The promise of Curcumin: A potential breakthrough in cancer treatment and drug delivery systems

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Abstract:

Cancer is one of the leading deaths causing health problem in the modern era. We have developed different advanced techniques but the mortality rates are still high. So, we have to develop a more efficient and less toxic methods for the treatment of different types of Cancers. Curcumin is known for its antibacterial, antioxidant, anti-inflammatory and anti-cancer properties. This review gives us the information about Medicinal Chemistry and pharmacology of curcumin derivatives works as an anticancer agent, their mode of action and celluar targets on the basis of literature, scientific, experimental data and clinical research of curcumin in cancer cell lines, humans project, and animal models. In addition, we can include how curcumin is delivered into the cancer cells through advanvced techniques that we can use in drug delivery.

Abbreviations used:

COX-2: Cyclooxygenase 2
DMC: Demethoxycurcumin
NF-kB: Nuclear factor kappa B
BDMC: bis-demethoxycurcumin
LPPC: Liposomal complexes of curcumin
DOPC: dioleoyl-sn-glycro-3-phosphocholine
DLPC: 1,2-Dilauroyl-sn-glycro-3-phosphocholine
5LOX: 5-Lipoxygenase
MMP: Metalloproteinase
BAX: Bcl-2-associated protein x

Keywords: Curcumin; Drug Delivery System; Targeted Delivery; Mode of action; cellular Pathway; interleukins; Polyethylene glycol

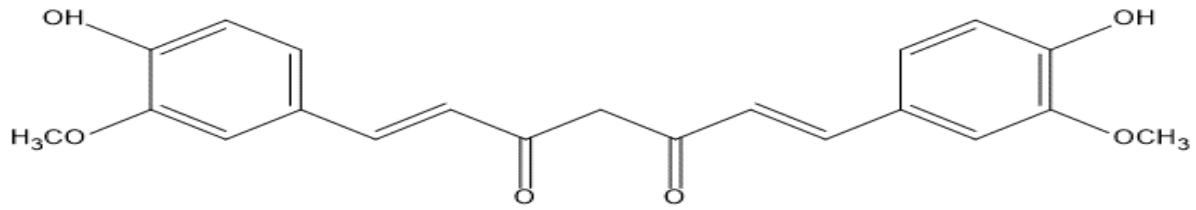
1. Introduction

In the current period, cancer is one of the main health issues that cause deaths. Even with the development of several cutting-edge procedures, the death rates remain high. Therefore, we need to create less harmful and more effective ways to treat the many kinds of cancer. Antibacterial, anti-inflammatory, antioxidant, and anti-cancer activities are well-known benefits of curcumin. Based on published literature, scientific research, experimental data, and clinical studies on curcumin in cancer cell lines, human subjects, and animal models, this review provides us with information about the medicinal chemistry and pharmacology of curcumin.

Cancer is merely an unchecked cell development that invades other organs and results in an individual's death. In the USA alone, 1.95 million new instances of cancer were reported in 2023, resulting in 609,824 cancer-related deaths [1]. Although there has been significant progress in cancer therapy, the death rate and reported incidence of the disease have not changed [2]. Understanding the molecular changes that cause cancer to form and spread can help with cancer treatment and prevention. It is possible to target specific cancer cells to prevent tumour growth, metastasis, and progression utilising a number of widely used methods without suffering from serious adverse effects [3]. One of the phenol-based components known as 1,7-Bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene 3,5-dione is extracted from the rhizome of Curcuma longa. Curcumin is a chemical with a yellow colour and several of biological characteristics, such as anti-inflammatory, anti-cancer, neuroprotective, and antioxidant actions. Additionally, curcumin has been shown to be helpful in treating a variety of illnesses, including cancer, pancreatitis, arthritis, psoriasis, and cardiovascular disease. Curcumin exhibits both therapeutic and preventative benefits on cancers such as brain tumours, glioblastoma, lung cancer, and prostate cancer [5–17]. The main purpose of curcumin is to target stem cells, a subset of cells that are resistant to chemotherapy and can lead to the recurrence of cancer. According to a number of studies, curcumin, when used as an aiding therapy, can sensitise cancer cells and lessen the severe side effects of radiation and chemotherapy [14–17].

Curcumin suppresses several cellular system pathways to cause programmed cell death and to slow down the growth and invasion of tumours. By focusing on many cell lines, curcumin exhibits anti-cancerous properties against various cancers, including brain tumours and lung, prostate, and breast cancers [19]. Curcumin has a number of benefits, however its restricted solubility in water leads to poor oral bioavailability, and it also has a lower chemical stability [20]. Due to its hydrophobicity and limited cellular absorption, curcumin can pass through cell membranes and form hydrophobic interactions and hydrogen bonds with fatty acyl chains, which reduces the amount of curcumin that is available inside the protoplasm [21, 22]. Curcumin's structure is altered in multiple ways to boost its anti-cancer effects overall and to raise its bioavailability and specific cancer-fighting capabilities. To improve the overall anti-cancer properties of curcumin its structure undergoes several modifications to increase its properties towards specific cancer and its bioavailability and stability also enhanced. Mervia, is a clinically enhanced form of curcumin that shows higher absorption when compared with regular curcumin [4,23]. Phospholipid is type of fat when attached with curcumin increases its absorption and increases its bioavailability in cytoplasm [24].

Different delivery systems can also be used to increase curcumins anti-cancer activity and its physiochemical properties [25]. This review highlights the use of curcumin and its derivatives with different cancer therapies for increasing anti-cancer effects in different cancer cell lines, human clinical trials, and animal models. Curcumin is beneficial in different type of diseases but cannot reviewed there as we only reviewed here only anti-cancerous properties of curcumin [4,26].



Fig; Diferuoloymethane

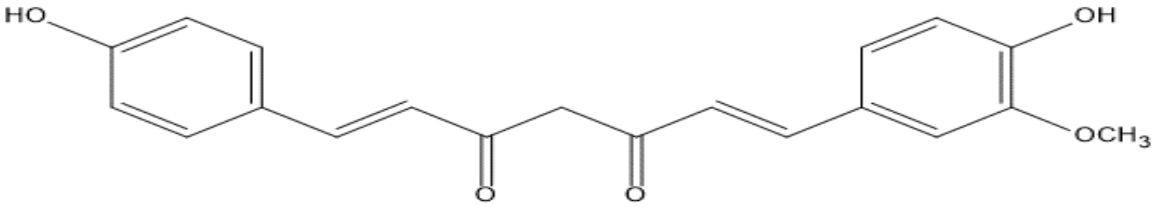


Fig ; Demethoxycurcumin

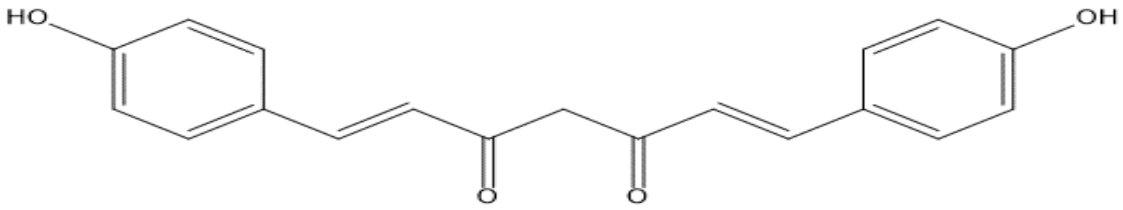


Fig ; Bisdemethoxycurcumin

Figure 1. - Isolated extracted substances from the turmeric plant. (A) Curcumin (diferuloloymethane), (B) demethoxycurcumin and (C) bisdemethyoxycurcumin.

2. Structure Activity Relationship of Curcumin and its Derivatives

Modifications in Curcumins structure alters its pharmacokinetics and physiochemical properties and also affects the receptor bindings and pharmacological activity of a drug molecule [4]. By studying the natural and synthetic analogues we can find the essential molecule which is responsible for the molecule's biological activity [27]. The structure of curcumin is shown in Figure 2 A. Curcumin also called (Di feruloyl methane) is a symmetric molecule with chemical formula C21H20O6 and molecular weight of 368.38g/mol. [28-31,32].

Curcumin structure contains three chemical entities: two aromatic rings containing ortho-methoxy phenolic groups which are substituted with methoxyl and hydroxyl and are connected with seven carbon keto-enol linker [32,33]. Curcumin is derived naturally form curcuma longa but its analogues are produced by reaction between acetylacetone and aryl-aldehydes. Curcuma longa is the natural source of curcumin; nevertheless, acetylacetone and aryl-aldehydes react to make curcumin's derivatives [34]. The Structural activity relationship (SAR) research of curcumin demonstrates that the anti-androgenic action for the treatment of prostate cancer requires the presence of (β-diketone) moiety and coplanar hydrogen doner group [34]. Dimethyl curcumin, having the chemical formula C23H24O6 and a molecular weight of 396.4 g/mol, is a derivative of curcumin. It is a novel anti-androgen that promotes the breakdown of androgen receptors [35,36]. Dimethyl curcumin also shows a noteworthy antiproliferative impacts on breast cancer cells that are dependent on estrogen [37].

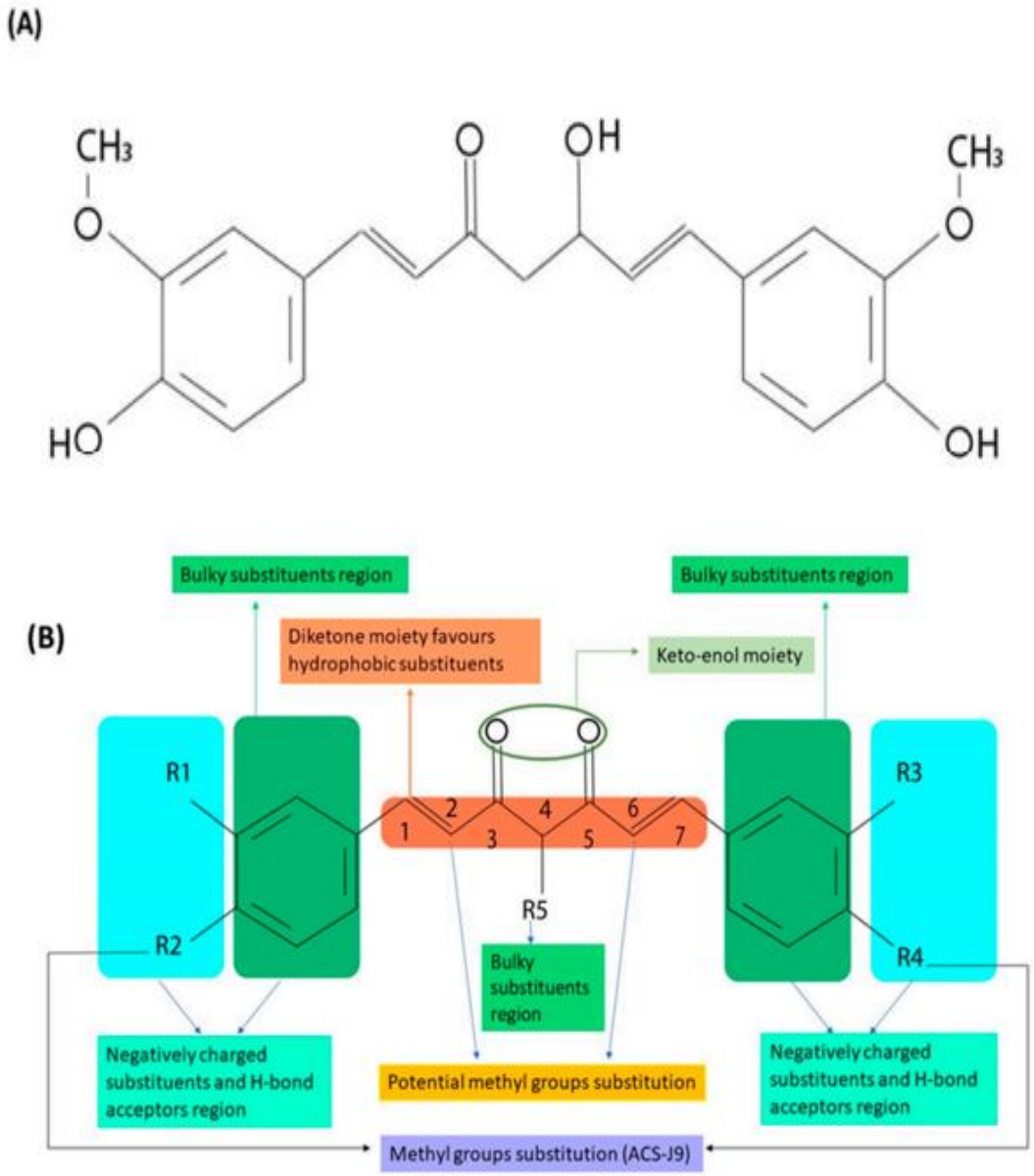


Figure 2. (A) Curcumin's Biochemical Structure (B) The Major pharmacophores and potential alteration sites.

