

CHALCONES: THE PROMISING COMPOUNDS TO PROVIDE NEW WAYS FOR CANCER TREATMENT

Retno Arianingrum

*Department of Chemistry Education, Faculty of Mathematics and Natural Science,
Yogyakarta State University*

Abstract

Chalcones (1,3-diphenylpropen-1-ones), a biosynthetic product of the shikimate pathway, belonging to flavanoid family are precursors of open chain flavonoids and isoflavonoids, which are abundant in edible plants. They have a wide variety of cytoprotective and modulatory functions, which may have therapeutic potential for multiple diseases, especially as antitumor drugs. Several natural and synthetic chalcones and their derivatives appear as promising anticancer activities. Their chemical structure evaluation will be critical to assess their therapeutic utility. Those for which the mechanism of action is well defined can serve as lead compounds for the design of new, more promising molecules. The present review highlights the recently natural synthesized chalcones and their derivatives possessing important pharmacological activities as anticancer and how the mechanism pathways of these compounds in inhibiting cancer cells.

Key words: chalcones; cancer treatment.

INTRODUCTION

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is caused by both external factors (tobacco, infectious organisms, chemicals, and radiation) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism). These causal factors may act together or in sequence to initiate or promote the development of cancer. Cancer is treated with surgery, radiation, chemotherapy, hormone therapy, biological therapy, and targeted therapy (American Cancer Society, 2012).

In the United States and many other parts of the world, cancer is a serious public health issue. 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 (Jemal et al., 2010). According to the data base of health research (Riskesdes, Health Department of Republic of Indonesia), the prevalence of tumors in Indonesia was 4.3 per 1000 population (Depkes RI, 2007). 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 . So it is the time to better understand the prognosis, diagnosis and treatment of cancer .

Chalcones (α,β -unsaturated ketones) are promising candidates in the new era of medicines on account of their wide spectrum of antitumor, antibacterial and anti-inflammatory activities (Sasayama et al., 2007; Ye et al. 2004; Ye et al., 2005; Lee et al., 2006; Haraguchi et al., 1998; Hsieh et al., 1998; Flechtner et al., 1979; Chang et al., 2007; Rauf et al., 2005; and Pandey et al., 2007). However, the mechanisms of actions of this class of compounds are not yet fully understood, especially in anticancer. The purpose of this review is to provide an overview

of the anticancer activity of naturally occurring and synthetic chalcones. This review highlights more recent pharmacological screening of these compounds, their mechanisms of action and relevant structure-activity relationships.

DISCUSSION

1. Structure and Synthesis of Chalcones

Chalcones, one of the major classes of natural products with widespread distribution in spices, tea, beer, fruits and vegetables, have been recently subject of great interest for their pharmacological activities (Dicarlo et al., 1999). Chalcones are precursor compounds for flavonoid synthesis in plants. Naturally occurring chalcones are found mostly in their hydroxylated forms, and have been reported to possess antiinflammatory, antimicrobial, antioxidant and anticancer properties (Echeverria et al., 2009; Nowakowska et al., 2007; Miranda et al., 1999; Shah et al., 2008; Boumendjel et al., 2009; Katsori et al., 2009; Dimmock et al., 1999 and Go et al., 2005).

Chalcones have crystal structure. They are α,β -unsaturated ketones consisting of two aromatic rings (ring A and B) having diverse array of substituents (figure 1). Rings are interconnected by a highly electrophilic three carbon α,β -unsaturated carbonyl system that assumes linear or nearly planar structure. They contain the ketoethylenic group ($-\text{CO}-\text{CH}=\text{CH}$). Chalcones possess conjugated double bonds and a completely delocalized π -electron system on both benzene rings (Rahman, 2011).

