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REVIEW ARTICLE



Curcumin: a bioactive compound with molecular targets for human malignancies

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ABSTRACT

Cancer is the second leading cause of death in the world and one of the major public health problems. Curcumin has anticancer activity including inducing apoptosis and inhibiting proliferation and invasion of tumours by suppressing a variety of cellular signalling pathways. It also possesses anti-tumour activity on different human cancers such as breast cancer, lung cancer, head and neck squamous cell carcinoma, prostate cancer, and brain tumours. In vitro and in vivo trails, curcumin inhibits tumour development and metastasis by inhibiting many pathways that regulate signalling in malignant cells, including Ras, p53, extracellular signal-regulated kinases (ERK), Wnt-protein kinase B (Akt), MAPKs, and PI3K. Curcumin can also inhibit IKK, EGFR, -catenin, cyclin D1, tumour necrosis factor (TNF), and anti-apoptotic genes such as Bcl-X and Bcl-2 along with downregulating nuclear transcription factors like NF- κ B, which reduces the formation of pro-inflammatory cytokines like chemokines, TNF-, Interleukins and IL-1, IL-2, IL-6, IL-8, IL-12.

Abbreviations: AP-1, activated protein 1; Bax, BCL-2-associated X protein; Bcl-XL, B-cell leukaemia extralarge; Cdc, cell division cycle; COX, cyclooxygenase; CY, cytochrome; DPPC, dipalmitoyl-

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phosphatidylcholine; EGFR, epidermal growth factor receptor; eIF, eukaryotic initiation factors; FOX, Forkhead box; FPTase, farnesyl protein transferase; HIF, hypoxia-inducible factor; histone deacetylase inhibitors, HLJ, DnaJ-like heat shock protein; Hsp, heat shock proteins; IL, interleukin; miRNA, micro ribonucleic acid; MMC, mitomycin-C; mTOR, mammalian target of rapamycin; NF- κ B, nuclear transcription factor-kappa-B; PG, prostaglandins; PKB, protein kinase B; Ras, reticular activating system; TargOncol, human small cell lung cancer cell lines; TGF, transforming growth factor; TNF, tumour necrosis factor; TP, thymidine phosphorylase; TPA3, 12-O-tetradecanoylphorbol-13-acetate; u-PA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factors; XIAP, Xlinked inhibitor of apoptosis

Introduction

Curcumin is a polyphenol chemical obtained naturally from turmeric (*Curcuma longa*) (Vyas et al., 2013). Curcumin makes up 1%-5% of turmeric formulations with a molecular mass of 368.37 and it has chemical formula $C_{21}H_{20}O_6$. The usage of curcumin as a culinary colouring ingredient (for example, in famous Indian curry), as well as in herbal medicine (Wong et al., 2021). Curcumin is insoluble in water and unstable. The solubilizing characteristics of rubusoside might be used to improve curcumin solubility (Shahbaz et al., 2023). Moreover, targeted transportation of synthetic analogues and nanotechnology-based curcumin preparations to cancer can boost chemotherapeutic and chemo-preventive effects (Park et al., 2013). Curcumin has various health benefits shown in Figure 1, but nowadays it is being extensively used in research to be used against various cancers.

Diferuloylmethane, the source of curcumin, which comes from the rhizome herb *Curcuma longa* as well, is renowned as turmeric, it has a polyphenolic composition and it owns a vast range of biological tasks involving antioxidant, anti-inflammatory, hepato-protective, immunomodulatory, anti-depressant, anti-dyslipidemic, antidiabetic, analgesic, and defensive factors against pulmonary diseases. Of specific concern, there have been various studies proposing the effectiveness of curcumin as a chemo protective anti-carcinogenic, and chemo-sensitizing complex besides a variation of cancer forms. Moreover, the US Food and Drug Administration has permitted curcumin's safety. Because of multiple medical research on the safety and harmfulness of curcumin, a tolerable dosage of 4–8 g per day is regarded to achieve the best therapeutic results (Yu et al., 2013).

The novelty of using curcumin as an anti-cancerous agent lies in its unique ability to target multiple cancer cell signalling pathways by inducing apoptosis, suppressing cell proliferation, inhibiting inflammation and blocking angiogenesis. Different delivery systems for the administration of curcumin have been developed by using various technologies to improve the properties of curcumin and its target ability. Liposome loading is an effective method. Curcumin-loaded liposomes are utilized to promote the inhibition of the production of IL-6 inside macrophages. Liposomes developed by mix solution of curcumin with HAS (human serum albumin) solution and then subsequently addition to a lipid mixture of cholesterol, DPPC (1, 2-dipalmitoyl-sn-glycero-3-phosphocholine)

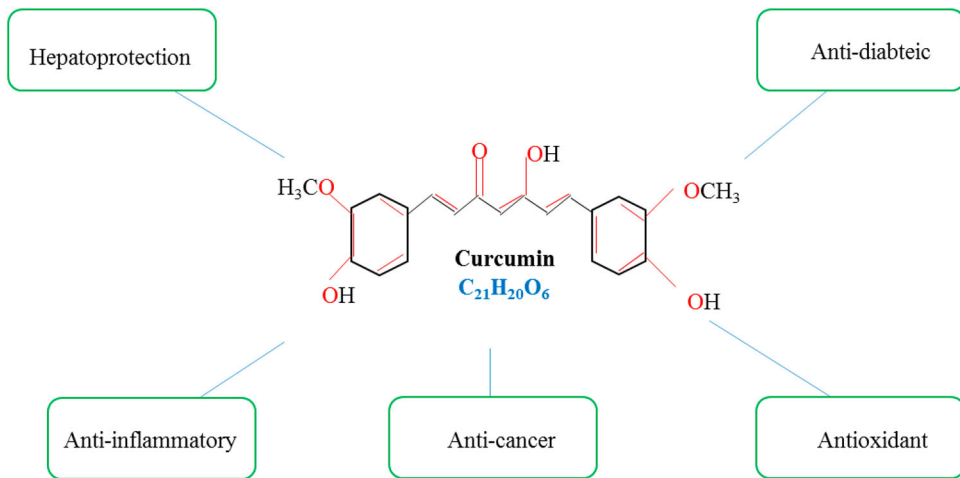


Figure 1. Various health benefits of curcumin.

and DPPS (1, 2-dipalmitoyl-sn-glycero-3-phospho-L-serine sodium salt). This system effectively induces suppression of IL-6 as well as a significant reduction in total number of macrophages (Tomeh et al., 2019). Pictorial depiction of the curcumin-liposome system playing a role in the reduction in number of macrophages. HAS; (human serum albumin), DPPC; (1, 2-dipalmitoyl-sn-glycero-3-phosphocholine), DPPS; (1, 2-dipalmitoyl-sn-glycero-3-phospho-L-serine) shown in Figure 2.

This paper includes an in-depth evaluation and integration of recent developments in the field of anticancer research, offering an up-to-date review of curcumin's anticancer perspectives. This paper thoroughly reviews the existing literature on the anticancer effects of curcumin, which includes a variety of studies and experimental results. We want to give a thorough review that encompasses the most recent advancements in curcumin research by analysing and synthesizing this abundance of data. Our study has a strong emphasis on incorporating the latest developments in the subject. We have carefully examined and highlighted recent discoveries and developing ideas mentioned in recent papers. Papers were selected based on the year of publication and not older than five years with very few older than five years owing to their high relevancy and importance to the subject. Papers relating to drug formulations, drug application and drug delivery using curcumin were excluded. The paper reporting the main effects of curcumin on cancer and describing the underlying pathways were included. The largest database google scholar was primarily used. Some closely related papers are "Modulatory properties of curcumin in cancer: a narrative review on the role of interferons," and "Curcumin, calebin A and chemo sensitization: How are they linked to colorectal cancer?" "Functionalization of curcumin nanomedicines: a recent promising adaptation to maximize pharmacokinetic profile, specific cell internalization and anticancer efficacy against breast cancer." The main gap is the absence of collecting of data on the main anticancer effects of curcumin as per recent literature. This paper includes recently revealed mechanisms of action, potential interactions between different substances and the use of curcumin in particular cancer types. Our paper provides new insights and

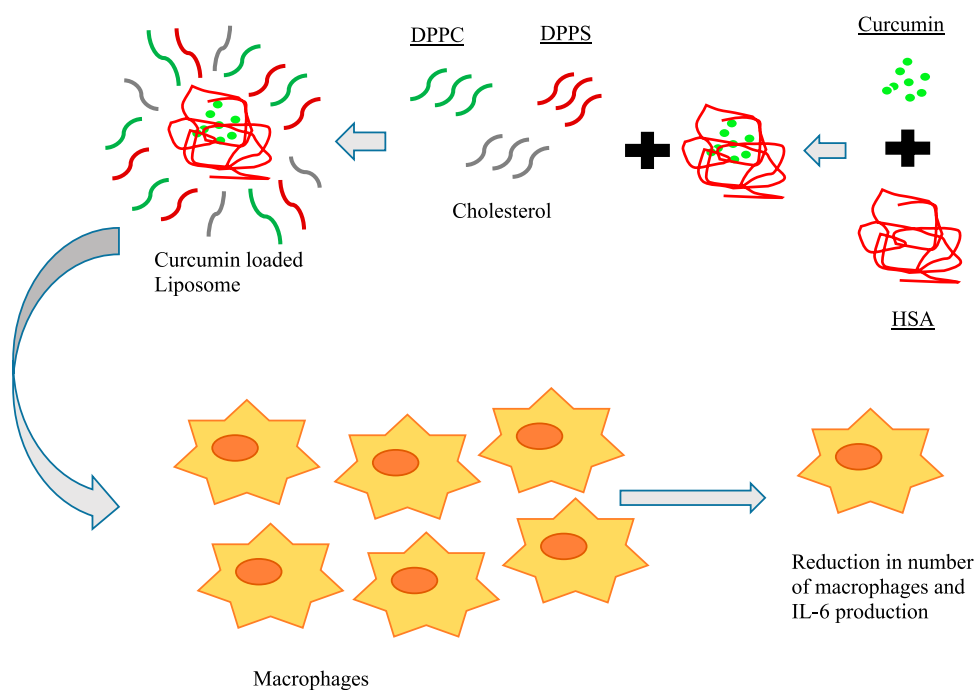


Figure 2. Pictorial depiction of curcumin-liposome system playing role in reduction in number of macrophages. HAS; (human serum albumin), DPPC; (1, 2-dipalmitoyl-sn-glycero-3-phosphocholine), DPPS; (1, 2-dipalmitoyl-sn-glycero-3-phospho-L-serine).

increases knowledge of the potential of curcumin as an anticancer agent by encompassing these most recent discoveries.

