Review Article

Chalcone-xanthine Hybrid: Its Expected Role in Treatment of Non-small Cell Lung Cancer

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Abstract

Cancer is a complex illness that kills millions of people globally each year. Its origin and growth are highly complicated. The treatment of cancer includes surgery, chemotherapy, and radiation, which can be used separately or in conjunction. However, side effects and multidrug resistance (MDR) are serious obstacles to effective cancer treatment. Chalcone family members have received high interest because of their synthetic and biosynthetic production, besides the broad range of their biological activities. Chalcone targets a wide range of molecular cascades that share in the control of apoptosis and cell cycle growth. Chalcone hybrids especially with xanthine derivatives have approved antineoplastic activity. This review highlights the mechanisms of action of chalcone alone or in hybrids in cancer cells with an impact on lung cancer, especially non-small cell lung cancer. It also clears the expected mechanisms that regulate apoptosis and cell cycle arrest as an important target in cancer.

Keywords: B-cell lymphoma 2 protein (Bcl-2), Chalcone, Non-small Cell Lung Cancer (NSCLC), Multidrug Resistance (MDR)

Citation. Elrehany OM, Ahmed AFF, Nazmy MH. Chalcone-xanthine Hybrid: Its Expected Role in Treatment of Non-small Cell Lung Cancer. J Vet Med Res., 2024; 32(2): 59–63. https://doi.org/10.21608/jvmr.2024.336602.1109

Article History: **Received**: 01-Oct-2024 **Accepted**: 07-Nov-2024

1. Introduction

Lung cancer is an important cause of mortality. Individuals who have cancer suffer from lowered life quality due to the bad effects linked with cancer. Chemotherapy is one of the most efficient ways to inhibit tumor development besides its related side effects such as nausea, vomiting, anemia, and thrombocytopenia (Miller et al., 2016).

Through 2018, statistics showed a high number of new cases of lung cancer reached 2.1 million, besides 1.8 million deaths, making it the principal cause of cancer mortality worldwide (Bray et al., 2018). The early detection of lung cancer is becoming more common each year, while death rates are decreasing due to the new detection and diagnosis procedures. However, in less developed nations, Lung cancer is often classified as either progressed or locally advanced. As a result, overall in 2019, the 5-year survival rate stays at 19% (Siegel et al., 2019). As a result, the development and identification of new candidate molecules implicated in lung cancer therapy is critical.

Lung cancer was shown to be common in high-income countries/ regions. This reflects high rates of consumption of tobacco (Chavan et al., 2014; Bray et al., 2018). However, the particular incidence of small cell lung cancer (SCLC) in various countries/regions is not completely clear. SCLC is a high-grade neuroendocrine carcinoma that mostly affects current or former smokers and has a very bad prognosis (DeVita et al., 2015). SCLC accounts for roughly 15% of lung cancer cases. Patients with SCLC typically present with respiratory symptoms such as cough, dyspnea, or hemoptysis, with imaging showing a centrally located lung mass and sometimes combined with bulky thoracic lymph nodes (Hou et al., 2012). SCLC accounts for 250,000 new cases annually and at least 200,000 deaths worldwide (Chavan et al., 2014). SCLC therapy remains identical for subtypes regardless of transcription factor expression profiles that classify SCLC (Kalemkerian et al., 2018).

The incidence of SCLC globally is high in males (Govindan et al., 2006). SCLC incidence in the United

States has been reduced in a descending manner through the last three decades reflecting a decreased frequency of cigarette smoking (Breitling et al., 2019). Although the a high frequency of smoking among African Americans, SCLC is less common than in white Americans (Bade and Dela Cruz, 2020).

Methylxanthines over theophylline show anticancer properties. Furthermore, Pentoxifylline is used in adjuvant therapy to increase the effect of chemotherapy and radiotherapy (Bravo-Cuellar et al., 2013). Anticancer cotherapy with pentoxifylline and doxorubicin showed a synergistic effect and inhibited the proliferation of neoplastic cells in a manner higher than each drug alone (Goel and Gude, 2014).

