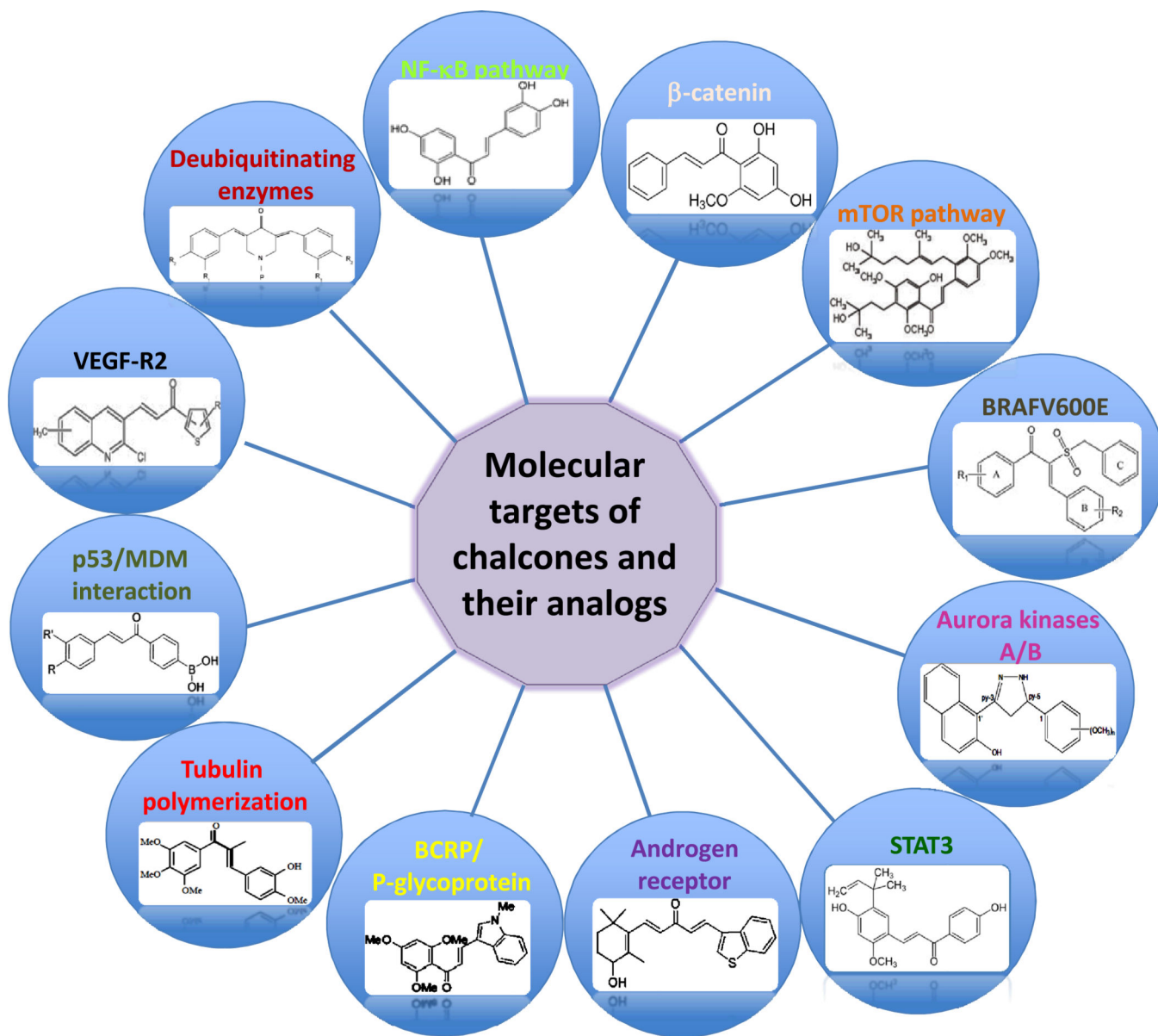


Fig. (4). Schematic presentation of different structural types of chalcones on a wide variety of molecular targets for their anti-cancer mechanisms.

