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The Anticancer Activity of Curcumin: A Literature Review

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A B S T R A C T

Cancer is the world's second-largest cause of mortality and one of the most serious public health issues. Despite significant advancements in cancer treatment, cancer incidence and mortality rates remain high. Current research is still focused on developing more effective and less hazardous cancer treatment options. Curcumin has gotten a lot of press in the last two decades as an anti-oxidant, anti-inflammatory, and cancer-fighting agent Curcumin modulated intracellular signaling pathways that affect tumor growth, angiogenesis, metastasis, inflammation, invasion, and apoptosis, among other things. Curcumin suppresses tumor cell growth and enhances apoptosis via upregulating the expression and activity of p53. Curcumin also has a strong inhibitory impact on the NFB and COX2 activity, which are involved in the upregulation of antiapoptotic genes like Bcl2. It can also reduce the control of antiapoptosis PI3K signaling and enhance MAPK expression, resulting in endogenous reactive oxygen species generation. The goal of this research is to review curcumin's anticancer properties.

1. Introduction

Cancer is the second most lethal disease and one of the world's most serious public health issues. Despite significant advancements in cancer treatment, the disease's reported incidence and mortality have not decreased in the last 30 years. Understanding the molecular changes that contribute to cancer's formation and progression is crucial to cancer prevention and treatment. There are various popular ways for inhibiting tumor development, progression, and metastasis without producing significant adverse effects by targeting specific cancer cells. Several anticancer substances with various mechanisms of action have been isolated from plant sources in addition to chemically manufactured anticancer medicines.[1]

Zingiberaceous plants have been utilized as spices and medicines in traditional Chinese and Indian medicine since ancient times. Curcuma longa, C. aromatica, and C. xanthorrhiza are among the more than 30 Curcuma species (Zingiberaceae) found in Asia and several of them have been extensively examined, particularly Curcuma longa, C. aromatic, and C. xanthorrhiza. Curcumin, a molecule generated from turmeric (Curcuma longa), has been intensively explored for its possible anti-inflammatory and/or anti-cancer benefits, and the genus is a rich source of it chemically. Desmethoxycurcumin (DMC) and bis-desmethoxycurcumin (BDC) are the other two curcuminoids derived from Curcuma longa (BDMC). Curcumin is also deemed pharmacologically safe, and the US Food and Drug Administration has classified it as safe for human ingestion. It's extensively used as a condiment and has no known negative effects.[2]

Curcumin and its derivatives have gotten a lot of

press during the last two decades because of their biofunctional qualities including anti-tumor, antioxidant, and anti-inflammatory properties. The main components in the curcumin molecule are responsible for these effects. This review has primarily focused on the anticancer activity of curcumin due to the importance of cancer as a primary cause of mortality and the ongoing search for more effective and less toxic anticancer medicines.

2. Methods

The search for article sources was conducted using the terms "curcumin" and "anticancer action" or "cancer apoptosis" on Google, Google Scholar, and NCBI. National and international journals published in the last ten years were the key data sources.

3. Discussion

Curcumin structure and Chemical Composition Polish scientists proposed the curcumin structure for the first time in 1910. (Figure 1). It consists of two phenyl rings replaced with hydroxyl and methoxyl groups and linked by a seven-carbon keto-enol linker, as can be seen (C7). Polish scientists proposed the curcumin structure for the first time in 1910. (Figure 1). It consists of two phenyl rings replaced with hydroxyl and methoxyl groups and linked by a seven-carbon keto-enol linker, as can be seen (C7).[1,3]

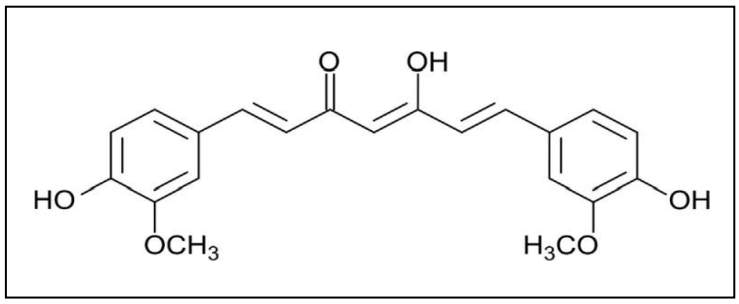

Figure 1. Chemical structure of curcumin.[3]

