AN OVERVIEW ON ANTICANCER ACTIVITY OF TURMERIC

Karan Babasaheb Katkar* and Rushikesh Atmaram Dahiphale

Dr. Kolpe College of Pharmacy, Kolpewadi Tel- Kopargaon Dist- Ahmednagar.

ABSTRACT

Natural products have received much attention due to their low toxicity, ability to overcome multiple targets involved in cancer, and their effectiveness in eliminating cancer stem cells for decades. Compounds, especially phytochemicals and their synthetic conjugates, have been extensively investigated for their potential in cancer prevention and treatment. The genus Curcuma belongs to the Zingiberaceae family. The genus includes about 80 species. Its geographical distribution extends to Southeast Asia, China, India, New Guinea and northern Australia. Turmeric is a herbaceous plant with thick, fleshy rhizomes, pseudostems, and leaf blades. Turmeric contains three curcumin analogues, curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC), collectively referred to as curcuminoids. Although the three compounds differ in their aromatic ring substitution, curcumin has two symmetrical o-methoxyphenols linked by a β,β-unsaturated β-diketone moiety, and BDMC is also symmetrical, but with two o- It has methoxy substitution, and DMC has an asymmetric structure. There is only one o-methoxy substitution. The number of chemopreventive and direct therapeutic effects of curcumin suggests that it may be a potential anticancer agent. has been shown to be active in various other in vitro models at doses comparable to humans. The effect of curcumin on ovarian cancer was evaluated in groups of animals treated with curcumin alone or in combination with docetaxel. Curcumin alone reduced mean tumor growth by 49-55% compared to controls, while the combination of curcumin and docetaxel reduced mean tumor growth by 77% compared to controls.

KEYWORDS:- Curcumin, Cancer, Chemotherapies, Potency of curcumin, Pharmacological action, Chemistry of curcumin.
INTRODUCTION
Recently, natural products have received a great deal of attention due to their low toxicity, their ability to negotiate multiple targets involved in cancer, and their effectiveness in eliminating cancer stem cells. New lead compounds inspired by natural products have accounted for nearly 50% over the last few decades. Naturally occurring compounds, especially phytochemicals and their synthetic conjugates, have been extensively studied to explore their therapeutic potential for cancer prevention and treatment, but recent studies have shown that cancer cells can be chemo-aggregated.\[1\]

A role in sensing and overcoming MDR has also been demonstrated. Curcumin is one such phytochemical that has been extensively studied. It targets multiple types of cancer and aims to raise awareness of anticancer drugs in multidrug-resistant cancers. Although this compound showed promising activity in preclinical studies, its clinical application is limited due to its limited water solubility and faster metabolism. Analogue have been synthesized and preclinically tested for better therapeutic activity. Numerous studies reported and increasing research interest, curcumin has become one of the most popular natural products in the fight against cancer.\[2\]

The claim that it is one of the Cancer has become her second leading cause of death worldwide. In 2018, about 1.73 million new cases and her more than 609,000 cancer deaths were reported in the United States alone. Despite remarkable advances in medical science and technology for treating cancer, new cases and deaths from the same disease have not declined in recent decades.\[3\]

Normal somatic cells are controlled by signaling pathways that direct and function as needed. They divide when the body needs new cells, but old or damaged cells die naturally. Cancer is the overgrowth of cells. An internal or external trigger reaction causes the cell to begin dividing and continually divides again even when the body doesn't need it. Also, the old cells survive and start dividing like normal cells. These undifferentiated cells form clump-like structures called tumors. Most cancers form solid tumors, but connective tissue cancers such as leukemia and blood cancers are in a liquid state.\[4\]
Cancer is one of the most important non-communicable diseases, affecting 18.1 million patients worldwide. Mortality decreased by 29% from 1991 to 2017, but he is reported to be the second deadliest disease in the United States.

The federal government said he spent $147.3 billion on cancer treatment in 2017, but this amount will drop considering he expects new cases to rise to 23.6 million by 2030. estimated to increase further3. Age-Standardized Rates (ASR) for cancer incidence and mortality across all cancer types combined worldwide (24 regions of the world), India ranks 18th in cancer incidence with ASR 279.8 and deaths with ASR 1231 Rate ranks lowest (24th).

