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REVIEW ARTICLE **OPEN ACCESS**

Curcumin as an Anticancer Agent: Review

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ABSTRACT

Curcumin (diferuloylmethane) is a polyphenol derived from the Curcuma longa plant, commonly known as turmeric. Curcumin has a long history of use in ayurvedic medicine as a treatment for anti-inflammatory conditions. It consists of three main types of curcuminoid i.e., diferuloylmethane (which is the primary constituent and responsible for its vibrant yellow colour), demethoxycurcumin, and bisdemethoxycurcumin. It is non-toxic and has a variety of therapeutic properties such as antioxidant, analgesic, anti-inflammatory, and antiseptic. Most recently it has been found to possess anti-cancer activities via its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis, and metastasis. Curcumin has fewer side effects compared to chemotherapeutic drugs. It aids in the management of oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety, and hyperlipidaemia. It may also help in the management of exercise-induced inflammation and muscle soreness, thus enhancing recovery and performance in active people. The purpose of this review is to provide a brief overview of research regarding the health benefits of curcumin and anticancer activity of curcumin in human beings. Keyword: Curcumin; Anticancer, Structure-activity relationship, Mechanism of action, Anticancer activity, Anti-inflammatory activity, Antioxidant activity.

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INTRODUCTION

Despite the substantial advances in cancer therapy, the reported incidences of the disease and the mortality have not declined in the past 30 years [1]. An important factor in cancer prevention and treatment is understanding the molecular alterations that contribute to cancer development and progression. There are several common strategies for targeting specific cancer cells to inhibit tumour development, metastasis, and progression without causing severe side effects [2]. Additionally, the chemically synthesized anticancer agents, several anticancer compounds with different modes of action are extracted from plant sources, like Pacific yew, periwinkle, Betula alba, Cephalotaxus species, Taxusbrevifolia, Catharanthusroseus, Erythroxylumprevillei, Curcuma longa, and many others [3]. Curcuma longa or turmeric is grown and naturally available in tropical regions native to southern and southeastern tropical Asia. Among them, curcumin is that the most vital component of the rhizomes of turmeric L. (turmeric) [4] which was extracted from a turmeric plant in a pure crystalline form for the first time in 1870 [5].

In the past two decades, Curcumin and its derivatives have received immense attention due to their bio functional properties such as anti-tumour, antioxidant, and anti-inflammatory activities [6]. These properties are assigned to the key elements in the curcumin structure [7]. Curcumin (1, 7-bis (4hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also called diferuloylmethane, is that the most natural polyphenol found within the rhizome of Curcuma longa (turmeric) and others Curcuma spp. [8]. Curcumin is usually used as a colouring agent also as a food additive; curcumin has also shown some therapeutic activities. Curcumin curcumin has the power to manage a spread of signalling pathways involved in cell growth, apoptosis, invasion, metastasis, and angiogenesis in preclinical studies elicited scientific interest in its potential as an anticancer agent in tumour therapy [9]. Many registered phase I/II clinical trials are designed to investigate the effectiveness of curcumin alone or with first-line treatment in patients with breast, prostate, pancreatic, lung, or colorectal cancer are underway [10].

Curcumin has been found to inhibit plat elet aggregation in vitro [11,12], suggesting a potential for curcumin supplementation to increase the risk of bleeding in people taking anticoagulant or antiplatelet medications, such as aspirin, heparin, and warfarin (Coumadin), clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), and ticlopidine (Ticlid).

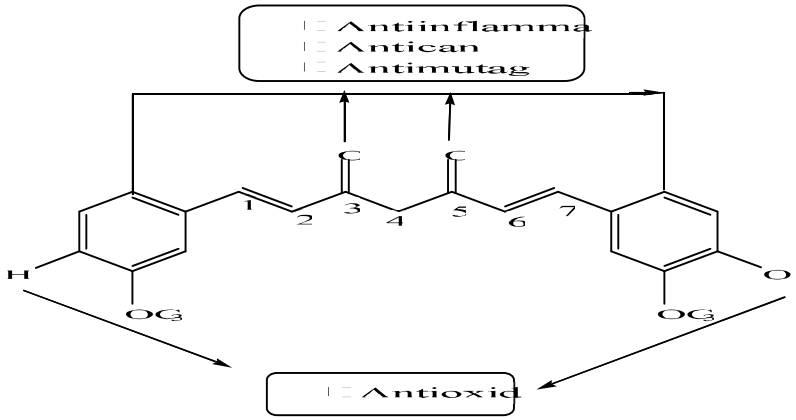
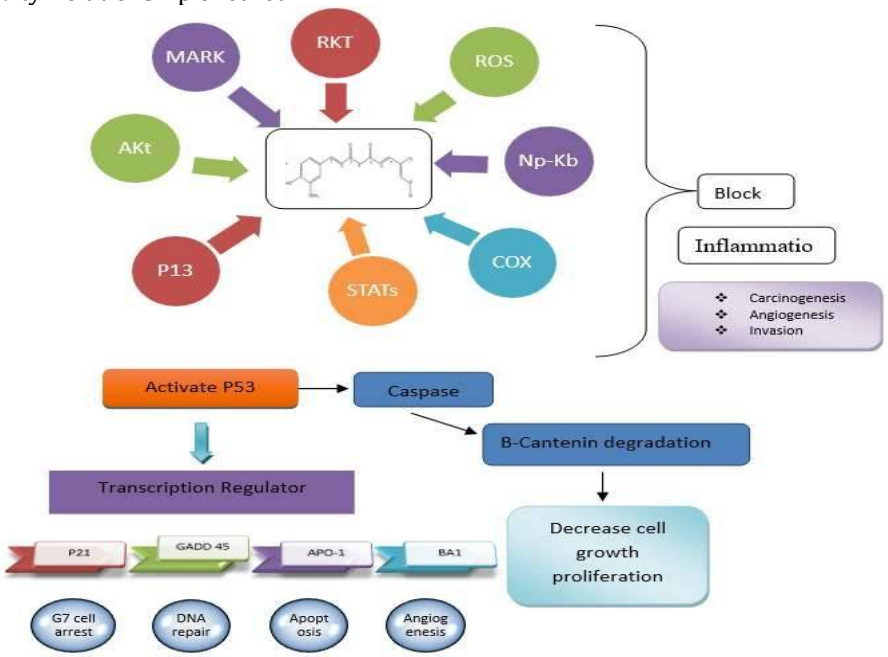


Fig.1 Structural Activity Relationship of curcumin



P13: Phosphatidylinositol-3kinase, Akt: ProteinkinaseB (PKB),ROS:ReactiveOxygenSpecies,NP-KB: Nuclearfactorkappa-light-chain-enhancerofactivatedBcells, COX: Cyclooxygenase, signaltransducerand Activatoroftranscription (STAT)

Fig 2: Mechanism of Action of Curcumin

Curcumin a well-known chemo protective agent extracted from turmeric, has a history of 5,000 years. In recent years studies have indicated that curcumin is been able to inhibit proliferation and survival , induce apoptotic and non-apoptotic cell death, and reduce invasion and migration in various types of malignant cancer cells. Through regulation of the expression of genes associated with programmed cell death, curcumin causes a high degree of apoptosis in human breast cancer cells.

Curcumin and its derivatives were first extracted from the turmeric plant in a pure crystalline form. It has been shown in several studies to have anti-tumour activity against a variety of cancer cell line including those found in breast, lung, head and neck, prostate and brain tumour.

Curcumin's distinct anticancer activity is primarily mediated by inducing apoptosis and inhibiting tumour growth and invasion by silencing a variety of cellular signalling pathways. The polyphenolic phytochemical curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], isolated from the powdered rhizome of Curcuma longa L. (Zingiberaceae), interacts with numerous biological targets, including inflammatory mediators, growth factors, enzymes, carrier proteins, metal ions, tumour suppressors, transcription factors, oncoproteins and cellular nucleic acids. Curcumin and its derivatives have attracted a lot of attention in the past 20 years due to their bio functional properties such as anti-tumour, anti-oxidant.

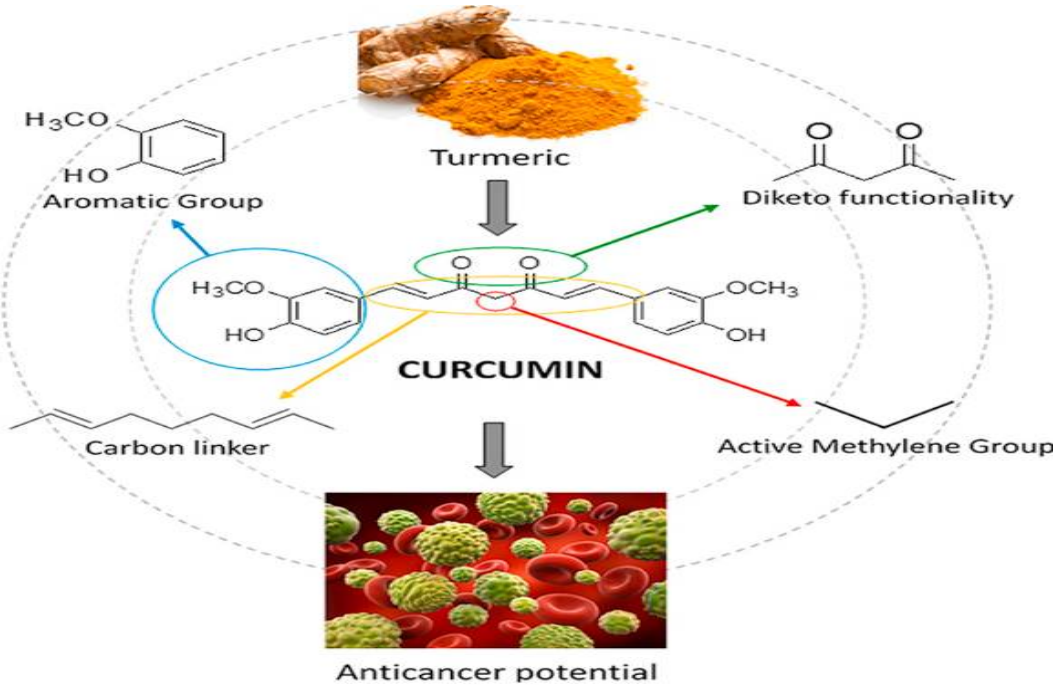
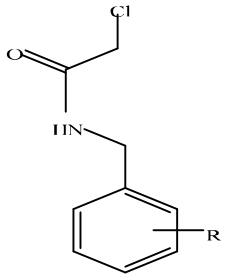


Fig 3: Development in the anticancer activity of C

REVIEW OF LITRATURE

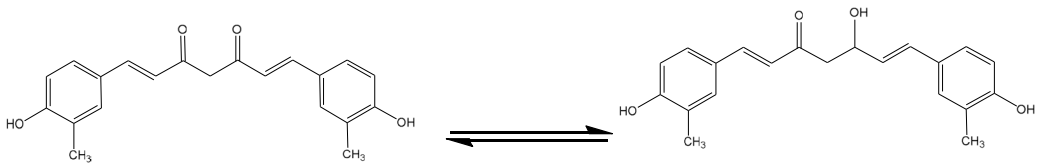
Amit Anthwal et al (2014) [13] Synthesis of a series of C-5 curcumin analogues was carried out. The new compounds demonstrated good cytotoxicity against chronic myeloid leukaemia (KBM5) and colon cancer (HCT116) cell lines. Further, these compounds were found to have better potential to inhibit TNF-α-induced NF-κB activation in comparison to curcumin, which show their potential to act as anti-inflammatory agents. Some compounds were found to show higher cytotoxicity against cancer cell lines in comparison to curcumin used as standard.



