

## Mini-Review



# Therapeutic activities and biological effects of curcumin, as a natural multi-target compound, on human health: A mini-review

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## Abstract

**Background and aims:** Curcumin or diferuloylmethane is derived from ferulic acid. This herbal compound has a particular chemical structure and various biological/medical properties. The functional groups in the curcumin structure and its analogs are involved in the formation of specific biological activities. This natural compound has high bioactivity, as well as the potential to treat diseases such as cancer, Alzheimer's, diabetes, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Considering the spread of infectious diseases and cancers in recent years, as well as an increase in drug resistance and side effects, providing effective and available treatments is necessary.

**Methods:** This review explained the chemical structure of curcumin and covered its biological properties, including anti-inflammation, antioxidant, anti-cancer, neuroprotective, anti-diabetic, and anti-SARS-CoV-2 activities. Scientific databases were studied to gather the required information.

**Results:** Curcumin affected several molecular pathways, including activating transcription factors, cell growth factors, anti-inflammatory agents, protein kinases, cytokines, and apoptotic pathway factors. Thus, it had beneficial therapeutic effects on health.

**Conclusion:** By targeting a wide range of molecular mechanisms, curcumin has the potential to treat various diseases. Knowledge of curcumin's pharmacological/biological activities and its action mechanisms can enhance the applications of curcumin as a potentially bioactive and therapeutic compound.

**Keywords:** Curcumin, Biological activities, Molecular effect targets, Curcuminoids

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## Introduction

Curcumin is a yellow-orange herbal compound that is extracted from *Curcuma longa* (1). It is known as the main component of turmeric, and its yellow-orange color is due to the presence of curcuminoids (2). The curcuminoid compounds of turmeric include curcumin, demethoxy-curcumin, and bis-demethoxy-curcumin, which form about 77%, 17%, and 3% of the dry weight, respectively (3).

The therapeutic and biological properties of curcumin have received much attention (4). Anti-cancer, anti-diabetes, anti-SARS-CoV-2 (5), anti-microbial, anti-inflammatory, and anti-apoptotic activities have been reported for curcumin (6-8). This herbal compound affects several molecular targets such as transcription factors, cell cycle regulating proteins, cytokines, growth factors, enzymes, and anti-inflammatory agents due to its low selectivity (9, 10). In addition, it has a chemotherapeutic effect without any side effects on normal cells, which is a promising drug candidate for cancer treatment (11).

Despite the unique biological properties of curcumin, low solubility in the physiological environment, rapid metabolism, and poor absorption have limited the clinical applications of curcumin (12). The increased plasma concentrations and bioavailability of curcumin

through its formulation have been reported as well (13). In recent years, multiple strategies such as the use of nano-based drug delivery systems have been proposed for the formulating and encapsulating of curcumin that can improve its medical applications (10,14). For example, an enhanced protective effect of nano-curcumin has been reported compared to curcumin to prevent lung damage caused by pesticides. Nano-curcumin exerts a protective effect by modulating oxidative stress (15). In another study, Asadi et al used the nano-formulation of curcumin in their experiments to increase the bioavailability of curcumin. Their results showed that nano-curcumin is effective in reducing anxiety in patients with diabetic polyneuropathy (16). Therefore, the therapeutic properties of curcumin are improved using nanotechnology methods (17).

Recently, herbal remedies have become an attractive topic in pharmaceutical research due to their low side effects and availability. This review covers the chemical structure and biological activities of curcumin. In addition, it focuses on the anti-cancer, neuroprotective, anti-diabetic, anti-inflammation, antioxidant, and anti-SARS-CoV-2 activities of curcumin, which could be effective in expanding the researchers' perspective on the therapeutic benefits and clinical applications of curcumin.

## Chemistry of curcumin

Curcumin (IUPAC: (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione) with molecular formula  $C_{21}H_{20}O_6$  is known as a polyphenolic and hydrophobic herbal compound (18-20). It shows keto/enol tautomeric forms (Figure 1), and a methylene bridge connects the two ferulic acid residues in the curcumin structure. Methoxyphenol and methylene groups are bioactive groups in the structure of curcumin (18,21,22).

