Review Article

# How Effective is Curcumin in Prevention of Cancer

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**Received:** 23-11-2020; **Revised:** 12-07-2021; **Accepted:** 25-07-2021; **Published on:** 15-08-2021.

**ABSTRACT**

The human physiology is a significant and a complex process, which is designed accordingly with multitude of functions. Phytochemicals are naturally occurring compounds found in plants, have modulating potential which is useful regarding chemoprevention. Curcumin (diferuloyl methane) is the dried ground rhizome of the perennial herb "Curcuma Longa" Linn, under the family of "Zingiberaceae". It is readily soluble in ethanol or acetone, dimethyl sulfoxide (DMSO), glacial acetic acid, poorly soluble in water since it is lipophilic in nature. In India, the average intake of turmeric is reported to as high as 2.0-2.5 g/day (approx. up to 0.1g of curcumin) no adverse effects have been studied at the population level. Curcumin triggers multiple biological mechanisms in tumour environment at different stages. Curcumin act on different cancer types such as colorectal, prostate, pancreatic, skin, head-neck squamous cell carcinoma, breast, brain and glioblastoma. Various formulations have been prepared to improve the bioavailability and solubility of curcumin which includes nanoparticles, liposomes, phospholipid complexes, structural analogs, cyclodextrins, nanogels, solid dispersions etc.,

**Keywords:** Curcumin, cell cycle arrest, anti-apoptotic signals, signalling pathways, nano formulation.

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**DOI:** 10.47583/ijpsrr.2021.v69i02.001

**DOI link:** http://dx.doi.org/10.47583/ijpsrr.2021.v69i02.001

## INTRODUCTION

The human physiology is a significant and a complex process, which is designed accordingly with multitude of functions. Each day 130 billion cells expire and are replaced by new cells to continue the activity that are assigned. The strength of the cancer cell to develop a typical tumour microenvironment is predisposed due to genetic instability and environmental features. Based on the origin of tumours, 90% of cancers arise from epithelial cell lines, called carcinoma (breast, lungs etc.,) approx., 2% of cancers are sarcoma (which arise in fibrous tissue, bone etc.), the cancers arising from blood forming cells, immune system are called leukaemia and lymphoma respectively.[1] Cancer is called to be the second leading cause for deaths. The International Agency for Research on Cancer (IARC) released the latest estimates on the global burden of cancer, stated that the burden has raised to 18.1 million new cases and 9.6 million deaths. One in 6 women and one in 5 men are affected worldwide during their lifetime, and 1 in 11 women and 1 in 8 men die out of the disease. Global data suggest that about a half of new cases and more than half of the deaths are reported in as an estimate in Asia, as it occupies 60% of global population.[2]Curcumin which is a small molecular weight polyphenolic compound, stable at an acidic and a neutral pH, lipophilic in nature is effective as anti-cancer and anti-inflammatory agent. Though curcumin is an effective natural chemo preventive agent, due to its low bioavailability and aqueous solubility, results in sub-therapeutic concentration at the target site. To overcome the limitation, advanced drug delivery systems of cancer were developed for targeted delivery of curcumin, thereby result in improved therapeutic effects such as cellular targeting of many other chemo-preventives. Different types of curcumin delivery systems include polymeric nanoparticles, liposomes, nanogels, cyclodextrin complexes etc., Our concern towards the article mainly focus on how effective does curcumin works to fulfil its role in prevention on tumour development (colorectal, pancreatic, prostate, brain -glioblastoma, skin, head –neck squamous cell carcinoma, breast cancer) and also providing a brief on the mechanisms involved.

### Cancer

An uncontrolled cell division, with an alteration in the cell cycle leading to destruction of body tissue is called as a cancer (or) neoplasm (or) tumor. The abnormal cell growth, gain the strength to invade and spread to distant areas by regulating growth factors and suppressing the control mechanisms. Benign tumors are localized and slow growing which do not cause any difficulty to the host system, whereas malignant tumor proliferate rapidly and

spread throughout the body, which may lead to death. New blood capillaries generate around the tumor mass to supply nutrients (angiogenesis). The inner (or) core of the tumor tends to necrose at times due to lack of oxygen and nutrients. Carcinogenesis is a typical process, which undergo initiation, promotion, progression of tumors cell. The hallmarks of cancer constitute 6 biological capabilities. a) reducing growth suppressor's action, b) ability to sustain proliferative signalling, c) resisting cell death, d) inducing angiogenesis, e) enabling replicate mortality, f) activating metastasis during tumor development at different stages. There are many cellular and molecular signalling pathways responsible for tumor development in different organs, which are the triggers of chemotherapeutic agents, traditionally; phytochemicals (of natural origin) show an immense activity towards tumour restriction at different levels., one such crude-natural compound is curcumin.

**The Role of Phytochemicals in Chemo-Protective Effects[3]**

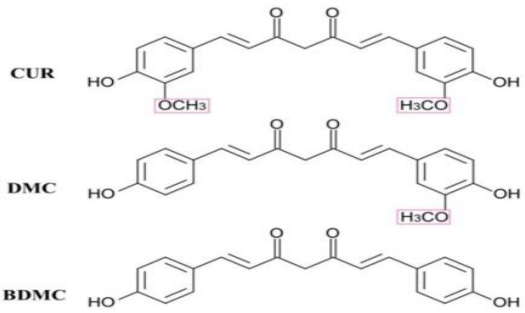
Phytochemicals are naturally occurring compounds found in plants, have modulating potential which is useful regarding chemoprevention. The mechanisms of phytochemicals are as follows.,

- Anti-oxidative effects
- Carcinogen modification by inhibition of specific enzymes
- Carcinogen detoxification through CYP450 activation
- Modification of hormone receptors and inhibitory effects on the vascularisation of tumour.
- Regulation of gene expression during cell proliferation and apoptosis.

**Curcumin**

Curcumin (diferuloyl methane) is the dried ground rhizome of the perennial herb "Curcuma Longa" Linn, under the family of "Zingiberaceae" which grow up to 1m and has been used in Asian medicine for second millennium BC.[4] It is well known dietary polyphenol derived from rhizome of turmeric, an Indian spice which is usually used in preparation of mustard and curry. It is found to be the principle component in turmeric (curry spice). The WHO monograph enlisted 76 names which are synonymous to each other.[5] World's supply of turmeric is produced in India.[6] Curcumin comprises approximately 2-5% of turmeric.[7] Turmeric which is available commercially may contain essential oils, fat, protein, polyphenols, carbohydrates, moisture, and minerals. The aromatic properties of turmeric are thought to be attributable to its volatile essential oils (turmerones, atlantones, and zingiberene).[8] The yellow colour of turmeric is due to the presence of polyphenolic curcuminoids, which constitute approx. 3-5% of most turmeric preparation. The alcoholic extract of turmeric constitute 3 curcuminoids (non- volatile compounds), namely, diferuloylmethane (77%), desmethoxy curcumin (18%), bisdesmethoxy curcumin (approx. 5%).[9,10] Among the 3 polyohenols that are isolated from Curcuma Long, curcumin (bis α,β- unsaturated β-diketone) is the potent, abundant and extensively investigated.[11]There are many alternative sources of curcumin and its analouges have been reported from other curcumin species such as *Curcuma zedoaria*, *Curcuma mangga, Curcuma xanthorrhiza, Curcuma aromatic, Costus speciosus, Etlingera elatior, Curcuma phaeocaulis* and *Zingiber cassumunar*.[12]

