Published in final edited form as:

Int Immunopharmacol. 2011 March ; 11(3): 295–309. doi:10.1016/j.intimp.2010.12.006.

The Role of Chalcones in Suppression of NF- κ B-Mediated Inflammation and Cancer

Vivek R. Yadav, Sahdeo Prasad, Bokyoung Sung, and Bharat B. Aggarwal*

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston 77030, Texas, USA

Abstract

Although consumption of fruits, vegetables, spices, cereals and pulses has been associated with lower incidence of cancer and other chronic diseases, how these dietary agents and their active ingredients minimize these diseases, is not fully understood. Whether it is oranges, kawa, hops, water-lilly, locorice, wax apple or mulberry, they are all connected by a group of aromatic ketones, called chalcones (1,3-diaryl-2-propen-1-ones). Some of the most significant chalcones identified from these plants include flavokawin, butein, xanthoangelol, 4-hydroxyderricin, cardamonin, 2',4'-dihydroxychalcone, isoliquiritigenin, isosalipurposide, and naringenin. These chalcones have been linked with immunomodulation, antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, anticancer, and antidiabetic activities. The current review, however, deals with the role of various chalcones in inflammation that controls both the immune system and tumorigenesis. Inflammatory pathways have been shown to mediate the survival, proliferation, invasion, angiogenesis and metastasis of tumors. How these chalcones modulate inflammatory pathways, tumorigenesis and immune system is the focus of this review.

Keywords

Chalcone; nuclear factor- κ B; Inflammation; tumor cell proliferation; invasion and angiogenesis; apoptosis

1. Introduction

Cancer is a serious public health issue in the United States and many other parts of the world. Currently, 1 in 4 deaths in the United States is due to cancer. It is estimated that 1,529,560 new cancer cases and 569,490 deaths from cancer are projected to occur in the United States in 2010 [1]. Besides this, it is also predicted that cancer will overtake heart disease as the world's top killer by 2010 and this trend would make more than a double the global cancer cases and deaths by 2030. Underlying all this is an expected expansion of the world's population, there will be more people around to get cancer. The “unprecedented” gathering of organizations is an attempt to draw attention to the global threat of cancer, which isn't recognized as a major, growing health problem in some developing countries. So it is the time to better understand the prognosis, diagnosis and treatment of cancer.

*For correspondence: Dr. Bharat B. Aggarwal, aggarwal@mdanderson.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The term “cancer” refers to more than 100 different types of diseases. After a half century of research it is now clear that cancer is a disease which can not be developed by the modification of a single gene. It is a complicated, multi step process where it takes 20 to 40 years to develop in human and which occurs with the involvement of a number of genes [2]. During this process, the genomes of incipient cancer cells acquire mutant alleles of proto-oncogenes, tumor-suppressor genes, and other genes that control, directly or indirectly, cell proliferation [3,4]. It can be found that these different types of genes are involved in development of human cancer in different combinations. As these combinations increase, it leads to neoplastic transformation [5]. Now we know that development of cancer involves a number of genes. Early studies were done in animal model with one or few gene mutation. However, a single gene mutation is not sufficient to accomplish the entire process of transformation. Instead, pairs of cooperation oncogene mutation, such as Ras and Myc [6], or Ras and adenovirus E1A protein, are necessary for transformation of the cells to malignancy [7]. As we know that only 5% to 10% of all cancers are caused by inheritance of mutated genes and somatic mutations, whereas the remaining 90% to 95% have been linked to lifestyle factors and environment [8]. Almost 30% of all cancers have been attributed to tobacco smoke [8], 35% to diet [9], 14% to 20% to obesity [10], 18% to infections [11], and 7% to radiation and environmental pollutants [12]. The underlying mechanisms by which these risk factors induce cancer are becoming increasingly evident. One process that seems to be common to all these risk factors is inflammation.

Inflammation, which occurs as a response to cancer, has two stages, acute and chronic. Acute inflammation, the initial stage of inflammation, represents innate immunity; it is mediated through the activation of the immune system, lasts for a short period and generally is regarded as therapeutic inflammation. If the inflammation persists for a long period of time, however, the second stage, chronic inflammation, sets in [13]. Chronic inflammation has been linked with most chronic illnesses, including cancer, cardiovascular disease, diabetes, obesity, pulmonary disease, and neurologic disease [14].

In the past two decades numerous new compounds have been identified with potential to suppress inflammation, including synthetic drugs and antibodies. These include steroids, NSAID, and Immune Selective Anti-Inflammatory Derivatives (ImSAIDs). Most of these modern drugs are costly and target single genes, while inflammation is regulated by multiple genes. For example a COX-2 inhibitor inhibits only the COX-2 gene. But inhibition of a single gene may not prevent the development of cancer or inhibit its growth, and yet knocking down even a single gene may cause a deleterious side effect. Because cancer develops as a result of the modification of a number of genes, there is a need to dial down multiple genes. Among the candidates for such an approach is the dietary consumption of food and herbal medicines, which are multitargeting in nature and cost-effective. Based on various investigations it is showed that, they never knock down the single gene, but they tune-up all genes. This review focuses on the role of one class of dietary compound, called chalcone, in targeting inflammatory pathways for immune modulation and prevention and treatment of cancer.

2. Source, Structure and Biosynthesis of Chalcones

Natural dietary agents including those from fruits, vegetables, and spices have drawn a great deal of attention from both the scientific community and the general public owing to their demonstrated ability to suppress cancers [15]. Chalcones, a group of aromatic enones, forms the central core of a variety of important biological compounds obtained from plants (Figure 1 A). These phenolic compounds all bear a 1,3-diphenyl-2-en-1-one framework [16]. They belong to the flavonoid family and are often responsible for the yellow pigmentation in plants.

Chalcones participate in the biosynthetic pathway of flavonoids, i.e., they are precursors of flavones. They can be easily cyclized by a Michael addition on the α,β -double bond to form flavanones, due to minimum energy conformation. An interesting finding is that ring A and B have different energy barriers to rotation [17]. Due to their easy availability, their simple structure, variety and different ways of cyclization, this class of compounds has emerged as important in the search for molecules with therapeutic potential. The simplest chalcone can be prepared by an aldol condensation between a benzaldehyde and an acetophenone in the presence of sodium hydroxide as a catalyst (Figure 1 B).

The key enzymes of chalcone biosynthesis catalyze the formation of the chalcone skeleton by stepwise addition of L-phenylalanine, which normally occurs in plants and removes one molecule of ammonia to form trans-cinnamate to form a compound that can be easily converted to *p*-coumarate in the presence of trans-cinnamate 4-monooxygenase. This *p*-coumarate undergoes ligation with CoA-SH to form a basic structure of 4-coumaroyl-CoA. 4-Coumaroyl-CoA and other byproducts of chalcone lead to the formation of the flavonoid skeleton [18]. In the final step of chalcone biosynthesis, these three units of 4-coumaroyl-CoA and three units of malonyl-CoA are linked in the presence of enzyme chalcone synthase to form naringenin chalcone [19,20]. A schematic of chalcone synthesis is presented in Figure 2.

Chalcones have a variety of biological properties, including analgesic, antioxidant, antifungal [21], antibacterial, antiprotozoal [22,23], gastric “protectant”, antimutagenic, antitumorogenic [24] and anti-inflammatory properties [17,22,25]. However, the mechanisms of actions of this class of compounds are not yet fully understood. A detailed list of different chalcones used in treatment of different types of chronic diseases is listed in Table 1. The purpose of this review article is to summarize the recent developments in anti-inflammatory and anticancer research of natural and synthetic chalcones with unaltered skeleton and their mechanism of action and Structure Activity Relationship (SARs) based activity.

3. Regulation of inflammatory pathways by Chalcones

3.1. NF- κ B

To understand how chalcones work, it is first necessary to understand some of the molecular details of cancer regulation. At the simplest level, cancer is regulated by a number of genes, which are in turn regulated by transcription factors. Among these transcription factors, NF- κ B plays a major role in development and progression of cancer because it regulates more than 400 genes involved in inflammation, cell survival, cell proliferation, invasion, angiogenesis, and metastasis. NF- κ B was discovered by Sen and Baltimore in 1986 as a nuclear factor that binds to the enhancer region of the κ B chain of immunoglobulin in B cells [48]. It has been shown since to be a ubiquitous transcription factor present in all cell types. It consists of homo- or heterodimers of the Rel family proteins, p50/NF κ B1, p52/NF κ B2, p65/RelA, and c-Rel. In most cell types studied to date, in resting stage NF- κ B dimers are retained in the cytoplasm through a physical association with inhibitor proteins, termed I κ B α [49]. Following cell activation, I κ B α becomes hyperphosphorylated on distinct serine residues, and a mounting body of evidence indicates that this hyperphosphorylation targets the inhibitor for proteolytic degradation [50]. The degradation of I κ B eventually leads to its dissociation from NF- κ B dimers, thereby allowing the movement of the latter towards the nucleus, where they may bind with high specificity to enhancer sequences in the 5' regulatory region of target genes.

The kinase that causes the phosphorylation of I κ B α is called I κ B α kinase or IKK. IKK β of IKK mediates the classical/canonical NF- κ B activation pathway, whereas IKK α mediates

the noncanonical pathway. What causes the activation of IKK is not well understood. More than a dozen different kinases have been described that can activate IKK including AKT, mitogen-activated protein/extracellular signal-regulated kinase kinase kinase 1 (MEKK1), MEKK3, transforming growth factor-activating kinase 1, NF- κ B-activating kinase, NF- κ B-inducing kinase, protein kinase C, and the double-stranded RNA-dependent protein kinase PKR.

The agents that activate NF- κ B include endotoxin, carcinogens (such as cigarette smoke), radiation, chemotherapeutic agents, hyperglycemia, tumor promoters, inflammatory cytokines [e.g., tumor necrosis factor (TNF) and interleukin (IL)-1] and growth factors [e.g., epidermal growth factor (EGF)] [51]. How all these diverse agents activate NF- κ B is not fully understood. However, we have shown that cigarette smoke and EGF activate NF- κ B through a mechanism different from that of TNF [52], whereas TNF-induced NF- κ B activation was found to be IKK dependent; for example, EGF activated NF- κ B through an IKK-independent mechanism [53]. Similarly, the mechanism of NF- κ B activation by UV, the major risk factor for melanoma, has been shown to be different from that of TNF [54]. In a majority of tumor cell lines, both solid and hematologic tumors, NF- κ B is constitutively active. What causes the constitutive activation of NF- κ B in these tumor cells is not fully understood. Many different mechanisms have been described, including overexpression of growth factor receptors, mutation of I κ B α such that it cannot bind to NF- κ B, constitutive activation of ras protein, high proteolytic activity directed to I κ B α , and autocrine secretion of inflammatory cytokines. In most tumor cells, constitutive activation of NF- κ B is responsible for proliferation, because inhibition of NF- κ B leads to abrogation of proliferation [55].

3.2. STAT3

Signal-transducer-and-activator-of-transcription (STAT) is also an important transcription factor. It is a family of six different transcription factors, first discovered in 1993 by James Darnell. They play major roles in cytokine signaling [56,57]. STAT3 can be activated by phosphorylation through Janus kinase (JAK) or cytokine receptors, G-protein-coupled receptors, or growth factor receptors (such as EGFR); by platelet-derived growth factor receptors that have intrinsic tyrosine kinase activity; or by intracellular non-receptor tyrosine kinase recruitment [58,59]. Of the seven STAT proteins identified so far, STAT3 and STAT5 have been implicated in multiple myeloma, lymphomas, leukemias, and several solid tumors, making these proteins logical targets for cancer therapy. These STAT proteins contribute to cell survival and growth by preventing apoptosis through increased expression of anti-apoptotic proteins, such as Bcl-2 and Bcl-XL, and angiogenic protein VEGF. Elevated STAT3 activity has been detected in head and neck squamous cell carcinoma [60], leukemias [61], lymphomas [62], multiple myeloma [63], gastric cancer [64], lung cancer [65], and laryngeal carcinoma [66].

STAT3 is activated by cytokines, growth factors, radiation, and carcinogens. The activation of STAT-3 is regulated by phosphorylation of tyrosine 705 by receptor and nonreceptor protein tyrosine kinases. The phosphorylation of STAT-3 in the cytoplasm leads to its dimerization, translocation into the nucleus, and DNA binding; as a result genes that regulate cell proliferation, differentiation, and apoptosis are expressed. In addition, numerous serine kinases have been implicated in the phosphorylation of STAT-3 at serine 727. Activated STAT3 resulted in dysfunctional cells. It mediates inflammation [67] and transformation of cells [68], promotes cell survival [69], suppresses apoptosis [70], and induces angiogenesis and metastasis [71].

3.3 Activator protein-1 (AP-1)

AP-1 is a transcription factor that is a heterodimer composed of proteins belonging to the c-Fos, c-Jun, ATF and JDP families. These dimers can bind AP-1 DNA recognition elements (5'-TGAG/CTCA-3'), also known as TREs. It is activated by several stimuli including cytokines, serum, growth factors, oncoproteins, stress, UV radiation, and bacterial and viral infections [72]. AP-1 has been implicated in regulation of genes involved in apoptosis and proliferation and may promote cell proliferation by activating the cyclin D1 gene, and repressing tumor-suppressor genes, such as p53, p21cip1/waf1 and p16. These oncogenic properties of AP-1 are primarily dictated by the dimer composition of the AP-1 family proteins and their post-transcriptional and translational modifications [72].

3.4 NRF2

Nuclear factor (erythroid-derived 2)-like 2, also known as NFE2L2 or Nrf2, is a transcription factor, is encoded by the NFE2L2 gene in humans. It regulates expression of several detoxification or antioxidant enzymes and is therefore, capable of protecting oxidative stress-related injury and inflammatory disease in animals. In response to antioxidants, xenobiotics, metals, and UV irradiation, Nrf2 protein binds strongly to antioxidant response elements (ARE) sequence and regulates ARE-mediated antioxidant enzyme gene expression and induction. NRF2 is negatively regulated by Kelch-like ECH-associated protein 1 (KEAP1). Mammalian KEAP1 proteins typically a metalloproteins that contain a Broad-complex, Tramtrack, Bric-a-brac (BTB) dimerization domain, an intervening region (IVR) enriched with Cys residues, and a domain comprising six Kelch repeats that represents a protein docking site [73-76]. Li et al characterized in Nrf2 a nuclear export signal (NES) in the leucine zipper domain (NESzip) and in the Neh5 transactivation domain (NES_{TA}) [77,78]. A nuclear localization signal (NLS) was also identified as a bipartite NLS in the basic region (bNLS) of Nrf2 [77,79], or a monopartite at the N-terminus (NLSN) and C-terminus (NLSC) of Nrf2 [80]. Activation of the Nrf2 pathway, by naturally-occurring compounds or synthetic chemicals at low-toxic doses, confers protection against subsequent toxic/carcinogenic exposure. Thus, the use of dietary compounds or synthetic chemicals to boost the Nrf2-dependent adaptive response to counteract environmental insults has emerged to be a promising strategy for cancer prevention.