## Biological activities of curcumin

### Anti-inflammatory and antioxidant activities

Inflammation occurs in the body against infections, injuries, and toxins. The immune system responds to the development and progression of cancer by inflammation. Many anti-inflammatory drugs have been proposed to relieve the chronic inflammatory response. Several studies have suggested that curcumin may be a promising anti-inflammatory agent (23,24).

The inflammatory process consists of three main phases, including increased vascular permeability, tissue infiltration of leukocytes, and granuloma formation. Curcumin is effective in controlling inflammation by modulating this process (25). Some special enzymes such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase, and lipoxygenase mediate inflammatory processes. According to evidence (26), curcumin can inhibit the functions of the enzymes by inhibiting the production of cytokines such as interferon- $\gamma$ , and tumor necrosis factors, suppressing transcription factors such as activating protein-1, and nuclear factor- $\kappa$ B (NF- $\kappa$ B). The inhibition of NF- $\kappa$ B signaling by curcumin diminishes macrophage activation. Moreover, curcumin can reduce the expression of the NF- $\kappa$ B-regulated gene products, including interleukin-1 (IL-1), IL-6, IL-8, COX-2, tumor necrosis factor (TNF), adhesion molecules, macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ ), C-X-C motif chemokine receptor-4, and C-reactive protein (27,28). Furthermore, the controlling activity of curcumin on immune cells such as T-regulatory and T-helper 17 cells

is advantageous in the inflammatory disease therapy. T-helper 17 cells accelerate the inflammatory process by producing IL-17, IL-22, and IL-23 (29).

In addition to anti-inflammatory activity, curcumin inhibits lipid peroxidation and DNA damage caused by free radicals through its antioxidant activity (30). The antioxidant properties of curcumin are attributed to the presence of methylene hydrogen and methoxy-phenol groups in their structure. Activation of antioxidant enzymes has been reported as a result of the increased expression of heme oxygenase-1 and nuclear factor erythroid-2 related factor-2 (Nrf2) pathway activation by curcumin (31). The association and interaction of oxidative stress and inflammation trigger intracellular signal cascades that are involved in the pathological processes of a wide range of diseases. Curcumin disrupts the oxidative stress/inflammation chain by increasing the activity of antioxidants and eliminating various types of free radicals such as hydroxyl, superoxide anion, and nitrogen oxide radicals (32,33).

### Anti-cancer activities

Cancer results from a defect in the mechanisms that usually control cell growth and proliferation. In this case, the cells often change their connections with the cells adjacent to the cell matrix, break the loose connections, and undergo an oncogenic transformation. In addition, cancer cells contain the active enzyme telomerase, which prevents apoptosis (34).

As shown in Figure 2, curcumin suppresses cancer cells by activating transcription factors, cell growth factors, protein kinases, inflammatory cytokines, and elucidating apoptotic pathway factors (35-38).

The effect of curcumin on the inhibition of telomerase activity in leukemia cancer has been reported in some studies (39,40). Curcumin increases the expression of proapoptosis genes by controlling various signaling pathways (41). For example, in breast cancer, curcumin activates the apoptotic pathway by positively regulating the Bad and Bax factors and reducing the expression of BCL2 and BCLXL (42). It has been shown that curcumin modulates the process of caspase activation and ultimately cell death by increasing the expression of PUMA, Bim, Noxa, Bak, Bax, and the like (36). Further, increased expression of the p53 gene, as a tumor suppressor gene and one of the downstream targets of apoptotic processes, has been reported in curcumin-treated cancer tissues (43). Studies have demonstrated the ability of curcumin to kill apoptotic resistant cancer cells through non-apoptotic mechanisms such as the activation of the aberrant mitotic mechanism (44). Natural killer (NK) cells are a group of human immune system lymphocytes that can detect and kill cancer cells without the need for prior activation. Cancer cells can inhibit the anti-tumor function of NK cells. Curcumin enhances apoptosis induction and cancer cell death by improving NK cell activity (45). Among the various anti-cancer mechanisms of curcumin, its

