Narrative Review Article

Curcumin as A Dual Treatment for Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD) is the most common form of dementia, hallmarked by amyloid-beta (Aβ) plaques, tau tangles, and neuroinflammation. Available therapeutic options have shown only marginal symptomatic relief and have not shown efficacy in halting the progression of the disease, calling for additional therapeutic options. Recently, Curcumin, a bioactive polyphenol extracted from the rhizome of Curcuma longa or turmeric, has gained popularity for its potential neuroprotective activity. However, Curcumin has its own disadvantages, making it important to evaluate synergistic nutraceutical approaches designed to overcome Curcumin's barriers. Combining Curcumin with other compounds has been shown to compensate for Curcumin's disadvantages and enhance the efficacy of Curcumin treatment. For example, combining Curcumin with Piperine, Berberine, Resveratrol, and Vitamin D3 has been shown to enhance the bioavailability of Curcumin treatment while helping reduce neuroinflammation, improve memory, or improving the Blood Brain Barrier (BBB). This review explores the combination of Curcumin and several different compounds and found that the Curcumin Piperine combination remains the most promising candidate for clinical standardization due to its direct role in preventing Aβ aggregation. However, current literature is limited by a reliance on in vitro and animal models, alongside inconsistent cognitive outcomes in existing human trials. While these natural synergies still need further research, they represent promising low-toxicity alternatives to traditional pharmaceuticals, but further well-designed, long-term clinical research is essential to establishing them as viable therapeutic options for AD patients.

Keywords: Alzheimer's Disease; Natural Compounds; Antioxidants; Dual Treatment; Anti-amyloid; Cognitive Function; Neuroinflammation

INTRODUCTION

Alzheimer's Disease (AD) is the most common cause of dementia and is estimated to affect around 55 million people around the world. It is one of the leading causes of death, characterized by progressive cognitive deterioration, exhibited through behavioral changes and a decline in daily activity (1). The estimate of its prevalence is one in nine people aged 65 years and older, with 7.2 million of the same demographic diagnosed with AD in the United States (2).

AD is caused by two key pathologies: the accumulation of amyloid beta (Aβ) plaques and tau tangles. These malformations harm neurons in the entorhinal cortex and hippocampus, areas responsible for memory, later affecting the cerebral cortex, an area in charge of language, reasoning, and social behavior (3).

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In AD, Aβ aggregates hinder cell-to-cell communication between neurons. The overphosphorylation of tau protein, integral to the structural support of nerve cells, forms tangles in the brain, blocking neuronal transport systems and leading to cell death (4). AD primarily manifests as memory loss and executive dysfunction, leading to a change in behavior, vision, language, and ultimately death (5).

Curcumin (*Curcuma longa*) is a spice that can be extracted from the rhizome of Curcuma longa (6). It is popularly used in Southeast Asian cuisine and possesses impressive herbal remedies that have long been used to treat respiratory conditions and abdominal pain. In vitro, Curcumin has antioxidant, anti-inflammatory, anti-tumoral, and antimicrobial effects (6), and has been extensively studied through experiments in vivo and in vitro to progress chemotherapy (7).

Studies have found Curcumin to possess a higher binding affinity to Aβ plaques, demonstrating it as a critical compound in the inhibition of the formation of Aβ plaques (11). A study showed that a low dosage of Curcumin was injected peripherally in mice; the natural compound bound with smaller Aβ species, thus inhibiting the Aβ aggregation, demonstrating Curcumin as a promising treatment for AD (8).

The abundance of pre-clinical animal studies and literature exemplifies curcumin's efficacy as a potential treatment for AD. However, the few clinical human studies, most being less than 4 years, examining the use of Curcumin to treat AD have yielded mixed results. One study conducted in 2012 observed no significant impact of Curcumin on cognition after 6 months of treatment (9). Noting the current ambiguity of Curcumin efficacy in human trials, this review aims to evaluate the therapeutic potential of combining Curcumin with specific natural compounds, namely Piperine, Berberine, Resveratrol, and Vitamin D3, to address its inherent pharmacological limitations, such as poor bioavailability and rapid metabolism. This review looks at how the combined effect is hypothesized to have greater efficacy than Curcumin alone, providing alleviation of Curcumin's disadvantages and showing the dual treatments' potential viability as low-toxicity, multifaceted alternatives to traditional pharmaceuticals.