Table 1

Chalcones and the p53 pathway

Lead Compounds	Chemical structures	Mechanisms of Action	Reference
Chalcone carboxylic acid		Disrupts p53/MDM2 interaction to restore p53 activity. IC ₅₀ = 49 μM (ELISA) Kd = 90 μM (NMR)	Stoll <i>et al</i> 2001 [8]
Boronic chalcones		Preferentially inhibit the growth of human breast cancer cells (MCF-7, MDA-MB-231, MDA-MB-435) versus non-malignant breast epithelial cell lines (MCF-10A and MCF-12A).	Kumar <i>et al</i> 2003 [9]
Trans-4-Iodo, 4'-boranyl-chalcone (TLBC)		Decreases p53 ubiquitination in lung cells.	Chen <i>et al</i> 2007 [13]
3,5-Bis-(4-boronic acid-benzylidene)-1-methyl-piperidin-4-one (AM114)		Inhibits the chymotrypsin-like activity of the 20S proteasome, induces p53 accumulation, and preferentially inhibit the growth of HCT116, p53+/+ versus p53 -/-.	Achanta <i>et al</i> 2006 [12]
Flavokawain A		Effects on cell cycle arrest vary in p53 wild-type (RT4) versus mutant human bladder cancer cell lines (T24, UMUC3, TCCSUP, 5637, HT1376, HT1197)	Tang <i>et al</i> 2008 [20]
Imidazothiazole chalcones		Induces p53 expression and G1 phase arrest.	Kamal <i>et al</i> 2010 [17].
3, 2',3',4'-Tetrahydroxychalcone		Inhibits the SIRT1-mediated deacetylation of a p53 acetylated peptide and recombinant protein in vitro, and induces SIRT1-mediated hyperacetylation of p53 in cells	Kahyo <i>et al</i> 2008 [22]

Table 2

Chalcones affect tubulin polymerization

Lead Compound	Chemical structure	Mechanisms of Action	Reference
Trans-1-(2,5-dimethoxyphenyl)-3-[4-(dimethylamino)phenyl]-2-methyl-2-propen-1-one], MDL 27048		Binds to tubulin at the colchicine-binding site, and inhibits microtubule assembly. IC ₅₀ 1 μM	Peyrot <i>et al</i> 1989 [23]
The crude extract of <i>Calythropsis aurea</i> (Myrtaceae). Calythrospins and dihydrocalythrospins are active compounds from the extract		Produce a pattern of differential cytotoxicity in the NCI 60 cell line assay which was similar to those of known tubulin-interactive compounds	Boumendjel <i>et al</i> 2008 [24]
Combretastatin-like, alpha-methyl chalcones SD400		Combretastatin-like analogues populate the colchicine-binding site of beta-tubulin	Ducki <i>et al</i> 2009 [25]
A series of Combretastatin-like alpha-aryl chalcones		Inhibits tubulin assembly/antimitotic activity	Ducki <i>et al</i> 2009 [26]
Thiophene analogues of chalcones; (3,4,5-Trimethoxyphenyl) (5-(2-methoxyphenyl) thiophen-2-yl)methanone		Inhibits tubulin assembly/antimitotic activity	Romagnoli <i>et al</i> 2008 [27]

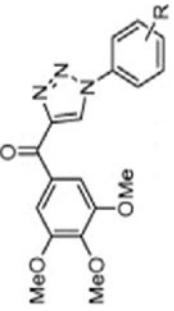
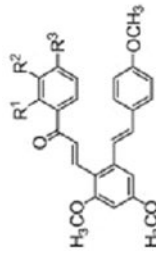
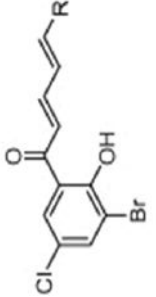
Lead Compound	Chemical structure	Mechanisms of Action	Reference
Triazole or tetrazole analogues of Chalcones		Inhibits tubulin assembly/ antimitotic activity	Mesenzani <i>et al</i> 2011 [37]
Resveratrol derivatives with a chalcone moiety		Inhibits tubulin assembly/ antimitotic activity	Ruan <i>et al</i> 2011 [36]
Dihalogenated chalcones and structurally related dienones	 <p>R=1-benzyl-1H-indol-3-yl</p>	Stabilizes tubulin assembly/ antimitotic activity	Dyrager <i>et al</i> 2011 [38]

