The Anticancer Activity of Curcumin: A Literature Review

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ABSTRACT

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 antioxidant, 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 NFκB 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. aromatica, and C. xanthorrhiza. Curcumin, a molecule generated from turmeric (Curcuma longa), has been intensively explored for its possible anti-inflammatory and/or anticancer benefits, and the genus is a rich source of it chemically. Desmethoxycurcumin (DMC) and bis-desmethoxycurcumin (BDC) are the other two curcumoids 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 include 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).¹³

![Figure 1. Chemical structure of curcumin.³](image)

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 through modulating VEGFR 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/β-catenin signaling pathway is also a viable cancer treatment strategy. Wnt/β-catenin overexpression has been linked to human malignancies, and curcumin can cause cell cycle arrest at the G2/M phase via modulating Wnt/β-catenin signaling. Curcumin can also reduce colon cancer by suppressing the Wnt/β-catenin pathways via miR-130a, according to Dou et al. (2017). Curcumin's anticancer 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 theirs intact. Curcumin inhibited the expression of proliferating cell nuclear antigen (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 cells3

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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 antiapoptotic 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 its capacity to reduce a variety of cancers by interacting with several molecular targets (Figure 3).\textsuperscript{1,5,6}

### Table 1. Curcumin anticancer effect and mechanisms\textsuperscript{3}

<table>
<thead>
<tr>
<th>Study type</th>
<th>Subjects</th>
<th>Dose / frequency</th>
<th>Outcome &amp; Mechanisms</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>in vitro</td>
<td>MCF-7 breast cancer cell line</td>
<td>50 µg/mL</td>
<td>Decreasing M6-1 gene expression</td>
<td>Chazaei Koohpar et al., 2015</td>
</tr>
<tr>
<td>in vitro</td>
<td>HNSCC cells (FaDu and Ca27)</td>
<td>12.5 µM</td>
<td>Increasing pro-apoptotic protein Bax and Bim</td>
<td>Xi et al., 2015</td>
</tr>
<tr>
<td>in vitro</td>
<td>MCF-7 breast cancer cell line</td>
<td>2.5 µM</td>
<td>Reducing phosphorylation of NF-κB and STAT-3</td>
<td>Zhao et al., 2015</td>
</tr>
<tr>
<td>in vitro</td>
<td>MCF-7 and MDA-MB-231 breast cancer cells</td>
<td>2–10 µM</td>
<td>Suppressing the EGFR expression</td>
<td>Zhang et al., 2016</td>
</tr>
<tr>
<td>in vitro</td>
<td>MCF7, MDA-MB-231, and 5KBRI breast cancer cells</td>
<td>40 µM</td>
<td>Activating the ERK signaling pathway</td>
<td>Momeni et al., 2017</td>
</tr>
<tr>
<td>in vitro</td>
<td>Ratul9888 pancreatic cell line</td>
<td>10, 15 and 20 µM</td>
<td>Inducing cell cycle arrest at G1 and G2/M phases</td>
<td>Zhou et al., 2019</td>
</tr>
<tr>
<td>in vitro</td>
<td>PANC1 and BxPC3 cell lines</td>
<td>10 - 80 µg/mL</td>
<td>Inducing cell cycle arrest at the G2/M phase</td>
<td>Zhu and Bu, 2017</td>
</tr>
<tr>
<td>in vitro</td>
<td>HCT116 colon cancer cell line</td>
<td>5, 10 and 20 µM</td>
<td>Downregulating Bax and Bax expression</td>
<td>Wang et al., 2016a</td>
</tr>
<tr>
<td>in vitro / in vivo</td>
<td>SW480 colon cancer cell line</td>
<td>200 mg/kg b.w. for 5 days</td>
<td>Upregulating the Notch signaling pathway</td>
<td>Duan et al., 2017</td>
</tr>
<tr>
<td>in vivo</td>
<td>Male Sprague-Dawley rats</td>
<td>25, 50, and 75 mg/kg b.w.</td>
<td>Downregulating the P38/MAPK pathway via mTOR</td>
<td>Pana et al., 2015</td>
</tr>
<tr>
<td>in vivo</td>
<td>Male nude BALB/c mice</td>
<td>100 mg/kg b.w. each 2 days</td>
<td>Downregulating Notch and HIF-1 signaling pathway</td>
<td>Li et al., 2016a</td>
</tr>
<tr>
<td>in vivo</td>
<td>Human lung cancer cells (NCI-H1299, NCI-H460, NCI-H520 and NCI-H698)</td>
<td>5-40 µM</td>
<td>Upregulating the IGF-1 and NF-κB pathway</td>
<td>Man et al., 2018</td>
</tr>
<tr>
<td>in vivo / in vivo</td>
<td>HCT11 and HT29 colon cancer cells</td>
<td>10, 20, 30 and 40 µM, 40 mg/kg b.w.</td>
<td>Downregulating the NF-κB pathway</td>
<td>Zhang et al., 2017</td>
</tr>
<tr>
<td>in vivo</td>
<td>Male nude BALB/c mice</td>
<td>50 and 100 nM</td>
<td>Activating the NF-κB signaling pathway</td>
<td>Li et al., 2019a</td>
</tr>
</tbody>
</table>
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 metastasir 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 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 analogues’ potential as effective chemotherapeutic drugs will be determined by further research in the future.
5. References


