Review Article

Curcumin: A Systematic Review

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ABSTRACT

Many pharmacologically active compounds can be found in medicinal plants. Phytochemicals are currently being studied by scientists to treat a variety of human illnesses. Turmeric (*Curcuma longa*), a rhizomatous perennial plant in the Zingiberaceae family, is widely used as a food ingredient and in traditional medicine to cure a variety of diseases. Anti-inflammatory, antifungal, anti-angiogenesis, virucidal, anti-mutagenic, and antioxidant activities are all present in it. Angiogenesis, or the formation of new blood vessels, is an important homeostatic mechanism that controls vascular populations in response to physiological and pathological demands, such as chronic inflammation and cancer. Curcumin, a natural polyphenol compound has an activity to inhibit angiogenesis by suppressing tumor neovasculature formation. This study aims to investigate the anti-angiogenesis effect of curcumin.

Keywords: Curcumin, Angiogenesis, Biological activity, Anti-Angiogenesis activity, Vascular endothelial growth factor, Tumor growth factor.

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INTRODUCTION

Tumors are composed of cancerous cells & stroma, which consist of fibroblasts, macrophages, mast cells, and vascular & lymphoid endothelium, pericytes cell for the immunity response, nerves, and extracellular matrix proteins. The biological behavior of a tumor depends on the context in which cancer cells exist [1].

Angiogenesis, or the formation of new capillaries from existing blood vessels, is a multistep process involving a sequence of biological events that result in neovascularization. Angiogenesis is important in a variety of physiological processes in the human body, including pre-natal development and tissue healing following surgery or trauma. The beginning of this process is known as˝ angiogenic switch, through which tumors acquire the ability to grow & proliferate beyond their primary site. Proteolytic enzymes are created after angiogenic stimuli, activate endothelial cells, degrading the perivascular extracellular matrix (ECM) and basement membrane. Endothelial primary sprouts arise when cells proliferate and move into the perivascular region. The creation of capillary loops follows the lumination of these primary sprouts, which is followed by the synthesis of a new basement membrane and the maturity of blood vessels into complete tube-like structures through which blood can flow [4].

Curcumin, one of the most promising natural polyphenol compounds, is found in Curcuma longa with an asymmetric chemical structure. It is a long-lived herb distributed throughout tropical and sub-tropical regions of the world including India, Pakistan, Bangladesh. It has been reported that *Curcuma longa* exerts various pharmacological activity including: anti-oxidant, anti-inflammatory, anti-diabetic, anti-cancer & anti-angiogenesis also [2,3].

Morphology and chemistry of curcumin

Biological source: Turmeric is the dried rhizome of *Curcuma longa* Linn. (syn.C.domesticaValeton)., belonging to the family Zingiberaceae.

Morphology: The plant is normally erect, growing to a height of 0.5 to 1.0 m, and is divided into an underground big ovoid tuberous rhizome known as root-stock and an erect aerial shoot with leaves and flowers. Externally, the medicine has a yellowish color, a distinctive odor, and a slightly bitter taste.

Rhizome: The rhizome is tuberous, short, fleshy, and sympodial in shape and size, with a camphoraceous pleasant odor and bitter flavor. It is sessile, laterally flattened, and covered with adventitious roots, root scars, and warts; it also has longitudinal circular wrinkles on the surface that give the rhizome the appearance of nodal and inter-nodal zones. The rhizome's surface (cork) is dark brown, bluish-black, or buff, with circular groupings of the scaly leaf remains that give the appearance of growth rings. The inside was off-white, while the outside was light brownish. White or off-white cylindrical tubers, on the other hand, get shorter as they get closer to the end. The mature rhizome has a diameter of 0.5- 1.5 cm and a length of 0.5 -3.5 cm. The aerial stems are almost always short and leafless. Leaf scars, though are visible. The inter-scar distance was 0.3 cm. Tuberous roots with a diameter of 0.2- 0.6 cm and a length of 0.3 cm terminate each rhizome. The primary fingers are pale white and have roots, rootlets, or no roots at all. Because the plants were grown in rocky areas surrounded by natural water sources, they were all disrupted in their growth.