**Figure 1[13]**



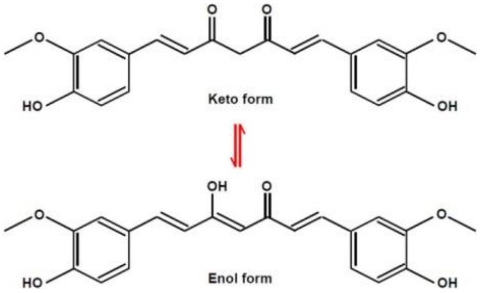

**History of Curcumin**

Curcumin is extracted in a pure crystalline form for the first time in 1870.[14] It is first purified by Vogel and Pelletier in 1815.[15] Its structure as diferuloylmethane was developed in 1910.[16] The chemical structure was confirmed by Roughley and Whiting in 1973 by using NMR technique[17]. The solution structure was confirmed by Payton et al only in 2007.[18]

**Chemistry and Chemical Properties of Curcumin**

Curcumin with a chemical name [E,E-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5 dione], chemical formula [C21 H20 O6] is a yellowish crystalline, odourless powder with a melting point 179 - 183° C and molecular weight 368.38.[19]Absorption spectra of curcumin and curcuminoids are (ƛmax) 429nm and 424nm respectively.[20] It is readily soluble in ethanol or acetone, dimethyl sulfoxide (DMSO), glacial acetic acid, poorly soluble in water since it is lipophilic in nature. The keto form of curcumin predominates and act as a potent donor of H-atoms in acidic and neutral solution as well as in solid state, where as in alkaline condition (>pH 8); the enolic form predominates and the phenolic part of the molecule play the major role as electron donor. This mechanism is responsible for scavenging activity of phenolic compounds. At alkaline pH, yellow curcumin changes to dark red colour.[21] Curcuminoids in the herb C. longa are synthesized by the collaboration of type III polyketide synthases, diketide Co A synthase (DCS) and curcumin synthase I (CURS 1). CURS and DCS catalyse the formation of curcumin.[22] The antioxidant activity of curcumin is either due to the presence of OH group or $CH_2$ group of the β-diketone (heptadiene-dione) moiety, where the OH group play an important role in biological activity of curcumin.[23,24] Replacement of the phenolic OH group inhibits lipid peroxidation inhibitory action and free radical scavenging property of curcumin.[25,26]

**Figure 2:** [27]




**Safety and Toxicity Profile of Curcumin**

In India, the average intake of turmeric is reported to as high as 2.0-2.5 g/day (approx. up to 0.1g of curcumin) no adverse effects have been studied at the population level.[28]Clinical trials reported no curcumin – related toxicity in patient who were given curcumin (8g/day) via oral route for 3 months (Liu et al 2012). A study by (Lao et al) explained the safety of curcumin in healthy volunteers by using curcumin capsules (75% curcumin, 23% demethoxy curcumin, 2% bisdemethoxy curcumin) with single escalating doses from 0.5 to 12.0 gm. The maximum tolerable doses cannot be determined, because a dose more than 12gm of curcumin is considered as bulky.[29]Among the 24 enrolled healthy subjects, 7 of them developed adverse effects (diarrhoea, yellowish stools, rashes, headache) which are observed to be of grade 1 and are not related to the dose. Based on the repeated studies, the US FDA reported that turmeric is Generally Recognized As Safe (GRAS) and an acceptable daily intake level of curcumin was determined to be 0.1-3mg/kg bw, which is granted by Joint Expert Committee of the Food and Agriculture Organisation/ World Health Organisation (FDA/WHO).[30]An allergic reaction to turmeric- related was described in one of the healthy volunteer enrolled in the phase 1 study testing the safety profile of turmeric oil and turmeric extract.[31]Curcumin is a widely used as colouring and flavouring agent in food industry. A study by (Crooke et al 2018) shows that curcumin have the capacity of enchanting therapeutic efficacy of other chemotherapeutic agents such as cisplatin, vinca alkaloid, gemcitabine, 5-FU(5-Fluorouracil), vinorelbine etc., it is known that drug-drug interactions include pK alterations besides pharmacological interaction. Curcumin have a tendency to competitively inhibiting CYP's (CYP1A2, CYP3A4) and also participate in non-competitive inhibition on CYP2D6, CYPP2D9 (Liu et al 2012) shown that curcumin had the ability to inhibit UGT1A1 and UGT2B7. This inhibitory effect of curcumin towards CYP's and UGT's make it have an ability to reduce the degradation of CYP substrates and clearance of UGT substrates. However, the dose of chemotherapeutic agents which are the transporters and enzymes of above substrates should be adjusted with narrow therapeutic range, when they are co-administered with curcumin, as curcumin has the ability to increase absorption and reduce the clearance.[32]

**Pharmacokinetic Properties of Curcumin**

The pharmacokinetic properties of curcumin in humans remains unclear and data is very limited. Various studies indicated that curcumin has poor absorption due to low solubility in water,[33]poor distribution, rapid rate of metabolism and rapid excretion from body.[34]After oral administration, curcumin shows low bioavailability in both humans and in animals due to rapid metabolic reduction and conjugation.[35-39]Metabolites of curcumin observed in plasma of rats and humans were curcumin glucuronide and curcumin sulfate in high amounts and hexahydrocucumin, hexahydrocurcuminol and hexahydrocurcumin glucuronide in less amounts.[40]No toxicity has been observed in animals but at very high doses few adverse events has been observed in humans.[41]

**The action Plan of Curcumin in Carcinogenesis**

Carcinogenesis is a typical process which comprises three phases: initiation (normal cell to initiated cell), promotion (initiated to pre-neoplastic cell), and progression (pre-neoplastic to neoplastic cell.[42] Cancer initiation is produced by chronic inflammation and oxidative stress, where inflammation is the main regulator in promoting the initiated cells, probably by providing proliferating signals and preventing apoptosis.[43,44] The inflammatory response secretes cytokines which act as angiogenic factors lending to conversion of transformed cells to proliferate and undergo promotion. Leucocytes produce angiogenic factors, cytokines, matric degrading proteases, which allow tumour cells proliferate, invade and metastasize.[45] The tumour infiltrating lymphocytes produce matrix degrading proteinases (matrix metallopeptidase 9, MMP 9) which exert their proteolytic activity and degrades the physical barriers thereby facilitating angiogenesis, invasion and metastasis.[46] The frequent up regulation of inflammatory mediators (NF –KB), play a role in inflammation in cancer. Curcumin inhibits the action of NF-κB signalling pathway, thereby reducing tumour development and progression. Curcumin interacts with arsenals of molecules which include growth factors, carriers proteins, metal ions, inflammatory mediators, tumour suppressors, transcription factors, onco-proteins and cellular nucleic acids.[47]The interaction can be either directly or indirectly through hydrogen, non-covalent hydrophobic, covalent bonding.[48]