Gastric cancer

Gastric cancer is the third biggest origin of cancer-related mortality and it is the fourth most frequent cancer in the world, creating a severe public health burden (Hassanalilou et al., 2019). Because early stages of stomach cancer are clinically asymptomatic, most patients are detected in the late stage (Najafi et al., 2020). The primary threat factors for the development of stomach cancer include gastroesophageal reflux ailment, obesity, dietary variables, and helicobacter pylori inflammation (Liu et al., 2016). Gastric cancer etiology and development is a complicated multistep process including changes in many genetic and epigenetic patterns, cell cycle regulators, tumour suppressor genes, DNA healing genes, and signalling chemicals. Most of the molecular processes that accrue in gastrointestinal carcinogenesis include oncogene initiation, overexpression of development tissues with their receptors, deactivation of tumour inhibitor genes, cell linkage particles and restoration genes of DNA. Nuclear factors such as kappa B transcription factor (NF- κ B) are a major modulator of tumour advancement that includes cellular survival, inhibition of cell mortality, oncogenesis and alteration (Li et al., 2017). Leukocytes and macrophages create nitrosamines and certain reactive oxygen species (ROS) during chronic inflammation, causing elevated oxidative pressure and

cell damage. Furthermore, cytokine and chemokine stimulation may promote not just leukocyte movement but also carcinogenesis. The host defense system is recognized to be a key factor in the development of stomach cancer. Instead of, the latest breakthroughs in our understanding of gastric cancer science, treating individuals with advanced stomach cancer remains a severe challenge. Phototherapy, radiation, surgery and chemotherapy are the current treatments available for stomach cancer. However, chemotherapy is the most often used treatment for people with stomach cancer. Natural anticancer drugs have established enough consideration over the last decade because of their strong therapeutic potential and few side effects in comparison to chemotherapy techniques. Curcumin, a kind of phytochemical, has demonstrated potential cancer chemo-preventive benefits in animal systems (Cai et al., 2013).

Curcumin inhibits tumour development and metastasis by inhibiting many pathways that regulate signalling in malignant cells, including Ras, p53, extracellular signal-regulated kinases (ERK), Wnt-protein kinase B (Akt), MAPKs, and PI3K. Curcumin can also inhibit several clinically essential molecules like IKK, EGFR, -catenin, cyclin D1, tumour necrosis factor (TNF), and anti-apoptotic genes such as Bcl-X and Bcl-2 (Huang et al., 2017). Curcumin can reduce inflammation by downregulating nuclear transcription factors like NF- κ B, which reduces the formation of pro-inflammatory cytokines like chemokines, TNF-, Interleukins and IL-1, IL-2, IL-6, IL-8, IL-12.

Curcumin lowered the growth of SGC7901, BGC823, MGC803 and MKN1 cancer cell outline in vitro in a dose-dependent (50-100 M) sequence. Curcumin was discovered to limit the growth of intestinal cancer MGC-803 cells by the initiation of cell mortality via the mitochondrial route, which was characterized by a reduction in the potential for mitochondrial membranes (MMP), the discharge of cytochrome c, decreased phosphorylation of ERK and Akt. Curcumin (15-60 M) was found to lower the growth of SGC-7901 gastric cells in a dose-dependent way that gives rise to MMP lowering by releasing cytochrome c within the cytosol and damaging ATP-sensitive potassium channel opening, thus enhancing the degree of apoptosis and reducing the energy source within the cell. Curcumin (5-40 M) inhibited proliferation and induced apoptosis in BGC-823 and SGC-7901 cell lines by modifying the manifestation of (miR-33b) micro-RNA 33b by decreasing the production of the X-linked regulator of certain apoptosis proteins. Curcumin was also discovered to decrease cell growth within the KATO-III gastric cell line via cell cycle arrest by lowering the magnitude of cell cycle regulators cyclin B and D. By activating two major apoptosis mediators such as caspase-3 and PARP curcumin can promote apoptosis in the KATO-II cell line. As a consequence, curcumin at concentrations ranging from 1 to 100 M may substantially slow down the propagation and survival of gastric tumour cells in vitro due to cell cycle inhibition and death in mitochondrial-independent and dependent mechanisms (Bahrami & Ferns, 2021).

Oesophageal cancer

Oesophageal carcinoma is the eighth most prevalent type of cancer and the sixth most common cause of cancer-related deaths. Although there have been advancements in surgery and neoadjuvant therapy, the 5-year survival rates for oesophageal cancer remain low. The pathophysiology of this malignancy is still unknown, resulting in an uncertain response to existing chemotherapy regimens. It is critical to find new

medications to combat the symptoms of this malignancy, which necessitates a more creative and integrated strategy for diagnosis, prevention and therapy (Komal et al., 2019).

Oesophageal cancer arises in the cells that line the muscular tube called the oesophagus, which moves food from the mouth to the gastrointestinal tract. The anti-inflammatory properties of curcumin make it a promising therapeutic option for oesophageal cancer prevention and treatment. Curcumin not only suppresses NF- κ B, but it also enhances apoptosis and drug accumulation in oesophageal cancer cells. Curcumin also prevented bile acid-induced COX-2 production and suppressed gene expression linked with sodium dismutase-1 in oesophageal HET-1A epithelial cell lines (Subramaniam et al., 2012). Curcumin affects several molecular pathways and triggers apoptosis-independent mortality in oesophageal cancer cells via strategies such as autophagy. Curcumin has recently been shown to alter Notch-1 signalling and inhibit NF- κ B and its subsequent inhibition such as cyclin D1, Bcl2, MMP-9, and VEGF in oral squamous cell carcinomas. Moreover, it was found that curcumin effectively suppressed NF- κ B activity and DNA damage induced by bile, and increased apoptosis *in vivo*, suggesting its potential as a chemo-preventive agent for oesophageal cancer in rats. When curcumin was administered to rats during the cancer initiation and post-initiation stages, it was observed to reduce the incidence of oesophageal carcinogenesis by 27% and 33%, respectively (Zheng et al., 2018).

Considerable evidence implies that curcumin can cause cell death in apoptosis-resistant cells. Numerous investigations have indicated that curcumin causes cell cycle pauses in the G2/M phases, as well as mitotic spindle disintegration, cytokinesis abnormalities, and micronucleation, which is associated with a kind of cell death known as mitotic catastrophe (MC). Recent studies have also demonstrated that curcumin therapy can induce autophagic cell death in tumour tissues. This kind of cell death is distinguished by the production of autophagic vacuoles and occurs without chromatin fragmentation (Hesari et al., 2019).

In an interesting study, the squamous and adenocarcinoma cell lines from human oesophageal cancer OE21, OE19 and OE33 were used. The cells were kept at 37°C in 95% air and 5% CO₂ in RPMI 1640, 1% penicillin/streptomycin and 10% (v/v) fetal calf serum, both Gibco, Paisley, UK. Curcumin was dissolved in dimethyl sulphoxide (DMSO). Dilution in culture medium yielded final curcumin dosages ranging from 5 to 50 micromolars, with the final DMSO content remaining below 0.07%. All studies included controls with 0.07% DMSO. After 24-h treatment with curcumin (5–50 micro molar), the cells were harvested and fixed in 70% ethanol overnight at 4°C. The cell cycle was analysed using flow cytometry. Anti-cancer activities were shown by curcumin in the subjected cell lines (Shehzad et al., 2013).

Based on an investigation, vulnerable cells have a similar morphology to MC. A distinct extra subpopulation also exists in the two top vulnerable cell lines. The OE21 cells exhibit a small proportion of cells with apoptotic morphology, whereas the KYSE450 cells show an additional population with autophagic features. Similarly, in OE19 cells, a minor population with autophagic characteristics can be observed, and in O33E cells, a small proportion of cells exhibit apoptotic morphology. The results indicated that curcumin sensitivity is dependable with MC induction (with a minor initiation of apoptosis in OE21 cells). Yet, another sort of cell death is present in the KYSE450 cell line and, to a lesser extent, in the more susceptible OE19 cells. These KYSE450 batteries had

substantial cytoplasmic vacuolization, which is compatible with the morphology reported for autophagy. Autophagy is a mechanism that transports cytoplasmic proteins or organelles to a lytic compartment for disintegration and regeneration. This can help cells survive during times of stress; nevertheless, uncontrolled phagocytosis can lead to cell death. We employed the MDC assay, a specific fluorescent marker of autophagic vesicles, to see if autophagy coexisted in the cell lines following curcumin therapy. When autophagy is activated, the dye is internalized into punctate vesicular staining rather than diffuse labelling. We investigated the dispersion in three curcumin-sensitive cell lines of the dye (OE33, OE21 and KYSE450) following curcumin therapy (Zhang et al., 2015).

Intestinal cancer

Intestinal cancer refers to the development of cancerous cells in the small intestine, which is responsible for transporting food from the abdomen to the colon during ingestion. Curcumin (0.15%) was tested in C57BL/6J-Min/+ (Min/+) mice, who have a germline variant in the APC gene that leads to the uncontrolled formation of intestinal adenomas by 15 weeks of age. Curcumin has been demonstrated to reduce tumour growth in Min/- mice by 63% via increasing enterocyte death and multiplication. Curcumin treatment also reduced -catenin expression in Min/+ mice erythrocytes. Curcumin has also been studied for its ability to prevent the formation of adenocarcinomas in the intestinal tracts of the Min/+ mice model of human familial adenomatous polyposis. Curcumin at 0.2% and 0.5% dosages was observed to lower adenoma multiplicity by 39% and 40%, respectively, over 15 weeks. Curcumin's effects on intestinal carcinogenesis were studied in APC (Min/+) mice aged 4–18 weeks (Shehzad et al., 2013). Their intestines were examined for polyp prevalence, and the reports revealed that curcumin minimized the number of intestinal polyps by 75%, perhaps due to decreased mRNA expression related to IL-6, IL-1, TNF-, and chemokine ligand 2 (CCL2). In a medical experiment investigating the effect of curcumin (0.5%, 12 g/day) on intestinal adenomas in patients with familial adenomatous polyposis, patients with premalignant lesions improved (Kabir et al., 2021).

In many epithelial models, curcumin prevented carcinogenesis at the beginning, activation, and advancement phases. Curcumin topical administration inhibited TPA-induced epidermal DNA production, tumour development, and ear oedema in mice, and prohibited DMBA-induced skin cancers. The management of curcumin was found to prevent the development of azoxymethane-induced malignancies in rats and mice, which was attributed to its ability to suppress cyclooxygenase and lipoxygenase movement in the intestinal mucosa. Curcumin inhibition of epithelial angiogenesis and prostaglandin activation has been linked to a decrease in COX2 (Cyclooxygenase 2) gene transcription. It remains uncertain whether the effect on cell propagation is a direct result of the suppression of COX2 activity or the reduction of prostaglandin production. Additionally, curcumin was found to reduce tumour growth in the Min/1 mouse model, which produces multiple intestinal adenomas due to a germline mutation in one Apc allele. The inclusion of 0.10% curcumin in the Min/1 mice's diet resulted in a 70% decrease in tumour development. Its chemo-preventive action was linked to enhanced enterocyte apoptosis and reduced b-catenin activation in the intestinal mucosa (Weng

& Goel, 2022). To gain a better consideration of the role of mucosal immune surveillance in a genetic colon tumour model and examine variations in immune effector cells that may be related to detection and therapy, immunohistochemistry was employed to describe the mucosal lymphoid population of Min/1 mice following oral ingestion of a tumour-preventing amount of curcumin. The number of B and T monocytes or lymphocytes in the intestinal mucosa of Min/1 mice did not differ significantly from that of their wild-type littermates. However, animals managed with curcumin displayed a higher incidence of B cells and CD4+ T cells in the mucosa of the small intestine at a dietary intake of 0.10%, a level that was associated with approximately 70% inhibition of intestinal tumour growth. Curcumin appears to regulate T and B cell-mediated immunological processes, according to this study (Pari et al., 2008).