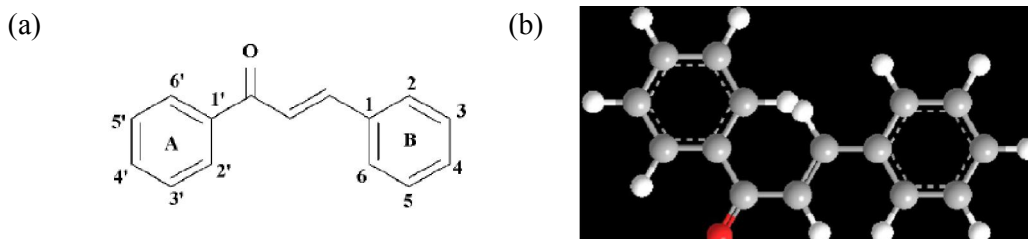


Figure 1. (a) Structure of chalcone, (b) The energy minimized 3D structure of chalcone

Chalcones can be readily synthesized in laboratory by the Claisen-Schmidt reaction which is very easy and simple to conduct as well as inexpensive. 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 (Arty, 2010).

2. The Potential of Chalcones in Cancer Treatment

a. Inhibition of activation NF- κ B by chalcone

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, apoptosis, cell cycle and metastasis. Incorrect regulation of NF- κ B may cause inflammatory and autoimmune diseases, viral infection and cancer (Yadav et al., 2011 and Pahl, 1999).

In tumor cells, NF- κ B is active either due to mutations in genes encoding the NF- κ B transcription factors themselves or in genes that control NF- κ B activity (such as I κ B genes); in addition, some tumor cells secrete factors that cause NF- κ B to become active. Blocking NF- κ B can cause tumor cells to stop proliferating, to die, or to become more sensitive to the action of anti-tumor agents. Thus, NF- κ B is the subject of much active research among pharmaceutical companies as a target for anti-cancer therapy (Escárcega et al., 2007).

NF- κ B 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 (Bauerle et al., 1988). The classic form of NF- κ B is a heterodimer p50 and p65 subunits. 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 (Finco et al., 1995). 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 (figure 2).

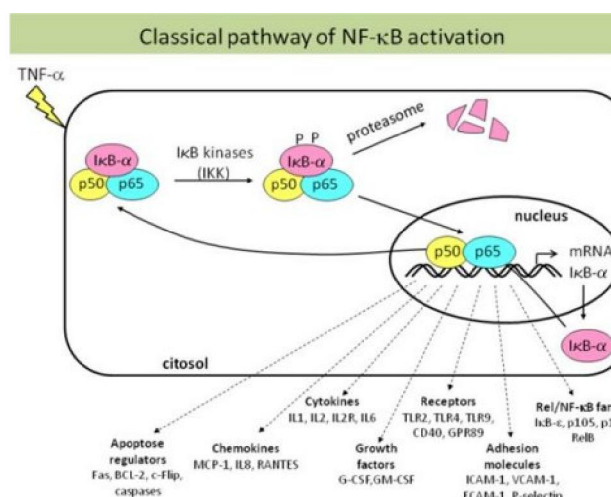


Figure 2. The classical pathway of NF- κ B activation (<http://redox.fc.ul.pt/research.html>.)

NF- κ B is often excessively activated in human solid tumor dan leukumias. Activation NF- κ B in cancer cell may enhance cancer progression through the activation of cancer cell growth, apoptotic resistance, and increased metastatic activity. To treat or prevent diseases such as cancer that have an etiology based in inflammation, the agents that inhibit the inflammation and have no side effects be required. Among the candidates is chalcone, which is known as a potent anti-inflammatory agent.

Chalcone and some derivate chalcones have been known to inhibit the activation of NF- κ B such as 2',5'-dihydroxy-4-chloro-dihydrochalcone; Brousochalcone A; 3,4,5-trimethoxy-4'-fluorochalcone; 3',4',5',3,4,5-hexamethoxy-chalcone; Xanthoangelol D; 4-Hydroxylonchocarpin; Flavokawain A, B; 2'-hydroxychalcone; Cardamomin; Isoliquiritigenin; 1,3-diphenyl-2-propenone (chalcone); 2'-hydroxy-3-bromo-6'-methoxychalcone; 2'-methoxy-3,4-dichlorochalcone; Butein; Cardamonin; Hydroxysafflor yellow A; Licochalcone A; 2',4',6'-tris(methoxymethoxy) chalcone; 3-hydroxy-4,3',4',5'-tetramethoxychalcone; Xanthohumol; and Isoliquiritigenin 2'-methyl ether (Yadav et al., 2011) through several mechanisms. 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 (Folmer et al., 2006). Butein (3,4,2',4'-tetrahydroxychalcone), natural compound obtained from stem-bark of cashews (*Semecarpus anacardium*), 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 (Pandey et al., 2007).

