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CHALCONE AFFILIATES: SIGNIFICANCE IN ANTINEOPLASTIC THERAPY

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Abstract

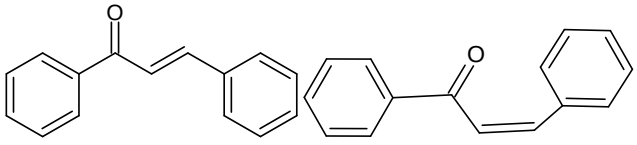
Cancer is most serious public health issue and lead by numerous factors. Chalcones are the building blocks of several heterocyclic componds and flavonoids. These compounds are advantageous due to their least side effects, simple structural modifications, easy availability, many biological features. Furthermore, for discovery of new anticancer drugs, chalcones serves as precursor or starting point. Both synthetic and natural chalcones produce anticancer effects in-vitro and in-vivo. Tubulin inhibition is most important mechanism of action of anticancer activity of chalcones. For efficient activity, chalcone hybridization with cancer pharmacophore is favourable. For example, coumarin conjugation with chalcone lead increase in pharmacological properties and can improve or change lipophilic character or parameters.

Keywords: Cancer, Cell lines, Tubulin inhibition, MDR inhibition, Chalcone

1. INTRODUCTION

Cancer is most of leading cause of deaths worldwide each year. Number of treatments are used for cancer such that radiotherapy, surgery, chemotherapy and multidrug resistance (MDR).[1] Global research is becoming increasingly interested in the chemistry of chalcones. The name "Chalcone" was given by Tambor and Kostanecki (1899). Chalcone have gained attention due to scope of its pharmacological activities including antidiabetic [2], antioxidant, anticancer [3,4], antimicrobial [5], antimalarial [6]. The unsaturated ketones known as chalcones (1,3-diaryl-2-propen-1-ones) are composed of two aromatic rings and variety of substitutions. In chalcone structure both rings (aromatic) joined by aliphatic chain having three carbons. A highly electrophilic three carbon unsaturated carbonyl system with a nearly planar and linear structure connects the two chalcone rings. On both aromatic rings, they have fully delocalized-electrons and conjugated double bonds. Chalcone scaffold exist in two isomeric forms one in cis and other in trans. Trans isomer is more stable at temperature variations (Figure 1). Chalcones serves as best synthons for a number of new heterocycles with strong pharmaceutical potential. [7,8]

In 21st century, the chemistry of chalcones remains interest for various therapeutic activities such as antigout (Hofmann et al., 2016), anticancer (Hsieh et al., 2019; Khanapure et al., 2018; Özdemir et al., 2017; 2014; Sashidhara et al., 2010), anti-inflammatory (Dhar et al., 2018; Fu et al., 2019; Gan et al., 2018; Li et al., 2017; Mahapatra et al., 2017; Md Idris et al., 2018), antimicrobial (Benouda et al., 2019; Lal et al., 2018), antimicrobial (Benouda et al., 2019; Lal et al., 2018). Chalcone has a very good moiety, for creating novel heterocyclic compounds with improved therapeutic properties. Broad spectrum biological activities shown by naturally occurring as well as synthetic chalcones. To prevent molecular damage and to survive from microorganism attack, chalcones serves as plant defence mechanism. [9]



(E)-Chalcone (Z)- Chalcone

Figure 1: Isomeric forms of chalcone

2. BIOSYNTHESIS OF CHALCONES

Chalcone synthase with its second active site and phenylalanine are major enzyme and precursor in chalcone biosynthesis respectively. Two major biomolecules i.e., malonyl CoA and coumaroyl CoA also needed for chalcone formation. [10,11] Cinnamic acid is formed after deamination of phenylalanine with enzyme PAL. After that hydroxylation occur and P-coumaric acid is formed, which converts into P-coumaroyl CoA by substitution of succinyl-CoA. This reaction followed by cyclization, decarboxylation and aromatization of malonyl-CoA. Obtained chalcone is act as biosynthetic precursor for flavones, flavonones, flavonols, isoflavonoids etc. [12] Biosynthetic pathway is described in Figure 2.