Curcumin's antioxidant qualities may be involved in the process of tumour suppression. There is a considerable body of evidence indicating that reactive oxygen species (ROS) are connected with cancer elevation. Reactive oxygen species and oxidant defense enzyme activity have been noticed in human colon carcinoma cells, normal mucosal biopsies tumour tissues and rat azoxymethane-induced colonic malignancies. According to research, both *in vivo*, colonic tumours and cultured human tumour cells had greater amounts of ROS than non-tumour tissues. These sensitive compounds are hypothesized to function as secondary messengers in signalling trials that control cell growth. Antioxidants are thought to suppress malignancy by lowering intracellular peroxides (McFadden et al., 2015). Gene expression and membrane-related signalling both of which are vulnerable to oxidative pressure, are crucial in sustaining immune cells' proper activity and capacity to protect against malignancies or invading antigens. Susceptible effector cells are subjected to elevated oxidative pressure because sensitive oxygen intermediates are created during normal activity. To accommodate this, immune effector cells have greater antioxidant nutrient availability than other cells. Moreover, deficits in numerous antioxidants, including vitamin E, vitamin C, zinc, glutathione, and selenium cause immune system abnormalities. Antioxidant substances in the diet can change the antioxidant-oxidant equilibrium, reducing the consequences of oxidative stress. Human and animal studies reveal that antioxidant consumption alters cell-mediated immunity, inflammatory response, and cytokine creation. To summarize, tumour suppression with the antioxidant curcumin was related to alterations in the immune effector cell population of the small intestine in Min/1 mice. These alterations, as demonstrated by an increase in mucosal B-cell and CD41 T-cell populations, are identical to those seen by other researchers in curcumin-treated mouse splenocytes. As a result, our study extends curcumin's immunomodulatory function to the intestinal mucosa. Further research is needed to determine if curcumin's immunomodulatory qualities are required for tumour-inhibitory efficacy (Shehzad et al., 2017).

Hepatic cancer

The hepatic tumour is named (HCC) hepatocellular carcinoma or liver malignancy because the liver is the site from which cancer initiates. Many researches have highlighted the possible efficiency of curcumin in the treatment of HCC. curcumin lowered MMP-9 emission in the (CBO140C12) HCC cells and decreased the migration and adhesion of laminin and fibronectin. Curcumin inhibited the impression of the Chk1 protein by

arresting the cell cycle at the G2/M stage and by inducing apoptosis in many hepatoma cell ranks. It is also recognized that curcumin encourages DNA growth arrest and damage by increasing lipid peroxidation and ROS generation in the treatment of the HepG2 cells. Moreover, it has been revealed that CUR interrupts Notch-1 signalling in the Notch intracellular domain in SK-Hep-1, SNU449 and HEP3B cellular lines. The pharmacological impacts of curcumin in carcinogenic-induced HCC have been conducted during *in vitro* and *in vivo* investigations. Curcumin provides protection against hyperplasia that is diethylnitrosamine (DEN)-induced and hepatocellular carcinoma in rodents by decremental impression of P53, NF- κ B and p21-Ras. Curcumin also provides enhanced purpose of lipid peroxidation and certain antioxidant liver enzymes such as glutathione and also protects alongside the induced hepatic carcinomas in some rodents that are managed with (DHPN) 2,2'-dihydroxy-di-*n*-propylnitrosamine. Curcumin has revealed its effective efficiency in the rodent's xenograft model that consists of intrahepatic metastasis in CBO140C12 cells. Many other researchers have also shown that curcumin plays its role in mice that are implanted with hepatoma cells to mediate tumour inhibition. The antiangiogenic and anti-proliferative impacts of curcumin in nude mice that were inserted with the human HepG2 cells have been approved (Soni et al., 2021).

The expression of IAPs such as XIAP can be stimulated by (NF- κ B) nuclear factor-kappa-B that is commonly stimulated in HCC. So the reduction of transcription factor provides help in antagonizing the effect of IAPs and other NF- κ B target genes such as COX-2, c-myc and Bcl-XL that are tangled in the negative effects of this cancer. To address this issue, the impacts of curcumin were examined either unaccompanied or in amalgamation with the conventional anti-tumour mediators such as doxorubicin and cisplatin on HCC cell line HA22T/VGH. Curcumin owing to its anti-tumour and anti-inflammatory properties can downregulate activation of NF- κ B. Because the HA22T/VGH cell line plays a role in the expression of activated NF- κ B, the anti-tumour activities of curcumin were examined and the effect of curcumin on initiation of NF- κ B, impression of NF- κ B target genes and IAPs were also reported (Cao et al., 2021).

Curcumin promotes apoptosis and it was evaluated by the method of flow cytometry experiments through DNA marked with the propidium iodide, the levels of caspase-3 activation and within cells the penetration of propidium iodide were also examined. The drug altered the dispersal of cells in phases of the cell cycle by changing it from G0 to G1 to S and then G2-M. Curcumin reduced 30% of cell death by antioxidant NAC which was examined in a separate experiment by the increase in generation of free radicals. Moreover, results of treatments with Caspase-9, Caspase-8 and Caspase 3 inhibitors showed that apoptosis from curcumin in HA22T/VGH cells is due to initiation of caspase 9 besides by caspase 3 rather than caspase 8. A definite synergy between cisplatin and curcumin occurred in caspase-3 activation and induction of apoptosis whereas the combination of doxorubicin and curcumin-caused effects on apoptosis that were sub-additive. Therefore, the effects of treatments were examined and results demonstrated that cytotoxicity only occurred when curcumin was administered before cisplatin, suggesting that it was curcumin that sensitized the cells to cisplatin. The combined impacts of doxorubicin and curcumin were significantly improved (Naeini et al., 2019).

Possible strategies for decreasing resistance to apoptosis and drug resistance are related to the expression of inhibitors of apoptosis (IAP) proteins, which are associated with poor prognosis in cancers such as hepatocellular carcinoma (HCC). Treatment with curcumin can help suppress NF- κ B, thereby inhibiting NF- κ B target genes and IAP expression in tumours. Curcumin is a polyphenolic compound with several mechanisms that add to its anti-tumour and anti-infectious properties. Additionally, studies have shown that curcumin can hinder the activation of NF- κ B and enhance cancer cell response to several NF- κ B stimulating anticancer drugs, including doxorubicin. Furthermore, results have demonstrated that initiation of NF- κ B is necessary for the cytotoxic effects of doxorubicin and its analogues, suggesting that curcumin may interfere with their anti-cancer actions. It has also been described that curcumin encourages significant growth inhibition and apoptosis in a human HCC cell line that expresses initiated NF- κ B. Curcumin-induced cell mortality is primarily dependent on caspase-3 and is mediated by caspase-9, the activator for apoptosis in the mitochondrial pathway, instead of caspase-8, which is a mediator of the extrinsic trials. Earlier research has indicated that curcumin-induced apoptosis can occur via various pathways, depending on the presence or absence of enhanced levels of free radicals, and may involve caspase-8, caspase-9, or both. Additionally, in some conditions, curcumin-induced apoptosis may occur independently of caspase activation (Bian & Guo, 2020).

Breast cancer

Breast cancer is a prevalent form of cancer among women worldwide, making up about 25% of all female cancer cases, with higher rates in developed countries. It is also the second most common cause of cancer-related deaths in women globally. The antioxidant curcumin, also known as 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, possesses anti-proliferative and apoptotic effects. Curcumin promoted death in MCF-7 cells and G2/M cell cycle stop, decreased cell growth by decreasing microtubule construction dynamics, and triggered the mitotic checkpoint. Curcumin inhibited the expression of the zeste homologue 2 gene through the activation of three key components of the mitogen-activated protein kinase trail: (JNK) c-Jun NH2-terminal kinase extracellular signal-regulated kinase and p38 kinase. Curcumin-induced tumour cell growth suppression is mediated through apoptosis. Curcumin was discovered to decrease the expression of PCNA, Ki-67, and p53 mRNAs in mammary tumour cells, as well as stimulate Bax mRNA expression while downregulating p21 mRNA in the human breast lines of epithelial cells (Talib et al., 2018). The aberrant stimulation of the Wnt/-catenin signalling pathway is linked to the expansion of breast carcinoma, and curcumin reduces the production of -catenin, slug, and cyclin D1, both MDA-MB-231 and MCF-7 cells. Maspin is a suppressor of serine protease that inhibits cancer development and metastasis *in vivo* while also inhibiting mobility and tumour cell incursion *in vitro*. Curcumin boosted maspin gene expression in MCF-7 cells, which was linked with an elevation in p53 protein and a reduction in Bcl-2. Another study found that curcumin decreased Bcl-2 expression in MCF-7 cells by increasing the expression of miR-16 and miR-15a. Also, in curcumin-treated malignant mammary carcinomas, the Alix/AIP-1 protein, which is a paraptosis inhibitory protein, was gradually down-regulated. Mitochondrial superoxide was a significant

early indication in curcumin-triggered paraptosis, and proteasomal failure was primarily accountable for the paraptotic alterations associated with (ER) oestrogen receptor dilatation. Curcumin was also discovered to impede mammary cancer cell attack and motility by spontaneously dropping the activity of integrin 64. The majority of anticancer drugs stimulate nuclear factor- κ B, which regulates proliferation, metastasis and cell survival. Curcumin has been discovered to lower the travelling behaviour of cancerous breast cells, as well as their adhesion, proliferative rate, and invasion, by downregulating the expression of NF- κ B p65. Human epidermal growth factor 2 is an essential oncoprotein found in 15% to 25% of mammary tumours. Curcumin reduced Akt, HER2 oncoprotein, MAPK phosphorylation and NF- κ B impression in both SK-BR-3-hr and BT-474 cells. Curcumin also improved chemotherapy effectiveness by adjusting p53-NF- κ B-p300 dialogue in approval of p53-p300 in malignancy. Curcumin may potentially play a therapeutic effect in inhibiting RON tyrosine kinase-mediated occupation of tumour cells by influencing transcriptional activity and p65 protein expression via NF- κ B (Bimonte et al., 2015).