Additionally, research on the kinetic stability of synthetic curcumin derivatives have shown that the compounds water solubility is increased by glycosylation of the aromatic ring pharmacophore, which improves the compounds kinetic stability and improves the therapeutic response overall [38]. Phase I and phase II metabolism involve oxidation, reduction, and conjugation events to change curcumin into a more excretable form. The hydroxyl groups (4-OH) that are connected to curcumin phenyl rings are the site of conjugation process. Therefore, hiding the 4-OH groups can improve the kinetic stability of curcumin [39]. Cu2+/Ni2+/Zn2+ metal ions have been used to create metallo-curcumin-conjugated DNA complexes, which increase curcumin solubility and strengthen DNA binding capacity [40]. Cu2+, Fe2+, and Pb2+ metal complexes increase the chelating activity of derivatives of curcumin. Significant toxicity to many prostate cancer cell lines is seen in these metallo-curcumin complexes, along with improved antibacterial action [40]. Curcumin root's unsaturated diketone group is a phase II enzyme inducer and a Micheal reaction accepter, which may be in charge of suppressing NF-kB in cancer cells [4]. Nonetheless, a study examining seventy-two distinct curcumin derivatives failed to discover a connection between antioxidant activity and the NF-kb mediated prevention of tumour growth [41]. The naturally occurring chemicals demethoxycurcumin (DMC) and bis-demethoxycurcumin (BDMC) have enhanced anti-cancer effects in-vitro [42] and are distinct from curcumin in terms of quantity and location of hydroxy and methoxy substitutions [43]. Curcumins methoxy and hydroxyl groups are essential in determining a range of biological actions [44,45]. Curcumin capacity to scavenge radicals is increased when phenolic groups are present, hence augmenting its antioxidant action [46]. There are two distinct forms of hydroxyl groups found in curcumin: the phenolic moiety and enolic moiety respectively[44,47]. Enolic portion exhibits stronger anticancer characteristics, and the presence of hydroxyl groups boosts the molecules anti-oxidant properties while also strengthening its ability to form hydrogen bonds, which increase the molecules hydrophilicity [48,49,50]. Curcumin-phenoxyl radicals, which are less reactive and more stable than the original free forms, are created when curcumin reacts with reactive oxygen species (ROSs) [51]. Boron trioxide mediated aldol condensation is the process used to create derivatives of cyclic curcumin, and it is crucial for enhancing the compound’s cytostatic, anticancer, and antioxidant properties [52]. Hydrazinocurcumin is made by substituting the diketone moiety with a hydrazine derivative. It is more effective at inhibing the progression of colon cancer by opposing the action of Ca2+/CaMe [53,54].

Table 1. Alterations in the pharmacological activity of metabolites of curcumin in relation to curcumin

Curcumin Derivative	Chemical Modification	Activities Shown	References
Dimethyl Curcumin (C23H24O6) (ASC-J9)	Substitution of methyl groups on R2 and R4	Increased action against breast and prostate cancer	[37,55,56,68]

Curcumin carbocyclic analogues	A carboxyl group is added to the diketone moiety	increased antioxidant capacity and more potent HIV 1 protease inhibition	[57,68]
Tetrahydrocurcumin (C21H24O6) (THC)	Moiety of hydrogenated diketones	Increased antioxidant capacity but diminished DNA binding and STAT3 inhibitory qualities	[58,59,68]
Vanadium, gallium, and Indium complexes	β-Diketones mediate metal complexation	Higher levels of cytotoxicity	[60,68]
Modified aromatic rings curcumin compounds	Cyclohexane bridge introduction	Enhanced permeability of the mitochondrial membrane during cancer treatment	[61,68]
Metallo-curcumin (Cu2+/Ni2+/Zn2+)	β-Diketones mediate metal complexation	Better DNA binding and increased solubility in water	[40,68]
Glycosylated curcumin derivative	Substitution of glycol groups on aromatic rings	Increased strength, water solubility, and chelating characteristics	[62,68]
Cu2+ conjugate of synthetic curcumin analogues	Conjugation reaction on the keto-enol moiety	Greater resistance against TNF-induced NF-κB activation in leukemic KBM-5 cells	[63,68]
Cyclic curcumin derivatives	Aldol condensation mediated by boron trioxide	Increased antioxidant, cytostatic, and anticancer activities	[64,68]
Hydrazinocurcumin (C21H20N2O4)	substituting a hydrazine derivative for the diketone moiety	Increased effectiveness in preventing the spread of colon cancer by antagonistic action on Ca2+/CaM functions	[66,65,68,]
Semicarbazone	NNHCONH2 is introduced at the keto-enol moiety	increased activity against radicals, proliferators, and antioxidants	[67,68]

3. Curcumin Administration Protocol

Curcumin has been termed "pharmacodynamically fierce" due to its wide range of biochemical actions and consequences in various disorders. Conversely considering its rapid clearance, low bioavailability, and poor absorption its pharmacokinetic profile has been categorized as “fragile” [51,69]. To boost curcumin’s bioavailability, various strategies have been employed, including creation of structural analogues of curcumin and combining curcumin with adjuvant substances. Additionally advanced drug delivery system include of liposomal curcumin, cyclodextrin complexes, peptide and protein formulations, nanoparticles, nanospheres, and cell derived nanovesicles [70].

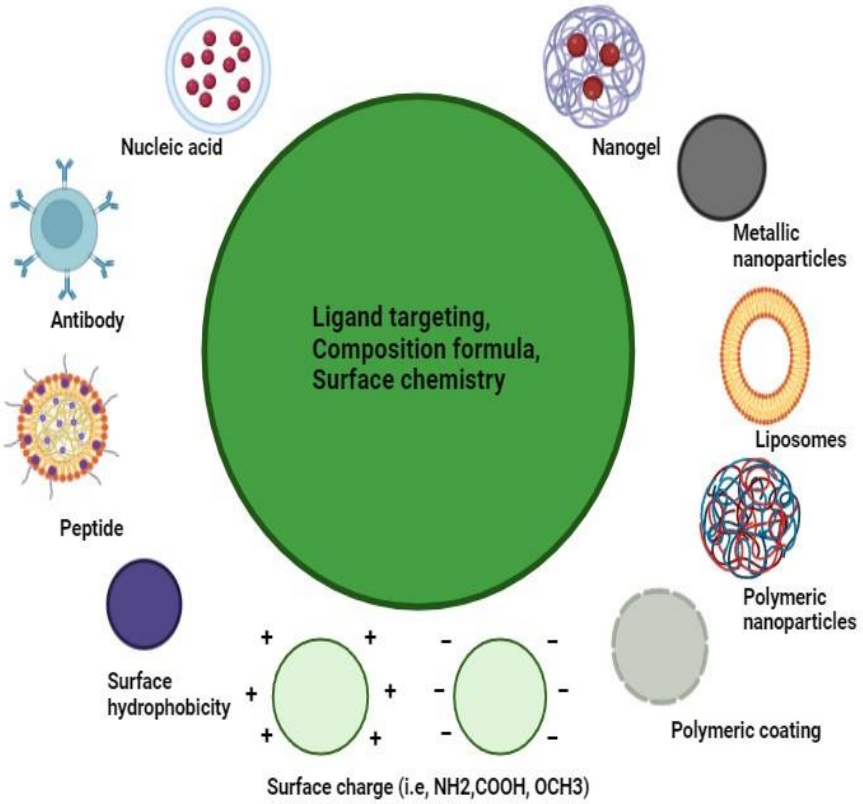


Figure 3. Examples of contemporary techniques to construct nanoparticles that facilitate targeting.

3.1 Nanoparticles

The uptake of lipophilic drugs has been greatly improved by the introduction of novel drug delivery methods. Many nano-particulate drug delivery technologies have made it possible for formulation professionals to prepare and administer curcumin and other hydrophobic drugs, which was previously unfeasible [71]. Nanoparticles administration methods can raise the therapeutic index of encapsulated medications so these methods gain enormous popularity in the last ten years. This can be accomplished by limiting the enzymatic breakdown of medications [72], modifying their pharmacokinetics [73], reducing their toxicity [74], or allowing for a controlled release over an extended period of time [75]. Nanoparticle delivery systems can contain pharmaceuticals that are conjugated, disseminated, adsorbed, or encapsulated with particle size ranging from 1-100 nm [76].

Curcumin can be formulated as PLGA and PEG NPs for parenteral administration utilizing the nano-precipitation process which can increase the curcumins biological half life and improves its suppression of TNF-induced NFKB activation in comparison to its free form [77].

3.2 Liposomes

The aqueous interior of spherical bilayer vesicles known as liposome is created when cholesterol molecules and amphiphilic phospholipids self-associate. Three types of liposomes exist: large unilemellar, fragile unilemellar, and multilamellar. Alternatively they can be categorized into traditional liposomes, pH sensitive liposomes, cationic, immune, and long circulating liposomes based on mechanism underlying drug releaseThe solubility of chemopreventives that are weakly soluble in water can be considerabaly increased by the lipid based particle carriers [78].

L-glutamic acid, N-(3-carboxyl-1-oxopropyl)-, 1,5-dihexadecyl ester, and 1,2-dimyristoyl-sn-glycro-3-phosphocholine (DMPC)have been used to successfully create lipid based curcumin nanoparticles [79]. Another finding is that curcumin plasma can be increased by using eggphosphatidylcholine (EPC) liposomes [80,81].