b. Chalcones arrests cell cycle progression and induces apoptosis

Both normal cells and cancer cells have growth through a cell cycle. Regulation of cell cycle determines process of cell growth. In cancer cells occurs abnormal regulation of the cell cycle. Cell Cycle consists of proliferative phase, in the resting state (no cells divides, Go), and not permanently divide. Cells that are dividing divided into 4 (four) major phases: the gap phase 1 (G1), synthesis phase (S), gap phase 2 (G2), and mitosis phase (M) (Foster et al., 2001 and Vermeulen et al., 2003). In normal cell, the cell cycle dependent on growth signals from the environment. If the signal is not sufficient growth, the cells are in the G1 phase of the cell cycle exit can enter the Go phase (Van den Heuvel, 2005).

G1 phase is the phase when the cells prepare for DNA replication that will occur in the S phase, when DNA synthesis is complete the cell then enters the G2 phase, in this phase the cells prepare for cell division, when the cell is ready to enter the mitotic phase (M). Cells that are in the G1 phase may decide to enter into S phase or enter the Go phase. Go phase is the phase for on-proliferating cells (Lodish et al., 2000 and Vermeulen et al., 2003). The move from one phase to the next phase of the cell cycle is regulated by three main groups, namely cyclin proteins (cyclin D, cyclin E, cyclin A, and cyclin B), cyclin dependent kinases (CDKs, especially CDK4, CDK6, and CDK2), and cyclin dependent kinase inhibitors (CKIs) (King, 2000).

Disturbance in the cell cycle regulator will cause disruption of the program of cell cycle. In cancer cells, the cell cycle cannot be regulated so that cells become divided continually. Therefore, the development of research on cancer, cell cycle regulators is the potential for targeted anticancer drugs.

Cancer cells are also able to avoid apoptosis mechanism. Apoptosis is cell death program that occurs as a result of the induction of the cell itself. Apoptosis can occur due to intrinsic factors when cells undergo irreversible damage DNA. Triggers apoptosis caused by extrinsic factors involving the role of tumor necrosis factor receptor, called the death receptors, viz. TNF - 2 receptor CD95 (Fas/APO-1), and TRAIL receptor (Lodish et al ., 2000). Proteins that play a role in the regulation of apoptosis are p53, Bcl-2 family proteins, Apaf, Caspase inhibitors pro apoptosis protein (as well as receptors that respond to death signals). Cells undergoing apoptosis has several characteristics, among others, increased expression pro apoptosis proteins (Bax , Bid and Bak) and suppression antiapoptosis protein expression (Bcl - 2 and Bcl - xL), increased levels of cytosolic cytochrome C, caspase activation, PARP1 activation, DNA fragmentation, and cell membrane damage. Accumulation of these characteristics led to the emergence of a variety of apoptotic bodies that result from cell fragmentation (Gerl and Vaux, 2005) .

Chalcone have been found to act through the intrinsic as well as extrinsic apoptosis pathway to prevent tumor progression. Basic structure of chalcone (1,3-diphenyl-1-2-propenone) has proven to have a chemopreventive effect in human breast cancer cell lines: MCF-7 and MDA-MB-231 (Hsu et al. 2006) and human bladder cancer cell lines: T24 and HT-1376 (Shen et al. 2007). The research showed that chalcone inhibits the proliferation of T24 and HT-1376 cells by inducing apoptosis and blocking cell cycle progression in the G2/M phase. Chalcone significantly increases the expression of p21 and p27 proteins, and decreases the levels of cyclin B1, cyclin A and Cdc2, thereby contributing to cell cycle arrest. In addition, chalcone increased the expression of Bax and Bak, but decreased the levels of Bcl-2 and Bcl-XL and subsequently triggered mitochondrial apoptotic pathway (release of cytochrome c and activation of caspase-9 and caspase-3). The induction of mitochondrial pathway and inhibition of the nuclear factor kappa B survival system may play important roles in the antiproliferative activity of chalcone in T24 and HT-1376 cells.