Curcumin inhibited mammary tumour angiogenesis by inhibiting VEGF impression generated by medroxyprogesterone acetate and osteopontin. Curcumin suppressed 64 signalling and activities by changing its intracellular location and preventing it from interacting with signalling stimulants like Akt and the epidermal growth factor receptor. Moreover, the amalgamation of curcumin and (EGCG) epigallocatechin gallate is effective in each *in vivo* and *in vitro* model of ER-breast cancer. The modulation of (Vascular Endothelial Growth Factor Receptor-1) VEGFR-1 may play a crucial part in anti-tumour actions in these processes (Farghadani & Naidu, 2022).

Prostate cancer

Diseases related to the prostate are the most important disorders found in males, especially in Western countries and prostate cancers are 3rd most common cause of death (Choi et al., 2019). Currently, available therapies (namely; chemotherapy, hormone-therapy radical prostatectomy, or local radiotherapy), although it is effective in curing androgen-depending, localized, prostate cancers are of inadequate efficiency against androgen-independent, metastatic ailment. The goal of chemoprevention is to decrease of rate of cancer incidences, by simultaneously reducing treatment side effects as well as mortality (Teiten et al., 2012). Innovative therapeutic modalities are required to cure several hormone-resilient cancers and to avert the advancement of sensitive to hormones in prostate cancers the hormone-resistant phase. Principal inhibition seems to be a striking tactic to eliminate prostate cancer if the individual reflects the maximum incidence of prostate cancers and minimum advanced growth of vigorous prostatic epithelium to (PIN) prostatic intraepithelial neoplasia, dysplasia, locally intrusive adenocarcinoma and metastatic ailment (Rivera et al., 2017).

Comparison of curcumin with its available equivalents, conforming to its demethoxy counter parts (bisdemethoxycurcumin and demethoxycurcumin) and with its stimulated hydrogenated-metabolites (hexahydrocurcumin, octahydrocurcumin and tetrahydrocurcumin) exhibited structure–activity correlation. The studies demonstrated that a higher number of ortho-methoxy substitutions and a higher degree of hydrogenation of the heptadiene moiety of curcumin particles are accountable for the increased radical inhibiting

capacity of curcuminoids. In comparison, the utmost anti-tumoural and anti-inflammatory capacity of curcuminoids is associated with a lesser degree of hydrogenation, to maximum degree of unsaturation of diketone moiety and the greatest methoxylation stage of the subject molecules. Numerous curcumin analogues have been calculated and analysed as possible androgen-stimulant antagonists to be utilized against androgen-depending and androgen-independent prostate cancerous cells. The experimental studies exhibited that the co-planarity of β -diketone moiety as well as the existence that is a powerful hydrogen bond donor group is vital for the anti-androgenic action of the said curcumin analogues. Through this mechanism, these curcumin analogues are significant agents to control androgen-receptor-mediated prostate cancerous development as they might work as 17α -substituted dihydrotestosterone. Research demonstrated the fact that a progressive composition to activity association for the proposal of fresh curcumin derivatives can be utilized as a likely anti-prostate tumour element. Firstly, aromatic rings are compulsory for anti-androgenic and cytotoxic mechanisms. The C-2' position of the phenyl ring should remain unsubstituted. The C-4' and C-3' positions should be substituted by 3'-methoxy-4'-hydroxy 3' and 4'-dimethoxy substitutes on the phenyl ring. Elongated association results in the damage of anti-androgenic and cytotoxicity action. An unsaturated and conjugated association is essential for the anti-androgenic and cytotoxic actions. Current conclusions led to the proposal of a very particular analogue, which comprised one pentadienone moiety. Reportedly it is said to be fifty times more effective than curcumin in the inhibition potential and growth of the prostate with androgen sensitivity and without cancerous cells of series with sub micro-molar (Dorai et al., 2014).

Curcumin has exhibited a positive impact on the impression intensity of typical prostate indicator protein. In reaction to certain curcumin treatments, the AR-impression was found significantly down-regulated and the AR-binding action to androgen-response of the (prostate-specific antigen protein) PSA gene, as well as the PSA impression in LNCaP cells. This mechanism is linked to removing these cells of critical development benefit and thus this as a phytochemical and non-toxic methodology towards the administration of AR-depending prostate cancers. Numerous analogues of curcumin have been established to act as an androgen-receptor antagonist. This type of downregulation of AR impression and these type blockages of its DNA binding activities by curcumin inhibit the homeobox gene NKX3.1, an androgen-administered NK-class homeobox gene that is said to show significant role in normal prostate carcinogenesis and organogenesis. Anti-cancer mechanisms of curcumin against prostate cancer are shown in Figure 3.

Lung cancer

Lung malignant cells are the majority frequent form of tumour around the globe and the primary factor of cancer-relating fatalities. Despite breakthroughs in treatment, the 5-year survival proportion for all phases joined is only 16%. Non-small cell lung tumour is the most common variety of lung cancer, responsible for over 85% of all incidences. Around 20% of early-stage NSCLC patients are considered therapeutically incurable. Radiation therapy and platinum-based chemotherapy are the usual treatments for those who have modified stage and incurable NSCLC and who have an

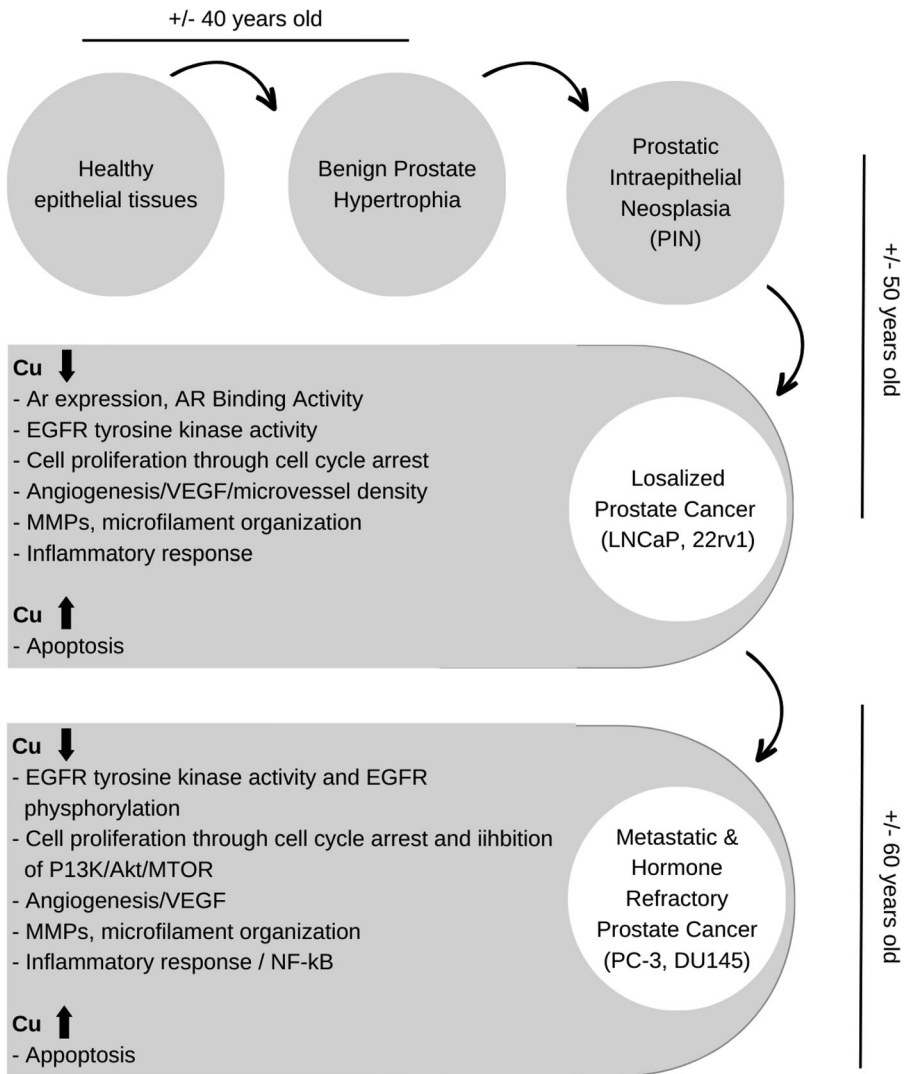


Figure 3. Possible anti-cancer mechanisms of curcumin.

effective performance status. Traditional lung cancer therapy is mostly unsuccessful (LelLelli et al., 2017).

Chemotherapy and radiation can also cause numerous undesirable side effects, some of which are permanent. Long-term fibrosis/radiation pneumonitis and radiation pneumonitis are typical adverse effects of radiotherapy. Platinum-based chemotherapy has hazardous side effects that are dosage-reliant and comprise otologic bone marrow and renal suppression (Mehta et al., 2014).

As a result, research into potential substitutes and less poisonous medicines for lung tumours is ongoing, to reach a better clinical consequence while minimizing therapeutic mortality (Chen et al., 2012). Programmed cell death is a critical step in eukaryotic growth and homeostasis of cells. This process must be tightly controlled since errors

in the apoptotic machinery might prolong cell life, creating a favourable environment for mutation accumulation and genetic instability (Satar et al., 2021).

Cell adhesive molecules are transmembrane proteins that allow cells to attach to various cells or extracellular substances. Endothelial cell impression of numerous cells outside adhesive molecules such as CAM-1 intercellular cell adhesive molecule, endothelial leukocyte CAM-1 and vascular CAM-1 is crucial for tumour progression. Curcumin has been shown in recent research to reduce (TNF) tumour necrosis factor-mediated adherence to endothelial cells by reducing the production of binding proteins via inhibiting NF- κ B (Ye et al., 2012).

TNF has been proven to show a significant function in cancer development, development, and metastasis. TNF is a growth factor for the majority of cancerous cells. Curcumin inhibits protein expression and TNF messenger ribonucleic acid (mRNA) by suppressing TNF expression at both the transcriptional and posttranscriptional stages. Curcumin's suppression of TNF can further decrease NF- κ B activation and consequently cell expansion (Zhan et al., 2017).

In the human lung, curcumin triggers apoptosis in tumour cells in a variety of ways, including simultaneous stimulation of apoptosis and cell death with apigenin, as well as by inhibiting cell cycle progression in A549 cells during the growth/mitotic (G2/M) phase. Curcumin can depolymerize interphase microtubules and impede the reassembly of freezing depolymerized microtubules by adhering to pure microtubules, according to the researchers. Curcumin, along with other naturally occurring chemicals, might aid in the development of anticancer combination medicines from inexpensive and widely accessible nutraceuticals. Moreover, co-culturing curcumin with immediately reproducing tumour cells induces cell death without damaging healthy tissue and controls tumour development by making tumours more susceptible to pharmacologic cell-killing therapies. Curcumin dramatically reduces micro ribonucleic acid (miRNA) production in A549 cells, as indicated by straight repression of caspase-10, which has been established as a receptor of mRNA-186. This causes apoptosis in 549 cells via the mRNA mechanism (Li et al., 2014).