Polyethylenimine (PEI) and polyethylene glycol (PEG) containing polycationic liposome complexes of curcumin (LPPC) was assessed by Lin et al. [82] . Using 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) and 1,2-Dilauroyl-sn-glycro-3-phosphocholine (DLPC), LPPC were produced. The cytotoxic activity of curcumin/LPPC was seen to be 3.9 to 20 times higher than that of nonencapsulated curcumin in a range of cancer cell lines, including curcumin sensitive and resistant cells. By enabling a quick distribution of the medication into the cells, curcumin/LPPC liposomes were also able to stop the cell cycle at the G2/M phase and cause apoptosis at a lower dose than noncapsulated curcumin. Curcumin/LPPC liposomes also significantly inhibited the growth of tumours in vivo, possibly as a result of the drug's increased delivery and accumulation in tumour area [82].

3.3 Polymer Based Hydrogels

Polymers have abundant OH groups in their structure including poly(vinyl alcohol) so they have demonstrated appropriate film forming characterstics [83]. El-Nashar et al.'s work suggest that a composite film consisting of poly(vinyl alcohol) and curcumin may be used to treat liver cancer [84]. A promising delivery method for the treatment of liver and breast malignancies is the curcumin-loaded film. The goal was accomplished by incfresing the efficiency of loaded curcumin through a sustained release profile and enhancing encapsulation efficiency with the help of cellulose nanocrystals. Curcumin reduced fast metabolism and blood clearence and exhibited an extended-release profile that enhanced bioavailability [85]. A surfactant containing water soluble formulations called polyethylene glycol d-α-tocopheryl succinate 1000 (TPGS) is made from vitamin E. In aqueous solution this substance can produce micellar NPs [86]. The HT-29 colon cancer cells underwent apoptosis and the concentration of reactive oxygen species was significantely reduced in vitro when curcumin was delivered by this method, albeit at a sluggish release. Moreover, as compare to free curcumin, it appears that the oral curcumin formulations made via TPGS has a higher bioavailabilty [87].

Implementation of injectable thixotropic hydrogels derived from silk fibrion/hydroxyl propyl cellulose is a promising new strategy for combting the hydrophilic nature of curcumin. Comparing the long term sustained anticancer effects to the free drug or single drug loaded hydrogels formulations, in vitro and in vivo drug release and cytotoxicity experiment shown [86]. Drug delivery methods utilizing polymeric micelles are frequently employed to address the limited solubility of hydrophobic medicines [88].

Glycyrrhetinic acid was utilized to create supramolecular curcumin pro-gelator (Ga-Cur), which is curcumin delivery strategy targeted for the functioning of liver [89]. Through ester bond hydrolysis, the targeted delivery system achieved continues drug release from the formulations. GA-Cur is a potentially effective targeted method for curcumin administration to the liver [90].

3.4 Cyclodextrin complexes

Cyclodextrins are water loving oligosaccharides that have a lipophilic core cavity and a hydrophilic outside [91]. Covalent interaction of lipophilic drug moieties within the lipophilic cavity of cyclodextrin result in the formation of drug-cyclodextrin inclusion complexes [91]. The solubilizing action of CD molecule is provided by its polar outer surface, while the lipophilic cavity shields the lipophilic guest molecule from the aqueous environment [91]. The polarity within the hollow is hypothesized to be comparable to that to that of an ethanol 40% solution in water [91,92]. Curcumin was found to form 1:1 inclusion complexes in the solution state, generating an AL type of phase solubility graphs with βCD, γCD, MβCD, and HPβCD [91]. Curcumin solubility was enhanced by CD in the following order: HPβCD>MβCD>γCD>βCD [91]. Bulky side groups on the phenyl moiety of the curcumin molecule appeared to fit better into the HPβCD cavity than the MβCD cavities, leading to a considerable increase in solubility when compared to the pure substance.

The synthesis of β-CD-curcumin inclusion complexes and their incorporation within liposomes was reported by Rahman et al. [93]. Experimental lung and colon cancer cell lines were used to analyze the in vitro cytotoxicity of the complexes. According to Maestrelli et al., liposomes were created utilizing the film hydration approach, which can entrap hydrophobic as well as βCD complexed hydrophobic molecules [94].

In both colon cancer and lung cancer cell lines studied, all formulations, including liposomal curcumin and liposomal β-CD-curcumin complexes, maintained their anti-cancer efficiency and had comparatively low median effective dose (EC50) values. Using curcumin entrapped liposomes, 1.9 μM for curcumin, 2.95 μM for βCD-C complexes, and 3.25 μM for liposomes containing βCD-curcumin were determined to be the formulations EC50 in colon cancer (Figure 3A) [93]. The same trend was absorbed in EC50 values for the formulation of lung cancer cells: 0.90 μM for curcumin entrapped liposomes, 1.5 μM for curcumin, 2.4 μM for β-CD-curcumin, and 2.9 μM for liposome containing β-CD-curcumin (Figure 3B) [93].

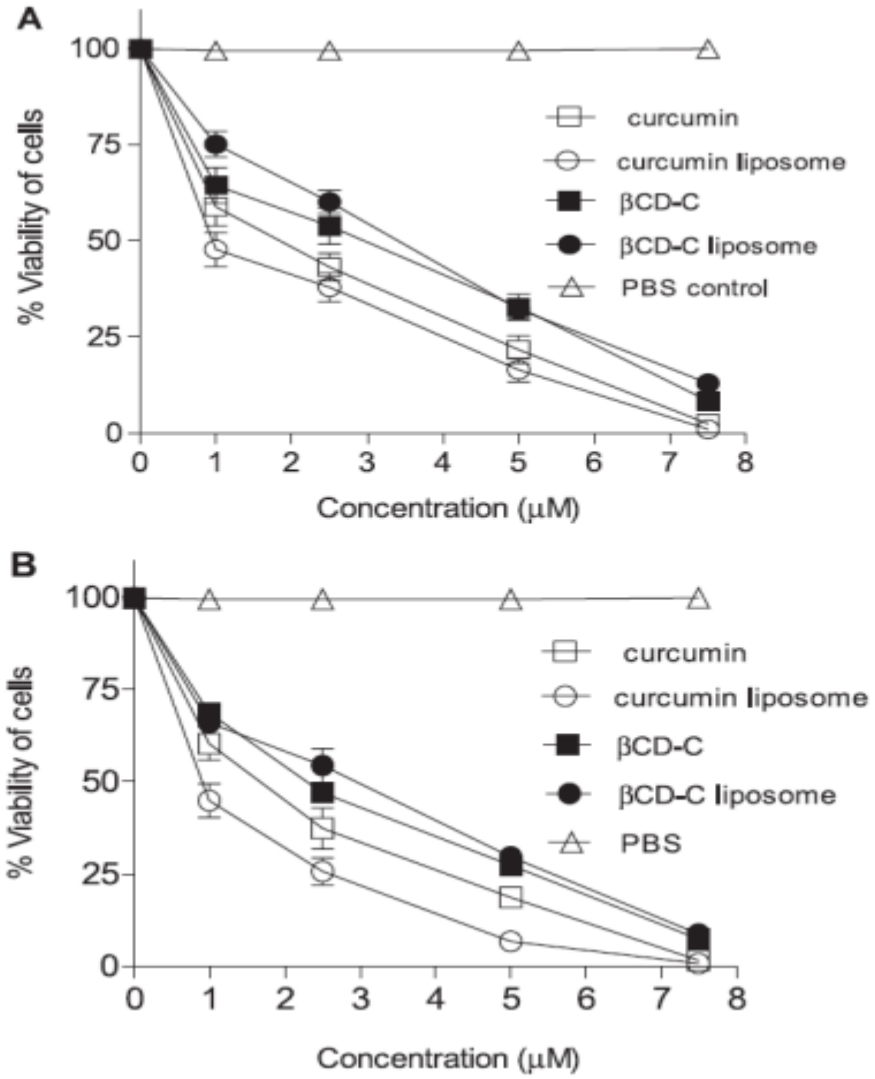


Figure 4: Cytotoxicity of curcumin formulations in SW-620 colon cancer cells (A) and A-549 lung cancer cells (B) Bars indicate SEM of three replicates [93,95]

4. Anticancer Activity of Curcumin

The onset of cancer is greatly impacted by generation of free radicals and oxidative damage, especially when it comes to destruction of DNA and peroxidation of lipids. Curcumin ability to scavenge free radicals may help prevent malignancy [96,97,98]. Moreover it inhibits the activation of the STAT-3 pathway, NF-kB, and signal transducer, postponing the initial stages of cancer [97,99]. Angiogenesis and tumour formation are two main processes that curcumin inhibits to prevent carcinogenesis, according to research conducted both in vitro and in vivo [100]. Several associated pathways are used by curcuminoids and turmeric to affect tumour angiogenesis [101]: i) Attenuation of IL-8 expression in pancreatic and head and neck cancer cell lines and prevention of VEGF synthesis induction through procedure at the level of transcription factors NF-kB, AP-1 (associated with inflammatory process), and early growth response protein 1; ii) suppression of angiogenesis caused by NO and iNOS; iii) inhibition of COX-2 and 5LOX; iv) action at the level of extracellular matrix's stability and coherence, which induces the elevated levels of tissue inhibitor of metalloproteinase-1 and reduction of MMP-2 and MMP-9. Turmeric also prevents the release of angiogenic factors that are kept in the extracellular matrix [101].

Leukemia, melanoma, and carcinomas of the breast, lung, colon, kidney, ovary, and liver are among the animal and human cell lines in which curcumin causes cell death [102]. Turmeric in varying doses, may also influence the kind of cell death. More intense doses result in decreased formation of reactive oxygen species, decreased ATP, and premature cell death, whereas lower amount cause oxidative stress and apoptosis [103]. It also seems that curcumin can induce cell death in a number of apoptosis resistant cell lines. This could be because curcumin triggers cell death processes aside from apoptosis, such as mitotic catastrophe, which is defined by abnormal mitosis and the development of multinucleated and large cells [104].

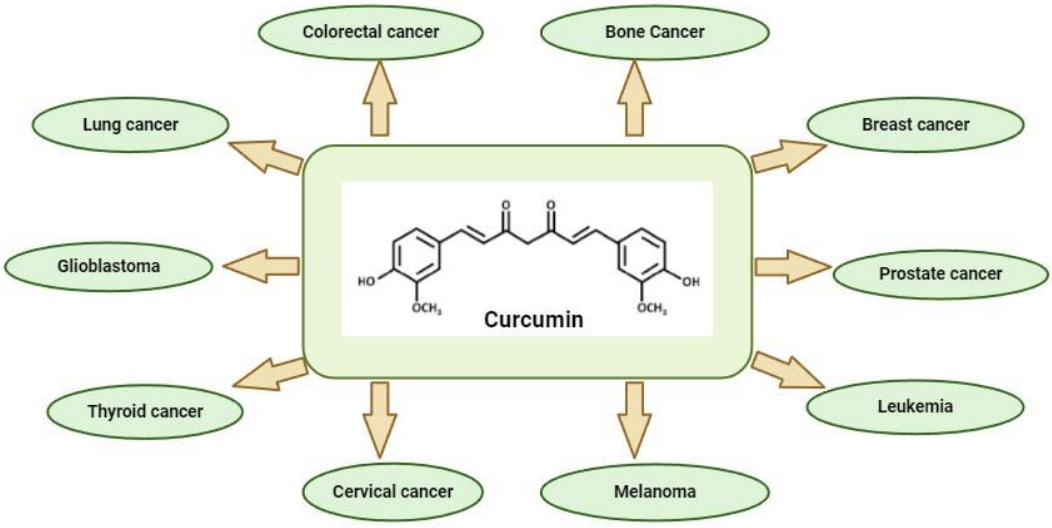


Figure 5. Descriptions of tumours that curcumin may be capable to alleviate and prevent.