The use of hybrid molecules is an important way to improve the potency of antineoplastic drugs and minimize drug resistance. Naturally occurring chalcones are compounds that have large-scale biological activities like anticancer that exert their effect through many mechanisms (Ahmed et al., 2018).

2. Chalcone

Phytochemicals such as chalcone can affect important mechanisms that contribute to cancer's origin and development. Therefore, scientists integrated folk medicine and knowledge about the use of medicinal plants to synthesize novel, potent, and more effective therapeutic anticancer medicines by application of various molecular processes (Manzo, 2021). A molecule called chalcone can be found in a variety of natural goods, such as teas, fruits, vegetables, and spices. Chalcone belongs to the family of flavonoids and according to its structural heterogeneity, it targets many drug destinations (Zhuang et al., 2017). Chalcone family members have received a lot of attention because of their potential for synthetic and biosynthetic production, as well as the broad range of their biological activities. They include antioxidant, anti-diabetic, anti-cancer, anti-leishmanial, antimicrobial, anti-malarial, anti-inflammatory, and cancer chemopreventive properties. More significantly, numerous chalcone compounds have been authorized for clinical use as vascular, neuroprotective, and diuretic agents (Cheng et al., 2020).

2.1. Expected Mechanisms of Action of Chalcone

Chalcone targets many molecular pathways that may contribute to their anti-neoplastic activity which are summarized as follows:

2.1.1. Chalcone and NF-κB Pathway

The transcription factor, nuclear factor kappa B (NF-κB), affects inflammation, cancer, and innate immunity. Signaling through the NF-κB pathway contributes to the progression of cancer by up-regulating survival genes and cytokines predisposing to cancer (e.g., Bcl-2), inhibiting apoptosis while increasing angiogenesis resulting in an invasive cancer phenotype (Hoesel and Schmid, 2013). NF-κB inhibitors (IKKs) may trigger an anticancer response or enhance the sensitivity of antitumor drugs. IKKs control NF-κB activity, which plays a key role in immunological responses and inflammation. Inhibiting NF-κB activity by IKK inhibition can reduce NF-κB translocation from cytoplasm to the nucleus, making it a possible therapy method for diseases including inflammation and cancer (Baldwin, 2012). Chalcone inhibits NF-κB by covalently modifying the Ikappa B kinase (IKK) proteins. Lee et al. (2012) and his colleagues discovered that chalcone derivative butein can downregulate NF-κB gene expression and activity by conjugation with cysteine residue 179 of IKK protein and also inhibits phosphorylation and degradation of IκBα. Chalcone derivatives suppress the expression of inflammatory mediators, including TNF-α, COX-2, and iNOS, by inhibiting the NF-κB signaling pathway. Finally, chalcone evolved as new mechanisms targeting inflammation and invasion to produce neoplastic chemopreventive treatments (Gan et al., 2018).

2.1.2. Chalcone as Inhibitors of MDR Channels

Chalcone has been investigated for its ability to generate resistance to famous anticancer drugs by modulation of transporters controlling drug efflux, which plays an important role in the accumulation of drugs in cancer cells. The majority of the investigated chalcone inhibited three members of the ATP-binding cassette transporter family; breast cancer-resistance protein (BCRP, ABCG2), multidrug resistance-associated protein 1 (MRP1) and P-glycoprotein, all of which contribute significantly to multidrug resistance (MDR) in cancer cells. As a result, chalcone has sparked substantial importance as chemotherapeutics to neglect drug resistance and to improve the pharmacokinetics of anticancer medications with delayed absorption (Vasan et al., 2019).