C-5 curcumin analogues

Hussain Al-Amiery et al (2010) [14] Studied anticancer activity of the active components of plants and use it as drugs. Curcumin [(1E, 6E)-1, 7-bis (4-hydroxy-3- methoxyphenyl) hepta-1, 6-diene-3,5dione] is the major yellow pigment extracted from turmeric, a commonly used spice, derived from the rhizome of the plant Curcuma longa. In India and Southeast Asia, turmeric has long been used as a treatment for inflammation, skin wounds and tumours. Curcumin has broad spectrum cancer chemo preventive activity in preclinical animal models. The extract of the herb curcumin, from Iraqi curcumin, was done by using of 95% ethanol as a solvent, then isolation of curcumin from the ethanolic extract by column chromatography, curcumin was characterized by UV Visible, FT-IR and proton NMR spectroscopy. The study of anticancer activity of the curcumin and ethanolic extract were done in vivo on mice and in vitro

on cell line. The extract showed a considerable anticancer activity against the cell line of human hepato cellular liver carcinoma.

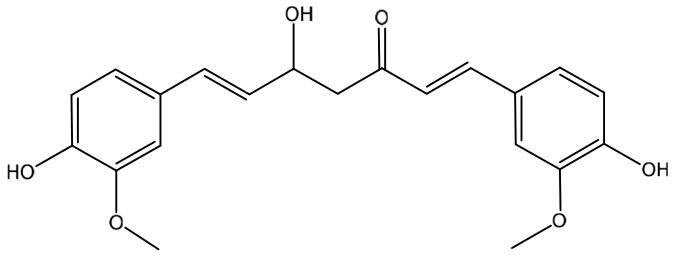


Stable Structure of Curcumin

A P Gupta et al (2017) [15] Studied curcuminoids, the principal bioactive component of Curcuma species, share a common unsaturated alkyl-linked two phenyl structural feature. Curcumin [diferuloylmethane, 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3, 5dione], a broad-spectrum anticancer polyphenolic derivative extracted from the rhizome of C. longa L., is a nontoxic compound and has been classified as "generally recognized as safe" (GRAS) by the National Cancer Institute. Several studies in literature survey revealed anticancer properties of curcumin against prostate cancer, cervical cancer, colorectal carcinoma, leukaemia, and human breast cancer cells. However, the clinical use of curcumin has been hampered by its poor solubility, absorption, bioavailability, and rapid metabolism. To overcome these limitations, various synthetic bioactive curcumin analogues were developed based on the structure-activity relationship (SAR) studies. This chapter highlights the research-based importance of curcumin and its analogues. Based on the available data, the chapter summarizes the potential and future of curcumin in anticancer therapy. Sorush Niknamian et al., (2018) [16] In spite of great progress in therapeutic practices over the past decade, neither the incidence nor the deaths from cancer have changed over the past thirty years. Existing anticancer drugs have limited efficacy, severe complications, and high costs expensive. Hence, identifying pharmaceutical agents lacking these disadvantages is required.

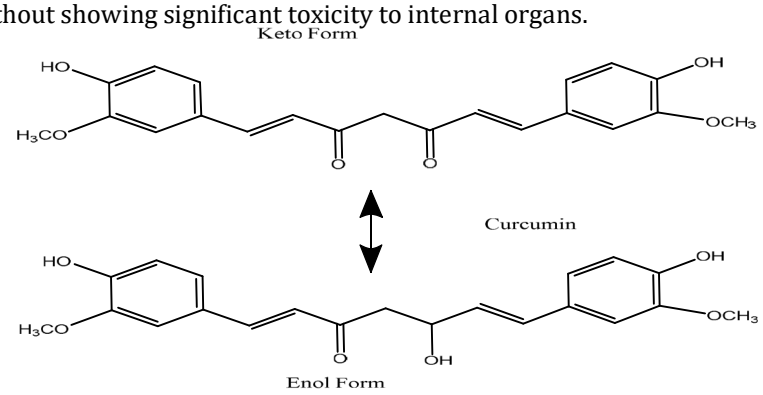
Zeynep Busra Bolat et al (2020)[17] In this study Curcumin, isolated from turmeric, and piperine, isolated from black long pepper, are two dietary polyphenols studied for their intrinsic anti-cancer properties against various cancer types including colorectal cancer (CRC). Furthermore, piperine improves the therapeutic effect of curcumin. Addressing this mutual behaviour, this study combines curcumin and piperine within emulsome Nano formulations. Curcumin- (CurcuEmulsomes) and piperine-loaded emulsomes (Piperine Emulsomes) have established a uniform, stable, spherical dispersion with average diameters of 184.21 and 248.76 nm, respectively. The solid tripalmitin inner core achieved encapsulation capacities of up to 0.10 mg/ml curcumin and 0.09 mg/ml piperine content. While piperine treatment alone – in its both free and emulsome forms – showed no inhibition in the proliferation of HCT116 cells in vitro, its presence as the second drug agent enhanced curcumin's effect. Combination of 7 μM Piperine Emulsome and 25 μM Curcumin Emulsome concentrations was found to be most effective with an inhibition of cell proliferation of about 50% viability. Cell cycle arrest at G2/M phase and induced apoptosis verified the improved anti-cancer characteristics of the therapy. While Curcumin Emulsomes achieved a fourfold increase in Caspase 3 level, combination of treatment with Piperine Eulsomes achieved a six fold increase in the level of this apoptotic marker. Combinational treatment of HCT116 cells with Curcumin Emulsomes and Piperine Emulsomes improved the anticancer activity of the compounds and highlighted the potential of the approach for further in vivo studies.

Shireen Parsai et al [18] the present study tested the anticancer activity of new curcumin like compounds (E21cH and Q012095H). Also, the use of new medicaments requires an understanding of their pharmacokinetic profiles and targets. Thus, molecular modelling methods were used to identify the targets of curcumin and curcumin-like compounds compared with other anticancer drugs (Q012138 and Q012169AT), which were used as the controls. The present study identified several enzymes that are targeted by curcumin, aldoketo reductase family 1 member B10 (AKR1B10), serine/threonine-protein kinase, protein kinase C, matrix metalloproteinase (MMP), cyclooxygenase and epidermal growth factor receptor, which were tested as targets for these anticancer chemicals. All the examined small compounds demonstrated anticancer activity in the in vitro experiments and may impact cancer cells by acting on AKR1B10, MMP-9 and their targets.

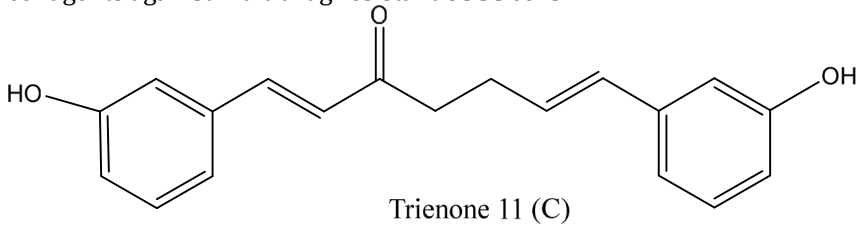


Curcumin

Puneet Khandelwal et al (2018) [19] In this report, studied to conjugate the curcumin molecules on the surface of gold quantum clusters (Au QCs) by a novel in situ synthesis method which provides an alternative route to not only reduce the metallic content but also increase the water solubility of curcumin and the loading efficiency. Here, curcumin itself acts as a reducing and capping agent for the synthesis of Au QCs. The UV−vis absorption, fluorescence, transmission electron microscopy, and electrospray ionization mass spectrometry results confirmed the synthesis of fluorescent Au QCs. Curcumin-conjugated Au NPs (C-Au NPs) and glutathione (GSH)- conjugated Au QCs (GSH-Au QCs) were also synthesized to visualize the effect of particle size and the capping agent, respectively, on the cytotoxicity to normal and cancer cells. The 3-(4,5-dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide assay showed that the curcumin conjugated Au QCs (C-Au QCs) were less cytotoxic to normal cells while almost the same cytotoxic to cancer cells in comparison to curcumin itself, which indicates that curcumin preserves its anticancer property even after binding to the Au QCs. However, C-Au NPs and GSH-Au QCs did not show any cytotoxicity against the normal and cancer cells at the concentration used. The western blot assay indicated that C-Au QCs promote apoptosis in cancer cells. Further, the in vivo study on severe combined immunodeficiency mice showed that C-Au QCs also inhibited the tumour growth efficiently without showing significant toxicity to internal organs.



