Exploring Curcumin and Its Derivatives: Insights into Their Structure–Activity Relationship as Anticancer Agents

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ABSTRACT

Purpose: *Curcumin, a bioactive compound from turmeric (Curcuma longa), exhibits multiple therapeutic properties such as anti-inflammatory, antimalarial, antifungal, antibacterial, antioxidant, and antitumor effects. To highlights the Indian origin medicinally important plant and its extract, this review is carried out.*

Methodology: *On the basis of literature availability data, this review has been carried out and structural activity relationship is illustrated on the basis of variation of activity with structural changes.*

Analysis/Results: *The two methoxy phenolic groups in curcumin are essential for its bioactivity. Modifications of curcumin's β-diketone and methylene α-hydrogen groups are a focus to enhance its stability and efficacy. Derivatives with electron-withdrawing groups like fluorine or nitro groups enhance bioactivity. Modifications such as substituting phenolic groups or reducing the flexibility of the molecule show improved therapeutic profiles.*

Originality/Value: *In the present article, importance of the curcumin and its derivatives in the field of anticancer agent is extensively discussed on the basis of literature available reports.*

Type of Paper: *Review Paper.*

Keywords: Curcumin, SAR study, anticancer agents, turmeric, bioactivity.

1. INTRODUCTION :

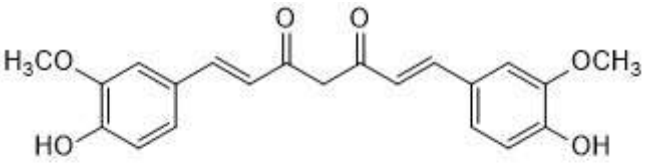
Ayurveda is 5,000 year old Indian traditional medical treatment system to fight against diseases. Turmeric has been used to treat variety of disorders including skin diseases, digestive issues, arthritis, and inflammation. Turmeric is also used in traditional Chinese medicine and other Eastern Asian medical systems [1].

Curcumin, or diferuloylmethane, is a bioactive compound found in turmeric (*Curcuma longa*) and *Curcuma xanthorrhiza* oil. This versatile molecule demonstrates a wide range of biological activities, including antibacterial, anti-inflammatory, hypoglycemic, antioxidant, wound-healing, and antimicrobial properties [2]. Curcumin derivatives are chemical compounds that are derived from curcumin, a polyphenolic compound found in turmeric [3], polyphenolic compounds of turmeric are classified as follows [4]:

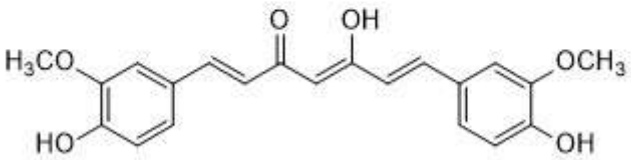
- **Demethoxycurcumin (DMC)**: A curcuminoid that occurs in turmeric in lesser amounts than curcumin,
- **Bis-demethoxycurcumin (BDMC)**: A curcuminoid that occurs in turmeric in lesser amounts than curcumin,
- **DiAcetylCurcumin (DAC)**: A derivative that is more stable than curcumin in physiological medium,

Curcumin (Figure 1) is a key member of the curcuminoid family and is also referred to as diferuloylmethane. It is derived from the rhizome of *Curcuma longa L.* [5, 6]. The primary roots of the plant, located underground, take on shapes resembling eggs and pears, while the lateral roots develop as tuberous structures (rhizomes). It is the compound responsible for turmeric's vibrant yellow color