Curcumin is high in terpene derivatives, with monocyclic sesquiterpenes and oxygenated derivatives like turmerone and zingibrene dominating. 3-5 percent curcuminoids and 2-7 percent essential oil are found in the rhizome. Curcumin has a melting point of 183°C and is insoluble in water. It is soluble in organic solvents such as dimethyl sulfoxide, ethanol, methanol, or acetone. Curcumin has a maximum spectrophotometric absorption of 430 nm in methanol and 415-420 nm in acetone, with 1,650 absorbance units in a 1 percent solution.[4]

Anticancer activity of curcumin

Extensive preclinical research evaluating curcumin's anticancer activity can be found in the literature, with growing attention being paid to its linked mechanism of action (Table 1). Curcumin has been found to inhibit carcinogenesis by inhibiting angiogenesis and cancer cell proliferation. It also inhibits cancer cell metastasis and promotes apoptosis in cancer cells. Figure 2 depicts the several molecular targets through which curcumin operates, either downregulating or upregulating.[3]

Angiogenesis is well-known for its role in cancer. Proangiogenic substances can actually stimulate cancer cells to generate new blood vessels. Curcumin has been demonstrated to block angiogenic factor stimulators such as VEGF and basic fibroblast growth factor, resulting in antiangiogenic action. In fact, curcumin has been shown to inhibit IL-8 expression via downregulating VEGF expression via NF-kB and AP-1 regulation. Curcumin can decrease angiogenesis by modulating VEFGR and the PI3K/Akt signaling pathway, according to Astinfeshan et al. (2019). Curcumin has also been reported to inhibit MMP-2 and MMP-9 while increasing the tissue inhibitor

metalloproteinase-A. One of the most essential tumor suppressor proteins, p53 regulates cell growth, death, and DNA damage. A link between p53 and cancer-related miRNAs has been discovered in several research. In non-small cell lung cancer, Ye et al. (2015) discovered that curcumin's proapoptotic impact is mediated by miR- 192-5p and miR-215, which activate p53. Curcumin-induced apoptosis in HT-29 colon cancer cells has been demonstrated to be p53-independent in other research. CDKs are serine/threonine kinases that form a complex with their cyclin partner to regulate cell cycle progression. The expression of CDKs is always altered in cancer cells. Curcumin treatment of the triple-negative breast cancer cell line MDA-MB-231 resulted in a disruption of CDKs/cyclin complexes required for cell cycle progression and down-regulation of cyclin D1, which is required for cell cycle progression through the G1/S phase and whose overexpression is associated with most breast cancers, resulting in cell cycle arrest at G1.[3,4,5]

Curcumin has been shown to be particularly beneficial in the treatment of cancers where Ras is overexpressed. Curcumin suppresses the proliferation of AGS gastric cancer cells by downregulating Ras proteins and upregulating ERK, according to Cao et al. (2015). Curcumin-based intervention alters the oncogenic Ras-induced MEK/ERK pro-proliferative pathway toward p38MAPK/JNK1, according to Banerjee et al. (2017). In cancer models, curcumin was also found to be able to block and downregulate the PI3K/Akt signal pathway. Targeting the Wnt/ß-catenin signaling pathway is also a viable cancer treatment strategy. Wnt/ß-catenin overexpression has been linked to human malignancies, and curcumin can cause cell cycle arrest at the G2/M phase via modulating Wnt/ß-catenin signaling. Curcumin can also reduce colon cancer by suppressing the Wnt/b-catenin pathways via miR-130a, according to Dou et al. (2017). Curcumin's anti-cancer properties allow it to target cancer transcription factors. It has been found in numerous studies to inhibit the transcriptional factors NF-kB and AP-1. Curcumin was examined in curcumin-sensitive and curcumin-resistant liver cancer cell lines by Marquardt et al. (2015). The investigators discovered that curcumin-sensitive cells had their NF-kB function suppressed, while curcumin-resistant cells had their intact. Curcumin inhibited the expression of proliferating cell nuclear antigens (PCNA), pPI3K, and NFkB in lung cancer cells. Curcumin therapy increased the sensitivity of human and rat glioma cells to radiation, and it inhibited both AP-1 and NF-kB expression. Curcumin has also been proven to inhibit STAT expression. In pancreatic cancer cells, curcumin reduced the expression of STAT3-regulated cyclin D1, BCL-2, and Bcl-xL. Curcumin inhibited IL-6-induced STAT-3 phosphorylation and nuclear translocation in multiple myeloma cells, according to Shanmugam et al. (2015). Furthermore, curcumin inhibited cell proliferation, migration, and invasion while promoting death in retinoblastoma cells, with their anticancer properties appearing to be mediated through up-regulation of miR-99a and thus suppression of the JAK/STAT pathway.[2,3,5,6]

