A Comprehensive Review: Revealing Curcumin's Multifaceted Journey Through Various Cellular Pathways

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***Abstract*- Curcumin, a polyphenolic derivative of turmeric, is a naturally occurring compound isolated from Curcuma longa that suppresses and inverts carcinogenesis via multifaceted molecular targets and has attracted a lot of interest due to its wide range of biological activities. This review explores the complex connections that curcumin has with important signaling networks as it travels via cellular pathways. Numerous in vitro and in vivo experimental models have also revealed that curcumin regulates several molecules in the cell signal transduction pathway including NF-κB, Akt, MAPK, p53, Nrf2, Notch-1, JAK/STAT, β-catenin, and AMPK. Curcumin shows promising therapeutic implications for a variety of illnesses, including cancer, neurological disorders, metabolic syndromes, and inflammation, due to its diverse modulatory actions and potential as a powerful medication in contemporary medicine which offers priceless insights into its pharmacological processes. To fully realize the medicinal potential of curcumin thorough investigation seeks to close the gap between basic science and practical application. This review article focuses on curcumin's potential in cancer therapy by modulating the WNT/β-catenin pathway, suppressing chronic inflammation and oxidative stress. Curcumin has been shown to downregulate this pathway by controlling tumor growth. In this article, we begin by evaluating its molecular targets and mechanism of action underlying curcumin's anticancer effects, including its modulation of cell signaling pathways, inhibition of tumor growth, and induction of apoptosis.**

***Keywords*: Curcumin, signaling pathways, WNT/β-catenin pathway, Apoptosis**

Introduction

Curcumin is a plant-derived polyphenolic yellowish active compound and curcumin is one of the major active constituents obtained from the turmeric plant (Curcuma longa). It is obtained from dried rhizomes of Curcuma longa plant belonging to the family Zingiberaceae. From ancient times till now this plant has been used for various purposes, for example, in foods as spices and for therapeutic uses widely in India [1-3]. It is a perennial herb that reaches a height of up to 1 meter with a compact and short stem. It is mainly found in various tropical and subtropical regions worldwide and extensively cultivated in Asian countries, particularly in Nepal, India, and China. In India, it is commonly referred to as "Haldi" and its economic significance has been extensively studied in Malaysia, Indonesia, and India. The rhizomes of this herb are oblong, and ovate, and often have a pyriform shape with short branching. They are widely used as a household remedy in Nepal [4]. In the form of a powder known as turmeric, it has been consistently utilized for its aromatic properties, serving as a spice in both vegetarian and non-vegetarian culinary preparations, while also possessing digestive properties [5].

According to current traditional Indian medicine, turmeric powder is believed to be effective against various ailments such as biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorder, rheumatism, and sinusitis [6]. The active compound responsible for its anti-inflammatory effects, curcumin, was isolated in the 19th century.

In ancient Hindu medicine, turmeric was extensively employed for treating sprains and swelling resulting from injuries [7]. Additionally, traditional Chinese medicine utilizes C. longa L. in the treatment of abdominal pain-related conditions. Turmeric continues to be utilized in various forms for religious ceremonies. One of the most widely used dietary supplements worldwide is curcuma longa [8]. Plant-based curcumin is a polyphenolic compound with a broad spectrum of antibacterial effects. It can prevent the growth of germs because of its special structure and capacity to produce anti-oxidation compounds. Through the bacterial quorum sensing control system, curcumin may also restrict bacterial adhesion to host receptors, reduce biofilm development, and hamper virulence factors in bacteria. Curcumin functions as a photosensitizer in response to blue light, causing phototoxicity and further preventing the development of germs. Moreover, curcumin can have a synergistic impact when used with other antimicrobial agents [9].

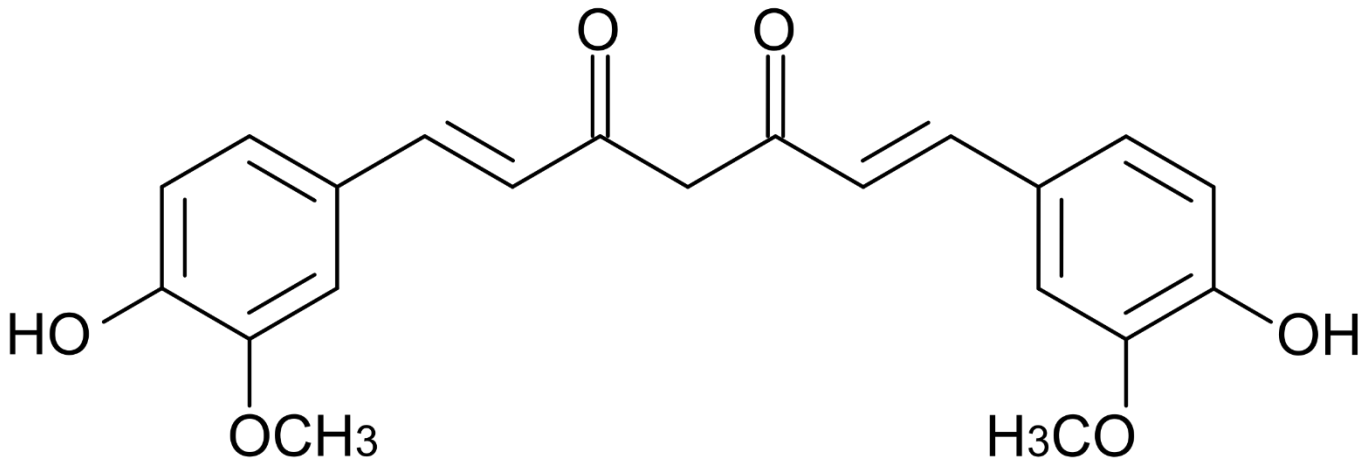
Curcumin has been the subject of several investigations and has been shown to have a wide range of benefits. Curcumin affects the functioning of high-density lipoproteins and reduces insulin resistance and hyperlipidemia [10–12]. In individuals with non-alcoholic fatty liver disease, it decreases liver fat [13]. Curcumin acts as an anticancer drug [14]. it has positive effects on head and neck squamous cell carcinoma [15]. effectively suppresses stomach, colon, and breast cancer [16, 17]. It can prevent liver cancer caused by tobacco smoke [18]. This drug has demonstrated antimetastatic properties recently. Additionally, curcumin is cytotoxic to tumors. it suppresses lung cancer stem cells [19]. Furthermore, curcumin Nano formulations have been used in cancer therapy [20].