Tanyarath Utaipan et al [20]The objective of this study was to investigate cytotoxicity and anticancer mechanisms of a synthetic trienone analogue of curcumin, 1,7-bis(3-hydroxyphenyl)-1,4,6heptatrien-3-one (trienone 11), against human oral squamous cell carcinoma (OSCC) cells exhibiting multidrug resistance (CLS-354/DX). The study of cytotoxicity showed that trienone 11 exerted threefold stronger cytotoxicity to CLS-354/DX cells than curcumin. Trienone 11 (15–30 μM) markedly induced intracellular reactive oxygen species (ROS) resulting in apoptotic cell death within 24 h, through activation of caspase-3/7 and caspase-9. A ROS inhibitor, N-acetylcysteine (NAC) prevented apoptotic cell death via decreasing caspase activation. Thus, the cytotoxicity of trienone 11 against CLS354/DX cells was ROS-mediated intrinsic apoptosis. Overall, trienone 11 could be an interesting lead for developing anti-cancer agents against multidrug resistant OSCC cells.



Trienone 11 (C)

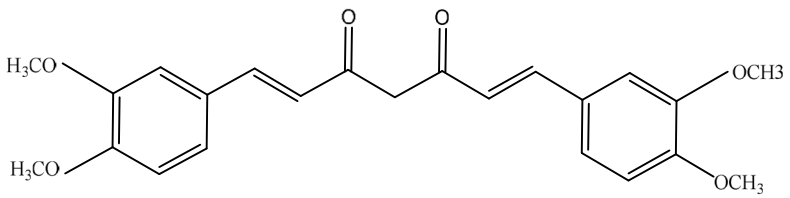
Alicja Karabasz et al (2019) [21] In this study analyse in vivo toxicity and antitumor activity of AA-Cur in two different mouse tumour models. Potential toxicity of intravenously injected AA-Cur was evaluated by: i) analyses of blood parameters (morphology and biochemistry), ii) histology, iii) DNA integrity (comet assay), and iv) cytokine profiling (flow cytometry). Antitumor activity of AA-Cur was

evaluated by measuring the growth of subcutaneously inoculated colon MC38-CEA- or orthotopically injected breast 4T1 tumour cells in control mice vs mice treated with AA-Cur. Injections of four doses of AA-Cur did not reveal any toxicity of the conjugate, thus indicating the safety of its use. AA-Cur elicited moderate anti-tumour activity toward colon MC38-CEA or breast 4T1 carcinomas. The tested conjugate of alginate and curcumin, AA-Cur, is non-toxic and safe, but exhibits limited anticancer activity.

Qiuyan Zhang et al [22] Three curcumin analogues (S1-S3) containing sulfone were investigated for their effects on human prostate cancer PC-3, colon cancer HT-29, lung cancer H1299 and pancreatic cancer BxPC-3 cells. The three compounds were approximately 16- to 96-fold more active than curcumin in these cell lines as determined by the MTT assay. The effects of these compounds on cell growth were further studied in prostate cancer PC-3 cells in both two-dimensional (2D) and three dimensional (3D) cultures. S1-S3 strongly inhibited the growth and induced cell death in PC-3 cells, and the effects of these compounds were associated with suppression of nuclear factor kappa B (NFκB) transcriptional activity. Moreover, treatment of PC-3 cells with all three compounds caused a decrease in the level of phosphorylated signal transducer and activator of transcription-3 (p-STAT3) (Tyr705), but not p-STAT3 (Ser727). Only S1 and S2 decreased the presence of phosphorylated Akt (p-Akt) in PC-3 cells. These curcumin analogues warrant further in vivo studies for anticancer activities in suitable animal models

Prajakta H Paradkar et al [23] The aim of study was to explore anti-inflammatory and antiproliferative potential and to understand the mechanism of action of these medicinal plants extracts individually or synergistically on cervical cancer cell lines. Anti-inflammatory activity of 5 extracts (curcumin, turmeric oil and poly sachharides from Curcuma longa and berberine and polysaccharides from Tinosporacordifolia) and mixture of the extracts was evaluated by in vitro macrophage activation assay and modulation of TNF-α and IL-6 release. Extracts were assessed for their cytotoxicity by sulforhodamine B (SRB) assay on SiHa and C33a cervical cancer cell lines. Indole amine 2, 3- dioxygenase (IDO) assay for immune modulation and flow cytometry with propidium iodide (PI) staining for cell cycle analysis were also performed. The results indicated that curcumin, berberine and the mixture of all 5 extracts could significantly reduce cytokine release in the supernatant from lipopolysaccharide (LPS) activated macrophages. All the extracts showed cytotoxicity in a dose dependent manner in both cell lines. Mixture of the extracts showed better activity than individual extracts in all the experiments. Study reveals that Curcuma longa and Tinosporacordifoila extracts synergistically demonstrate anti-inflammatory and antiproliferative activity. There is therefore scope for using these plant bio actives as complementary therapy or for chemoprophylaxis.

Constantin Tamvakopoulos et al [24] The synthetic curcumin analogue dimethoxycurcumin was compared with curcumin for ability to inhibit proliferation and apoptosis of human HCT116 colon cancer cells in vitro by estimating the GI50 and LC50 values and detecting the extent of apoptosis by flow cytometry analysis of the cell cycle. Metabolic stability and/or identification of metabolites were evaluated by recently developed mass spectrometric approaches after incubation with mouse and human liver microsomes and cancer cells in vitro. Additionally, circulating levels of dimethoxycurcumin and curcumin were determined in mice following i.p. administration. Dimethoxycurcumin is significantly more potent than curcumin in inhibiting proliferation and inducing apoptosis in HCT116 cells treated for 48 h. Nearly 100% of curcumin but 30% of dimethoxycurcumin was degraded in cells treated for 48 h, and incubation with liver microsomes confirmed the limited metabolism of dimethoxycurcumin. Both compounds were rapidly degraded in vivo but dimethoxycurcumin was more stable. Compared with curcumin, dimethoxycurcumin is (a) more stable in cultured cells, (b) more potent in the ability to kill cancer cells by apoptosis, (c) less extensively metabolized in microsomal systems, and (d) more stable in vivo. It is likely that the differential extent of apoptosis induced by curcumin and dimethoxycurcumin in vitro is associated with the metabolite profiling and/or the extent of stability.



Dharmalingam Subramaniam et al [25] Diphenyl difluoroketone (EF24), a molecule having structural similarity to curcumin, was reported to inhibit proliferation of a variety of cancer cells in vitro. However, the efficacy and in vivo mechanism of action of EF24 in gastrointestinal cancer cells have not been investigated. Here, we assessed the in vivo therapeutic effects of EF24 on colon cancer cells. Using hexosaminidase assay, we determined that EF24 inhibits proliferation of HCT-116 and HT-29 colon and

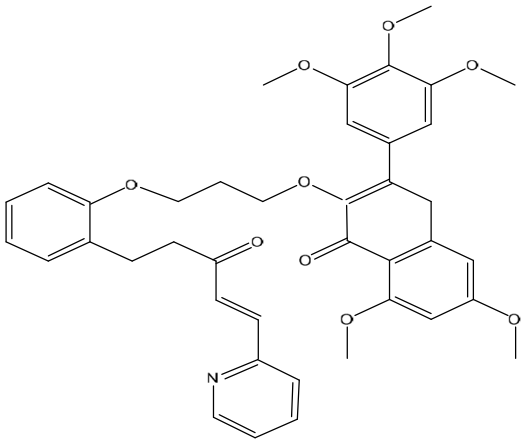
AGS gastric adenocarcinoma cells but not of mouse embryo fibroblasts. Furthermore, the cancer cells showed increased levels of activated caspase-3 and increased Bax to Bcl2 and Bax to Bcl-xL ratios, suggesting that the cells were undergoing apoptosis. At the same time, cell cycle analysis showed that there was an increased number of cells in the G2-M phase. To determine the effects of EF24 in vivo, HCT-116 colon cancer xenografts were established in nude mice and EF24 was given i.p. EF24 significantly suppressed the growth of colon cancer tumour xenografts. Immunostaining for CD31 showed that there was a lower number of micro vessels in the EF24-treated animals coupled with decreased cyclooxygenase-2, interleukin8, and vascular endothelial growth factor mRNA and protein expression. Western blot analyses also showed decreased AKT and extracellular signal-regulated kinase activation in the tumours. Taken together, these data suggest that the novel curcumin-related compound EF24 is a potent antitumor agent that induces caspase-mediated apoptosis during mitosis and has significant therapeutic potential for gastrointestinal cancers.

Zeinab Khazaei Koohpar et al[26] the present study examined the anti-proliferative activity of curcumin and its effect(s) on the apoptosis of breast cancer cells. This study was performed by an in vitro assay and the anticancer effects of curcumin were determined by MTT (3-[4, 5-dimethylthiazol2-yl]-2, 5 diphenyl tetrazolium bromide). In this study used quantitative real time Polymerase Chain Reaction (PCR) for detection of Mcl-1 gene expression in treated groups and then compared them to control samples. In the treatment group, there were higher levels of cell death changes than the control group. The results also showed that the Mcl-1 gene expression declined in the tested group as compared to the control group. Our present findings indicated that curcumin significantly inhibited the growth of human breast cancer cell MCF-7 by inducing apoptosis in a dose- and time- dependent manner, accompanied by a decrease in MCF-7 cell viability. Furthermore, results showed that quantitative real-time PCR could be used as a direct method for detection Mcl-1 gene expression in tested samples and normal samples.

Ramadasan Kuttan et al [27] Anticancer activity of the rhizomes of turmeric was evaluated in vitro using tissue culture methods and in vivo in mice using Dalton's lymphoma cells grown as ascites form. Turmeric extract inhibited the cell growth in Chinese Hamster Ovary (CHO) cells at a concentration of 0.4 mg/ml and was cytotoxic to lymphocytes and Dalton's lymphoma cells at the same concentration. Cytotoxic effect was found within 30 min at room temperature (30°C). The active constituent was found to be 'curcumin' which showed cytotoxicity to lymphocytes and Dalton's lymphoma cells at a concentration of 4 μg/ml. Initial experiments indicated that turmeric extract and curcumin reduced the development of animal tumours.