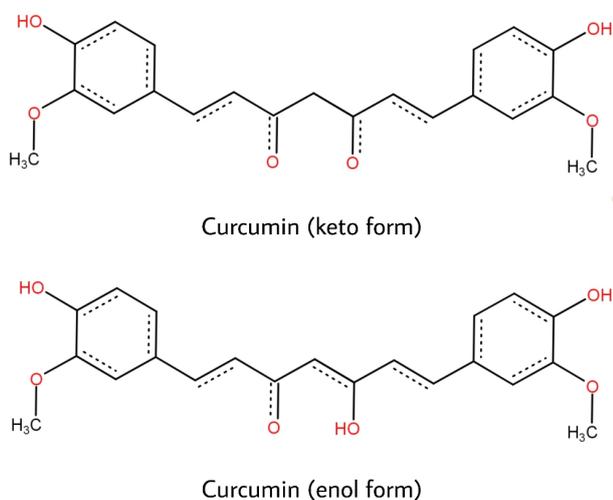
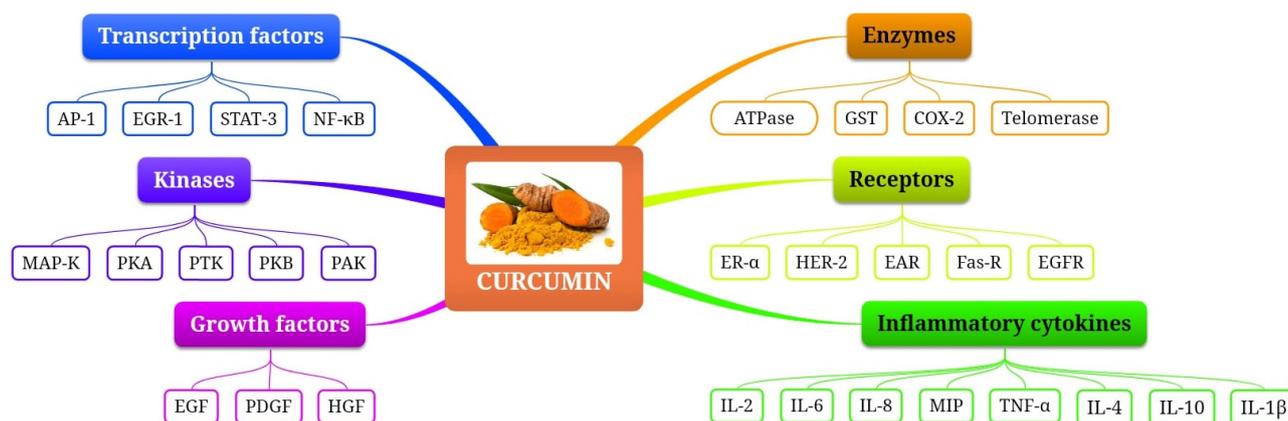


Figure 1. Chemical structures of curcumin.



**Figure 2.** Schematic of curcumin-influenced molecules. *Note.* AP-1: Activating protein-1; EGR-1: Early growth response-1; STAT-3: Signal transducer and activator of transcription-3; NF-κB: Nuclear factor-κB; MAP-K: Mitogen-activated protein kinase; PKA: Protein kinase A; PTK: Protein tyrosine kinase; PKB: Protein kinase B; PAK: p-21 activated kinase; EGF: Epidermal growth factor; PDGF: Platelet-derived growth factor; HGF: Hepatocyte growth factor; GST: Glutathione S-transferase; COX-2: Cyclooxygenase-2; ER-α: Estrogen receptor-α; HER-2: Human epidermal growth factor receptor-2; EAR, Fas-R: Fas-receptor; EGFR: Epidermal growth factor receptor; IL: Interleukin; MIP: Macrophage inflammatory protein; TNF-α: Tumor necrosis factor-α.

ability to induce apoptosis plays a more important role in the treatment of cancer (46). Inflammatory reactions are known as the side effect of radiation therapy and chemotherapy. Inflammation can increase the resistance and growth of cancer cells. Curcumin inhibits the growth of cancer cells through its anti-inflammatory mechanisms, controlling the NF-κB, and its downstream signaling pathways (24).