Curcumin is a chemosensitizer that lessens the harmful and toxic effects of chemotherapy medications. It also has favorable benefits in immunotherapy. Further evidence of curcumin's radioprotective properties for normal cells has been shown [21]. properties that offer protection against UVB damage [22]. The health of the skin is positively impacted by curcumin and turmeric It is possible to treat osteoarthritis using curcumin because of its shown anti-inflammatory properties. Psoriasis can be effectively treated by using turmeric topically. Antiviral, antifungal, and antibacterial properties are also present in curcumin [23]. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin are present in turmeric ethanolic extract, which has anti-diabetic properties and can lower blood sugar levels in mice while preventing blood sugar spikes [24].

Historical Background and Chemistry of Curcumin

Henri Auguste Vogel and Pierre Joseph Pelletier reported the first separation of a "yellow coloring matter" from the turmeric rhizomes in 1815 when the term curcumin was introduced [25]. It was eventually discovered to be a combination of turmeric oil and resin. Curcumin's chemical composition was described as diferuloylmethane by Milobedzka and Lampe in 1910 [26]. The compound's synthesis was completed by the same group later in 1913. Roughley and Whiting (1973) identified the chemical structure of curcumin, also known as diferuloylmethane, the main ingredient and most significant portion of Curcuma longa L. Curcumin may react with alkalis to generate reddish-brown salts, and it has a melting point between 176 and 177°C. It stays insoluble in water but becomes soluble in ethanol, alkalis, ketone, acetic acid, and chloroform. Curcumin is an aliphatic, unsaturated compound with a potentially substituted aryl group [27].

Curcumin consists of three main functional groups: an aromatic O-methoxy-phenolic group, an α, β-unsaturated β-diketone moiety, and a seven-carbon linker [28,29]. The phenolic aromatic ring systems are linked by a pair of α, β-unsaturated carbonyl groups [28,30] It is a tautomer of a diketone that exists in water in the keto form and organic solvents in the enolic form. In [31] The diketones may be easily deprotonated to produce enolates, forming stable enols; the α, β-unsaturated carbonyl group is a suitable Michael acceptor and can be added nucleophilic ally. Curcumin is poorly soluble in water due to its hydrophobic nature [28] and dissolves readily in organic solvents [29]. One complexometric indicator for boron is curcumin. It combines with boric acid to produce rosocyanine, a reddish-colored chemical [28, 32].

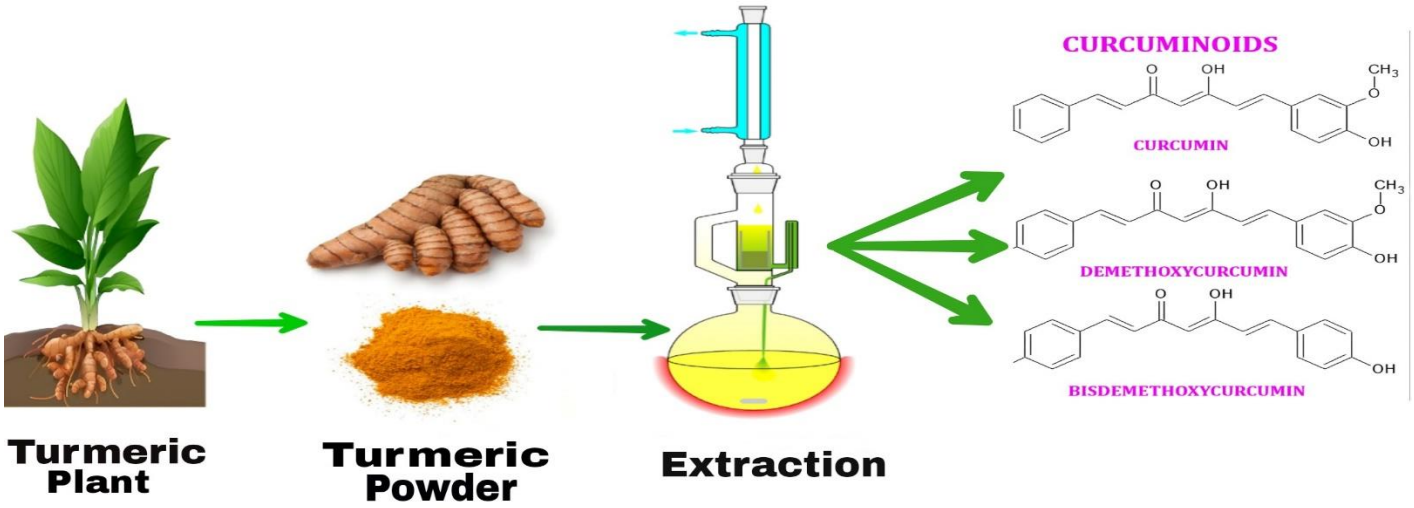


Curcumin

Method of extraction

Since 1815, researchers have been working to extract and separate curcumin from turmeric powder. Even after 200 years, scientists are still finding and publishing ever more advanced extraction techniques [33, 34]. Solvent extraction is the most popular method for isolating curcumin from turmeric, and it is followed by column chromatography. For this, a variety of polar and non-polar organic solvents have been used, including methanol, acetone, hexane, and ethyl acetate. Ethanol has become the go-to option among these solvents for curcumin extraction. Nevertheless, because of their unacceptability, chlorinated solvents—despite being incredibly effective in extracting curcumin—are not frequently utilized in the food sector. There have been attempts at zone-refining, dipping, Soxhlet, ultrasonic, and microwave extractions; among these, Soxhlet, ultrasonic, and microwave extractions are the most often used [35].

The extraction process can have an impact on curcumin's properties and structural attributes. It is possible to extract curcumin from turmeric roots using both: traditional (Soxhlet extraction, hydro distillation, and maceration) and innovative (ultrasound-assisted extraction, high hydrostatic pressure extraction, microwave-assisted extraction, enzyme-assisted extraction, supercritical fluid extraction, enzyme-assisted extraction, zone refining, and dipping methods) techniques [36].