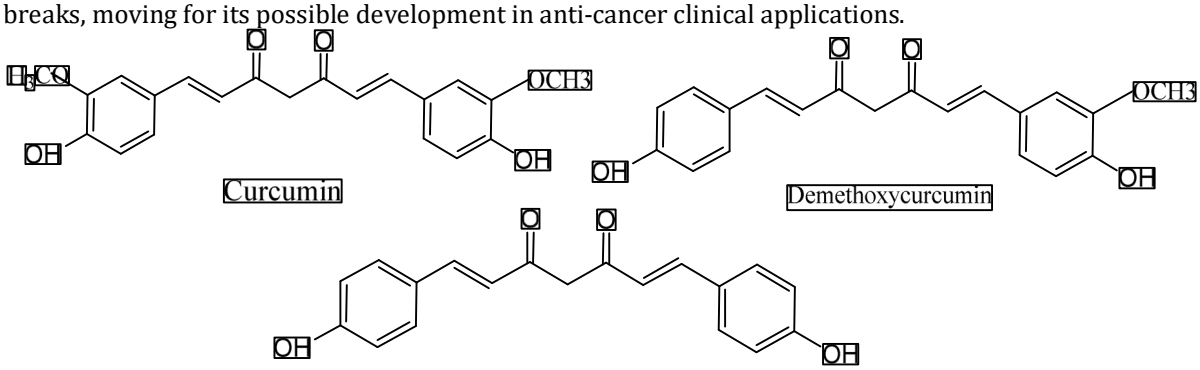
Chuan He Yang et al [28] EF24 is a curcumin analogue that has improved anticancer activity over curcumin, but its therapeutic potential and mechanism of action is unknown, which is important to address as curcumin targets multiple signalling pathways. EF24 inhibits the NF-κB but not the JAKSTAT signalling pathway in DU145 human prostate cancer cells and B16 murine melanoma cells. EF24 induces apoptosis in these cells apparently by inhibiting miR-21 expression, and also enhances the expression of several miR-21 target genes, PTEN and PDCD4. EF24 treatment significantly suppressed the growth of DU145 prostate cancer xenografts in immunocompromised mice and resulted in tumour regression. EF24 enhanced the expression of the miR-21 target PTEN in DU145 tumour tissue, but suppressed the expression of markers of proliferating cells (cyclin D1 and Ki67). In syngeneic mice injected with B16 cells, EF24 treatment inhibited the formation of lung metastasis, prolonged animal survival, inhibited miR-21 expression and increased the expression of miR-21 target genes. Expression profiling of miRNAs regulated by EF24 in vitro and in vivo showed that the antitumor activity of EF24 reflected the enhanced expression of potential tumour suppressor miRNAs as well as the suppressed expression of oncogenic miRNAs, including miR-21. Taken together, data suggest that EF24 is a potent anticancer agent and selectively targets NF-κBsignaling and miRNA expression, indicating that EF24 has significant potential as a therapeutic agent in various cancers.

JieQuan Wang et al [29] Twenty curcumin analogue hybrids as potential anticancer agents through regulation protein of TrxR were designed and synthesized. Results of anticancer activity showed that 5,7-dimethoxy-3-(3-(2-((1E, 4E)-3-oxo-5-(pyridin-2-yl)penta-1,4-dien-1yl)phenoxy)propoxy)-2-(3,4,5-trimethoxyphenyl)-4H-chromen-4-one(compound 7d) could induce gastric cancer cells apoptosis by arresting cell cycle, break mitochondria function and inhibit TrxR activity. Meanwhile, western blot revealed that this compound could dramatically up expression of Bax/Bcl-2 ratio and high expression of TrxRoxidation. These results preliminarily show that the important role of ROS mediated activation of ASK1/MAPK signalling pathways by this title compound.



5,7-dimethoxy-3-(3-(2-((1E, 4E)-3-oxo-5-(pyridin-2-yl) penta-1,4-dien-1- yl) phenoxy) propoxy)-2-(3,4,5-trimethoxyphenyl)-4H-chromen-4-one

Valentina Basile et al (2009) [30] Curcumin, a phenolic compound from the plant Curcuma longa L., has shown a wide-spectrum of chemo preventive, antioxidant and antitumor properties. Although its promising chemotherapeutic activity, preclinical and clinical studies highlight Curcumin limited therapeutic application due to its instability in physiological conditions. To improve its stability and activity, many derivatives have been synthesized and studied, among which bis-DemethoxyCurcumin (bDMC) and diAcetylCurcumin (DAC). In this report, we show that both bDMC and DAC are more stable than Curcumin in physiological medium. To explore the mechanism of their chemotherapeutic effect, studied their role in proliferation in the HCT116 human colon cancer cells. Correlated kinetic stability and cellular uptake data to their biological effects. Both bDMC and DAC impair correct spindles formation and induce a p53- and p21CIP1/WAF1-independent mitotic arrest, which is more stable and long-lasting for bDMC. A subsequent p53/p21CIP1/WAF1dependent inhibition of G1 to S transition is triggered by Curcumin and DAC as a consequence of the mitotic slippage, preventing post-mitotic cells from re-entering the cell cycle. Conversely, the G1/S arrest induced by bDMC is a direct effect of the drug and concomitant to the mitotic block. Finally, demonstrate that bDMC induces rapid DNA double-strand breaks, moving for its possible development in anti-cancer clinical applications.



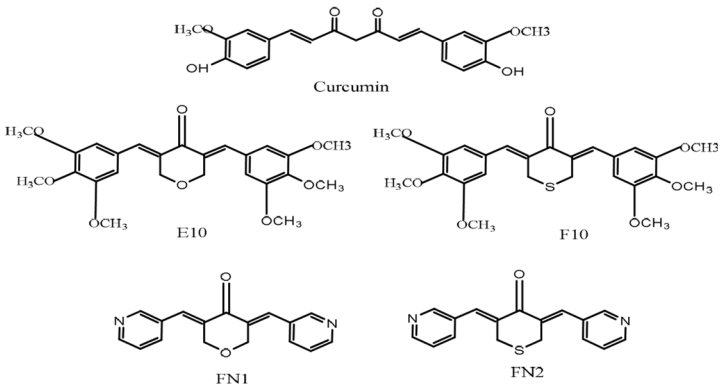
Farah J. Hashim et al[31] Studied the evaluation of Ethanolic turmeric extracts (ETE) as anticancer agent by detect the apoptotic induction and DNA damage activity of ETE which were investigated against two human leukemic cell lines, U937 (human monocytic leukaemia cell line) and Molt4 (human lymphoblastic cell line). ETE obtained by extraction of turmeric by ethanol solvent, apoptosis activity was performed by using 4, 6-diamidino-2-phenylindole dihydrochloride [DAPI] stain; also comet assay which is sensitive method of detection double strand break (DSB) of DNA was used. showed that apoptotic activity of ETE against U937, Molt4 cell lines were 58.06% and 39.07% respectively while apoptotic activity of Melphalan were 92.04% and 89.03% respectively by using DAPI stain, otherwise apoptotic percentage of ETE were 92.44% and 61.95% against U937, Molt4 respectively while by Melphalan were 100% against both of leukemic cell lines which evaluated by comet assay. Ethanolic turmeric extracts (ETE) showed that have apoptogenic and DNA damage activity against two human leukemic cell lines. Otherwise DAPI stain and comet assay prove to be suitable tools to detect DNA damage of U937 and Molt4 leukemic cell lines by ETE.

Hisatsugu Ohori et al (2006) [32] Synthetic chemical modifications of curcumin had studied intensively in an attempt to find a molecule with similar but enhanced properties of curcumin. In this study, a series of novel curcumin analogues were synthesized and screened for anticancer activity. New analogues that

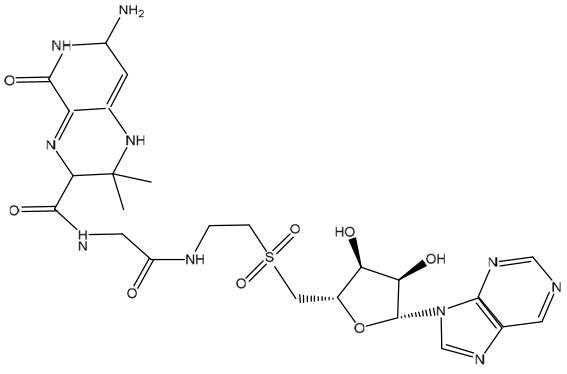
exhibit growth-suppressive activity 30 times that of curcumin and other commonly used anticancer drugs were identified. Structurally, the new analogues are symmetrical 1,5diarylpentadienone whose aromatic rings possess an alkoxy substitution at each of the positions 3 and 5. Analysis of the effects of the analogues on the expression of cancer-related genes usually affected by curcumin indicated that some induced the down-regulation of β-catenin, Ki-ras, cyclin D1, c-Myc, and ErbB-2 at as low as one eighth the concentration at which curcumin normally has an effect. The analogues, however, exhibited neither harmful nor growth-suppressive effects on normal hepatocytes where oncogene products are not activated. They also exhibited no toxicities in vivo that they may provide effective alternative therapies for the prevention and treatment of some human cancers. Sri Vishnu Kiran et al (2017) [33] Developed a novel, biocompatible, amenable to industrial scale up and affordable solid lipid nanoparticles (SLN) preparation of curcumin and evaluate the therapeutic efficacy in vitro using cancer cells. We have incorporated cholesterol as the lipid to prepare SLN along with the Poloxamer-188 as stabilizer. High shear homogenization was used to prepare the SLN and formulation was optimized using Quality by Design the optimized Chol CUR SLN exhibited a narrow size distribution with a particle size of 166.4 ± 3.5 nm. Percentage encapsulation (%EE) was found to be 76.9 ± 1.9%. The SLN were further characterized by DSC, FTIR, XRD and drug release. In vitro cell studies in MDA-MB-231 (Human Breast cancer) cell line revealed that the Chol CUR SLN showed superior cytotoxicity and uptake in comparison to the free curcumin. Furthermore, Chol CUR SLN induced a significantly higher apoptosis compared to free CUR treatment. These results indicated that the curcumin encapsulated in Chol SLN was able to significantly improve the cytotoxic potential and induction of apoptosis in MDA-MB-231 cells. The promising result from our study could lead a further exploration of this nanoparticle formulation to be utilized clinically for cancer treatment.