**The Effect of Curcumin in Tumour Initiation**

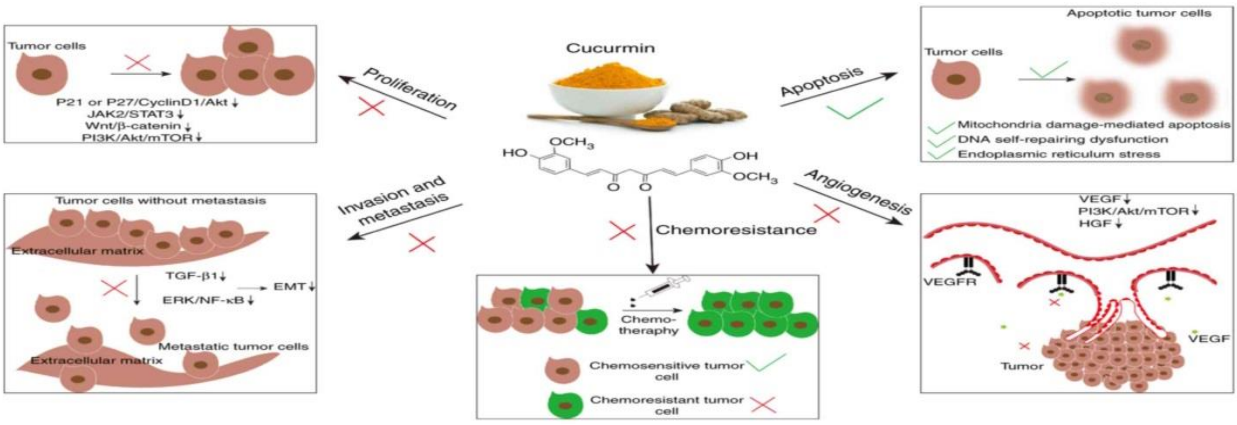
The inflammation of cancer cells occur through the production of reactive oxygen species(ROS) and reactive nitrogen species by activated macrophages and neutrophils, which cause the cancer to cause mutations.[49]Curcumin show a significant reduction in the levels of inducible nitric oxide synthesis (iNOS) by inhibiting the induction of nitric oxide synthase and is also a potent scavenger of nitric oxide (free radicals).[50]NF-κB influences the induction of iNOS which produce oxidative stress; curcumin prevents phosphorylation and degradation of inhibitor of κ B α, thereby blocking NF –κB activation which

suppress iNOS gene transcription, through which cancer cells gain the strength to overcome oxidative stress. It inhibits the cell proliferation and cytokine production by inhibiting NF-κB target genes which are involved in IL-2 production, NO generation, and mitogen induction of T cell proliferation.[51] It also inhibits reduction induced overexpression of cytokines (IL -6,10,18) which is accompanied by NF –κB induction. Curcumin induce HO-1(heme oxygenase 1) expression which counteract oxidative stress, modulate apoptosis, inhibit tumor cell proliferation by signaling through NF –κB, NRF-2, thereby attain the potential to reduce oxidative stress.[52,53]NRF-2(nuclear receptor factor-2) is a transcription factor that regulate glutathione-s-transferase (conjugatory enzyme) via an antioxidant response element (AGR).[54]

**The Role of Curcumin in Tumour Promotion And Progression Suppression[55]**

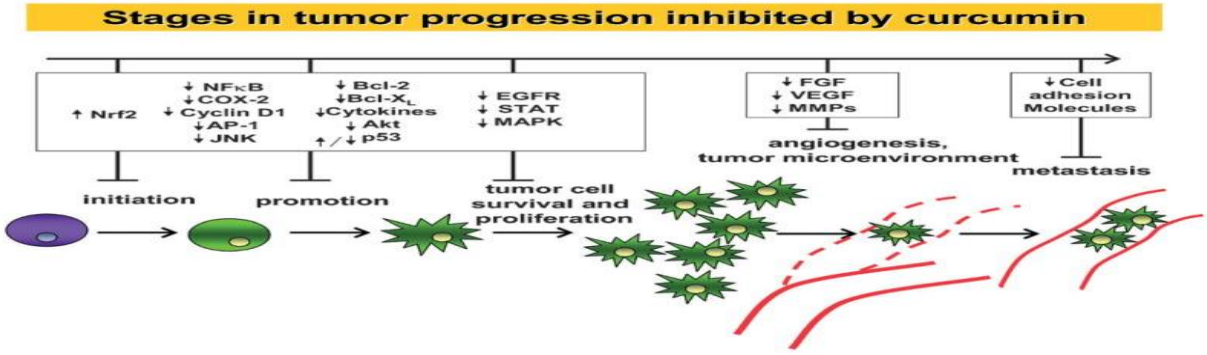
Curcumin blocks NF –κB signaling which occur primarly via the inhibitor κB kinase (IKK) mediated phosphorylation of inhibitory molecules**.** It induces apoptosis by caspase activation of poly (ADP ribose) polymerase (PARP) cleavage. Regulation of NF –κB by curcumin is associated with decreasing Bcl-X (L) mRNA , increasing Bcl-X (S) and c-IAP-2 mRNA, activation of caspase 3 and 9. COX –2(cyclooxygenase) catalyzes the rate limiting step in PG (prostaglandin) synthesis from arachidonic acid, which play an important role in tumor promotion, it is said that NF –κB intracellular signaling pathway mediates COX-2 induction.[56] Especially, in colon cancer cells, COX-2 is down regulated by curcumin.[57]MMP play a role in mediating neo-vascularization, endothelial cell migration, tube formation, and is increased during tumour progression. By inhibiting NF –κB and AP-L which are binding to the DNA promoter region, curcumin down regulates MMP-9 expression. It cause a significant inhibition of TNF- α (tumor necrosis factor –α) induced VCAM-1(vascular cell adhesion molecule -1) expression which is related to the activation of MAPK NF-κB pathway.[58]It reduced pre-neoplastic cell migration and invasion induced by osteopontin (extracellular matrix protein) via NF-κB pathway . Curcumin downregulated IL-1,8 induced receptor internalization, thereby inhibiting cell growth. Certain molecular targets like β-catenin/T cell factor (TCF), lymphoid enhance factor (LEF) which are often disrupted in many cancer cells. It is found to decrease nuclear β-catenin, TCF-4, thus inhibit β-catenin/TCF signalling in various cell lines. Curcumin suppresses the promotion and progression of cancer through NF-κB repression and reduced β- catenin signalling.