Table 3

Mechanisms of chalcone induced Cell death

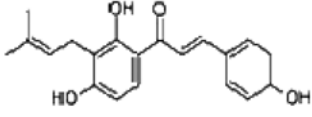
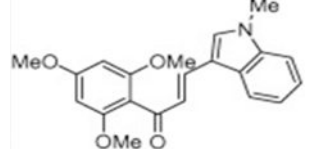
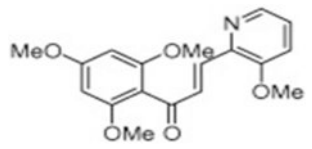
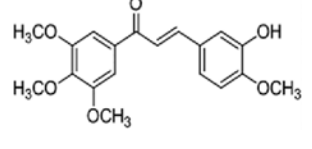
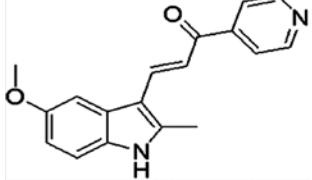
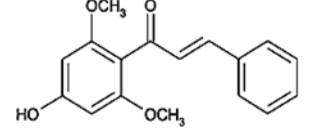
Lead Compound	Chemical Structure	Mechanisms of Action	Reference
Isobavachalcone		Increases Bak and Bax expression and decreases Bcl2 expression, as well as activates caspase-9 and -3	Nishimura <i>et al</i> [55]
JAI-51		Increases Bax/Bcl2 ratio and activates caspases-8, -9 and -3, leading to apoptosis in glioblastoma cell lines	Champelovier <i>et al</i> [71]
MBL-II-58		Induces ROS production and autophagic cell death	Champelovier <i>et al</i> [71]
Chalcone-24 (Chal-24)Chal-24		Inducing autophagy-mediated necroptosis and c-IAP1 and c-IAP2 degradation and ripoptosome formation	He <i>et al</i> 2013 [72]
3-(5-methoxy, 2-methyl-1H-indol-3-yl)-1-(4-pyridinyl)-2-propen-1-one (i.e., MOMIPP)		An inducer of methuosis	Robinson <i>et al</i> 2012 [73]
Flavokawain B		Increases the expression of death receptor-5, Bim and Bax and down-regulates the expression of survivin and XIAP, leading to apoptosis.	Tang <i>et al</i> [64]

Table 4Mechanisms of chalcones inhibiting the NF- κ B pathway

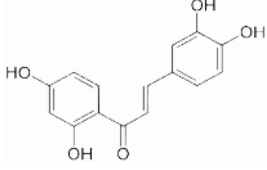
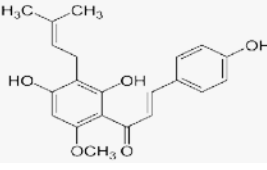
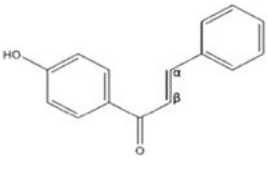
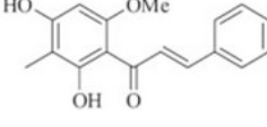
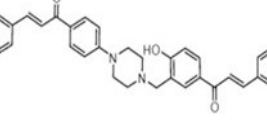
Lead Compound	Chemical structure	Mechanisms of Action	Reference
Butein		Conjugation of cysteine 179 residue of the IKK β and then stabilization of I κ B α protein	Pandey <i>et al</i> 2007 [78]
Xanthohumol		Prevents the degradation of I κ B α and in turn blocks NF- κ B activation	Harikumar <i>et al</i> 2009 [81]
4'-Hydroxychalcone		Inhibits proteasome function and then stabilizes I κ B α via an IKK-independent mechanism	Orlikova <i>et al</i> 2006 [86]
2',4'-Dihydroxy-6'-methoxy-3'-methylchalcone (stercurensin)		Inhibits TAK1-TAB1 complex formation	Kim <i>et al</i> 2011 [87]
Bichalcones		Blocks the nuclear translocation of NF- κ B p65	Reddy <i>et al</i> 2011 [88]