Yuee Cai et al (2015) [34] Curcumin (CUR), a nontoxic polyphenol derived from the rhizome of turmeric (Curcuma longa), has been recognized as an anti-cancer and chemo-preventative agent. However, its clinical application for cancer treatment has been greatly limited due to its poor water solubility and low bioavailability. To tackle this problem, Pluronic F68–CUR (F68–CUR) conjugate micelles, which are amphiphilic copolymers, were designed and synthesized in this study. These highly stable micelles with CUR concentrated in the core were formulated using the solvent evaporation method and were confirmed by Fourier transform infrared spectroscopy and nuclear magnetic resonance. Physicochemical characterization of F68–CUR conjugate micelles revealed that high drug loading content (DL%; 0.248 mg CUR/1 mg F68) was achieved, and the average particle size of micelles was 115.2 ± 3.0 nm. Compared with free CUR, a significantly higher cytotoxicity against human breast cancer cell line MDA-MB-231 was observed in F68–CUR conjugate micelles. The IC50 value of F68–CUR conjugate micelles was 1.95-fold lower than that of free CUR, indicating that the anti-cancer activity of CUR was significantly improved in the micelles. Furthermore, apoptotic studies demonstrated that F68–CUR conjugate micelles induced more cell apoptosis than that of free CUR. Taken together, these results demonstrate that F68–CUR conjugate micelles are promising to improve the clinical effectiveness of CUR in cancer treatment.

XingchuanWei et al[35]Sixty-one curcumin-related compounds were synthesized and evaluated for their anticancer activity toward cultured prostate cancer PC-3 cells, pancreas cancer Panc-1 cells and colon cancer HT-29 cells. Inhibitory effects of these compounds on the growth of PC-3, Panc-1 and HT-29 cells were determined by the MTT assay. Compounds E10, F10, FN1 and FN2 exhibited exceptionally potent inhibitory effects on the growth of cultured PC-3, Panc-1 and HT29 cells. The IC50 for these compounds was lower than 1 μM in all three cell lines. E10 was 72-, 46- and 117-fold more active than curcumin for inhibiting the growth of PC-3, Panc-1 and HT-29 cells, respectively. F10 was 69-, 34- and 72-fold more active than curcumin for inhibiting the growth of PC3, Panc-1 and HT-29 cells, respectively. FN1 and FN2 had about the same inhibitory effect as E10 and F10 toward Panc-1 cells but were less active than E10 and F10 toward PC-3 and HT-29 cells. The active compounds were potent stimulators of apoptosis. The present study indicates that E10, F10, FN1 and FN2 may have useful anticancer activity.



Mina Karimpour et al [36] Gemini–Cur polymerases were synthesized through Nanoprecipitation method and characterized by dynamic light scattering (DLS), transmission and scanning electron microscopies, HPLC and X-ray diffraction (XRD). The anticancer effect of Gemini–Cur nanoparticles was studied on three different breast cancer cell lines including MCF-7,
SkBr-3 and MDA-MB-231 through uptake kinetics, viability & cytotoxicity recordings and apoptotic assays. Furthermore, qRT-PCR was performed to evaluate the expression of apoptotic genes including p16INK4a, p14ARF, Bax and Bcl-2.According to physicochemical analysis, the average particle size, zeta potential value and drug entrapment efficiency for Gemini–Cur compound were recorded as 161 ± 6.2 nm, +5.32 mV and 89.13% ± 0.93, respectively. XRD analysis also confirmed the incorporation of curcumin in gemini surfactant micelles. Regarding the enhanced cellular uptake of sphere-shaped Gemini–Cur, our data showed that this nano compound suppresses cancer cell proliferation via induction of apoptosis. Moreover, qRT-PCR analysis revealed that Gemini–Cur could effectively up regulate the expression of p16INK4a, p14ARF and Bax, while significantly decreasing the Bcl-2 expression in these breast cancer cells. Our data demonstrates the great potential of gemini surfactants for efficient delivery of curcumin and subsequently, the improvement of its anticancer effect. Therefore, it is sagacious to support the idea that Gemini–Cur nano compound might have the potential to be considered as an anticancer agent.
Sharvil Patil et al [37] The objective of the current work was to prepare novel curcumin loaded mixed micelles (CUR-MM) of Pluronic F-127 (PF127) and Gelucire® 44/14 (GL44) in order to enhance its oral bioavailability and cytotoxicity in human lung cancer cell line A549.32 Factorial design was used to assess the effect of formulation variables for optimization of mixed micelle batch.CUR-MM was prepared by a solvent evaporation method. The optimized CUR-MM was evaluated for size, entrapment efficiency (EE), in vitro curcumin release, cytotoxicity and oral bioavailability in rats The average size of CUR-MM was found to be around 188 ± 3 nm with an EE of about 76.45 ± 1.18% w/w. In vitro dissolution profile of CUR-MM revealed controlled release of curcumin. Additionally, CUR-MM showed significant improvement in cytotoxic activity (3-folds) and oral bioavailability (around 55-folds) of curcumin as compared to curcumin alone. Such significant improvement in cytotoxic activity and oral bioavailability of curcumin when formulated into mixed micelles could be attributed to solubilization of hydrophobic curcumin into micelle core along with Pgp inhibition effect of both, PF127 and GL44.Thus the present work proposes the formulation of mixed micelles of PF127 and GL44 which can act as promising carrier systems for hydrophobic drugs such as curcumin with significant improvement in their oral bioavailability.



Gelucire structure

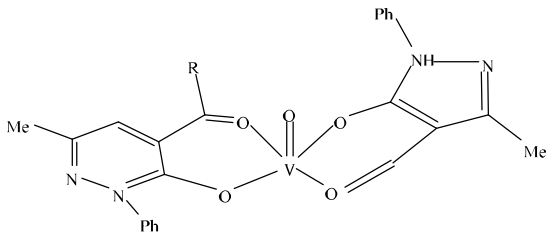
Nattika Saengkrit et al (2014) [38] the delivery of curcumin had explored in the form of liposomal nanoparticles to treat various cancer cells. Since curcumin is water insoluble and an effective delivery

route is through encapsulation in liposomes, which were modified with three components of DDAB, cholesterol and non-ionic surfactant. The purpose of this study was to establish a critical role of DDAB in liposomes containing curcumin at cellular response against two types of cell lines (HeLa and SiHa). Here, demonstrate that DDAB is a potent inducer of cell uptake and cell death in both cell lines. The enhanced cell uptake was found on DDAB-containing liposome, but not on DDAB-free liposome. However, the cytotoxicity of DDAB-containing liposomes was high and needs to be optimized. The cytotoxicity of liposomal curcumin was more pronounced than free curcumin in both cells, suggesting the benefits of using nanocarriers. In addition, the anticancer efficiency and apoptosis effect of the liposomal curcumin formulations with DDAB was higher than those of DDAB-free liposomes. Therefore, curcumin loaded liposomes indicate significant potential as delivery vehicles for the treatment of cervical cancers.

Murali M. Yallapu et al [39] the objective of this study was to evaluate therapeutic potential of novel poly (lactic-co-glycolic acid) - CUR nanoparticles (PLGA-CUR NPs) for prostate cancer treatment. Results indicate that PLGA-CUR NPs efficiently internalize in prostate cancer cells and release biologically active CUR in cytosolic compartment of cells for effective therapeutic activity. Cell proliferation (MTS), clonogenic, and Western blot analyses reveal that PLGA-CUR NPs can effectively inhibit proliferation and colony formation ability of prostate cancer cells than free CUR. PLGA-CUR NPs showed superior tumour regression compared to CUR in xenograft mice. Further investigations reveal that PLGA-CUR NPs inhibit nuclear β-catenin and AR expression in cells and in tumour xenograft tissues. It also suppresses STAT3 and AKT phosphorylation and leads to apoptosis via inhibition of key anti-apoptotic proteins, Mcl-1, Bcl-xL and caused induction of PARP cleavage. Additionally, significant downregulation of oncogenic miR21 and up-regulation of miR-205 was observed with PLGA-CUR NPs treatment as determined by RT-PCR and in situ hybridization analyses. A superior anti-cancer potential was attained with PSMA antibody conjugated PLGA-CUR NPs in prostate cancer cells and a significant tumour targeting of labelled PSMA antibody was achieved with PLGA-CUR NPs in prostate cancer xenograft mice model. In conclusion, PLGA-CUR NPs can significantly accumulate and exhibit superior anticancer activity in prostate cancer.

Ahmad Safety et al [40] Conjugates of curcumin to two differently sized poly(ethylene glycol) molecules were synthesized in an attempt to overcome the low aqueous solubility of this natural product with cytotoxic activity against some human cancer cell lines. The soluble conjugates exhibited enhanced cytotoxicity as compared to that of the parent drug. Synthesis, analyses of the rate of drug release, and cytotoxicity studies are herein reported. The water-soluble conjugates may provide information useful for the development of injectable curcumin conjugates.

Babu Balaji et al (2013) [41]Oxovanadium (IV) complexes [VO(Fc-pic) (acac)](ClO4), [VO(Fcpic)(cur)](ClO4), [VO(Ph-pic)(acac)](ClO4) and [VO(Ph-pic)(cur)](ClO4) ,where Fc-pic and Ph-pic are ferrocenylmethyl-bis-(2-pyridylmethylamine) and bis-(2-pyridylmethyl)benzylamine, respectively, acac is acetylacetonate anion and cur is curcumin anion were prepared, characterized and their photo-induced DNA cleavage and anticancer activity studied. The crystal structure of as its PF6− salt shows the presence of a VO2+ moiety in VO3N3 coordination geometry. The complexes show a d–d band at ~790 nm in DMF and display V(IV)/V(III) redox couple near −1.45 V vs. SCE in DMF - 0.1 M TBAP. The complexes are avid binders to calf thymus DNA. Complex efficiently photo-cleaves plasmid DNA in near-IR light of 785 nm forming OH radicals. The curcumin complexes show photocytotoxicity in HeLa cancer cells in visible light of 400–700 nm with significant cellular uptake within 4 h of incubation time.