Roots: The primary roots are not visible because the plant propagates by rhizome; however, yellow-brown long fibrous and tapering adventitious roots can be observed all over the surface of the rhizome. The tips of the roots were pointed.

Shoot: Turmeric is a perennial herb that is planted as an annual in the United States. The leafy shoot shoots are erect and rarely reach 1 m in height, containing 6-10 leaves with a pseudostem formed by the leaf sheaths. The narrow petiole broadens suddenly as it approaches the sheath. A ligule is a tiny lobe that measures roughly 1 mm in length. The lamina is lanceolate, acuminate, and thin, with a dark green upper surface and a pale green underside with pellucid spots. It can be up to 30 cm long and 7-8 cm wide, and seldom exceeds 50 cm in length. The margins of the leaf sheath near the ligule are ciliate.

Chemistry of curcumin

The marked yellow color of turmeric is due to the presence of curcuminoids which essentially contain curcumin.

Commercially˝curcumin˝ is a mixture of three curcuminoids.

(A) 71.5% curcumin (Curcumin 1)

(B) 19.4% demethoxycurcumin (Curcumin 2)

(C) 9.1% bisdemethoxycucumin (curcumin 3)

These three major curcuminoids are also found in some other species of Curcuma but lesser concentration – e.g- *C.amada*, C. aromatic some minor and rare curcuminoids of *C.longa* or their analogs may be identified in other species e.g, cyclo-curcumin with cyclization of seven carbon units as a ring found in C. longa.

Curcuminoids have shown different activities. A recent study suggests that curcumin had a relatively higher potency for suppression of tumor necrosis factor (TNF-α) induce nuclear factor-κβ activation than that of demethoxycurcumin and bisdemethoxycurcumin. The result suggests that the methoxy group on the phenyl ring has a critical role but conjugated bond in the central seven-carbon chain is also important for curcuminoids NF-κβ activity. However, the suppression of proliferation of various tumor cells lines by curcumin, demethoxycurcumin, and bis-demethoxycurcumin was found to be comparable; indicating the methoxy group plays a minimum role in the anti-proliferative effects of curcuminoids [5,15].

The chemical formula of the main three principle derivative of curcumin are:-

(A) Curcumin 1:- chemical formula- $C_{21}H_{20}O_6$ (Molecular weight=368)

(B) Curcumin 2:- chemical formula $C_{20}H_{18}O_5$ (Molecular weight=338)

(C) Curcumin 3:- chemical formula $C_{19}H_{16}O_4$ (Molecular weight=308)

A minor amount of oil may be naturally present in curcumin. The predominant constituent of this oil appears to be sesquiterpene ketone and alcohol, α-turmerone, β-turmerone, m-eugenol, turmerone-A, turmerone–B.

About Angiogenesis

Angiogenesis, or the formation of new capillaries from existing blood arteries, is a complicated multistep process involving a succession of biological events, resulting in neovascularization. The discovery that tumor growth is linked to the formation of new blood vessels led us to research the chemical components that mediate angiogenesis, broadening our understanding of pathological processes and thus opening up new avenues for disease diagnosis and therapy.

Angiogenic factors are substances that cause blood vessels to constrict (1) soluble growth factors (e.g. hyaluronic acid, hyalFibroblast growth factors that are acidic and basic (aFGF and bFGF) (2) inhibitory factors that inhibit the proliferation and accelerate the differentiation of ECs, such as transforming growth factor (TGF-β), angiogenin, and various low molecular weight compounds and (3) extracellular matrix-bound cytokines that are released by proteolysis.

How does Curcumin affect Angiogenesis

C. longa has been used to treat a variety of ailments since prehistoric times. Turmeric and ginger its active ingredients are multi-targeted phytochemicals for the treatment of cancer. Apoptosis, for example, is a type of cell death. Their use can alter autophagy and cell cycle halt.

1) Colorectal Cancer (CRC) has recently emerged as a serious public health concern. Obesity and its associated metabolic issues have been linked to colorectal carcinogenesis, according to research. There have been numerous biological mechanisms discovered in the relationship between obesity and the progression of CRC. As a result, turmeric's regulation of the NF-κB and STAT-3 pathways can effectively hinder tumor cell proliferation.