**Figure 3[59]**




**Molecular Targets**

Curcumin triggers multiple biological mechanisms in tumour environment at different stages. One main cause of cancer is the imbalance between cell proliferation and cell death.[60]The cellular and molecular targets are the important elements for the life of tumour. These targets play an empirical role for drug-development to treat cancer. Off -late natural compound i.e., curcumin is found to show its effects on the targets either by up-regulation or down- regulation. The role of curcumin in multi-step development of tumour is shown in **Figure 4** [61]



Chemo-therapeutic agents act on the targets at different stages of tumour development. Cancer is a multi-step process and also occur at different proportions in the host system. Few molecular targets are confined to specific tissue or organ, but most of the targets are common in all organs, such as NF-κB, Bcl-2, STAT-3, p53,etc.,

**Table 1:** The Role of Curcumin on Targets

| Target | Mechanism | Role of curcumin on target |
|---|---|---|
| NF-κB (Nuclear Factor Kappa B) | It is the transcription factor which regulates genes that implicate in growth factor regulation, inflammation, carcinogenesis and apoptosis. The upregulation of NF-κB in tumour cells support in proliferation. The survival signals such as NF-κB, Akt and their downstream cascades lead to up regulation of Bcl-2 proteins(anti-apoptotic).[62,63] | At multiple levels, curcumin modulate these signals by inhibiting NF-κB pathway.[64,65] |
| STAT-3 (Signal Transducer and Activator of Transcription) | It is activated by tyrosine phosphorylation via upstream receptors (PDGF, EGF, IL-6). The oncogenic effect of activated STAT-3 on cell proliferation, angiogenesis, apoptosis, and immune system invasion. The active STAT-3 induces the resistance to apoptosis via the expression of cyclin D1 and Bcl-xL .[66-68] | Curcumin inhibit STAT-3. |
| Cyclin D | The expression of cyclin D is mediated by NF-κB pathway, it is overexpressed in many cancers. [69]The suppression of cell cycle progression mediated by cyclin D1 is led by the suppression of NF-κB pathway.[70] | Curcumin downregulates cyclin D1 |
| TNF –α (Tumour Necrosis Factor-alpha) | The pro-inflammatory effects of TNF-α are due to its ability to activate NF-κB. When a cell is exposed to TNF-α, it activates NF-κB, thereby leading to expression of inflammatory genes (chemokines, iNOS, 5-LOX, COX-2, adhesion molecules). It mediate tumour initiation, promotion, metastasis.[71-73] | Both at transcriptional and post-translational levels, curcumin suppress the expression of TNF-α |
| Nrf-2 (Nuclear factor erythroid 2–related factor 2 ) | The transcription factor Nrf-2-keap interaction initiate Nrf-2 to translocate to nucleus and bind to ARE (anti-oxidant response element), thus initiating transcription of genes encoding for detoxifying and anti-oxidant enzymes via HO-1, glutathione, NADPH quinone oxidoreductase-1.[74-75] | Increase in expression of Nrf-2 (especially in renal epithelial cells) was observed on curcumin treatment. |
| Wnt/ β-catenin | Wnt glycoproteins signalling is one of the fundamental mechanisms that is responsible for cell proliferation and tissue homeostatsis. The development of gene expression program is controlled by Wnt in association with the transcriptional co-activator β-catenin.[76] | It inhibit Wnt and cell-cell adhesion pathway resulting in induction of apoptosis (especially in HCT-116 colon cancer cells).[77] |
| PPAR-γ (Peroxisome Proliferator Associated Receptor γ) | Activation of PPAR-γ involved in inducing differentiation and inhibiting proliferation of cancer cells. It functions as a transcription factor, regulating the gene expression.[78,79] | It activates PPAR-with subsequent inhibition of EGFR gene, cyclin D1 results in inhibiting growth of Moser cells.[80] |
| AP-1 (Activator Protein) | It expresses the cancer-relevant genes, that activate pro-angiogenic, anti-apoptotic, mitogenic signals. The high levels of AP-1, NF-κB expression (in gliomas) is in part responsible for increased radio resistance and chemo resistance. It is associated with tumour progression.[81,82] | Curcumin downregulates AP-1. |
| COX-1,2 (cyclooxygenases) | COX is responsible for the conversion of arachidonic acid to PG, thromboxanes. COX-2 overexpression has been implicated in caners such as colon, prostate, lung, pancreas etc.[83] | It reduces COX-2 expression at transcription level.[84] It can also inhibit COX-1 transcription which is responsible for local spread malignancy .(Dr. S. Plummer, unpublished data) |
| Angiogenesis and cell adhesion | Angiogenesis is regarded as the important aspect to the transition of pre-malignant lesions in a hyper-proliferative state to malignant type, thereby facilitating tumour growth and metastasis. Cell-cell adhesion proteins (β-catenin, E-cadherin), APC are important for cell adhesion.[85] | Curcumin inhibits angiogenic growth factor production which is integral to the formation of new vessels.[86,87]It affects the proteins related to cell adhesion, inhibits the secretion of cytokines relevant to tumour growth.[88] |
| NO (Nitric oxide) | NO has an unpaired electron, hence, it is a free radical species. The bioavailability of NO is related to the production of many intermediates that are reactive in nature; most of these reactive nitrogen species are capable of hindering DNA repair. [89] | Curcumin is a free radical scavenger |

| | | |
|---|---|---|
| ROS (Reactive oxygen species) | ROS cause DNA mutations in carcinogenesis. | It is a ROS scavenging enzyme inducer, in some areas curcumin uses ROS to kill cancer cells.[90] |
| Apoptotic signals | Various cell stresses in intrinsic pathway include defective cell cycle, loss of growth factor, irreversible DNA damage; can generate death signals which pass them to mitochondria. In the extrinsic pathway, external environment initiate death signals via Fas, DR, INF. [91] | Curcumin activates both intrinsic and extrinsic pathways to promote apoptosis. |
| p 53 | It is the 1st tumour suppressor gene. It proofreads DNA and recognizes the mutational changes which cannot be changed, at this point; it arrests cell cycle of tumour cells and leads the cell towards apoptosis. p 53 inactivation and NF-κB activation play a major role in carcinogenesis .[92] | It was shown to upregulate the expression of p 53 followed by an increase in p 21(CIP-1) resulting in cell cycle arrest at G2/M and/ or G0/G1 phase .[93] |
| Sp-1 | It is highly expressed in breast, thyroid, gastric tumour cells in comparison to normal cells, it interacts with co-repressors and co-activators, thereby activate multiple biological functions (carcinogenesis).[94] | Curcumin suppress Sp-1 activation |
| Fak (Focal adhesion kinase) | The Fak activity produce intracellular signal transduction pathway which promote the turn-over rate of cell contacts with the extra cellular matrix., promoting cell migration. | It inhibits Fak phosphorylation and enhances several extracellular matrix component expression, which play a role in invasion and metastasis of tumour cells.The inhibition regulates cell adhesion that said to be anti-invasive effect of curcumin.[95] |
| Bcl-2 and Bax | Apoptotic and pro-apoptotic in nature. Bax is a central cell death regulator and a member of Bcl-2 family. Bax let mitochondria to open the transitional channels, leading to release of cytochrome C and caspase activation, to activate downstream triggering apoptosis. Bcl inhibits calcium release, whereas Bax promote calcium release into mitochondria. Bcl promote cell death (apoptosis), either by inducing (pro-apoptotic) or inhibiting (anti-apoptotic) apoptosis. [96] | Curcumin mediate the mitochondrial outer membrane permeability, by down-regulating Bcl expression and up-regulating Bax expression. In simple words, curcumin controls Bax and Bcl expression to induce calcium overload into mitochondria, thereby result in cancer cell apoptosis. |