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,

cardamomin, licochalcone A, and butin (Table 1). These triterpenoids have a common target, Bcl-2 protein, which can induce apoptosis in cancer cells.

Table 1. Molecular targets of known synthetic and natural chalcones for anticancer and anti-inflammatory activities chalcones

Chalcone	Targets
2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone	NF- κ B, KDR tyrosine kinase, Bim, Bcl-2, caspase-3, erbB-2 receptor, PARP, TNF- α , IL-6, IL-1 β , iNOS
4-Hydroxyonchocarpin	NF- κ B, MMP-2, iNOS
Brousochalcone A	NF- κ B, iNOS, PKC, NADPH oxidase
Butein	NF- κ B 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
Cardamomin	NF- κ B, TNF- α , COX-2, Akt, DR4/5, Bcl-xL, CHOP
Cardamomin	NF- κ B, COX-1/2, TNF- α , iNOS, mTOR, P70S6K, 4E-BP1
Flavokawain A	NF- κ B, Bax, Bcl-xL, XIAP, survivin, p27, p27, CDK1/2, Myt1, Wee1, cyclin B1, cdc25C
Flavokawain B	NF- κ B, DR5, Bim, Puma, survivin, GADD153, PARP, Bid, caspase-8, Bak, cytochrome C, Bcl-2, iNOS, COX-2, TNF- α , caspase-3/9, Bax, XIAP
Hydroxysafflor yellow A	NF- κ B, TNF- α , ICAM-1, IL-1 β , IL-6, IL-10, VEGF, p53, Bcl-2/ Bax ratio, HIF-1 α , VHL, ET-1, iNOS
Isobavachalcone	caspases -3/9, Bax, A
Isoliquiritigenin	LOX-5/12, caspase-3/8/9, p53, p21, Fas/APO-1 receptor, FasL, Bax, NOXA, NF- κ B, Bcl-xL, cIAP-1/2, COX-2, iNOS, cytochrome C, PARP, quinone reductase, GADD153 ICAM-1, VCAM-1, Bcl-2, MMP-2, ATM, Chk2, topoisomerase II, HO-1, IL-1 β , 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
Licochalcone A	NF- κ B, COX-1/2, Bax, Bcl-2, STAT3, CD31, Ki-67, VEGFR2, iNOS, CCL2/MCP-1, CXCL1/KC, mTOR, TNF α , topoisomerase-1, cyclin B1/D1/E, Rb, cdc2, CDK4/6
Naringenin chalcone	IL-2, IL-4, IL-5, IL-13, INF- γ , TNF- α , MCP-1, p38 MAPK
Xanthoangelol	NF- κ B, caspases -3/9, VEGF, thromboxane B2, ET-1
Xanthohumol	NF- κ B, 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, STAT1 α , IRF-1, IL-1 β , p21, p53, Bcr- Abl, IL-2, IFN- γ , MCP-1, GRP78, Hsp70, PERK, ATF6, CHOP, Mcl-1, XBP-1, IL-8, IL-12

Chalcones influence invasion, metastasis and angiogenesis

Tumor progression is a complex and multifaceted process that involves initiation, growth, invasion, and metastasis. Tumors would not grow beyond the limits of diffusion without stimulating a vascular system for the delivery of nutrients. Key stimulators and inhibitors of angiogenesis along with the tumor microenvironment regulate tumor growth. The relative concentrations of these stimulators and inhibitors determine endothelial cell phenotype, with the change from a quiescent to angiogenic phenotype referred to as the “angiogenic switch.” The tumor vasculature also provides tumor cells with a pathway through which to enter the circulation and metastasize.

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 (Noren et al., 2000 and Sahai et al., 2002). 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 (Noujaim et al., 2002).

Vascular endothelial growth factor (VEGF) plays a unique role in physiological and pathological angiogenesis. VEGF promotes endothelial cell proliferation and migration, increases vascular permeability and inhibits apoptosis of endothelial cells lining newly formed vessels. There are numerous splice isoforms of VEGF that bind with varying degrees of affinity to VEGF receptors (VEGFR) on the surface of endothelial cells. Most of the angiogenic effects attributed to VEGF are a result of activation of VEGFR-2, which signals through the phosphatidylinositol 3 kinase (PI3K)/Akt pathway (Zachary, 2003).

