1. INTRODUCTION

1.1 CANCER

Cancer is a comprehensive terminology for a multitudinous group of maladies characterised by growth of abnormal cells which then invades adjoining parts of the body or proliferates to other organs through blood and lymphatic systems. Earliest description of cancer dates back to 3000 B.C. Origin of the word ‘cancer’ is credited to Greek physician Hippocrates, whose terms ‘carcinos’ and ‘carcinoma’ were later translated into Latin term ‘cancer’ referring to a crab, because the finger-like spreading projections from a cancer resembles the shape of a crab. Similarly the term ‘oncos’ which means swelling was given by Greek physician Galen. The branch dealing with the study and treatment of tumors is hence referred to as oncology. Chief types of cancers include carcinoma, sarcoma, leukemia, lymphoma and CNS cancers. According to WHO, cancer is the second leading cause of mortality worldwide. As per statistics of centers for disease control and prevention (CDC, an US federal agency), prostate, lung and colorectal cancers are most common amongst men and breast, lung and colorectal cancers are most usual amongst women. But cancer can affect any part of the human body. Major causes for cancer include smoking, poor lifestyle habits, unhealthy diet, infection, pollution, radiation, lack of awareness.

1.2 CANCER TREATMENT METHODS

Several treatment methods like surgery, chemotherapy, radiation therapy, hormone therapy, immunotherapy, stem cell therapy and targeted drug therapy are in practice. In cancer therapeutics, staging is crucial to choose between local treatment (surgery, radiation therapy, etc) and systemic treatment (chemotherapy,
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Commonly most types of cancers have four stages where stage 1 refers to a condition where cancer is relatively small and contained within an organ it originated. Stage 2 refers to a phase where tumor has grown in size but has not started to spread into surrounding tissues. Stage 3 is where cancer has started to spread into surrounding tissues and there are cancer cells in the lymph nodes in that region. Stage 4 is a plight where cancer has spread to other body organs and is referred to as metastasis.

1.3 TARGETED DRUG THERAPY

Targeted drug therapy is a genre of therapeutic method where drugs specifically attack cancer cells thereby sparing normal cells. Pharmaceutical instability in conventional dosage form, biopharmaceutical low absorption, high membrane binding, biological instability, pharmacokinetic/pharmacodynamic short half-life, large volume of distribution, low specificity, low therapeutic index are reasons for requirement of targeted drug therapy. Targeted drug therapy is advantageous as it specifically attacks cancer cells by targeting specific genes/proteins which are overexpressed in cancer cells or by inhibiting enzymes which instruct cancer cells by sending signals to grow and divide uncontrollably thereby sparing normal cells. Targeted drug therapy may change proteins within cancer cells, stop making new blood vessels, trigger immune system to kill cancer cells, etc. Main categories of targeted drug therapy include use of small molecules like Gleevec, Gefitinib, etc or monoclonal antibodies like Rituximab, Trastuzumab, Cetuximab, etc. Other merits of targeted drug therapy are its improved efficacy, use of relatively smaller dose of drugs and fewer side effects. This method can be used in combination with other treatment methods. Strategies for targeted drug therapy include passive targeting, inverse targeting, active...
targeting, ligand mediated targeting, physical targeting, dual targeting, double targeting. In targeted drug therapy, drug toxicity, biocompatibility, biodegradability, physiochemical stability, extent of target specificity, controllability of rate of drug release and its impact on drug activity, leakage issues during transit, nature of carriers, optimisation of overall strategy are to be taken into account.

1.4 ROLE OF NATURAL PRODUCTS IN DRUG THERAPY

Natural products (NPs) or natural product based drugs have received considerable attention in drug therapy due to their chemical diversity, biochemical specificity and biocompatibility. The use of NPs dates back to ancient Mesopotamian days. Even ancient texts on Ayurveda such as Charaka Samhita and Sushruta Samhita have articulated about the use of NPs as early as 900 B.C. and 600 B.C. respectively. Some of the NPs and NP based drugs which possess anticancer potential include vincristine, vinblastine, paclitaxel, docetaxel, topotecan, irinotecan, etoposide. Though NPs are widely used in drug therapy, they have some limitations such as difficulties in access and use, high cost of collection of natural product samples, requirement of several separation cycles, concerns about intellectual property rights, etc. Most importantly, safety and toxicity are crucial to determine the effectiveness of natural product based drug research. Therefore these issues have led to a significant decrease in natural product based drug research in the last decade.  