3.5 PPAR- γ

Peroxisome proliferator-activated receptor gamma (PPAR- γ or PPARG), is also known as the glitazone receptor. It is a group of nuclear receptor proteins that function as transcription factors regulating the expression of different genes. PPAR- γ is a member of the nuclear receptor super family. It plays an important role in the regulation of cellular differentiation, development, metabolism, and tumorigenesis [81]. There are three forms of PPAR receptor: alpha, beta/delta and gamma [82]. PPAR- γ is normally expressed in adipocytes, skeletal muscle cells, osteoclasts, osteoblasts and several immune-type cells. It also play important role in modulation of immune system through its ability to inhibit the expression of inflammatory cytokines by direct differentiation of immune cells towards anti-inflammatory sites.

It is a ligand-activated transcription factor that regulates gene expression in response to various mediators such as 15-deoxy-12,14-prostaglandin J2 (15d-PGJ2) and oxidized linoleic acid (9-and 13-HODE). It also activated by phosphorylation, which increases the ligand-independent transcriptional activity [83]. Apart from its role as a transcription factor, PPAR γ also acts as a trans-repressor of macrophage inflammatory genes [84]. In this mechanism the ligand-dependent sumoylation of PPAR γ represses inflammatory gene expression. Binding of sumoylated PPAR γ to DNA-bound repressor complex blocks the expression of inflammatory gene products by preventing the 19S proteasome-mediated

degradation of the repressor complex. Ligand-independent activation of PPAR β/δ can suppress bowel disease by down regulation of inflammatory signaling [85]. PPAR- γ is therefore not only a target of the pharmaceutical industry, but also of great potential interest to the food industry, since it is activated by several natural dietary constituents.

3.6 beta-Catenin/wnt signaling

β -catenin is a subunit of the cadherin protein complex and has been implicated as an integral component in the Wnt signaling pathway. β -catenin, homologue of *Drosophila* Armadillo, is a dual purpose protein of great interest to those biomedical researchers concerned with tumor study. In normal epithelial cells, β -catenin is found at the plasma membrane where it provides a mechanical linkage between cell-to-cell junctional proteins (e.g., E-cadherin) and cytoskeletal proteins (e.g., β -catenin and actinin-4) [86,87]. By contrast, in tumor cells, β -catenin is often found in the cytoplasm and nucleus where it associates with ternary complex factor (TCF) family members to form a complex, which activates transcription of pro-mitotic proteins including c-Myc and cyclin-D1. β -catenin is normally undergo phosphorylation by Src and Src is also necessary for its dissociation from E-cadherin [88]. In addition to this, β -catenin also phosphorylated by the glycogen synthase kinase 3- β : adenomatous polyposis coli (GSK3 β :APC) complex leading to its ubiquitination and proteasome-mediated degradation. Canonical Wnt signaling pathway plays an important role in decreasing GSK3 β activity significantly. It involves in the regulation of growth factor Wnt, the Wnt receptor Frizzled, and associated regulatory proteins such as Disheveled and Frat [89]. Thus, increased Wnt signaling results in diminished phosphorylation and reduced degradation of β -catenin, and accumulation of β -catenin in the cytoplasm and nucleus. It can also act as oncogene [90]. Once β -catenin production increases in patients with basal cell carcinoma, it increases proliferation of tumors.

4. Role of Chalcone in Cancer

4.1. Role of chalcones in inflammation

The suffix “itis” is used typically to denote inflammation. Bronchitis, colitis, cervicitis, gastritis, and hepatitis, for example, reflect inflammation of the bronchus, colon, cervix, stomach, and liver, respectively. It seems that most cancers, especially solid tumors, are preceded by inflammation. It is already proven that inflammation is a major risk factor for type 2 diabetes, atherosclerosis, cancer, and other chronic diseases. Several natural compounds have been shown to exhibit activity against inflammation through antioxidant and anti-inflammatory mechanisms. As early as 2500 years ago, Hippocrates recognized and professed the importance of various foods both natural and those derived from human skill in the primary constitution of the person. So these natural compounds are believed to suppress the inflammatory processes that lead to transformation, hyperproliferation, and initiation of carcinogenesis. Their inhibitory influences may ultimately suppress the final steps of carcinogenesis as well, namely angiogenesis and metastasis.

Development of cancer is a multistep process that can be activated by different types of environmental carcinogens (such as cigarette smoke, industrial emissions, gasoline vapors), inflammatory agents (such as tumor necrosis factor (TNF) and H₂O₂), and tumor promoters (such as phorbol esters and okadaic acid). We and others have proved that these agents modulate transcription factors (e.g., NF- κ B, AP-1, STAT3). We know that NF- κ B regulates such proinflammatory stimuli as TNF, IL-1, IL-6, cyclooxygenase-2 (COX-2), and 5-lipoxygenase. It has been shown that these proinflammatory stimuli are expressed in bronchitis, colitis, cervicitis, gastritis, or hepatitis. Overexpression of COX-2, for example, has been shown in colitis, bronchitis, and gastritis [91]. It is also known that TNF is overexpressed in head and neck squamous cell carcinoma and mediates tumor cell

proliferation [92]. Similarly, TNF expression and its proliferative role have been shown in mantle cell lymphoma [52], acute myeloid leukemia [93], cutaneous T-cell lymphoma [94], and glioblastoma [95]. IL-6, whose expression is regulated by NF- κ B, has been shown to induce proliferation of multiple myeloma cells through activation of the STAT3 pathway [96]. If these processes are disturbed NF- κ B is activated and releases inflammatory cytokines, thus contributing to tumor initiation and progression [97]. To treat or prevent diseases such as cancer that have an etiology based in inflammation, we need agents that inhibit the inflammation and have no side effects. Among the candidates is chalcone, which is known as a potent anti-inflammatory agent (Table 2) (Figure 3,4) [41,98,99].

Brousochalcone A (BCA), isolated from *Broussonetia papyrifera* Vent, inhibits iron-induced lipid peroxidation in rat brain homogenate in a concentration-dependent manner with an IC(50) of 0.63 $\pm$ 0.03 μ M. It is as potent as butylated hydroxytoluene, a common antioxidant used for food preservation. It also inhibits NO production in RAW 264.7 macrophages stimulated by lipopolysaccharid (LPS). This effect may be attributed to the suppression of iNOS protein expression. NF- κ B is activated by LPS or cytokines; the inhibitory subunit I κ B α is postulated to be phosphorylated and then degraded, thereby releasing it from the NF- κ B-I κ B α complex. BCA prevents the degradation of I κ B α and iNOS protein expression, which would in turn block NF- κ B activation and iNOS protein expression (Cheng Z 2001). Another compound such as 4-hydroxylonchocarpin obtained from *Psoralea corylifolia* and 2',5'-dihydroxy-4-chloro-dihydrochalcone (DCDC) also inhibit LPS-stimulated increase of iNOS expression; however, DCDC has little effect on iNOS enzyme activity, suggesting that the inhibitory action is mainly due to the inhibition of iNOS expression rather than iNOS enzyme activity. 4-Hydroxylonchocarpin and DCDC significantly inhibit LPS-evoked degradation of I κ B α and the nuclear translocation of NF- κ B. DCDC also inhibits COX-2 activity in RAW 264.7 cells [100,104].

Sugii et al found that anti-inflammatory and anticancer activities of xanthoangelol, and xanthoangelol D, which are isolated from the root of *Angelica keiskei*, may be mediated through NF- κ B activation and endothelin-1 (ET-1) gene expression in cultured porcine aortic endothelial cells (PAECs). This result indicates that xanthoangelol D may be useful for the treatment of various vascular diseases involving NF- κ B activation. Cardamomin, isolated from the fruits of *Alpinia rafflesiana*, has demonstrated anti-inflammatory activity in cellular models of inflammation. Anti-inflammatory activity of cardamomin is due to suppression of NO and PGE2 synthesis, iNOS and COX-2 expression and enzymatic activity, and key molecules in the NF- κ B pathway in order to determine its molecular target. Cardamomin suppressed the production of NO and PGE2 in interferon-gamma (IFN- γ)- and lipopolysaccharide (LPS)-induced RAW 264.7 cells [40,103]. Flavokavains A and B obtained from *Piper methysticum* cause inhibition of both I κ B degradation and subsequent translocation of p50 and p65 NF- κ B subunits from the cytoplasm to the nucleus. Additionally, kinase selectivity screening demonstrates that flavokavain A, but not flavokavain B, inhibits the I κ B kinase (IKK) as well as PRAK (p38-regulated/activated kinase), MAPKAP-K3 (MAPK-activated protein kinase 3), DYRK1A (dual-specificity tyrosine-phosphorylated and regulated kinase 1A) and Aurora B kinase [37]. Lee et al identified cardamomin, 2',4'-dihydroxy-6'-methoxychalcone, as an inhibitor of NF- κ B, obtained from *Alpinia conchigera* Griff (Zingiberaceae). LPS-induced production of TNF- α and NO, as well as expression of inducible nitric-oxide synthase, and COX-2, was significantly suppressed by the treatment of cardamomin in RAW264.7 cells. Also, cardamomin inhibited not only LPS-induced degradation and phosphorylation of I κ B α but also activation of IKK. Further analyses revealed that cardamomin did not directly inhibit IKK, but rather significantly suppressed LPS-induced activation of Akt. Moreover, cardamomin suppressed transcriptional activity and phosphorylation of Ser536 of RelA/p65 subunit of NF- κ B. However, this compound did not inhibit LPS-induced activation of

extracellular signal-regulated kinase and stress-activated protein kinase/c-Jun NH(2)-terminal kinase, but significantly impaired activation of p38 mitogen-activated protein kinase. They also demonstrated that pretreatment of with cardamomin rescued C57BL/6 mice from LPS-induced mortality and decreased the serum level of TNF- α . These data taken together indicate that cardamomin could be valuable candidate for treating such NF- κ B - dependent pathological conditions as inflammation [106].

The natural compound butein (3,4,2',4'-tetrahydroxychalcone) is obtained from stem-bark of cashews (*Semecarpus anacardium*), the heartwood of *Dalbergia odorifera*, and the traditional Chinese and Tibetan medicinal herbs *Caragana jubata* and *Rhus verniciflua* Stokes. It exhibits anti-inflammatory, anti-cancer, and anti-fibrogenic activities. Pandey et al found that butein suppressed the NF- κ B activation induced by various inflammatory agents and carcinogens; and inhibited the NF- κ B reporter activity induced by TNFR1, TRADD, TRAF2, NIK, TAK1/TAB1, and IKK-beta. They also found that butein blocked the phosphorylation and degradation of I κ B α by inhibiting IKK activation which is direct and involved cysteine residue 179. This correlated with the suppression of phosphorylation and the nuclear translocation of p65 [41]. Shen et al demonstrated the anti NF- κ B effect of basic structure of chalcone (1,3-diphenyl-2-propenone). Furthermore, the expression of Bcl-X_L, the downstream target of NF- κ B, decreased in chalcone-treated cells. Therefore, reduction in the antiapoptotic effect of NF- κ B may contribute to apoptosis induced in T24 and HT-1376 cells by chalcone [108]. Hydroxysafflor yellow A (HSYA) is a main active monomer purified from *Carthamus tinctorius* L. HSYA shown the inhibition of both I κ B degradation and subsequent translocation of p50 and p65 NF- κ B subunits from the cytoplasm to the nucleus. At the same time, HSYA suppressed p65 binding activity and the transcriptional level of pro-inflammatory cytokines including TNF- α , IL-1 β and IL-6, and promoted the mRNA expression of anti-inflammatory cytokine IL-10 [110].

Xanthohumol (XN), a prenylated chalcone isolated from the hop plant, exhibits anti-inflammatory, antiproliferative, and antiangiogenic properties through an undefined mechanism. XN down-regulates both constitutive and inducible NF- κ B activation. This effect is due to inhibition of phosphorylation and degradation of I κ B α , suppression of p65 nuclear translocation, and NF- κ B -dependent reporter gene transcription. In recent studies, XN directly inhibited tumor necrosis factor-IKK activation, and a reducing agent abolished this inhibition, indicating the role of cysteine residue. XN had no effect on the IKK activity when cysteine residue 179 of IKK was mutated to alanine. It also inhibited direct binding of p65 to DNA [98,115]. In another study Isoliquiritigenin 2'-methyl ether (ILME), which is obtained from *Caesalpinia sappan* L, inhibited activated NF- κ B transcription factors, phosphorylated the MAPK, JNK (c-Jun N-terminal kinase) and ERK (extracellular signal-regulated kinase). Furthermore, ILME treatment upregulated HO-1 expression through activation of Nrf2 (NF-E2-related factor 2) pathway, and induced the expression of heme oxygenase-1 (HO-1). Tin protoporphyrin, an HO-1 inhibitor, dose-dependently attenuated the growth-inhibitory effect of ILME and blocked ILME-induced expression of the p21 and p53 cell cycle-regulatory proteins [114]. Kim et al found that licochalcone A, 3-a,a-dimethylallyl-4,4'-dihydroxy-6-methoxychalcone, from the root of *Glycyrrhiza inflata* Beta (Leguminosae) (Xin-jiang liquorice), significantly inhibited the receptor activator of NF- κ B ligand (RANKL)-induced activity of tartrate-resistant acid phosphatase (TRAP) activity and formation of osteoclasts without any effect on cell viability. Interestingly, licochalcone A inhibited the RANKL-induced activation of extracellular signal-regulated kinase, translocation of NF- κ B into nucleus and mRNA expression of Fra-2 [111].

Chalcones bear a structural similarity to stilbene, a synthon found in several selective estrogen receptor modulators like tamoxifen [116]. The enone linkage in chalcones is chemically reactive and can bind to receptors leading to increased activities of phase II

enzymes like glutathione S-transferase and quinone reductase, which are involved in the metabolism of xenobiotics. Part of the chalcone backbone is similar to curcumin and quercetin, naturally occurring chemoprotective agents. Based on the substitution pattern of chalcone, different groups have synthesized chalcone derivatives like hydroxyl and methoxy chalcones, halogenated chalcone, boronic chalcone, minochalcone, etc. Srinivasan et al found that simple chalcone candidates with only hydroxyl and methoxy substitutions in basic chalcone ring demonstrate single-digit micromolar NF- κ B inhibitory activities. 3-Hydroxy-4,3',4',5'-tetramethoxychalcone demonstrates potent cytotoxicity against lung cancer cells in vitro with most GI₅₀ in single-digit micromolar range, consistent with their NF- κ B inhibitory potency. This compound effectively suppresses lung cancer growth in vivo at a dose of 1 mg/mouse/day via IP administration [113]). Kim et al showed that brominated or halogenated chalcone can increase its activity via direct iNOS inhibition and lead to inhibition of NF- κ B even when it is given at low concentrations [109]. In another study of a synthetic chalcone 3',4',5',3,4,5-hexamethoxy-chalcone (CH) showed an anti-inflammatory activity able to reduce nitric oxide (NO) production by inhibiting inducible NO synthase protein synthesis. It also inhibits NF- κ B translocation into the nucleus, by direct DNA binding and transcriptional activity. It was also found that this compound activates Nfe2-related factor (Nrf2) and induces heme oxygenase-1 (HO-1) [102]. Rojas et al showed NF- κ B inhibition by 3,4,5-trimethoxy-4'-fluorochalcone at 10 μ M, which indicates that halogenation increases chalcone activity [101].

