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The Effect of Curcumin on Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most prevalent type of dementia, affecting approximately 50 million individuals globally, and projections indicate that this number will increase to 139 million by 2050. It is one of the main factors contributing to cognitive decline in the aging population. Existing treatments do not produce the intended therapeutic benefits; therefore, it is imperative to identify alternative pharmacological and biological techniques. As the precise pathogenic pathways underlying AD remain unknown, existing therapies only address symptoms rather than promote prevention or treatment. Curcumin has attracted increasing attention owing to its distinct molecular structure. It affects antioxidant and inflammatory pathways as well as amyloid aggregation, which is one of the main characteristics of Alzheimer's disease. Many human ailments have been treated with medicinal plants, owing to their antioxidant properties. Curcumin has been used as a traditional food and medicine in Asia for a long time. Numerous studies have shown that curcumin has several advantageous properties including anti-inflammatory and antioxidant activities. Numerous clinical trials have been conducted to clarify the impact of curcumin on cancers, owing to its documented effects on tumors. Recent findings suggest that curcumin may have therapeutic potential in the pathogenesis of Alzheimer's disease (AD). The overall memory of patients with AD has improved because of several benefits of curcumin, including decreased beta-amyloid plaques, delayed neuronal degradation, metal chelation, anti-inflammatory and antioxidant effects, and decreased microglial production.

Keywords

Alzheimer's, Curcumin, Beta-Amyloid, Anti-Inflammatory, Antioxidant, Microglia

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by pro-

gressive destruction of cortical neurons and hippocampal cells, which impairs cognitive and memory functions. Deterioration of short-term memory is the initial clinical symptom of the illness, whereas recovery of distant memory occurs later in the disease. It represents 60% - 70% of all dementia cases. Cognitive decline is the first indication of AD, followed by a decline in social and behavioral functioning. Amyloid-β (Aβ) plaques, which result from modifications in the proteolytic processing of amyloid precursor protein (APP) and neurofibrillary tangles (NFTs) caused by tau protein hyperphosphorylation, are the primary histological characteristics of AD. [1] As the longevity of the elderly population increases, the World Health Organization (WHO) reports state that 35.6 million individuals worldwide suffer from this condition; it is predicted that this frequency will double by 2030 and triple by 2050. Currently, no pharmacological interventions are available to prevent or reverse cognitive deterioration. [2] Additional cognitive capacity and the capacity to utilize and interpret everyday equipment and objects are compromised by the onset of the disease. [3] Randomized controlled clinical trials are lacking to verify the protective or therapeutic efficacy of natural antioxidant agents, such as polyphenols, fatty acids, and vitamin-rich foods, although epidemiological studies suggest that they may postpone the onset of neurodegenerative diseases. [4] The aim of this review is to summarize the research evidence with an emphasis on recent studies on the protective potential of Curcumin against Alzheimer's disease.

2. Alzheimer

Alzheimer's disease (AD) is a neurodegenerative condition that is often distinguished by two features: amyloid plaques and neurofibrillary tangles. Globally, more than 50 million individuals suffer from this condition, and by 2050, this number is expected to increase to 139 million. Despite the high incidence, the pathogenic mechanisms underlying this condition remain unclear. Although preventive and curative measures have not yet been launched, treatments that concentrate solely on symptom management have been developed. To mitigate the global incidence and morbidity of AD, it is imperative to enhance our understanding of its etiology and to identify plausible therapeutic targets that may serve as preventive or remedial measures. Currently, the primary pathways implicated in the pathogenesis of AD are the amyloid and tau hypotheses. The amyloid hypothesis remains the most widely accepted explanation for the pathophysiology of AD despite the wealth of evidence supporting the critical role of amyloid beta (Aβ) in AD pathology over the past few decades. However, this hypothesis does not provide a complete explanation for the causative mechanisms of the disease. [5] The ATN framework establishes a clear distinction between dementia and Alzheimer's disease by supporting the roles of tau and amyloid β as defining features of the disease. This framework suggests that biomarkers alone can be used to diagnose Alzheimer's disease. [3]