and is widely used in culinary, cosmetic, and medicinal applications. Curcumin has poor solubility in water but dissolves well in organic solvents like ethanol, methanol, acetone, and dimethyl sulfoxide [7]. First identified in 1815, its chemical structure was elucidated in 1973 by Roughley and Whiting, with its melting point recorded between 176°C and 177°C [8-9]. The chemical name of curcumin is 1,7-bis(4-hydroxy-3-methoxyphenyl)- 1,6-heptadiene-3,5-dione. Recognized as the primary bioactive and non-toxic compound in turmeric, curcumin is valued for its safety and its broad spectrum of biological activities [10]. However, a significant challenge associated with curcumin is its limited bioavailability and poor absorption in the body [11]. Curcumin and its derivatives are known for their biological activities, including: anti-inflammatory, antioxidant, and antitumor. Curcumin and its derivatives have been studied for their potential therapeutic applications in treating neurodegenerative disorders and brain tumors. They have also been studied for their potential as molecular probes for diagnostic imaging [12]. Curcumin is valued for its extensive pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, and anticancer effects. It has been recognized as a safe and non-toxic compound, making it a key focus in both traditional medicine and modern therapeutic research. However, curcumin's potential is limited by challenges such as poor water solubility, low stability, and limited bioavailability. These drawbacks have spurred scientific efforts to develop innovative formulations and delivery systems to enhance its therapeutic applications. Its diverse biological actions and its significant role in health and wellness continue to make curcumin a prominent subject of study in natural product research.



Keto form of Curcumin



Enol form of Curcumin

Fig. 1: Structure of Curcumin

2. OBJECTIVES :

(1) Carryout literature survey on importance of the curcumin and curcuminoid in the anticancer activity.
(2) Identifying the structural changes requirements to enhance anti-cancer activity.
(3) To know structure activity relationship in curcuminoid and anti-cancer activity.

3. IMPORTANCE OF CURCUMIN :

Curcumin has major application in the field of pharmaceutical foiled, along with this, shows diversified activity in many branches of chemistry.

3.1 Food additive:

Curcumin is used as a food additive to colour and flavour foods. It's the E100 colouring in the European Union and is approved by the FDA in the US.

3.2 Biomedical applications:

Curcumin is used in tissue engineering, drug delivery, and biosensors.

3.3 Complexometric indicator:

Curcumin is used as a complexometric indicator for boron. It reacts with boric acid to form a red-coloured compound called rosocyanine.

3.4 Therapeutic properties:

Biocompatibility of the curcumin has made this moity integral part of the traditional medicine, many therapeutic properties, including antioxidant, anti-inflammatory, analgesic, antiseptic, and anticancer properties. It may also help with arthritis, depression, and heart health [13].

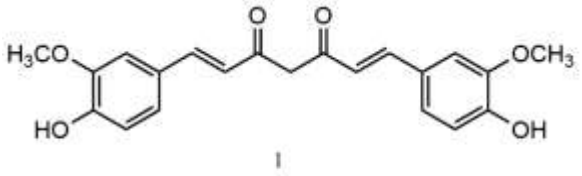
3.5. Photodynamic Therapy:

Photosensitizers, have the ability to produce reactive oxygen species (ROS) when exposed to light of a specific wavelength. This process triggers potent phototoxic effects that can target malignant cells and various pathogens. Among the extensively studied phytochemicals, curcumin stands out for its broad spectrum of therapeutic applications. It has demonstrated significant photocytotoxic activity at micromolar concentrations against numerous cancer cell lines. Curcumin and its natural derivative, bisdemethoxycurcumin both shows photosensitization and useful in photodynamic therapy [14-15].

4. REVIEW OF LITERATURE :

Curcumin and curcuminoid are the marked for the excellent anti-cancer activity [16]. In the present review article, brief literature survey on curcumin and its derivatives has been carried out to explore the structural diversity required for the exhibit superior activity to anti-cancer agents. Even though the many review articles are available for the curcumin in the literature they are focusing on different aspects such as mechanism of action, various bioactivity etc. moreover this article give the insights of anticancer activity and their mechanism of action.

Chemo-preventive effects of curcumin (1) and its derivative and tetrahydrocurcumin (THC) (2) were examined by Kim et al., and found to exhibit potential as chemo preventive agents against colon carcinogenesis. these compounds influence on proliferation of colonic crypt epithelial cells was also assessed in terms of 5-bromo-29-deoxyuridine (BrdU) incorporation [17].