A:R=CH_3

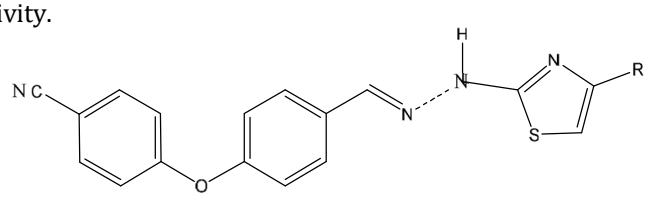
B: R=CH2Cl

C: R=CF3

Oxovanadium (IV) complexes

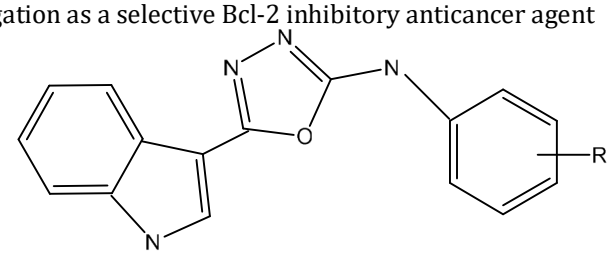
MehlikaDileketal[42] In an attempt to developed potent anticancer agents targeting Akt, new thiazole derivatives (1–10) were synthesized and investigated for their cytotoxic effects on A549 human lung adenocarcinoma, C6 rat glioma, and NIH/3T3 (healthy) mouse embryonic fibroblast cell lines. The most

potent compounds were also investigated for their effects on apoptosis and Akt pathway. The most promising anticancer agent was found to be 2-[2-((4-(4-cyanophenoxy)phenyl)methylene)hydrazinyl]-4-(4-cyanophenyl)thiazole (6), due to its selective inhibitory effects on A549 and C6 cells with IC50 values of 12.0 ± 1.73 μg/mL and 3.83 ± 0.76 μg/mL, respectively. Furthermore, compound 6 increased early and late apoptotic cell population (32.8%) in C6 cell line more than cisplatin (28.8%) and significantly inhibited the Akt enzyme. The molecular docking study was performed to predict the possible binding modes of compounds A, 6, and 8 inside the active site of Akt (PDB code: 4EJN). Molecular docking simulations were found to be in accordance with in vitro studies and, hence, supported the biological activity.



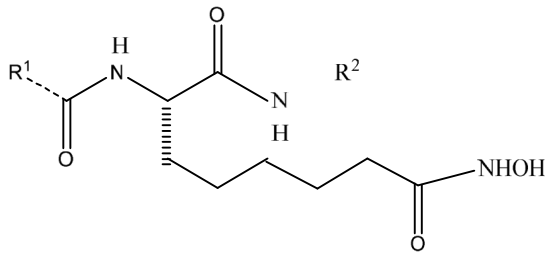
2-[2-((4-(4-cyanophenoxy) phenyl) methylene) hydrazinyl]-4-(4-cyanophenyl) thiazole

Rania Hamdy et al (2020)[43]A series of 2-(1H-indol-3-yl)-5-substituted-1,3,4-oxadiazoles, 4a–m, were designed, synthesized and tested in vitro as potential pro-apoptotic Bcl-2 inhibitory anticancer agents based on our previously reported hit compounds. Synthesis of the target 1, 3, 4-oxadiazoles was readily accomplished through a cyclization reaction of indole carboxylic acid hydrazide 2 with substituted carboxylic acid derivatives 3a–m in the presence of phosphorus oxychloride. New compounds 4a–m showed a range of IC50 values concentrated in the low micromolar range selectively in Bcl-2 positive human cancer cell lines. The most potent candidate 4-trifluoromethyl substituted analogue 4j showed selective IC50 values of 0.52–0.88 μM against Bcl-2 expressing cell lines with no inhibitory effects in the Bcl-2 negative cell line. Moreover, 4j showed binding that was two-fold more potent than the positive control gossypol in the Bcl-2 ELISA binding affinity assay. Molecular modelling studies helped to further rationalize anti-apoptotic Bcl-2 binding and identified compound 4j as a candidate with drug-like properties for further investigation as a selective Bcl-2 inhibitory anticancer agent



2-(1H-indol-3-yl)-5-benzo-1, 3, 4-oxadiazoles

Pia Kahnberg et al [44] studied on structure–activity relationships are now reported for 43 compounds derived from 2-aminosuberic acid that kill a range of cancer cells, 26 being potent cytotoxins against MM96L melanoma cells (IC50 20 nM–1 μM), while 17 were between 5- and 60fold more selective in killing MM96L melanoma cells versus normal (neonatal foreskin fibroblasts, NFF) cells. This represents a 10- to 100-fold increase in potency and up to a 10-fold higher selectivity over previously reported compounds derived from cysteine. Selectivity is also an underestimate, because the normal cells, NFF, are rarely all killed by the drugs that also induce selective blockade of the cell cycle for normal but not cancer cells. Selected compounds were tested against a panel of human cancer cell lines (melanomas, prostate, breast, ovarian.



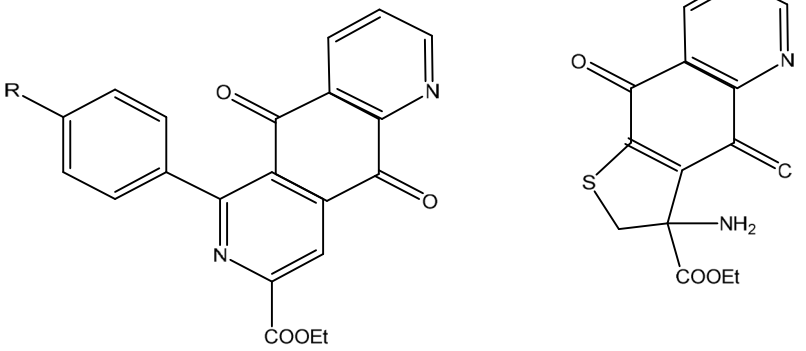
2-aminosuberic acid

Ahmed A.Gaber et al [45] All the newly synthesized compounds were evaluated in vitro for their inhibitory activities against EGFRWT. Compounds 15b, 15j, and 18d potently inhibited EGFRWT at sub-micron molar IC50 values comparable to that of erlotinib. Moreover, thirteen compounds that showed promising IC50 values against EGFRWT were tested in vitro for their inhibitory activities against mutant

EGFRT790M. Compounds 17d and 17f exhibited potent inhibitory activities towards EGFRT790M comparable to osimertinib. Compounds that showed promising IC50 values against EGFRWT were further tested for their anti-proliferative activities against three cancer cell lines bearing EGFRWT (MCF-7, HepG2, A549), and two cancer cell lines bearing EGFRT790M (H1975 and HCC827). Compounds 15g, 15j, 15n, 18d and 18e were the most potent anticancer agents against the EGFRWT containing cells, while compounds 15e, 17d and 17f showed promising anti-proliferative activities against EGFRT790M containing cells.

Paul A. Wender et al [46] studied on Modern methods for the identification of therapeutic leads include chemical or virtual screening of compound libraries. Nature's library represents a vast and diverse source of leads, often exhibiting exquisite biological activities. However, the advancement of natural product leads into the clinic is often impeded by their scarcity, complexity, and nonoptimal properties or efficacy as well as the challenges associated with their synthesis or modification. Function-oriented synthesis represents a strategy to address these issues through the design of simpler and therefore synthetically more accessible analogues that incorporate the activity-determining features of the natural product leads. This study illustrates the application of this strategy to the design and synthesis of functional analogues of the bryostatin marine natural products.

Adele Bolognese et al (2004) [47] New Antiproliferative compounds, the 1-aryl-3-ethoxycarbonylpyrido[2,3-g] isoquinolin-5,10-diones (PIQDs, 1−7), were designed on the basis of a molecular model obtained by aligning the common quinolinquinone substructure of 5H-pyrido[3,2-a] phenoxazin-5one (PPH) and some known anticancer agents. A Diels−Alder reaction between quinolin-5,8-dione (QD) and a 2-azadiene, formed by demolition of 2-aryl-1,3-thiazolidine ethyl esters (T compounds), was used to produce 1−7 and the isomeric 1-aryl-3-ethoxycarbonylpyrido[3,2-g] isoquinolin-5,10diones (8−14). Two other compounds, the 3-amino-3-ethoxycarbonyldihydrothieno[2,3-g] quinolin4,9-dione (15) and the 3-amino-3-ethoxycarbonyldihydrothieno [3,2-g] quinolin-4,9-dione (16), arising from a 1,4 Michael reaction of QD with a thiolate species formed by opening of T compounds, were recovered from the reaction mixture. The antiproliferative activity of 1−16 was evaluated against representative human liquid and solid neoplastic cell lines. The IC50 of these compounds had median values in the range 2.00−0.01 μM, with 2−4 and 15 exhibiting significantly higher in vitro cytotoxic activity

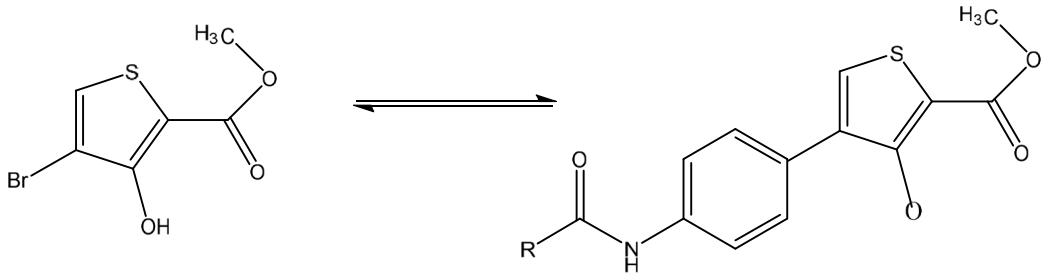


R= H, NO_2, Cl, Br, Me, OMe, $M(Me)_2$

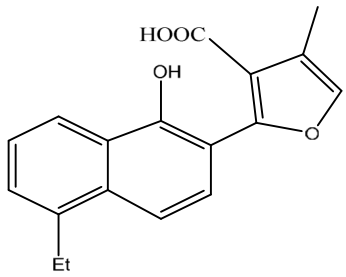
1-aryl-3-ethoxycarbonyl-pyrido [2, 3-g] isoquinolin-5, 10-diones

Amer M. Alanazi et al (2014) [48] studied on A novel series of 6-chloro-2-p-tolylquinazolinone and substituted-(4-methylbenzamido) benzamide (1–20) were designed, synthesized and evaluated for their in-vitro antitumor activity. Compounds 3, 14 and 16 possessed remarkable broad-spectrum antitumor activity. Compound 16 was found to be a particularly active growth inhibitor of the renal cancer (GI50 = 4.07 μM), CNS cancer (GI50 = 7.41 μM), ovarian cancer (GI50 = 7.41 μM) and nonsmall cell lung cancer (GI50 = 7.94 μM). Compound 16 ranks as nearly 1.5-fold more potent (mean GI50 = 15.8 μM) compared to 5-FU (mean GI50 = 22.6 μM).