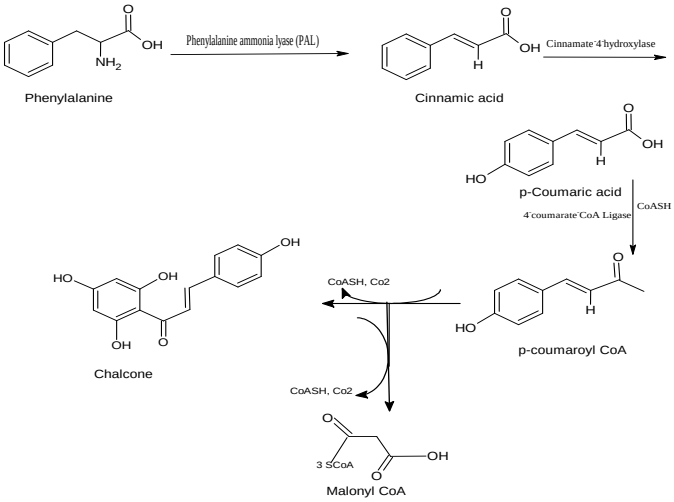
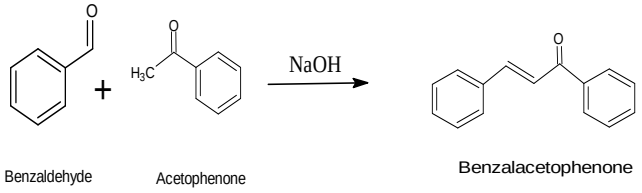


Figure 2: Biosynthetic pathway of chalcones

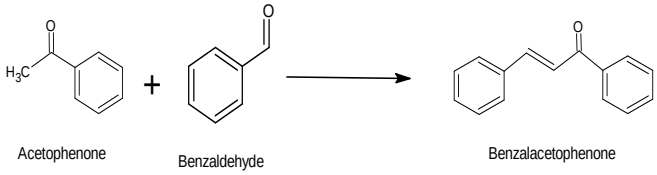
2.1. SYNTHETIC METHODS FOR CHALCONES

For synthesis of chalcone moiety two aromatic ring systems are condensed. Various chemical reactions like carbonylative Heck coupling reaction, aldol condensation, Claisen-Schmidt condensation, coupling reaction are present but most useful and common method is Claisen–Schmidt condensation. [7,13]. Two most common methods are discussed here.

Claisen Schmidt Condensation: This is the easiest method for chalcone synthesis by reacting aryl aldehyde with aryl methyl ketone and alcoholic base like sodium hydroxide as catalyst [14].



Aldol Condensation: Benzaldehyde and acetophenone reacts and lose water molecule by heat give chalcones [15].



2.2. APPROACHES SELECTED TO GENERATE ANTITUMOUR AGENTS

For development of antitumour drugs, chalcone moiety is best model. We can get potent antitumour- chalcones by applying three spiked approaches (Figure 3).

1. Molecular hybridization with other therapeutically effective scaffolds.
2. Aryl rings substitution.
3. Altering structure of aryl rings. [4]