4.1 prostate cancer

In western countries, prostate cancer ranks second among cancer related deaths among males [105]. Mostly, androgen receptor (AR) dependent signelling is responsible for the disease's start and development [106]. Prostate cancer was responsible for 378,000 deaths and 1,29,8000 new cases worldwide. Prostate cancer risk factors include weight, family history, age, and ancestry [107]. Currently, prostate cancer can be treated with surgery, radiation, chemotherapy, and hormone therapy. Numerous investigation have been conducted to assess curcumin's anticancer properties on both androgen sensitive and androgen resistant prostate cancer cell lines [108]. Curcumin can lower the development rate to 20-30% when compared to untreated LNCaP cells (a cell line that is sensatiuve to androgen). This was reported by T Doroi et al. in 2000 [109]. Additionally, they observed that BAX protein levels remain constant under the same circumstances, but that the antiapoptotic proteins BcL-XL BcL-2 were markedly decreased [109]. Curcumin may reduce NF-kB activation in prostate cancer cells, leading to tumour necrosis factor (TNF)-induced apoptosis, according to Asok Mukhopadhyay et al. [110].

Curcumin similarly impects numerous other proteins and pathways, including c-jun/activator protein 1, cyclin D1, CDK-4, phosphatidylinositol 3-kinase (PI3K)/mechanistic target of rapamycin (mTOR)/E-twenty six proto-oncogene 2 (EST2) pathway to decrease cell cell growth and proliferation in androgen sensitive prostate cancer cell lines [111,112,113]. Curcumin has also been demonstrated in studies to have anticancer effects on androgen insensitive prostate cancer cell lines. A typical androgen insensitive prostate cancer cell line is DU-145. When treated with curcumin, DU-145 prostate cancer cells had decreased NF-kB expression along with decreased growth and higher apoptosis [110]. Many scientific research works have explained the effects of curcumin therapy in vivo on mice that were xenografted with different types of human prostate cancer cells. On athymic naked mice injected with LNCap cells, Thambi Dorai et al. (2001) investigated the effects of curcumin. Enhanced pycnotic brown staining nuclei in situ, which indicated a considerable increase in apoptosis and a decrease in LNCap cell growth [114].

4.2 Colorectal Cancer

Men and women are equally impacted by colorectal cancer, which is one of the most common cancers. Patient hardly recovered from its malignent features, and relapse is frequent. Curcumin demonstrated its therapeutic activity in colorectal cancer by competing with multiple cell signelling pathways. Curcumin suppressed the growth of in vitro cultured HT 29 cell line and rat colorectal carcinogenesis induced by DMH (1,2-Dimethylhydrazine) via decreasing the PPARy signel transduction pathway [143]. Likewise curcumin inhibit the production of p53, pre-mRNA processing factor 4B (Prp4B), and cyclooxygenase-2 (COX-2) [144,145]. The suppression of NF-κB, urokinase-type plasminogen activator (uPA) activator, and matrix metalloproteinase-9 (MMP9) by AMPK has been reported to be the mechanism by which curcumin reduces colorectal cancer colonization [146].

Curcumin markedly reduced the development of human colon cancer cells. More-over it induced apoptosis via enroute mediated by mitochondria. In LoVo cells, curcumin produced the release of cytochrome C, markedly raised Bax and p53, and dramatically decreased Bcl-2 and surviving [147]. Curcumin increased the splitting of hexokinase II (HKII) from mitochondria, leading to mitochondrial mediated apoptosis, and diminished HKII expression and activity in humen colorectal cancer HCT116 and HT29 cells in a concentration dependent manner [148].

Furthermore, curcumin inhibit the WNT/catechin pathway in colon cancer cells SW480 by lowering the amount of miR-130a. This allowed curcumin to carry out its antitumour effects by preventing cells from proliferation as apposed to encouraging cell death [149]. Additionally, curcumin inhibit colon cancer cell proliferation and induced apoptosis by targeting the miR-491/PEG10 pathway [150].

4.3 Breast cancer

Breast cancer is one of the most common causing cancer in the world in women. Its rapidly spreading across all over the world at exponential rate. It is one of the life- threatening disease with higher mortality rate. About 70% of breast cancers are classified as estrogen receptor (ER) positive and could be treated with antiestrogens [151,152]. Breast cancers are mostly caused due to abnormal growth of breast cells which grows out of control at a rapid rate and generally forms tumours.

If it remains unchecked for sometimes, it starts affecting other part of body and generally becomes fatal if left untreated for longer duration and becomes fatal. Symptoms in breast cancer includes – a lump on breast or thickened area at some part of breast muscles that generally feels different from surrounding region or tissues, changes in colour of breast skin, change in shape size or appearance of breast, nipple or areola that is turned inwards, etc. These symptoms are significant part for developing breast cancer and should get medical attention as soon as possible. Drug combinations targeting different pathology signaling pathways have been considered as a major trend in drug design and discovery for killing endocrine-resistant breast cancer cells [153]. Curcumin has lots of medicinal properties and is one of the promising active ingredient for treatment of breast cancer. Particularly, curcumin has been recognized as an effective anticancer agent that regulates multiple intracellular signaling pathways, including transcription factors (e.g., STAT3, NF-κB, and AP-1), receptors (e.g., IL-8, HER2, and CXCR4), kinases (e.g., EGFR, ERK, and JAK), cytokines (e.g., TNF, IL, and MIP), enzymes (e.g., MMP, iNOS, and GST), and growth factors (e.g., EGF, NGF, and HGF) [154]. Curcumin possesses the property to inhibit the proliferation of various tumour cells in humans. In breast cancer cells, the survival signaling molecules, such as NF-κB, play a pivotal role in cell proliferation [155] . Liu et al. reported that curcumin was able to inhibit NF-κB expression and toggled many downstream signaling pathways, which silenced inflammatory cytokines, such as CXCL1 and CXCL2, and mediated the expression of matrix metalloproteinase 9 (MMP-9), urokinase plasminogen activator (uPA), uPA receptor (uPAR), intercellular adhesion molecule 1 (ICAM-1), and chemokine receptor 4 (CXCR4) [156,157]. Apoptosis is the term related to cancer of the process of programmed cell death. It is one of the method of the body to get rid of unwanted or abnormal cells. In breast cancer cell lines, curcumin is able to induce apoptosis by transfection of IGFBP-3 resulting in a higher of Bcl-2 family members. Curcumin also induced apoptosis in MCF-7 cells via a p53 dependent pathway [158].

4.4 Lung cancer

Lung cancer is one of the most common causing cancers that is spread globally affecting people's life. It is generally caused by uncontrolled growth of cell or rapid cell division in lungs. The genetic damage to the DNA of the cells lining the airways that results from smoking cigarettes or breathing harmful substances is what causes lung cancer. Tumour growth results from damaged airway cells' unregulated ability to reproduce. Tumour spread throughout the lung and impair lung function if left untreated. Lung tumours eventually metastasis, or spread to other bodily regions. Early lung cancer has no symptoms at all, they are very hard to detect and can only be detected by medical imaging technology. Lung cancer is divided into small cell lung cancer (SCLC) and Non-small cell lung cancer (NSCLC). Often, plant derived compound such as Curcumin are known to have curative property for lung cancer. Curcumin (diferuloylmethane), an active component of the spice turmeric, is able to suppress cancer cell proliferation, invasion, angiogenesis, and metastasis [159] through a diversity of signalling pathways involving nuclear factor-κB, IκBα kinase, Akt, activator protein (AP-1), mitogen-activated protein kinase, cyclooxygenase-2 (COX-2), lipoxygenase, inducible nitric-oxide synthase, urinary plasminogen activator, tumour necrosis factor, chemokines, cell surface adhesion molecules, cyclin D1, and others [160,161].

Interestingly, one of the target genes is a heat shock protein (HSP), HLJ1, also known as DNAJB4, which was recently cloned and classified as a member of the HSP40 family [162]. HSPs are believed to function as chaperones (a functionally related group of proteins assisting protein folding in the cell under physiological conditions) for molecule. Some HSPs have recently been discovered to be linked to the advancement of several human malignancies and may influence the growth, differentiation, metastasis, and death of cancer cells [163,164]. Longer overall survival for patients with non-small cell lung cancer (NSCLC) and lower cancer reoccurrence are linked to high expression of HLJI in tumour specimens [165]. According to these findings, curcumin prevents the invasion and metastasis of lung cancer cells by modifying by expression of E-cadherin and transcriptionally controlling the expression of HLJ1 via the JNK/JunD pathway.

4.5 Curcumin for other cancers

It has been found that curcumin exhibits pharmacological efficiency against a variety of different cancer types, including liver, colorectal, stomach, and osteosarcoma. Curcumin, oxaliplatin, and 5-fluorouracil together had a potent inhibitory impact in xenograft gastric tumour (BGC-823 cancer cells) by downregulating Bcl-2 and cleaving caspase-3 and PARP through upregulating BAX, according to Xiang Zhou et al. [115]. Curcumin has been shown to have a dose dependent chemopreventive effect in HCT-116 and LoVo cells, which are human colon cancer cell lines. This effect may be attribute to either the activation of caspase-3 and caspase-9 or the inhibition of NF-kB [116]. Curcumin has been shown to have an antiproliferative effect on liver cancer by Biqiong Ren et al. They also found that curcumin works by inhibiting the heat shock protein 70 toll like receptor 4 (HSP70-TLR4) signelling pathway [117]. Fibrosarcoma is an uncommon malignant tumour of the fibrous connective tissue around the bones that has been shown to be resistant to curcumins antiproliferative action. Curcumin the ability to suppress the expression of cytokine genes in periodontal diseased tissue, according to MR Guimaraes et al. They found that p38 MAPK was not inhibited by curcumin, but that L-6 and IL-11 were inactivated in a dose dependent manner [118]. The main chemicals and cell signaling pathways that curcumin affects in different cancer types are given in table 2.