(Figure-1. Method of Extraction of Curcumin)

Conventional extraction techniques have some drawbacks, including the need for high temperatures, which can be harmful to compounds that are sensitive to heat, the need for a considerable amount of organic solvent, extended processing times, and low extraction yields [37]. Owing to these disadvantages, researchers frequently turn to alternative methods that can include highly efficient extraction and environmentally friendly technologies [38]. Common advanced techniques for extracting curcumin have been reported to include pressured liquid extraction, ultrasound-assisted extraction, microwave-assisted extraction, pressurized liquid extraction, supercritical fluid extraction (involving costly instruments), and enzyme-assisted extraction [36, 39].

Novel approaches for extracting curcumin have been the subject of recent investigations, which have demonstrated that these procedures generate better results, take less time, and have stronger antioxidant efficacy. Choi et al.'s research [40] demonstrated that applying high hydrostatic pressure to turmeric is a viable way to increase its antioxidant activity. They also found that extracts containing more ferulic and vanillic acid concentrated with time. According to a comparison study by Wakte et al. [41], in terms of yield and time needed, microwave-assisted extraction of curcumin from C. longa is more effective than Soxhlet, ultrasonic, and supercritical carbon dioxide-assisted extractions. The extraction yield for the following methods was reported in the same study, in decreasing order: Soxhlet extraction (2.1%), supercritical carbon dioxide extraction (69.36%), microwave-assisted extraction (90.47%), and ultrasound-assisted extraction (71.42%). Furthermore, Liang et al. [42] have demonstrated that ionic liquid-based microwave-assisted extraction is a quick, efficient, and environmentally friendly way to extract curcumin.

It has also been revealed recently that extraction techniques using microwave and pulse ultrasonic assistance are superior than continuous approaches [43]. It has been discovered that improving the extraction involves raising the temperature to between 60 and 80 °C [44]. Due to its growing usage in nutritional supplements, scientists are creating extraction techniques that provide high yields using food-grade solvents such triacylglycerols [45]. Supercritical carbon dioxide is another effective and economically feasible extraction technique [46, 47]. In a number of nations, supercritical carbon dioxide-based pilot facilities have been set up to extract curcumin from turmeric. This is typically operated at temperatures of 318 K and pressures of 25 to 30 MPa.

A few studies on enzyme-assisted extraction have also been published, in which curcumin output was significantly increased by pre-treating turmeric with enzymes such α-amylase and glucoamylase [48]. However, this approach is not financially feasible due to the rise in extraction costs. By utilizing combinations of solvents such as dichloromethane/acetic acid or methanol/chloroform to adsorb the mixture on silica gel, curcumin may be isolated from curcumin mix—a mixture of curcumin, demethoxycurcumin, and bisdemethoxycurcumin—by column chromatography, resulting in the formation of three distinct fractions. Chloroform/dichloromethane and ethanol/methanol combinations are used as eluents in the subsequent purification of the curcumin fraction on silica gel [49,50].

Detection of Curcumin

The high-performance liquid chromatography (HPLC) technology has been primarily used in methods for curcumin detection and quantification. Different gradients of solvents comprising acetonitrile/water or chloroform/methanol have been utilized as the mobile phase, while reverse phase C18 columns are often utilized as the stationary phase [51,52]. A common detection wavelength of 250–270 nm may be used in the UV area or for curcumin detection, making absorption detectors in the 350–450 nm range or in

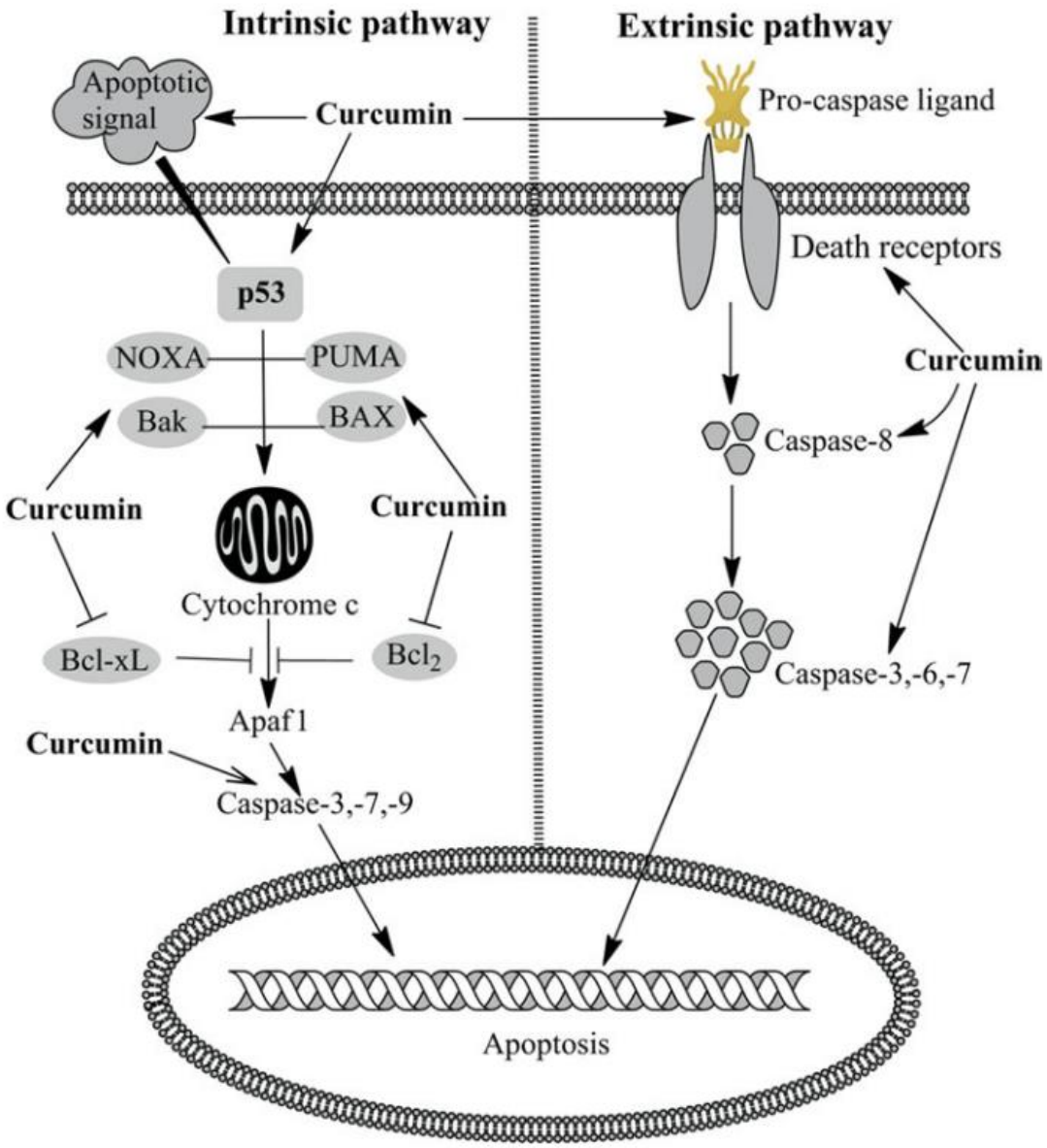
the UV region very easily and effectively used. A number of studies have also employed fluorescence detection techniques and HPLC-diode arrays [53].
Curcumin detection with liquid chromatography-coupled mass spectrometry has shown to be another effective method. The most sensitive technique for detecting curcumin (up to 1 ng/mL) among all of them is fluorescence, which is stimulated in the 400–450 nm range. For both detection and separation, high-performance thin layer chromatography techniques employing aluminium plates precoated with silica gel as the stationary phase and chloroform-methanol as the solvent have proven to be highly beneficial. Curcumin in turmeric powders was effectively separated and detected by Ali et al. [54] via an HPLC approach with a phenyl column and acetonitrile-methanol-water as the mobile phase. The extraction and quantification of curcumin in food and drug samples using microemulsion electrokinetic chromatography with oil droplets and surfactants has been proven to be effective [55]. One common method for estimating curcumin/turmeric in food items is to use capillary electrophoresis with Amperometric detection [56].