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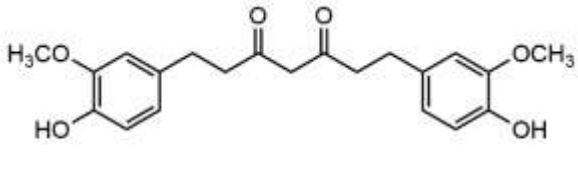

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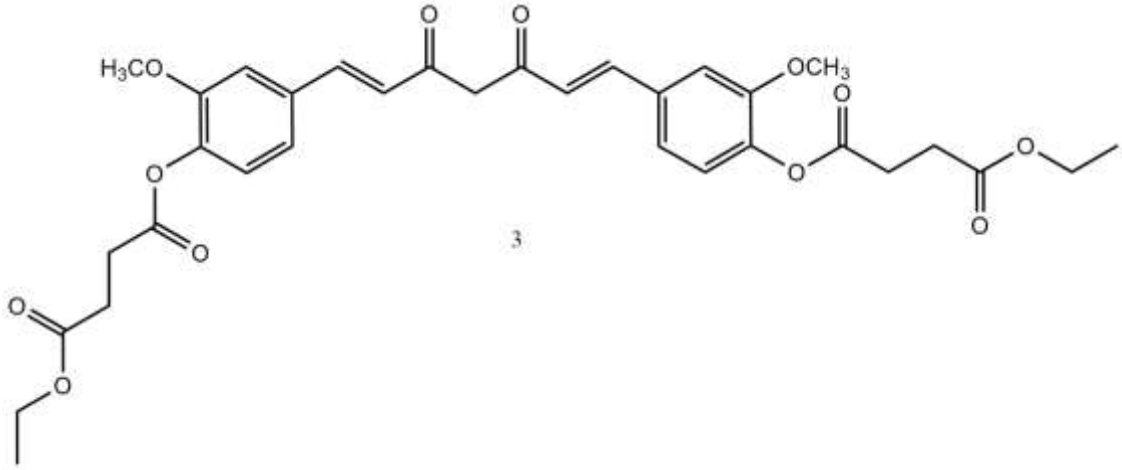
Wichitnithad et al., synthesized a series of curcumin derivatives with ester linkage, via aldol condensation, showed activity against anti-colon cancer activity. Compound 3 with prominent activity 1.84 IC_{50} values in the series of synthesized curcumin analogoues [18].



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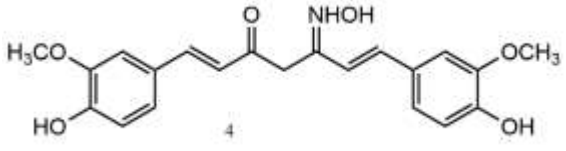
Agrawal and Mishra synthesized new curcumin derivatives, were also evaluated for antiproliferative effects against MCF-7 estrogenic-dependent breast cancer cell line [19],



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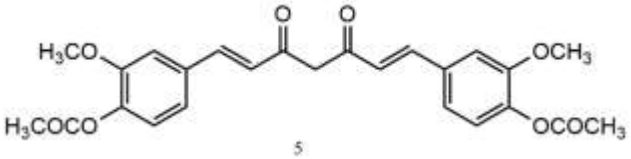

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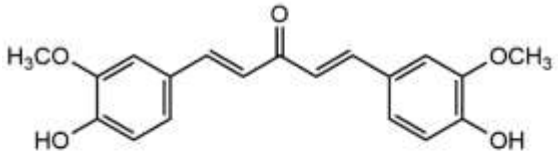
In the series of the curcuminoid derivatives by Yellapu et a., compound 6 and 7 displayed significant anticancer action when compared to curcumin alone in various ER+ and ER- human breast cancer cells with IC_{50} values 0.3 to 5.7 µM, respectively. Here introduction of methoxy group, ie electron donating group increases the activity [20].



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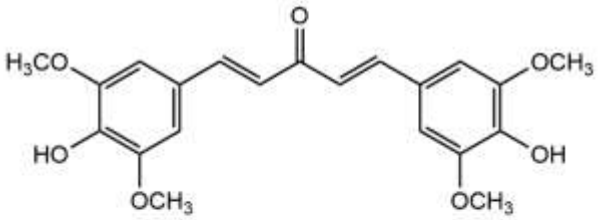

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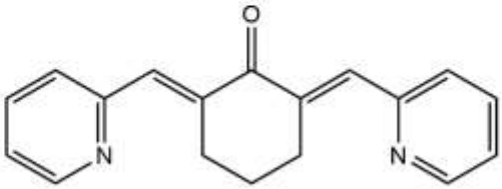