4.2. Role of chalcones in tumor cell survival, apoptosis, and proliferation

Apoptosis, or programmed cell death, occurs naturally in multicellular organisms. Because deregulation of apoptosis is a major contributor to the survival of tumor cells, there is much interest in identifying new ways to activate this process for the treatment of cancer cells. The process can be divided into two parts, sensors and effectors. The sensors (extrinsic pathway) are responsible for monitoring the extracellular and intracellular environment for conditions that influence whether a cell should live or die. These signals regulate the second class of components (intrinsic pathway), which function to induce apoptotic death. The intrinsic apoptosis pathway is also referred to as the mitochondrial apoptosis pathway because it requires the release of proapoptotic factors from the mitochondria such as cytochrome c [117]. This process is controlled by Bcl-2 family. Cytochrome c interacts with apoptosis protease activating factor-1 (Apaf-1). This complex provides a platform for activation of the initiator caspase procaspase-9. Once caspase cleaves it activates caspase-3, leading to death of the cell. The second pathway is the extrinsic pathway, in which apoptosis is triggered by the activation of proapoptotic receptors such as death receptors 4 and 5 (DR4 and DR5) and Fas, which are present on the cell surface. The activation of the death receptor pathway leads to receptor aggregation, which then initiates the recruitment and activation of initiator caspase-8 [118,119].

Chalcone have been found to act through the intrinsic as well as extrinsic apoptosis pathway to prevent tumor progression. For example, many natural chalcones have been shown to induce apoptosis in different types of cancer cells through a wide variety of mechanisms. Among the most important of these are xanthoangelol, flavokawain B, xanthohumol, isoliquiritigenin, flavokawain A, isobavachalcone, cardamonin, licochalcone A, and butin (Table 3). These triterpenoids have a common target, Bcl-2 protein, which can induce apoptosis in cancer cells.

Today, this is an important pathway for development of new drugs and their synthetic derivatives. Chalcone derivatives, xanthoangelol for example, was found to have anti-tumor-promoting activity in mouse skin carcinogenesis induced by 7,12-dimethylbenz[a]anthracene (DMBA) plus 12-O-tetradecanoylphorbol 13-acetate (TPA) [183]. Xanthoangelol inhibited DNA synthesis in LLC cells at concentrations of 10 and 100

μ M. Antitumor and/or antimetastatic activities of xanthoangelol may be due to inhibition the binding of VEGF to HUVECs [35]. In addition to this it reduced the level of precursor caspase-3, 9 and increased the level of cleaved caspase-3, 9, but Bax and Bcl-2 proteins were not affected [29,184].

Flavokawain A and B are the major chalcones in kava extracts, causing strong antiproliferative and apoptotic effects in cancer cells. Zi and Simoneau found that the apoptotic effect of flavokawain A is mediated through a decrease in the association of Bcl-xL with Bax, and an increase in the active form of Bax protein. In addition, it down-regulates the expression of X-linked inhibitor of apoptosis and survivin proteins. Ultimately showing a protective effect against bladder tumors implanted in nude mice [140]. This anticancer effect was due to a significant reduction in expression of the CDK1-inhibitory kinases, Myt1 and Wee1, and caused cyclin B1 protein accumulation, which lead to CDK1 activation in T24 cells. Suppression of p53 expression by small interfering RNA in RT4 cells restored Cdc25C expression and down-regulated p21/WAF1 expression, which allowed Cdc25C and CDK1 activation, which then led to a G(2)-M arrest and an enhanced growth-inhibitory effect by flavokawain A [185]. Whereas Flavokawain B induces apoptosis via up-regulation of death-receptor 5 and Bim expression in androgen receptor-negative, hormone-refractory prostate cancer cell lines and leads to reduction in tumor growth [141]. Kuo et al showed that the apoptotic effect of flavokawain B occurs through the intrinsic pathway by involving ROS and GADD153 upstream of mitochondria-dependent apoptosis [142].

Xanthohumol, a naturally occurring chalcone, induced apoptosis in cancer cells: initial induction of PARP cleavage led to activation and cleavage of the effector caspases-3 and -7, induced by activation of the initiator caspases -8 and -9. Expression of anti-apoptotic Bcl-2 was down regulated [175]. XN also inhibited K562 cell viability as well as inducing apoptosis, increasing p21 and p53 expression, and decreasing survivin levels (Monteghirfo S 2008). This enhancement of apoptosis correlated with down-regulation of bcl-xL, XIAP, cIAP1, cIAP2, cyclin D1, and c-myc [98].

Butein, a plant polyphenol, was shown to be a specific protein tyrosine kinase inhibitor [186]. Pandey et al showed that the apoptotic effect of butein was due to its inhibition of the expression of such NF- κ B-regulated gene products as IAP2, Bcl-2, and Bcl-xL [41]. Butein increased caspase-3 activity and expression of death receptor DR5 [125]. Moon et al found that it induces G(2)/M phase arrest and apoptosis in human hepatoma cancer cells through ROS generation [137]. A topical application of a chalcone derivative, 4,2',4'-trihydroxychalcone (isoliquiritigenin), inhibited epidermal ornithine decarboxylase induction and ear edema formation, i.e. inflammation [148]. It also exhibited varying degrees of estrogen receptor (ER) agonism in different tissues in vitro and in vivo. It also decreases PGE2-dependent COX-2 expression, and the decrease in NO appeared due to a decrease in inducible nitric oxide synthase (iNOS) protein expression [151]. Isoliquiritigenin dose-dependently increased the levels of cleaved caspase-9, caspase-7, caspase-3, and PARP and downregulated Bcl-2, cdk 2/4, and E2F [187,188]. Combined treatment with suboptimal concentrations of isoliquiritigenin and TRAIL markedly induced apoptosis. The effect was blocked by a pan-caspase inhibitor and a caspase-3, 8, 9, or 10 inhibitor, suggesting that the combination facilitates caspase-dependent apoptosis [189]. Nishimura et al found Isobavachalcone, a chalcone constituent of *Angelica keiskei*, induces apoptosis in neuroblastoma through reduction in pro-caspase-3 and pro-caspase-9, and subsequently increased the level of cleaved caspase-3 and cleaved caspase-9. Moreover, Bax was markedly induced by isobavachalcone application [29].

Caramonin and cardamomin are structural isomers of each other that are extracted from the *Alpinia* plant. They showed anti-inflammatory effects through direct involvement of COX-2 and DR5. This effect was due to a decrease in the Bcl-xL level in TRAIL-resistant DLD1 cells. Up-regulation of DR5 paralleled that of CCAAT/enhancer-binding protein-homologous protein (CHOP) [106,138].

Hydroxysafflor yellow A (HSYA), a component of the flower *Carthamus tinctorius* L, showed neuroprotective and cardioprotective activities in animal studies. This effect of HSYA is due to changes of Bcl-2, Bax, p53 and eNOS [190]. 2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC), which is isolated from the buds of *Cleistocalyx operculatus*, significantly inhibits the growth of human liver cancer SMMC-7721 cells and induces apoptosis of SMMC-7721 cells in vitro due to down-regulation of Bcl-2 protein [121]. Xanthoangelol, a major chalcone constituent of *Angelica keiskei*, induces apoptosis in neuroblastoma and leukemia cells. This effect is due to reduction in the level of precursor caspase-3 and an increase in the level of cleaved caspase-3, but Bax and Bcl-2 proteins are not affected. Xanthoangelol induces apoptotic cell death by activation of caspase-3 in neuroblastoma [173]. Licochalcone-A (LA), a chalcone extracted from licorice root, has antiparasitic and anti-tumor activity. LA induced apoptosis in MCF-7 and HL-60 cell lines, as demonstrated by cleavage of PARP, the substrate of ICE-like proteases. LA has shown activity against anti-apoptotic protein bcl-2 and altered the bcl-2/bax ratio in favor of apoptosis [164]. Chalcone such as methyl hydroxychalcone found in cinnamon has been used as insulin mimetic, improving insulin response of diabetics [191].

4.3. Role of chalcones in invasion, metastasis, and angiogenesis

A critical step in the development of a malignant tumor is characterized by a gain in the tumor cells' migratory and invasive capabilities. In metastasis the cancer cells migrate from their origin to other parts of the body, via either the bloodstream or lymphatic system. Migration and invasion of tumor cells are promoted by the loss of interaction of adherens junctions with the cytoskeleton, subsequent changes in the activities of Rho family small GTPases (most prominently Rac1, Cdc42, and RhoA), and the concomitant reorganization of the actin cytoskeleton [192,193]. Among the factors influencing invasion, which affects whether or not a tumor will metastasize, are matrix metalloproteinase (MMPs) and ICAM-1. MMPs (specifically MMP2 and MMP9) are endopeptidases that degrade the basement membrane components separating the cells from their surrounding tissue and enabling them to move freely and spread to other tissues [194]. MMPs play a role in a wide variety of physiological and pathological conditions, among which their role in cancer has been the most extensively studied. The MMPs are required in invasive processes during reproduction, growth and development, leukocyte mobilization and inflammation, and wound healing. Increased MMP activity has been observed in a variety of pathological conditions including cancer, inflammation, infective diseases, degenerative diseases of the brain, and vascular diseases [195]. MMP-2 is abundantly expressed in normal fibroblasts and endothelial and epithelial cells, as well as in many transformed cells [196-198]. MMP-9 expression is observed in normal leukocytes as well as in transformed cells [199,200]. ICAM-1 is a type of intercellular adhesion molecule that is constantly present in low concentrations on the surface of leukocytes and endothelial cells. It is expressed at a low basal level in fibroblasts, leukocytes, keratinocytes, and endothelial and epithelial cells, but in the presence of various cytokines its expression is increased. ICAM-1 mRNA levels have been shown to be elevated in breast tumor compared with adjacent normal tissue [201].

A few chalcones derived from natural sources have been shown to inhibit tumor cell invasion and metastasis by targeting one or more molecules (Table 3). Isoliquiritigenin, inhibited basal and EGF-induced cell migration, invasion and adhesion dose dependently. It decreased EGF-induced secretion of urokinase-type plasminogen activator (uPA), MMP-9,

tissue inhibitor of metalloproteinase-1 (TIMP-1), and VEGF, but increased TIMP-2 secretion in a concentration-dependent manner. It also decreased the protein levels of integrin- α 2, ICAM and VCAM [162]. Butein induces down-regulation of MMP-9 gene in human leukemia cells in vitro [41]. Nagameni et al found that different compounds, kanzonol C, 4-hydroxyonchocarpin, paratocarpin, stipulin and dorsamanin A, are potential, naturally-occurring antitumor drugs that inhibit MMP-2 secretion from brain tumor-derived glioblastoma cells [123].

Chalcones also have potential to inhibit tumor angiogenesis, an important consideration because the growth of human tumors and development of metastases depends on the de novo formation of blood vessels [202]. These vessels enhance tumor growth by providing oxygen and nutrition. They also help tumor cells to migrate, invade, and metastasize. Inhibition of the VEGF tyrosine kinase signaling pathway blocks new blood vessel formation in growing tumors, leading to stasis or regression of tumor growth.

Kimura et al found that in LLC cells xanthoangelol inhibits tumor-induced neovascularization, inhibiting the formation of capillary-like tubes by vascular endothelial cells and inhibiting the binding of VEGF to vascular endothelial cells. This compound also exhibited strong inhibitory effects on the human umbilical vein endothelial cell tube formation in an in vitro model [35]. Dell'Eva and Bertl found that xanthohumol dose-dependently reduces capillary formation. Moreover, xanthohumol also effectively inhibited microcapillary tube formation of immortalized human microvascular endothelial cells (HMEC-1) cells. This effect of xanthohumol is associated with induction of apoptosis and reduced VEGF secretion [174,203]. Isoliquiritigenin significantly decreased microvessel density within xenograft tumors, along with reducing VEGF production and suppressing the mTOR pathway co-regulated by JNK and ERK [160]. 2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone, a component from Chinese herbal medicine, inhibited growth of human vascular endothelial HDMEC cells in the presence of VEGF preferentially through MAPK and AKT in vitro and in vivo. Systemic administration of this chalcone resulted in an inhibition of subcutaneous growth of human hepatocarcinoma Bel7402 and lung cancer GLC-82 xenografts and a decrease in the tumor vessel density [120].

Recently, Lee et al. confirmed the antiangiogenic effects of synthetic chalcones in in vitro as well as in vivo conditions. 2'-Hydroxy-4'-methoxychalcone decreased angiogenesis in both chick embryos in the chorioallantoic membrane assay and basic fibroblast growth factor (bFGF)-induced vessel formation in the mouse Matrigel plug assay. This compound also reduced the proliferation of calf pulmonary arterial endothelial cells and was found to possess relatively weak gelatinase/collagenase inhibitory activity in vitro [204].

5. Structure Activity Relationship of Chalcones

Chalcones, both those derived from nature and synthetic versions, have shown a wide variety of pharmacological activities, including anti-inflammatory and anticancer as already described. As a result some chalcones have been approved for clinical trials for the treatment of cancer and viral and cardiovascular diseases (Ni L 2004). In the next section, we explain the relationship of NF- κ B, anti-inflammatory and anticancer activities with respect to structure activity relationship (SAR) (Table 4).