Molecular Mechanisms of Curcumin and Signal Transduction

Curcumin has intriguing pharmacological actions and has been found to benefit cancer cell proliferation, growth, survival, apoptosis, migration, invasion, angiogenesis, and metastasis [57-63]. Curcumin has been proven in several studies to suppress cancer development by anti-inflammatory, antioxidant, anti-proliferation, and pro-apoptotic pathways [57–60]. Curcumin is thought to have interactions immediately with a variety of molecular proteins, including inflammatory molecules, cells that survive proteins, the histone acetyltransferases (HATs), histone deacetylases (HDAC), protein kinases and reductases, glyoxalase I (GLOI), proteasome, sarcoplasmic reticulum Ca2-ATPase (SERCA), the type 1 human immunodeficiency virus (HIV1) integrase and protease, DNA methyltransferases 1 (DNMT1), FtsZ protofilaments, carrier proteins, DNA, RNA and metal ions [58,64].
Additionally, curcumin has indirect interactions with several transcription factors, such as peroxisome proliferator-activated receptor y (PPARy), activator protein 1 (AP-1), beta-catenin, signal transducer and activator of transcription (STAT) protein, and nuclear factor-kappa-B (NF-kB) [65]. The expression of B cell lymphoma 2 (Bcl2), cyclin D1, cyclooxygenase-2 (COX-2), matrix metalloproteinase-9 (MMP9), Akt, mitogen-activated protein kinase (MAPK), NF-E2-related factor 2 (Nrf2), b-catenin, and cell–cell adhesion is among the genes that are intrinsically and extrinsically regulated by p53, NF-kB, and NF-kB-regulated gene expression. According to reports, Notch signaling, one of the inflammatory cytokines that regulate NF-kB, is substantially elevated in human cancer patients. It has been demonstrated that curcumin inhibits NF-kB and associated gene products to mediate anti-apoptotic actions [61-63].

1. Induction of Apoptotic Signaling Cascade/pathways of Curcumin

Strong scientific and nutritional data have shown that curcumin can cause apoptosis in a variety of cancer cells. 104 of the 214 apoptosis-associated genes had their expression changed by curcumin therapy, according to microarray research that previously identified the apoptotic genes regulated by curcumin in human breast cancer and mammary epithelial cell lines [66]. Curcumin has been shown to play a strong role in apoptosis in a variety of cancer cell lines. It also modulates intrinsic (mitochondrial) and extrinsic cell signaling pathways [67].



(Figure-2. Induction of apoptosis signal cascade)

p53: Tumor Protein 53, PUMA: p53 Upregulated Modulator of Apoptosis, NOXA: Latin for "damage" or "harm", Bak: Bcl-2, Homologous Antagonist/Killer, BAX: Bcl-2 Associated X protein, Bcl2: B-cell lymphoma 2, Bcl-xL: B-cell lymphoma-extra-large, Apaf1: Apoptotic Protease-Activating Factor 1, Caspase-3: Cysteine-aspartic Acid Protease-3, Caspase-7: Cysteine-aspartic Acid Protease-7, Caspase-9: Cysteine-aspartic Acid Protease-9 [68].

Tumor suppressor protein p53 and members of the Bcl2 family of proteins promote the initiation of mitochondrial apoptosis, which causes mitochondrial membrane permeability and the release of pro-apoptotic proteins into the cytosol (Fig. 3) [57,69]. Furthermore, the endoplasmic reticulum (ER) engages in intricate interactions with the mitochondria and is a crucial membrane organelle during apoptosis. But when ER function is disrupted, the misfolded protein accumulates and causes ER stress, which is a crucial first step in the cellular apoptotic cycle [70].

According to reports, extended endoplasmic reticulum stress causes Ca2+ to be released from the ER lumen at the mitochondria-associated membrane (MAM), which in turn increases the amount of Ca2+ absorbed into the mitochondrial medium. This increased intake of Ca2+ results in an imbalance between the amount of Ca2+ within the mitochondria and the surrounding buffering environment, which in turn prolongs the buildup of Ca2+ within the mitochondria and opens the mitochondrial permeability transition pore. Consequently, the mitochondrial membrane swells and ruptures, releasing pro-apoptotic proteins into the cytosol [71]. In human lung cancer A-549 cells, curcumin (30 lM) has been demonstrated to cause ER stress and DNA damage, which in turn activates caspase-3 to cause mitochondrial-dependent apoptosis [72].

