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A REVIEW ARTICLE ON: CANCER THERAPY AND CHALCONE AS ANTICANCER AGENT

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Abstract: In this article we discuss the cause of cancer, type of cancer, sites of cancer in human body and different ways of treatment of cancer. We also discuss the chemotherapy of cancer and classification of chemotherapeutic agent on the basis of mode of action. Chalcone is a biosynthetic product of Shikimate pathway. Chalcone (1,3-diaryl propenone or 1,3-diphenyl-2-propen-1-one), constitutes an important natural product which possess a wide range of biological activities, such as antiviral, antioxidant, antibacterial, antifungal, antitumor, anti-inflammatory, antimutagenic and antimicrobial. In this article we represent an integrated overview on chalcone as anticancer agent.

Keywords **- Cancer, chalcone, anticancer agent and therapy.**

INTRODUCTION

Cancer is a group of diseases characterised by abnormal and uncontrolled cell division. Invasion and metastasis are the two mechanisms by which cancer spread in the various part of body. Detection of cancer in early stage is almost completely curable while in later stage may become non-curable and lead to death. A tumour is a lump or growth of tissue made up of abnormal cells. Tumours are divided into two types i) benign tumour and ii) malignant tumour. Benign tumours grow slowly and do not spread to other tissues in the body. Malignant tumours tend to grow quickly, and invade into nearby tissues and organs which can cause severe cell damage. The original site where a tumour first develops is called a primary tumour. Malignant tumour may also spread to other part of the body to form secondary tumours (metastases).

Causes of cancer

Three main factors, viz, chemicals, radiations and viruses or bacteria contribute to the growth of cancer. They all trigger changes in a cell's genes. Chemicals and radiation act by damaging genes and causing DNA mutations whereas viruses introduce their own genes into the cells. People can reduce the risk of cancer by avoiding the carcinogenic agents like tobacco, alcohol, radiations & environmental pollutants or by taking adequate amounts of fruits & vegetables which contains antioxidants, vitamins, flavonoids & resveratrol.

Types of cancer

Cancer originates within a single cell. Cancer can be classified depending on the origin and the location of the cell. For example, carcinomas originate in epithelial cell, viz, skin, digestive tract or glands. Leukemia starts in bone marrow stem cells. Sarcoma begins in the connective tissues of bones & muscles and teratoma occurs within germ cells.

Most common sites of cancers are: prostate, thyroid, lungs & bronchus, stomach, colon & rectum, brain, urinary bladder, multiple myeloma, non-Hodgkin lymphoma, oesophagus, breast, liver & intrahepatic bile duct, kidney & renal pelvis, cervix, pancreas, larynx, oral cavity & pharynx, acute myeloid leukemia, ovary, chronic lymphocytic leukemia, soft tissues including heart, Hodgkin-lymphoma, testis, small intestine & gastrointestinal carcinoid, tumours, chronic myeloid leukaemia, anus, anal canal & anorectal,

vulva, gall bladder, bones & joints. Further the less common sites of cancer areeyes & noses, nasal cavity & middle ear.

Therapy of Cancer

Cancer can be treated by

1. Radiation therapy involves treatment of cancer cells with ionizing agents.
2. Surgery involves removing of tumour growth,
3. Chemotherapy treatment by usage of anti-cancer drugs, destroying cancer cells by inhibiting growth at one or several life cycle stages.
4. Immunotherapy (Biological Therapy) by involving body's immune system.
5. Hormone therapy involves use of hormones to balances hormones in biological system.
6. Alternative and complimentary therapy involves Acupuncture and Homeopathy.

Cancer Chemotherapy

The anticancer drugs have specific action mechanism that may vary in effects on normal and cancer cells. Further, normal cells and cancer cells have only few known biochemical differences. The effectiveness of many anticancer drugs is limited by their toxicity to normal rapidly growing cells in the intestinal and bone marrow area. Moreover, cancerous cells which are initially suppressed by specific drug, may develop a resistance to that drug. Chemotherapeutic agents can be divided into three main categories on the basis of their action mechanism [1]:

1.Inhibition of synthesis of pre-DNA molecule blocks: DNA building blocks are synthesized within cells by a series of reactions. Some agents interfere in biosynthesis of nucleotides or deoxynucleotide and halt the synthesis of DNA and RNA so that cells cannot replicate. For example, methotrexate, fluorouracil, hydroxyurea and 6-mercaptopurine as given in Figure-1. Hydroxyurea blocks an enzyme, which converts the cytosine nucleotide into deoxy derivative. 6-MP, an adenine analog inhibits the biosynthesis of adenine nucleotide by acting as an antimetabolite.