Chalcone compounds have ortho- (i.e. 2', 3'- and 3',4'-) and para- (i.e. 2,5'-) substitutions. Chalcones possess conjugated double bonds and a completely delocalized Π -electron system on both benzene rings. Molecules possessing such a system have relatively low redox potentials and have a greater probability of undergoing electron transfer reactions. Shen et al, in working on a basic structure of chalcone (1,3-diphenyl-2-propenone), they found NF- κ B inhibitory activity at the concentration of 50 μ M [108]. Chalcones with substituents that

increase the electronic density of the B-ring, such as methoxy, butoxy or dimethylamine groups, did not show significant activity in the inhibition of the nitrite production. The B-ring has a flexible ring structure and can easily convert cis-chalcone to trans-chalcone or vice versa. Because of this reason, some of the chalcones that have a single substitution at the B-ring, like xanthohumol, isoliquiritigenin, butein, cardamonin, 2',5'-dihydroxy-4-chloro-dihydrochalcone [40,41,98,100,107], work best at higher concentrations. At the same time some natural and synthetic chalcones with trimethoxy in the B-Ring act by inhibiting nitrite production. If there is 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, then they are better inhibitors of NF- κ B [37,109]. Srinivasan et al synthesized chalcones with trimethoxy substitutions in the A-ring and hydroxyl substitutions in the B-ring. They found that the synthetic compound 1, 2, 3, and 4 inhibited NF- κ B even at lower concentrations between 1-8 μ M [113]. All the chalcones showing NF- κ B inhibition contained a highly electrophilic α,β -unsaturated carbonyl moiety, which has been reported to result in Nrf2 activation and the induction of phase II detoxifying enzyme expression [205]. This α,β -unsaturated carbonyl moiety can act as an electrophile and react with free sulfhydryl groups of thioredoxin and cysteine residues in proteins [206]. Foresti et al and Srinivisan et al indicated that electrophilic phytochemicals could give rise to thiyl radicals leading to alkene reduction through a covalent Michaelis addition of nucleophiles, such as SH from cystin from DNA, which binds to NF- κ B [113,205].

6. Role of Chalcones in Cancer Treatment

Chalcones have a long history in the treatment of various human diseases such as gastric ulcer, duodenal ulcers, bronchial asthmas, addison's disease, skin disease, diabetes, and cardiac disease [207-209]. Sofalcone was used (oral delivery) in combination with other drugs for *Helicobacter pylori* eradication with encouraging results [210]. Some chalcones have shown to reach interesting plasma concentrations without marked toxicity [211]. It has been noted that the chalcones normally exert their activities in the middle to low micromolar range, with fewer examples of activity in the nanomolar range. Skilful structural manipulation of the chalcone framework may narrow its range of biological activities and enhance its potency for a targeted pharmacological profile. Chalcones are easy to synthesize, further enrich the structural diversity of the template through the introduction of features normally associated with ligand-receptor interaction, namely hydrophobic groups, hydrogen bond donor and acceptor features. Chalcones are highly multifunctional and thus are promising as agents in the treatment of cancer because of their ability to block the NF- κ B activation, induce apoptosis, and to inhibit proliferation, invasion, metastasis and angiogenesis. So these natural chalcone may serve as lead compound for drug development.

7. Conclusion

Natural dietary agents including those from fruits, vegetables, and spices have drawn a great deal of attention of scientists from all over the world due to their demonstrated ability to suppress cancers. The questions that remain to be answered are which of these dietary agents are responsible for the anti-cancer effects and what is the mechanism by which they suppress cancer. At the same time most modern medicines currently available for treating cancers have disadvantages of being very expensive, toxic, and less effective in treating the disease.

This review delineates the role of various natural and synthetic chalcones in particular to their role in suppression of NF- κ B-mediated inflammation and cancer. Because NF- κ B is a critical transcription factor that regulates the production of various proinflammatory proteins

and cytokines in activated macrophages during the process of inflammation, the inhibition of this transcription factor by chalcone might be an effective therapeutic approach for treatment of inflammatory diseases.

Acknowledgments

Dr. Aggarwal is the Ransom Horne, Jr., Professor of Cancer Research. This work was supported by a grant from a program project grant from National Institutes of Health (NIH CA-124787-01A2), and a grant from Clayton Foundation for Research, USA.

We would like to thank Walter Pagel for his careful reading of the manuscript.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin.* 2010; 60:277–300. [PubMed: 20610543]
2. Golub TR, Slonim DK, Tamayo P, Huard C, Gaasenbeek M, Mesirov JP, et al. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. *Science.* 1999; 286:531–7. [PubMed: 10521349]
3. Bhattacharjee A, Richards WG, Staunton J, Li C, Monti S, Vasa P, et al. Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses. *Proc Natl Acad Sci U S A.* 2001; 98:13790–5. [PubMed: 11707567]
4. Garber ME, Troyanskaya OG, Schluens K, Petersen S, Thaesler Z, Pacyna-Gengelbach M, et al. Diversity of gene expression in adenocarcinoma of the lung. *Proc Natl Acad Sci U S A.* 2001; 98:13784–9. [PubMed: 11707590]
5. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. *Nature.* 2000; 406:747–52. [PubMed: 10963602]
6. Land H, Parada LF, Weinberg RA. Tumorigenic conversion of primary embryo fibroblasts requires at least two cooperating oncogenes. *Nature.* 1983; 304:596–602. [PubMed: 6308472]
7. Ruley HE. Adenovirus early region 1A enables viral and cellular transforming genes to transform primary cells in culture. *Nature.* 1983; 304:602–6. [PubMed: 6308473]
8. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, et al. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res.* 2008; 25:2097–116. [PubMed: 18626751]
9. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst.* 1981; 66:1191–308. [PubMed: 7017215]
10. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* 2003; 348:1625–38. [PubMed: 12711737]
11. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer.* 2006; 118:3030–44. [PubMed: 16404738]
12. Belpomme D, Irigaray P, Hardell L, Clapp R, Montagnier L, Epstein S, et al. The multitude and diversity of environmental carcinogens. *Environ Res.* 2007; 105:414–29. [PubMed: 17692309]
13. Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *J Clin Invest.* 2007; 117:1175–83. [PubMed: 17476347]
14. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? *Biochem Pharmacol.* 2006; 72:1605–21. [PubMed: 16889756]
15. Aggarwal BB. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. *Annu Rev Nutr.* 2010; 30:173–99. [PubMed: 20420526]
16. Bohm, BA. Introduction to Flavonoids. Amsterdam: Harwood Academic; 1998.
17. Lopez SN, Castelli MV, Zacchino SA, Dominguez JN, Lobo G, Charris-Charris J, et al. In vitro antifungal evaluation and structure-activity relationships of a new series of chalcone derivatives and synthetic analogues, with inhibitory properties against polymers of the fungal cell wall. *Bioorg Med Chem.* 2001; 9:1999–2013. [PubMed: 11504637]

18. Spribille R, Forkmann G. Chalcone synthesis and hydroxylation of flavonoids in 3'-position with enzyme preparations from flowers of *Dianthus caryophyllus* L. (carnation). *Planta*. 1982; 155:176–82.
19. Kuhn B, Forkmann G, Seyffert W. Genetic control of chalcone-flavanone isomerase activity in *Callistephus chinensis*. *Planta*. 1978; 138:199–203.
20. Forkmann G, Kuhn B. Genetic control of chalcone isomerase activity in anthers of *Petunia hybrida*. *Planta*. 1979; 144:189–92.
21. Opletalova V, Sedivy D. Chalcones and their heterocyclic analogs as potential antifungal chemotherapeutic agents. *Ceska Slov Farm*. 1999; 48:252–5. [PubMed: 10748740]
22. Herencia F, Ferrandiz ML, Ubeda A, Guillen I, Dominguez JN, Charris JE, et al. Novel anti-inflammatory chalcone derivatives inhibit the induction of nitric oxide synthase and cyclooxygenase-2 in mouse peritoneal macrophages. *FEBS Lett*. 1999; 453:129–34. [PubMed: 10403389]
23. Hsieh HK, Lee TH, Wang JP, Wang JJ, Lin CN. Synthesis and anti-inflammatory effect of chalcones and related compounds. *Pharm Res*. 1998; 15:39–46. [PubMed: 9487544]
24. Makita H, Tanaka T, Fujitsuka H, Tatematsu N, Satoh K, Hara A, et al. Chemoprevention of 4-nitroquinoline 1-oxide-induced rat oral carcinogenesis by the dietary flavonoids chalcone, 2-hydroxychalcone, and quercetin. *Cancer Res*. 1996; 56:4904–9. [PubMed: 8895742]
25. Ban HS, Suzuki K, Lim SS, Jung SH, Lee S, Ji J, et al. Inhibition of lipopolysaccharide-induced expression of inducible nitric oxide synthase and tumor necrosis factor- α by 2'-hydroxychalcone derivatives in RAW 264.7 cells. *Biochem Pharmacol*. 2004; 67:1549–57. [PubMed: 15041472]
26. Mohamad H, Abas F, Permana D, Lajis NH, Ali AM, Sukari MA, et al. DPPH free radical scavenger components from the fruits of *Alpinia rafflesiana* Wall. ex. Bak. (Zingiberaceae). *Z Naturforsch C*. 2004; 59:811–5. [PubMed: 15666539]
27. Jayasinghe L, Rupasinghe GK, Hara N, Fujimoto Y. Geranylated phenolic constituents from the fruits of *Artocarpus nobilis*. *Phytochemistry*. 2006; 67:1353–8. [PubMed: 16730759]
28. Yu X, Wang W, Yang M. Antioxidant activities of compounds isolated from *Dalbergia odorifera* T. Chen and their inhibition effects on the decrease of glutathione level of rat lens induced by UV irradiation. *Food Chemistry*. 2007; 104:715–20.
29. Nishimura R, Tabata K, Arakawa M, Ito Y, Kimura Y, Akihisa T, et al. Isobavachalcone, a chalcone constituent of *Angelica keiskei*, induces apoptosis in neuroblastoma. *Biol Pharm Bull*. 2007; 30:1878–83. [PubMed: 17917255]
30. Motani K, Tabata K, Kimura Y, Okano S, Shibata Y, Abiko Y, et al. Proteomic analysis of apoptosis induced by xanthoangelol, a major constituent of *Angelica keiskei*, in neuroblastoma. *Biol Pharm Bull*. 2008; 31:618–26. [PubMed: 18379052]
31. Aoki N, Muko M, Ohta E, Ohta S. C-geranylated chalcones from the stems of *Angelica keiskei* with superoxide-scavenging activity. *J Nat Prod*. 2008; 71:1308–10. [PubMed: 18558745]
32. Vogel S, Heilmann J. Synthesis, cytotoxicity, and antioxidative activity of minor prenylated chalcones from *Humulus lupulus*. *J Nat Prod*. 2008; 71:1237–41. [PubMed: 18611049]
33. Kim JY, Park SJ, Yun KJ, Cho YW, Park HJ, Lee KT. Isoliquiritigenin isolated from the roots of *Glycyrrhiza uralensis* inhibits LPS-induced iNOS and COX-2 expression via the attenuation of NF- κ B in RAW 264.7 macrophages. *Eur J Pharmacol*. 2008; 584:175–84. [PubMed: 18295200]
34. Agnihotri VK, Elsohly HN, Khan SI, Smillie TJ, Khan IA, Walker LA. Antioxidant constituents of *Nymphaea caerulea* flowers. *Phytochemistry*. 2008; 69:2061–6. [PubMed: 18534639]
35. Kimura Y, Baba K. Antitumor and antimetastatic activities of *Angelica keiskei* roots, part 1: Isolation of an active substance, xanthoangelol. *Int J Cancer*. 2003; 106:429–37. [PubMed: 12845685]
36. Hsu YL, Kuo PL, Lin CC. Isoliquiritigenin induces apoptosis and cell cycle arrest through p53-dependent pathway in Hep G2 cells. *Life Sci*. 2005; 77:279–92. [PubMed: 15878356]
37. Folmer F, Blasius R, Morceau F, Tabudravu J, Dicato M, Jaspars M, et al. Inhibition of TNF α -induced activation of nuclear factor κ B by kava (*Piper methysticum*) derivatives. *Biochem Pharmacol*. 2006; 71:1206–18. [PubMed: 16464438]

38. Delmulle L, Bellahcene A, Dhooge W, Comhaire F, Roelens F, Huvaere K, et al. Anti-proliferative properties of prenylated flavonoids from hops (*Humulus lupulus* L.) in human prostate cancer cell lines. *Phytomedicine*. 2006; 13:732–4. [PubMed: 16678392]
39. Amor EC, Villasenor IM, Antemano R, Perveen Z, Concepcion GP, Choudhary MI. Cytotoxic C-methylated chalcones from *Syzygium samarangense*. *Pharm biol*. 2007; 45:777–83.
40. Israf DA, Khaizurin TA, Syahida A, Lajis NH, Khozirah S. Cardamonin inhibits COX and iNOS expression via inhibition of p65NF-kappaB nuclear translocation and Ikappa-B phosphorylation in RAW 264.7 macrophage cells. *Mol Immunol*. 2007; 44:673–9. [PubMed: 16777230]
41. Pandey MK, Sandur SK, Sung B, Sethi G, Kunnumakkara AB, Aggarwal BB. Butein, a tetrahydrochalcone, inhibits nuclear factor (NF)-kappaB and NF-kappaB-regulated gene expression through direct inhibition of IkappaB kinase beta on cysteine 179 residue. *J Biol Chem*. 2007; 282:17340–50. [PubMed: 17439942]
42. Li F, Awale S, Tezuka Y, Kadota S. Cytotoxic constituents from Brazilian red propolis and their structure-activity relationship. *Bioorg Med Chem*. 2008; 16:5434–40. [PubMed: 18440233]
43. Yagura T, Motomiya T, Ito M, Honda G, Iida A, Kiuchi F, et al. Anticarcinogenic compounds in the Uzbek medicinal plant, *Helichrysum maracandicum*. *J Nat Med*. 2008; 62:174–8. [PubMed: 18404319]
44. Nozawa H. Xanthohumol, the chalcone from beer hops (*Humulus lupulus* L.), is the ligand for farnesoid X receptor and ameliorates lipid and glucose metabolism in KK-A(y) mice. *Biochem Biophys Res Commun*. 2005; 336:754–61. [PubMed: 16140264]
45. Ogawa H, Ohno M, Baba K. Hypotensive and lipid regulatory actions of 4-hydroxyderricin, a chalcone from *Angelica keiskei*, in stroke-prone spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol*. 2005; 32:19–23. [PubMed: 15730429]
46. Wright DC, Geiger PC, Han DH, Holloszy JO. Are tyrosine kinases involved in mediating contraction-stimulated muscle glucose transport? *Am J Physiol Endocrinol Metab*. 2006; 290:E123–E8. [PubMed: 16159907]
47. Semwal DK, Rawat U, Semwal R, Singh R, Krishan P, Singh M, et al. Chemical constituents from the leaves of *Boehmeria rugulosa* with antidiabetic and antimicrobial activities. *J Asian Nat Prod Res*. 2009; 11:1045–55. [PubMed: 20183275]
48. Sen R, Baltimore D. Inducibility of kappa immunoglobulin enhancer-binding protein NF-kappa B by a posttranslational mechanism. *Cell*. 1986; 47:921–8. [PubMed: 3096580]
49. Baeuerle PA, Baltimore D. Activation of DNA-binding activity in an apparently cytoplasmic precursor of the NF-kappa B transcription factor. *Cell*. 1988; 53:211–7. [PubMed: 3129195]
50. Finco TS, Baldwin AS. Mechanistic aspects of NF-kappa B regulation: the emerging role of phosphorylation and proteolysis. *Immunity*. 1995; 3:263–72. [PubMed: 7552992]
51. Aggarwal BB. Nuclear factor-kappaB: the enemy within. *Cancer Cell*. 2004; 6:203–8. [PubMed: 15380510]
52. Shishodia S, Amin HM, Lai R, Aggarwal BB. Curcumin (diferuloylmethane) inhibits constitutive NF-kappaB activation, induces G1/S arrest, suppresses proliferation, and induces apoptosis in mantle cell lymphoma. *Biochem Pharmacol*. 2005; 70:700–13. [PubMed: 16023083]
53. Sethi G, Ahn KS, Chaturvedi MM, Aggarwal BB. Epidermal growth factor (EGF) activates nuclear factor-kappaB through IkappaB kinase-independent but EGF receptor-kinase dependent tyrosine 42 phosphorylation of IkappaB kinase. *Oncogene*. 2007; 26:7324–32. [PubMed: 17533369]
54. Kato T Jr, Delhase M, Hoffmann A, Karin M. CK2 Is a C-Terminal IkappaB Kinase Responsible for NF-kappaB Activation during the UV Response. *Mol Cell*. 2003; 12:829–39. [PubMed: 14580335]
55. Bargou RC, Emmerich F, Krappmann D, Bommert K, Mapara MY, Arnold W, et al. Constitutive nuclear factor-kappaB-RelA activation is required for proliferation and survival of Hodgkin's disease tumor cells. *J Clin Invest*. 1997; 100:2961–9. [PubMed: 9399941]
56. Shuai K, Stark GR, Kerr IM, Darnell JE Jr. A single phosphotyrosine residue of Stat91 required for gene activation by interferon-gamma. *Science*. 1993; 261:1744–6. [PubMed: 7690989]
57. Levy DE, Darnell JE Jr. Stats: transcriptional control and biological impact. *Nat Rev Mol Cell Biol*. 2002; 3:651–62. [PubMed: 12209125]