1.5 CURCUMIN – AN EXCEPTIONAL NATURAL PRODUCT

But curcumin ((1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (Fig. 1.1) is an exceptional natural product as it is
extremely safe, does not show any undesirable side effects and its efficacy is also manifested. Curcumin is a hydrophobic phytopolyphenolic compound isolated from the rhizomes of Indian herb *Curcuma Longa* along with other curcuminoids like demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC).

![Figure 1.1 Curcuminoi](image)

**Figure 1.1 Curcuminoi: curcumin, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC)**

Ever since curcumin was isolated for the first time in 1815 by Vogel and Pelletier, there are several modified and improved methods reported for isolation of curcumin. Approximately, a century after isolation of curcumin, first report on synthesis of curcumin was published in 1918. Pabon HJ reported the synthesis of curcumin from vanillin and acetylacetone-B$_2$O$_3$ complex. Rao EV et al., have reported new strategy for synthesis of curcuminoids using acetylacetone difluoroboronite complex (AADFB). Curcumin (C$_{21}$H$_{20}$O$_6$, Mol. Wt = 368.38 g mol$^{-1}$) is a yellow solid. It is insoluble in water but soluble in solvents like dimethyl sulfoxide (DMSO), methanol, ethanol, acetonitrile, etc.
In non polar solvents, almost 90% of curcumin exists as the enol tautomer due to stabilisation by intramolecular hydrogen bonding between enolic hydroxyl group and keto carbonyl group whereas in polar solvents, the keto form predominates (Fig. 1.2). pH also plays a crucial role in determining the form of existence. In acidic and neutral pH, curcumin exists as keto tautomer whereas in alkaline solutions, enol form predominates.

![Figure 1.2 Keto-enol tautomerism in curcumin](image)

The UV absorption spectrum of curcumin exhibits two strong absorption bands at 410-430 nm and 265 nm. Fourier Transform Infrared (FTIR) spectrum of curcumin has a broad band at 3293 cm\(^{-1}\) and a strong band at 1626 cm\(^{-1}\) which correspond to phenolic and \(\alpha,\beta\)-unsaturated carbonyl groups respectively. Characterisation of curcumin is preferably done using Nuclear Magnetic Resonance (NMR) spectroscopy where the methoxy protons appear as a sharp singlet at \(\delta\) 3.95 ppm, -CH proton flanked between two carbonyl groups appear at \(\delta\) 5.8 ppm as a singlet and the aromatic and vinylic protons appear in the range of \(\delta\) 6.48-7.59 ppm.

\(\alpha\)-Methoxyphenolic group, \(\alpha,\beta\)-unsaturated ketone moiety and a seven carbon linker are the important functionalities present in curcumin.
1.6 BIOLOGICAL ACTIVITIES OF CURCUMIN AND RELATED COMPOUNDS