2. Directly damage the DNA and RNA in the cell nuclei: These agents chemically damage DNA and RNA by either disrupting the replication of DNA or causing the manufacture of non-sense DNA or RNA which does not code the synthesis of useful proteins. Example: cisplatin and antibiotics doxorubin and cerubidine.

3. Disrupt the formation or break down of the mitotic spindles: Mitotic spindle appear on north and south - pole of cells during cell division. These spindles help to split newly copied DNA in such a way that a copy goes to each of two new daughter cells during cell division. These drugs disrupt the formation of these spindles and therefore interrupt cell division. Example: vincristine, vinblastine and paclitaxel.

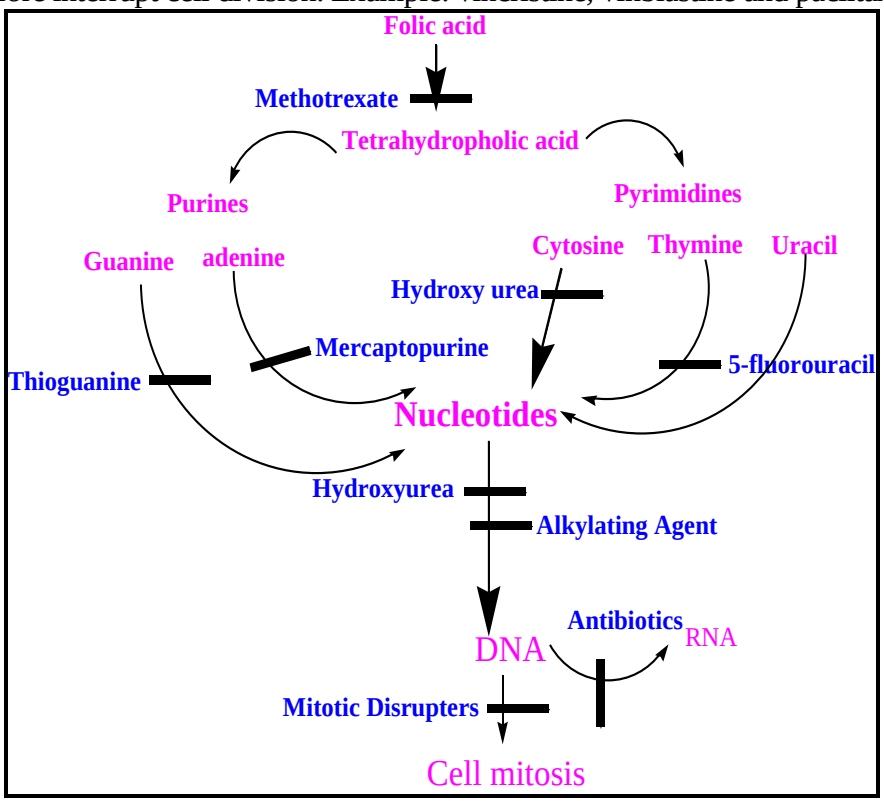
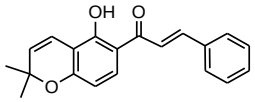


Figure 1:Mechanism of action of anti-cancer drugs [1]

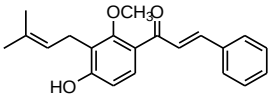
Chalcone as anticancer agent

Chalcone is a unique template that is associated with several biological activities. Cytotoxicity against tumour cells may be the result of disruption of the cell cycle, inhibition of angiogenesis [2], interference with p53-MDM2 interaction[3,4], mitochondrial uncoupling [5] or induction of apoptosis[6,7]. Lonchocarpin (**1)** and derricin (**2)** (two chalcone present in the root of *Lonchocarpussericeus*, a common plant found in north-eastern Brazil) are cytotoxic against a leukemic cell line (IC_{50}=17.6 mg/mL) [8].

Derricin is a prenylated chalcone and lonchocarpin may be considered as a derivative in which the prenyl side chain and the adjacent methoxy group are cyclized to form an additional ring.

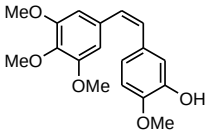


Lonchocarpin (1)

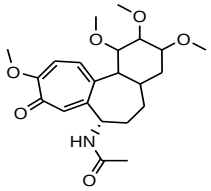


Derricin(2)

Comberstatin A-4 (CA-4) is isolated from the bark of *combretum coffarum* [9], having strong antitubulin activity CA-4 **(3),** binds to colchine binding site and exhibit strong anticancer activity against different cancer cell line [10]. Structurally in CA-4 two phenyl ring are spaced by two carbon atoms. CA-4 analogues possessing space of three carbon atom are very few and the present study is focused on it. It is attractive and lead to compound for the development of anticancer agent.