58. Yu CL, Meyer DJ, Campbell GS, Lerner AC, Carter-Su C, Schwartz J, et al. Enhanced DNA-binding activity of a Stat3-related protein in cells transformed by the Src oncoprotein. *Science*. 1995; 269:81–3. [PubMed: 7541555]
59. Bromberg JF, Horvath CM, Besser D, Lathem WW, Darnell JE Jr. Stat3 activation is required for cellular transformation by v-src. *Mol Cell Biol*. 1998; 18:2553–8. [PubMed: 9566875]
60. Grandis JR, Drenning SD, Chakraborty A, Zhou MY, Zeng Q, Pitt AS, et al. Requirement of Stat3 but not Stat1 activation for epidermal growth factor receptor- mediated cell growth *In vitro*. *J Clin Invest*. 1998; 102:1385–92. [PubMed: 9769331]
61. Carlesso N, Frank DA, Griffin JD. Tyrosyl phosphorylation and DNA binding activity of signal transducers and activators of transcription (STAT) proteins in hematopoietic cell lines transformed by Bcr/Abl. *J Exp Med*. 1996; 183:811–20. [PubMed: 8642285]
62. Weber-Nordt RM, Egen C, Wehinger J, Ludwig W, Gouilleux-Gruart V, Mertelsmann R, et al. Constitutive activation of STAT proteins in primary lymphoid and myeloid leukemia cells and in Epstein-Barr virus (EBV)-related lymphoma cell lines. *Blood*. 1996; 88:809–16. [PubMed: 8704235]
63. Bharti AC, Donato N, Aggarwal BB. Curcumin (diferuloylmethane) inhibits constitutive and IL-6-inducible STAT3 phosphorylation in human multiple myeloma cells. *J Immunol*. 2003; 171:3863–71. [PubMed: 14500688]
64. Kanda N, Seno H, Konda Y, Marusawa H, Kanai M, Nakajima T, et al. STAT3 is constitutively activated and supports cell survival in association with survivin expression in gastric cancer cells. *Oncogene*. 2004; 23:4921–9. [PubMed: 15077160]
65. Haura EB, Zheng Z, Song L, Cantor A, Bepler G. Activated epidermal growth factor receptor-Stat-3 signaling promotes tumor survival *in vivo* in non-small cell lung cancer. *Clin Cancer Res*. 2005; 11:8288–94. [PubMed: 16322287]
66. Liu B, Ren Z, Shi Y, Guan C, Pan Z, Zong Z. Activation of signal transducers and activators of transcription 3 and overexpression of its target gene CyclinD1 in laryngeal carcinomas. *Laryngoscope*. 2008; 118:1976–80. [PubMed: 18758380]
67. Pfitzner E, Kliem S, Baus D, Litterst CM. The role of STATs in inflammation and inflammatory diseases. *Curr Pharm Des*. 2004; 10:2839–50. [PubMed: 15379672]
68. Frank DA. STAT3 as a central mediator of neoplastic cellular transformation. *Cancer Lett*. 2007; 251:199–210. [PubMed: 17129668]
69. Masuda M, Suzui M, Yasumatu R, Nakashima T, Kuratomi Y, Azuma K, et al. Constitutive activation of signal transducers and activators of transcription 3 correlates with cyclin D1 overexpression and may provide a novel prognostic marker in head and neck squamous cell carcinoma. *Cancer Res*. 2002; 62:3351–5. [PubMed: 12067972]
70. Konnikova L, Kotecki M, Kruger MM, Cochran BH. Knockdown of STAT3 expression by RNAi induces apoptosis in astrocytoma cells. *BMC Cancer*. 2003; 3:23. [PubMed: 13678425]
71. Xie TX, Wei D, Liu M, Gao AC, Ali-Osman F, Sawaya R, et al. Stat3 activation regulates the expression of matrix metalloproteinase-2 and tumor invasion and metastasis. *Oncogene*. 2004; 23:3550–60. [PubMed: 15116091]
72. Eferl R, Wagner EF. AP-1: a double-edged sword in tumorigenesis. *Nat Rev Cancer*. 2003; 3:859–68. [PubMed: 14668816]
73. Adams J, Kelso R, Cooley L. The kelch repeat superfamily of proteins: propellers of cell function. *Trends Cell Biol*. 2000; 10:17–24. [PubMed: 10603472]
74. Zipper LM, Mulcahy RT. The Keap1 BTB/POZ dimerization function is required to sequester Nrf2 in cytoplasm. *J Biol Chem*. 2002; 277:36544–52. [PubMed: 12145307]
75. Li X, Zhang D, Hannink M, Beamer LJ. Crystal structure of the Kelch domain of human Keap1. *J Biol Chem*. 2004; 279:54750–8. [PubMed: 15475350]
76. Dinkova-Kostova AT, Holtzclaw WD, Wakabayashi N. Keap1, the sensor for electrophiles and oxidants that regulates the phase 2 response, is a zinc metalloprotein. *Biochemistry*. 2005; 44:6889–99. [PubMed: 15865434]
77. Li W, Jain MR, Chen C, Yue X, Hebbar V, Zhou R, et al. Nrf2 Possesses a redox-insensitive nuclear export signal overlapping with the leucine zipper motif. *J Biol Chem*. 2005; 280:28430–8. [PubMed: 15917227]

78. Li W, Yu SW, Kong AN. Nrf2 possesses a redox-sensitive nuclear exporting signal in the Neh5 transactivation domain. *J Biol Chem.* 2006; 281:27251–63. [PubMed: 16790425]
79. Jain AK, Bloom DA, Jaiswal AK. Nuclear import and export signals in control of Nrf2. *J Biol Chem.* 2005; 280:29158–68. [PubMed: 15901726]
80. Theodore M, Kawai Y, Yang J, Kleshchenko Y, Reddy SP, Villalta F, et al. Multiple nuclear localization signals function in the nuclear import of the transcription factor Nrf2. *J Biol Chem.* 2008; 283:8984–94. [PubMed: 18238777]
81. Belfiore A, Genua M, Malaguarnera R. PPAR-gamma Agonists and Their Effects on IGF-I Receptor Signaling: Implications for Cancer. *PPAR Res.* 2009; 2009:830501. [PubMed: 19609453]
82. Glass CK, Rosenfeld MG. The coregulator exchange in transcriptional functions of nuclear receptors. *Genes Dev.* 2000; 14:121–41. [PubMed: 10652267]
83. Diradourian C, Girard J, Pegorier JP. Phosphorylation of PPARs: from molecular characterization to physiological relevance. *Biochimie.* 2005; 87:33–8. [PubMed: 15733734]
84. Pascual G, Fong AL, Ogawa S, Gamliel A, Li AC, Perissi V, et al. A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. *Nature.* 2005; 437:759–63. [PubMed: 16127449]
85. Peters JM, Hollingshead HE, Gonzalez FJ. Role of peroxisome-proliferator-activated receptor beta/delta (PPARbeta/delta) in gastrointestinal tract function and disease. *Clin Sci (Lond).* 2008; 115:107–27. [PubMed: 18616431]
86. Morin PJ. beta-catenin signaling and cancer. *Bioessays.* 1999; 21:1021–30. [PubMed: 10580987]
87. Hayashida Y, Honda K, Idogawa M, Ino Y, Ono M, Tsuchida A, et al. E-cadherin regulates the association between beta-catenin and actinin-4. *Cancer Res.* 2005; 65:8836–45. [PubMed: 16204054]
88. Coluccia AM, Benati D, Dekhil H, De Filippo A, Lan C, Gambacorti-Passerini C. SKI-606 decreases growth and motility of colorectal cancer cells by preventing pp60(c-Src)-dependent tyrosine phosphorylation of beta-catenin and its nuclear signaling. *Cancer Res.* 2006; 66:2279–86. [PubMed: 16489032]
89. Krishnan V, Bryant HU, Macdougald OA. Regulation of bone mass by Wnt signaling. *J Clin Invest.* 2006; 116:1202–9. [PubMed: 16670761]
90. Wang X, Goode EL, Fredericksen ZS, Vierkant RA, Pankratz VS, Liu-Mares W, et al. Association of genetic variation in genes implicated in the beta-catenin destruction complex with risk of breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2008; 17:2101–8. [PubMed: 18708403]
91. Dannenberg AJ, Lippman SM, Mann JR, Subbaramaiah K, DuBois RN. Cyclooxygenase-2 and epidermal growth factor receptor: pharmacologic targets for chemoprevention. *J Clin Oncol.* 2005; 23:254–66. [PubMed: 15637389]
92. Jackson-Bernitsas DG, Ichikawa H, Takada Y, Myers JN, Lin XL, Darnay BG, et al. Evidence that TNF-TNFR1-TRADD-TRAF2-RIP-TAK1-IKK pathway mediates constitutive NF-kappaB activation and proliferation in human head and neck squamous cell carcinoma. *Oncogene.* 2007; 26:1385–97. [PubMed: 16953224]
93. Estrov Z, Kurzrock R, Pocsik E, Pathak S, Kantarjian HM, Zipf TF, et al. Lymphotoxin is an autocrine growth factor for Epstein-Barr virus-infected B cell lines. *J Exp Med.* 1993; 177:763–74. [PubMed: 8382256]
94. Giri DK, Aggarwal BB. Constitutive activation of NF-kappaB causes resistance to apoptosis in human cutaneous T cell lymphoma HuT-78 cells. Autocrine role of tumor necrosis factor and reactive oxygen intermediates. *J Biol Chem.* 1998; 273:14008–14. [PubMed: 9593751]
95. Aggarwal BB, Schwarz L, Hogan ME, Rando RF. Triple helix-forming oligodeoxynucleotides targeted to the human tumor necrosis factor (TNF) gene inhibit TNF production and block the TNF-dependent growth of human glioblastoma tumor cells. *Cancer Res.* 1996; 56:5156–64. [PubMed: 8912851]
96. Akira S, Kishimoto T. The evidence for interleukin-6 as an autocrine growth factor in malignancy. *Semin Cancer Biol.* 1992; 3:17–26. [PubMed: 1643291]
97. Coussens LM, Werb Z. Inflammatory cells and cancer: think different! *J Exp Med.* 2001; 193:F23–6. [PubMed: 11257144]