Kali Charan Gulipalli et al [49] Studied on a series of novel methyl 4-(4-amidoaryl)-3methoxythiophene-2-carboxylate derivatives were designed against the active site of protein tyrosine phosphatise 1B (PTP1B) enzyme using MOE.2008.10. These molecules are also subjected for in silico toxicity prediction studies and considering their corresponding drug scores, it implied that, the molecules are promising as anticancer agents. The designed compounds were synthesized by using suitable methods and characterized. They were subjected to inhibitory activity against PTP1B and in vitro anticancer activity by MTT assay.



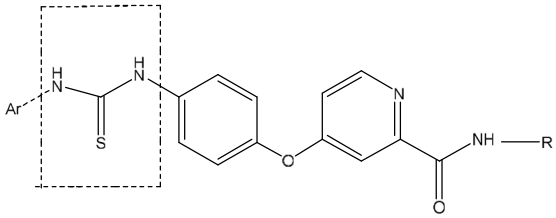
Yizhou Dong et al [50] in a continuing study, explored how the individual rings in neotanshinlactone influence it's potent and selective in vitro anti breast cancer activity. Accordingly, discovered a novel class of anti-breast cancer agents, 2-(furan-2-yl) naphthalen-1-ol derivatives, based on an active C-ring opened model compound 5. Further optimization led to 18 and 21, which showed decreased cytotoxic potency but better selectivity than neo-tanshinlactone analogue 2. Interestingly, 20 showed broad cytotoxicity against human cancer cell lines.



2-(furan-2-yl) naphthalen-1-ol

Junjie Ma et al [51] a series of novel benzothiazole derivatives bearing the ortho-hydroxyNcarbamoylhydrazone moiety were designed and synthesized and their cytotoxic activities against five cancer cell lines (NCI-H226, SK-N-SH, HT29, MKN45, and MDA-MB-231) were screened in vitro. Most of them showed moderate to excellent activity against all the tested cell lines. Among them, compounds 15g (procaspase-3 EC50 = 1.42 μM) and 16b (procaspase-3 EC50 = 0.25 μM) exhibited excellent antitumor activity with IC50 values ranging from 0.14 μM to 0.98 μM against all cancer cell lines, which were 1.8–8.7 times more active than the first procaspase activating compound (PAC-1) (procaspase-3 EC50 = 4.08 μM). The structure–activity relationship (SAR) analyses indicated that the introduction of a lipophilic group (a benzyloxy or heteroaryloxy group) at the 4-position of the 2hydroxy phenyl ring was beneficial to antitumor activity, and the presence of substituents containing nitrogen that are positively charged at physiological pH could also improve antitumor activity. It was also confirmed that the steric effect of the 4-position substituent of the benzyloxy group had a significant influence on cytotoxic activity.

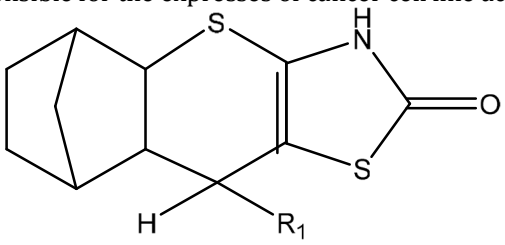
Jianwen Yao et al [52]a novel series of diarylthiourea containing sorafenib derivatives 9a– t was designed and synthesized. The structures of all the newly synthesized compounds were determined by 1H NMR, 13C NMR and HRMS. Their antiproliferative activities against HCT116 and MDA-MB-231 cell lines and their inhibitory activities against the phosphorylation of VEGFR were evaluated and described. Some of the compounds showed significant activities against both cell lines and VEGFR. Compounds 9g, 9m, 9o and 9p demonstrated competitive antiproliferative activities to sorafenib, the reference standard, while compounds 9d, 9m, and 9p showed significant inhibitory activities against the phosphorylation of VEGFR.



DiarylThiourea

Mohammad Rashid et al (2020) [53] some of the substituted thiazolidinedione molecules were designed for the treatment of human cancers cell line through different molecular mechanism such as EGFR &

Mushroom Tyrosine kinase inhibitor, COX enzyme inhibitors, Histone deacetylase inhibitors, Alpha glucosidase inhibitor, DNA intercalation and Protein tyrosine phosphatase 1B (PTP1B) inhibitor, basically in which PPAR gamma express are in high levels. Peroxisome proliferator-activated receptor (PPAR) gamma ligands effect on apoptosis, cell proliferation and cell differentiation on different types of cell. The most commonly cascades in human cancers cell are Raf/MEK/ERK, Wnt and PI3/Akt. This article highlights and embraces a concise overview of recent approaches for the synthesis of new thiazolidinedione molecules with its structure activity relationship strategy and effects on various signalling pathways, which is responsible for the expresses of cancer cell line activity.



Thiazolidinedione

Mohmmad R Selim et al (2010) [54] Fused pyrazolopyrimidoquinolines 3a-d, Schiff bases 5, 6a-e, two hybridized systems: pyrazolochromenquinoline 7 and pyrazolothiazolidinquinoline 8, different substituted thiazoloquinolines 13-15 and thiazolo [3, 2-a] pyridine derivatives 16a-c were synthesized. Their chemical structures were characterized through spectral and elemental analysis, cytotoxic activity on five cancer cell lines, caspase-3 activation, tubulin polymerization inhibition and cell cycle analysis were evaluated.

Ngoc Hong Nguyen et al (2011) [55] the present study aimed to discover the potential cytotoxicity of ethanol extract and its derived fractions (chloroform, ethyl acetate, butanol, and aqueous) of AdenosmabracteosumBonati. (A. bracteosum) on human large cell lung carcinoma (NCI-H460) and hepatocellular carcinoma (HepG2). Among these fractions, the chloroform showed significant activity in the inhibition of proliferation of both cancerous cells because of the presence of bioactive compounds including xanthomicrol, 5,4'-dihydroxy-6,7,8,3'-tetramethoxyflavone, and ursolic acid which were clearly revealed by nuclear magnetic resonance spectroscopy 1H-NMR, 13C-NMR .Minghui Wan et al (2011)[56]Based on the structure of sanguinarine, fourteen phenanthridine derivatives were designed and synthesized in the current study. The cytotoxic activities of synthesized compounds were evaluated against five human cancer cell lines (MCF-7, PC3, Hela, A549, and HepG2 cell lines) via MTT assay. Among all the compounds tested, molecule 8a exhibited significant cytotoxic activity against MCF-7 cells with a IC50 value of 0.28 μM. A following up enzymatic assay indicated that compound 8a could inhibit the activity of DNA topoisomerase I/II. Further mechanistic studies performed in the MCF-7 cell line revealed that compound 8a could arrest cell cycle in S phase and induce cell apoptosis via downregulation of Bcl-2 and upregulation of Bax. Collectively, a potent DNA topoisomerase inhibitor (8a) was discovered, which exhibited potential as a candidate chemotherapeutic agent for the management of tumours in the present study.

Boon KuiHo et al (2012) [57] Studied on 4-[(Halo phenyl) diazenyl] phenol was prepared prior to esterification from coupling reaction of aniline derivatives and phenol in basic solution. All compounds were characterized using elemental analysis, FTIR, and 1H and 13C NMR spectroscopies. All compounds were screened for their anticancer activities against nasopharyngeal cancer (NPC) HK1 cell lines and the viability of cultured cells was determined by MTS [3-(4,5-dimethylthiazol-2-yl)5-(3-carboxylmethoxylphenyl)-2-(4-sulfophenyl)-2H-tetrazolium]-based colorimetric assay. 4-[(E) (Fluorophenyl) diazenyl] phenol showed the highest anticancer activity against NPC HK-1 cell lines compared to other synthesized compounds. 4-[(Halo phenyl) diazenyl] phenylaspirinate showed low cytotoxicity against NPC HK-1 cell lines compared to 4-[(halo phenyl) diazenyl] phenol but better anticancer activity than aspirin alone.

Victor Kuete et al (2020) [58] Natural products are well recognized as sources of drugs in several human ailments. In the present work, carried out a preliminary screening of six natural compounds, xanthone V1 (1); 2-acetylfuro-1,4-naphthoquinone (2); physcion (3); bisvismiaquinone (4); vismiaquinone (5); 1,8-dihydroxy-3-geranyloxy-6-methylanthraquinone (6) against MiaPaCa-2 pancreatic and CCRFCEM leukaemia cells and their multidrug-resistant subline, CEM/ADR5000. Compounds 1 and 2 were then tested in several other cancer cells and their possible mode of action were investigated.

Katayoon Hafeji et al (2019) [59] This study aimed to investigate the anticancer activity and molecular mechanisms of α-conidendrin on breast cancer cell lines. The results of the present study showed that α-conidendrin possesses potent anti-proliferative effects on breast cancer cell lines MCF-7 and MDAMB-231. α-Conidendrin significantly induced apoptosis in breast cancer cells via reactive oxygen species generation, upregulation of p53 and Bax, downregulation of Bcl-2, depolarization of mitochondrial membrane potential (MMP), release of cytochrome c from mitochondria, and activation of caspases.
Anna Lichota et al (2011) [60] this paper describes the substances of plant and marine origin that have anticancer properties. The chemical structure of the molecules of these substances, their properties, mechanisms of action, their structure–activity relationships, along with their anticancer properties and their potential as chemotherapeutic drugs are discussed in this paper. This paper presents natural substances from plants, animals, and their aquatic environments. These substances include the vinca alkaloids, mistletoe plant extracts, podophyllotoxin derivatives, taxanes, camptothecin, combretastatin, and others including geniposide, colchicine, artesunate, homoharringtonine, salvicine, ellipticine, roscovitine, maytanasin, tapsigargin, and bruceantin.
Ignas Grigalius et al (2013) [61] studied was to evaluate antioxidant and anticancer activity of seventeen trihydroxyflavone derivatives, including apigenin (API) and baicalein (BCL). Also, wanted to find out if there is a correlation between those two effects. Cell growth inhibition testing was carried out using MTT assay in three different human cancer cell lines: lung (A549), breast (MCF-7) and brain epithelial (U87). Antioxidant activity was determined by the DPPH radical scavenging method. Thirteen trihydroxyflavones possessed anticancer activity against at least one tested cancer cell line. They were more active against the MCF-7 cell line, and the lowest activity was determined against the U87 cell line. The majority of compounds inhibited cancer cell growth at EC50 values between 10–50 μM. The most active compound was 3', 4',5-trihydroxyflavone 7, especially against A549 and MCF-7 cell lines Lili Zhang et al (2016)[62]the objective of this study was to investigate the use of curcumincyclodextrin complexes (CD15) as an approach to cancer chemoprevention. In this study, CUR encapsulation into the β-cyclodextrin (CD) cavity was achieved by the saturated aqueous solution method. CD15 was characterized by Fourier transform infrared (FTIR) and UV spectra analyses. An optimized CD15 was evaluated by cellular uptake and anti-cancer activity. As a result, CD15 enhanced curcumin delivery and improved its therapeutic efficacy compared with free curcumin in vivo and in vitro. Therefore, through regulation of MAPK/NF-κB pathway, CD15 up-regulated p53/p21 pathway, down-regulated CyclinE-CDK2 combination and increased Bax/caspase 3 expression to induce cellar apoptosis and G1-phase arrest. In conclusion, these results suggested that CD15 formulation should be used as a system for improving curcumin delivery and its therapeutic efficacy in lung cancer.