Curcumin and its analogues, derivatives, hybrids, physically modified forms and formulations exhibit wide range of biological activities including antiviral, antidiabetic, antihypertensive and antihypercholesterolemic, antiretroviral, antiallergic, antibacterial, antifungal and antioxidant properties. Especially there are quite a few reports on anticancer activity of curcumin and related compounds. Curcumin is proven to interdict the survival and metastasis of prostate cancer cells via the Notch-1 pathway. There are several molecular targets and mechanisms of action proposed to account for the anticancer property of curcumin and its counterparts. Curcumin functions as an antiproliferative agent, antioxidant and carcinogen-blocking agent and it targets transcription factors, growth factors, receptors, enzymes, kinases, oncogenes, etc. Either one or combination of survival signal reduction, induction of apoptosis, arrest of cell cycle progression, generation of reactive oxygen species (ROS) are proven to be mechanisms of action for curcumin against different cancers. As per the results of tubulin polymerisation assay, few curcumin analogues are
affirmed to inhibit microtubule assembly.\textsuperscript{29} According to a study, curcumin is shown to increase the levels of intracellular free calcium, which involves B-cell lymphoma 2 (Bcl-2) mediated Inostol 1,4,5-triphosphatre receptors (IP3R) phosphorylation. These features are attributed to cytotoxic effect of curcumin on lung cancer cell line A549.\textsuperscript{30} Curcumin inhibits metastasis through the adiponectin/NF-κβ/MMPs signaling pathway\textsuperscript{31} and it instigates upregulation of tumor-suppressive miR-34a and downregulation of miR-27a in colorectal cancer cells.\textsuperscript{32} A curcumin analogue is found to inhibit SERCA2 expression and proven to exhibit enhanced inhibitory effect against colorectal cancer cells as compared to curcumin.\textsuperscript{33} Two analogues of curcumin are ascertained to inhibit cell cycle progression and downregulate levels of Thymidylate synthase (TS) in colorectal cancer cells.\textsuperscript{34} As per a study, curcumin could be a plausible annihilator for cancer harboring PTEN mutations.\textsuperscript{35} Curcumin inhibits breast cancer metastasis via down-regulation of inflammatory cytokines\textsuperscript{36} and there is a report according to which it could be used as an adjuvant agent to chemotherapy in treatment of triple negative breast cancer.\textsuperscript{37} Curcumin arrests progression of breast cancer cells through Nrf2-mediated down-regulation of Fen1 expression.\textsuperscript{38} Curcumin induces apoptosis by suppressing sarco/endoplasmic reticulum Ca\textsuperscript{2+} ATPase activity in ovarian cancer cells.\textsuperscript{39} Curcumin could be used in the treatment of pancreatic cancer as it is demonstrated to target miR-7.\textsuperscript{40} Curcumin induces apoptosis in leukemia cells.\textsuperscript{41,42} There are several reports on anticancer activity of this natural product against hepatocellular carcinoma.\textsuperscript{43-45} Though curcumin is a multitherapeutic agent displaying broad spectrum of biological activities and is safe and efficacious, it suffers from limitations due to poor aqueous solubility and
bioavailability. Some of the reported degradation pathways of curcumin are listed below.

Scheme 1.1 Chemical degradation of curcumin at neutral/basic pH
Scheme 1.2 Oxidative cyclisation of heptadienone moiety\textsuperscript{48}

Scheme 1.3 Photodegradation of curcumin\textsuperscript{49}
1.7 STRUCTURAL MODIFICATIONS OF CURCUMIN

In order to overcome the above mentioned problems and to improve the biological activity of curcumin, several strategies have been adopted which include use of adjuvants, nanoparticles, liposomes, micelles and phospholipid complexes, derivatives, analogues, etc.  

There are several reports on structural modification of curcumin which include changes in aromatic ring portion, phenolic hydroxyl group, seven carbon linker chain, double bond (ene) and enone part.

Figure 1.4 Structural modifications possible with curcumin

A few examples of phenolic hydroxyl modifications reported in literature are represented below.  

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Synthesis and Evaluation of Novel Curcumin Conjugates and Hybrids as Potential Anticancer Agents

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One more type of change involves modification at active methylene group.\textsuperscript{51}

Analogues obtained by varying the linker chain length are listed below.\textsuperscript{52}
Reduction of double bond(s) in the seven carbon linker chain has led to new set of compounds.\textsuperscript{52}

Another strategy involves synthesis of pyrazole and isoxazole conjugates of curcumin.\textsuperscript{53}

Carbocyclic analogues of curcumin have also been reported.\textsuperscript{54,55}
Another genre of compounds are obtained by varying the aromatic rings with heterocyclic ring systems.\textsuperscript{52,56}

Metal complexes of curcumin have also been reported.\textsuperscript{56}

In fact there is a dedicated repository of curcumin related compounds called curcumin research database (CRDB) which has a huge list of research publications and patents about curcumin analogues and their molecular targets.
In the present study, synthesis, characterisation and determination of anticancer potential of chalcones (which have structural resemblance with curcumin) derived from vanillin and isovanillin are presented in chapter 2.

Synthesis, characterisation and determination of in vitro cytotoxicity of glycosides of curcumin and isocurcumin are discussed in chapter 3.

Synthesis and evaluation of cytotoxic potential of curcumin-quinolone hybrids are compendiously discussed in chapter 4.

Molecular docking studies of most potent chalcones and curcumin-quinolone hybrids are recapitulated in chapter 5. Drug likeness (Lipinski’s rule) and ADMET properties of all chalcones and curcumin-quinolone hybrids reported in the study have also been ascertained.
1.8 REFERENCES