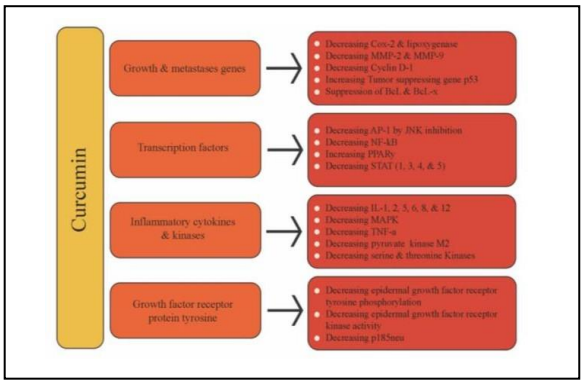

Figure 2. Curcumin molecular targets in cancer cells[3]

Table 1. Curcumin anticancer effect and mechanisms.[3]

Study type	Subjects	Dose / frequency	Outcome & Mechanisms	Reference
In vitro	MCF-7 breast cancer cell line	50 μg/mL	Decreasing *Mcl-1* gene expression Inducing apoptosis	(Khazaei Koohpar et al., 2015)
In vitro	HNSCC cells (FaDu & Cal27)	12.5 μM	Increasing pro-apoptotic protein Bik and Bim Reducing phosphorylation of NF-κB and STAT-3 Suppressing cyclin D1 and D2 expression	(Xi et al., 2015)
In vitro	MCF-7 breast cancer cell line	2.5 μM	Inducing Bcl-2 expression (apoptosis) Suppression of the EGFR expression	(Zhan et al., 2014)
In vitro	MCF-7 and MDA-MB-231 breast cancer cells	2–10 μM	Activating the ERK signaling pathway Autophagy induced by activation of JNK	(Wang et al., 2016b)
In vitro	MCF7, MDA-MB-231, and SKBR3 breast cancer cells		Increasing *Tusc7* and *GAS5* expression	(Esmatabadi et al., 2018)
In vitro	MDA-MB-231 breast cancer cell	40 μM	Activating p38-MAPK Decreasing CDK2, CDK4, cyclin D1, and cyclin E levels Inducing cell cycle arrest at G1/ and G2/M phases	(Meena et al., 2017)
In vitro	Patu8988 pancreatic cell line	10, 15 and 20 μM	Suppressing cell growth, inhibiting migration and invasion, and inducing apoptosis Downregulating YAP and TAZ expression Suppressing *Notch-1* expression.	(Zhou et al., 2016)
In vitro	PANC1 and BxPC3 cell lines	10 - 80 μg/mL	Inducing cell cycle arrest at the G2/M phase Upregulating of Bax and LC3II expression Downregulating Bcl2 expression	(Zhu and Bu, 2017)
In vitro	HCT116 colon cancer cell line	5, 10 and 20 μM	Inhibiting EIF2, eIF4/p70S6K, and mTOR signaling pathways Inhibiting *de novo* protein synthesis Increasing ROS levels due to mitochondrial dysfunction	(Wang et al., 2016a)
In vitro / In vivo	SW480 colon cancer cell line	200 mg/kg b.w. for 5 days	Decreasing β-catenin expression Upregulating of Nkd2 Suppressing the Wnt/β-Catenin Pathway via miR-130a	(Dou et al., 2017)
In vivo	Male Sprague–Dawley rats	25, 50, and 75 mg/kg b.w.	Downregulating the PI3-K/Akt/PTEN pathway Increasing pro-apoptotic Bad and Bax expression Inhibiting Bcl2 expression	(Rana et al., 2015)
In vivo	Male nude BALB/c mice	100 mg/kg b.w. each 2 days	Downregulating Notch and HIF-1 mRNA expression Suppressing VEGF and NF-κB expression VEGF and NF-κB expression	(Li et al., 2018b)
In vitro	Human lung cancer cells (NCI-H1299, NCI-H460, NCI-H520 and NCI-H446)	5-40 μM	Upregulating IGFBP-1 Suppressing the PCNA and NF-κB pathway Activating JNK phosphorylation	(Man et al., 2018)
In vitro / In vivo *In vitro*	HCT11 and HT29 colon cancer cells Male nude BALB/c mice Mouse prostate cancer cells TRAMP-C1	10, 20, 30 and 40 μM, 40 mg/kg b.w. 50 and 100 nM	Downregulating NF-κB activation Inhibiting AMPK/ULK1-dependent autophagy Activating Nrf2 expression Reducing the methylation rate of the Nrf2 promoter Reducing H3k27me3 enrichment on the Nrf2 promoter region	(Zhang et al., 2017) (Li et al., 2018a)