A few chalcones derived from natural sources have been shown to inhibit tumor cell invasion and metastasis by targeting one or more molecules (Table 1). Butein induces down-regulation of MMP-9 gene in human leukemia cells *in vitro* (Pandey et al., 2007). The 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 (Ngameni et al., 2006).

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 (McMahon, 2000). 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. 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.

Recently, the molecular docking study of chalcone derivative i.e. 3 - (4'-hydroxy-3'-methoxyphenyl)-1-phenyl-2-propene-1-one showed that the binding energy of this compound with VEGFR (2P2I) almost had the same energy binding compared with ATP binding on VEGFR. Docking results between these compounds with the target protein VEGFR tyrosine kinase receptor showed the similarity of amino acids involved in their interaction (figure 3). It is expected this compound has potential as a cancer chemopreventive agent especially as anti angiogenesis (Arianingrum et al., 2013).

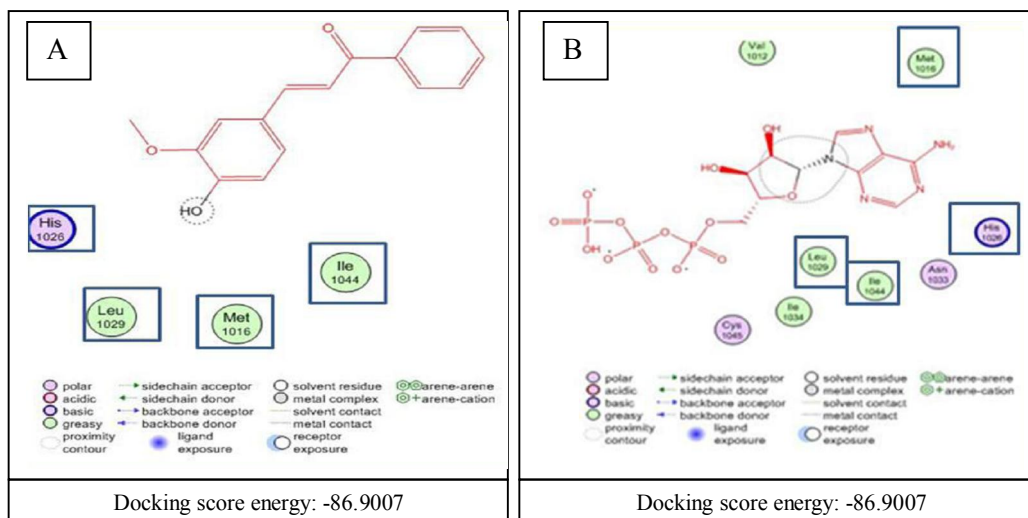


Figure 4. Interaction of 3 - (4'-hydroxy-3'-methoxyphenyl)-1-phenyl-2-propene-1-on (A) and ATP (B) with VEGFR (2P2I), showed the similarity of amino acid involved in their interaction (marked with boxes).

Structure Activity Relationship of Chalcones

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. The basic structure of chalcone (1,3-diphenyl-2-propenone) has NF- κ B inhibitory activity at the concentration of 50 μ M (Shen et al., 2007).

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, work best at higher concentrations (Israf et al., 2007); Pandey et al., 2007; Harikumar et al., 2009; Huang et al., 2001; Kumar et al., 2007). 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 (Folmer et al., 2006 and Kim et al., 2007).

Srinivasan et al (2009) 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. All the chalcones showed NF- κ B inhibition contained a highly electrophilic α,β -unsaturated carbonyl moiety. This α,β -unsaturated carbonyl moiety can act as an electrophile and react with free sulfhydryl groups of thioredoxin and cysteine residues in proteins. Foresti et al (2005) and Srinvisan et al (2009) indicated that electrophilic phytochemicals could give rise to thyl 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.