PIPERINE

Piperine (1-piperoylpiperidine) is an alkaloid that is present in many spices (10): black pepper (Piper nigrum), long pepper (Piper longum), and other plants in the Piperaceae family (11). Most notably, Piperine is used in black pepper, being one of the most used flavor-enhancers in the world. However, Piperine is not only a flavor-enhancing bioactive compound (12), it has also shown multiple health benefits: it has antioxidant, anti-inflammatory, anti-cancer, anti-hypertensive, and neuroprotective effects (13). Piperine has also been established as favorable in altering gastrointestinal disorders and being beneficial in diabetes, breast cancer, cardiovascular diseases, kidney diseases, inflammatory diseases, and more. Piperine is not genotoxic, the ability for a substance to damage the genetic material of a cell, and, in the murine model, does not exhibit major detrimental impacts following supraphysiological doses that are even 5-20 times higher than the human average (14).

Piperine has a bioavailability enhancement effect on the digestive system due to piperine's ability to inhibit enzymes responsible for metabolizing nutritional substances. These enzymes include cytochrome P450, isoenzymes, and UDP-glucuronosyltransferase (UGT), which are present in the liver and intestines (15). Researchers have also theorized that Piperine and the complexes it forms with other compounds are both apolar, increasing the absorption across intestinal barriers (16). This shows piperine's ability to enhance Curcumin's weak bioavailability in the gut.

Piperine has also been demonstrated to benefit AD through its anti-inflammatory, antioxidant, and neuroprotective effects. In a mouse model of sporadic AD, intracerebroventricular infusion of streptozotocin (STZ) induced AD-like symptoms in mice, and then they were bilaterally injected with Piperine daily for 15 days. Piperine ameliorated inflammation and cognitive deficits seen in the control group, demonstrating it as a prospective therapeutic agent against cognitive deficits in mice with AD (17). In another study, U87MG cell lines were administered with Aβ and Okadaic acid before being administered with Piper Longum Extract (PLE), an extract that Piperine is a component of, to determine PLE's effects on toxins associated with AD. PLE showed neuroprotective effects on the U87MG cell lines with increased cell viability and decreased levels of LCN2 and p-Tau levels (23).

Piperine and Curcumin have exhibited promising synergetic effects on a myriad of different viruses, digestive diseases, lessening inflammatory pain, and more. In Figure 1, Piperine and Curcumin have compatible molecular structures, as seen by the aromatic rings on the ends, and as they are both lipophilic. Due

to both compounds offering numerous advantages, many studies and clinical trials suggest that synergized lower concentrations of Curcumin and Piperine establish better outcomes compared to utilizing them independently.

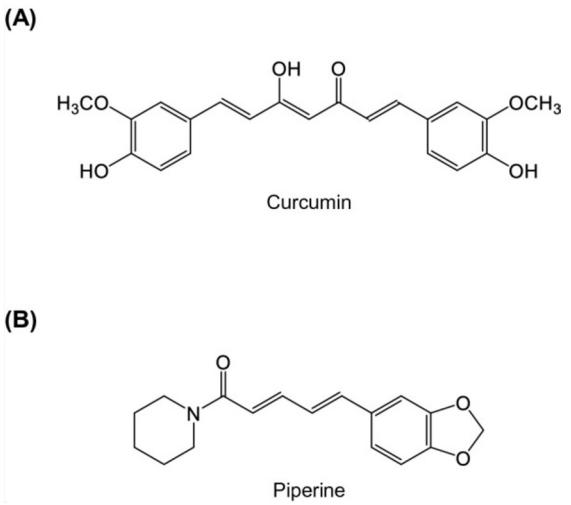

Figure 1. *Molecular structures of the bioactive compounds Curcumin (A) and Piperine (B) (18).*

Oral Curcumin treatment for AD has exhibited mixed results due to digestive enzymes metabolizing the treatment in a short timeframe; however, piperine's ability to inhibit digestive enzymes allows Curcumin to prolong its duration in the body in order to demonstrate its anti-inflammatory and neuroprotective effects. One study looked at the separate effects of Curcumin and Piperine as anti-amyloidogenic agents by applying molecular docking when screening in order to predict the conformation of Curcumin and Piperine ligands when bound to the Aβ42 peptide. Compared to piperine, Curcumin possessed a binding affinity to Aβ42 peptide (-5.6 kcal/mol and piperine's binding energy was -5.4 kcal/mol, making it a more promising treatment for AD (18). When combined in vitro, Curcumin and Piperine were able to inhibit aggregation of Aβ, disaggregate fibrillar Aβ (Aβ42), and reduce neuronal oxidative stress (19). This established synergizing Piperine and Curcumin as a potential dual curative treatment for AD. In another study, 35 μM of Curcumin and Piperine were used to treat Aβ42 fibrils. In the Piperine and Curcumin treatment group, a myriad of mechanistic pathways were modulated, ultimately altering expression profiles of genes in the neuronal cell model and inhibiting Aβ expression. This highlights a possible remedial approach using Curcumin and Piperine as a dual treatment (20).