Curcumin also causes a rise in intracellular Ca2+ concentration, ER stress, and the production of reactive oxygen species (ROS), which is followed by the activation of caspase-3 and loss of mitochondrial membrane potential [73]. It has also been demonstrated that curcumin increases apoptosis in hepatocellular carcinoma HCC J5 cells by breaking down the mitochondrial membrane,

producing ROS, and increasing the intracellular absorption of Ca2Í into the mitochondria. Cytochrome c release mediates this kind of apoptotic cell death [74]. It was recently demonstrated that curcumin is directly bound with SERCA to cause ER stress. C/EBP homologous protein (CHOP) and its transcription target death receptor 5 (TRAIL-R2) were expressed more when curcumin specifically reduced the activity of SERCA2 in SW872 cells both in vitro and in vivo. This led to caspase-3 and -8 cascade-dependent apoptosis [75]. Additionally, in LoVo cells, curcumin was found to release lactate dehydrogenase, activate caspase-3 and -9, and reduce mitochondrial membrane potential in a dose- and time-dependent manner. It was discovered that in the same cell type, the mechanism of curcumin-induced apoptosis was dependent on cytochrome c release, increased Bax and p53 expression, and decreased Bcl2 and surviving expression [76].

2. Curcumin's Effects on p53 Signaling Pathway

The p53 protein is referred to as a tumor suppressor protein because it is essential for apoptosis, cell cycle regulation, genomic integrity, cellular response to DNA damage, and signal transmission in cells. The p53 protein, by inhibiting DNA replication, also plays a significant role in DNA repair [77]. The production of proteins involved in DNA repair, cell-cycle arrest, redox control, protein degradation, and eventually death is driven by the activation of p53 [78]. While Bcl2 and Bax primarily regulate cell development and initiate apoptosis, it has been suggested that p53 activates two sets of genes, p21cip1/waf-1 and GADD45, for inhibitory effects [79]. Curcumin therapy has been demonstrated to dose-dependently enhance the p53 pathway by upregulating p53 and p21 expression and suppressing CDC2 and retinoblastoma protein (Rb) via boosting CDKN2A/p16 in glioblastomas [80]. Curcumin caused apoptosis in stage 4 MYCN-amplified neuroblastoma cell lines by serine phosphorylating p53, up-regulating Bax, and down-regulating Bcl2 [81]. Additionally, curcumin-induced apoptosis was linked to p53 expression being upregulated and nuclear translocation of p53, which was followed by stimulation of a protein involved in the cell cycle and apoptosis [81]. Phosphorus phosphorylated p53 at several N-terminal p53 sites, including Ser-15, -20, and -33. Crucially, phosphorylating Ser-15 within the N-terminal activation domain perturbs the interaction between p53 and mouse double minute 2 (MDM2), which causes p53 to stabilize and activated through the reversal of MDM2-mediated transcriptional inhibition or degradation of p53 [82].

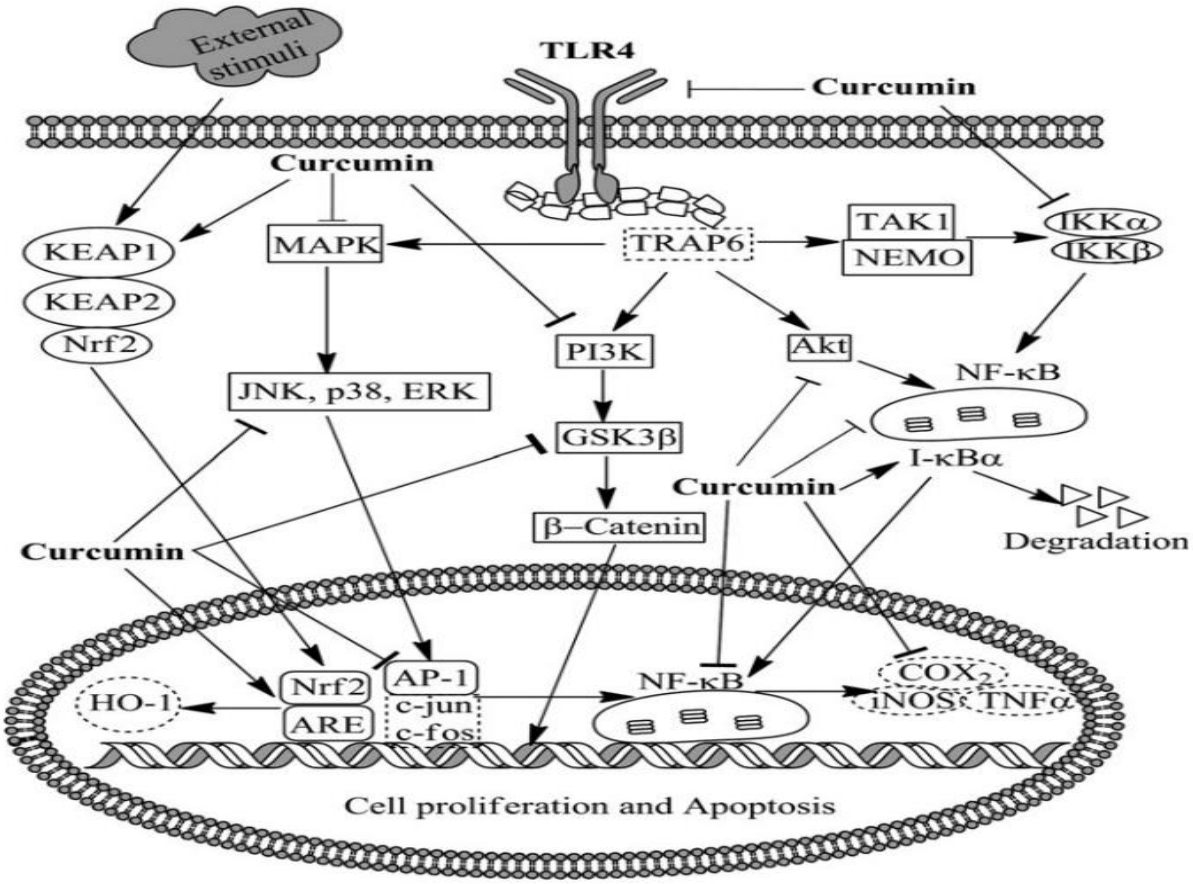
Numerous strong pieces of evidence have demonstrated that AMP-activated protein kinase (AMPK), which is known to favorably control p53 phosphorylation at Ser-15 and relieve p53 protein as well as its downstream effectors p21 and p27, is one of the cellular kinases that mediates p53 phosphorylation [83]. It has been documented that curcumin activates AMPK and phosphorylates p53 at Ser15 to cause the death of CaOV3 ovarian cancer cells. In particular, the investigation found that AMPK is essential for the up-regulation of p53 phosphorylation and activation of apoptosis that is brought about by curcumin [84].