Table 2: Curcumin's impacts on key cell signalling pathways and chemicals in different forms of cancer

Nucleus kappa B, or NF-kB; EGFR: epidermal growth factor receptor; p53: tumor protein P53; KRAS: Kirsten rat sarcoma viral oncogene homolog; EGFR-TK: epidermal growth factor receptor-tyrosine kinase; PI3K/Akt/mTOR: phosphatidylinositol 3-kinase/serine/threonine-protein kinase/mammalian target of the rapamycin;; and JAK/STAT: Janus kinase and signal transducer and activator of transcription; COX-2: cyclooxygenase-2; JNK/ERK/AP1: c-Jun NH2-terminal kinase/extracellular signal-regulated kinase/activator protein 1; MAPKKK1-JNK: mitogen-activated protein kinase kinase 1-c-Jun NH(2)-terminal kinase; Bcl-2: B-cell lymphoma-2; p38 MAPK: mitogen-activated protein kinases; PI3K/mTOR/ETS2: phosphatidylinositol 3-kinase/mechanistic target of rapamycin/E-twenty six proto-oncogene 2; HSP70-TLR4: heat shock protein 70-toll like receptor 4; IL-6: interleukin 6; IL-11: interleukin 11

Cancer types	Principal cell signaling pathways and compounds impected by curcumin	Reference
Breast cancer	p53, HER2-TK, NF-kB, EGFR, and ERK1/2	[119,120,121,122,123]
Lung cancer	EGFR-TK, NF-kB, KRAS, PI3K/Akt/mTOR, JAK/STAT, and COX-2	[124,125,126,127,128]
Haematological cancer	JNK/ERK/AP1, JAK/STAT, Bcl-2, MAPKKK1-JNK, NF-kB, and p38-MAPK	[129,130,131,132]
Prostate Cancer	NF-kB, PI3K/mTOR/ETS2, cyclin D1, CDK-4, c-Jun/activator protein 1 (AP-1)	[133,134,135.136]
Osteosarcoma	Bcl-2 and Caspace-3	[137,138]
Gastric, Colon, Liver Cancer and Sarcoma	PARP, IL-6, IL-11, Bcl-2, NF-kB, Caspase-9, HSP70-TLR4, and Caspase-3	[139,140,141,142]

CONCLUSION

This paper demonstrates the use of curcumin and its derivatives as an anticancer agent. Over the past several decades, a great deal of research conducted on curcumin, the active component of curcuma longa extract, to examine its potential as an anti-inflammatory, antioxidant, anticancer, antiandrogenic agent. Curcumin has demonstrated significant anticancer effects against different types of cancers both in-vivo and invitro. These cancer types include prostate cancer, lung cancer, liver cancer, colorectal cancer, and head and neck cancer. Curcumin is a known cancer therapeutic medication that impacts several targets at different phases of the disease, such as angiogenesis, proliferation, metastasis, and apoptosis. A through investigation has been conducted into curcumin's molecular mode of action. It accomplishing this by causing and inhibiting synthesis of certain growth factors like enzymes and cytokines, as well as interfering with a number of cells signalling pathways. Several structural modifications and different drug delivery systems are used to increase bioavailability, potency, solubility and anti-cancerous properties of curcumin.

But most of these formulations are at the proof of principal level, and more clinical trials are needed to confirm the effect of curcumin as an anticancer agent. Furthermore, the majority of curcumin drug delivery methods that are currently under development lack target tissue selectivity. Therefore, in terms of selectivity for particular tumour tissue, there is still tremendous space for advancement in curcumin delivery system. Higher efficiency (at lower doses of curcumin) and fewer side effects are the outcomes of tissue-specific curcumin administration, which increase local drug concentration at the site of action. However, more research is required to better understand curcumin's pharmacokinetics, improve its distribution to target tissue, increase its bioavailability, and assess its mechanical properties.

References:

1. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2018. CA Cancer J. Clin. 2018, 68, 7–30.
2. Gupta, A.P.; Pandotra, P.; Sharma, R.; Kushwaha, M.; Gupta, S. Chapter 8—Marine Resource: A Promising Future for Anticancer Drugs. In Studies in Natural Products Chemistry; Elsevier: Amsterdam, The Netherlands, 2013; Volume 40, pp. 229–325.
3. Umar, A.; Dunn, B.K.; Greenwald, P. Future directions in cancer prevention. Nat. Rev. Cancer 2012, 12, 835.
4. Mundekkad, D.; Cho, W.C. Applications of Curcumin and Its Nanoforms in the Treatment of Cancer. Pharmaceutics 2023, 15, 2223.
5. Motofei, I.G. Biology of cancer; from cellular and molecular mechanisms to developmental processes and adaptation. Semin. Cancer Biol. 2022, 86, 600–615.
6. Piña-Sánchez, P.; Chávez-González, A.; Ruiz-Tachiquín, M.; Vadillo, E.; Monroy-García, A.; Montesinos, J.J.; Grajales, R.; Gutiérrez de la Barrera, M.; Mayani, H. Cancer Biology, Epidemiology, and Treatment in the 21st Century: Current Status and Future Challenges From a Biomedical Perspective. Cancer Control 2021, 28, 10732748211038735.
7. Yip, H.Y.K.; Papa, A. Signaling Pathways in Cancer: Therapeutic Targets, Combinatorial Treatments, and New Developments. Cells 2021, 10, 659.
8. Martini, M.; De Santis, M.C.; Braccini, L.; Gulluni, F.; Hirsch, E. PI3K/AKT signaling pathway and cancer: An updated review. Ann. Med. 2014, 46, 372–383.
9. Glaviano, A.; Foo, A.S.C.; Lam, H.Y.; Yap, K.C.H.; Jacot, W.; Jones, R.H.; Eng, H.; Nair, M.G.; Makvandi, P.; Geoerger, B.; et al. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Mol. Cancer 2023, 22, 138.
10. Stefani, C.; Miricescu, D.; Stanescu-Spinu, I.I.; Nica, R.I.; Greabu, M.; Totan, A.R.; Jinga, M. Growth Factors, PI3K/AKT/mTOR and MAPK Signaling Pathways in Colorectal Cancer Pathogenesis: Where Are We Now? Int. J. Mol. Sci. 2021, 22, 10260.
11. Zhang, Y.; Kwok-Shing, N.P.; Kucherlapati, M.; Chen, F.; Liu, Y.; Tsang, Y.H.; de Velasco, G.; Jeong, K.J.; Akbani, R.; Hadjipanayis, A.; et al. A Pan-Cancer Proteogenomic Atlas of PI3K/AKT/mTOR Pathway Alterations. Cancer Cell 2017, 31, 820–832.
12. Li, Q.; Li, Z.; Luo, T.; Shi, H. Targeting the PI3K/AKT/mTOR and RAF/MEK/ERK pathways for cancer therapy. Mol. Biomed. 2022, 3, 47.

13. Fleming-de-Moraes, C.D.; Rocha, M.R.; Tessmann, J.W.; de Araujo, W.M.; Morgado-Diaz, J.A. Crosstalk between PI3K/Akt and Wnt/β-catenin pathways promote colorectal cancer progression regardless of mutational status. Cancer Biol. Ther. 2022, 23, 1–13.
14. Mundekkad, D.; Cho, W.C. Applications of Curcumin and Its Nanoforms in the Treatment of Cancer. Pharmaceutics 2023, 15, 2223.
15. Kah, G.; Chandran, R.; Abrahamse, H. Curcumin a Natural Phenol and Its Therapeutic Role in Cancer and Photodynamic Therapy: A Review. Pharmaceutics 2023, 15, 639.
16. Kyritsis, A.P.; Bondy, M.L.; Levin, V.A. Modulation of glioma risk and progression by dietary nutrients and antiinflammatory agents. Nutr. Cancer 2011, 63, 174–184.
17. Hassanizadeh, S.; Shojaei, M.; Bagherniya, M.; Orekhov, A.N.; Sahebkar, A. Effect of nano-curcumin on various diseases: A comprehensive review of clinical trials. Biofactors 2023, 49, 512–533.
18. Kunnumakkara, A.B.; Bordoloi, D.; Padmavathi, G.; Monisha, J.; Roy, N.K.; Prasad, S.; Aggarwal, B.B. Curcumin, the golden nutraceutical: Multitargeting for multiple chronic diseases. Br. J. Pharm. 2017, 174, 1325–1348.
19. Anand, P.; Sundaram, C.; Jhurani, S.; Kunnumakkara, A.B.; Aggarwal, B.B. Curcumin and cancer: An “old-age” disease with an “age-old” solution. Cancer Lett. 2008, 267, 133–164.
20. Nagahama, K.; Utsumi, T.; Kumano, T.; Maekawa, S.; Oyama, N.; Kawakami, J. Discovery of a new function of curcumin which enhances its anticancer therapeutic potency. Sci. Rep. 2016, 6, 30962.
21. Barry, J.; Fritz, M.; Brender, J.R.; Smith, P.E.; Lee, D.K.; Ramamoorthy, A. Determining the effects of lipophilic drugs on membrane structure by solid-state NMR spectroscopy: The case of the antioxidant curcumin. J. Am. Chem. Soc. 2009, 131, 4490–4498.
22. Tsukamoto, M.; Kuroda, K.; Ramamoorthy, A.; Yasuhara, K. Modulation of raft domains in a lipid bilayer by boundary-active curcumin. Chem. Commun. 2014, 50, 3427–3430.
23. Koo, H.-J.; Shin, S.; Choi, J.Y.; Lee, K.-H.; Kim, B.-T.; Choe, Y.S. Introduction of Methyl Groups at C2 and C6 Positions Enhances the Antiangiogenesis Activity of Curcumin. Sci. Rep. 2015, 5, 14205.
24. Agrawal, A.K.; Gupta, C.M. Tuftsin-bearing liposomes in treatment of macrophage-based infections. Adv. Drug Deliv. Rev. 2000, 41, 135–146.
25. Aggarwal, B.B.; Deb, L.; Prasad, S. Curcumin differs from tetrahydrocurcumin for molecular targets, signaling pathways and cellular responses. Molecules 2014, 20, 185–205.
26. Gera, M.; Sharma, N.; Ghosh, M.; Huynh, D.L.; Lee, S.J.; Min, T.; Kwon, T.; Jeong, D.K. Nanoformulations of curcumin: An emerging paradigm for improved remedial application. Oncotarget 2017, 8, 66680–66698.
27. Anand, P.; Sundaram, C.; Jhurani, S.; Kunnumakkara, A.B.; Aggarwal, B.B. Curcumin and cancer: An “old-age” disease with an “age-old” solution. Cancer Lett. 2008, 267, 133–164.
28. Grykiewicz, G.; Silfirski, P. Curucmin and curcuminoids in quest for medicinal status. Acta Biochim. Pol. 2012, 59, 201–212.
29. Esatbeyoglu, T.; Huebbe, P.; Insa, M.A.; DawnChin, E.; Wagner, A.E.; Rimbach, G. Curcumin—From Molecule to Biological Function. Angew. Chem. Int. Ed. 2012, 51, 5308–5332.