### Neuroprotective activities

Progressive neurological diseases such as Parkinson's, Alzheimer's, multiple sclerosis, and Huntington's rapidly spread in human societies (47). In Alzheimer's disease, when cholinergic neurons release neurotransmitter cell acetylcholine, folding and abnormal accumulation of amyloid-β (Aβ) peptides cause aging plaques and hyperphosphorylation of Tau node microtubules in the brain, which impairs cerebral skeletal integrity (48,49). In Alzheimer's disease, extensive research has been performed on the treatment and prevention of this disease, which can be referred to as the extraordinary effect of curcumin in treating this disease (50). Curcumin is shown to be effective in inhibiting (κ) nuclear factor signaling and reducing pro-inflammatory cytokines such as IL-6, IL-1B, and TNF-α due to its anti-inflammatory potential (51,52). Furthermore, curcumin prevents lipid peroxidation, mitochondrial dysfunction, and neuronal death by increasing glutathione levels and decreasing the level of reactive oxygen species (53).

There are many studies on plasma cholesterol levels and Alzheimer's disease; for example, plasma cholesterol levels have been reported to be 10% higher in Alzheimer's patients compared to levels in healthy individuals. ApoE protein transports free cholesterol to the brain and causes the accumulation of the Aβ peptide. Curcumin reduces the synthesis of cholesterol and fatty acids in the liver by inhibiting the expression of sterol regulatory element-binding proteins (54-56). In Alzheimer's disease, the Aβ peptide is transported by copper molecules to form an

interdisciplinary histidine brace, allowing the formation of the beta-sheet structure in the plaque. Curcumin has metallic chelation properties and chelates copper in the presence of the Aβ peptide (57-59).

Parkinson's disease after Alzheimer's is the most common disease associated with aging, which has pathological features, including α-synuclein protein phosphorylation and the formation of proteinaceous inclusions such as Lewy bodies in axons and neurons, along with the degeneration of dopaminergic nigrostriatal neurons (60). Curcumin treats Parkinson's disease by stimulating the human α7-nicotinic acetylcholine receptor and neuroprotection against the reduction of dopaminergic neurons (61).

Nowadays, heavy metal poisoning is one of the challenges that causes nervous system disorders. These metals (e.g., cadmium) enter the central nervous system through the nasal mucosa and olfactory tract and cause adverse structural and functional effects on the brain. The effect of curcumin on hippocampal (DCX, CREB, BDNF, and synapsin II) cells underwent investigation. When these cells were exposed to cadmium, they caused behavioral disorders through oxidative stress, decreased neurogenesis-related proteins in the hippocampus, and destructed central cortical neurons. When these cells were treated with different concentrations of curcumin, neurogenesis proteins in the hippocampus increased in a way that reduced cadmium toxicity (62).

### Anti-diabetics activities

Insulin is a protein hormone that plays an essential role in blood glucose homeostasis. In response to the levels of blood glucose, the islet cells of Langerhans secrete insulin, then enter the bloodstream and are transported to the skeletal muscle, liver, and adipose tissue. Disruption of the insulin-signaling pathway leads to insulin resistance, known as diabetes II, which is spreading worldwide (63-65). Studies examining the link between diabetes II and obese people have demonstrated that plasma free-fatty

acids impair insulin's ability to suppress hepatic glucose (66-70).

Many studies have focused on the effects of plant compounds on the treatment of diabetes II. One of these plant compounds is curcumin (71-73). According to studies, curcumin is effective in treating diabetes by controlling apoptosis-dependent pathways and the PI3K/AKT signaling pathway (17,74). Inflammatory reactions and oxidative stress are considered to be effective factors in the progression of diabetes. Cellular exposure to curcumin has been associated with a reduction in inflammatory factors such as TNF $\alpha$ , IL-6, and the like, and the modulation of antioxidant enzyme serum levels, including catalase and superoxide dismutase, confirming the role of curcumin in the diabetes treatment (75).