The breakdown of equilibrium between cell proliferation and cell death is one of the fundamental causes of cancer. Uncontrolled cell proliferation occurs when cells skip death due to a lack of apoptotic signals, leading to various forms of cancer. The intrinsic and extrinsic routes are the two primary pathways that create apoptotic signals. The intrinsic route inhibits the expression of anti-apoptotic proteins Bcl-2 and Bcl-Xl by activating the mitochondrial membrane. Curcumin disrupts the mitochondrial membrane potential balance, resulting in increased inhibition of the Bcl-xL protein. The death receptors (DRs) on cells are increased, and the tumor necrosis factor is triggered, in the extrinsic apoptotic pathway. Curcumin also plays a role in this pathway by increasing the expression of the death receptors DR 4 and DR 5. Curcumin and its derivatives have been shown in vitro to have a remarkable potential to trigger apoptosis in several cell lines by blocking or downregulating intracellular transcription factors. NF-B, activator protein 1 (AP- 1), cyclooxygenase II (COX-2), nitric oxide synthase, matrix metalloproteinase-9 (MMP-9), and STAT3 are some of these factors [33,73]. Curcumin has been discovered to have a new anticancer mechanism in which it reduces glucose uptake and lactate synthesis (Warburg effect) in cancer cells by downregulating pyruvate kinase M2 (PKM2). The mammalian target of rapamycin-hypoxia-inducible factor 1 (TOR-HIF1) was suppressed in order to inhibit PKM2. Curcumin and its derivatives have been studied for their capacity to reduce a variety of cancers by interacting with several molecular targets (Figure3).[1,5,6]

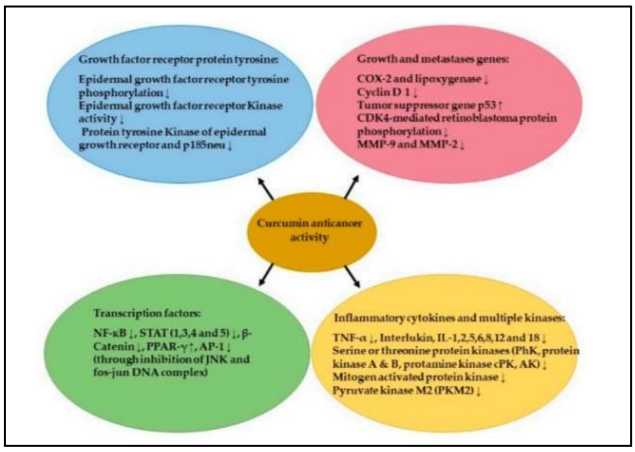

Figure 3. The main molecular targets of curcumin in cancer cells.[1]

Inflammation also plays a crucial role in carcinogenesis and therapeutic response in all of its forms. STAT3 and NF-B activation and interaction are critical in the control of cancer and inflammatory cells. TNF-, VEGF, IL-10, MMP-2 and MMP-9, MCP, CD4+ T, AP-1, Akt, PPAR-, MAP kinases, and mTORC1 are all key mediators of inflammation and cancer.[7]