30. Gupta, S.; Prasad, S.; Ji, H.K.; Patchva, S.; Webb, L.J.; Priyadarsini, K.I.; Aggarwal, B.B. Multitargeting by curcumin as revealed by molecular interaction studies. Nat. Prod. Rep. 2011, 28, 1937–1955.
31. Priyadarsini, K.I. Chemical and structural features influencing the biological activity of curcumin. Curr. Pharm. Des. 2013, 19, 2093–2100.
32. Priyadarsini, K.I. Photophysics, Photochemistry and Photobiology of Curcumin: Studies from organic solutions, bio-mimetics and living cells. J. Photochem. Photobiol. C 2009, 10, 81–96.
33. Chen, W.-F.; Deng, S.-L.; Zhou, B.; Yang, L.; Liu, Z.-L. Curcumin and its analogues as potent inhibitors of low density lipoprotein oxidation: H-atom abstraction from the phenolic groups and possible involvement of the 4-hydroxy-3-methoxyphenyl groups. Free Radic. Biol. Med. 2006, 40, 526–535.
34. Ohtsu, H.; Xiao, Z.; Ishida, J.; Nagai, M.; Wang, H.K.; Itokawa, H.; Su, C.Y.; Shih, C.; Chiang, T.; Chang, E.; et al. Antitumor agents. 217. Curcumin analogues as novel androgen receptor antagonists with potential as anti-prostate cancer agents. J. Med. Chem. 2002, 45, 5037–5042.
35. Shi, Q.; Shih, C.C.; Lee, K.H. Novel Anti-Prostate Cancer Curcumin Analogues That Enhance Androgen Receptor Degradation Activity. Anti-Cancer Agents Med. Chem. 2009, 9, 904–912.
36. Lin, T.H.; Izumi, K.; Lee, S.O.; Lin, W.J.; Yeh, S.; Chang, C. Anti-androgen receptor ASC-J9 versus anti-androgens MDV3100 (Enzalutamide) or Casodex (Bicalutamide) leads to opposite effects on prostate cancer metastasis via differential modulation of macrophage infiltration and STAT3-CCL2 signaling. Cell Death Dis. 2013, 4, e764.
37. Verderio, P.; Pandolfi, L.; Mazzucchelli, S.; Marinozzi, M.R.; Vanna, R.; Gramatica, F.; Corsi, F.; Colombo, M.; Morasso, C.; Prosperi, D. Antiproliferative Effect of ASC-J9 Delivered by PLGA Nanoparticles against Estrogen-Dependent Breast Cancer Cells. Mol. Pharm. 2014, 11, 2864–2875.
38. Ferrari, E.; Lazzari, S.; Marverti, G.; Pignedoli, F.; Spagnolo, F.; Saladini, M. Synthesis, cytotoxic and combined cDDP activity of new stable curcumin derivatives. Bioorg. Med. Chem. 2009, 17, 3043–3052.
39. Cao, Y.K.; Li, H.J.; Song, Z.F.; Li, Y.; Huai, Q.Y. Synthesis and biological evaluation of novel curcuminoid derivatives. Molecules 2014, 19, 16349–16372.
40. Vellampatti, S.; Chandrasekaran, G.; Mitta, S.B.; Lakshmanan, V.-K.; Park, S.H. Metallo-CurcuminConjugated DNA Complexes Induces Preferential Prostate Cancer Cells Cytotoxicity and Pause Growth of Bacterial Cells. Sci. Rep. 2018, 8, 14929.
41. Dairam, A.; Limson, J.L.; Watkins, G.M.; Antunes, E.; Daya, S. Curcuminoids, curcumin, and demethoxycurcumin reduce lead-induced memory deficits in male Wistar rats. J. Agric. Food Chem. 2007, 55, 1039–1044.
42. Weber, W.M.; Hunsaker, L.A.; Roybal, C.N.; Bobrovnikova-Marjon, E.V.; Abcouwer, S.F.; Royer, R.E.; Deck, L.M.; Vander Jagt, D.L. Activation of NFκB is inhibited by curcumin and related enones. Bioorg. Med. Chem. 2006, 14, 2450–2461.
43. Shabaninejad Z, Pourhanifeh MH, Movahedpour A, Mottaghi R, Nickdasti A, Mortezapour E, Shafiee A, Hajighadimi S, Moradizarmehri S, Sadeghian M, Mousavi MS, Mirzaei H. Therapeutic potential of curcumin in the treatment of glioblastoma. Eur J Med Chem. 2020;188:112040.

44. Gupta AP, Khan S, Manzoor MM, Yadav AK, Sharma G, Anand R, Gupta S. Anticancer curcumin: natural analogues and structure activity relationship. Stud Nat Prod Chem. 2017;54:355–401.
45. Priyadarsini KI. Chemical and structural features influencing the biological activity of curcumin. Curr Pharm Des. 2013;19:2093–2100.
46. Parvathi KS, Negi PS, Sarinivas P. Antioxidant, Antimutagenic and antibacterial activity with β-diglucoside. Food Chem. 2009;115:265–271.
47. Bonaccorsi PM, Labbozzetta M, Barattucci A, Salerno TMG, Poma P, Notarbartolo M. Synthesis of curcumin derivatives and analysis of their antitumor effects in triple negative breast cancer (TNBC) cell lines. Pharmaceuticals. 2019;12:161.
48. Sribalan R, Kirubavathi M, Banuppriya G, Padmini V. Synthesis of biological and evaluation of new symmetric curcumin derivatives. Bioorg Med Chem Lett. 2015;25:4282–4286.
49. Masuda T, Toi Y, Bando H, Maekawa T, Takeda Y, Yamaguchi H. Structural Identification of new curcumin dimers and their contribution to the antioxidant mechanism of curcumin. J Agric Food Chem. 2002;50:2524–2530.
50. Feng JY, Liu ZQ. Phenolic and enolic hydroxyl groups in curcumin: which plays the major role in scavenging radicals? J Agric Food Chem. 2009;57:11041–11046.
51. Nelson, K.M.; Dahlin, J.L.; Bisson, J.; Graham, J.; Pauli, G.F.; Walters, M.A. The Essential Medicinal Chemistry of Curcumin. J. Med. Chem. 2017, 60, 1620–1637.
52. Youssef, D.; Nichols, C.E.; Cameron, T.S.; Balzarini, J.; De Clercq, E.; Jha, A. Design, synthesis, and cytostatic activity of novel cyclic curcumin analogues. Bioorg. Med. Chem. Lett. 2007, 17, 5624–5629.
53. Shim, J.S.; Kim, D.H.; Jung, H.J.; Kim, J.H.; Lim, D.; Lee, S.K.; Kim, K.W.; Ahn, J.W.; Yoo, J.S.; Rho, J.R.; et al. Hydrazinocurcumin, a novel synthetic curcumin derivative, is a potent inhibitor of endothelial cell proliferation. Bioorg. Med. Chem. 2002, 10, 2987–2992.
54. Shim, J.S.; Lee, J.; Park, H.-J.; Park, S.-J.; Kwon, H.J. A New Curcumin Derivative, HBC, Interferes with the Cell Cycle Progression of Colon Cancer Cells via Antagonization of the Ca2+/Calmodulin Function. Chem. Biol. 2004, 11, 1455–1463.
55. Cheng, M.A.; Chou, F.-J.; Wang, K.; Yang, R.; Ding, J.; Zhang, Q.; Li, G.; Yeh, S.; Xu, D.; Chang, C. Androgen receptor (AR) degradation enhancer ASC-J9® in an FDA-approved formulated solution suppresses castration resistant prostate cancer cell growth. Cancer Lett. 2018, 417, 182–191.
56. Soh, S.F.; Huang, C.K.; Lee, S.O.; Xu, D.; Yeh, S.; Li, J.; Yong, E.L.; Gong, Y.; Chang, C. Determination of androgen receptor degradation enhancer ASC-J9((R)) in mouse sera and organs with liquid chromatography tandem mass spectrometry. J. Pharm. Biomed. Anal. 2014, 88, 117–122.
57. Bhullar, K.S.; Jha, A.; Youssef, D.; Rupasinghe, H.P. Curcumin and its carbocyclic analogs: Structure-activity in relation to antioxidant and selected biological properties. Molecules 2013, 18, 5389–5404.
58. Anand, P.; Thomas, S.G.; Kunnumakkara, A.B.; Sundaram, C.; Harikumar, K.B.; Sung, B.; Tharakan, S.T.; Misra, K.; Priyadarsini, I.K.; Rajasekharan, K.N.; et al. Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. Biochem. Pharm. 2008, 76, 1590–1611.

59. Hahn, Y.-I.; Kim, S.-J.; Choi, B.-Y.; Cho, K.-C.; Bandu, R.; Kim, K.P.; Kim, D.-H.; Kim, W.; Park, J.S.; Han, B.W.; et al. Curcumin interacts directly with the Cysteine 259 residue of STAT3 and induces apoptosis in H-Ras transformed human mammary epithelial cells. Sci. Rep. 2018, 8, 6409.
60. Mohammadi, K.; Thompson, K.H.; Patrick, B.O.; Storr, T.; Martins, C.; Polishchuk, E.; Yuen, V.G.; McNeill, J.H.; Orvig, C. Synthesis and characterization of dual function vanadyl, gallium and indium curcumin complexes for medicinal applications. J. Inorg. Biochem. 2005, 99, 2217–2225.
61. Thompson, K.H.; Böhmerle, K.; Polishchuk, E.; Martins, C.; Toleikis, P.; Tse, J.; Yuen, V.; McNeill, J.H.; Orvig, C. Complementary inhibition of synoviocyte, smooth muscle cell or mouse lymphoma cell proliferation by a vanadyl curcumin complex compared to curcumin alone. J. Inorg. Biochem. 2004, 98, 2063–2070.
62. Benassi, R.; Ferrari, E.; Grandi, R.; Lazzari, S.; Saladini, M. Synthesis and characterization of new beta-diketo derivatives with iron chelating ability. J. Inorg. Biochem. 2007, 101, 203–213.
63. Zambre, A.P.; Kulkarni, V.M.; Padhye, S.; Sandur, S.K.; Aggarwal, B.B. Novel curcumin analogs targeting TNF-induced NF-kappaB activation and proliferation in human leukemic KBM-5 cells. Bioorg. Med. Chem. 2006, 14, 7196–7204.
64. Youssef, D.; Nichols, C.E.; Cameron, T.S.; Balzarini, J.; De Clercq, E.; Jha, A. Design, synthesis, and cytostatic activity of novel cyclic curcumin analogues. Bioorg. Med. Chem. Lett. 2007, 17, 5624–5629.
65. Shim, J.S.; Kim, D.H.; Jung, H.J.; Kim, J.H.; Lim, D.; Lee, S.K.; Kim, K.W.; Ahn, J.W.; Yoo, J.S.; Rho, J.R.; et al. Hydrazinocurcumin, a novel synthetic curcumin derivative, is a potent inhibitor of endothelial cell proliferation. Bioorg. Med. Chem. 2002, 10, 2987–2992.
66. Shim, J.S.; Lee, J.; Park, H.-J.; Park, S.-J.; Kwon, H.J. A New Curcumin Derivative, HBC, Interferes with the Cell Cycle Progression of Colon Cancer Cells via Antagonization of the Ca2+/Calmodulin Function. Chem. Biol. 2004, 11, 1455–1463.
67. Dutta, S.; Padhye, S.; Priyadarsini, K.I.; Newton, C. Antioxidant and antiproliferative activity of curcumin semicarbazone. Bioorg. Med. Chem. Lett. 2005, 15, 2738–2744.
68. Tomeh, M.A., Hadianamrei, R., & Zhao, X. (2019). A Review of Curcumin and Its Derivatives as Anticancer Agents. International Journal of Molecular Sciences, 20.
69. Zoi, V.; Galani, V.; Tsekeris, P.; Kyritsis, A.P.; Alexiou, G.A. Radiosensitization and Radioprotection by Curcumin in Glioblastoma and Other Cancers. Biomedicines 2022, 10, 312.
70. Sohn, S.I.; Priya, A.; Balasubramaniam, B.; Muthuramalingam, P.; Sivasankar, C.; Selvaraj, A.; Valliammai, A.; Jothi, R.; Pandian, S. Biomedical Applications and Bioavailability of Curcumin-An Updated Overview. Pharmaceutics 2021, 13, 2102.
71. Bawarski WE, Chidlowsky E, Bharali DJ, Mousa SA. Emerging nanopharmaceuticals. Nanomedicine. 2008;4:273–282.
72. Khan JA, Kainthan RK, Ganguli M, Kizhakkedathu JN, Singh Y, Maiti S. Water soluble nanoparticles from PEG-based cationic hyperbranched polymer and RNA that protect RNA from enzymatic degradation. Biomacromolecules. 2006;7:1386–1388.
73. Schluep T, Hwang J, Hildebrandt IJ, Czernin J, Choi CH, Alabi CA, et al. Pharmacokinetics and tumor dynamics of the nanoparticle IT-101 from PET imaging and tumor histological measurements. Proc Natl Acad Sci U S A. 2009;106:11394–11399.