Curcumin increases the impression of the cyclic-dependent kinase suppressor genes p27 and p21 while inhibiting the impression of several other genes such as cyclin D1, Bcl-2, CDK4, CDK2, and CDK6. Curcumin's anticancer effect is primarily mediated by the upregulation of GADD45 and GADD153. Curcumin's effects on (MMC) mitomycin-C-mediated cytotoxicity have also been investigated. Curcumin increased MMC-mediated cytotoxicity via lowering TP impression and activation of ERK1/2. Curcumin reduces Protein levels of ERK1/2 and MKK1/2, two mitogen-activated protein kinases in response to MMC in human cell types for NSCLC H1650 and H1975. Moreover, curcumin reduces MMC-triggered TP protein levels via increasing protein instability and TP mRNA. Augmentation of ERK1/2 stimulation by constitutively vigorous (MKK1/2-CA) MKK1/2 enhances cell survival and TP pr levels of protein in cells co-treated by MMC and curcumin. Small interfering RNA (siRNA)-mediated TP inhibition dramatically improves cell development inhibition and MMC-induced cell death. Curcumin causes a rapid drop in activation of Caspase-3 and Caspase-9, a reduction in the potential of the mitochondrial membrane, and the cytosolic release of cytochrome C are all events that cause death via activating the mitochondrial ROS-mediated pathway. Curcumin, interestingly, dose- and time-dependently, increases the percentage of apoptotic cells

in human A549 cells. In A549 cells, curcumin elevates the Bax/Bcl-2 ratio by upregulating Bax protein expression and downregulating Bcl-2 expression.

Chemo prevention is distinct as the use of natural or manufactured substances to inhibit, delay, or invert carcinogenesis. Chemo-defensive agents have minimal side effects and adverse effects, and they counter carcinogens. Curcumin, as a separate kind of chemo-preventive agent that possesses protective abilities cells from carcinogenesis and mutagenesis. By generating Ras protein, the reticular activating system oncogene is thought to be a crucial factor in carcinogenesis. To prolong their biological activity, Ras proteins must be isoprenylated at a conserved cysteine residue at the carboxyl terminus. Farnesyl protein transferase (FPTase), an isoprenyl group donor is one of the primary enzymes related to Ras oncogene activation via oxidative metabolism. Curcumin may be able to shut off the Ras oncogene and have a significant impact in inhibiting carcinogenesis by suppressing FPTase activity (Tang et al., 2021).

Pancreatic cancer

Pancreatic tumour is one of the worst forms of cancer worldwide and the bulk of patients are detected not on time for therapeutic surgery. Yet in individuals who have had curative resection, the disease return speed is more than eighty percent within 2 years. Since 1997, when a Gemcitabine monotherapy has been demonstrated to be safe in randomized phase III studies and considerably alleviated cancer-related complaints as compared to 5-fluorouracil, systemic gemcitabine-based chemotherapy has been the normal treatment for individuals with higher pancreatic malignancy (Ma et al., 2014). Several attempts have been undertaken over the last decade to enhance the overall life expectancy of individuals using this illness by merging gemcitabine with a second cytotoxic drug. The majority of these gemcitabine combination treatments, however, have failed to provide substantial survival improvements above gemcitabine mono therapy. As a result, alternative techniques, other than just adding more cytotoxic agents to gemcitabine, are required. Furthermore, while selecting palliative chemotherapy, it is critical to examine the balance of quality and efficacy of life, as patients with pancreatic cancer frequently experience cancer-related indications such as appetite loss, exhaustion, and discomfort. In contrast to traditional cytotoxic medications, which can cause vomiting, nausea, or fatigue, curcumin has low toxicity (Kanai, 2014). This is a significant benefit for treating pancreatic disease patients, who often have low tolerance to rigorous therapy as a result of clinical circumstances. Another benefit of this mediator is its safety. The World Health Organization and the Food and Drug Administration have both confirmed curcumin's safety. Curcumin has been shown to influence the activity of a broad variety of molecules involved in cancer advancement, with over 30 molecular targets discovered so far. Among these compounds, NF- κ B appears to be one of curcumin's key targets. Importantly, recent research has shown that changes in miRNA expression levels after curcumin or a curcumin analogue therapy are important in the anticancer actions of these drugs. Curcumin, for example, can increase the expression of micro RNA-200, which regulates the epithelial-to-mesenchymal transition and cancer progression. Curcumin, on the other hand, can suppress the expression of miR-21, which is abundantly expressed in several cancers, it is hypothesized to be an oncogenic miRNA that causes pancreatic cancer. Angiogenesis is a complicated

procedure that is dependent on top of the interplay of various growth factors including (vascular endothelial growth factor), fibroblast growth factor, angiopoietin, tumour growth factor and platelet-derived growth factor (Bimonte et al., 2016). Nuclear factor κ -B and hypoxia are transcription factors induced factor influence the expression of these growth factors. HSP90, a chaperone protein plays a significant role in the stability as well as activation of more than a few transcription factors. Increased cytokines, the presence of hypoxia, the activation of proto-oncogenes, and the suppression of tumour inhibitor genes all activate NF- κ B and HIF-1, resulting in the production and release of angiogenic factors in pancreatic cancer. Hence, inhibiting angiogenesis by targeting HIF-1 and NF- κ B is a sensible approach for pancreatic cancer treatment (Sun et al., 2013).

Previous research found that curcumin, UBS109 and EF31 have antiangiogenic properties on PANC-1 and MIA PaCa-2 cells utilizing three different assays: egg CAM test, HUVEC tube formation, and *in vivo* matrigel analysis. When the tubes are formed experiment media from pancreatic cells treated with curcumin UBS 109 and EF31 dramatically reduced HUVEC's capacity to form tubes as contrasted to medium from the contemporaneous control and treated pancreatic cancer cells (fresh medium). In the media from pancreatic cells treated with curcumin, UBS109, EF31, or HUVEC generated considerably fewer tubes than contemporaneous control cells. The antiangiogenic impact of UBS109 or EF31 was much higher than that of curcumin. The culture PANC-1 and MIA PaCa-2 cell line media (simultaneous control) significantly improved angiogenesis in the egg CAM experiment as compared to the middle from curcumin-treated cells. When compared to the control media and the medium from the curcumin-treated cell lines, UBS109 and EF31 suppressed angiogenesis. Curcumin was outperformed by UBS109 and EF31 in terms of antiangiogenic activity. In the matrigel assay, mice treated with UBS109 or EF31 showed considerable suppression of angiogenesis as compared to untreated animals. Both cell lines had comparable results (Osterman et al., 2015).

Colon cancer

Colorectal cancer, which is among the major reasons for tumour mortalities in women and men in the United States, claims approximately 56,000 lives each year. Though nutritious interference may not be enough to secure the risk of high patients from developing colon cancer, a complementary and substitute actual methodology for a minor cure has been to pinpoint chemo-preventive agent's therapeutic potential and calculate them in high-threat patients with nutritious involvement simultaneously (McFadden et al., 2015).

Curcumin, the primary pigment found in turmeric, has antioxidant as well as anti-inflammatory qualities. Curcumin has been shown to suppress DNA adduct brought on by benzo(a)pyrene formulation as well as the progress of fur cancers in addition to tumour promotion and Epidermal DNA synthesis induced by TPA3. Curcumin has a substantial inhibitory impact on cell growth in the human colon cancer cell lines HCT-29 and HCT-15 (Guo et al., 2018).

Many PG (Prostaglandins) synthesis inhibitors, including ibuprofen, aspirin, sulindac, and piroxicam, have previously been proven to reduce colon carcinogenesis in

experimental animal model studies. Colon carcinogenesis suppression was strongly linked with a reduction in COX activity in colon cancers. Curcumin may potentially limit cell growth and increase apoptosis, according to evidence. Curcumin suppresses colon cancer cell growth in vitro, irrespective of its capability to decrease PG production. Additionally, a transition of colonic epithelium into adenocarcinomas and adenomas has been linked to increasing apoptosis suppression, indicating that apoptosis inhibition in colon carcinogenesis may contribute to cancer development and increase neoplastic advancement (Buhrmann et al., 2014).

Curcumin, a naturally existing antioxidant and anti-inflammatory mediator given as a nutritional addition throughout the promotion period still hinders tumour genesis in the colon, implying that curcumin management may slow the development/growth of pre-existing malignant tumours in the colon. This also shows that this product might be effective as a chemo-preventive therapy for patients who are at greater threat of emerging colon cancer, like sufferers with polyps. Synthetic NSAIDs, such as sulindac and piroxicam, protect rats from colon cancer throughout the progression/promotion stage. Curcumin, unlike artificial NSAIDs, does not cause gastrointestinal damage, even at extremely high dosages, which may give it an edge over synthetic medicines (Wang et al., 2016).

In terms of chemo-preventive effect, curcumin has a wide range of cellular, metabolic, and molecular actions, including the suppression of arachidonic acid production and subsequent conversion to eicosanoids. Our research has shown that dietary curcumin suppresses phosphor-lipase A2 in tumours anti-intestinal mucosa, causing the Arachidonic acid discharge from phospholipids, affects LOX and COX activity, and modulates PGE2 levels. Various lines of indication also point to that the process of action of curcumin is not restricted to PG suppression. A study discovered that dietary curcumin suppresses LOX activity as well as the generation of LOX byproducts like 5(S), 8(S), 12 and 15(S)-HETEs the tumours and intestinal mucosa (Zhang et al., 2016).

Significantly, LOX metabolites such as 12(S)-HETE have been demonstrated to boost cancer cell adherence, drive tumour cell dissemination, and increase metastatic potential. TPA-induced hyper-proliferation and tumour growth were also found to have a positive connection with 8(S)-HETE levels. Moreover, curcumin suppresses the activation of nuclear factor B and activator protein-1 as well as many enzymes and mediators induced in cell mitogenic signal transduction pathways. In colonic cancer cell lines HT-29 and HCT-15, curcumin suppresses cell proliferation and produces cell cycle alterations, and this impact is independent of its potential to decrease PG production. Curcumin's suppressive effects during the progression/elevation phase of chemically triggered carcinogenesis are related to elevated cell death, indicating that enhanced cell death by Apoptosis could be among the ways by which nutritional curcumin influences this suppression. The findings of this and other research support the idea that many chemo-preventive drugs can trigger apoptosis. This has undoubtedly been demonstrated for NSAIDs and other drugs that reduce colon carcinogenesis, indicating that reactions to these compounds may influence chemo-preventive effects. Curcumin's actions are similar to those of NSAIDs, and it appears to work aggressively by inhibiting arachidonate metabolism, lowering cellular proliferation, and triggering mortality (Selvam et al., 2019).