CONCLUSION AND SUGGESTION

From the above review, it can be said that chalcones and their derivatives display a wide range of anticancer activities in particular to their role in suppression of NF- κ B-mediated inflammation and cancer. 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 and synthetic chalcones may serve as lead compound for cancer drug development.

REFERENCES

- American Cancer Society. 2012. *Cancer Facts & Figures 2012*. Atlanta: American Cancer Society: 1-6.
- Arianingrum, R., Hermawan, A., Meiyanto, E., and Purnomo, H., 2013, Molecular Docking Studies and Anticancer Activity of Chalcone Derivate Compound MPHc on MCF-7 & Doxorubicin Resistant Cell. Proceeding in 44th World Chemistry Congress 11-16 August, 2013, Istanbul Turkey, 427.
- Arty, I.S., 2010, Synthesize and Cytotoxicity Test of Several Compounds of Mono Para Hydroxy Chalcone, *Indo. J. Chem.*, 10 (1), 110-115
- Baeuerle PA, Baltimore D. 1988. Activation of DNA-binding activity in an apparently cytoplasmic precursor of the NF-kappa B transcription factor. *Cell.*: 53:211-7.
- Boumendjel, A.; Ronot, X.; Boutonnat, J. 2009. Chalcones derivatives acting cell cycle blockers: Potential anticancer drugs? *Curr. Drug Targets*, 10, 363-371.
- Chang, H.J.; Yoon, G.; Park, J.S.; Kim, M.H.; Baek, M.K.; Kim, N.H.; Shin, B.A.; Ahn, B.W.; Cheon, S.H.; Jung, Y.D. 2007. Induction of apoptosis by the licochalcone E in endothelial cells via modulation of NF-B and Bcl-2 family. *Biological and Pharmaceutical Bulletin*, 30, 2290- 2293
- Departemen Kesehatan Republik Indonesia. 2007. Riset Kesehatan Dasar, Badan Penelitian dan Pengembangan (Balitbang), Jakarta.
- Dicarlo, G.; Mascolo, N.; Izzo, A.A.; Capasso, F. 1999. Flavonoids: Old and new aspects of class of natural therapeutic drugs. *Life Sci.*, 65, 337-353.
- Dimmock JR, Elias DW, Beazely MA, Kandepu NM 1999. Bio- activities of chalcones. *Curr Med Chem*;6:1125-49.
- Echeverria, C.; Santibanez, J.S.; Donoso-Taouda, O.; Escobar, C.A.; Ramirez-Tagle, R. 2009. Structural antitumoral activity relationships of synthetic chalcones. *Int. J. Mol. Sci.*, 10, 221-231.
- Escárcega RO, Fuentes-Alexandro S, García-Carrasco M, Gatica A, Zamora A .2007. The transcription factor nuclear factor- κ B and cancer. *Clinical Oncology (Royal College of Radiologists (Great Britain))* 19 (2): 154-61
- Flechtner, T.W. Carbohydrate triflates: reactions with bases. *Carbohydr. Res.* 1979, 77, 262-266.
10. Chang, H.J.; Yoon, G.; Park, J.S.; Kim, M.H.; Baek, M.K.; Kim, N.H.; Shin, B.A.; Ahn, B.W.; Cheon, S.H.; Jung, Y.D. Induction of apoptosis by the licochalcone E in endothelial cells via modulation of NF-B and Bcl-2 family. *Biological and Pharmaceutical Bulletin* 2007, 30, 2290- 2293.
- Finco TS, Baldwin AS.1995. Mechanistic aspects of NF-kappa B regulation: the emerging role of phosphorylation and proteolysis. *Immunity* : 3:263-72.
- Folmer F, Blasius R, Morceau F, Tabudravu J, Dicato M, Jaspars M, et al. 2006. Inhibition of TNF α induced activation of nuclear factor kappaB by kava (Piper methysticum) derivatives. *Biochem Pharmacol.* : 71:1206-18.
- Foresti R, Hoque M, Monti D, Green CJ, Motterlini R. 2005. Differential activation of heme oxygenase-1 by chalcones and rosolic acid in endothelial cells. *J Pharmacol Exp Ther.* :