**Effect of curcumin in different set of cancers**

**Colorectal cancer**

Colorectal cancer is the most common form of malignant cancer and third leading cause of death in United states. [97,98]NF-kB plays a key role in progression of colorectal cancer. NF-kB induces inflammation, anti-apoptosis, angiogenesis and cell proliferation.[99]Curcumin suppresses activation of NF-kB by inhibiting inhibitor k B kinase(IKK) mediated phosphorylation of inhibitory molecules [100,101] and activation of cascade 3 and 9, increasing BCL-X(S), c-IAP-2 mRNA and decreasing BCL-X(L) mRNA.[102]Curcumin reduces proliferation, invasion and migration of cancer cells by inhibiting NF-kB intracellular signalling pathway mediated COX-2 and osteopontin, an extracellular matrix protein.[103-105]Curcumin suppresses MMP expression, specifically MMP-9 which induces tumour angiogenesis by matrix degrading capacity by inhibiting AP-1 binding to DNA and NF-kB.[106,107] Molecular targets of curcumin in colorectal cancer are Beta- catenin, β-catenin/T cell factor(TCF), lymphoid enhance factor(LEF).[108,109]Curcumin has been found to inhibit signalling of molecular targets, IL-1,IL-8, increased localization of β-catenin and reduction of E-cadherin in the nucleus are associated with metastatic cancer progression, cancer cell growth and poor prognosis. [110-112]

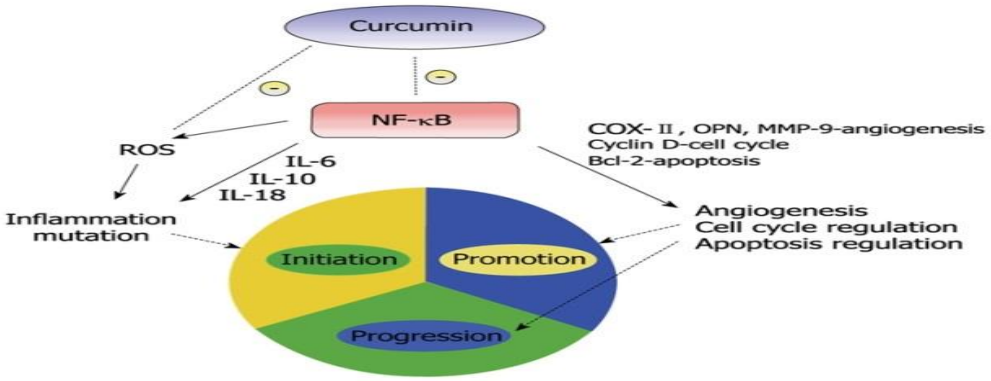



**Figure 4:** Role of curcumin in colorectal cancer [113]

**Breast Cancer**

It is the most common and second leading cause of cancer deaths among females[114] Curcumin reduces the expression of zeste homolog 2(E2H2) gene by stimulating c-Jun NH 2 –terminal kinase (JNK), ERK (extracellular signal regulated kinase), p38 kinase which are members of MAPK pathway.[115] By inhibiting microtubular assembly, curcumin inhibit cell proliferation and also induce G2/M phase arrest and activate mitotic checkpoint in MCF -7 cells.[116]Abnormal activation of Wnt/β catenin signaling pathway is associated with breast cancer development, curcumin inhibit cyclin D1, β catenin and slug in both MCF 7, MDA –MB-231 cells.[117]Curcumin shows the anti-tumour effects by inhibiting the expression of PCNA (proliferating cell nuclear antigen), p53 mRNA, KI-67 and down-regulates p21 mRNA which induces Bax mRNA expression in breast cancer cells.[118]Curcumin increases maspin gene in MCF-7 cells , a serine protease inhibitor which inhibits metastasis and tumor growth with down-regulation of Bcl-2 and up-regulation[119] of p53 protein. By up-regulating the expression of miR-15a and miR-16 in MCF-7 cells, curcumin reduces Bcl-2 expression.[120]It inhibits MDA-MB-231 cells proliferation by either up-regulation of p21 or Bax to Bcl-2 ratio.[121]Curcumin induces paraptosis by down-regulating AIP-1 protein, which acts as early signal and proteasome dysfunction was associated with the estrogen receptor(ER) dilation.[122] Presence of mitochondrial superoxide, proteosomal dysfunction and down-regulation of AIP-1/Alix protein associated with ER dilation, were found to be the paraptotic changes induced by curcumin. It inhibits invasion and cancer cell motility, by inhibiting α6β4 integrin function.[123]Curcumin reduces the expression of NF-κB in BT-474 and SK-BR-3-h cells phosphorylation of Akt, MAPK (mitogen activated protein kinase) and HER-2 (Human Epidermal Growth Factor) expression, which result in inhibition of proliferation and migration, metastasis, cell survival.[124-127]It inhibits receptor d' origine nantais (RON) tyrosine-kinase mediated invasion of cancer cells by acting on p 65 protein and NF-κB transcriptional activity . Curcumin inhibits α6β4 signalling functions, osteopontin or medroxy-progesterone acetate induced VEGF (vascular endothelial growth factor) expression and prevents its association with signalling receptors such as Akt and EGFR, VEGFR-1 resulted in prevention of breast cancer angiogenesis.[128-131]Inhibition of skp 2 (a F box protein S-phase kinase associated protein 2) results in cell growth arrest and p27 expression and phosphorylation of Src and STAT 3 plays a key role in treatment of malignant tumour and ER/MER 2 negative breast cancer.[132,133]