Synergized Curcumin and Piperine have exhibited a plethora of benefits in AD treatment, including up to 2000% bioavailability of Curcumin when co-administered with Piperine and a strong combined anti-inflammatory and antioxidant effect when easing AD symptoms. Curcumin is easily absorbed in the presence of piperine, which slows it down through inhibition. However, although there exists an abundance of mouse models and in vitro studies examining the potential for Piperine and Curcumin as a dual treatment for AD, there are very few clinical trials exploring this dual treatment. This also limits knowledge on the optimal dosage window when treating patients with the treatment, as Curcumin has demonstrated gastrointestinal side effects when overadministered. To identify synergized Curcumin and Piperine as a potential dual treatment for AD, longer, well-designed clinical studies would be required that indicate consistent, promising results in easing AD symptoms and inhibiting Aβ aggregation. Curcumin and Piperine have not yet yielded sufficient clinical results; however, in vitro studies as well as Curcumin and piperine's beneficial effects establish synergized Curcumin and Piperine as an auspicious potential treatment for AD.

BERBERINE

Berberine is a bioactive alkaloid that can be found in a plethora of plants (21). Berberine has notably been used in Traditional Chinese Medicine for hundreds of years because of its healing properties, which have been accentuated by modern medicine. Berberine has shown promising health benefits in promoting weight loss, lowering blood sugar, lowering cholesterol, improving heart health, and having antioxidant and anti-inflammatory effects (22). Studies on the therapeutic effects of berberine identified its potential use against cancer, metabolic disorders, obesity, and heart and cardiovascular diseases, and it has been demonstrated to combat inflammation, atherosclerosis, neurodegenerative diseases, and rheumatoid arthritis (23).

Berberine exhibits multiple health benefits through altering an abundance of significant signaling pathways, including but not limited to metabolic, inflammatory, and immune pathways. Berberine is an AMP-activated Protein Kinase (AMPK) activator, a key enzyme that regulates homeostasis of the body

through serving as a pivotal energy-sensing system in cells that monitor cellular energy levels. AMPK's role includes the production of beta-amyloid protein and tau phosphorylation, both of which are critical parts of AD pathology (24, 25). Therefore, the current therapeutic effects of AMPK on AD are controversial, but it is involved in the pathogenesis of AD (35).

Berberine also has the potential to regulate the WNT pathway regarding cancer; the WNT pathway is also correlated with neurogenesis, synaptic formation, memory, and learning, and the dysfunction of the WNT signaling pathway may lead to neurodegenerative diseases such as AD (26). In a model of in vitro studies studying hepatocellular carcinoma (HCC), berberine mechanistically regulates the WNT pathway through the hepatocellular carcinoma cell line (SMMC-7721) (27).

Berberine also notably affects the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which is a protein transcription factor that regulates innate immunity and is involved in immune function and inflammation (28). In AD inflammation, the activation of NF-κB releases cytokines and chemokines from the microglia (29). In a rat model of Myocardial ischemia/reperfusion injury (MI/RI), berberine suppressed NF-κB pathways, resulting in the inhibition of inflammatory responses, establishing it as an effective anti-inflammatory compound (30).

Berberine's neuroprotective properties regarding signaling pathways establish it as a promising therapeutic curative agent for AD. Berberine has been characterized as a second-generation anti-AD drug inhibiting human acetylcholinesterase (30), a cholinergic enzyme known to catalyze the hydrolysis of acetylcholine (31, 32). In an AD mouse study, AD mice and their neuroinflammation-related markers and Aβ pathology were studied and demonstrated berberine's efficacy in improving cognitive performance, lowering amyloid pathology, and easing abnormal neuroinflammation (33). Another study utilized immunofluorescence staining in order to assess changes in Aβ plaques, neuroinflammation, neurons, and autophagy-related markers. The staining revealed that berberine mitigated Aβ plaque buildup, lowered neuron damage, and calmed neuroinflammation. According to behavioral tests, berberine has been revealed to benefit AD mice and their spatial memory deficits (34). Altogether, these studies present berberine as a promising therapeutic agent for AD through preventing neurodegeneration.