98. Harikumar KB, Kunnumakkara AB, Ahn KS, Anand P, Krishnan S, Guha S, et al. Modification of the cysteine residues in IkappaBalpha kinase and NF-kappaB (p65) by xanthohumol leads to suppression of NF-kappaB-regulated gene products and potentiation of apoptosis in leukemia cells. *Blood*. 2009; 113:2003–13. [PubMed: 18952893]
99. Cheng Z, Lin C, Hwang T, Teng C. Brousochalcone A, a potent antioxidant and effective suppressor of inducible nitric oxide synthase in lipopolysaccharide-activated macrophages. *Biochem Pharmacol*. 2001; 61:939–46. [PubMed: 11286985]
100. Huang YC, Guh JH, Cheng ZJ, Chang YL, Hwang TL, Lin CN, et al. Inhibitory effect of DCDC on lipopolysaccharide-induced nitric oxide synthesis in RAW 264.7 cells. *Life Sci*. 2001; 68:2435–47. [PubMed: 11350014]
101. Rojas J, Paya M, Devesa I, Dominguez JN, Ferrandiz ML. Therapeutic administration of 3,4,5-trimethoxy-4'-fluorochalcone, a selective inhibitor of iNOS expression, attenuates the development of adjuvant-induced arthritis in rats. *Naunyn Schmiedebergs Arch Pharmacol*. 2003; 368:225–33. [PubMed: 12904830]
102. Alcaraz MJ, Vicente AM, Araico A, Dominguez JN, Terencio MC, Ferrandiz ML. Role of nuclear factor-kappaB and heme oxygenase-1 in the mechanism of action of an anti-inflammatory chalcone derivative in RAW 264.7 cells. *Br J Pharmacol*. 2004; 142:1191–9. [PubMed: 15249426]
103. Sugii M, Ohkita M, Taniguchi M, Baba K, Kawai Y, Tahara C, et al. Xanthoangelol D isolated from the roots of *Angelica keiskei* inhibits endothelin-1 production through the suppression of nuclear factor-kappaB. *Biol Pharm Bull*. 2005; 28:607–10. [PubMed: 15802795]
104. Lee MH, Kim JY, Ryu JH. Prenylflavones from *Psoralea corylifolia* inhibit nitric oxide synthase expression through the inhibition of I-kappaB-alpha degradation in activated microglial cells. *Biol Pharm Bull*. 2005; 28:2253–7. [PubMed: 16327160]
105. Abuarqoub H, Foresti R, Green CJ, Motterlini R. Heme oxygenase-1 mediates the anti-inflammatory actions of 2'-hydroxychalcone in RAW 264.7 murine macrophages. *Am J Physiol Cell Physiol*. 2006; 290:C1092–9. [PubMed: 16291820]
106. Lee JH, Jung HS, Giang PM, Jin X, Lee S, Son PT, et al. Blockade of nuclear factor-kappaB signaling pathway and anti-inflammatory activity of cardamomin, a chalcone analog from *Alpinia conchigera*. *J Pharmacol Exp Ther*. 2006; 316:271–8. [PubMed: 16183703]
107. Kumar S, Sharma A, Madan B, Singhal V, Ghosh B. Isoliquiritigenin inhibits IkappaB kinase activity and ROS generation to block TNF-alpha induced expression of cell adhesion molecules on human endothelial cells. *Biochem Pharmacol*. 2007; 73:1602–12. [PubMed: 17276410]
108. Shen KH, Chang JK, Hsu YL, Kuo PL. Chalcone arrests cell cycle progression and induces apoptosis through induction of mitochondrial pathway and inhibition of nuclear factor kappa B signalling in human bladder cancer cells. *Basic Clin Pharmacol Toxicol*. 2007; 101:254–61. [PubMed: 17845507]
109. Kim YH, Kim J, Park H, Kim HP. Anti-inflammatory activity of the synthetic chalcone derivatives: inhibition of inducible nitric oxide synthase-catalyzed nitric oxide production from lipopolysaccharide-treated RAW 264.7 cells. *Biol Pharm Bull*. 2007; 30:1450–5. [PubMed: 17666802]
110. Chen TT, Du YJ, Liu XL, Zhu HB. Inhibitory action of hydroxysafflor yellow A on inflammatory signal transduction pathway related factors in rats with cerebral cortex ischemia. *Yao Xue Xue Bao*. 2008; 43:570–5. [PubMed: 18822957]
111. Kim SN, Kim MH, Min YK, Kim SH. Licochalcone A inhibits the formation and bone resorptive activity of osteoclasts. *Cell Biol Int*. 2008; 32:1064–72. [PubMed: 18539489]
112. Lee SH, Kim JY, Seo GS, Kim YC, Sohn DH. Isoliquiritigenin, from *Dalbergia odorifera*, up-regulates anti-inflammatory heme oxygenase-1 expression in RAW264.7 macrophages. *Inflamm Res*. 2009; 58:257–62. [PubMed: 19169644]
113. Srinivasan B, Johnson TE, Lad R, Xing C. Structure-activity relationship studies of chalcone leading to 3-hydroxy-4,3',4',5'-tetramethoxychalcone and its analogues as potent nuclear factor kappaB inhibitors and their anticancer activities. *J Med Chem*. 2009; 52:7228–35. [PubMed: 19883086]

114. Lee YM, Jeong GS, Lim HD, An RB, Kim YC, Kim EC. Isoliquiritigenin 2'-methyl ether induces growth inhibition and apoptosis in oral cancer cells via heme oxygenase-1. *Toxicol In Vitro*. 2010; 24:776–82. [PubMed: 20040371]
115. Cho YC, Kim HJ, Kim YJ, Lee KY, Choi HJ, Lee IS, et al. Differential anti-inflammatory pathway by xanthohumol in IFN-gamma and LPS-activated macrophages. *Int Immunopharmacol*. 2008; 8:567–73. [PubMed: 18328448]
116. Dimmock JR, Elias DW, Beazely MA, Kandepu NM. Bioactivities of chalcones. *Curr Med Chem*. 1999; 6:1125–49. [PubMed: 10519918]
117. Liu X, Kim CN, Yang J, Jemmerson R, Wang X. Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome c. *Cell*. 1996; 86:147–57. [PubMed: 8689682]
118. Fulda S, Debatin KM. Signaling through death receptors in cancer therapy. *Curr Opin Pharmacol*. 2004; 4:327–32. [PubMed: 15251124]
119. Debatin KM, Krammer PH. Death receptors in chemotherapy and cancer. *Oncogene*. 2004; 23:2950–66. [PubMed: 15077156]
120. Zhu XF, Xie BF, Zhou JM, Feng GK, Liu ZC, Wei XY, et al. Blockade of vascular endothelial growth factor receptor signal pathway and antitumor activity of ON-III (2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone), a component from Chinese herbal medicine. *Mol Pharmacol*. 2005; 67:1444–50. [PubMed: 15703376]
121. Ye CL, Qian F, Wei DZ, Lu YH, Liu JW. Induction of apoptosis in K562 human leukemia cells by 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone. *Leuk Res*. 2005; 29:887–92. [PubMed: 15978939]
122. Kim YJ, Ko H, Park JS, Han IH, Amor EC, Lee JW, et al. Dimethyl cardamonin inhibits lipopolysaccharide-induced inflammatory factors through blocking NF-kappaB p65 activation. *Int Immunopharmacol*. 2010; 10:1127–34. [PubMed: 20609401]
123. Ngameni B, Touaibia M, Patnam R, Belkaid A, Sonna P, Ngadjui BT, et al. Inhibition of MMP-2 secretion from brain tumor cells suggests chemopreventive properties of a furanocoumarin glycoside and of chalcones isolated from the twigs of *Dorstenia turbinata*. *Phytochemistry*. 2006; 67:2573–9. [PubMed: 17070879]
124. Wang JP, Tsao LT, Raung SL, Lin CN. Investigation of the inhibitory effect of broussonchalcone A on respiratory burst in neutrophils. *Eur J Pharmacol*. 1997; 320:201–8. [PubMed: 9059855]
125. Kim N. Butein sensitizes human leukemia cells to apoptosis induced by tumor necrosis factor-related apoptosis inducing ligand (TRAIL). *Arch Pharm Res*. 2008; 31:1179–86. [PubMed: 18806962]
126. Hayashi K, Nagamatsu T, Honda S, Suzuki Y. Butein (3,4,2',4'-tetrahydroxychalcone) ameliorates experimental anti-glomerular basement membrane antibody-associated glomerulonephritis (3). *Eur J Pharmacol*. 1996; 316:297–306. [PubMed: 8982701]
127. Iwashita K, Kobori M, Yamaki K, Tsushida T. Flavonoids inhibit cell growth and induce apoptosis in B16 melanoma 4A5 cells. *Biosci Biotechnol Biochem*. 2000; 64:1813–20. [PubMed: 11055382]
128. Kim NY, Pae HO, Oh GS, Kang TH, Kim YC, Rhew HY, et al. Butein, a plant polyphenol, induces apoptosis concomitant with increased caspase-3 activity, decreased Bcl-2 expression and increased Bax expression in HL-60 cells. *Pharmacol Toxicol*. 2001; 88:261–6. [PubMed: 11393587]
129. Yang EB, Guo YJ, Zhang K, Chen YZ, Mack P. Inhibition of epidermal growth factor receptor tyrosine kinase by chalcone derivatives. *Biochim Biophys Acta*. 2001; 1550:144–52. [PubMed: 11755203]
130. Lee SH, Nan JX, Zhao YZ, Woo SW, Park EJ, Kang TH, et al. The chalcone butein from *Rhus verniciflua* shows antifibrogenic activity. *Planta Med*. 2003; 69:990–4. [PubMed: 14735434]
131. Takano-Ishikawa Y, Goto M, Yamaki K. Inhibitory effects of several flavonoids on E-selectin expression on human umbilical vein endothelial cells stimulated by tumor necrosis factor-alpha. *Phytother Res*. 2003; 17:1224–7. [PubMed: 14669262]
132. Lee SH, Seo GS, Sohn DH. Inhibition of lipopolysaccharide-induced expression of inducible nitric oxide synthase by butein in RAW 264.7 cells. *Biochem Biophys Res Commun*. 2004; 323:125–32. [PubMed: 15351711]

133. Pandey MK, Sung B, Ahn KS, Aggarwal BB. Butein suppresses constitutive and inducible signal transducer and activator of transcription (STAT) 3 activation and STAT3-regulated gene products through the induction of a protein tyrosine phosphatase SHP-1. *Mol Pharmacol*. 2009; 75:525–33. [PubMed: 19103760]
134. Moon DO, Kim MO, Lee JD, Choi YH, Kim GY. Butein suppresses c-Myc-dependent transcription and Akt-dependent phosphorylation of hTERT in human leukemia cells. *Cancer Lett*. 2009; 286:172–9. [PubMed: 19560862]
135. Moon DO, Kim MO, Choi YH, Kim GY. Butein sensitizes human hepatoma cells to TRAIL-induced apoptosis via extracellular signal-regulated kinase/Sp1-dependent DR5 upregulation and NF-kappaB inactivation. *Mol Cancer Ther*. 2010; 9:1583–95. [PubMed: 20515942]
136. Moon DO, Choi YH, Moon SK, Kim WJ, Kim GY. Butein suppresses the expression of nuclear factor-kappa B-mediated matrix metalloproteinase-9 and vascular endothelial growth factor in prostate cancer cells. *Toxicol In Vitro*. 2010; 24:1927–34. [PubMed: 20696233]
137. Moon DO, Kim MO, Choi YH, Hyun JW, Chang WY, Kim GY. Butein induces G(2)/M phase arrest and apoptosis in human hepatoma cancer cells through ROS generation. *Cancer Lett*. 2010; 288:204–13. [PubMed: 19643530]
138. Ohtsuki T, Kikuchi H, Koyano T, Kowithayakorn T, Sakai T, Ishibashi M. Death receptor 5 promoter-enhancing compounds isolated from *Catimbum speciosum* and their enhancement effect on TRAIL-induced apoptosis. *Bioorg Med Chem*. 2009; 17:6748–54. [PubMed: 19682913]
139. Zhou P, Gross S, Liu JH, Yu BY, Feng LL, Nolta J, et al. Flavokawain B, the hepatotoxic constituent from kava root, induces GSH-sensitive oxidative stress through modulation of IKK/NF- κ B and MAPK signaling pathways. *FASEB J*. 2010
140. Zi X, Simoneau AR. Flavokawain A, a novel chalcone from kava extract, induces apoptosis in bladder cancer cells by involvement of Bax protein-dependent and mitochondria-dependent apoptotic pathway and suppresses tumor growth in mice. *Cancer Res*. 2005; 65:3479–86. [PubMed: 15833884]
141. Tang Y, Li X, Liu Z, Simoneau AR, Xie J, Zi X. Flavokawain B, a kava chalcone, induces apoptosis via up-regulation of death-receptor 5 and Bim expression in androgen receptor negative, hormonal refractory prostate cancer cell lines and reduces tumor growth. *Int J Cancer*. 2010; 127:1758–68. [PubMed: 20112340]
142. Kuo YF, Su YZ, Tseng YH, Wang SY, Wang HM, Chueh PJ. Flavokawain B, a novel chalcone from *Alpinia pricei* Hayata with potent apoptotic activity: Involvement of ROS and GADD153 upstream of mitochondria-dependent apoptosis in HCT116 cells. *Free Radic Biol Med*. 2010; 49:214–26. [PubMed: 20398749]
143. Lin CT, Senthil Kumar KJ, Tseng YH, Wang ZJ, Pan MY, Xiao JH, et al. Anti-inflammatory activity of Flavokawain B from *Alpinia pricei* Hayata. *J Agric Food Chem*. 2009; 57:6060–5. [PubMed: 19537711]
144. Xi S, Zhang Q, Xie H, Liu L, Liu C, Gao X, et al. Effects of hydroxy safflor yellow A on blood vessel and mRNA expression with VEGF and bFGF of transplantation tumor with gastric adenocarcinoma cell line BGC-823 in nude mice. *Zhongguo Zhong Yao Za Zhi*. 2009; 34:605–10. [PubMed: 19526794]
145. Ji DB, Zhu MC, Zhu B, Zhu YZ, Li CL, Ye J, et al. Hydroxysafflor yellow A enhances survival of vascular endothelial cells under hypoxia via upregulation of the HIF-1 α -VEGF pathway and regulation of Bcl-2/Bax. *J Cardiovasc Pharmacol*. 2008; 52:191–202. [PubMed: 18670359]
146. Lian ZQ, Zhao DL, Zhu HB. Hydroxysafflor yellow A up-regulates HIF-1 α via inhibition of VHL and p53 in Eahy 926 cell line exposed to hypoxia. *Yao Xue Xue Bao*. 2008; 43:484–9. [PubMed: 18717335]
147. Jing H, Zhou X, Dong X, Cao J, Zhu H, Lou J, et al. Abrogation of Akt signaling by Isobavachalcone contributes to its anti-proliferative effects towards human cancer cells. *Cancer Lett*. 2010; 294:167–77. [PubMed: 20167420]
148. Yamamoto S, Aizu E, Jiang H, Nakadate T, Kiyoto I, Wang JC, et al. The potent anti-tumor-promoting agent isoliquiritigenin. *Carcinogenesis*. 1991; 12:317–23. [PubMed: 1899810]