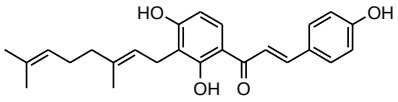


CA-4 (3)

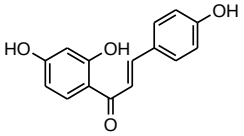


Colchicine (4)

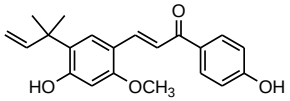
For example, xanthoangelol was reported to induce apoptosis and inhibit tumor promotion and metastasis in several cancer cell lines [11,12]. Licochalcone-A (7), isoliquiritigenin (6) and flavokawain A (8) have also been indicated to induce apoptosis and cell cycle arrest in various cancer cells [13-15].



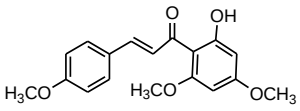
Xanthoangelol (5)



Isoliquiritigenin (6)



Licochalcone-A (7)



FlavokawainA (8)

Edwards et al.[16] have also shown that chalcones were effective antimitotic agents by binding to tubulin and noticed that reduction of the carbonyl group of chalcone diminished this activity. They noted that thiol-containing reagent present at the colchicine's binding site on tubulin, binds with enone moiety and stopped tubulin polymerisation as given in Figure-2. Natural and synthetic chalcones have been reported to possess strong antiproliferative effects in primary as well as established ovarian cancer cells[17] and in gastric cancer (HGC-27) cells [18]**.** Hydroxyl chalcones and isoliquiritigenin have shown to be potent inhibitors of skin carcinogenesis [19].The remarkable biological potential of these chalcones is due to their possible interactions with various proteins related to cell apoptosis and proliferation. Recent studies have shown that these chalcones induce apoptosis in a variety of cell types, including breast cancers [20-22]**.**

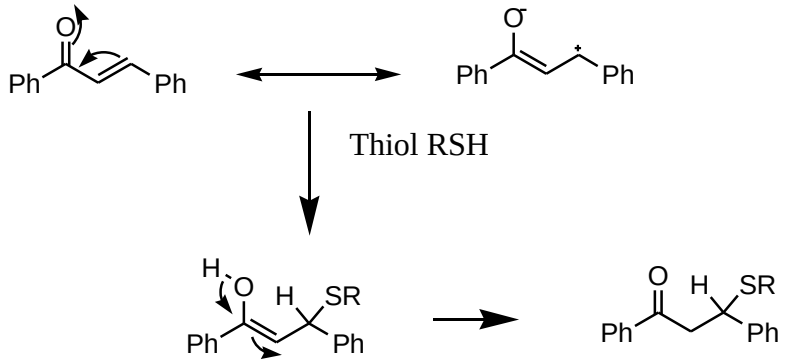


Figure 2: Reaction of a representative chalcone (Michael reaction acceptor) and a nucleophilic thiol (RSH)

CONCLUSION AND FUTURE PROSPECTS

In current scenario cancer is emerging as a major cause of morbidity and mortality. At present there are two ways of treatment of cancer is chemotherapy and radiotherapy.Clinical practice of cancer chemotherapy has achieved considerable success; however, it still holds scope to improve, particularly in terms of efficacy and safety of enrolled chemotherapeutic regimes. Thus, there is an urgent need to identify new chemo types or re-examine old molecules to transform them into appropriate clinical candidates. This review has summarized some chalcone derivatives as anticancer agent very concisely, which will be useful to scientists working on the synthesis of more chalcone derivatives and biological testing for cancer cure.