74. Italia JL, Bhatt DK, Bhardwaj V, Tikoo K, Kumar MN. PLGA nanoparticles for oral delivery of cyclosporine: nephrotoxicity and pharmacokinetic studies in comparison to Sandimmune Neoral. J Control Release. 2007;119:197–206.
75. Grabovac V, Bernkop-Schnurch A. Development and in vitro evaluation of surface modified poly(lactide-co-glycolide) nanoparticles with chitosan-4-thiobutylamidine. Drug Dev Ind Pharm. 2007;33:767–774.
76. Koo OM, Rubinstein I, Onyuksel H. Role of nanotechnology in targeted drug delivery and imaging: a concise review. Nanomedicine. 2005;1:193–212.
77. Shaikh J, Ankola DD, Beniwal V, Singh D, Kumar MN. Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer. Eur J Pharm Sci. 2009;37:223–230.
78. Bawarski WE, Chidlowsky E, Bharali DJ, Mousa SA. Emerging nanopharmaceuticals. Nanomedicine. 2008;4:273–282.
79. Ghosh M, Singh AT, Xu W, Sulchek T, Gordon LI, et al. (2011) Curcumin nanodisks: formulation and characterization. Nanomedicine 7: 162-167.
80. Yallapu MM, Jaggi M, Chauhan SC (2012) Curcumin nanoformulations: a future nanomedicine for cancer. Drug Discov Today 17: 71-80.
81. Pandelidou M, Dimas K, Georgopoulos A, Hatziantoniou S, Demetzos C (2011) Preparation and characterization of lyophilised egg PC liposomes incorporating curcumin and evaluation of its activity against colorectal cancer cell lines. J Nanosci Nanotechnol 11: 1259-1266.
82. Lin YL, Liu YK, Tsai NM, Hsieh JH, Chen CH, et al. (2012) A Lipo-PEG-PEI complex for encapsulating curcumin that enhances its antitumor effects on curcumin-sensitive and curcumin-resistance cells. Nanomedicine 8: 318-327.
83. Bernal-Ballen, A.; Lopez-Garcia, J.-A.; Ozaltin, K. (PVA/chitosan/fucoidan)-ampicillin: A bioartificial polymeric material with combined properties in cell regeneration and potential antibacterial features. Polymers **2019**, 11 (8), 1325, DOI: 10.3390/polym11081325
84. El-Nashar, D. E.; Rozik, N. N.; Soliman, A. M.; Helaly, F. Study the release kinetics of curcumin released from PVA/curcumin composites and its evaluation towards hepatocarcinoma. Journal of Applied Pharmaceutical Science **2016**, 6 (7), 67– 72, DOI: 10.7324/JAPS.2016.60710
85. Hussein, Y.; Loutfy, S. A.; Kamoun, E. A.; El-Moslamy, S. H.; Radwan, E. M.; Elbehairi, S. E. I. Enhanced anti-cancer activity by localized delivery of curcumin form PVA/CNCs hydrogel membranes: preparation and in vitro bioevaluation. Int. J. Biol. Macromol. **2021**, 170, 107– 122, DOI: 10.1016/j.ijbiomac.2020.12.133
86. Zhang, J.; Tao, W.; Chen, Y.; Chang, D.; Wang, T.; Zhang, X.; Mei, L.; Zeng, X.; Huang, L. Doxorubicin-loaded star-shaped copolymer PLGA-vitamin E TPGS nanoparticles for lung cancer therapy. J. Mater. Sci.: Mater. Med. **2015**, 26 (4), 165, DOI: 10.1007/s10856-015-5498-z
87. Li, H.; Yan, L.; Tang, E. K.; Zhang, Z.; Chen, W.; Liu, G.; Mo, J. Synthesis of TPGS/curcumin nanoparticles by thin-film hydration and evaluation of their anti-colon cancer efficacy in vitro and in vivo. Frontiers in pharmacology **2019**, 10, 769, DOI: 10.3389/fphar.2019.00769
88. Gong, C.; Xie, Y.; Wu, Q.; Wang, Y.; Deng, S.; Xiong, D.; Liu, L.; Xiang, M.; Qian, Z.; Wei, Y. Improving anti-tumor activity with polymeric micelles entrapping paclitaxel in pulmonary carcinoma. Nanoscale **2012**, 4 (19), 6004– 6017, DOI: 10.1039/c2nr31517c

89. Park, J. H.; Saravanakumar, G.; Kim, K.; Kwon, I. C. Targeted delivery of low molecular drugs using chitosan and its derivatives. Advanced drug delivery reviews **2010**, 62 (1), 28– 41, DOI: 10.1016/j.addr.2009.10.003
90. Chen, G.; Li, J.; Cai, Y.; Zhan, J.; Gao, J.; Song, M.; Shi, Y.; Yang, Z. A glycyrrhetinic acid-modified curcumin supramolecular hydrogel for liver tumor targeting therapy. Sci. Rep. **2017**, 7 (1), 1– 8, DOI: 10.1038/srep44210
91. Yadav VR, Suresh S, Devi K, Yadav S (2009) Effect of cyclodextrin complexation of curcumin on its solubility and antiangiogenic and anti-inflammatory activity in rat colitis model. AAPS Pharm Sci Tech 10: 752-762.
92. Fromming KH, Szejtli J (1994) Cyclodextrins in pharmacy. Dordrecht: Kluwer Academic.
93. Rahman S, Cao S, Steadman KJ, Wei M, Parekh HS (2012) Native and Î²- cyclodextrin-enclosed curcumin: entrapment within liposomes and their in vitro cytotoxicity in lung and colon cancer. Drug Deliv 19: 346-353.
94. Maestrelli F, González-Rodríguez ML, Rabasco AM, Mura P (2005) Preparation and characterisation of liposomes encapsulating ketoprofen-cyclodextrin complexes for transdermal drug delivery. Int J Pharm 298: 55-67.
95. Dutta and Ikiki, J Bioequiv Availab 2013, 6:1 http://dx.doi.org/10.4172/jbb.1000172
96. Abd El-Hack, M.E.; El-Saadony, M.T.; Swelum, A.A.; Arif, M.; Abo Ghanima, M.M.; Shukry, M.; Noreldin, A.; Taha, A.E.; El-Tarabily, K.A. Curcumin, the active substance of turmeric: Its effects on health and ways to improve its bioavailability. J. Sci. Food Agric. **2021**, 101, 5747–5762.
97. Mansouri, K.; Rasoulpoor, S.; Daneshkhah, A.; Abolfathi, S.; Salari, N.; Mohammadi, M.; Rasoulpoor, S.; Shabani, S. Clinical effects of curcumin in enhancing cancer therapy: A systematic review. BMC Cancer **2020**, 20, 791.
98. Ojo, O.A.; Adeyemo, T.R.; Rotimi, D.; Batiha, G.E.-S.; Mostafa-Hedeab, G.; Iyobhebhe, M.E.; Elebiyo, T.C.; Atunwa, B.; Ojo, A.B.; Lima, C.M.G. Anticancer properties of curcumin against colorectal cancer: A review. Front. Oncol. **2022**, 12, 881641.
99. Fuloria, S.; Mehta, J.; Chandel, A.; Sekar, M.; Rani, N.; Begum, M.Y.; Subramaniyan, V.; Chidambaram, K.; Thangavelu, L.; Nordin, R.; et al. A Comprehensive Review on the Therapeutic Potential of Curcuma longa Linn. in Relation to its Major Active Constituent Curcumin. Front. Pharmacol. **2022**, 13, 820806.
100. Maheshwari RK, Singh AK, Gaddipati J and Srimal RC: Multiple biological activities of curcumin: A short review. Life Sci. 78:2081–2087. 2006.
101. Yance DR Jr and Sagar SM: Targeting angiogenesis with integrative cancer therapies. Integr Cancer Ther. 5:9–29. 2006.
102. Karunagaran D, Rashmi R and Kumar TR: Induction of apoptosis by curcumin and its implications for cancer therapy. Curr Cancer Drug Targets. 5:117–129. 2005.
103. Helson L: Curcumin (diferuloylmethane) delivery methods: A review. Biofactors. 39:21–26. 2013.
104. Salvioli S, Sikora E, Cooper EL and Franceschi C: Curcumin in cell death processes: A challenge for CAM of age-related pathologies. Evid Based Complement Alternat Med. 4:181–190. 2007.
105. Siegel R.L., Miller K.D., Jemal A. Cancer statistics, 2020. CA Cancer J. Clin. 2020;70:7–30. doi: 10.3322/caac.21590.

106. Lonergan P.E., Tindall D.J. Androgen receptor signaling in prostate cancer development and progression. J. Carcinog. 2010;10:20
107. Leslie SW, Soon-Sutton TL, Sajjad H, et al. StatPearls [Internet] Treasure Island (FL): StatPearls Publishing; 2022. Prostate cancer.
108. Curcumin against prostate cancer: current evidence. Termini D, Den Hartogh DJ, Jaglanian A, Tsiani E. https://doi.org/10.3390/biom10111536 Biomolecules. 2020;10:1536.
109. Therapeutic potential of curcumin in human prostate cancer-I. curcumin induces apoptosis in both androgen-dependent and androgen-independent prostate cancer cells. Dorai T, Gehani N, Katz A. Prostate Cancer Prostatic Dis. 2000;3:84–93.
110. Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines. Mukhopadhyay A, Bueso-Ramos C, Chatterjee D, Pantazis P, Aggarwal BB. Oncogene. 2001;20:7597–7609.
111. Curcumin down-regulates AR gene expression and activation in prostate cancer cell lines. Nakamura K, Yasunaga Y, Segawa T, Ko D, Moul JW, Srivastava S, Rhim JS. Int J Oncol. 2002;21:825–830.
112. Curcumin-induced suppression of cell proliferation correlates with down-regulation of cyclin D1 expression and CDK4-mediated retinoblastoma protein phosphorylation. Mukhopadhyay A, Banerjee S, Stafford LJ, Xia C, Liu M, Aggarwal BB. Oncogene. 2002;21:8852–8861.
113. Curcumin, a dietary component, has anticancer, chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway. Li M, Zhang Z, Hill DL, Wang H, Zhang R. Cancer Res. 2007;67:1988–1996.
114. Therapeutic potential of curcumin in human prostate cancer. III. curcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells in vivo. Dorai T, Cao YC, Dorai B, Buttyan R, Katz AE. Prostate. 2001;47:293–303.
115. Curcumin enhances the effects of 5-fluorouracil and oxaliplatin in inducing gastric cancer cell apoptosis both in vitro and in vivo. Zhou X, Wang W, Li P, Zheng Z, Tu Y, Zhang Y, You T. Oncol Res. 2016;23:29–34
116. Curcumin effects on cell proliferation, angiogenesis and metastasis in colorectal cancer. Calibasi-Kocal G, Pakdemirli A, Bayrak S, et al. https://pubmed.ncbi.nlm.nih.gov/31646795/ J BUON. 2019;24:1482–1487.
117. Curcumin inhibits liver cancer by inhibiting DAMP molecule HSP70 and TLR4 signaling. Ren B, Luo S, Tian X, et al. Oncol Rep. 2018;40:895–901.
118. Potent anti-inflammatory effects of systemically administered curcumin modulate periodontal disease in vivo. Guimarães MR, Coimbra LS, de Aquino SG, Spolidorio LC, Kirkwood KL, Rossa C Jr. J Periodontal Res. 2011;46:269–279.
119. Molecular targets of curcumin in breast cancer (review) Song X, Zhang M, Dai E, Luo Y. Mol Med Rep. 2019;19:23–29.
120. Curcumin: getting back to the roots. Shishodia S, Sethi G, Aggarwal BB. Ann N Y Acad Sci. 2005;1056:206–217.
121. Curcumin and its analogues (PGV-0 and PGV-1) enhance sensitivity of resistant MCF-7 cells to doxorubicin through inhibition of HER2 and NF-kB activation. Meiyanto E, Putri DD, Susidarti RA, et al. Asian Pac J Cancer Prev. 2014;15:179–184.
122. Curcumin induces apoptosis in human breast cancer cells through p53-dependent Bax induction. Choudhuri T, Pal S, Agwarwal ML, Das T, Sa G. FEBS Lett. 2002;512:334–340.