2.1. Antioxidant

Oxidative stress plays a crucial role in the development of redox imbalance, which may include the accumulation of reactive oxygen species (ROS) or a decline in antioxidant defense. Owing to its high oxygen consumption rate, low enzymatic defence against oxidative stress, and readily damaged lipid composition, the brain is particularly vulnerable to oxidative stress. In addition to lipids, ROS can interact with other molecules such as proteins and nucleic acids, causing harmful modifications to their structures and activities. Oxidative stress can lead to cell death by the end of the day. Aberrant transition metal accumulation and/or mitochondrial malfunction may result in the overabundance of reactive metals in AD. Tau and A proteins may also exacerbate this redox imbalance, and oxidative stress can accelerate tau phosphorylation and polymerization as well as enhance the synthesis and aggregation of A, which can lead to a vicious loop that promotes disease progression. Restoring redox balance could be a viable treatment for AD because of the harmful effects of ROS on the disease. [6]

2.2. Amyloid B and Tau Protein in Alzheimer's Disease

Amyloid beta (Aβ) has traditionally been regarded as a defining characteristic of the AD pathophysiology. Patients with Alzheimer's disease typically have severe neuronal loss, neurofibrillary tangles, and senile plaques in their brains. This type of abnormality is primarily dependent on two critical proteins, tau and amyloid-β (Aβ), where tau is responsible for the production of neurofibrillary tangles, and Aβ is responsible for the formation of senile plaques. AD is a rapidly progressive neurodegenerative disease characterized by behavioral abnormalities and loss of cognitive function in developing countries. Increased levels of Aβ fibril deposition in the AD brain cause neuropathology, including neuronal death and impaired function. The colocalization of the amyloid protein precursor gene at chromosome 21 and the prior discovery that trisomy 21 always results in the neuropathology of AD have been previously reported. Additionally, it shows how Aβ accumulation is the main event in the pathogenesis of AD. A mutation near the Aβ region of the APP gene coding sequence, which was subsequently broken down by proteases known as α-, β-, and γ-secretases, has also been reported. Therefore, alterations in APP metabolism via secretases or abnormal APP metabolism may play a significant role in AD pathophysiology. Similarly, significant tau deposition in neurofibrillary tangles in the brain, which causes frontotemporal dementia with parkinsonism without any Aβ deposition, is linked to the same type of mutation in the tau protein-coding area. We might infer from these data that the initial pathogenic event leading to AD is the accumulation of Aβ in the brain.

Despite this, Aβ contains two species: Aβ40 and Aβ42. The C-terminus of Aβ ends at the 40th or 42nd amino acid and distinguishes these two species from one another.

Aβ42 can show signs of plaque formation as early as 12 years of age, whereas Aβ40 plaque formation is not observed until at least 20 years of age, according to

earlier reports. According to additional research, Aβ42 aggregation occurs far more quickly than Aβ40 aggregation, and is essential for amyloid deposition in the parenchyma and vasculature. [7]

3. Curcumin

One phenolic antioxidant alternative is curcumin. Curcumin is an active hydrophobic polyphenol extracted from the rhizomes of the herb Curcuma Longa Linn, also known as turmeric, which belongs to the family of Zingiberaceae. [2] Yellow curry species derived from turmeric. This spice is used as a food preservative and herbal medicine in India, where the prevalence of AD in patients aged 70 - 79 years is 4.4-fold lower than that in the United States. [8] Curcuminoids are the active components responsible for most of the medicinal properties of turmeric and consist of a mixture of curcumin (75% - 80%), demethoxycurcumin (15% - 20%), and bisdemethoxycurcumin (3% - 5%) (**Figure 1**) [9]. Modern medicine has shown that curcumin exhibits a wide variety of biological and pharmacological activities, including anti-inflammatory, antioxidant, neuroprotective, and chemoprotective properties, owing to its ability to modulate numerous signaling molecules. [2] Many studies concerning the antitumor activity of curcumin have been conducted, and the clinical benefits of curcumin against tumors are being actively investigated, although clinical trials are still in a relatively early phase. Current consumption in old age has recently been associated with improved cognitive functions. Furthermore, some reports have suggested possible beneficial effects of curcumin on experimental models of Alzheimer's disease (AD). In recent years, the focus has shifted to the neuroprotective effects of curcumin on cognition. Epidemiological data has shown that regular curcumin intake may be associated with improved cognitive function in healthy elderly individuals. [10]

However, there are drawbacks that limit the development of curcumin as a potential therapeutic agent, such as its instability at a pH above 7, low bioavailability, and poor solubility. The antioxidant curcumin can be categorized into two series: phenolic compounds and Î²-diketones. [11]

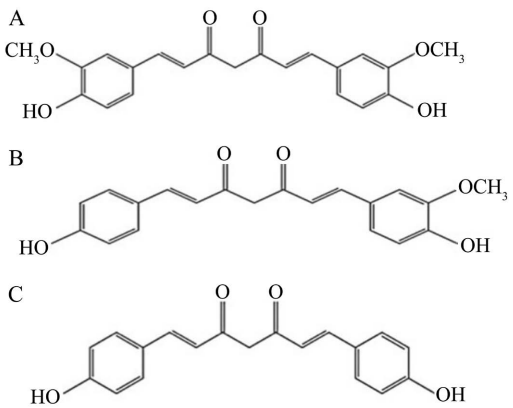

Figure 1. Chemical structures of curcumin (A), demethoxycurcumin (B), and bisdemethoxycurcumin (C).