2) Hepatic cancer is another type of complicated disease in which human hepatoma SMMC-7721 cells are affected. Curcumin inhibits the development of SMMC-7721 cells by triggering apoptosis via modification of the bax/bcl-2 pathway. Curcumin stimulates the apoptotic pathway and inhibits cell growth and proliferation, resulting in cell death.

3) Million people are affected by lung cancer due to mainly smoking cessation. C. longa is now known to possess tumor-inhibiting gears, both in vitro and in vivo. Curcumin has been shown to promote tumor progression, reducing the efficacy of docetaxel in lung cancer patients. Similarly, synchronized curcumin and docetaxel treatment causes minor toxicity in normal organs, as well as the bone marrow and liver.

Curcumin reduces T cells in significant numbers, but a modest dose of curcumin boosts T cells retrieved from mice with the 3LL tumor. As a result, increased CD8+ T cells demonstrated improved IFN-c discharge and proliferation, especially against 3LL tumor cells; all of this resulted in tumor-suppressing abilities.

A research of the anti-proliferative effects of turmeric components on human cancer cell lines MDAMB- 231, MCF-7, and HepG2, as well as the immune-modulatory effects of turmerones on human blood mononuclear cells, found that alpha-turmerone and curcuminoids significantly decrease cancer cell formation. There has been progressing in the proliferation of peripheral blood mononuclear cells and the composition of cytokines after the use of alpha-turmerone and aromatic-compounds turmerone [7,10,13].

The curcumin shows the other activities like as:-

1) *Anti-diabetic activity:-* Curcumin has been shown to have anti-diabetic properties. Curcumin's antioxidant properties may be responsible for its anti-diabetic properties. Curcumin has been shown in recent research to have the ability to directly quench reactive oxygen species (ROS), which can contribute to oxidative damage. This feature is thought to contribute to curcumin's overall protective benefits. Curcumin can help prevent cell death caused by oxidative stress by inducing and/or activating antioxidant/cytoprotective enzymes like heme oxygenase-1 (HO-1). Curcumin was tested in a pre-diabetic human population for its ability to prevent type 2 diabetes [8].

2) Wound healing activity:- Wound healing is a complex process that involves inflammation, granulation, and tissue remodeling. The mechanism of action of the wound healing effect of curcumin include:- Curcumin-treated wounds had higher immune histochemistry localization of transforming growth factor-1 than untreated wounds, modifying collagen, and reducing reactive oxygen species. Early re-epithelialization, enhanced neovascularization, greater migration of numerous cells into the wound bed, including dermal myofibroblasts, fibroblasts, and macrophages, and higher collagen content were all seen with curcumin.

3) Anti-angiogenesis activity:- Pathological angiogenesis is a sign of cancer and several ischemic and inflammatory diseases. In recent years, significant progress has been made in understanding the process of angiogenesis in many pathophysiological conditions. Curcumin inhibits angiogenesis directly, while also inhibiting the expression of numerous pro-angiogenesis factors. Curcumin has an anti-angiogenesis action. Curcumin inhibits angiogenesis directly while also inhibiting the expression of numerous pro-angiogenesis factors. Curcumin impacts the entire process of angiogenesis by downregulating transcription factors like NF-κB and pro-angiogenesis factors like VEGF, bFGF, and MMPs all of which are associated with cancer and are involved in curcumin's convoluted regulating process [6,7,12].

a) Fibroblast growth factor:-. Highly angiogenic and extensively expressed in normal and malignant tissues, bFGF was isolated from the bovine pituitary. Because of its effects on smooth muscle cells and endothelial cells, as well as its role as a chemoattractant and aid in the proliferation of fibroblasts and epithelial cells, bFGF stimulates angiogenesis. During tumor neo-vascularization and anti-proliferative disorders, bFGF is expressed in the vascular endothelium. FGFs are important for wound healing in addition to their angiogenic action. Curcumin and its derivatives have been shown to reduce corneal neovascularization caused by basic fibroblast growth factors [1].