Lymphoma cancers are a heterogeneous group of malignancies with a wide spectrum of disease, comprising 70 different subtypes and the most frequently observed in children after leukemia.[4,5]

The estimated incidence of NHL in India in 2012 was 22, with a mortality rate of 1.5 per million population, 2.2, and a mortality rate of 0.15 per 100,000 population. Asia is said to lead in both cancer incidence (57.3%) and cancer mortality (48.4%).[5]

**General features of curcuma**

The genus Curcuma belongs to the *Zingiberaceae* family. There are about 80 species in the genus. They are found in China, India, New Guinea, Southeast Asia, and northern Australia. The rhizomes, pseudostems and leaf blades of herbaceous turmeric plants are thick and fleshy. They have flower spikes that emerge directly from the rhizome, sometimes on a black separate stem from the tip of the pseudostem.[6]
Turmeric rhizomes have been used as food, seasonings, toppings, and sauces in recipes. Various diseases and conditions have traditionally been treated with many species of this genus. The following turmeric species have been studied and reported for their antiproliferative, apoptotic, and anti-cancer properties.\(^\text{[7]}\)

**Chemical composition**

Curcuminoids consist of two methoxylated phenols linked by two α, β-unsaturated carbonyl groups. Curcumin is rich in terpene derivatives, primarily monocyclic sesquiterpenes, and oxygenated derivatives such as turmerone and zingiberene. The rhizome contains 3-5% curcuminoids and 2-7% essential oils. Curcumin is sparingly soluble in water and soluble in organic solvents such as dimethyl sulfoxide, ethanol, methanol, and acetone, with a melting point of 183°C. Curcumin has an absorbance maximum of 430 nm in methanol and 415-420 nm in acetone, whereas a 1% solution of curcumin has an absorbance of 1,650 units. Curcumin contains a seven-carbon linker and three main functional groups.\(^\text{[8]}\)

α,β-unsaturated β-diketone moieties and aromatic methoxy phenol groups. The phenolic aromatic ring system is joined by two α,β-unsaturated carbonyl groups. It is a diketone tautomer that exists in the enol form in organic solvents and the keto form in water. Diketones form stable enols and are readily deprotonated to form enolates. α- and β-unsaturated carbonyl groups are good Michael acceptors and undergo nucleophilic addition. Due to its hydrophobicity, curcumin is poorly soluble in water.\(^\text{[9]}\)

![Chemical constituent in Curcumin & Its structure](image-url)
Curcumin Metabolites and Synthetic analogues
Turmeric contains three curcumin analogues, collectively referred to as curcuminoids: curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC). Although the three compounds differ in their aromatic ring substitution, curcumin has two symmetrical o-methoxyphenols linked by a β,β-unsaturated β-diketone moiety, and BDMC is also symmetrical but has two o- There are no methoxy substitutions. DMC has an asymmetric structure. There is only one o-methoxy substitution. Curcumin, the three curcuminoids, is most abundant in turmeric, followed by he DMC and BDMC.\[10\]

A lesser-known curcuminoid from turmeric is cyclocurcumin, which is said to have biological activity in both DMC and BDMC. The bright yellow color of turmeric is primarily due to fat-soluble polyphenols known as curcuminoids. It comes from pigments. Curcumin, the main curcuminoid found in turmeric, is widely considered to be the most active ingredient. Other curcuminoids found in turmeric include demethoxy curcumin and bisdemethoxy curcumin.

Other components in turmeric are volatile oils such as thumeron, atlanthone and zingiberene, as well as sugars, proteins and resins. The curcuminoid complex is also known as Indian saffron. Curcumin is a lipophilic polyphenol, sparingly soluble in water, but fairly stable at the acidic pH of the stomach.\[12\]

Absorption of curcumin in the therapy of carcinoma
Curcumin has multiple pharmacological effects, but its low bioavailability reduces its therapeutic efficacy. This is likely due primarily to poor absorption, rapid metabolism, and rapid excretion. Due to its poor qualitative properties and its low bioavailability, it remained a potential cancer therapeutic candidate for many years without finding a suitable application. It is unstable in aqueous media and undergoes rapid hydration. It undergoes degradation, which limits its usefulness as an anticancer agent. There are several ingredients that increase bioavailability.\[13\]

Developments in chemotherapies
The advances and milestones achieved in cancer chemotherapy over nearly 80 years are historic in their impact. Start with Nitrogen Mustard, a highly non-specific cytotoxic agent. In the early 1940s, Vinca revolutionized the study of alkaloids such as vinblastine. In 1968, the focus shifted to using natural products to treat various types of cancer. It was one
breakthrough. Further insight into systems biology led to the development of monoclonal antibodies (MABs) for cancer therapy in 1997, followed by the FDA approval of rituximab for the B-cell lymphoma protein tyrosine kinase involved in promoting cell proliferation signaling. followed. In 2001, the derivative now known as imatinib was granted the first FDA-approved tyrosine kinase inhibitor to treat chronic myelogenous leukemia., cancer treatment of drug-resistant cancer remains a serious challenge.\[14\]

**Anti-inflammatory mechanisms**

The desirable prophylactic or putative therapeutic properties of curcumin are also related to its antioxidant and anti-inflammatory properties. Curcumin's anti-inflammatory effects are most likely mediated by its ability to inhibit cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS). LOX, and iNOS are key enzymes that mediate inflammatory processes. Defective upregulation of COX-2 and/or iNOS has been implicated in the pathophysiology of certain human cancers and inflammatory diseases.