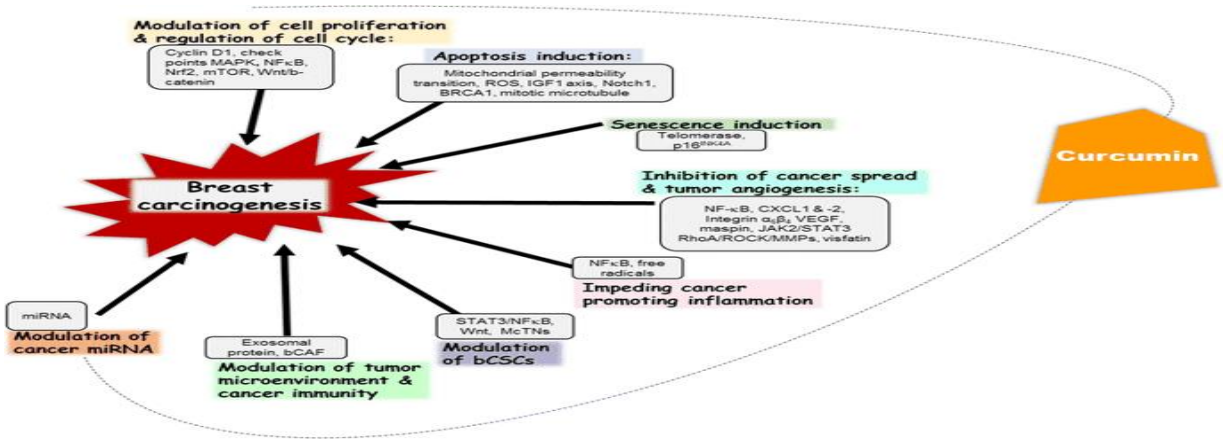



**Figure 5:** Role of curcumin in breast cancer [134]

**Prostate Cancer**

Prostate cancer has been treated with chemotherapy, local radiotherapy, hormone-therapy, radical prostatectomy. These therapies are effective in the treatment of localized, androgen dependent and ineffective in metastasis and androgen independent prostate cancer.[135] Androgen receptor r(AR) mutations, uncontrolled gene amplification, over expression of AR are the major reasons for the progression of prostate cancer. Curcumin has been found to be effective and non-toxic management for non- cancerous chronic bacterial prostatitis[136], androgen dependent DU145, androgen sensitive LNCaP and 22rv1 and bone metastatic LNCaP derived C4-2B prostate cancer cells.[137] Some curcumin analogues were also act as AR antagonists.[138] Curcumin reduces AR expression, AR binding activity to prostate specific antigen protein (PSA) gene and PSA expression in LINPAC cells[139] leads to inhibition of home box gene NKX 3.1[140] which induces prostate organogenesis and carcinogenesis[141] Imbalance between cell cycle checkpoints and different cycling(D1,E) deregulation of EGFR and VEGFR signalling pathways, increased expression of EGFR, EGFR tyrosine kinase activity[142] and ligand induced activation of EGFR are involved in the proliferation of cancer cells. By inhibiting endothelial growth factor receptor(EGFR) signalling, EGFR phosphorylation in PC-3 cells[143], cycling D1[144] and E [145] in LINPAC cells cur cumin reduces EGFR expression in LINPAC cells[146], disruption of cell cycle, proliferation and cell death. Curcumin prevents tumorigenesis and metastasis[147] by inhibiting phosphorylation of mTOR(mammalian target of rapamycin) in PC-3 and DU 145 cells, phosphatidylinositol 3-kinase (PI3K)/AKt(protein kinase B), P110, P85 subunits and phosphorylation of Ser 473 AKT target.[148]Curcumin shows its anti angiogenic effects by reducing proliferation

of human endothelial cells, pro-angiogenic genes such as VEGF, angiopoietin 1 and 2, kinase domain region(KDR).[149]Inhibition of MMP-2 and MMP-9 , auto-phosphorylation of EGFR and CSF1-R involved in development of osteomimetic properties, binding factor a-1 and osteoblast or stromal cells resulted in prevention of bone metastasis and tumour invasion.[150]Suppression of IKB-alpha proteosomal degradation, phosphorylation, phosphorylated AKT kinase and up regulation of mitogen activated protein kinase phosphatase-5(MKP 5) which dephosphorylates Jun N-terminal kinase(JNK) and protein kinase P38 resulted in decreased activation of NF-kB, TNF-α, COX-2, IL-6 by anti-inflammatory property of curcumin High levels of COX-2 are survival factors for prostate cancer.[151-154]Curcumin induced apoptosis is resulted by upregulation of pro-apoptic proteins and down regulation of anti-apoptic proteins (XIAP,BCL-2,BCL-XL)[155] TRAIL(TNF-alpha related apoptosis inducing ligand)acts as an inducer of apoptosis, thus TRAIL mediated immunotherapy is considered as choice of treatment for advanced cancers but DU 145,PC-3 and LNCaP cancer cells are resistant to TRAIL. Sensitization of these cells with curcumin results in TRAIL induced apoptosis by inducing DNA fragmentation, cleavage of procaspase-3,8 and 9 and release of cytochrome C.[156,157] Curcumin exhibits a potent radiosensitizing effect by increasing radiation induced clonogenic inhibition and apoptosis when combined with radiotherapy.[158]

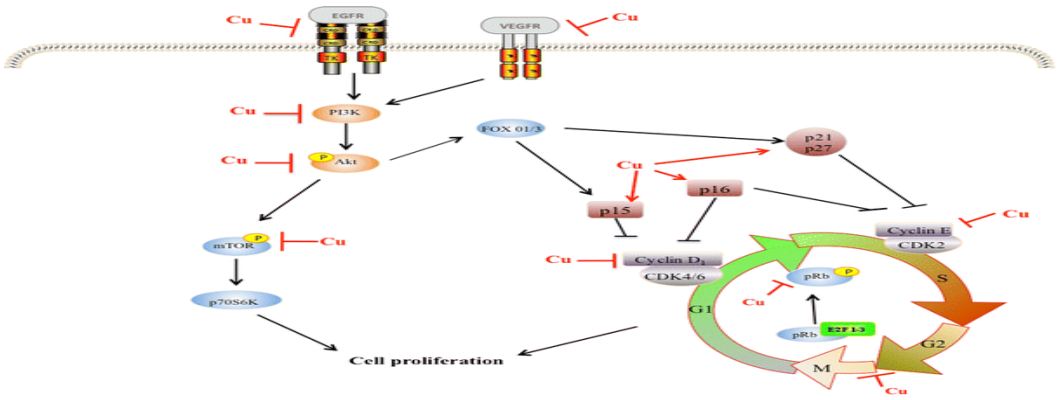



**Figure 6:** Role of curcumin in prostate cancer [159]

**Pancreatic Cancer**

Curcumin has been considered as an effective treatment for pancreatic cancer due to its low toxicity and antitumor effects via blocking multiple signalling pathways which are essential for tumor initiation and progression.[160] IAP (inhibitor of apoptosis) proteins maintain balance between cell survival and cell death. IAP family includes surviving, cellular IAPs1&2 (CIAP), X-chromosome linked IAP(XIAP). Resistance to chemotherapy, radiotherapy and pancreatic cancer cells overexpresses these IAP proteins and thus leads to poor outcomes.[161-163] Curcumin was found to inhibit IAP proteins in pancreatic cancer cells. Curcumin induces apoptosis through forehead box O1 (FOXO1) and by inhibiting STAT 3 signalling, NF-kB activity, PI3K/AKt pathway and reduces MMP-9, VEGF, Cyclin D1 and surviving.[164,165] miRNA-7 plays a key role in tumour growth and metastasis in chemo resistant cancer cells.[166] Curcumin inhibits downregulation of SET 8, upregulation of miRNA-7,Notch-1 which are associated with promotion of tumorigenesis, activation of p53 and pancreatic cancer cell growth.[167,168] By inhibition of cyclin B1/CDK -1 expression, G2/M cell cycle arrest, DNA damage, activation of ataxia tel-angiectasia mutated (ATM)/checkpoint kinase 1(chk1)/cell division cycle 25c (Cdc25C), curcumin suppresses the proliferation of BXPC-3 human pancreatic cancer cells.[169] Curcumin downregulates specific protein Sp1 which inhibits NF-kB expression, panc-1 and L3.6pL cancer cell growth.[170]