b) Matrix Metalloproteinases.:- MMPs play a larger role in tumor angiogenesis because they are required for the formation and maintenance of supportive growth and angiogenesis. Endothelial cells secrete MMPs, which are important in neo-vascularization. MMP-9, like all MMPs, has a regulatory role in angiogenesis, but it does so in a unique way not just through proteolytic action, but also through other downstream mechanisms factors that promote angiogenesis. Curcumin inhibits angiogenesis by modulating MMP levels. MMP-2 and MMP-9 levels in prostate and breast cancer cells treated with curcumin were shown to be significantly reduced. These findings showed that MMP-9 inhibition is one of the key causes of demethoxycurcumin-induced vasculature suppression. Curcumin and its synthetic analogs have been found to suppress the expression of genes involved in angiogenesis and wound healing. VEGF and MMP-9 are two more angiogenesis factors.

c) Vascular Endothelial Growth Factor:- VEGF, the most well-known angiogenesis factor, was first found in 1986 by Senger and colleagues and has since been regarded as the most important factor in angiogenesis regulating mechanisms. It is known to be essential for both normal and pathological angiogenesis in a variety of tissues, as well as playing a role in cancer biology and neo-vascularization. In vitro and in vivo, curcumin has an anti-angiogenesis impact predominantly in tumors. Curcumin inhibited angiogenesis generated by hypoxia in vitro and downregulated VEGF expression in an in vitro model of endometriosis, as well as reducing VEGF suppression. Curcumin is used to treat corneal disorders, diabetic retinopathy, diabetic nephropathy, and ectopic endometrium by inhibiting angiogenesis by downregulating VEGF [14].

4) Anti-arthritis activity:- Rheumatoid arthritis is an auto-immune disease in which there is joint inflammation, synovial proliferation, and destruction of articular cartilage. Immune complexes composed of IgM activate complement and release cytokines, mainly TNF-α, IL-1 which are chemotactic for neutrophils. Curcumin's antioxidant, anti-proliferative, anti-inflammatory, and immune-suppressive properties are thought to help individuals with rheumatoid arthritis relieve their symptoms. Reduced apoptosis could be one of the most serious outcomes of RA. Curcumin inhibited the development of synovial fibroblasts and induced apoptosis when they were exposed to it. These findings suggest that curcumin may aid in the prevention of synovial fibroblast hyperplasia in RA [6].

5) Anti-oxidant activity:- Curcumin's antioxidant processes have recently attracted the attention of biologists and free-radical chemists. Curcumin is renowned for its ability to protect biomembranes from oxidative damage. Peroxidation of lipids is known to be a free-radical-mediated chain process that damages cell membranes, and curcumin's suppression of peroxidation is mostly due to the scavenging of reactive free radicals implicated in peroxidation. Curcumin is a unique antioxidant that includes the B-keto group, carbon-carbon double bonds, and phenyl rings with different quantities of hydroxyl and methoxy substituents. The enol form of curcumin is substantially more stable than the di-keto form, and the bond dissociation enthalpy (BDE) of the phenolic O: H bond is significantly lower than the BDE of the central O: H bond, implying that hydrogen atom abstraction occurs in the phenolic group. The relative contribution of the phenolic group and the core methylenic group to antioxidant activity is also dependent on the attacking radical's activity and the reaction media.

6) Anti-inflammatory activity:- Curcumin has been discovered to have amazing anti-inflammatory properties. Curcumin's natural anti-inflammatory action is comparable to that of steroidal and nonsteroidal medications such as indomethacin and phenylbutazone, both of which have serious side effects negative consequences. It appears to have anti-inflammatory properties via inhibiting COX-2, LOX, iNOS, and the generation of cytokines like interferon and tumor necrosis factor, as well as activating transcription factors like NF-κB and AP-1 [15].