Since inflammation is closely associated with tumor promotion, curcumin, with its potent anti-inflammatory properties, is expected to exert chemopreventive effects against carcinogenesis. Therefore, curcumin's antioxidant and anti-inflammatory properties have been extensively studied in recent decades.\[15,16\]

**Anticancer activity**

A number of activities of curcumin, which are exerted in a chemopreventive and a directly therapeutic manner, indicate that it may be a potential anticancer remedy. Although the results have been obtained in animal models, curcumin has been demonstrated to be active in various other in vitro models, and the dosages are comparable to those used in humans. In vitro and in vivo studies have indicated that curcumin prevents carcinogenesis by affecting two primary processes: Angiogenesis and Tumor growth. Turmeric and curcuminoids influence tumor angiogenesis through multiple, interdependent processes. Action at the level of transcription factors NF-κB, AP-1 (associated with inflammatory processes) and early growth response protein 1, which attenuates the expression of IL-8 in pancreatic and head and neck cancer cell lines and prevents the induction of VEGF synthesis, inhibition of angiogenesis mediated by NO and iNOS, inhibition of COX-2 and 5-LOX; iv) action at the level of angiogenic factors.\[17\] VEGF, the primary factor for migration, sprouting, survival and proliferation during angiogenesis, and basic fibroblast growth factor; and v) action at the level of stability and coherence of the ECM, including the downregulation of MMP-2 and
MMP-9, and upregulation of tissue inhibitor of metalloproteinase-1. Turmeric also interferes with the release of angiogenic factors stored in the ECM. Curcumin induces cell death in numerous animal and human cell lines, including leukemia, melanoma, breast, lung, colon, kidney, ovarian and liver cancer. This appears to function through caspase-dependent and -independent (mitochondrial) mechanisms associated with the presence or absence of p53. Certain data show that curcumin exhibits a biphasic effect acting on the proteasome, activating at low doses and inhibiting at high doses. Depending on the dose used, curcumin may lead to apoptosis or survival. Additionally, varying doses of turmeric can also affect the type of cell death.[18]

Low doses lead to oxidative stress and apoptosis, while high doses lead to reduced reactive oxygen species production, ATP depletion, and necrotic cell death. Curcumin also appears to be able to induce cell death in various cell lines resistant to apoptosis, possibly by activating cell death mechanisms other than apoptosis. The mitotic catastrophe induced by curcumin is associated with decreased gene expression of various anti-apoptotic proteins, particularly survivin.

In addition, previous studies have shown that curcumin administration can significantly reduce the levels of the cell cycle regulators CDK4 and Cyclin D1 and inhibit the expression of p53, an upstream regulator of the CDK4-Cyclin D1 complex. I was. Recently, Vallianou et al. demonstrated the ability of curcumin to induce tumor cell apoptosis by inducing severe endoplasmic reticulum stress, which has a key function in the apoptotic process. This study suggests that curcumin may have acted by suppressing specific protein 1 activation and, as a result, failed to prevent cancer development, migration and invasion.[19]

**Liver cancer**

In Wistar rats, curcumin has been shown to prevent the development of hepatic hyperplastic nodules, hypoproteinemia, and body weight loss. N nitrosodimethylamine (DENA), a potent hepatocarcinogen, was administered intraperitoneally to five-week-old C3H/HeN mice in an experiment. From four days before the DENA injection until the conclusion of the study, one group of mice consumed a diet containing 0.2% curcumin. When compared to the non-treated group, the curcumin group had an 81% lower multiplicity and a 62% lower incidence of hepatocarcinoma at 42 weeks. In rats inoculated with Yoshida AH-130 ascites hepatoma, a rapidly growing tumor that causes death 10 days or less after inoculation, Busquets et al.
investigated the chemopreventive potential of curcumin. Curcumin markedly reduced tumor growth by 31%.\textsuperscript{[20,21]}