Curcumin-induced apoptosis was demonstrated to entail superoxide anion generation and phosphorylation of oxidative stress proteins, including phosphorylation of Chk2 at Thr68, independent of p53 in colon cancer cells, notwithstanding p53 phosphorylation and up-regulation [85]. According to the explanation given above, curcumin's involvement in the function of the p53 tumor suppressor may be tissue- and cell-specific. Additionally, curcumin has demonstrated possible advantages in vivo. By preventing the activation of hepatic stellate cells, causing apoptosis by up-regulating p53 and Bax, and down-regulating Bcl2 at the mRNA level, curcumin treatment shielded BALB/c animals from hepatic fibrosis [86]. Curcumin was also tested in patients with colon cancer; after being administered, the patient's body weight grew, their blood TNF-a levels dropped, and their tumor's apoptotic cell count increased due to increased p53 molecule production in the tumor tissue [87].

3. Curcumin's Effects on the NF-κB pathway

It is present in nearly every kind of animal cell and plays a role in how cells react to various stimuli such stress, cytokines, free radicals, heavy metals, UV radiation, oxidized low-density lipoprotein, and antigens from bacteria or viruses. Numerous physiological processes, including inflammation, cell proliferation, apoptosis, and the stress response, are regulated by the nuclear NF-κB signaling system. NF-κB is a transcription factor family consisting of five genes: NF-κB1 (p50/p105), NF-κB2 (p52/p100), RelA (p65), c-Rel, and RelB. NF-κB is not a single gene. NF-κB can be activated by signaling pathways that are initiated by different cytokines, growth factors, and kinases. Numerous chemical pathways have been hypothesized [88,89] for the activation of NF-κB (Fig. 4).

RelA or c-Rel-containing dimers bind to p50 in the so-called "canonical" or classical NF-κB pathway. Because of their combination with an inhibitor of κB (IκB) protein, the dimers are rendered inactive in the cytoplasm [90]. The IKKb subunit is principally in charge of IκB phosphorylation at serine residues during activation. IκB proteins are phosphorylated, after which the proteasome degrades them in a ubiquitin-dependent manner. NF-κB is then translocated to the nucleus, where it functions as a nuclear transcription factor. According to the conventional mechanism, TNF-a and other stimulating substances cause the nuclear translocation of the RelA subunit. The alternative route states that lymphotoxin B and B-cell activating factor (BAFF) stimulate cell-differentiating and developmental processes.



(Figure-3. NF-κB pathway)

According to this pathway concept, IKKa activation phosphorylates p100, which is then proteolyzed to produce the mature form of p52 [91]. It has been said that NF-κB is an important protein and a main therapeutic target for medications in the development of inflammation and cancer [92]. Several studies have shown that the dietary component curcumin suppresses NF-κB activation, which suppresses COX-2 gene expression in human colon epithelial cells triggered by phorbol 12-myristate 13-acetate (PMA), TNF-a, or fecapentaene12. Curcumin may prevent NF-B transactivation mediated by tumor promoters by preventing the NF-B-inducing kinase (NIK)/IKK signaling complex, most likely at the level of IKKa/b [92,93].

Additionally, curcumin has been shown to increase TNF-a-induced apoptosis and reduce IKK. It has also been shown to inhibit both constitutive and inducible NF-κB activation [94]. Additionally, curcumin has been shown to have an inhibitory effect on additional signaling pathways, including Ras/MAPK and phosphoinositide 3-kinase (PI3K)/Akt, which are similarly implicated in the activation of NF-κB (Fig. 4) [95].

Curcumin prevents NF-κB from being activated by TLR4 via IKKa and IKKb. Curcumin enhanced the ability to degrade IκB and prevented Akt-induced NF-κB activation. Curcumin suppressed p38 and ERK, which are activated by MAPK and stimulate the transcription of AP-1, c-for, and c-jun. Moreover, curcumin suppressed COX-2, iNOS, and TNFa. Curcumin causes apoptosis by inducing Nrf2 and increasing HO-1 production. Curcumin inhibits the modification of b-catenin numerous signaling molecules by GSK3b and PI3K, which promotes apoptosis and prevents uncontrolled cellular growth. Arrowhead lines demonstrate activation or up-regulation in signaling pathways, whereas blunt-headlines suggest that curcumin can block or downregulate these molecules [96].

4. Effects on the Wnt/beta-Catenin Signaling Pathway

A complex consisting of axin, adenomatous polyposis coli (APC), b-catenin, and GSK-3 is formed via the Wnt/b-catenin signaling pathway, which is crucial for the control of several cellular activities [97]. Normally, the axin/GSK-3/APC complex stimulates the ubiquitin-proteasome pathway to degrade b-catenin. Stabilized b-catenin translocates to the nucleus when Wnt attaches to Frizzled family receptors, where it binds to transcription factors of the T-cell factor (TCF)/lymphoid-enhancer factor (LEF) family to control the expression of Wnt target genes [98]. In a variety of cancer cell lines, curcumin has been shown to block the b-catenin/TCF/LEF pathway [99]. Curcumin also suppresses the activation of transcription factors through the Wnt/b-catenin signaling pathway, which is important in curcumin-induced adipogenesis suppression [100]. These transcription factors include peroxisome PPARc and C/EBPa. The Wnt/b-catenin pathway's genes, such as b-catenin and cyclin D1, may be silenced by curcumin, and it can also cause apoptosis in the cell lines MCF-7 and MDA-MB-231. When curcumin was administered, Wnt signaling, GSK-3b, and E-cadherin activation were all decreased in the same cells [101]. Additionally, curcumin suppressed intestinal tumors by lowering the expression of b-catenin and triggering apoptosis through Wnt/b-catenin in both in vitro and animal models of familial adenomatous polyposis [102].