Oral cancer

Oropharyngeal and oral cancers, the great majority of which are squamous cell carcinomas (SCCs), are among the top ten malignancies in the world (Nagpal & Sood, 2013). Despite comprehensive treatment (radiation, surgery, and/or chemotherapy), OSCC is linked with second primary tumours and recurrence, which are responsible for dismal overall survival rates (50%) that have not considerably improved over the last three decades. This might be ascribed in part to genetic susceptibility, which can be a major concern in the pathogenesis of oral cancer because tumours frequently form within pre-neoplastic domains of genetically manipulated cells. Moreover, components of the tumour microenvironment that are in constant molecular interaction with cancer cells have been demonstrated to accelerate tumour invasion and dissemination, and hence play a critical role in the poor prognosis of OSCC patients. Patients with OSCC who appear to have been effectively treated must deal with substantial side effects, particularly after radiation. As a result, there have been concentrated efforts to identify alternative medicines that result in better clinical outcomes and reduced morbidity among such patients (Kabir et al., 2021).

Curcumin has been utilized in traditional oriental herbal medicine over many years as a therapeutic agent. Epidemiologic research poses an association between the broad procedure of nutritional curcumin and the small occurrence of gastrointestinal mucosal distortions in south-east Asia. These findings may be explained by the concurrent excessive frequent use of cigarettes, alcohol, and other carcinogenic drugs. Curcumin has been deemed pharmacologically safe due to its long history of use as a spice for food at levels of up to 100 mg per day. Moreover, its tolerability and safety were demonstrated in phase I investigations at dosages as high as 8 g per day (Gupta et al., 2013).

There is evidence of curcumin in recent research to have anti-cancer activity by modulating several critical components of the tumour microenvironment that govern tumour growth. Curcumin appears to modify fibroblast cell behaviour such as migration, proliferation, and apoptosis, according to increasing research. Curcumin also alters inflammatory processes and immune cells by increasing the cytotoxicity of CD8 (+) T lymphocytes against malignancies (Kim et al., 2012).

A recent research investigated the impact of different dosages of curcumin on OSCC cells. Curcumin (0–40 micro molar) was applied to cells for 24 h, and cell feasibility was determined using the MTT test. Curcumin inhibited OSCC cell survival in a concentration-dependent approach, according to the findings. Curcumin doses ranging from 10 to 40 micro molar effectively triggered the death of OSCC cells. Concentrations ranging from ten micromolars to twenty micromolars exhibited inhibitory activity on the survival of OSCC cells. The impact of both dosages (10 and 20 micro molar) on OSCC cell shape was investigated further. Following twenty-four hours, twenty micro molar curcumin produced cell rounding, shrinkage, and partial detachment, showing that curcumin's cytotoxic effects on OSCC cells might be apoptotic. Curcumin-treated cells, on the other hand, were morphologically different from apoptotic cells and displayed cytoplasmic vacuolization. FACS measurement of the sub-G0/G1 population was undertaken to determine if the reduction in OSCC viability caused by ten micro molar curcumin happened by apoptosis. The proportion of sub-G1 cells, which indicate apoptotic cells, does not rise significantly (3.9%) in curcumin-treated cells. This apoptotic

cell ratio did not explain the thirty percent loss in cell viability seen using the MTT test, showing that a non-apoptotic form of cell mortality predominates in OSCC cells after ten micro molar curcumin therapy. Treatment with thirty micro molar Taxol, on the other hand, is known to trigger apoptosis in cancerous cells (Zlotogorski et al., 2013).

In addition to promoting IGFBP-5 promoter activity in SAS oral cancer cells, curcumin enhances IGFBP-5 impression in a range of oral keratinocytes. According to promoter deletion mapping, curcumin-mediated IGFBP-5 overexpression needs a C/EBP-binding element (nt-71 to nt-59 comparative to the transcription process start point). Chromatin immunoprecipitation experiments revealed that curcumin significantly increased the *in vivo* requirement of C/EBP in this area. Curcumin improved nuclear IGFBP-5 and C/EBP expression through p38 stimulation, which was inhibited by SB203580 administration. In addition, MKK6 expression increased IGFBP-5 agent movement and impression by activating C/EBP and p38. Ultimately, CUR-induced IGFBP-5 impression is linked to a reduction in xenograft tumourigenesis in rodents caused by oral cancerous cells. Curcumin stimulates p38, which then activates the C/EBP trans-activator by engaging with binding sites in the IGFBP-5 promoter. The ensuing increase in IGFBP-5 and C/EBP caused by curcumin is essential for preventing oral carcinogenesis (Shanmugam et al., 2015).

Cervical cancer

Cervical cancer is one of the most frequent and lethal malignancies in females across the world, and it is linked to chronic Human Papillomavirus infection. In raft cultures, organotypic produced from a cell line derived from cervical intraepithelial neoplasia type I, BaP treatment increases viral morphogenesis in cells with the high-risk HPVs infected 16, 31 and 18. Furthermore, micro RNAs, which are non-coding little RNAs that influence the role that protein-coding genes play in humans a significant in the development of cancer. Confrontation to radio/chemotherapies, which results in an advanced type of cancer, necessitates the evolution of innovative beneficial approaches to overcome and chemo-resistance to increase the average lifespan of patients (Ghasemi et al., 2019).

Many studies and pre-clinical trials have shown that chemotherapeutic and chemopreventive effects are dose-dependent. Curcumin has harmful effects on cells on cells from cervical cancer that are its activity is concentration and time-dependent is greater in HPV-infected cells. Curcumin has been shown to block HPV18 transcription by specifically decreasing AP-1 activity, hence reversing the dynamics of fra-1 and c-fos and expression in cervical cancerous cells (Sreekanth et al., 2011).

Curcumin's superior inhibitory impact against cervical cancer cells was attributed to its suppression of telomerase expression, the ERK and Ras signalling pathways, COX-2, cyclin D1, and iNOS activity, as well as the mitochondrial system. Curcumin, interestingly, worked on many pathways and, as a result of pretreatment, was able to reverse the regenerative cervical cancer cells' impacts. According to new proteomic research, curcumin causes substantial alterations in tumour-related proteins linked with cell cycle, cell metabolism, and carcinogenicity in HeLa cells. Curcumin also functions as a sensitizer for radiation and chemotherapy in cervical cancer treatment. Curcumin has been shown to play a comprehensive cellular suppressive functional role in a three-dimensional carcinoma raft culture system. Curcumin suppressed cellular proliferation,

triggered apoptosis, lowered the expression of HPV onco proteins, and restored tumour inhibitor proteins (Roy & Mukherjee, 2014).

Several investigations have revealed that when 4–12 g/day of curcumin was provided, a trace quantity of curcumin was detectable in human serum. While curcumin has aroused tremendous attention due to its wide range of physiological actions, its low bioavailability limits its therapeutic use (Singh & Singh, 2011). In clinical studies, it has shown no harm to healthy organs at greater levels such as 8 g/day. Nevertheless, it has low systemic accessibility, poor pharmacokinetics, poor penetrability, a fast metabolic rate, metabolic product inactivity, and quick excretion and clearance from the body (Zaman et al., 2016).

Leukaemia

Leukaemia is related to a heterogeneous group of haematological malignancies that mainly include bone marrow and peripheral blood. 8% of all cases of cancer are due to leukaemia which includes all age groups and executes heavy expense during its identification and therapy (Kouhpeikar et al., 2019). There are many selections for the management of leukaemia such as radiation therapy, chemotherapy and bone marrow transplantation. Common therapy approaches that are used for AML contain an arrangement of daunorubicin (DNR) and cytarabine. Likewise, combinations of four standard medications are used in ALL including vincristine, asparaginase, corticosteroids and anthracycline usually (DOX) doxorubicin or DNR. Regardless of improvements in therapy choices for leukaemia, patients undergo many difficulties including poor prognosis, degeneration of disease and high death rate. Radiotherapy and chemotherapy frequently have side effects such as mouth ulcers, hair loss, vomiting, loss of appetite, diarrhoea neurological disorders and liver damage. So, identifying novel therapeutic methodologies with greater efficacy and lesser side effects for leukaemia is important. In this regard, curcumin is a highly significant phytochemical (Yang et al., 2012).

Chronic myeloid leukaemia (CML)

CML is considered a (BCR-ABL) breakpoint cluster region-Abelson fusion gene that is accountable for the pathogenesis of chronic myeloid leukaemia. BCR-ABL is composed of three breakpoint cluster regions: (1) major (M-bcr), (2) minor, (3) micro (μ -bcr). M-bar is the main breakpoint which codes 210 kDa protein and also creates a 190 kDa protein but μ -bcr codes for a 230 kDa protein. For the pathogenesis of CML, the P210 BCR-ABL protein is important (Martínez-Castillo et al., 2018).

It is an appealing therapeutic strategy to target this oncoprotein. When the effects of curcumin were observed on K562 cells it was determined that curcumin reduced the proliferation of K562 cells by suppressing p210 BCR-ABL thus causing a reduction in Ras signal transduction pathways. So, curcumin increases the efficiency of (IM) imatinib mesylate in the CML cells. K562 cells were experimented with various meditations of imatinib mesylate alone and with curcumin (30 μ M). The MTT assay showed that curcumin considerably enhanced the toxicity of imatinib mesylate. Western blotting indicated that IM alone and a combination of IM plus of the curcumin both suppressed the impression of survivin, p210 BCR-ABL, NF- κ B subunits as p65 and p50 and heat

shock protein 90, e.g. Hsp90. Moreover, they revealed that combined treatment of curcumin and 1M enhanced the activity of caspases 8, 9 and 3. The researchers also discovered that a combination of curcumin and phosphorothioate antisense oligonucleotides resulted in a synergistic inhibition of K562 cell proliferation by suppressing NF- κ B, P210 BCR-ABL, and Hsp90. (Mutlu Altundağ et al., 2018).

Curcumin reduced levels of the anti-apoptotic markers such as X-linked and BCL-2 inhibitors of certain apoptosis proteins. In addition, curcumin enhanced the expression of (tumour suppressor protein) p73 causing apoptosis into k562 cells. NF- κ B is a transcription aspect that disturbs biological procedures including cell cycle progression and cell survival. During the pathogenesis of leukaemia, NF- κ B is very important. Reports revealed the effects of curcumin in K562 cells on 84 TNF- α -activated genes of the NF- κ B trails. Of the genes examined, an impression of 10 mRNAs is enhanced and 29 are reduced by the curcumin (Bilajac et al., 2023).

Acute myeloid leukaemia

The classification of acute myeloid leukaemia is done into myeloblastic M0, M0 with maturation M2, M0 without maturation M1, promyelocytic M3, myelomonocytic M4, erythroleukaemia M6, megakaryocytic M7 and monocytic M5 according to French American British Classification system. Curcumin synergistically reduced cell proliferation and enhanced DNR's cytotoxic effects by cell cycle seizure into G1/the Synthesis phase. Caspase-3 activation is induced and reduced impression of both protein and Bcl-2 mRNA were observed by curcumin. The transfer of methyl group to DNA is catalysed by DNA methyltransferase 1 which is the mediator of DNA methylation. The pathogenesis of cancer is due to aberrant DNA methylation that causes tumour inhibitor gene silencing and it has been testified in many cancers (Yu et al., 2013).