3.1. Anti-Inflammatory Mechanism of Curcumin

Curcumin reduces inflammation by blocking the synthesis of inflammatory mediators and by controlling inflammatory signaling pathways. By binding to toll-like receptors (TLRs), curcumin controls many signaling pathways such as mitogen-activated protein kinase (MAPK), Activator Protein 1 (AP-1), and downstream nuclear factor Kappa-B (NF-κB). This helps control inflammatory mediators and treat inflammatory illnesses. Curcumin acts on peroxisome proliferator-activated receptor gamma (PPARγ) to downregulate NF-κB. Curcumin exerts anti-inflammatory effects by controlling the Janus kinase/signal transducer and activator of transcription (JAK/STAT) inflammatory signaling pathway. Cytosolic multiprotein complexes, known as the NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome, have been implicated in the etiology of numerous inflammatory disorders. The three components of the NLRP3 complex are protease caspase-1, an apoptosis-associated speck-like protein with a caspase recruitment domain, and sensor protein. One possible mechanism of action of curcumin in the treatment of inflammatory illnesses is the direct inhibition of NLRP3 inflammasome assembly or NLRP3 inflammasome activation via the NF-κB pathway inhibition. [12]

3.2. Curcumin for AD

Many studies have examined the interaction between curcumin and β-amyloid *in vitro* and *in vivo*, given the significance of β-amyloid accumulation in the etiology of AD. The dose-dependent neuroprotective effects of curcumin against β-amyloid-induced damage in cultured neuronal cells have been the subject of numerous studies. Several theories have been proposed to explain this protective effect. It has been demonstrated that curcumin, which blocks nuclear factor-κB, can inhibit β-amyloid-induced cell death in human neuroblastoma cells. Additionally, curcumin prevented nuclear factor-κB-induced suppression of peroxiredoxin-6, which decreased hypoxia-induced cell death in rat hippocampal cells. Curcumin has been shown to inhibit β-amyloid-induced expression of the cytokines tumor necrosis factor-α and interleukin-1β in a human acute monocytic leukemia cell line (Sigma-Aldrich), as well as activation of mitogen-activated protein kinase and phosphorylation of extracellular signal-regulated kinase-1/2. Curcumin was added to rat prefrontal cortex neurons, where it blocked the β-amyloid-mediated rise in capsase-3 and triggered the neuroprotective pathway involving Akt. In rat cortical cells, curcumin reduced reactive oxygen species and oxidative stress indicators while preserving cell viability following β-amyloid exposure. In APPswe-transfected SY5Y cells, curcumin reduced β-amyloid toxicity by promoting the Wnt/β-catenin pathway and by lowering GSK-3β activity. Thus, curcumin appears to function at multiple levels to mitigate the neuronal damage induced by exposure to β-amyloid, oxidative stress, or inflammation. β-Amyloid formation and deposition, which has long been considered a trigger for neurodegeneration in Alzheimer's disease (AD), may also be affected by curcumin. Curcumin caused

a dose-dependent reduction in fibrillary β-amyloid1-40 and β-amyloid1-42 production in rat cortical neurons as well as in solution. It also destabilizes fibrils that have already been formed, thereby disrupting the β-sheet shape observed in the AD plaques. Although the exact mechanism underlying this effect remains unknown, it may bind to β-amyloid and inhibit its aggregation. Curcumin analogs that optimize the suppression of β-amyloid aggregation are currently under development. [13]

3.3. Mechanisms of Action of Curcumin in Alzheimer's Disease

The multipurpose mechanisms of action of curcumin A and tau are the two histological markers of AD. They also affect other pathophysiological processes. In addition, it can bind to collagen, decrease cholesterol, alter microglial activity, block acetylcholinesterase, improve the insulin signaling pathway, and possess antioxidant properties (**Figure 2**). [14]