Additionally, it has been demonstrated that curcumin activates protein kinase D1 (PDK1), which prevents nuclear b-catenin transcription activity in prostate cancer cells and increases b-catenin signaling levels. After intratumorally injecting curcumin into the xenograft mouse model, the tumor volume was assessed. In mice treated with curcumin, tumor development was substantially suppressed by a factor of more than two. This resulted in a reduction in cofilin, a downstream target of PDK1, and an increase in b-catenin's membrane localization [103].

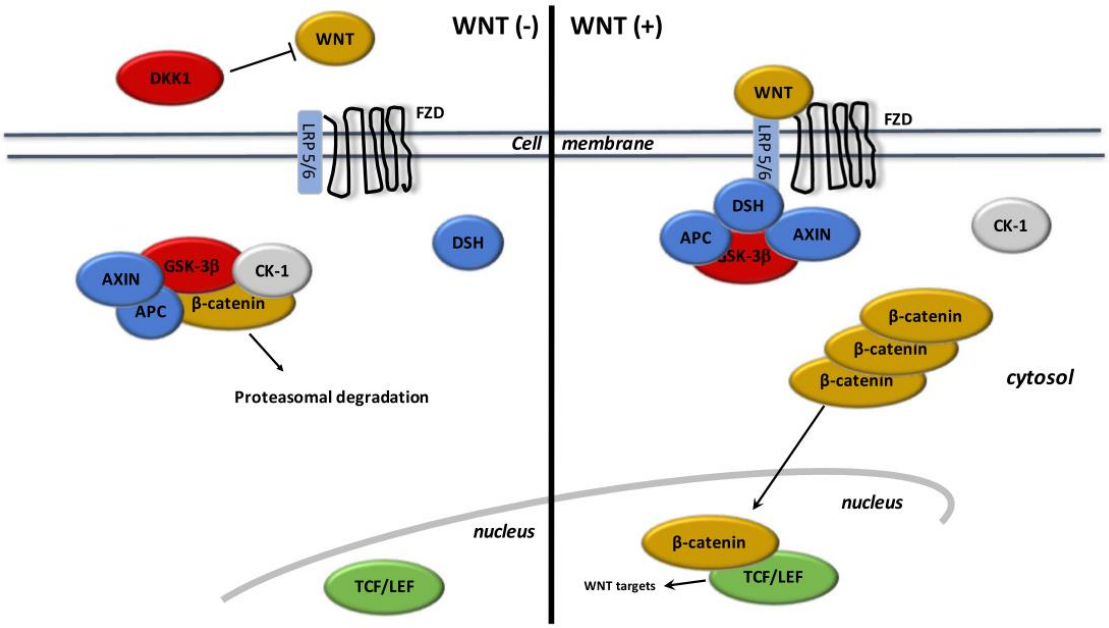
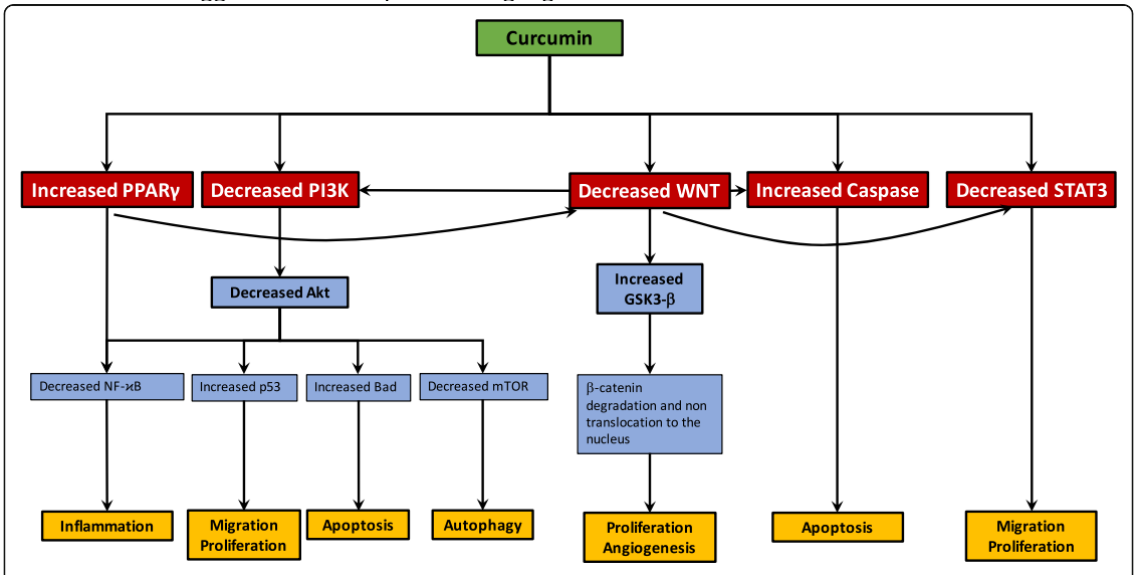


Figure-4. the canonical WNT/β-catenin pathway. WNT (−). Under resting condition, the cytoplasmic β-catenin is bound to its destruction complex, consisting of APC, AXIN, and GSK-3β. After CK-1 phosphorylates on Ser45 residue, β-catenin is further phosphorylated on Thr41, Ser37, and Ser33 residues by GSK-3β. Then, phosphorylated β-catenin is degraded into the proteasome. Therefore, the cytosolic level of β-catenin is kept low in the absence of WNT ligands. If β-catenin is not present in the nucleus, the TCF/LEF complex cannot activate the target genes. DKK1 inhibits the WNT/β-catenin pathway by binding to WNT ligands or LRP5/6. WNT (+). When WNT ligands bind to both FZD and LRP5/6, DSH is recruited and phosphorylated by FZD. Phosphorylated DSH in turn recruits AXIN, which dissociates the β-catenin destruction complex. As a result, β-catenin avoids being phosphorylated and ends up building up in the cytoplasm. As cytosolic β-catenin accumulates, it enters the nucleus, attaches itself to TCF/LEF, and triggers the transcription of target genes [104].