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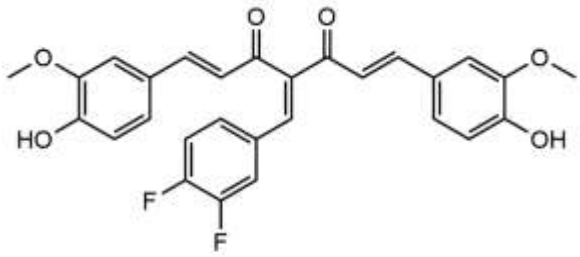
Pyridine derivatives of curcumin were prepared and tested against CWR-22Rv1 prostate cancer cell line, in the series of the synthesized compound 8 shows highest potent inhibitory efficacy with 0.53±0.1 µM concentration [21].

In vitro studies of a curcumin derivatives of difluorinated-curcumin (9) show activity on pancreatic cancer cell lines and has capacity to inhibit the growth and survival of these cancer cells [22]. Curcumin derivative (10) which has a more significant ability for inhibiting the pancreatic cell lines than curcumin. through the inhibition of the inhibition of STAT3 [23]



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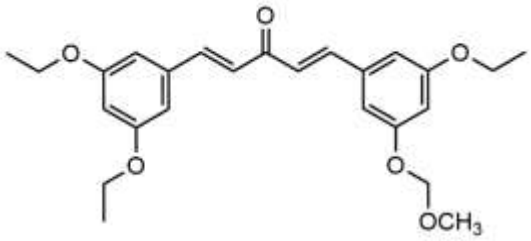

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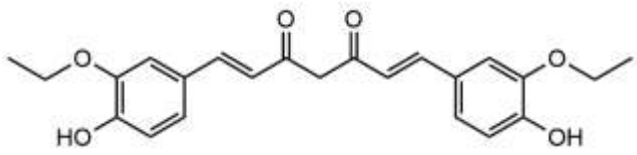
Slightly modification in the structure of parent curcumin or construction of the ring structure at alpha methylene position increases the anticancer activity. For example and 5-bis(4-hydroxy- 3-methoxybenzylidene)-N-methyl-4-piperidine (11) and 1,7-bis-(4-hydroxy-3-ethoxyphenyl)-1,6-heptadien-3,5- diene (12) shows superior activity against breast cancer cell lines compare to curcumin [24].



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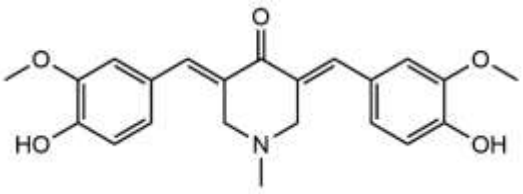

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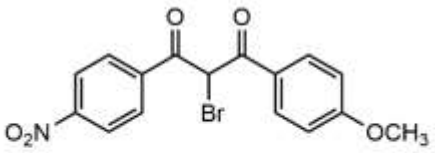
Junko.I.et al synthesized, curcumin derivatives and examined for in vitro cytotoxicity against a panel of human tumour cell lines. Bromo substituted on alpha methyl position (13) is marked for the most potent activity with ED_{50} vales 0.97 and <0.63 µg/mL for HOS (bone cancer) and 1A9 (breast cancer) cell lines respectively [25]. On insertion of cyclic six member ring at the position of the diketone, cytotoxicity in the NCI in vitro anti-cancer cell line and also effective in in-vitro anti-angiogenesis assays [26].



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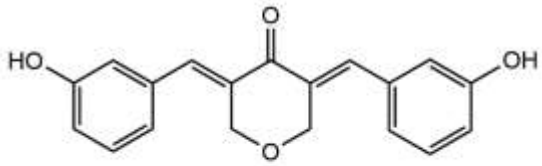

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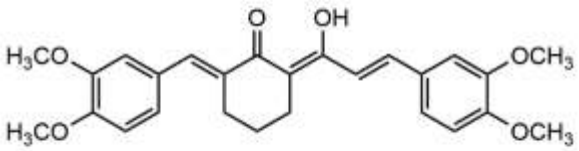