2.1.3. Chalcone Target the p53 Pathway

The tumor suppressor protein p53 controls cell cycle progress and suppresses tumors. p53 is essential for preserving cellular and genomic integrity, as well as limiting the development of cancer cells. p53 is destroyed by a variety of molecules, including MDM2 and Sirtuin-1. Inhibiting the tumor suppressor gene product p53 breakdown is an important anticancer therapeutic strategy (Stein et al., 2019). p53 is negatively regulated by MDM2. The E3 ubiquitin ligase, MDM2, suppresses the activity of p53 by continuous ubiquitinating p53, a mechanism needed for p53 degradation by proteasomes

in the nucleus and cytoplasm (Karni-Schmidt et al., 2016). Thus, disrupting p53-MDM2 complex formation is a cornerstone in the activation of p53. (Silva et al., 2016) reported that trans-chalcone (TChal) may inhibit expression of the transcription factor specificity proteins 1(Sp1), needed for cell differentiation and proliferation, while up-regulating expression of p53 in osteosarcoma cells.

2.1.4. Chalcone as Inhibitors of Angiogenesis

Angiogenesis is a prospective target for cancer therapy because it plays a significant role in cancer development and metastasis. Chalcone has been shown to affect various stages of angiogenesis, including VEGF, bFGF, TGF-$beta$ signaling, HIF-1, matrix metalloproteinase activity, migration, and proliferation of endothelial cells (Shanmugam et al., 2017).

Ma et al. (2020) and coworkers discovered that a 3',5'-diprenylated chalcone derivative inhibits Fli-1 (friend leukemia integration-1) and regulates the expression of ICAM-1 (intercellular cell adhesion molecule-1), vascular endothelial growth factor-1 (VEGF-1), MMP-1, TGF-$beta$2, and p53 genes. These genes are linked to prostate cancer invasion, migration, and apoptosis.

2.1.5. Chalcone Target Tubulin Polymerization

Tubulin is a protein that is essential for all eukaryotic cells during mitosis. It is made up of two subunits, α and $beta$, that are related but not identical. The discovery of chalcone as an antimitotic agent occurred about 3 decades ago. According to research on the structure-activity relationship between colchicine and tubulin, chalcone derivatives resemble colchicine and can bind to tubulin to stop its polymerization. This disrupts the assembly of the mitotic spindle, which interferes with the cytoskeleton's ability to function and mitosis completion (Mirzaei and Emami, 2016).

Many chalcones can bind to $beta$-tubulin and destabilize microtubule polymers, acting as analogs to combretastatin 4A. Ducki et al. (2009) and his coworkers synthesized and produced CA-4 type chalcone and α-phenyl chalcone that demonstrated strong suppression of polymerization of tubulin, arrest cell cycle at the G2/M phase and potential anti-vascular action.

3. Xanthine-Chalcone Hybrids

The purine base xanthine is found in some plants, urinary calculi, and many body fluids and tissues. Degradation of AMP into uric acid includes xanthine intermediate which is produced from hypoxanthine oxidation. Theophylline, theobromine, and caffeine are methylated xanthines used with their derivatives as bronchodilators (Hisham et al., 2019).

Xanthine derivatives were tested for their biological effects. They possess diverse biological activities that include anti-inflammatory, CNS stimulant, antimicrobial, adenosine receptor antagonists, antiasthmatic, inhibitors for PDE (phosphodiesterase) and PEPCK (phosphoenol pyruvate carboxykinase) and antitumor activity. Wu et al. (2019) found that theophylline and caffeine promote apoptosis, and enhance doxorubicin-induced cytotoxicity.

Hybrid molecules have the ability to increase the selectivity and activity of chemotherapeutics and beat drug resistance. As a result, the hybridization of anticancer pharmacophores with chalcone is a novel method for developing new anticancer medications. Many chalcone hybrids were synthesized and tested for their antineoplastic activity. Some have considerable in vivo and in vitro activity and this indicates their powerful anticancer medications (Feng et al., 2020).

It was found that apoptosis is induced in many human cancer cell lines through adjuvant therapy of theophylline with gemcitabine or cisplatin. The mechanism of apoptosis induction of theophylline is thought to be across reduction of intracellular levels of the anti-apoptotic protein Bcl2 (Hisham et al., 2019), targeting p53 or cell cycle arrest as mentioned later.