149. Chowdhury SA, Kishino K, Satoh R, Hashimoto K, Kikuchi H, Nishikawa H, et al. Tumor-specificity and apoptosis-inducing activity of stilbenes and flavonoids. *Anticancer Res.* 2005; 25:2055–63. [PubMed: 16158945]
150. Hsu YL, Kuo PL, Lin LT, Lin CC. Isoliquiritigenin inhibits cell proliferation and induces apoptosis in human hepatoma cells. *Planta Med.* 2005; 71:130–4. [PubMed: 15729620]
151. Takahashi T, Takasuka N, Iigo M, Baba M, Nishino H, Tsuda H, et al. Isoliquiritigenin, a flavonoid from licorice, reduces prostaglandin E2 and nitric oxide, causes apoptosis, and suppresses aberrant crypt foci development. *Cancer Sci.* 2004; 95:448–53. [PubMed: 15132774]
152. Kim SC, Byun SH, Yang CH, Kim CY, Kim JW, Kim SG. Cytoprotective effects of Glycyrrhizae radix extract and its active component liquiritigenin against cadmium-induced toxicity (effects on bad translocation and cytochrome c-mediated PARP cleavage). *Toxicology.* 2004; 197:239–51. [PubMed: 15033546]
153. Jang DS, Park EJ, Hawthorne ME, Vigo JS, Graham JG, Cabieses F, et al. Potential cancer chemopreventive constituents of the seeds of *Dipteryx odorata* (tonka bean). *J Nat Prod.* 2003; 66:583–7. [PubMed: 12762787]
154. Kanazawa M, Satomi Y, Mizutani Y, Ukimura O, Kawauchi A, Sakai T, et al. Isoliquiritigenin inhibits the growth of prostate cancer. *Eur Urol.* 2003; 43:580–6. [PubMed: 12706007]
155. Tanaka S, Sakata Y, Morimoto K, Tambe Y, Watanabe Y, Honda G, et al. Influence of natural and synthetic compounds on cell surface expression of cell adhesion molecules, ICAM-1 and VCAM-1. *Planta Med.* 2001; 67:108–13. [PubMed: 11301853]
156. Kang SW, Choi JS, Choi YJ, Bae JY, Li J, Kim DS, et al. Licorice isoliquiritigenin dampens angiogenic activity via inhibition of MAPK-responsive signaling pathways leading to induction of matrix metalloproteinases. *J Nutr Biochem.* 2010; 21:55–65. [PubMed: 19157825]
157. Park I, Park KK, Park JH, Chung WY. Isoliquiritigenin induces G2 and M phase arrest by inducing DNA damage and by inhibiting the metaphase/anaphase transition. *Cancer Lett.* 2009; 277:174–81. [PubMed: 19167809]
158. Lee YM, Lim do Y, Choi HJ, Jung JI, Chung WY, Park JH. Induction of cell cycle arrest in prostate cancer cells by the dietary compound isoliquiritigenin. *J Med Food.* 2009; 12:8–14. [PubMed: 19298190]
159. Park SJ, Song HY, Youn HS. Suppression of the TRIF-dependent signaling pathway of toll-like receptors by isoliquiritigenin in RAW264.7 macrophages. *Mol Cells.* 2009; 28:365–8. [PubMed: 19809799]
160. Sun ZJ, Chen G, Zhang W, Hu X, Huang CF, Wang YF, et al. Mammalian target of rapamycin pathway promotes tumor-induced angiogenesis in adenoid cystic carcinoma: its suppression by isoliquiritigenin through dual activation of c-Jun NH2-terminal kinase and inhibition of extracellular signal-regulated kinase. *J Pharmacol Exp Ther.* 2010; 334:500–12. [PubMed: 20484154]
161. Park SJ, Youn HS. Suppression of homodimerization of toll-like receptor 4 by isoliquiritigenin. *Phytochemistry.* 2010; 71:1736–40. [PubMed: 20701936]
162. Kwon GT, Cho HJ, Chung WY, Park KK, Moon A, Park JH. Isoliquiritigenin inhibits migration and invasion of prostate cancer cells: possible mediation by decreased JNK/AP-1 signaling. *J Nutr Biochem.* 2009; 20:663–76. [PubMed: 18824345]
163. Furusawa J, Funakoshi-Tago M, Tago K, Mashino T, Inoue H, Sonoda Y, et al. Licochalcone A significantly suppresses LPS signaling pathway through the inhibition of NF-kappaB p65 phosphorylation at serine 276. *Cell Signal.* 2009; 21:778–85. [PubMed: 19168128]
164. Rafi MM, Rosen RT, Vassil A, Ho CT, Zhang H, Ghai G, et al. Modulation of bcl-2 and cytotoxicity by licochalcone-A, a novel estrogenic flavonoid. *Anticancer Res.* 2000; 20:2653–8. [PubMed: 10953339]
165. Kim YH, Shin EK, Kim DH, Lee HH, Park JH, Kim JK. Antiangiogenic effect of licochalcone A. *Biochem Pharmacol.* 2010; 80:1152–9. [PubMed: 20637733]
166. Kim JK, Shin EK, Park JH, Kim YH. Antitumor and antimetastatic effects of licochalcone A in mouse models. *J Mol Med.* 2010; 88:829–38. [PubMed: 20383690]

167. Yo YT, Shieh GS, Hsu KF, Wu CL, Shiao AL. Licorice and licochalcone-A induce autophagy in LNCaP prostate cancer cells by suppression of Bcl-2 expression and the mTOR pathway. *J Agric Food Chem.* 2009; 57:8266–73. [PubMed: 19711916]
168. Yoon G, Kang BY, Cheon SH. Topoisomerase I inhibition and cytotoxicity of licochalcones A and E from *Glycyrrhiza inflata*. *Arch Pharm Res.* 2007; 30:313–6. [PubMed: 17424936]
169. Fu Y, Hsieh TC, Guo J, Kunicki J, Lee MY, Darzynkiewicz Z, et al. Licochalcone-A, a novel flavonoid isolated from licorice root (*Glycyrrhiza glabra*), causes G2 and late-G1 arrests in androgen-independent PC-3 prostate cancer cells. *Biochem Biophys Res Commun.* 2004; 322:263–70. [PubMed: 15313200]
170. Hirai S, Kim YI, Goto T, Kang MS, Yoshimura M, Obata A, et al. Inhibitory effect of naringenin chalcone on inflammatory changes in the interaction between adipocytes and macrophages. *Life Sci.* 2007; 81:1272–9. [PubMed: 17915259]
171. Iwamura C, Shinoda K, Yoshimura M, Watanabe Y, Obata A, Nakayama T. Naringenin chalcone suppresses allergic asthma by inhibiting the type-2 function of CD4 T cells. *Allergol Int.* 2010; 59:67–73. [PubMed: 20035147]
172. Fujita T, Sakuma S, Sumiya T, Nishida H, Fujimoto Y, Baba K, et al. The effects of xanthoangelol E on arachidonic acid metabolism in the gastric antral mucosa and platelet of the rabbit. *Res Commun Chem Pathol Pharmacol.* 1992; 77:227–40. [PubMed: 1439191]
173. Tabata K, Motani K, Takayanagi N, Nishimura R, Asami S, Kimura Y, et al. Xanthoangelol, a major chalcone constituent of *Angelica keiskei*, induces apoptosis in neuroblastoma and leukemia cells. *Biol Pharm Bull.* 2005; 28:1404–7. [PubMed: 16079483]
174. Dell'Eva R, Ambrosini C, Vannini N, Piaggio G, Albini A, Ferrari N. AKT/NF-kappaB inhibitor xanthohumol targets cell growth and angiogenesis in hematologic malignancies. *Cancer.* 2007; 110:2007–11. [PubMed: 17823911]
175. Pan L, Becker H, Gerhauser C. Xanthohumol induces apoptosis in cultured 40-16 human colon cancer cells by activation of the death receptor- and mitochondrial pathway. *Mol Nutr Food Res.* 2005; 49:837–43. [PubMed: 15995977]
176. Liu G, Eggler AL, Dietz BM, Mesecar AD, Bolton JL, Pezzuto JM, et al. Screening method for the discovery of potential cancer chemoprevention agents based on mass spectrometric detection of alkylated Keap1. *Anal Chem.* 2005; 77:6407–14. [PubMed: 16194107]
177. Vanhoecke B, Derycke L, Van Marck V, Depypere H, De Keukeleire D, Bracke M. Antiinvasive effect of xanthohumol, a prenylated chalcone present in hops (*Humulus lupulus* L.) and beer. *Int J Cancer.* 2005; 117:889–95. [PubMed: 15986430]
178. Monteghirfo S, Tosetti F, Ambrosini C, Stigliani S, Pozzi S, Frassoni F, et al. Antileukemia effects of xanthohumol in Bcr/Abl-transformed cells involve nuclear factor-kappaB and p53 modulation. *Mol Cancer Ther.* 2008; 7:2692–702. [PubMed: 18790751]
179. Gao X, Deeb D, Liu Y, Gautam S, Dulchavsky SA, Gautam SC. Immunomodulatory activity of xanthohumol: inhibition of T cell proliferation, cell-mediated cytotoxicity and Th1 cytokine production through suppression of NF-kappaB. *Immunopharmacol Immunotoxicol.* 2009; 31:477–84. [PubMed: 19555200]
180. Lupinacci E, Meijerink J, Vincken JP, Gabriele B, Gruppen H, Witkamp RF. Xanthohumol from hop (*Humulus lupulus* L.) is an efficient inhibitor of monocyte chemoattractant protein-1 and tumor necrosis factor-alpha release in LPS-stimulated RAW 264.7 mouse macrophages and U937 human monocytes. *J Agric Food Chem.* 2009; 57:7274–81. [PubMed: 19634869]
181. Dorn C, Weiss TS, Heilmann J, Hellerbrand C. Xanthohumol, a prenylated chalcone derived from hops, inhibits proliferation, migration and interleukin-8 expression of hepatocellular carcinoma cells. *Int J Oncol.* 2010; 36:435–41. [PubMed: 20043079]
182. Cho YC, You SK, Kim HJ, Cho CW, Lee IS, Kang BY. Xanthohumol inhibits IL-12 production and reduces chronic allergic contact dermatitis. *Int Immunopharmacol.* 2010; 10:556–61. [PubMed: 20144742]
183. Okuyama T, Takata M, Takayasu J, Hasegawa T, Tokuda H, Nishino A, et al. Anti-tumor-promotion by principles obtained from *Angelica keiskei*. *Planta Med.* 1991; 57:242–6. [PubMed: 1896522]

184. Akihisa T, Tokuda H, Hasegawa D, Ukiya M, Kimura Y, Enjo F, et al. Chalcones and other compounds from the exudates of *Angelica keiskei* and their cancer chemopreventive effects. *J Nat Prod.* 2006; 69:38–42. [PubMed: 16441065]
185. Tang Y, Simoneau AR, Xie J, Shahandeh B, Zi X. Effects of the kava chalcone flavokawain A differ in bladder cancer cells with wild-type versus mutant p53. *Cancer Prev Res (Phila).* 2008; 1:439–51. [PubMed: 19138991]
186. Yang EB, Zhang K, Cheng LY, Mack P. Butein, a specific protein tyrosine kinase inhibitor. *Biochem Biophys Res Commun.* 1998; 245:435–8. [PubMed: 9571170]
187. Jung JI, Lim SS, Choi HJ, Cho HJ, Shin HK, Kim EJ, et al. Isoliquiritigenin induces apoptosis by depolarizing mitochondrial membranes in prostate cancer cells. *J Nutr Biochem.* 2006; 17:689–96. [PubMed: 16517140]
188. Kim DC, Ramachandran S, Baek SH, Kwon SH, Kwon KY, Cha SD, et al. Induction of growth inhibition and apoptosis in human uterine leiomyoma cells by isoliquiritigenin. *Reprod Sci.* 2008; 15:552–8. [PubMed: 18487228]
189. Yoshida T, Horinaka M, Takara M, Tsuchihashi M, Mukai N, Wakada M, et al. Combination of isoliquiritigenin and tumor necrosis factor-related apoptosis-inducing ligand induces apoptosis in colon cancer HT29 cells. *Environ Health Prev Med.* 2008; 13:281–7. [PubMed: 19568915]
190. Ji DB, Zhang LY, Li CL, Ye J, Zhu HB. Effect of Hydroxysafflor yellow A on human umbilical vein endothelial cells under hypoxia. *Vascul Pharmacol.* 2009; 50:137–45. [PubMed: 19084079]
191. Jarvill-Taylor KJ, Anderson RA, Graves DJ. A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. *J Am Coll Nutr.* 2001; 20:327–36. [PubMed: 11506060]
192. Noren NK, Liu BP, Burridge K, Kreft B. p120 catenin regulates the actin cytoskeleton via Rho family GTPases. *J Cell Biol.* 2000; 150:567–80. [PubMed: 10931868]
193. Sahai E, Marshall CJ. RHO-GTPases and cancer. *Nat Rev Cancer.* 2002; 2:133–42. [PubMed: 12635176]
194. Noujaim D, van Golen CM, van Golen KL, Grauman A, Feldman EL. N-Myc and Bcl-2 coexpression induces MMP-2 secretion and activation in human neuroblastoma cells. *Oncogene.* 2002; 21:4549–57. [PubMed: 12085233]
195. Van den Steen PE, Dubois B, Nelissen I, Rudd PM, Dwek RA, Opdenakker G. Biochemistry and molecular biology of gelatinase B or matrix metalloproteinase-9 (MMP-9). *Crit Rev Biochem Mol Biol.* 2002; 37:375–536. [PubMed: 12540195]
196. Giannelli G, Falk-Marzillier J, Schiraldi O, Stetler-Stevenson WG, Quaranta V. Induction of cell migration by matrix metalloproteinase-2 cleavage of laminin-5. *Science.* 1997; 277:225–8. [PubMed: 9211848]
197. Hips DS, Hembry RM, Docherty AJ, Reynolds JJ, Murphy G. Purification and characterization of human 72-kDa gelatinase (type IV collagenase). Use of immunolocalisation to demonstrate the non-coordinate regulation of the 72-kDa and 95-kDa gelatinases by human fibroblasts. *Biol Chem Hoppe Seyler.* 1991; 372:287–96. [PubMed: 1647782]
198. Vartio T, Vaheri A. A gelatin-binding 70,000-dalton glycoprotein synthesized distinctly from fibronectin by normal and malignant adherent cells. *J Biol Chem.* 1981; 256:13085–90. [PubMed: 7309753]
199. Murphy G, Bretz U, Baggiolini M, Reynolds JJ. The latent collagenase and gelatinase of human polymorphonuclear neutrophil leucocytes. *Biochem J.* 1980; 192:517–25. [PubMed: 6263256]
200. Sopata I, Wize J. A latent gelatin specific proteinase of human leucocytes and its activation. *Biochim Biophys Acta.* 1979; 571:305–12. [PubMed: 508769]
201. Rosette C, Roth RB, Oeth P, Braun A, Kammerer S, Ekblom J, et al. Role of ICAM1 in invasion of human breast cancer cells. *Carcinogenesis.* 2005; 26:943–50. [PubMed: 15774488]
202. McMahon G. VEGF receptor signaling in tumor angiogenesis. *Oncologist.* 2000; 5 1:3–10. [PubMed: 10804084]
203. Bertl E, Becker H, Eicher T, Herhaus C, Kapadia G, Bartsch H, et al. Inhibition of endothelial cell functions by novel potential cancer chemopreventive agents. *Biochem Biophys Res Commun.* 2004; 325:287–95. [PubMed: 15522231]

204. Lee YS, Lim SS, Shin KH, Kim YS, Ohuchi K, Jung SH. Anti-angiogenic and anti-tumor activities of 2'-hydroxy-4'-methoxychalcone. *Biol Pharm Bull.* 2006; 29:1028–31. [PubMed: 16651739]
205. Foresti R, Hoque M, Monti D, Green CJ, Motterlini R. Differential activation of heme oxygenase-1 by chalcones and rosolic acid in endothelial cells. *J Pharmacol Exp Ther.* 2005; 312:686–93. [PubMed: 15537827]
206. Shibata T, Yamada T, Ishii T, Kumazawa S, Nakamura H, Masutani H, et al. Thioredoxin as a molecular target of cyclopentenone prostaglandins. *J Biol Chem.* 2003; 278:26046–54. [PubMed: 12709421]
207. Fenwick GR, Lutomski J, Nieman C. Liquorice, *Glycyrrhiza glabra* L.: composition, uses and analysis. *Food Chemistry.* 1990; 38:119–43.
208. Wegener JW, Nawrath H. Cardiac effects of isoliquiritigenin. *Eur J Pharmacol.* 1997; 326:37–44. [PubMed: 9178653]
209. Kang DG, Lee AS, Mun YJ, Woo WH, Kim YC, Sohn EJ, et al. Butein ameliorates renal concentrating ability in cisplatin-induced acute renal failure in rats. *Biol Pharm Bull.* 2004; 27:366–70. [PubMed: 14993804]
210. Isomoto H, Furusu H, Ohnita K, Wen CY, Inoue K, Kohno S. Sofalcone, a mucoprotective agent, increases the cure rate of *Helicobacter pylori* infection when combined with rabeprazole, amoxicillin and clarithromycin. *World J Gastroenterol.* 2005; 11:1629–33. [PubMed: 15786539]
211. Opletalova V, Jahodar L, Jun D, Opletal L. Chalcones (1,3-diarylpropen-1-ones) and their analogs as potential therapeutic agents in cardiovascular system diseases. *Ceska Slov Farm.* 2003; 52:12–9. [PubMed: 12685329]

Figure 1.
Chalcones, their sources and common name.