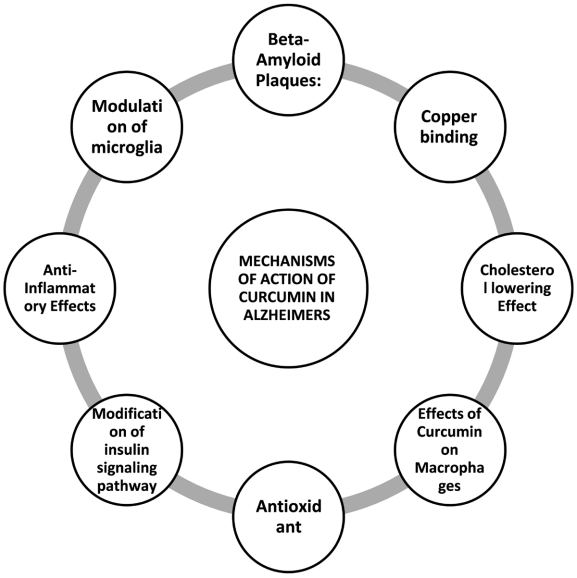

Figure 2. Different mechanisms of action of curcumin in AD.

3.3.1. Beta-Amyloid Plaques

The presence of β-amyloid plaques is the most noticeable sign of AD. In essence, these plaques are a build-up of tiny amyloid fibrils. An appealing therapeutic approach for the treatment of AD is to block the synthesis of A-beta, prevent the development of A-beta fibrils, and destabilize preformed A-beta because the deposition of beta-amyloid protein is a constant pathological hallmark of AD in the brain. When AD mice were administered low doses of curcumin, their beta-amyloid levels were approximately 40% lower than those of mice that did not receive any treatment. Furthermore, the so-called "plaque burden", which β-amyloid has on the brains of AD mice, was reduced by 43% with low-dose curcumin. It was found to be more effective in slowing the neurodegenerative process of Alzheimer's disease (AD) at surprisingly low levels when administered over an extended

period. At higher concentrations, curcumin bound to Aβ and prevented its self-assembly. The presence of two aromatic end groups is one of the primary chemical characteristics of Aβ and changes in these groups have a significant impact on protein function. [7]

3.3.2. Copper Binding

Additionally, to tau and A, the pathophysiology of AD could also be influenced by metal ions, specifically copper (Cu^{2+}). AD is associated with changes in metal homeostasis; in fact, serum Cu levels are higher in patients with AD than in healthy individuals. The precise mechanisms underlying neurological deterioration caused by the interaction between A and copper are unknown. Copper can facilitate plaque formation through multiple methods. It has been demonstrated that metal binds to a peptide to form an interstrand histidine brace, which permits the development of beta-sheet structures in plaques. Copper can be used in the Fenton reaction to produce hazardous reactive oxygen species (ROS), such as superoxide anions and hydroxyl ion radicals, in addition to changing protein structure. It has been shown that oxidative stress controls APP expression and causes an excess of A to be produced. According to previous studies, Cu may also play a role in APP processing. BACE1 interacts with copper and exposure to metal ions increases BACE1 mRNA and APP levels. Furthermore, it is important to note that Cu is also bound by cellular prion proteins, which have recently been discovered to be receptors for misfolded A oligomers. As AD is linked to copper, metal chelation could be a treatment option for AD. Curcumin does, in fact, possess metal chelation capabilities. Picciano and Vaden showed that curcumin chelated copper in the presence of peptides. Furthermore, curcumin prevents the peptide from spontaneously forming fibrils in the presence of Cu and Zn. [14]

3.3.3. Cholesterol Lowering Effect

Cholestery esters accumulate intracellularly in response to high-fat meals and elevated blood cholesterol levels and are associated with increased amyloid plaques. Increasing molecular, animal, and epidemiological research has indicated an association between AD and hypercholesterolemia. Plasma cholesterol levels are approximately 10% higher in patients with AD than in healthy controls. High cholesterol levels alter APP metabolism, which increases A generation. Additionally, individuals carrying the APOE 4 allele were more likely to develop AD. ApoE facilitates Aβ aggregation and cholesterol transport in the brain. Thus, there is a chance that lipid-lowering medication will lower the chance of AD. A population-based case-control study found that the early use of statins, a class of medications used to decrease cholesterol, was substantially related to a lower incidence of AD progression in individuals with mild-to-moderate AD than in those who did not take statins. Similar to statins, curcumin is controversial, but can also be used to decrease cholesterol levels. Sterol regulatory element-binding proteins (SREBPs) have been shown to be inhibited by curcumin. These transcription factors increase the synthesis of the enzymes responsible for lipogenesis, energy production,