In vitro and in vivo animal and human clinical trials for colorectal, liver, pancreatic, lung, breast, uterine, ovarian, prostate, bladder, kidney, renal, brain, non-Hodgkin lymphoma, and leukemia cancers, curcumin was revealed to have clinical therapeutic and preventive potential. Although there is no quantitative cause-and-effect relationship data, regular turmeric use has been linked to lower cancer rates in India. Curcumin modulated intracellular signaling pathways that affect tumor growth, angiogenesis, metastasis, inflammation, invasion, and apoptosis, among other things. NF-B pathways are activated by most carcinogens, resulting in the development of inflammatory enzymes and mediators such as COX-2, LOX-2, iNOS, inflammatory cytokines, including TNF-, and chemokines. Curcumin inhibits the transcription factor NF-B and downstream gene products (including fas, p53, VEGF, Cdc42, Bcl-2, COX-2, NOS, cyclin D1, TNF-, interleukins, and MMP-9) and has anti-proliferative properties. Curcumin suppressed COX-2 expression and inhibited NF-KB and STAT3 activation, making it a potential therapy for multiple myeloma. Curcumin induced apoptosis in cancer cells is mostly mediated by the mitochondrial route, according to Karunagaran et al. Curcumin reduces the expression of the proinflammatory cytokines CXCL1 and -2, which leads to a reduction in the growth of breast and prostate cancer metastases, according to Kronski et al. The chemopreventive curcumin induces MiR181b, which prevents breast cancer metastasis by downregulating the inflammatory cytokines CXCL1 and -2. As a result, curcumin could be a simple bridge to bringing metastatic modulation into the clinic for both preventive and therapeutic purposes. Prusty and Das investigated the redox regulatory pathway involved in HPV expression, which can be influenced by antioxidant-induced AP-1 transcription reconstitution. Curcumin completely inhibited AP-1 binding activity and restored normal c-fos/fra-1 transcription in the cervix, according to the researchers. A unique mechanism governing the transcription of harmful HPVs during keratinocyte differentiation and progression of cervical cancer was discovered in HeLa cancer cells.[5,6,7]

4. Conclusion

Curcumin and its equivalents have been shown to have anticancer activities in a number of cancer cell lines, including pancreatic, lung, ovarian, oral, colorectal, breast, and melanoma cells. Curcumin analogs' potential as effective chemotherapeutic drugs will be determined by further research in the future.

5. References

1. Tomeh M.A, Hadianamrei R, Zhao X. A Review of Curcumin and Its Derivatives as Anticancer Agents. Int J Mol Sci. 2019; 20(1033): 1-26. https:// doi:10.3390/ijms20051033.
2. Gupta A.P, Khan S, Manzoor M.M, et al. Anticancer Curcumin: Natural Analogues and Structure-Activity Relationship. Studies in Natural Products Chemistry. 2017; 54: 355-401. http://dx.doi.org/10.1016/B978- 0-444-63929-5.00010-3.
3. Sharifi-Rad J, Rayess Y.E, Rizk A.A, et al. Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications. Frontiers in Pharmacology.2020; 11: 1-23. https:// https://doi.org/10.3389/fphar.2020.01021.
4. Perrone D, Ardito F, Giannatempo G, et al. Biological and therapeutic activities, and anticancer properties of curcumin (Review). Experimental and Therapeutic Medicine. 2015; 10: 1615-1623. https:// doi:10.3892/etm.2015.2749.
5. Vallianou N.G, Evangelopoulos A, Schizas N, et al. Potential Anticancer Properties and Mechanisms of Action of Curcumin. Anticancer Research. 2015; 35: 645-652.
6. Mortezaee K, Salehi E, Mirtavoos-mahyari H, et al. (2018). Mechanisms of apoptosis modulation by curcumin: Implications for cancer therapy. J Cell Physiol. 2018; 1-14. https:// DOI: 10.1002/jcp.28122
7. He Y, Yue Y, Zheng X, et al. (2015). Curcumin, Inflammation, and Chronic Diseases: How Are They Linked?. Molecules. 2015; 20: 9183-9213.https://doi:10.3390/molecules20059183