123. Epidermal-growth-factor receptor status as predictor of early recurrence of and death from breast cancer. Sainsbury JR, Farndon JR, Needham GK, Malcolm AJ, Harris AL. Lancet. 1987;1:1398–1402.
124. Curcumin inhibits interferon-alpha induced NF-kappaB and COX-2 in human A549 non-small cell lung cancer cells. Lee J, Im YH, Jung HH, et al. Biochem Biophys Res Commun. 2005;334:313–318.
125. Curcumin suppresses stem-like traits of lung cancer cells via inhibiting the JAK2/STAT3 signaling pathway. Wu L, Guo L, Liang Y, Liu X, Jiang L, Wang L. Oncol Rep. 2015;34:3311–3317.
126. Antitumor activity of curcumin by modulation of apoptosis and autophagy in human lung cancer A549 cells through inhibiting PI3K/Akt/mTOR pathway. Liu F, Gao S, Yang Y, et al. Oncol Rep. 2018;39:1523–1531.
127. Curcumin lowers erlotinib resistance in non-small cell lung carcinoma cells with mutated EGF receptor. Li S, Liu Z, Zhu F, Fan X, Wu X, Zhao H, Jiang L. Oncol Res. 2013;21:137–144.
128. Curcumin overcome primary gefitinib resistance in non-small-cell lung cancer cells through inducing autophagy-related cell death. Chen P, Huang HP, Wang Y, et al. J Exp Clin Cancer Res. 2019;38:254.
129. Curcumin induces the apoptosis of human monocytic leukemia THP-1 cells via the activation of JNK/ERK pathways. Yang CW, Chang CL, Lee HC, Chi CW, Pan JP, Yang WC. BMC Complement Altern Med. 2012;12:22.
130. Inhibition of the c-Jun N-terminal kinase (JNK) signaling pathway by curcumin. Chen YR, Tan TH. Oncogene. 1998;17:173–178.
131. Curcumin reduces expression of Bcl-2, leading to apoptosis in daunorubicin-insensitive CD34+ acute myeloid leukemia cell lines and primary sorted CD34+ acute myeloid leukemia cells. Rao J, Xu DR, Zheng FM, et al. J Transl Med. 2011;9:71.
132. Curcumin induces apoptosis and suppresses invasion through MAPK and MMP signaling in human monocytic leukemia SHI-1 cells. Zhu GH, Dai HP, Shen Q, Ji O, Zhang Q, Zhai YL. Pharm Biol. 2016;54:1303–1311.
133. Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines. Mukhopadhyay A, Bueso-Ramos C, Chatterjee D, Pantazis P, Aggarwal BB. Oncogene. 2001;20:7597–7609.
134. Curcumin down-regulates AR gene expression and activation in prostate cancer cell lines. Nakamura K, Yasunaga Y, Segawa T, Ko D, Moul JW, Srivastava S, Rhim JS. Int J Oncol. 2002;21:825–830.
135. Curcumin down-regulates AR gene expression and activation in prostate cancer cell lines. Nakamura K, Yasunaga Y, Segawa T, Ko D, Moul JW, Srivastava S, Rhim JS. Int J Oncol. 2002;21:825–830.
136. Curcumin, a dietary component, has anticancer, chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway. Li M, Zhang Z, Hill DL, Wang H, Zhang R. Cancer Res. 2007;67:1988–1996.
137. JNK pathway mediates curcumin-induced apoptosis and autophagy in osteosarcoma MG63 cells. Zhang Y, Chen P, Hong H, Wang L, Zhou Y, Lang Y. Exp Ther Med. 2017;14:593–599.

138. Curcumin induces cell cycle arrest and apoptosis in human osteosarcoma (HOS) cells. Lee DS, Lee MK, Kim JH. https://ar.iiarjournals.org/content/29/12/5039.long. Anticancer Res. 2009;29:5039–5044.
139. Curcumin enhances the effects of 5-fluorouracil and oxaliplatin in inducing gastric cancer cell apoptosis both in vitro and in vivo. Zhou X, Wang W, Li P, Zheng Z, Tu Y, Zhang Y, You T. Oncol Res. 2016;23:29–34.
140. Curcumin effects on cell proliferation, angiogenesis and metastasis in colorectal cancer. Calibasi-Kocal G, Pakdemirli A, Bayrak S, et al. https://pubmed.ncbi.nlm.nih.gov/31646795/ J BUON. 2019;24:1482–1487.
141. Curcumin inhibits liver cancer by inhibiting DAMP molecule HSP70 and TLR4 signaling. Ren B, Luo S, Tian X, et al. Oncol Rep. 2018;40:895–901.
142. Desirable PEGylation for improving tumor selectivity of hyaluronic acid-based nanoparticles via low hepatic captured, long circulation times and CD44 receptor-mediated tumor targeting. Teng C, Chai Z, Yuan Z, et al. Nanomedicine. 2020;24:102105.
143. Liu L.B., Duan C.N., Ma Z.Y., Xu G. Curcumin inhibited rat colorectal carcinogenesis by activating PPAR-gamma: An experimental study. Zhongguo Zhong Xi Yi Jie He Za Zhi Zhongguo Zhongxiyi Jiehe Zazhi (Chin. J. Integr. Tradit. West. Med.) 2015;35:471–475.
144. Goel A., Boland C.R., Chauhan D.P. Specific inhibition of cyclooxygenase-2 (COX-2) expression by dietary curcumin in HT-29 human colon cancer cells. Cancer Lett. 2001;172:111–118. doi: 10.1016/S0304-3835(01)00655-3.
145. Shehzad A., Lee J., Huh T.L., Lee Y.S. Curcumin induces apoptosis in human colorectal carcinoma (HCT-15) cells by regulating expression of Prp4 and p53. Mol. Cells. 2013;35:526–532. Doi: 10.1007/s10059-013-0038-5.
146. Tong W., Wang Q., Sun D., Suo J. Curcumin suppresses colon cancer cell invasion via AMPK-induced inhibition of NFkappaB, uPA activator and MMP9. Oncol. Lett. 2016;12:4139–4146. Doi: 10.3892/ol.2016.5148
147. Guo L.D., Chen X.J., Hu Y.H., Yu Z.J., Wang D., Liu J.Z. Curcumin inhibits proliferation and induces apoptosis of human colorectal cancer cells by activating the mitochondria apoptotic pathway. Phytother. Res. 2013;27:422–430. doi: 10.1002/ptr.4731.
148. Wang K., Fan H., Chen Q., Ma G., Zhu M., Zhang X., Zhang Y., Yu J. Curcumin inhibits aerobic glycolysis and induces mitochondrial mediated apoptosis through hexokinase II in human colorectal cancer cells in vitro. Anti-Cancer Drug. 2015;26:15–24. doi: 10.1097/CAD.0000000000000132.
149. Dou H., Shen R., Tao J., Huang L., Shi H., Chen H., Wang Y., Wang T. Curcumin Suppresses the Colon Cancer Proliferation by Inhibiting Wnt/beta-Catenin Pathways via miR-130a. Front. Pharmacol. 2017;8:877. doi: 10.3389/fphar.2017.00877.
150. Li B., Shi C., Li B., Zhao J.M., Wang L. The effects of Curcumin on HCT-116 cells proliferation and apoptosis via the miR-491/PEG10 pathway. J. Cell. Biochem. 2018;119:3091–3098. doi: 10.1002/jcb.26449.
151. Sørlie, T.; Charles, M. P.; Robert, T.; et al. Gene Expression Patterns of Breast Carcinomas Distinguish Tumor Subclasses with Clinical Implications. Proc. Natl. Acad. Sci. U.S.A. 2001, 98 (19), 10869–10874

152.Anderson, W. F.; Chatterjee, N.; Ershler, W. B.; et al. Estrogen Receptor Breast Cancer Phenotypes in the Surveillance, Epidemiology, and End Results Database. Breast Cancer Res. Treat. 2002, 76 (1), 27–36.
153.Giordano, S.; Petrelli, A. From Single- to Multi-Target Drugs in Cancer Therapy: When Aspecificity Becomes an Advantage. Curr. Med. Chem. 2008, 15 (5), 422–432
154.7. Goel, A.; Kunnumakkara, A. B.; Aggarwal, B. B. Curcumin as “Curecumin”: From Kitchen to Clinic. Biochem. Pharmacol. 2008, 75 (4), 787–809.
155.Lin, M. T.; Chang, C. C.; Chen, S. T.; et al. Cyr61 Expression Confers Resistance to Apoptosis in Breast Cancer MCF-7 Cells by a Mechanism of NF-κB-Dependent XIAP Up-Regulation. J. Biol. Chem. 2004, 279 (23), 23915–23923.
156.Liu, Q.; Loo, W. T. Y.; Sze, S. C. W.; et al. Curcumin Inhibits Cell Proliferation of MDA-MB-231 and BT-483 Breast Cancer Cells Mediated by Down-Regulation of NFκB, CyclinD and MMP-1 Transcription. Phytomedicine 2009, 16 (10), 916-922.
157.Bachmeier, B. E.; Mohrenz, I. V.; Mirisola, V.; et al. Curcumin Downregulates the Inflammatory Cytokines CXCL1 and -2 in Breast Cancer Cells via NFκB. Carcinogenesis 2008, 29 (4), 779–789
158.Fuloria, S. et al. A comprehensive review on the therapeutic potential of Curcuma longa Linn. in relation to its major active constituent curcumin. Front. Pharmacol. **13**, 820806.
159.Menon LG, Kuttan R, Kuttan G. Anti-metastatic activity of curcumin and catechin. Cancer Lett 1999; 141:159–65.
160.Chen HW, Huang HC. Effect of curcumin on cell cycle progression and apoptosis in vascular smooth muscle cells. Br J Pharmacol 1998; 124: 1029–40.
161.Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res 2003; 23: 363–98.
162.Miernyk JA. The J-domain proteins of Arabidopsis thaliana: an unexpectedly large and diverse family of chaperones. Cell Stress Chaperones 2001; 6: 209–18.
163.Van 't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002; 415: 530–6.
164.Calderwood SK, Khaleque MA, Sawyer DB, Ciocca DR. Heat shock proteins in cancer: chaperones of tumorigenesis,Trends Biochem Sci. 2006; 31: 164–72.
165.Tsai MF, Wang CC, Chang GC, et al. A new tumor suppressor DnaJ-like heat shock protein HLJ1 and survival of patients with non-small cell lung carcinoma. J Natl Cancer Inst 2006; 98: 825–38.