Table 5

Chalcones affect androgen receptor and estrogen receptor signaling

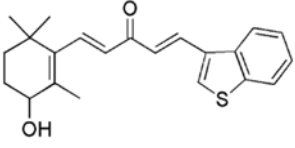
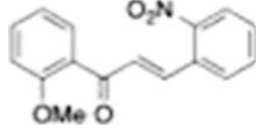
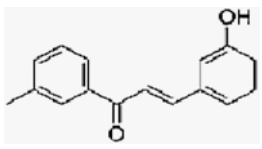
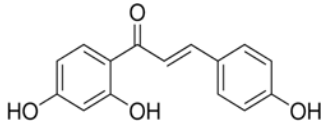
Lead Compound	Chemical structure	Mechanisms of Action	Reference
Ionone-based chalcones		A pan-inhibitor against the wild type and the clinically relevant T877A, W741C and H874Y mutated AR activities	Zhou <i>et al</i> 2010 [90]
Methoxychalcones		Inhibits androgen receptor nuclear translocation and AR mediated gene expression.	Kim <i>et al</i> 2012 [92]
3'-Methyl-3-hydroxychalcone		Blocks the binding of estradiol to type-II estrogen binding sites	Satomi <i>et al</i> 1993[93]
Isoliquiritigenin		Stimulates the estrogen receptor and downstream transcriptional activity at low concentrations (10 nM to 1 μM), and cytotoxic effect at higher concentrations (1 to 10 μM)	Maggiolini <i>et al</i> 2002 [97].

Table 6

Chalcones target multidrug resistance transporters

Lead Compound	Chemical structure	Mechanisms of Action	Reference
3', 4', 5'-Trimethoxy-4-chlorochalcone		Inhibits the transport activity of P-glycoprotein.	Ivanova <i>et al</i> 2008 [101]
3-(2,4-Dimethoxyphenyl)-1-(4-(piperazin-1-yl)phenyl)prop-2-en-1-one		inhibits both P-glycoprotein and BCRP	Liu <i>et al</i> 2008 [102]
JAI-51		An inhibitor of P-glycoprotein and BCRP in <i>in-vitro</i> and <i>in-vivo</i> glioblastoma models.	Boumendjel <i>et al</i> 2009 [105]
Bifendate-chalcone hybrids		P-glycoprotein inhibitors with minimal cytotoxicity and no stimulation on the P-gp ATPase activity	Gu <i>et al</i> 2012 [106]