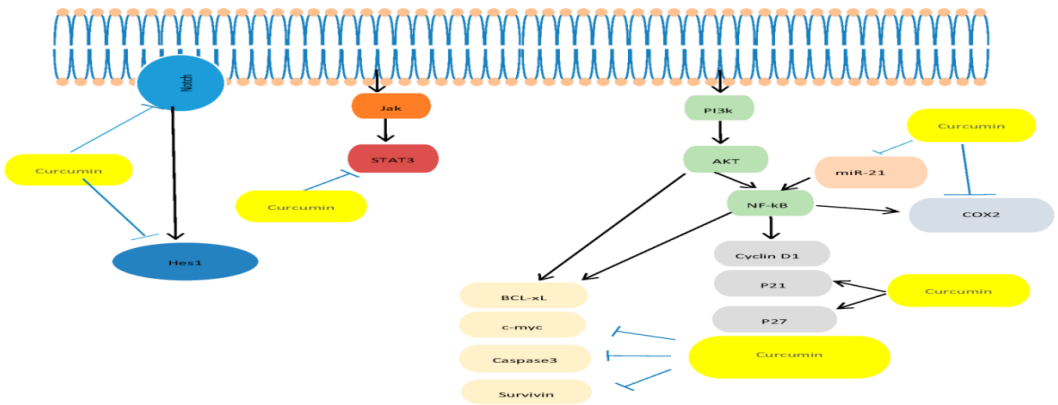



**Figure 7:** Role of curcumin in pancreatic cancer [171]

**Head and Neck Carcinoma**

Human papilloma virus (HPV), tobacco use, alcohol consumption and environmental exposures are the major risk factors for the development of hand and neck squamous cells. Curcumin suppresses cell growth of immortalized oral mucosal epithelial cells and SCC (squamous cell carcinoma) cells (UMSCC22B &SCC4) and cell survival by inhibiting NF-kB via inhibition of IkB-alpha, IL-6 mediated STAT3 phosphorylation, nuclear localization.[172,173] Curcumin inhibits IGFBP-5 and C/EBP-alpha by p38 activation and reduces phospho-IkB-alpha, COX-2, IL-6, IL-8, Mcl-1L, Mcl-1S, MMP-9, cyclin D1, Bcl-2, Bcl-xl levels and resulted in decreased tumorigenesis.[174,175] AKT signalling cascade is stimulated by EGFR. Curcumin induces AKT independent mechanism mediated inhibition of IkK. Curcumin enhances therapeutic efficacy by targeting EGFR/AKT signalling cascade and induces proteins such as insulin-like growth factor binding protein-5(IGFBP-5) and CCAAT/enhancer-binding protein alpha(C/EBP alpha) which suppresses development of head and neck cancer.[176] Curcumin reduces migration, invasion and angiogenesis of malignant oral squamous cells by inhibiting AKT/mTOR pathway and downregulating expression of MMP-9.

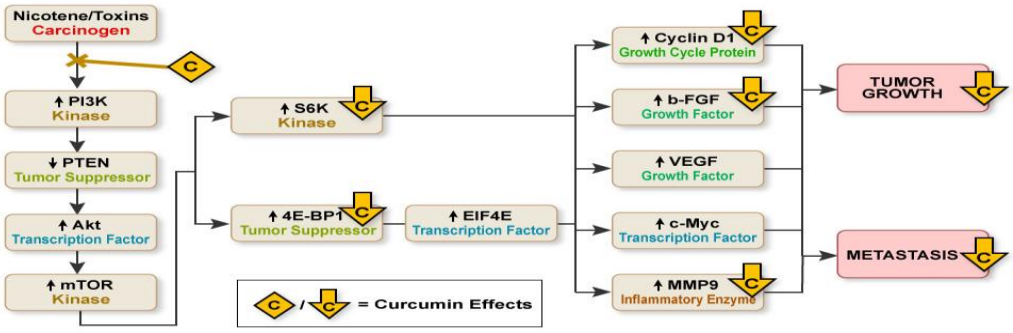



**Figure 8:** Role of curcumin in head and neck carcinoma [177]

**Brain Cancer and Glioblastoma**

Glioblastoma (GBM) is found to be most common primary malignant brain tumour. DAPK1 plays a key role in curcumin mediated cell death. Curcumin enhances DAPK1 mRNA in U251 GBM cell line which inhibits caspase-3 activation and by inhibiting NF-kB results in G2/M cell cycle arrest and apoptosis.[178] Curcumin downregulates Bcl-2, survivin, hTERT, inhibition of telomerase and increases caspase3,7,8 activity, BAX/Bcl-2 ratio and over expresssion of BAX thus results in DNA damage and apoptosis.[179,180] Inhibition of NF-kB transcription factor activity and caspase dependent pathway (caspase-3,8,9) resulted in increased apoptosis, DNA fragmentation , reduced cell proliferation and mitochondrial membrane potential.[181]Curcumin exhibits its antiproliferative effects by suppressing cyclin D1 and inducing p21. Egr-1,a transcription factor which activates transcription of p21 independent of p53 activation. Curcumin upregulates p53 expression and Egr-1 which is induced via ERK and JNK.[182] In B16F10 cells, curcumin reduces NF-kB, ERK, AKT, Bcl-XL and cyclin D1. In KNS60 and ONS76 cells of human GBM, curcumin arrest G2/M phase. Curcumin induces autophagy by inhibiting AKT/mTOR (mammalian target of rapamycin) /p70S6K pathway and by activating ERK 1/2 pathway.[183] Curcumin acts as an AP-1 inhibitor that down-regulates proganulin promoter activity and expression which involved in tumorigenesis and treatment resistance. Curcumin downregulates SHH( sonic hedgehog) signalling pathway which plays an important role in carcinogenesis of medulloblastoma leading to decreased downstream targets GLI1, PTCH1 and cytotoxicity in cell lines MED-4,5 and DAOY.[184] Curcumin induces tumour metastasis and invasion by inhibiting AP-1, MAP, MMP-1,3,9,14 expression in U87MG and U373MG GBM cell lines.[185] Curcumin induces anti-inflammatory, antioxidant and antitumor effects by inhibiting cellular glyoxalases resulted in decreased ATP and glutation and activates an antioxidant protein, thioredoxin in Nrf2 pathway.[186]

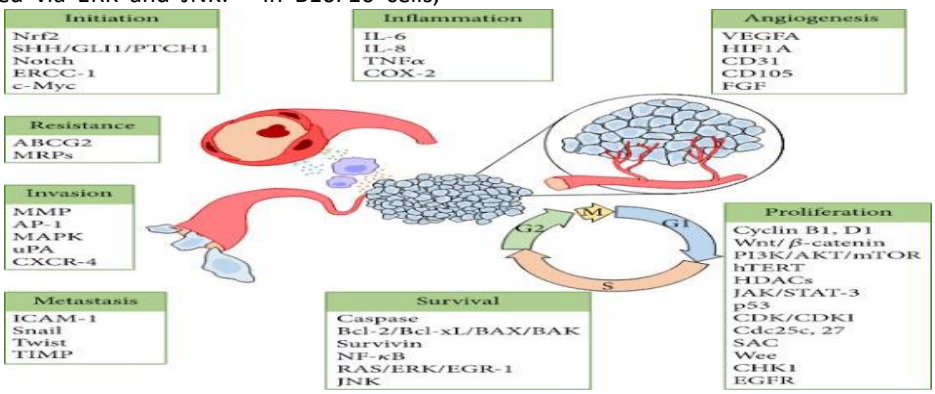



**Figure 9:** Role of curucmin in brain cancer and gliobastoma [187]

**SKIN CANCER**

Melanoma is one of the deadliest form of skin cancer. Curcumin inhibits cancer cell growth, invasion, inflammation and metastasis by inhibiting NF-kB, TNF-alpha, AKT/mTOR and ERK signalling, PI3k/AKT, MAPK, c-Jun N- terminal kinase, protein tyrosine kinase, protein serine define serine threonine kinase.[188,189] Curcumin acts as a selective inhibitor of phosphorylase kinase and results in anti-inflammatory and apoptosis by down regulating NF-kB, NF-kB mediated TGF-beta1 which converts fibroblasts to myofibroblasts leads to hypertrophic scarring, cycline kinases and adhesion molecules.[190-192] Curcumin also induces apoptosis by DNA damage repair(DDR) pathway through histone mediated DNA repair and mitochondrial pathway. [193]