**Skin carcinogenesis**

Topical application of curcumin in combination with the tumor promoter TPA to female CD-1 mice, twice weekly, significantly suppressed papilloma formation for 20 weeks. In an additional study, topical application of relatively low doses of curcumin (20 or 100 nmol) significantly inhibited TPA-induced tumor promotion. Topical application of commercial curcumin (containing approximately 77% curcumin, 17-methoxycurcumin, and 3% bis-demethoxycurcumin), pure curcumin, or demethoxycurcumin significantly reduced TPA in DMBA-induced mouse skin carcinogenesis induced tumors decreased.\textsuperscript{[22]}

It showed an almost equally strong inhibitory effect on facilitation. Moreover, her dietary administration of 2% turmeric to female Swiss mice significantly suppressed DMBA- and TPA-induced skin tumorigenesis. In a two-step skin tumorigenesis model initiated by benzopyrene and promoted by TPA, curcumin reduced the number of tumors per mouse and the number of mice with tumors. In another study, Huang et al. showed that curcumin suppressed UV-induced dermatitis in mouse skin. Jiang et al. showed that curcumin can induce apoptosis and inhibit melanoma cell proliferation. Furthermore, curcumin treatment altered the expression levels of the apoptosis-associated proteins NF-κB, p38, and p53.\textsuperscript{[23]}

**Pancreatic cancer**

Pancreatic cancer cells were injected subcutaneously into the side of the abdomen of female nude mice as part of a xenograft model study. Liposomal curcumin was subsequently injected into these animals. Curcumin appeared to inhibit tumour angiogenesis and suppress pancreatic carcinoma growth in murine xenograft models because it reduced tumour size and decreased CD31 expression in addition to VEGF and IL-8 expression. Difluorinated curcumin (CDF) was shown by Bao et al. to inhibit tumour growth in a way that was related to decreased expression of EZH2, Notch-1, CD44, EpCAM, and NANOG and increased expression of let-7, miR-26a, and miR-101, which are not typically expressed in pancreatic cancer. In addition, Ali et al. showed that CDF administration caused let-7 to re-express.\textsuperscript{[24,25]}

**Prostate cancer**

Androgen-dependent L-NCaP prostate cancer cells were injected subcutaneously into mice fed a diet containing 2% curcumin for up to 6 weeks. Curcumin significantly increased the
level of apoptosis measured by the in situ cell death assay and caused a decrease in cell proliferation measured by the BrdU incorporation assay. Furthermore, curcumin has been observed to induce a marked decrease in her MMP-2 and MMP-9 activity at tumor-bearing sites. A previous study showed significantly fewer metastatic nodules in the curcumin-treated group compared to the untreated group.\[26\]

Another study evaluated the antitumor, radiosensitizing, and chemo sensitizing effects of curcumin using a xenograft prostate cancer model. Prostate cancer cells were injected into the left groin of nude mice, curcumin was administered by gavage, and gemcitabine was introduced by intraperitoneal injection. Reduced expression of the Mdm2 oncogene was demonstrated in xenografts treated with curcumin alone, in addition to those treated with a combination of curcumin and gemcitabine or radiation. Furthermore, the researchers showed that GO-Y030, a curcumin analogue, decreased the expression of Bcl-XL in prostate cancer.\[27,28\]

**Ovarian cancer**

To evaluate the effects of curcumin on ovarian cancer, groups of animals were treated with curcumin alone or in combination with docetaxel. The combination of docetaxel and docetaxel resulted in a 77% reduction in mean tumor growth compared to controls. In both cases, curcumin induced a decrease in proliferation and microvessel density and a significant increase in tumor cell apoptosis. In a recent in vitro study, the authors showed that the combination of curcumin and triptolide can synergistically inhibit the proliferation of ovarian cancer cells.\[29\]

**Lung cancer**

In animal studies, curcumin administration reduced the number of lung tumor nodules and inhibited melanoma lung metastasis. Therefore, it is possible to stop the metastatic growth of tumor cells using curcumin. Furthermore, exposure of lung cells to curcumin has been shown to inhibit cigarette smoke-induced NF-κB activation. This correlates with the suppression of cyclin D1, COX-2, and MMP-9 expression by CS. Yang et al. Curcumin inhibits cell proliferation, alters expression of proliferative and antiproliferative proteins (survivin, Bcl-XL, and cyclin B1), cell cycle, migration and invasion, and invasive proteins downregulate VEGF. I observed that you can rate. MMP-2, MMP-7, and intercellular adhesion molecule-1. Furthermore, curcumin appeared to reduce angiogenesis by suppressing it STAT3 signaling pathway in small-cell cancer.\[30,31\]
Table no. 1: Anti-cancer activities of different curcuma species.