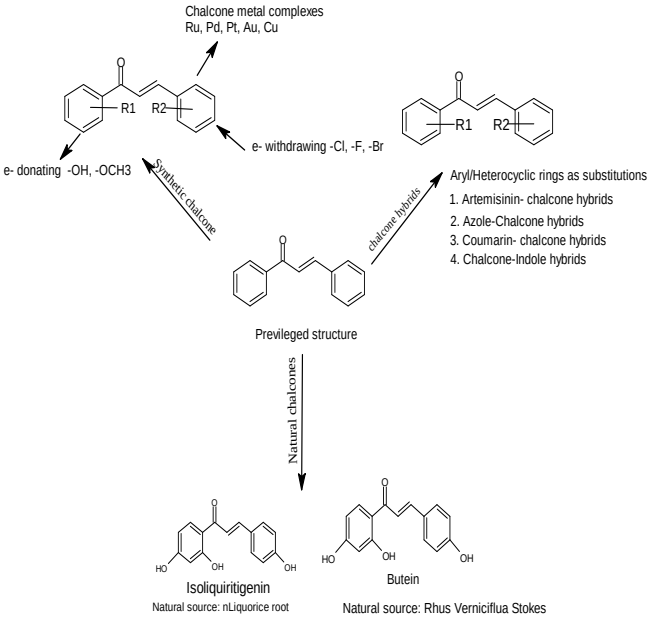


Figure 3: Approaches selected to generate antitumour agents

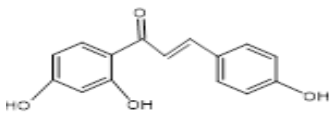
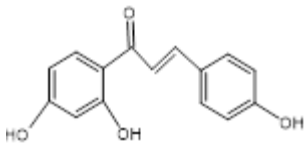
2.3. Natural chalcones

Chalcones made up of numerous natural originated biological compounds and studied for many years. The chalcone family has broad variety of structural variability and can be divided in two groups:

a. Hybrid
b. Simple

They are extensively dispersed in many plant parts like rhizome, leaves, seeds, roots, flowers. [16,8] Natural chalcones are mostly found in monomeric form. Some eminent examples of natural chalcones are Butein, Isoliquiritigenin. Potential antitumour actions described in Table 1

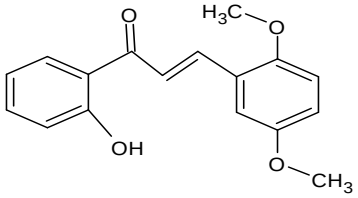
Table 1: Potential antitumour actions of natural chalcones

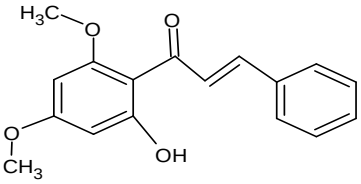
S. no	Compounds with chemical structure	Originated from	Therapeutic potential against	Mechanism of action	Reference
1	Butein 	Rhusverniciflua Stokes	HCC (Hepatocellular cancer), NSCLC (Non-small cell lung cancer),	Apoptosis and Endoplasmic Reticulam stress dependent ROS generation	17,18
2	Isoliquiritigenin (ISL) 	Liquorice root	Colon cancer	Inducing apoptosis, arresting cell cycle, suppress cell proliferation, inhibits angiogenesis and also enhance chemosensitivity	19-24

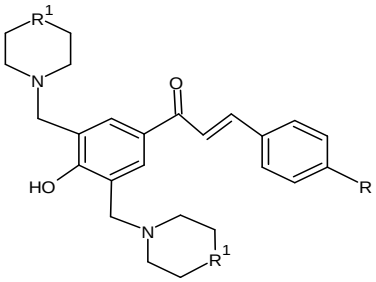
2.4. Synthetic chalcone derivatives

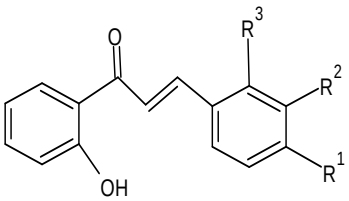
Many efforts have been made to produce new synthetic chalcones with antitumor activities, inspired by successful use of natural chalcones as cancer treatment drugs. Various studies found that position and number of -OCH_3 and -OH groups on aryl rings appear to be effective in anticarcinogenic property.[25]

Halogen containing chalcone, showed extensive cytotoxic properties. Padhye. et al and Zhang. et al reported fluorine and bromine bearing chalcones show anticarcinogenic activity against human breast, pancreatic and gastric cancer. [26-27] Some synthetic chalcones are given in Figure 4









1a-c

R=F, Cl, Br

1a R^1 = OH, R^2 = OH, R^3 = H

R^1 = -CH^2, -O-, -NH^3

1b R^1 = OH, R^2 = H, R^3 = OH

1c R^1 = F, R^2 = F, R^3 = H

Figure 4: Synthetic chalcones

Recently, in bioinorganic medicinal chemistry due to chelation property of chalcones they form complexes with different metals and have worldwide attention for effects on different antitumour targets. [28]

2.5. Hybrid chalcones

Hybridization is a promising and best technique to combat drug resistance and in activity enhancement. Recently, various hybrids of chalcone have been synthesised and analysed for anticancer potential. Structure of some remarkable potential chalcone hybrids is in Figure 5.