Table 7

Chalcones affect the tumor vasculature

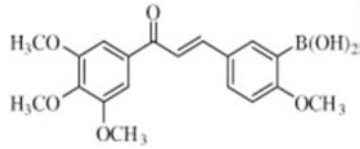
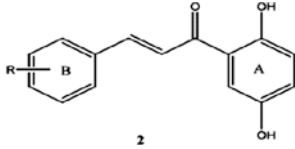
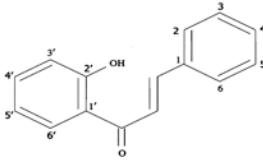
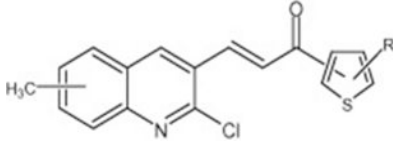
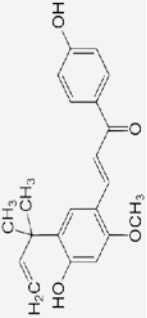
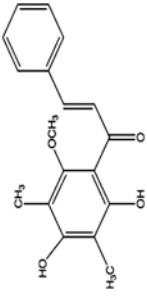
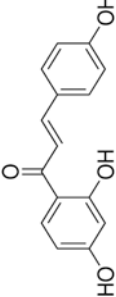
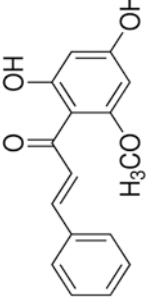
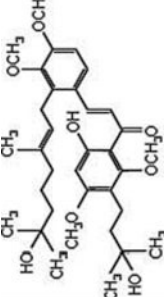
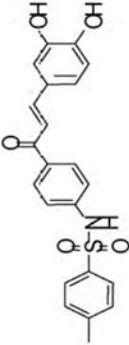
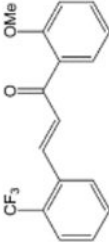
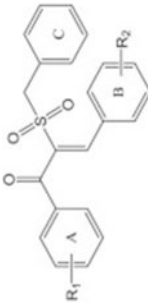
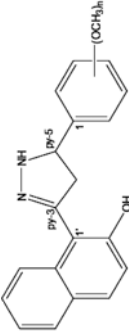
Lead Compound	Chemical structure	Mechanisms of Action	Reference
Boronic acid chalcone		Inhibits angiogenesis in HUVEC tube formation and aortic ring assays.	Kong <i>et al</i> 2009 [110]
2-Chloro-2',5'-dihydroxychalcone		Exhibit the highest 66 fold selective toxicity toward HUVECs versus HCT116 cells	Nam <i>et al</i> 2003 [112]
2'-Hydroxychalcone		Inhibiting the expression of ICAM-1, VCAM-1, and E-selectin and the adhesion of peripheral neutrophils to the endothelial cell monolayers	Madan <i>et al</i> 2000 [115].
Quinolyl-thienyl chalcones		Inhibition of VEGF-R2 (KDR) kinase activity	Rizvi <i>et al</i> 2012 [118]

Table 8

Miscellaneous targets

Lead compound	Chemical structure	Mechanisms of action	Reference
Licochalcone A		Prevents TEL-Jak2-mediated transformation through significant inhibition of the phosphorylation and nuclear localization of Stat3	Funakoshi-Tago M <i>et al</i> 2008 [119]
ON-III (2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone)		Inhibits ErbB-2 tyrosine kinase phosphorylation, disables AKT, MAPK, and downstream pathway, and induces apoptosis via induction of Bim	Li <i>et al</i> 2009 [122]
Isoliquiritigenin		Inhibits cell proliferation via inhibition of ErbB3 signaling and PI3K/Akt pathway	Jung <i>et al</i> 2006 [123]
Cardamonin		Promoting β -catenin degradation	Cho <i>et al</i> 2010 [125]
WJ9708011 (a methoxy chalcone derivative)		Inhibits mTOR signaling pathway	Sun <i>et al</i> 2010 [126]

Lead compound	Chemical structure	Mechanisms of action	Reference
Toluenesulfonylamido-chalcone, 4'-(p-toluene sulfonyl amino)-3,4-dihydroxy chalcone (TSHDC)		Increasing c-Myc-mediated reactive oxygen species production	Kim <i>et al</i> 2010 [129]
2-trifluoromethyl-2'-methoxychalcone		A potent activator of Nrf2, both in vitro and in vivo and independent of reactive oxygen species or redox changes.	Kumar <i>et al</i> 2011 [130]
A (E)- α -benzylsulfonyl chalcone derivative	 R1 = 4-Cl; R2 = 4-NO2	Exhibiting inhibitory activity with an IC ₅₀ value of 0.17 μ M for BRAFV600E and GI ₅₀ value of 0.52 μ M for mutant BRAF-dependent cells.	Li <i>et al</i> 2012 [131]
1-(5-(2,4-Dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)naphthalen-2-ol		A selective inhibitor of aurora kinases A and B	Shin <i>et al</i> 2013 [132]