Curcumin reduces the amount of free glucose in the blood through several methods, increases insulin secretion, and prevents diabetes (76), which is briefly described as follows:

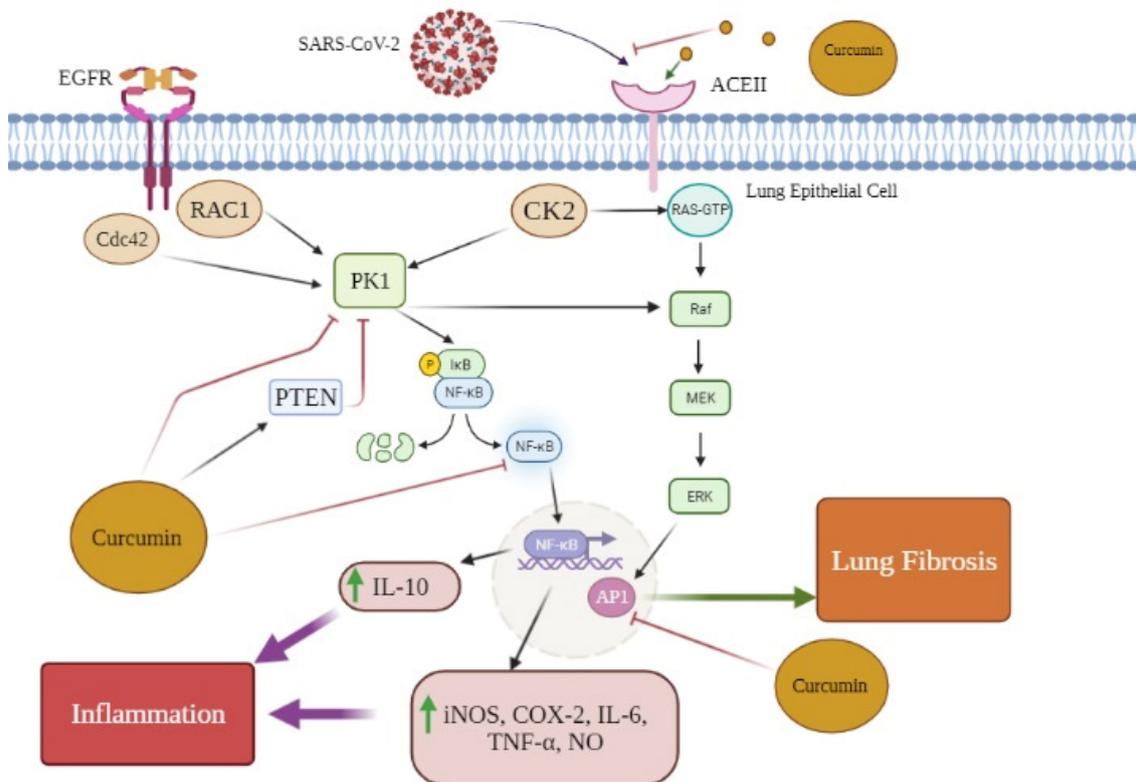
- Reducing glycerol release and increasing glucose uptake in 3T3-L1 adipocytes (77-79);
- Reducing the differentiation of fat cells (C/EBP $\alpha$ -PPAR $\gamma$ -C/CEBP $\beta$ ) and suppressing lipogenesis (80);
- Treating 3T3-L1 cells and primary adipocytes with curcumin resulted in the browning of fat white cells and mitochondrial biogenesis, indicating that curcumin treats obesity and insulin-resistant diabetes (81,82);
- Suppressing inflammation, hyperglycemia, and lipid

peroxidation by inhibiting the TNF $\alpha$ , HbA1c, IL-6, and monocyte chemotactic protein-1 (MCP-1) factors (83,84);

- Suppressing gluconeogenesis by inhibiting the enzyme carnitine palmitoyl transferase 1(CPT-1), which is associated with a decrease in blood sugar (63,85);
- Treating adipocytes with curcumin suppressed differentiation and decreased mRNA levels of carnitine kinase 1 and glycogen synthase kinase 1 (86).