So, the establishment of new techniques of DNA methylation suppressors with a low range of toxicity is needed. In vitro and *in vivo*, a new study has been conducted to exhibit the impacts of curcumin on the activity of DNMT in AML cells. Curcumin decreased the DNMT activity by suppressing the NF- κ B component and Transcription Factor1 (Sp1) which causes the recurrence of p15INK4B acts as a tumour inhibitor. In addition, when management of curcumin is done in mice it significantly decreases AML tumour growth (Martínez-Castillo et al., 2018).

Acute lymphoblastic leukaemia

Presently chronic lymphocytic leukaemia is not curable with current treatment modalities. Many side effects of anti-leukaemic drugs and haematopoietic stem cell transplantation are also currently present. Curcumin has multi-target actions and anti-carcinogenic properties and is valuable in leukaemia in the initial stages of chronic lymphocytic leukaemia. It inhibits the development of the disease, reduces CLL B-cell counts and it has also a synergistic effect when used with conventional anti-cancerous drugs in addition to reducing their side effects and dose. For repairing DNA, (PARP1) Poly (ADP-ribose) polymerase-1 is a protein that shows a significant role. PARP1 takes part in various pathological processes such as cell existence, angiogenesis, inflammation, and cell death. Overexpression of PARP1 is found in numerous primary cancer cell lines

of humans. Researchers found that curcumin lowers the propagation of RS4 and REH such as 11 cells that is an ALL cell line by cleavage of pathways of PARP1. Curcumin controls DNA methylation in cells of AML by suppressing the expression of (DNA methyl transferases-1) DNMT1, which results in stimulation of p15 (a cancer suppressor gene) that results in ALL cell apoptosis (Kuttikrishnan et al., 2019).

Curcumin lowers the activation of ABL/STAT5 AKT/mTOR. In addition, curcumin suppresses the expression of BCR/ABL and lowers the ratio of BAX to BCL-2. In the SUP-B15 cell line, curcumin has synergistic anti-tumour effects with the imatinib but curcumin also reduces cell propagation in the samples that were attained from imatinib-resistant and recently identified patients. Curcumin enhanced populations of T cells e.g. both CD8 and CD4 and NK cells, these cell types are intricate eradication of tumour carcinoma through immunomodulation. Curcumin also lowered the ALC due to immune response induction with elevating CD8, NK and CD4 cell numbers. At stage 0/1, curcumin efficiency with arabinoside was observed in 10 patients in the current study. Arabinoside can induce an immune response and it has both anti-inflammatory and proapoptotic effects. For 6 months, Ribraxx (2 g) and curcumin (6 g) were given to the patients at stage 0/1. The combination of arabinoside and curcumin decreased ALC (20%) in patients by 22% while CD8 and CD4-T cells increased. In addition, a clinical trial of Phase II examining the effects of cholecalciferol and curcumin combination in treating patients with formerly untreated Stage 0-II of CLL is ongoing (Guo et al., 2015).

Since curcumin has less bioavailability, research should be directed to form new curcumin formulations with the help of nanotechnology by chemically changing the hydrophobic component of the curcumin or by encapsulating or combining it with other therapeutics. Curcumin should be used for a longer time duration if it is used in anti-cancer therapy. To ensure the safety of high-dose administration of curcumin, there are no long-term clinical trials used currently. More long-term clinical trials should be done to assess the safety of higher doses of curcumin to ensure the utility of curcumin in chronic lymphocytic leukaemia and any cancer as an anticancer drug (Olivas-Aguirre et al., 2021).

Bone cancer

Curcumin plays an important role in many therapeutic actions and certain biological actions such as anti-oxidant, thrombosuppressive, chemo-preventive, anti-infectious, anti-inflammatory, anti-arthritic, and anti-carcinogenic properties. For example, over 40 clinical trials of curcumin have been done for the treatment of many human cancers and other inflammatory diseases. When a high dose of curcumin is administered in an organism then it is well tolerated due to its various biological activities (Kamble et al., 2020).

Curcumin controls many molecular targets in a diverse variety of cells that include transcription factors, e.g. β -catenin, activating protein-1, Peroxisome proliferator-activated receptor nuclear Factor- κ B. Lowering NF- κ B activity is the main biological effect of curcumin during which NF- κ B has to retain its bond with I κ B (inhibitor of NF- κ B) because curcumin obstructs the degradation and phosphorylation of I κ B α (Zhao et al., 2021).

The inactivated form of NF- κ B/I κ B complex is retained within cytoplasm so it cannot enter the nucleus. In the anti-cancer activities of curcumin, it is important to inactivate

signalling pathways of NF- κ B because NF- κ B is higher in tumour cells than the normal cells and this causes the formation of carcinogenesis like metastasis, malignancy, anti-apoptotic genes and tumour promotion. Due to the inactivation of NF- κ B, curcumin suppresses the expression of certain genetic products that are related to carcinogenesis such as inducible cyclooxygenase (COX-2), cell cycle proteins, e.g. cyclin p21 and D1 and Bcl-2. In addition, curcumin disrupts the activity of certain enzymes by downregulating their expression including inducible nitric oxide (NO) synthase and lipoxygenase. Moreover, curcumin also changes the expression of various cytokines, e.g. tumour necrosis factor- α , interleukin-1 (IL-1), IL-6 and chemokines, such as the receptor for epidermal growth factor, oestrogen receptor- α and low-density lipoprotein receptor and adhesion molecules of the cell surface (Dhatchayani et al., 2020).

Metastasis is a process that involves a sequence of events including invasion in circulations of blood and lymph, separation of primary tumour cells and metastatic site homing. For the propagation and adherence of cancer cells, bone provides a suitable specific microenvironment. The progression of cancer cells is stimulated by the profusion of various ions, cytokines and certain growth factors and it is just because of higher vascularity of bones. Bone metastasis causes destructive lesions in bone resulting in pain, hypercalcemia, morbidity, fractures and a significant decrease in the life of patients with certain diseases. For bone metastasis treatment, certain anti-cancerous therapies including radiotherapy, surgical resection and chemotherapy are used. Major side effects and increase in patient morbidity are linked with these invasive approaches. Cancer therapies that are based on alternative drugs are inadequate due to a deficiency of selections for the directed distribution of the drug that is directly injected into the bone at the metastatic site. So having a drug delivery system that can effectively deliver anti-cancer agents and specifically target the bone microenvironment would be a significant breakthrough. Nanoparticle-mediated targeted delivery of chemotherapeutic agents to specific sites is a promising approach to managing the toxic effects of certain drugs and minimizing the frequency of administration (Chang et al., 2014).

During bone metastasis, nanoparticles are used for drug delivery and active targeting to the site of tumour development by using the affinity between bone tissues and nanoparticles increasing the rate of accumulation of drug in bones. At the tumour site in the bone, medications or drug carriers conjugated with bisphosphonates (BPs) are accumulated to a higher extent during the bone-targeted drug delivery system. Curcumin has been used as an anti-cancer agent and it is a good suppressor of cyclooxygenase-2, activated protein-1 like AP-1, osteoclastogenesis, RANK signalling and expression of growth factor receptors in clinical studies. Osteolytic bone tumours are known to exploit the localized bone microenvironment by releasing pro-inflammatory factors that affect both osteoclasts and tumour cells, thereby promoting tumour growth. Hence, we assume that at the bone metastatic tumour sites, the release of curcumin can lower tumour invasion and growth by performing a dual action (1) by terminating metastatic cancer cells that are sited in the bone microenvironment and (2) by lowering bone resorption simultaneously so it disrupts the cycle of cytokine release that is self-perpetuating because it can trigger the growth of carcinomas (Chang et al., 2014).

This study is meant to form and design ALN-conjugated micelles that are encumbered with curcumin for their targeted delivery to bone during this study. In the bone microenvironment, ALN conjugation can cause an increase in localized accumulation of

micelles. This results in efficient therapy by lowering the dose and frequency of dose because of a targeted drug delivery system (Doan et al., 2017).

To eliminate metastatic bone cancer, the combination of bisphosphonates and curcumin plays a synergistic role. In an ovariectomized osteoporotic rat model, a combination therapy of raw curcumin (unformulated) and alendronate has been found to have synergistic anti-bone-resorptive effects. The combination therapy significantly increased bone density when compared to the groups that received curcumin only or alendronate only. Because of its ability to form stable micelles and biocompatibility, Pluronic F127 triblock copolymer was chosen to formulate curcumin-loaded micelles (Xu et al., 2019).

The study followed an organized approach to chemically modify Pluronic F127 with some alendronate and then fabricate curcumin-loaded micelles. The hydroxyl group present in Pluronic F127 was found to be converted into a carboxyl group by using a carbodiimide-mediated reaction and succinic anhydride. The carboxylic terminals of the HOOC-Pluronic-COOH during alendronate conjugation show higher efficiency because very low initial HOOC-Pluronic-COOH were found during final conjugate when observed by ¹H NMR. Conjugation reaction success is due to the qualitative success of ³¹P NMR of the ALN-Pluronic-ALN. Monodispersed nanoparticles are yielded due to conjugation of ALN-Pluronic-ALN from the preparation of curcumin micelle and it was confirmed by the DLS particle size measurement. In vitro, HA binding affinity study was used to demonstrate the affinity of Cur-ALN-NPs to bones. Although the primary objective of utilizing this technology was to transport curcumin, these developed nano-carriers can also serve as a delivery platform for various agents to bones for non-cancerous applications. Additionally, the carbodiimide method employed for conjugating alendronate to Pluronic F127 can serve as a model for binding alendronate or other bisphosphonates to other polymers for diverse drug delivery applications (Verma et al., 2019).

Thymic cancer

Thymic malignancy is a type of thymic epithelial cancer that is an infrequent malignant tumour obtained from mediastinum antierius that is attached to the pericardium and the aorta is closely related to it. The current research is dedicated to the natural compound and it is meant to discover effective treatment with minimum side effects of thymic carcinoma (Hamzehzadeh et al., 2018).

For 24 h, the cell line of thymic carcinoma TC1889 was used with curcumin. Curcumin reduced cell viability of TC1889 cells, e.g. 1 μ M, p ranges from 0.05–5 and 10 μ M, $p < .001$. Moreover, the influence of curcumin treatment on normal thymocytes was also checked. There was no significant change was observed in normal cell viability when treated with S1b, 5- μ M, and 1. While 10 μ M reduced MTEC1 cell viability. There was 4.908 μ M of IC₅₀ of Curcumin. So in the next experiments, TC1889 was treated with 5- μ M concentration of curcumin. Curcumin suppressed the impression level of cyclin E and c-myc that was shown by the western blot method. In addition, Curcumin increased cell apoptotic capacity. Moreover, curcumin altered the impression of anti-apoptotic and pre-apoptotic proteins. In the curcumin treatment group, the impression of Bcl-2 was lowered while the impression of cleaved caspase-nine, and Bax cleaved caspase-three was increased. Moreover, we also

Table 1. Different studies showing the anti-cancer mechanisms of curcumin summarized.