a) Effect of curcumin on cyclooxygenase and lipooxygenase:- Curcumin's anti-inflammatory activities have been related to its reduction of prostaglandin (PG) synthesis, at least in part. For more than two decades, scientists have recognized that PGs and other eicosanoids have a role in the development of human cancer. Importantly, an increase in PG synthesis has been shown to influence tumor growth in humans and experimental animals, and multiple studies have shown the impact of PG synthesis on carcinogen metabolism, tumor cell proliferation, and metastatic potential in humans and animals. The enzyme cyclooxygenase (COX) is involved in the conversion of arachidonic acid to PGs. COX-1 and COX-2 are the two isoforms that make up this enzyme. COX-1 is a constitutive isoform found in most tissues that are commonly referred to as a "housekeeping" enzyme, and its suppression causes major consequences such as peptic ulcers and renal blood flow impairment. COX-2, on the other hand, is expressed only in the brain and spinal cord. The hormones of ovulation can also cause it in a wide range of normal tissues, cytokines, growth factors, oncogenes, and tumor promoters, as well as pregnancy. Inhibitors of COX-2 activity are effective in the treatment of inflammation and the prevention or treatment of cancer.

b) Effect of curcumin on inducible nitric oxide synthase:- Inducible nitric oxide synthase is another enzyme that plays a key function in mediating inflammation (iNOS). NO, a strong pro-inflammatory mediator, is produced by iNOS catalyzing the oxidative deamination of l-arginine.NO has been shown to influence tumor progression by influencing angiogenesis and perhaps promoting the production of vascular endothelial growth factor (VEGF). In addition to COX-2, iNOS appears to be a target for curcumin's anti-inflammatory properties. Curcumin has been shown to decrease NO generation as well as the expression of iNOS protein and mRNA in RAW-264.7 cells treated with LPSs or interferon-γ.

c) Effect of curcumin on tumor necrosis factor:- Tumor necrosis factor (TNF) has been proven to play a role in tumor start, progression, and spread. Because TNF plays such a vital role in carcinogenesis, medicines that can inhibit TNF activity could be used to treat TNF-related disorders. Curcumin was discovered to have a spellbinding influence on TNF production. The autocrine production of TNF causes constitutive activation of NF-B in mantle cell lymphoma (MCL) cells. When TNF secretion was inhibited by curcumin, NF-B and cell proliferation were inhibited, as was the case when TNF secretion was neutralized with anti-TNF antibody. Curcumin protects against inflammatory illnesses by inhibiting COX, LOX, iNOS, NF-B, TNF, and other inflammatory mediators [11].

7) Anti-bacterial activity:- Curcumin has been shown to reduce the growth of periodontal bacteria and Porphyromonas gingivitis Arg- and Lys-specific proteinase (RGP and KGP, respectively) activities in antibacterial research. Curcumin also inhibited the production of P. gingivitis homotypic and *Streptococcus gordonii* biofilms in a dose-dependent manner. Curcumin at a dosage of 20 g/mL reduced the production of P. gingivitis biofilms by more than 80%. After treatment with curcumin at the MIC, various characteristics of a bacterial apoptosis-like response were identified, including membrane depolarization, Ca^{2+} influx, PS exposure, and DNA fragmentation. Curcumin induces a bacterial apoptosis-like response by generating reactive oxygen species production and DNA damage. Curcumin's inhibitory effect on FtsZ polymerization suppressed FtsZ assembly, resulting in disruption of prokaryotic cell division, according to a study on E.coli and B.subtilis. Curcumin loaded in zein (zein-CUR) fibers also shown good antibacterial action against S. aureus and E.coli, with the inhibitory efficacy increasing as the curcumin level rose. The antibacterial activity against S. aureus was better than that against E.coli due to differences in cell membrane constituents and structure. According to the findings, zein-CUR fibers could be a viable material for antimicrobial applications in food packaging, inhibiting bacterial growth and propagation.

CONCLUSION

Finally, it has been discovered that curcumin has potent anti-angiogenesis regulating properties. The wisdom and scientific knowledge of curcumin, a highly pleiotropic substance that has been employed in traditional medicine in many nations for its therapeutic properties. As indicated by the studies discussed above and the many more being reported every day, the pharmacological characteristics and applications of curcumin are a quickly growing, progressing, and increasing enterprise. Furthermore, designing current formulations (e.g., nanoparticles, liposomes, and microspheres) and evaluating their performance are proposed in terms of its constituents' bioavailability and drug delivery methods.

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