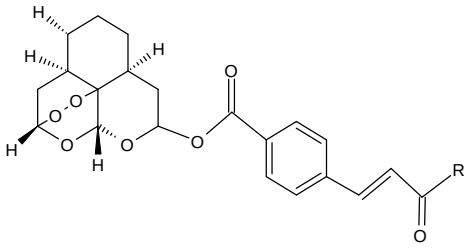
2.6. Artemisinin-Chalcone hybrids

Hybridization of these molecules provide potent antitumour agents. Smit et. Al reported potent artemisin-chalcone hybrids against Plasmodium falciparum and MCF-7 cell lines (IC50: 1.02-53.7). These hybrids are non-toxic in nature. [29] (Figure 5)

Chalcone-Azole hybrids: For antitumour drug development commonly used pharmacophores are azoles. Pyrazole, imidazole, tetrazole, oxadiazole, triazole, thiazole are common azoles having nitrogen containing 5-membered heterocyclic rings. Various studies revealed that hybrids of abovesaid azoles with chalcone showed broad spectrum activity against EGFR, HCC cell lines, Breast MCF-7 cell lines and also inhibit polymerization of tubulin, help to overcome cancer cell drug resistance. [30-32] (Figure5).

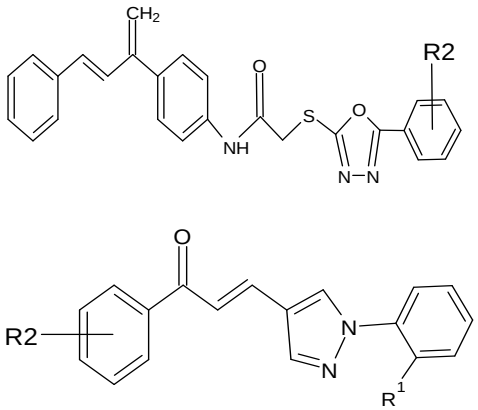
Chalcone-Coumarin hybrids: Coumarin and chalcone moieties hybridization gained attention for design of new antitumour agents. Recently, different studies reported coumarlcone conjugates activate apoptosis pathway, cervical cancer cells antiproliferation as well as exert moderate cytotoxic effect against liver cancer (HEPG2). They found to be more effective than cisplatin against breast cancer cell lines. [33-34] (Figure 5)

Chalcone-Indole hybrids: Chalcone-Indole hybrids are probable approaches to generate antitumour agents. These hybrids shown potent anticancer efficacy towards HepG2, HCT116, HCT-8/T, MCF-7 cancer cell lines. They act by inhibition of tubulin polymerization. Further systematic studies suggested that these hybrids show less cytotoxic in human cells. Various studies revealed that indole hybrids with chalcones can be potential drug molecule for antitumour drug development of MDR cancers. [35,36] (Figure 5)



Artemisinin-chalcone hybrid

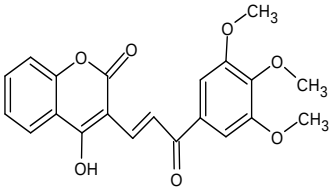
1(a-c) 1a= C6H5, 1b= 3-NO2-4-OCH3C6H5, 1c= 5-methyl-2-yl

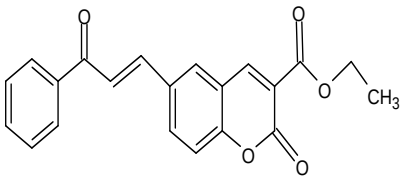


Chalcone-Azole hybrids

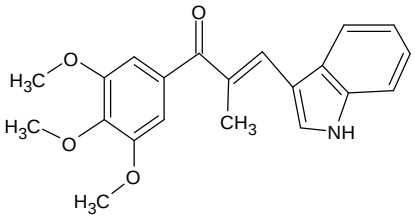
Chalcone-Oxadiazole hybrid
R1= 3,4,5- triOMe, R2= 4-Ome