4. Targeting Bcl-2 Family

The mitochondria-dependent intrinsic pathway is a key apoptotic route. Thus, targeting this pathway is a viable method for inducing apoptosis (Hassan et al., 2014). The Bcl-2 family plays an important role in intrinsic pathways that increase or inhibit mitochondrial membrane permeability, which is required for the release or inhibition of cytochrome-c and other apoptotic proteins (Green and Kroemer, 2004). Because anti-apoptotic proteins decrease apoptosis while increasing cell survival and proliferation, several studies have linked their overexpression to tumor growth and progression (Gautschi et al., 2001).

Nangia et al. (2018) and his colleagues revealed that the combined treatment of MEK and MCL1 inhibition produces apoptosis and tumor support in KRAS mutant NSCLC. This was synergized by the initial exposure to Bcl-XL inhibitors, which enhances the binding of pro-apoptotic Bcl-2 proteins to MCL-1. Graviola, a plant-derived molecule, has shown anticancer activity. Research discovered that it inhibits Bcl-2 proteins, boosts Bax, and induces apoptosis (Pfeffer and Singh, 2018). The specific mechanism is not yet fully known, although it shows promising efficacy as a cancer therapy.

5. Targeting the Tumor Suppressor Gene P53

Multiple anticancer drugs target p53-mediated pathways because it is a tumor inhibitor and pro-apoptotic pro-

tein that causes apoptosis. For decades, p53 has been known to begin DNA repair by increasing the expression of certain target genes by binding to their regulatory areas (Vogelstein et al., 2000). Repairing damaged DNA is the main goal. However, p53 activation will result in cell cycle arrest or death if DNA is significantly damaged (Vermeulen et al., 2003). P53 activity is necessary to stop tumors from growing. As a result, a lot of recently developed anticancer treatments aim to induce cell death by activating or refolding the mutant p53 pathway (Blaydes et al., 2000). This could be achieved by directly targeting p53 or by using small molecules that can restore p53 function. Additionally, focusing on its target gene products, like the pro-apoptotic Bax protein, which can activate the intrinsic apoptotic pathway, inhibit Bcl-2 expression, and induce apoptosis (Beberok et al., 2018).

6. Initiating Cell Cycle Arrest to Induce Apoptosis

One potential target for cancer treatment is the family of cyclin-dependent kinases (CDKs), which regulate and track the stages of the cell cycle. For many years, CDKs were thought to be the main players in the cell cycle, development, differentiation, and proliferation. But recently, interesting targets have been identified, including protein kinases that regulate mitosis and those that act on DNA damage (Fathy et al., 2017). DNA lesions cause cell cycle stop, which enables the cell to fix damaged DNA.

Two essential checkpoints, 1 and 2, are thought to preserve DNA integrity and function as self-cell defenses against cancer by stopping the cell cycle through the activation of serine-threonine protein kinase. The BCR-ABL protein kinase inhibitor "imatinib" from Gleevec; Novartis, which effectively targets tyrosine kinases for the treatment of chronic myelogenous leukemia, was developed as a result of trials for the manufacturing of kinase inhibitors as anticancer medicines. Targeting CDK family members—specifically, CDK-2, 4, and 5—is a useful addition to the list of therapies for inducing apoptosis, according to multiple studies. According to other studies, CDK1 may be involved in prostate cancer, while CDK5 plays a particular function in regulating cell motility and metastasis in this disease (Strock et al., 2006).

7. Conclusion

The anticancer effect of chalcone hybrid on HOP-92 cells was investigated. It reduced proliferation, triggered apoptosis, and stalled the G2/M phase. Furthermore, the chalcone hybrid decreased Bcl-2 expression while increasing P53, caspases 3, 8, 9, and the pro-apoptotic production of Bax at the transcriptional level. Furthermore, chalcone treatment suppressed the phosphorylation of downstream proteins involved in the propagation of cell cycle and apoptosis regulation. These findings emphasize the compound's possible anticancer properties, indicating that it might be used as a novel therapy for the treatment of NSCLC (Elrehany et al., 2024).

Article Information
Ethical Approval. Not Applicable.
Funding. The research received no external funding.
Conflict of Interest. The authors declare no conflict of interest.

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