APPLICATIONS OF CURCUMIN IN TREATMENT OF DIFFERENT TYPES OF CANCER

Because of the emergence of novel applications, research on the bioactive component content of the many species of turmeric in the Zingiberaceae family points to an increase in curcumin synthesis in the years to come. Curcumin is suggested as a possible adjuvant for the treatment of cancer and neurological illnesses because of its anti-inflammatory and antioxidant qualities. Applications for curcumin's antioxidant qualities can also be found in the dyeing of textiles, which led to the creation of fabrics with antimicrobial or anti-UV qualities. The variety of uses for curcumin indicates its adaptability and propensity to be applied in as many contexts as feasible where the given features are present. Curcumin has been demonstrated to be a potent antioxidant and has been the subject of numerous clinical and pharmacological investigations. Through the inhibition of peroxidated lipids and the neutralization of super oxidized and hydrolysed radicals, a curcumin-containing diet reduces oxidative stress. Curcumin's low solubility in water limits its applications even with these advantageous qualities. Several encapsulation techniques for curcumin have been tried in an effort to enhance the photo stability and solubility characteristics. Since the 1990s, curcumin's antiviral activity has been investigated through laboratory experiments on cells. The findings of these studies have demonstrated curcumin's activity against the hepatitis C virus and the human immunodeficiency virus; currently, research is being done on both DNA and RNA viruses. Curcumin's antiviral qualities were validated in 2007 after a study on acute respiratory syndrome associated with coronavirus (SARS-CoV) examined curcumin and 220 other phytocompounds. Curcumin is one of the 20 phytocompounds that have demonstrated notable and targeted anti-SARS CoV activity, along with a few diterpenes and triterpenes. As a result of improving on the preliminary findings in subsequent years, new classes of antiviral agents containing curcumin and carbon dots were created. Viral protein modification and suppression of RNA synthesis are the mechanisms by which the new structures work. Another way to lessen coronavirus infections is to promote the synthesis of pro-inflammatory and interferon-simulating cytokine genes. Another technique used in antiviral treatments is photodynamic inactivation, which involves depositing

curcumin on reduced graphene oxide as a photosensitizing agent. There are currently proposals for the use of curcumin to treat the COVID-19 virus that is currently circulating.

In 2016, studies showing the synergistic effect of curcumin and ciprofloxacin against Gram-positive bacteria brought curcumin to the attention of researchers as a potentiator of the effect of antibiotics. The process's capacity to produce ROS is the mechanism by which it operates. Curcumin exhibited superior antibiofilm activity in comparison to histidine and showed a comparable effect to chloramphenicol. In vitro tests confirmed that curcumin had an antibiofilm effect on A. baumannii. One of the most prevalent bacteria in nosocomial and chronic infections is A. baumannii, which has a strong resistance to antibiotics and other antimicrobials.

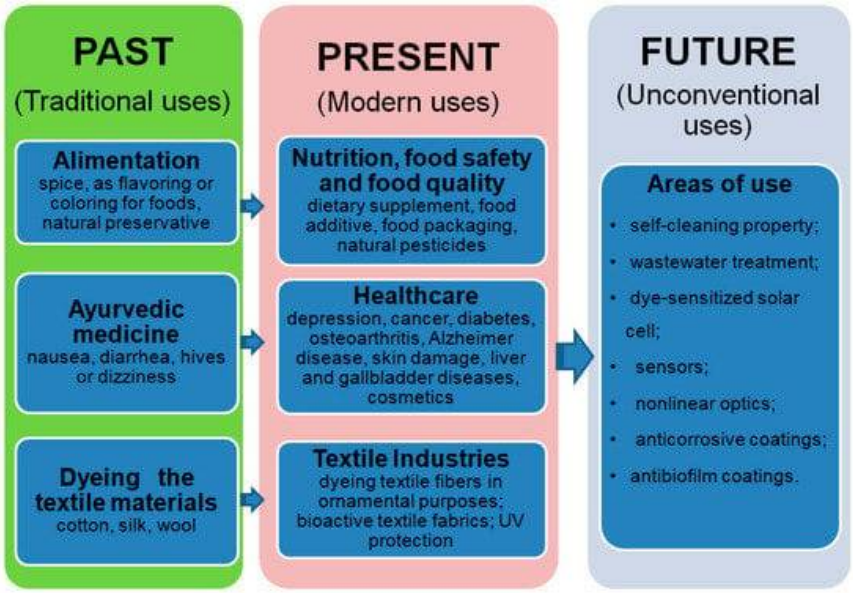


Fig 4: Areas of applications of Curcumin

A) Additive for the Prevention of Spoilage, Safety and Quality of Food:

In order to combat a variety of pathogens in the process of preserving and preventing fruit and vegetable rot degradation, curcumin is used in the form of natural extracts, nanocomposites, or deposited on nanoparticles with metal-organic structures. This allows for the optimization of the antifungal properties and insecticidal effects. Because of its antifungal properties, curcumin can be added to food as an additive, extending its shelf life. Simultaneously, curcumin encapsulated in β-cyclodextrin is employed in the process of manufacturing cheese, or encapsulated in sodium alginate for the mature cheeses' edible membranes, all without altering their original properties. Under white light irradiation, thin coatings with antimicrobial photodynamic activity have been created using curcumin incorporated in polyvinyl acetate films. Since curcumin is not able to undergo isomerization, its stability and fluorescence lifespan are prolonged when it is embedded in polymer matrix.

B) Additive for Health Care Products:

Because of its anti-inflammatory, antiviral, and antibacterial qualities, curcumin is well-known in traditional medicine, particularly in India, for the treatment of fever, skin infections, and digestive difficulties. Nosocomial infections have increased during the past two years as a result of hospital congestion brought on by the COVID-19 pandemic. In this context, numerous research using curcumin as a microemulsion have shown noteworthy findings. Curcumin is most heavily used in skin care products. Curcumin was once used in poultices and compresses to treat a variety of skin conditions. As its antibacterial, antifungal, and antioxidant qualities were established, cosmetic manufacturers became aware of curcumin. Afterwards, loading systems were created to boost curcumin's photostability and skin penetration effect. As a result, it was first used as a conditioning agent in cosmetics to preserve the skin's quality and to treat eczema, psoriasis, and acne. Additionally, research has focused on treating and preventing chronic wound infections, particularly in patients with diabetes whose healing process is sluggish.

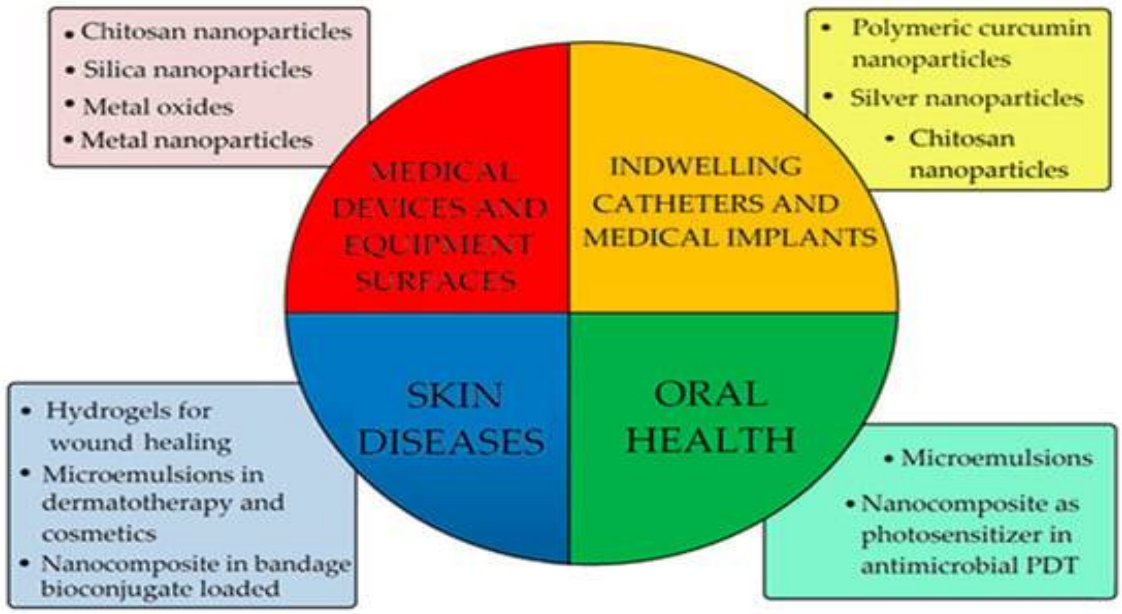


Fig 5: Applications of Curcumin in the medical field & its types of formulations

CONCLUSION

In conclusion, we have presented, in brief, highlights of the researchers and studies that have been directly linked to the field of oncology. Curcumin has considerable anticancer effects against several different types of cancer, viz. prostate cancer, breast cancer, colorectal cancer, pancreatic cancer and head and neck cancer both in vitro and in vivo. The results reviewed in the current study investigate that curcumin may exert positive effects against various types of tumour and anti-oxidant, anti-inflammatory, anticancer activity of curcumin analogues study.

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