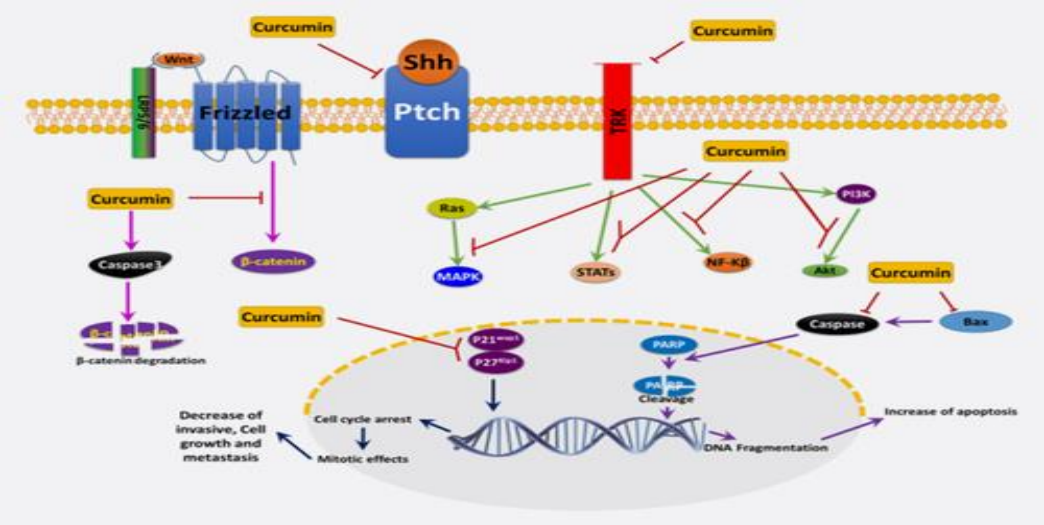



**Figure 10:** Role of curcumin in skin cancer [194]

**Available Types of Formulations**

Curcumin have low bioavailability and solubility, to overcome the limitations, nanoformulations are preferred. Several factors needed to be considered during preparation of nanoformulations to improve efficacy and cellular targeting of curcumin, which include[195]

- Ligand targeting : nucleic acid, peptide, antibody.
- Surface chemistry: polymeric coating, surface charge, surface hydrophobicity.
- Composition formula: nanogel, liposomes, polymeric nanoparticles, metallic nanoparticles, micelle, micro-emulsions/micro-encapsulation etc.

**Table 2:** Role of Nano-Formulations In Curcumin Delivery to the Target Site.

| Type of nano formulations | Comment | Example |
|---|---|---|
| Nanoparticles | They are used for encapsulation of curcumin, due to its bioavailability and biodegradability. Nanoparticle vehicles enable passive targeting of inflammed tissues and tumour by the increased production of cytokines and regulation of angiogenesis at the site, resulting in vascular leakiness, thereby lead to enhanced permeation and retention (EPR) effect.[196-198] | Curcumin encapsulated hyaluronic acid -polylactide nanoparticles (CEHPNP) |
| Cyclodextrins | They are cyclic oligo-saccharides, that solubilize curcumin (loaded drug) with the help of lipophilic core and allow permeation into the site of action via its hydrophilic outer layer. They improve bioavailability, solubility, stability, reduce non-selective toxicity and minimize degradation. [199] | β- cyclodextrin-curcumin self-assembling preparation. |
| Liposomes | They are generated from phospholipid bi-layers. The self-association of amphiphilic phospholipids with the cholesterol molecules, form the aqueous inner layer. The self-associating ability of phospholipids originates from their tendency to protect the hydrophobic groups from aqueous forces, while interacting with the aqueous phase of hydrophilic drugs. These lipid-based vehicles enhance solubility of the loaded drug (eg: curcumin). [200] | TMC(N-trimethyl chitosan chloride)-CUR liposomes. |

| | | |
|---|---|---|
| Micro-emulsions | Also called as micro-encapsulations, which have high drug-entrapment efficiency with long term stability of hydrophobic molecules. This micro-structure result in high-drug solubility capacity, fast and free drug diffusion, that coupled with the lipophilic nature give them a potential for transporting lipophilic compound (such as curcumin) through skin and also across lipophilic cell membrane. [201,202] | Turmeric oleoresin microencapsulation. |
| Polymeric nanoparticles | They are preferred in curcumin drug delivery as it enhances the biological activity, solubilty, bioavailability, reduce risk of toxicty and is biodegradable. [203] | PLGA-curcumin nano-formulation. |
| Solid lipid nanoparticles | They are capable enough of providing protection to the labile drugs from pH/light/heat-mediated degradation, controlled release and possess efficient bioavailability and tolerability. They can cross BBB due to its lipophilic nature (which can also act as vehicle for less lipophilic drugs which cannot cross BBB). This carrier protects the compound from photochemical/pH degradation, but also enables drug targeting and easy large scale production. [204] | Curcumin SLN(solid lipid nanoparticles) are formulated using di-mystroyl phosphatidylcholine (DMPC) |
| Implantable drug delivery systems | The localized delivery and bioavailability of implants into systemic circulation by releasing the encapsulated drug slowly at the site of implantation is achieved by homogeneous entrapment of compounds in a polymeric complex. Due to its slow release kinetics, it can improve patient compliance to compounds like curcumin, which is rapidly metabolized and poorly bioavailable. [205] | Poly(ε-caprolactone) (PCL) implants. |
| Micelles | They have high drug encapsulation efficiency and narrow size distribution capacity. The hydrophobic core of micelles helps in curcumin solubilization and delivery at target site. | TGPS (D-α Tocopheryl polyethylene glycol 1000 succinate), poloxamer-407 combined with curcumin micelle. |
| Nanogel | The swollen nature of these carriers mimics human tissue due to its high hydrophilicity. These hydrogel nanoparticles have swollen chemical/physically cross-linked networks that are composed of amphiphilic polymer chains. They possess large surface area for drug entrapment and porous structure for loading and release of drug. [206] | Cholesterol-hyaluronic acid nano gel curcumin |
| Dendrimers | They are suitable for conjugation and loading of curcumin. They are highly branched and star-shaped networks of macromolecules. | PAMAM dendrimer (Hyaluronic acid conjugated polyamidoamine-curcumin) |

## CONCLUSION

Curcumin, a phytochemical compound provides various therapeutic benefits by acting as anti-bacterial, anti - inflammatory, antioxidant, anti-tumour, neuroprotective and so on. Curcumin has low bioavailability and solubility and thus shows poor absorption. Various formulations have been prepared to improve bioavailability. It mediates multiple signalling pathways and involves in prevention of cancer cell growth, survival, invasion, angiogenesis, and metastasis and also improves therapeutic efficacy in radio and chemotherapy resistance. Curcumin shown to be effective in treatment of various cancers like colorectal cancer, pancreatic cancer, prostate cancer, head and neck cancer, brain cancer and glioblastoma, skin cancer, breast cancer, myeloid leukemia, lung cancer. Our review also presents the mechanism of curcumin in the 3 major steps of tumour development i.e., initiation, progression, promotion.

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**Source of Support:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Conflict of Interest:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.