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REFERENCES

[1] Virtual chembook, Elmhurst College. Ophardt, 2003: 0.
[2] Nam N.H., Kim Y., You Y.J., Hong D.H., Kim H.M.&Ahn, B.Z. (2003). Cytotoxic 2',5'-dihydroxychalcones with unexpected antiangiogenic activity. Eur. J. Med. Chem., 38 :179.
[3] Stoll R., Renner C., Hansen S., Palme S., Klein C., Belling A., Zeslawki W.,Kamionka M., Rehm T.,Muhlhahn P., Schumacher R., Hesse F., Kaluza B.,Voelter W,Engh R.A.&Holak T.A. (2001). Chalcone derivatives antagonize interactions between the human oncoprotein MDM2 and p53. Biochemistry, 40:336.
[4] Kumar S.K., Hager E., Pettit C.,Gurulingappa H., DavidsonN.E.& Khan S.R (2003). Design, synthesis, and evaluation of novel boronic-chalcone derivatives as antitumor agents.J. Med. Chem., 46: 2813.
[5] Sabzevari O., Galati G.,Moridani M.Y.,Siraki A.& O'Brien P.J, (2004). Molecular cytotoxic mechanisms of anticancer hydroxychalcones.Chemico-Biological Interactions, 148:57.
[6] De Vincenzo R.,Ferlini C., Distefano M.,Gaggini C., Riva A., Bombardelli E.,Morazzoni P.,Valenti P.,Belluti F.,Ranelletti F.O., Mancuso F.&ScambiaG. (2000). In vitro evaluation of newly developed chalcone analogues in human cancer cells. Cancer Chemother. Pharmacol., 46: 305.
[7] Saydam G.,Hakan Aydin H.,Sahin F.,Kucukoglu O.,ErciyasE.,Terzioglu E.,Buyukkececi F.&Omay S.D.(2003). Leukemia Res., 27: 57.
[8] De Andrade Cunha G.M.,Fontenele B.,Nobre Junior H.V.,De Sousa F.C.M., Silveira E.R., Nogueira N.A.P.,De Moraes M.O., Viana G.S.B., Costa-Lotufo L.V. (2003).Phytotherap. Res., 17:155.
[9] Petitt, G. R., Gragg G. M., Herald D. L., Schmidt J. M.&Lohavanijaya P.(1982). Isolation and structure of combretastatin. Can.J.Chem., 60:1374.
[10] Mc Gown A. T.& Fox B. W. (1990). Differential cytotoxicity of Combretastatins A1 and A4 in two daunorubicin-resistant P388 cell lines. Cancer Chemother. Pharmacol., 26 :79.
[11] Kimura Y.& Baba, K. (2003). Antitumor and antimetastatic activities of Angelica keiskei roots, part 1: Isolation of an active substance, xanthoangelol .Int. J. Cancer. , 106 :429–437.
[12] Tabata K.,Motani K.,Takayanagi N., Nishimura R.,Asami S., Kimura Y.,Ukiya M., Hasegawa D., Akihisa T.& Suzuki T.(2005). Xanthoangelol, a Major Chalcone Constituent of Angelica keiskei, Induces Apoptosis in Neuroblastoma and Leukemia Cells. Biol. Pharm.Bull., 28: 1404–1407.
[13] Fu Y., Hsieh T.C., Guo J.,Kunicki J., Lee M.Y.,Darzynkiewicz Z.& Wu J.M.(2004). 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., 322: 263–270.

[14] Hsu Y.L.,Kuo P.L., Chiang L.C.& Lin, C.C.(2004). Isoliquiritigenin inhibits the proliferation and induces the apoptosis of human non-small cell lung cancer. A549 Cells Clin. Exp. Pharmacol. Physiol., 31: 414–418.
[15] Zi X.&Simoneau A.R.(2005).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., 65:3479–3486.
[16] Edwards M.L., Stemerick D.M.& SunkaraP.S.(1990). Chalcones: a new class of antimitotic agents. J. Med.Chem., 33:1948.
[17] De Vincenzo R.,Scambia G.& Mancuso S. (1995).Anticancer Drug Des., 10: 481–490.
[18] Shibata S. (1994). Anti-tumorigenic chalcones. Stem Cells., 12: 44–52.
[19] Yamamoto S., Aizu E., Jiang H.,Nakadate T., Kiyoto I.,Wangand J. C.& Kato, R.(1991). The potent antitumor promoting agent isoliquiritigenin.Carcinogenesis, 12:317–323.
[20] Claude-Alain C., Jean-Chritophe L., Patrick T., Christelle P., Gerard H., Albert-Jose C.& Jean-Luc D. (2001). Anticancer Res. 21:3949–3956.
[21] Wei B. L., Teng C. H., Wang J. P., Won S. J., Lin C.N.(2007). Synthetic 2′,5′-dimethoxychalcones as G_2/M arrest-mediated apoptosis-inducing agents and inhibitors of nitric oxide production in rat macrophages. Eur. J.Med. Chem. 42 :660–668.
[22] Takahashi T.,Takasuka N.,Iigo M., Baba M., Nishino H.,Tsudaand H.&Okuyama T. (2004). Cancer Sci.,95:448–453.