glycolysis, and cholesterol synthesis. In addition to aiding cholesterol production, SREBP-1 activation has been demonstrated to be neurotoxic. Curcumin reduces the production of fatty acids and cholesterol in hepatocytes by inhibiting SREBP expression *in vitro*. Similarly, curcumin prevents cholesterol accumulation in muscle cells by blocking SREBP-1 nuclear translocation. In addition to influencing cholesterol synthesis, curcumin affects cholesterol uptake. Peschel *et al.* showed that curcumin reduces cholesterol levels by altering the expression of genes in the liver, which enhances the expression of the low-density lipoprotein (LDL) receptor that mediates endocytosis of cholesterol-rich LDL. Curcumin inhibits the production of the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene, which is responsible for the degradation of LDL receptors. Therefore, more LDL receptors are available to absorb cholesterol-rich LDL when curcumin reduces PCSK9 expression. In addition to hepatic proteins, curcumin also affects intestinal proteins. By suppressing the expression of the intestinal cholesterol transporter Niemann-Pick C1-like-1 (NPC1L1), curcumin reduced the absorption of dietary cholesterol. Soni *et al.* discovered that curcumin can quickly and efficiently reduce blood cholesterol levels in humans. Furthermore, curcumin and turmeric have been suggested to be antioxidants that can scavenge superoxides and radicals both *in vivo* and *in vitro*. [15] and [16], respectively.

3.3.4. Effects of Curcumin on Macrophages

A study conducted at UCLA found that curcumin may help macrophages to clear amyloid plaques found in Alzheimer's disease. Macrophages play an important role in the immune response. They help the body to fight foreign proteins and effectively clear them. Curcumin was administered to macrophages in blood collected from nine volunteers: six patients with AD and three healthy controls. Beta amyloid was then introduced. Patients with AD, whose macrophages were treated with curcumin, showed improved uptake and ingestion of plaques compared with patients whose macrophages were not treated with curcumin. Therefore, curcumin might support the immune system by clearing amyloid proteins. [15] and [17], respectively.

3.3.5. Modulation of Microglia

Curcumin, a natural antioxidant, has been shown to be effective in treating Alzheimer's disease (AD) by modulating microglial activation, signaling pathways, and product secretion. It also reduces microglial activation, inhibits the NF-B signaling pathway, and reduces cytokine production. The effects of curcumin occur both *in vivo* and *in vitro*, with *in vitro* results showing that phagocytosis increases by 50% in the microglia. Glial cells, which are non-neuronal cells of the immune system, play crucial roles in neural plasticity and brain development. Curcumin protects neurons by inhibiting the TLR4/MyD88/NF-κB signaling pathway and promoting M2 polarization. It enhances PPARγ activity, reduces cytokine production, and regulates the expression of the CC motif ligand 2 in astrocytoma cells. Curcumin also improves pathological deficits and memory impairment in

mice with AD, decreases astrogliosis and Aβ plaques, and enhances microglial Aβ phagocytosis *in vitro*. [14] and [18], respectively.

3.3.6. Anti-Inflammatory Effects

The AD brain has been shown to have inflammatory alterations (such as complement, cytokine, and acute-phase reactant overexpression), and inflammation is assumed to play a compounding, if not causal, role in the AD pathophysiology. Furthermore, although investigations of NSAIDs in people with established AD have been unsuccessful, epidemiological studies have consistently shown a link between NSAID use and decreased risk for the development of AD. Owing to its anti-inflammatory properties, curcumin may help halt AD progression. Researchers have shown that Curcumin inhibits lipoxygenase and cyclooxygenase 2, which are responsible for producing prostaglandins, thromboxanes, and leukotrienes, which are pro-inflammatory compounds. Additionally, it decreased the inflammatory processes of inducible nitric oxide synthase (iNOS) in activated macrophages and AP-1-mediated transcription linked to cytokine modulation *in vitro*. The antioxidant properties of curcumin help reduce inflammation, similar to that of lipid peroxides do the same. Curcumin has been shown to have anti-inflammatory properties that may explain how it slows AD. Researchers have shown that Curcumin inhibits lipoxygenase and cyclooxygenase 2, which are responsible for producing pro-inflammatory leukotrienes, prostaglandins, and thromboxanes [19]. *In vitro* cytokine regulation mediated by AP-1 is inhibited [20], and inducible nitric oxide synthase (iNOS) is suppressed in activated macrophages [21], both of which are mechanisms that lead to inflammation. The antioxidant properties of curcumin help reduce inflammation, similar to that of lipid peroxides do the same. [6]