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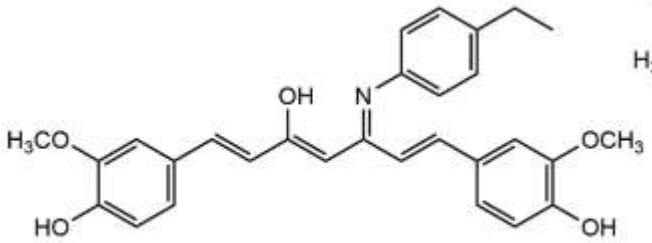

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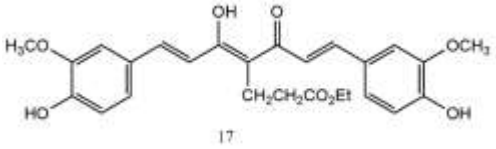
Cyclic derivatives of curcumin were marked for the significant anti-cancer activity against murine and human cancer cell lines [27]. Compound 15 has IC_{50} value 1.4±0.3 and 1.2 ± 0.2 µM against L1210 and Molt4C/8 cell lines respectively.

Zivdar et al., synthesized the curcumin derivatives via condensation reaction, exhibited the anticancer activity against BRC-9 breast cancer cells. In the series of the synthesized compounds para ethylamine substituted (16) marked for the superior activity [28].

Elias et al. synthesized curcumin derivatives and evaluated for cytotoxic anti-cancer activity against PC-3 and LN Ca Phumanprostate cancer cell lines, compound 18 is the prominent compound, activity on LNCaP cell line with an IC_{50} value of 0.2 µM, and compound 17 with IC50 value 1.5 µ molar concentration [29].



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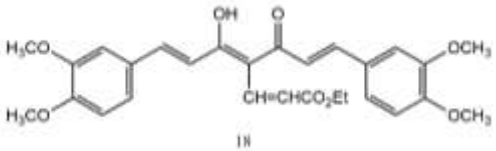
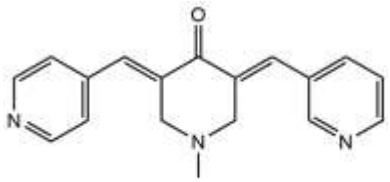


18

1-Methyl-3,5bis [(E)4pyridyl) methylidene-]4-piperidone is a curcuminoid (19 & 20) with nitrogen as a hetero atom in the ring, exhibits superior cytotoxicity towards a variety of ER negative breast cancer cells [30].



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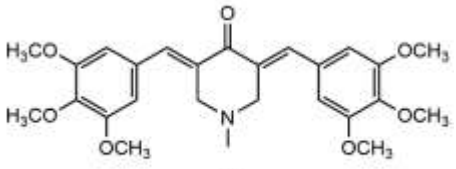

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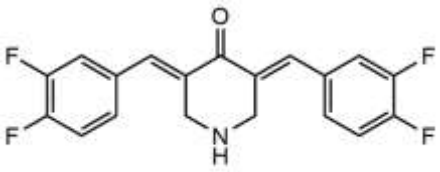
3,5-bis(3,4,5-trimethoxybenzylidene)-1-methylpiperidine-4-oneis (20) a curcumin derivative with group, is found to exhibit anti-cancer activity on canine histiocytic sarcoma cells with IC_{50} values 0.66 ± 0.057 µM and 0.79 ± 0.13 µM in the DH82 and Nike cell lines [31].

A large number of studies have showed that curcumin can modify the activation of NF-kB. Upon its activation by carcinogens it can suppress apoptosis and induce cellular transformation, proliferation, invasion, metastasis, chemoresistance, radio-resistance, and associated inflammation [32]. A new

curcumin analogue 21 has been synthesized and investigated for its anticancer effect on the lung cancer cell lines. It has presented an excellent anti-lung cancer activity by hindering the tumor growth, inducing the apoptosis and elevating the expression of apoptosis related proteins like caspase 3, Bax and p53 [33].



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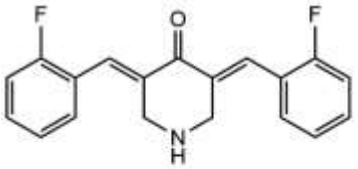
Curcumin can also act as an anti-metastatic agent and inhibit cancer cell migration and invasion invitro by reducing the expression and activity of many enzymes that facilitates matrix metalloproteinases MMP-2 and MMP-9. Moreover, curcumin has been proven to inhibit telomerase activity in the cervical cancer, A novel curcumin analogue (22) has displayed multiple potent bioactivities and enhanced bioavailability [34].