- 312:686–93.
- Foster, J.S., Henley, D.C., Ahamed, S., and Wimalasena, J., 2001, Estrogen and Cell Cycle Regulation in Breast Cancer, *Trend Endocr. Metab.* 12(7):320-327
- Gerl, R., and Vaux, D.L., 2005, Apoptosis in The Development and Treatment of Cancer, *Carcin.*, 26 (2), 263-270.
- Go ML, Wu X, Liu XL. 2005.Chalcones: an update on cytotoxic and chemoprotective properties. *Curr Med Chem* :12:481–99.
- Haraguchi, H.; Ishikawa, H.; Mizutani, K.; Tamura, Y.; Kinoshita, T. 1998. Antioxidative and superoxide scavenging activities of retrochalcones in *Glycyrrhiza inflata*. *Bioorg. Med. Chem.* : 6, 339-347.
- Harikumar KB, Kunnumakkara AB, Ahn KS, Anand P, Krishnan S, Guha S, et al. 2009. 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.* : 113:2003–13.
- Hsieh, H.K.; Lee, T.H.; Wang, J.P.; Wang, J.J.; Lin, C.N. 1998. Synthesis and anti-inflammatory effect of chalcones and related compounds. *Pharm. Res.* : 15, 39-46.
- Hsu, Y L, P L Kuo, W S Tzeng, and C C Lin. 2006. Chalcone Inhibits the Proliferation of Human Breast Cancer Cell by Blocking Cell Cycle Progression and Inducing Apoptosis. *Food and chemical toxicology* □: an international journal published for the British Industrial Biological Research Association 44(5): 704–13.
- Huang YC, Guh JH, Cheng ZJ, Chang YL, Hwang TL, Lin CN, et al. 2001. Inhibitory effect of DCDC on lipopolysaccharide-induced nitric oxide synthesis in RAW 264.7 cells. *Life Sci.*: 68:2435–47.
- Israf DA, Khaizurin TA, Syahida A, Lajis NH, Khozirah S. 2007. 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.*; 44:673–9.
- Jemal A, Siegel R, Xu J, Ward E. 2010. Cancer statistics. *CA Cancer J Clin.* ; 60:277–300.
- Katsori, A.M.; Hadjipavlou-Latina, D. 2009.Chalcones in cancer: Understanding their role in terms of QSAR. *Curr. Med. Chem.*, 16, 1062–1081.
- Kim YH, Kim J, Park H, Kim HP. 2007. 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.* ; 30:1450–5.
- King, R. J. B., 2000, *Cancer Biology*, Pearson Education, Second Edition, England. p.1-7,228-231, 263-264
- Kumar S, Sharma A, Madan B, Singhal V, Ghosh B. 2007. Isoliquiritigenin inhibits IkappaB kinase activity and ROS generation to block TNF-alpha induced expression of cell adhesion molecules on human endothelial cells. *Biochem Pharmacol.* ; 73:1602–12.
- Lee, Y.S.; Lim, S.S.; Shin, K.H.; Kim, Y.S.; Ohuchi, K.; Jung, S.H. Anti-angiogenic and anti-tumor activities of 2-hydroxy-4- methoxychalcone. *Biol. Pharm. Bull.* 2006, 29, 1028-1031.
- Lodish, H., Berk, A., Zipursky, S.L., Matsudaira, P, Baltimore, D., and Darnell, J., 2000, *Molecular Cell Biology*, 4th edition, New York: W.H. Freeman
- McMahon G. VEGF receptor signaling in tumor angiogenesis. *Oncologist.* 2000; 5 1:3–10.
- Miranda, C.L.; Stevens, J.F.; Helmrich, A.; Henderson, M.C.; Rodriguez, R.J.; Yang, Y.H.;Deinzer, M.L.; Barnes, D.W.; Buhler, D.R. 1999. Antiproliferative and cytotoxic effects of prenylated flavonoids from hops (*Humulus lupulus*) in human cancer cell lines. *Food Chem. Toxicol.*, 37,271–285.
- Ngameni B, Touaibia M, Patnam R, Belkaid A, Sonna P, Ngadjui BT, et al. 2006. 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*. ; 67:2573–9.