(Figure-5. Various pathways followed by curcumin to prevent diseases)

Effects of curcumin on the WNT pathway in cancer treatment. Curcumin regulates many signaling pathways, which in turn controls the course of cancer. When ligands bind to their respective receptors, downstream pathways including caspase, STAT, and PI3K are activated. Angiogenesis, migration, metastasis, apoptosis, and cell survival are all significantly impacted by these signaling pathways [105-107]. Curcumin inhibits the Akt pathway, which activates the p53 signaling cascade and the Bad-mediated apoptotic pathway, both of which promote the survival of cancer cells. Furthermore, the suppression of the NF-κB signaling pathway, which causes inflammation, is linked to the downregulation of the Akt pathway. Curcumin causes the WNT pathway to be inhibited, which activates GSK-3β activity and causes β-catenin to be phosphorylated and eventually degraded [108-110].

The regulation of angiogenesis and proliferation is linked to the suppression of the WNT pathway. Curcumin inhibits the STAT3 signaling pathway to prevent migration and proliferation while increasing the caspase pathway, which causes apoptosis. Curcumin activates PPARγ, which in turn causes the WNT pathway to be downregulated and inflammation to be controlled. WNT pathway downregulation causes the caspase signaling pathway to rise while the PI3K and STAT3 signaling pathways decline [111-115].

5. Curcumin's Effects on the AMPK/COX-2 Pathway

Maintaining the energy balance inside the cell, AMPK is an intracellular energy sensor that recognizes increased AMP levels and depletes cellular ATP [116]. According to reports, AMPK regulates the body's energy metabolism. As a result, medications aimed at preventing metabolic disorders including type II diabetes and obesity may find value in targeting this protein [117]. In vitro and in vivo investigations have shown that AMPK has anti-inflammatory properties in addition to its role as an energy regulator [118]. Numerous pieces of evidence suggest that AMPK activity inhibits NF-jB activation. It appears that the downstream mediators of SIRT1, the Forkhead box O (FoxO) family, and peroxisome proliferator-activated receptor c co-activator 1a (PGC-1a), which inhibit the production of inflammatory markers, are indirectly responsible for this suppression [119]. When galactosidase indicator (MAGI) cells were activated multinuclear, the application of curcumin triggered AMPK, undid Tat-induced downregulation of HDAC1 expression, and prevented p65/NF-κB binding to long terminal repeat promoters [120]. In HT-29 colon cancer cells, curcumin has been shown to activate AMPK, which is essential for the down-regulation of pAkt and COX-2 [121]. Through the down-regulation of PPARc by AMPK in 3T3-L1 adipocytes, curcumin can have anti-differentiation effects. In MCF-7 breast cancer cells, curcumin can have anti-proliferative effects through AMPKa/COX-2. This study found that in cancer cells, AMPK activation by curcumin downregulated Erk1/2, p38, and COX-2 [122].

Curcumin therapy (0.2% and 2.0%) was shown to activate AMPK and down-regulate COX-2 and NF-κB, resulting in a substantial decrease in the overall number of colonic premalignant lesions caused by azoxymethane in obese C57BL/KsJ-db/db mice. As a result, a mechanism that starts a cascade between AMPK and COX-2 presents a viable treatment option for stopping the growth of cancer cells [123].

6. Curcumin's Effects on the MAPK Pathway

Apart from the NF-κB pathway, MAPK has gained significant attention as a potential target molecule for cancer prevention and treatment. According to reports, phase II detoxifying enzymes may be induced by activating MAPK pathways, while AP-1-mediated gene expression is inhibited by inhibiting MAPK pathways (Fig. 4) [124]. The MAPK pathway is made up of a three-tiered kinase core in which MAP3K activates MAP2K, which in turn activates a MAPK (p38, Erk, and JNK). This process stimulates NF-κB, which promotes cell growth and survival. Through the lowering of phosphorylated PI3K-Akt, Erk, and JNK in the hepatic stellate cells, curcumin inhibited the signaling of the growth factors PDGF and EGF and triggered death. Curcumin's inhibiting method may cause apoptosis by adversely regulating the expression of the PPARc gene [125].

Furthermore, a great deal of data suggests that in several cell systems, ERK activation phosphorylates and degrades IkB protein, increasing NF-κB's nuclear translocation and subsequent DNA binding. In mouse skin, curcumin reduced NF-κB activation and ERK1/2's catalytic activity [126]. Curcumin also lessens inflammation and modifies the MAPK signaling pathway. Through a decrease in p38 MAPK activity, curcumin can mitigate experimental colitis [127]. It is thought that protein kinases are involved in many different physiological processes. Curcumin binds directly to PKC-a and -b2 and inhibits the membrane translocation of these proteins caused by diabetes. It also inhibits the elevated phosphorylation of p38-MAPK and ERK1/2 in diabetic rats. Growth factors (TGF-b, osteopontin), myocyte enhancer factor-2 protein expression, and nicotinamide adenine dinucleotide phosphate (NADPH-oxidase) subunits (p67phox, p22phox, gp91phox) were all reduced by curcumin [128]. Another study demonstrated curcumin's protective impact in the same animal by lowering MAPK activation and COX-2-mediated inducible nitric oxide (iNOS) production. Curcumin's apoptotic actions were mediated by the production of ROS and the inhibition of the transcriptional activities of JNK, P38, MAPK, and AP-1 [102].

Conclusion

In conclusion, this comprehensive exploration of curcumin's complex trip through cellular pathways sheds light on the drug's extraordinary potential for therapeutic use. Curcumin possesses a diverse range of biological activities, including anti-inflammatory actions that regulate immune responses and antioxidant qualities that fight oxidative damage. Its importance in several clinical scenarios is further highlighted by its capacity to modulate signaling pathways linked to angiogenesis, apoptosis, and cell proliferation. Moreover, the knowledge gained from this research and review clarified the significance of customized medical strategies. The optimization of curcumin-based therapies' effectiveness for a range of patient groups can be achieved by customizing them to certain cellular and molecular profiles.

Curcumin is a chemical that has uses beyond cooking, as we discover when we explore the complex geography of its cellular connections. Its passage via biological pathways provides access to novel treatment approaches for a variety of illnesses, including inflammatory ailments, metabolic syndromes, cancer, and neurodegenerative diseases. Thorough scientific research and multidisciplinary cooperation will be essential to realizing curcumin's full medicinal potential. We are in a position to see the revolutionary effects of curcumin on human health through continued research, launching a new age of individualized, focused therapies.

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