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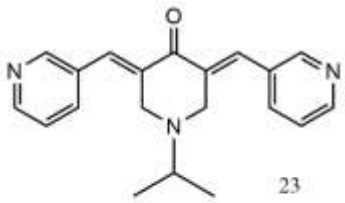

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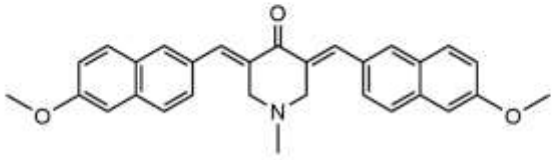

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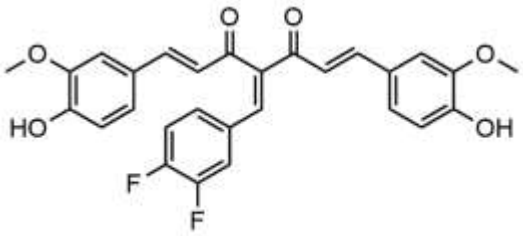
The curcumin analogues 23 and 24 displayed potent cytotoxicity on the prostatic cancer patients, It was noted that both these analogs enhanced the number of cell lines in G2/M phase of the cell cycle, induced apoptosis and cell cycle arrest.

In vitro studies of curcumin analogue, difluorinated curcumin on variety of pancreatic cell lines have proved its ability of hindering the cell growth and the survival of cancer cells. The curcumin derivative 26 has more capability of hindering the pancreatic cell lines due to improved solubility and inhibition of the STAT3 signaling pathway [35].



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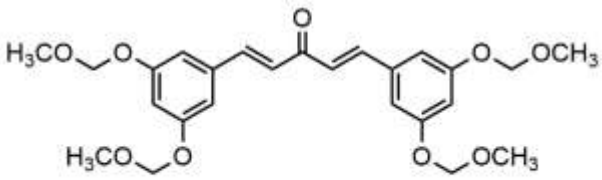

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5. MECHANISMS OF ANTICANCER ACTION OF CURCUMIN AND ITS DERIVATIVES :

Curcumin and its derivatives exhibit anticancer properties by targeting multiple signaling pathways that regulate cell proliferation, survival, apoptosis, metastasis, and angiogenesis. The multitargeted nature of these compounds makes them effective against various cancer types, often overcoming resistance to conventional therapies. Below is a detailed explanation of the key mechanisms underlying their anticancer activity:

5.1 Induction of Apoptosis:

Apoptosis, or programmed cell death, is a critical mechanism for eliminating cancer cells. Curcumin has been shown to induce apoptosis (programmed cell death) in cancer cells by modulating both intrinsic and extrinsic apoptotic pathways. These pathways involve:
Intrinsic Pathway: Curcumin triggers mitochondrial dysfunction, leading to the release of pro-apoptotic factors like cytochrome c, which activates caspase proteins (especially caspases 3, 8, and 9) and induces apoptosis [36].
Extrinsic Pathway: Curcumin can activate death receptors on the cell surface (e.g., Fas receptor) that initiate caspase-dependent apoptosis.
Curcumin's ability to promote apoptosis is particularly significant in cancer cells, which often evade normal apoptotic mechanisms [37].

5.2 Inhibition of Cell Proliferation:

Curcumin inhibits cancer cell proliferation by regulating various signaling pathways involved in cell cycle progression. It affects key cell cycle proteins, such as cyclins and cyclin-dependent kinases (CDKs), and causes cell cycle arrest at different phases (G0/G1, S, G2/M phases), preventing tumor cell growth.
Inhibition of Cyclin D1: Cyclin D1 is often overexpressed in many cancers, and curcumin suppresses its expression, leading to cell cycle arrest in the G1 phase.
Regulation of p53: Curcumin can activate the tumor suppressor protein p53, leading to the arrest of the cell cycle and induction of apoptosis [38].