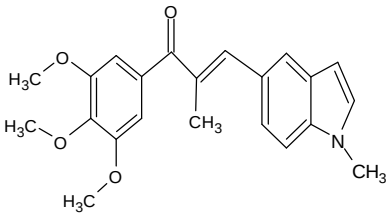
Chalcone- Pyrazole hybrid
R1= 2,4,5-triOMe, R2= Pyridin-3-yl





Coumarin-Chalcone hybrids





Chalcone-Indole hybrids

Figure 5: Structure of chalcone hybrids

2.7. Mechanism of action of chalcones as antitumour agent

In previous papers, biological activities and multitarget action of chalcones are discussed. [37,38] In this section, we represent summary of anticancer mechanism of chalcones in recent years. Main 4 pathway for antitumour action described in Table 2 and Figure 6.

- **P53 pathway:** P53 tumour protein act as tumour suppressor. P53 protein breakdown inhibition is best approach in antitumour treatment. Dos et al. revealed that halogen bearing chalcones produce antiproliferative effect for cancer of breast[39].
- Tubulin polymerization
- NF-ĶB pathway
- MDR channel inhibition

Table 2: Pathway for antitumour mechanism of action

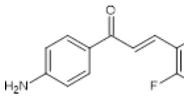
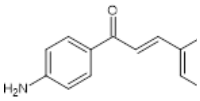
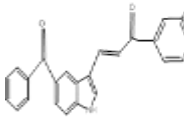
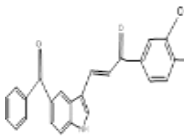
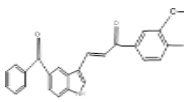
Pathway	Lead compound	Mode of action	Reference
P53 pathway	 2-fluoro-  4'aminochalcone 3-pyridyl-4'aminochalcone	P53 elevated regulation and insensitivity toward SP protein expression	39
Tubulin polymerization	 Indole-linked chalcone	Inhibit tubulin polymerization and cell integrity lost	40
NF-ϰB pathway	 Dihydrotriazinechalcone	Target dihydrofolate reductase (DHFR) and MDA-MB-231 migration (in-vitro) into cancer cells of breast	41
MDR channel inhibition	 Non-basic chalcone	Inhibition of ABCB1/ ABCG2	42

Figure 6: Mechanism of action of chalcones as antitumour

3. CONCLUSION

Chalcones are starting point for iso-flavonoids and flavonoids that are found in natural compounds as chemical scaffold. Derivative of chalcones prepared by convenient synthetic methods. Extensively, natural chalcones are modulated and studied. Because of broad spectrum biological efficiencies, they have potential /capability against different diseases especially cancer. Chalcone compound families observed potential in-vivo and in-vitro activity towards cancer through various mechanism, including apoptosis induction, cell cycle arrest, inflammation mediators, regulation of autophagy. Development of chalcones as potential anticancer drugs is a challenging approach. Furthermore, conjugation of therapies and chalcones enhance effectiveness of anticancer medications. In this review, we provide mechanism of action and new development of chalcones as possible antitumour agents. Additionally, scope of chalcones and potential uses in management of cancer are also highlighted. To add up, chalcones can be created as innovative and potential scaffold which target inflammation and invasion for antitumour therapies development.

4. LIST OF ABBREVIATIONS

20-HETE-20-Hydoxyeicosatetraenoic acid; AKT- protein kinase B; BCRP- Breast cancer resistance protein; COX-2- Cyclooxygenase-2;CRM1- Chromosome region maintenance 1;CYP- Cytochrome P450;HIF-1- Hypoxia-inducible factor-1;IKKs-IκBkinases; MDM2- the mouse double minute 2; MDR- Multidrug resistance; NF-κB- Nuclear factor kappa-light-chain-enhancer of activated B cells; P-gp- P-glycoprotein;ROS- Reactive oxygen species;TNF-Tumor necrosis factor;VEGF- Vascular endothelial factor; DHFR- Dihydrofolate reductase.

ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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