3.3.7. Modification of Insulin Signaling pathway

Alzheimer's disease (AD) is associated with metabolic abnormalities and cognitive deterioration that are linked to insulin resistance in the brain. Insulin is a hormone that facilitates glucose intake and controls various brain activities such as blood flow, inflammation, oxidative stress, tau phosphorylation, apoptosis, lipid metabolism, and memory formation. Studies conducted in patients with AD after death have revealed reduced insulin receptor binding, a drop in activated insulin receptors, and an increase in IRS-1 inhibitory phosphorylation. [14] Insulin resistance in AD brains has been confirmed by a study that compared the activity of the insulin signaling pathway in AD tissues to that in healthy tissues. Curcumin regulates the insulin signaling pathway and cognitive deficits associated with insulin resistance in AD. Compared to healthy tissue, insulin noticeably decreased the activation of its signaling pathway in the hippocampus, prefrontal cortex, and cerebellar cortex in AD tissues. Curcumin controls insulin signaling and cognitive impairment associated with insulin resistance in AD. [22]

3.3.8. Antioxidant

The antioxidant properties of curcumin have been investigated, both directly and

indirectly. The capacity of curcumin to chelate ferrous ions, decrease ferric ions, and scavenge free radicals has been demonstrated *in vitro*. Additionally, it increased the expression of antioxidant proteins and suppressed lipid peroxidation. In addition, curcumin increased the transcription of proteins that restored the levels of glutathione, an antioxidant. In addition, it avoids the negative consequences of reactive oxygen species (ROS) in Alzheimer's disease (AD). When hydrogen peroxide and curcumin were incubated together, lipid peroxidation, cytosolic calcium concentrations, and caspase-3 and -9 levels were decreased in SH-SY5Y neuronal cells. Curcumin regulates B-cell lymphoma 2 protein family to suppress A-induced mitochondria-mediated apoptosis in PC12 cells. It effectively prevented ROS-mediated DNA damage, caspase activation, and poly ADP ribose polymerase (PARP) cleavage. Studies have demonstrated that curcumin also protects against synaptic toxicity; pre-treated cells exhibit normal synaptic activity and decreased mitochondrial dysfunction [4].

Table 1 shows a summary of the most important effects of curcumin on AD.

Table 1. Summary of mechanisms of action of curcumin in AD.

Mechanisms involved in Alzheimer's disease	Effects of curcumin
β-amyloid	
·Increased production	·Decrease in β-amyloid
·β-sheet formation	·Inhibition of sheet formation
·Plaque burden	·Reduced plaque burden
·Metal homeostasis	·Prevents the peptide from spontaneously forming fibrils in the presence of Cu and Zn
·Cholesterol	·Decrease cholesterol levels ·Reduces the production of fatty acids and cholesterol in hepatocytes by inhibiting SREBP
·Macrophages	·Clear amyloid plaques
·Microglia	·Reduces microglial activation
·Anti-inflammatory	·Reduce inflammation
·Insulin	·Controls insulin signaling and cognitive impairment associated with insulin resistance
·Antioxidant	·Increases the expression of antioxidant proteins and suppresses lipid peroxidation

4. Conclusion

It has been demonstrated that curcumin improves cognition in both non-pathological aging and Alzheimer's disease (AD). Nevertheless, only a small number of human studies have been conducted, and the consistency of these findings is lower than that of the preclinical studies. Preliminary data suggests that curcumin may

stabilize or prevent cognitive decline in healthy individuals. Although the findings of the clinical trials are encouraging, the limited bioavailability of curcumin warrants caution. Another significant issue is the difficulty in diagnosing neurological illnesses, especially AD, and the misdiagnosis of these conditions. Animal models of AD have demonstrated antioxidant, anti-inflammatory, and anti-amyloid properties of curcumin. Important data regarding the bioavailability, safety, and tolerability of curcumin, particularly in older populations, are lacking despite its extensive use as a food additive.

5. Discussion

Knowing the causes of any disease is the best method for determining how to cure it. A study predicted a model using multiple logistic regression to predict Alzheimer's disease patients by selecting the relevant risk factors. Multiple risk factors and interactions have been found to significantly contribute to Alzheimer's disease [23]. Research has shown that curcumin helps to reduce risk factors. Thus, curcumin may be a promising treatment option for AD. Large-scale human research is required to determine their preventive and therapeutic benefits.

Conflicts of Interest

The authors declare no conflicts of interest.

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