Type of cancer	Mechanism	Dosage	Source/Intervention	Reference
Gastric	Curcumin was found to inhibit the accumulation of myeloid-derived suppressor cells (MDSCs) and their interaction with cancer cells. It was observed to induce the differentiation of MDSCs, leading to the inhibition of tumour growth.	2% curcumin in diet (20 g of curcumin per kg diet) for four weeks	Curcumin	Tu et al. (2012)
Gastric	Substantial changes of 75 proteins in cells treated with curcumin and protein-protein interactions affected by curcumin in gastric cancer cells.	1, 5, 10 & 30 micro moles of curcumin for 96 h	Curcumin	Cai et al. (2013)
Breast	In vitro cytotoxic activity of curcumin demonstrated its anticancer properties against the MCF-7 cell line.	20 µg/ml	Heterocyclic curcumin derivatives	Borik et al. (2018)
Breast	Inhibition of Akt, STAT3, and HER2/ Neu pathways and induction of apoptosis	10 µM	Curcumin derivatives	Cridge et al. (2013)
Prostate	Curcumin increases TAC and reduce SOD activity in the plasma	347 mg of curcumin, 84 mg desmethoxy-curcumin, 9 mg bisdemethoxycurcumin and placebo capsule 500 mg	Curcumin and curcuminoids	Hejazi et al. (2016)
Prostate	Demonstrated cytotoxic activity against PC-3 and LNCaP human prostate cancer cell lines in vitro.	0.5 and 0.1 µM	Curcumin derivatives	Elias et al. (2016)
Colon	Induces the apoptosis in (HCT116-cells) colon cancer cells	8 g per day	Dimethoxy-curcumin (DMC)	Tamvakopoulos et al. (2007)
Colon	The cell proliferation and development of aberrant crypt foci (ACF) were inhibited.	20 mg per kg of body weight, two times a week, for a period of 3 weeks	Tetrahydrocurcumin (THC) (Curcumin derivative)	Mbese et al. (2019)
Lung	Suppressed the proliferation of tumour cells and stimulated death of tumour cells.	100 mg per kg per day by intraperitoneal injections. Consecutive 15 days.	Curcumin	Tang et al. (2021)
Lung	Curcumin-induced apoptotic cell death in non-small cell lung cancer (NSCLC) cells by activating caspase-3 and -7.	0.78–100 µM, 48 h	Curcumin	Tunc et al. (2017)
Lung	Curcumin-induced DNA damage and inhibited invasion and migration of NCI-H460 human lung cancer cells.	2 µM	Curcumin	Chiang et al. (2015)
Pancreatic	Sensitization of gemcitabine and inhibition of growth and metastasis in pancreatic cancer	0.5–2 mg curcumin in 10 mg superparamagnetic iron oxide nanoparticles solution	Curcumin	Khan et al. (2019)
Oral	Inhibition of expression of oncogenes (cyclin D1), suppresses the expression of epithelial-mesenchymal transition markers in oral cancer cells.	PAC 0–10 µM, for 24 h	Curcumin analogue: PAC (3,5-Bis (4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperidone)	Semlali et al. (2021)
Oral	Inhibition of HGF-induced EMT and cell motility in HSC-4 and Ca9-22 cells via c-Met blockade	20 ng per ml hepatocyte growth factor and 15 micro moles of curcumin 48 h.	Curcumin	Ohnishi et al. (2020)
Cervical	Cytotoxic effect of curcumin-loaded FA-adorned hyper-branched polyglycerol @Fe ₃ O ₄ nanoparticles on HeLa cells and reduction in viability of cancer cells	-	Folic acid-adorned curcumin-loaded iron oxide nanoparticles	Ramezani et al. (2022)
Blood	Decreased ALC (20%) in patients while CD8 and CD4-T cells increased	6 months, Ribraxx (arabinoxylan) 2 g and curcumin 6 g	Curcumin and curcumin analogue arabinoxylan	Guo et al. (2015)

Table 2. Clinical trials of curcumin (combined treatments) against various cancers.

Type of cancer	Clinical trial period	Intervention	Results	Reference
Prostate	6 months	40 mg soy-isoflavones with 100 mg curcumin	Decrease in PSA levels	Ide et al. (2010)
Prostate	1 year	Nanocurcumin 120 mg per day	Non-significant reduction in the rate of proctitis	Saadipoor et al. (2019)
Breast	12 weeks	300 mg Curcumin combined with Paclitaxel 80 mg per m ² of body surface area (Intravenous once per week)	Significant reduction of solid tumours, better survival of curcumin group	Saghateluyan et al. (2020)
Breast	6 weeks	450 mg curcumin, 0.5–8.0 g per day, combined with intravenous docetaxel therapy	Reduced VEGF marker pointing to antiangiogenic effects, CEA tumour marker decreased	Bayet-Robert et al. (2010)
Lung	8 weeks	CURCUViva TM (Curcumin-based formulation) combined with EGFR-TKI treatment at 80 mg per day	No haematological toxicity observed. Overall, improved quality of life, and improved LCS of the FACT-L	Esfahani et al. (2019)
Skin	3 months	0.5–8.0 g curcumin per day; oral administration	Improved histological prominence of precancerous lesions at applied doses	Hsieh (2001)
Skin	1 week	1 g curcumin tablet, 900 mg curcumin + 80 mg desmethoxy-curcumin + 20 mg bisdesmethoxy-curcumin	Improved pain scores and lesions size; decreased MDA and 8-OHdG levels in all three groups	Rai et al. (2010)
Colorectal	1 week	Reduced M1-G level; curcumin metabolites detected in healthy and malignant colorectal tissues	Turmeric extract, oral intake; 3.6, 1.8 and 0.45 g per day	Garcea et al. (2005)
Colorectal	30 days	360 mg curcumin, 3 times per day, oral intake	Increased tumour apoptotic cells numbers, increased p53 and Bax expression levels; reduced serum TNF- α levels, inhibition of BIs-2 expression	He et al. (2011)

examined the effect of curcumin on cell migration and cell aggressive ability. Curcumin lowered cell migration level ($p < 0.05$). In addition, cell assault was reduced with curcumin treatment. The above facts recommended that the hindrance of curcumin lowered cell migratory level, cell growth and incursion in thymic carcinomas (Kumar et al., 2015).

Curcumin clogged Notch 1 and mTOR signalling trials by downregulation of miR-27a. Cells of TC1889 were transduced due to miR-27a mimic and negative control (NC) mimic when used with 5- μ M curcumin for about 24 h. By usage of the western blot method, the impression of t-mTOR and p-mTOR, tp70S6K and p-p70S6K was evaluated and by using the western blot procedure, the impression of Notch 1 was assessed. β -actin normalized the relative expression of the protein. To increase therapeutic efficiency and lessen adverse effects, it is necessary to discover new drugs against thymic carcinoma. Cell invasion, cell growth and migration of thymic tumour cells were decreased by curcumin as it is shown in our paper. In addition, in thymic malignant cells, miR-27a impression was stimulated and suppressed by curcumin in thymic carcinoma cells. Due to overexpression of miR-27a, the results of curcumin on cell behaviour of thymic malignant cells were reversed. According to these results, it was shown that by suppressing miR-27a, curcumin blocked Notch 1 and mTOR signalling pathways (Han et al., 2020).

Curcumin used in a dose-dependent manner, decreased cell proliferation and increased apoptosis in human glioblastoma. Experimental data showed that curcumin interferes with the cell malignant process in breast cancer by reducing cell growth and mitochondrial membrane potential. *In vivo* research showed that curcumin management delayed melanoma metastasis to the lung (Loch-Imran et al., 2023). In cell behaviour, no detailed investigations of the effects of curcumin were shown despite of previous study of thymic carcinoma showing that curcumin may influence inflammatory response by blocking the interleukin-1 signalling. As confirmed in other cancers, related results were found in thymic malignancy. It was found that curcumin not only improved cell propagation but also reduced cell invasive and cell migratory abilities of TC1889 cells. The results showed that curcumin applied for acute roles in the biological processes of thymic tumours (Pavlovic et al., 2016).

MicroRNAs (miRNAs) are a bunch of non-coding endogenous RNAs that are composed of a lesser amount of 22 nucleotides in length and they are used to reduce the mRNA transcription process so they are included in tumour development. A broad-ranging spectrum of results showed that curcumin has certain anticancer impacts by modifying miR-27a. Current indications recommended that curcumin reduced miR-27a expression by delaying cell propagation and formation of (ROS) in the colon tumour. Data showed that in thymic malignant tissues, miR-27a was overexpressed. Moreover, miR-27a impression was suppressed by curcumin of varied absorptions in the thymic malignant cells. Due to the overexpression of miR-27a, the anticancer impacts of curcumin on the thymic malignant cells were reversed. These results showed that curcumin has anti-migratory, anti-invasive and anti-growth effects by suppressing miR-27a in thymic carcinoma (Kumar et al., 2018). Different studies showing the anti-cancer mechanisms of curcumin are summarized in Table 1. Clinical trials of curcumin (combined treatments) against various cancers are shown in Table 2.

Conclusion

As evident from the studies, curcumin preferentially kills tumour cells through the control of several cell signalling pathways, according to many *in vivo* animal studies and *in vitro* cell cultures. Many studies showed that curcumin's anticancer activity is related to the activation of apoptosis via interference with cell viability signalling pathways. Previous studies have also shown that caspase is involved in curcumin-induced apoptosis. CUR has been shown to trigger caspase-3-independent cell death in human multidrug-resistant cells. Whilst it is not apparent if curcumin can produce ROS or has antioxidant potential, research has shown that curcumin-caused ROS generation and curcumin-induced ROS ultimately result in autophagy activation in cancerous cells. Moreover, curcumin was shown to activate JNK and reduce NF- κ B, indicating that these components are implicated in curcumin-induced ROS formation and apoptosis. Findings suggested that curcumin-induced apoptosis is a pro-death signal instead of a pro-survival signal. According to the findings, it was proposed that curcumin induces autophagy in glioma cells to show anticancer activity instead of eliciting a cytoprotective reaction. Since curcumin induces autophagic cell death and can inhibit cell growth, it might be an effective therapeutic drug for cancer therapies. As a polyphenolic, natural substance, it has generated interest as a possible cancer chemotherapeutic agent. Further investigations are required to identify the function of ROS and other relevant pathways in curcumin-induced autophagy in cancer cells. A complete understanding of underlying pathways will enable the researchers and pharmacists to develop a stand-alone or combined effective anticancer drug/medicine having more essential functionality than a conventional drug and none of the side effects.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

The data that support the findings of this study are available within the manuscript.

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