5.3 Inhibition of Angiogenesis:

Angiogenesis (the formation of new blood vessels) is crucial for tumor growth and metastasis. Curcumin inhibits angiogenesis by targeting various signaling pathways, including:
VEGF (Vascular Endothelial Growth Factor): Curcumin suppresses the expression of VEGF, a key molecule involved in angiogenesis.
HIF-1α (Hypoxia-Inducible Factor 1-alpha): Curcumin reduces HIF-1α levels, which is activated under low oxygen conditions in tumours to stimulate angiogenesis [39].

5.4 Suppression of Metastasis:

Curcumin can inhibit metastasis, the spread of cancer cells to distant organs, by affecting various molecular processes that contribute to tumor cell migration, invasion, and adhesion:
Matrix Metalloproteinases (MMPs): Curcumin inhibits MMPs, enzymes that degrade the extracellular matrix and facilitate cancer cell migration.
Epithelial-Mesenchymal Transition (EMT): Curcumin prevents EMT, a process where epithelial cells acquire migratory and invasive properties, contributing to cancer metastasis [40].

5.5 Modulation of Tumor Microenvironment

The tumor microenvironment, which includes stromal cells, immune cells, and extracellular matrix components, plays a critical role in cancer progression. Curcumin modifies the tumor microenvironment by:
Enhancing Immune Response: Curcumin activates immune cells like macrophages and dendritic cells and enhances the immune system's ability to target and destroy cancer cells.
Regulation of Fibroblasts: Curcumin suppresses the activity of cancer-associated fibroblasts (CAFs), which contribute to tumor growth and metastasis [41].

5.6 Inhibition of Stem Cell-Like Properties:

Cancer stem cells (CSCs) are a small subset of cancer cells that have self-renewal properties and are responsible for tumor initiation, recurrence, and resistance to chemotherapy. Curcumin has been shown to target CSCs by:
Downregulating Stem Cell Markers: Curcumin reduces the expression of stem cell markers like CD44, CD133, and ALDH.
Modulating Signaling Pathways: Curcumin affects key pathways involved in stem cell function, such as the Notch, Wnt/β-catenin, and Hedgehog pathways, reducing the self-renewal and tumorigenic potential of CSCs [42].

5.7 Synergy with Other Chemotherapeutic Agents:

Curcumin can enhance the efficacy of conventional chemotherapy and radiation therapy by: Chemosensitization: Curcumin sensitizes cancer cells to chemotherapeutic drugs (e.g., cisplatin, doxorubicin) and radiation by modulating drug resistance mechanisms, apoptosis, and DNA repair pathways [43].
Reducing Chemotherapy Resistance: Curcumin inhibits drug efflux pumps like P-glycoprotein (P-gp) and modulates multi-drug resistance (MDR), making cancer cells more susceptible to chemotherapy [44].

6. DISCUSSIONS :

Curcumin and curcuminoid derivatives exhibit the variety of the anti-cancer activity, at lower concentration. Two keto group which is separated by the methylene group in the moiety is main responsible for the observed activity. Structural changes also enhances the activity by proper insertion of electron donation group on alpha carbon atom of the diketone. Electron donating group on phenyl group also increases the activity. By constructing heterocyclic moiety between diketone enhances the activity. Some of the moiety with Flouro group also enhances the activity. By increasing the number of electron donating group more number of the sites are available for the binding.
Curcumin plays a role in various stages of carcinogenesis through multiple mechanisms, including: (a) preventing the initiation of tumors by exhibiting cytotoxic effects in early stages of cancer development, (b) reducing cellular proliferation, as demonstrated in antiproliferation studies, (c) promoting apoptosis, or programmed cell death, in cancer cells, (d) inhibiting angiogenesis (the formation of new blood vessels) and metastasis (the spread of cancer to other parts of the body), and (e) counteracting tumor-induced immunosuppression, thereby enhancing the immune response against cancer cells.

7. CONCLUSION :

Curcumin and curcuminoid derivatives are marked for the variety of anticancer activity, in the present review enlighten the structural importance of the moiety to show enhanced activity. Electron donating group and formation of heterocyclic moiety is mainly responsible for the enhancement of the activity. Mechanism of action is dependent on the structure of the moiety and type of the cancer cell lines.

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