**Anti-SARS-CoV-2 activities**

During the coronavirus disease 19 (COVID)-19 pandemic, a large body of research has been performed to identify the components that affect the SARS-CoV-2 virus. Various studies have suggested curcumin as an anti-SARS-CoV-2 drug. Curcumin acts against SARS-CoV-2 by inhibiting viral replication and proteases in virus-targeted cells. Moreover, the anti-inflammatory, inhibitory effects on cytokines and chemokines are the potential of curcumin against SARS-CoV-2 (87,88) (Figure 3). The other anti-SARS-CoV-2 activities of curcumin include the inhibition of virus binding and entering into host cells and the disruption of the viral structure. In-silico studies have demonstrated that curcumin has a dual inhibitory effect. Additionally, it has a strong affinity to bind to SARS-CoV-2 spike protein and its receptor in the host cell angiotensin-converting enzyme II. Thus, by inhibiting the receptor in the host cell and the viral antigen, the viral



**Figure 3.** Schematic illustration of the action mechanisms of curcumin against SARS-CoV-2. Note. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. Cdc42: Cell division cycle 42; RAC1: Rac family small GTPase 1; PK1: Protein kinase 1; CK2: Casein kinase 2; PTEN: Phosphatase and tensin homolog deleted on chromosome ten; MEK: Mitogen-activated protein kinase; ERK: Extracellular signal-regulated kinase; iNOS: Inducible nitric oxide synthase; COX-2: Cyclooxygenase-2; IL: Interleukin; NO: Nitric oxide.

entry into the cell is disrupted (89,90). Targeted curcumin delivery approaches such as drug nano-carriers have been proposed to increase bioavailability and therapeutic efficacy. This structure helps curcumin work better against the SARS-CoV-2 (89).

SARS-CoV-2 is one of the more recently oxidative stress-related diseases that progresses by oxidative stresses. Under cellular redox imbalance, Nrf2 controls the normal state of cellular redox by interacting with antioxidant response elements. There is strong evidence that curcumin has the potential to activate the Nrf2 pathway (91). Furthermore, the unbalanced ratio of T-regulatory/T-helper 17 cells is one of the effective mechanisms in the hyper inflammation of the immune system in COVID-19, which is related to high mortality. Curcumin affects the number of T-helper cells in different ways by reducing the number of T-helper 17 cells, and T-helper 17 cell-related factors (92). Notably, the incidence of acute respiratory distress syndrome and multiple organ damage in COVID-19 patients has been associated with elevated levels of inflammatory chemokines such as MIP1 $\alpha$  and MCP1, and inflammatory cytokines, including IL-6, IL-8, TNF- $\alpha$ , and IL-1 $\beta$ . Curcumin as an inflammatory response suppressor can prevent cytokine storms in COVID-19 patients (29).

### Conclusion and Future Perspectives

This review focused on studying the biological activity and therapeutic benefits of curcumin. Numerous studies have confirmed the strong potential of curcumin against microbial/viral agents by impairing their structure and function. The use of herbal compounds such as curcumin can be significantly effective in reducing drug resistance. Curcumin is effective in the prevention, control, and treatment of various diseases such as cancer, diabetes, neurological disorders, and COVID-19 by suppressing/activating several signaling pathways.

Nonetheless, curcumin has not been accepted as an ideal drug for clinical use due to poor solubility in water, rapid metabolism, short half-life, and low absorption in the gastrointestinal tract due to glucuronidation reactions and sulfation in the stomach. However, the use of new methods such as nanoparticles and nanoemulsions for curcumin formulation/encapsulation improves the effectiveness of curcumin. Therefore, curcumin can be a promising and eligible alternative to many current high-risk treatments since it is a natural, available, and safe compound.

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### Authors' Contributions

F.P., N.P., and N.N. equally contributed to this study. H.M. conceived the presented ideas and supervised the work. F.P. and H.M. reviewed the manuscript. All the authors read and approved the final manuscript. All figures were designed by the authors.

### Conflict of Interests

The authors declare that they have no conflict of interests.

### Ethical Approval

Not applicable.

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