<table>
<thead>
<tr>
<th>Name of species</th>
<th>Name of tested cell line</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcuma Amanda Roxb. (Common name-mango ginger)</td>
<td>Anti-cancer activity on lung cancer cell line H460 of the 60 cells lines from National Cancer Institute (NCIH460) and adenoca DNA ricomic human alveolar basal epithelial cells (A-549) is reported to be due to the presence of compounds</td>
<td>Herb acts through AKT (AK mice strain Transforming capabilities) also known as Protein kinase B (PKB) signalling pathway</td>
<td>[32]</td>
</tr>
<tr>
<td>Curcuma aromatica (Common name-wild turmeric)</td>
<td>Sesquiterpenoids β-element, Germacrone and Curcumin derivatives are present in Curcuma aromatica which showed Inhibition of human colon carcinoma cell (LS-174-T) anti-proliferation was observed.</td>
<td>It involves in induction of apoptosis via down regulation of cyclin B1 and Cyclin-dependent kinase 1 (CDK1) and without the participation of p53. C. aromatic oil was also found to exhibit antiproliferative effect on human hepatocellular carcinoma Hepa1-6 cells</td>
<td>[33]</td>
</tr>
<tr>
<td>Curcuma caesia (Common name- Black turmeric)</td>
<td>Antitumor activity of this herb was tested on three human-cancer cell lines-(MCF-7) human breast cancer, human colon cancer cell line (HCT-116) and ovarian Cancer cell line.</td>
<td>Anti-cancer activity was shown to be active through the tumour necrosis factor alpha (TNF α) mediated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathway</td>
<td>[34]</td>
</tr>
<tr>
<td>Curcuma longa (Common name Turmeric)</td>
<td>Curcuma longa have shown anti-tumour effect on human colon carcinoma cells lines (HCT116, SW480, CaCo2, HT29, and SW837) N-Hexane extract is more effective on human lung cancer cell line (A549).</td>
<td>Curcuma longa shows inhibition of telomerase activity in a dose-dependent manner</td>
<td>[35]</td>
</tr>
<tr>
<td>Curcuma zedoaria (Common name -white turmeric)</td>
<td>This herb shows specificity towards human oesophageal cancer cells (TE-8).</td>
<td>It induces apoptosis through caspase cascade dependent pathways, which involved activation of caspase-9, caspase-3 and Poly (ADP-ribose)</td>
<td>[36]</td>
</tr>
</tbody>
</table>
Table no. 02: Examples of new drug delivery system with curcumin.\textsuperscript{[37-40]}

<table>
<thead>
<tr>
<th>Nanoformulation</th>
<th>Application</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin-loaded liposomal PMSA a antibodies</td>
<td>Human prostate cancer (LNCa, C4-2B)</td>
<td>Enhanced antiproliferative efficacy and targeting</td>
</tr>
<tr>
<td>Curcumin-loaded magnetic silk nanoparticles</td>
<td>Human breast cancer (MDA-MB-231) cell</td>
<td>Enhanced cellular uptake and growth inhibition</td>
</tr>
<tr>
<td>Curcumin–chitosan nanoparticles</td>
<td>Melanomas</td>
<td>Enhanced antitumor effect</td>
</tr>
<tr>
<td>Curcumin loaded lipo-PEG f-PEI g complexes</td>
<td>Melanoma (B16F10) and colon carcinoma (CT-26) cells</td>
<td>Increased cytotoxicity</td>
</tr>
<tr>
<td>Curcumin loaded liposomes coated with N-dodecyl chitosan-HPTMA d chloride</td>
<td>Murine fibroblasts (NIH3T3) and murine melanoma (B16F10) cells</td>
<td>Specific toxicity in murine melanoma (but not in fibroblasts)</td>
</tr>
</tbody>
</table>

CONCLUSION

A literature review of different types of turmeric identifies many types that are traditionally used as spices and as remedies for various ailments and ailments. Several of the above species have been shown to have potential anti-cancer effects. In vitro and in vivo cancer models. Rich in active ingredients. It has also been identified as the most common of the various turmeric species. Some active ingredients derived from clonga are common among different species. However, many other types of dates have not been reported to have any activity. Its anticancer activity and potential for development as an anticancer agent used in combination with drugs or other drugs has been studied. To avoid it, the detailed mechanism of action should also be studied.

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Conflict of interests

Nil

REFERENCE