- Noren NK, Liu BP, Burrige K, Kreft B. 2000. p120 catenin regulates the actin cytoskeleton via Rho family GTPases. *J Cell Biol.* ; 150:567–80.
- Noujaim D, van Golen CM, van Golen KL, Grauman A, Feldman EL. 2002. N-Myc and Bcl-2 coexpression induces MMP-2 secretion and activation in human neuroblastoma cells. *Oncogene*. ; 21:4549–57.
- Nowakowska, Z. 2007. A review of anti-infective and anti-inflammatory chalcones. *Eur. J. Med. Chem.* 42, 125–137.
- Pahl, H L. 1999. Activators and Target Genes of Rel/NF-kappaB Transcription Factors. *Oncogene* 18(49): 6853–66. <http://www.ncbi.nlm.nih.gov/pubmed/10602461>.
- Pandey MK, Sandur SK, Sung B, Sethi G, Kunnumakkara AB, Aggarwal BB. 2007. Butein, a tetrahydrochalcone, inhibits nuclear factor (NF)-kappaB and NF-kappaB-regulated gene expression through direct inhibition of IkappaBalpha kinase beta on cysteine 179 residue. *J Biol Chem.* ; 282:17340–50.
- Rahman, M A. 2011. Chalcone □: A Valuable Insight into the Recent Advances and Potential. 2011(3): 1–16.
- Rauf, S.; Gooding, J.J.; Akhtar, K.; Ghauri, M.A.; Rahman, M.; Anwar, M.A.; Khalid, A.M. Electrochemical approach of anticancer drugs-DNA interaction. *J. Pharm. Biomed. Anal.* 2005, 37, 205-217.
- Sahai E, Marshall CJ. 2002. RHO-GTPases and cancer. *Nat Rev Cancer.* ; 2:133–42.
- Sasayama T, Tanaka K, Mizukawa K, Kawamura A, Kondoh T, Hosoda K, Kohmura E. 2007. Trans-4-Iodo,4-boranyl-chalcone induces antitumor activity against malignant glioma cell lines in vitro and in vivo. *J. Neu-Onc.* 85, 123-132.
- Shah, A.; Khan, A.M.; Qureshi, R.; Ansari, F.L.; Nazar, M.F.; Shah, S.S. 2008. Redox behavior of anticancer chalcone on a glassy carbon electrode and evaluation of its interaction parameters with DNA. *Int. J. Mol. Sci.* , 9, 1424–1434.
- Shen, Kun-hung, Jiunn-kae Chang, Ya-ling Hsu, and Po-lin Kuo. 2007. 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. 24: 254–61.
- Srinivasan B, Johnson TE, Lad R, Xing C. 2009. 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.* ; 52:7228–35.
- Van den Heuvel, S., 2005, *Cell-cycle Regulation*, WormBook, oi/10.1895/wormbook.1.28.1, [Http://www.wormbook.org](http://www.wormbook.org)
- Vermeulen, Katrien ., Bockstaele, D.R., and Berneman, Z.N., 2003. The Cell Cycle: a Review of Regulation, Deregulation and Therapeutic Targets in Cancer”, *Cell. Proliff.*, 36: 131-149.
- Vivek R. Yadav, Sahdeo Prasad, Bokyung Sung, and Bharat B. Aggarwal. 2011. The Role of Chalcones in Suppression of NF-κB-Mediated Inflammation and Cancer. *Int Immunopharmacol* 11(3): 295–309.
- Ye, C.L.; Liu, J.W.; Wei, D.Z.; Lu, Y.H.; Qian, F. 2004. In vitro anti-tumor activity of 2, 4-dihydroxy- 6-methoxy-3, 5-dimethylchalcone against six established human cancer cell lines. *Pharmacol. Res.* , 50, 505-510.
- Ye, C.L.; Liu, J.W.; Wei, D.Z.; Lu, Y.H.; Qian, 2005. F. In vivo antitumor activity by 2, 4-dihydroxy-6- methoxy-3, 5-dimethylchalcone in a solid human carcinoma xenograft model. *Canc. Chemo. Pharm.*, 55, 447-452.
- Zachary I. 2003. Vascular endothelial growth factor and antiangiogenic peptides as therapeutic and investigational molecules. *IDrugs* 6:224–231)