Figure 2.
Biosynthesis of chalcone.

Figure 3.
Chemical structures of different types of chalcones that inhibit NF-κB.

Figure 4. Chemical structures of different types of chalcones having anticancer activity with difference mode of action.

Table 1
Source and Chemistry of Natural Chalcones

Natural Source	Active compound	Reference
Antioxidant activity		
Alpinia rafflesiana	Flavokawin B	[26]
Alpinia rafflesiana	2',3'4',6'-Tetrahydroxychalcone	[26]
Artocarpus nobilis	3-Hydroxyxanthoangelol	[27]
Dalbergia odorifera	2'-O-Methylisoliquiritigenin	[28]
Angelica keiskei	Xanthoangelol H	[29]
	Xanthoangelol	[30]
	Xanthoangelol B	[31]
	xanthokeismins A,B,C	[31]
Humulus lupulus	Xanthohumol	[32]
Glycyrrhiza uralensis	Isoliquiritigenin	[33]
Nymphaea caerulea	Isosalipurposide	[34]
Anti-inflammatory and Anticancer activity		
Angelica keiskei	4-Hydroxyderricin	[35]
Plants metabolite	Chalcone	[36]
Piper methysticum	Flavokawin A,B	[37]
Humulus lupulus	Xanthohumol	[38]
Angelica keiskei	Xanthoangelol	[30]
Angelica keiskei	Xanthoangelol H	[29]
Syzygium samarangense	2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone	[39]
Alpinia rafflesiana	Cardamonin	[40]
Semecarpus anacardium	Butein	[41]
Dalbergia odorifera	2'-O-Methylisoliquiritigenin	[28]
Angelica keiskei	Isobavachalcone	[29]
Dalbergia ecastophyllum	2',4'-Dihydroxychalcone	[42]
Glycyrrhiza uralensis	Isoliquiritigenin	[33]
Helychrysium maracandicum	Isosalipurposide	[43]
Helichrysium maracandicum	Naringenin chalcone	[43]
Antidiabetic activity		
Humulus lupulus	Xanthohumol	[44]
Angelica keiskei	4-Hydroxyderricin	[45]
Rhus verniciflua	Butein	[46]
Boehmeria rugulosa	chalcone-6'-hydroxy-2',3,4-trimethoxy-4'-O-beta-D-glucopyranoside	[47]

Table 2
List of NF- κ B inhibitory chalcones

Chalcone	Source	Reference
2',5'-dihydroxy-4-chloro-dihydrochalcone	synthetic	[100]
Broussonchalcone A	Broussonetia papyrifera	[99]
3,4,5-trimethoxy-4'-fluorochalcone	synthetic	[101]
3',4',5',3,4,5-hexamethoxy-chalcone	synthetic	[102]
Xanthoangelol D	Angelica keiskei	[103]
4-Hydroxylonchocarpin	Psoralea corylifolia	[104]
Flavokawain A, B	Piper methysticum	[37]
2'-hydroxychalcone	synthetic	[105]
Cardamomin	Alpinia conchigera	[106]
Isoliquiritigenin	Glycyrrhiza uralensis	[107]
1,3-diphenyl-2-propenone (chalcone)	Plant Metabolite	[108]
2'-hydroxy-3-bromo-6'-methoxychalcone	synthetic	[109]
2'-methoxy-3,4-dichlorochalcone	synthetic	[109]
Butein	Semecarpus anacardium	[41]
Cardamonin	Alpinia rafflesiana	[40]
Hydroxysafflor yellow A	Carthamus tinctorius	[110]
Licochalcone A	Glycyrrhiza inflata Beta	[111]
2',4',6'-tris(methoxymethoxy) chalcone	synthetic	[112]
3-hydroxy-4,3',4',5'-tetramethoxychalcone	synthetic	[113]
Xanthohumol	Humulus lupulus	[98]
Isoliquiritigenin 2'-methyl ether	Caesalpinia sappan	[114]

Table 3
Molecular targets of Known Synthetic and Natural Chalcones for anticancer and anti-inflammatory activities

Chalcones	Targets	References
2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone	NF-κB, KDR tyrosine kinase, Bim, Bcl-2, caspase-3, erbB-2 receptor, PARP, TNF-α, IL-6, IL-1β, iNOS	[120,121], [104,122]
4-Hydroxylonchocarpin	NF-κB, MMP-2, iNOS	[123]
Broussouchalcone A	NF-κB, iNOS, PKC, NADPH oxidase	[41,99]
Butein	NF-κB IAP2, Bcl-2, Bcl-xL, cyclin D1, c-Myc, COX-2 MMP-9, DR5, STAT3, ICAM-1, Bax, caspase-3, EGFR TIMP-1, E-selectin, iNOS, JNK, IL-8, MMP-7, Mcl-1, hTERT, ATM, Chk1/2, cdc25C, Cdc2, Sp-1, VEGF, CXCR4	[124-137], [112]
Cardamomin	NF-κB, TNF-α, COX-2, Akt, DR4/5, Bcl-xL, CHOP	[106,138]
Cardamonin	NF-κB, COX-1/2, TNF-α, iNOS, mTOR, P70S6K, 4E-BP1	[40,114]
Flavokawain A	NF-κB, Bax, Bcl-xL, XIAP, survivin, p27, p27, CDK1/2, Myt1, Wee1, cyclin B1, cdc25C	[139-141]
Flavokawain B	NF-κB, DR5, Bim, Puma, survivin, GADD153, PARP, Bid, caspase-8, Bak, cytochrome C, Bcl-2, iNOS, COX-2, TNF-α, caspase-3/9, Bax, XIAP	[139-143]
Hydroxysafflor yellow A	NF-κB, TNF-α, ICAM-1, IL-1β, IL-6, IL-10, VEGF, p53, Bcl-2/Bax ratio, HIF-1α, VHL, ET-1, iNOS	[110,144-146]
Isobavachalcone	caspases -3/9, Bax, Akt	[29,147]
Isoliquiritigenin	LOX-5/12, caspase-3/8/9, p53, p21, Fas/APO-1 receptor, FasL, Bax, NOXA, NF-κB, Bcl-xL, cIAP-1/2, COX-2, iNOS, cytochrome C, PARP, quinone reductase, GADD153	[36,112,114,127,148-162],
	ICAM-1, VCAM-1, Bcl-2, MMP-2, ATM, Chk2, topoisomerase II, HO-1, IL-1β, TNF-α, cyclin B1/D1/E, CDK4, p27, cdc25c, IRF3, IP-10, RANTES, Nrf2, mTOR, VEGF, TLR4, uPA, MMP-9, TIMP-1	
Kanzonol C	MMP-2	[123]
Licochalcone A	NF-κB, COX-1/2, Bax, Bcl-2, STAT3, CD31, Ki-67, VEGFR2, iNOS, CCL2/MCP-1, CXCL1/KC, mTOR, TNFα, topoisomerase-1, cyclin B1/D1/E, Rb, cdc2, CDK4/6	[111,162-169]
Naringenin chalcone	IL-2, IL-4, IL-5, IL-13, INF-γ, TNF-α, MCP-1, p38 MAPK	[43,170,171]
Xanthoangelol	NF-κB, caspases -3/9, VEGF, thromboxane B2, ET-1	[35,103,172,173]
Xanthohumol	NF-κB, Bax, p53, Akt, survivin, Bcl-xL, XIAP, cIAP1/2 cyclin D1, c-myc, VEGF, PARP, caspase-3/7/8/9, Bcl-2 Keap1, E-cadherin, TLR4, MD2, STAT1α, IRF-1, IL-1β p21, p53, Bcr-Abl, IL-2, IFN-γ, MCP-1, GRP78, Hsp70, PERK, ATF6, CHOP, Mcl-1, XBP-1, IL-8, IL-12	[98,115,174-182]

4E-BP1, 4E-binding protein; ATF6, activating transcription factor 6; ATM, ataxia-telangiectasia-mutated; Bak, BCL2-antagonist; Bax, BCL2-associated X protein; Bcl-2, B-cell CLL/lymphoma 2; Bid, BH3 interacting domain death agonist; Bim, Bcl-2-interacting mediator of cell death; CCL2, Chemokine (C-C motif) ligand 2; cdc25C, cell division cycle 25 homolog C; CDK, cyclin-dependent kinase; Chk, checkpoint homolog; CHOP, CAAT/enhancer-binding protein homologous protein (also known as GADD153); COX, cyclooxygenase; CXCL1/KC, chemokine ligand 1; CXCR4, C-X-C chemokine receptor type 4; DR, death receptor; EGFR, epidermal growth factor receptor; ET-1, endothelin 1; FasL, Fas ligand; GADD153, growth arrest and DNA-damage-inducible protein 153; GRP78, glucose-regulated protein 78; HIF-1α, hypoxia inducible factor 1α; HO-1, heme oxygenase-1; Hsp70, heat shock protein 70; hTERT, human telomerase reverse transcriptase; IAP, inhibitor of apoptosis proteins; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon gamma; IL, interleukin; iNOS, inducible nitric oxide synthase; IP-10, IFNγ-induced protein 10; IRF, interferon regulatory factor; JNK, c-Jun N-terminal kinases; KDR, kinase insert domain; LOX, lipooxygenase; Mcl-1, myeloid cell leukemia-1; MCP-1, monocyte chemoattractant protein-1; MD2, lymphocyte antigen 96; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; Myt1, myelin transcription factor 1; NADPH oxidase, nicotinamide adenine dinucleotide phosphate-oxidase; NF-κB, nuclear factor-kappaB; Nrf2, NF-E2-related factor 2; p38 MAPK, p38 mitogen-activated protein kinase; p70S6K, p70-ribosomal S6 kinase; PARP, poly (ADP-ribose) polymerase; PERK, double-stranded RNA-activated protein kinase (PKR)-like ER kinase; PKC, protein kinase C; Puma, p53-upregulated modulator of apoptosis; RANTES, regulated upon activation, normal T cell expressed and secreted; Rb, retinoblastoma protein; Sp-1, specificity protein-1; STAT, signal transducer and activator of transcription; TIMP-1, tissue inhibitor of metalloproteinase 1; TLR4, toll-like receptor 4; TNF-

α , tumor necrosis factor- α ; uPA, urokinase type of plasminogen activator; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; VHL, Von Hippel-Lindau; XBP-1, X-box binding protein-1; XIAP, X-linked IAP

Table 4
Structure Activity Relationship Play Active Role in Anti-inflammation and Anti-cancer Activity of Chalcones

Activity	R'1	R'2	R'3	R'4	R'5	R1	R2	R3	R4	R5	Dose (µM)
1,3-diphenyl-2-propenone (Chalcone)											50
isoliquiritigenin 2'-methyl ether	OH		OH		OCH ₃			OH			25
3-hydroxy-4,3',4',5'-tetramethoxychalcone		OCH ₃	OCH ₃	OCH ₃			OH	OCH ₃			5
xanthohumol	OCH ₃		OH	X ₁	OH			OH			50
Hydroxysafflor yellow A	OH	OH+X ₂	OH	X ₂	=O			OH			?
Licochalcone A			OH			OCH ₃		OH	X ₃		5
Isoliquiritigenin	OH		OH					OH			40
2'-hydroxy-3-bromo-6'-methoxychalcone	OH				OCH ₃				Br		8
2'-methoxy-3,4-dichlorochalcone	OH				OCH ₃		Cl	Cl			20
butein	OH		OH					OH	OH		50
Cardamonin	OH		OH		OCH ₃						50
Flavokawain A	OH		OCH ₃		OCH ₃						15
Flavokawain B	OH		OCH ₃		OCH ₃			OCH ₃			15
2',4',6'-tris(methoxymethoxy) chalcone	X ₄		X ₄		X ₄						20
2'-hydroxychalcone	OH										15
cardanomin	OCH ₃		OH		OH						30
Xanthoangelol D		OH	X ₅								50
4-Hydroxylonchocarpin	X ₆										20
3',4',5',3,4,5-hexamethoxy-chalcone		OCH ₃	OCH ₃	OCH ₃			OCH ₃	OCH ₃	OCH ₃	OCH ₃	30

Activity	R'1	R'2	R'3	R'4	R'5	R1	R2	R3	R4	R5	Dose (µM)
3,4,5-trimethoxy-4'-fluorochalcone			F				OCH ₃	OCH ₃	OCH ₃		10
2',5'-dihydroxy-4-chloro-dihydrochalcone	OH			OH				Cl			50
Broussonchalcone A	OH		OH	X ₆			OH	OH			20
Synthetic-1		OCH ₃	OCH ₃				OH	OCH ₃			8
Synthetic-2		OCH ₃		OCH ₃			OH	OCH ₃			8
Synthetic-3		OCH ₃	OCH ₃	OCH ₃			OH				2.3
Synthetic-4		OCH ₃	OCH ₃	OCH ₃			OH	OH			1.9
Synthetic-5		OCH ₃	OCH ₃	OCH ₃			X ₇	OCH ₃			9
Synthetic-6		OCH ₃	OCH ₃	OCH ₃			X ₈	OCH ₃			6
Synthetic-7		OCH ₃	OCH ₃	OCH ₃							9

X₁ = -CH₂-CH₂-(CH₃)₂; X₂ = -2,4-di-beta-D-glucopyranosyl; X₃ = -C(CH₃)-CH=CH₂; X₄ = -CH-O-CH-O-CH; X₅ = CH-CH(OH)-C(C=O)(CH₂); X₆=R₂ , =CH-C(CH₃)₂-O . R₃; X₆=CH₂-CH=C(CH₃)₂; X₇=-O(CH₂)₂OH; X₈=-O(CH₂)₂NH₂