Berberine and Curcumin have been researched as a potential dual treatment when synergized to treat metabolic diseases, inflammatory diseases, and more due to both of their antioxidative, anticancer, anti-inflammatory, and neuroprotective effects. A study in Belgium, including 146 IBS patients, showed that, for those who took the dual treatment, less than 10% of patients experienced negative side effects and showed nearly 50% improvement in bloating, abdominal discomfort, and quality of life (35). Another study looking at Curcumin and berberine as a chemopreventive treatment against breast cancers revealed that Curcumin and berberine impeded the growth of breast cancer cells by inducing apoptosis and autophagic cell death. This shows how the similarities between Curcumin and berberine present it as an adequate dual treatment for diseases (36).

Due to berberine and curcumin's shared antioxidant, anti-inflammatory, and neuroprotective effects, utilizing them as a dual treatment for AD is promising. In a study of Parkinson's disease using berberine and curcumin-loaded transferosomes, berberine-curcumin was synthesized, and combined berberine and Curcumin transferosomes were synthesized. Ultimately, the berberine Curcumin combined group exhibited lower percentages of hemolysis, lower percentages of binding, greater acetylcholinesterase inhibition, decreased level of malondialdehyde, improved spatial memory, and the highest NO level decrease, establishing synergized Curcumin and berberine as a favorable dual treatment for AD (37). However, it is important to note that there is a significantly limited amount of research and clinical trials regarding combined berberine and Curcumin treatment and its effects on AD. Further studies, clinical trials, and research need to be conducted in order to determine berberine and curcumin's true potential in acting as therapeutic agents for AD.

RESVERATROL

Resveratrol is a polyphenol naturally existing in a variety of foods. This compound is prevalent in more than 70 species of plants, including grapes, and is known for opposing pathogens and being a potent antioxidant (38). Resveratrol has two isomeric forms: the trans-isomer and the cis-isomer. The trans-isomer is in the majority of grape cultivars in their berry skin, whilst the cis-isomer is only somewhat discernible in grapes and is produced by UV irradiation of Resveratrol's trans-isomer. Research regarding Resveratrol mainly utilizes trans-isomers due to their stability and greater natural

occurrence (39). This can be seen in Figure 2, where the trans isomer of Resveratrol has its phenol rings on opposite sides of the double bond, thus allowing the molecule to lie flat for easy movement of electrons.

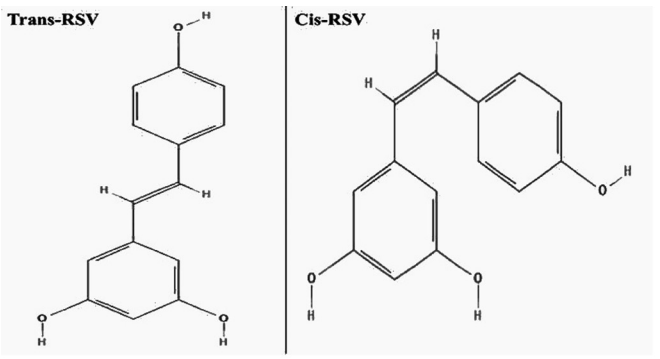

Figure 2. *Molecular structures of the trans- (left) and cis- (right) forms of Resveratrol (43).*

Although Resveratrol holds relatively inconsistent clinical study results, evidence points towards its use in managing inflammation, lowering blood sugar, and supporting the immune system. Resveratrol possesses antioxidant, immunomodulatory, anti-inflammatory, neuroprotective, and cardiovascular protective effects (40). Due to its health benefits, Resveratrol can help combat cardiovascular diseases, cancer, liver diseases, obesity, diabetes, Parkinson's disease, and AD. Resveratrol modulates antioxidant enzymes by inhibiting extracellular signal-regulated kinase (ERK), a protein kinase that's pivotal in the MAPK signaling pathway, which has implications in AD (55). Figure 3 shows how Resveratrol is involved in the modulation of neuroinflammation, autophagy, and oxidative stress, corroborating its efficacy regarding AD-related pathologies.

There exist many in vitro studies examining Resveratrol on cancer cells and pathways. Through promoting cell cycle arrest, Resveratrol can induce apoptosis in tumor cells and be an antioxidant that protects against damaged DNA (41). Resveratrol has also been shown to decrease the DNA binding activity of nuclear factor κB, a protein complex that ultimately reduces cancer cell proliferation and has implications in AD (42). In digestive tissues, Resveratrol has been shown to lower iNOS levels, reducing lipid peroxidation in neuronal cells for AD, and increasing heme oxygenase-1 (HO-1) production to mitigate oxidative damage (43). The longevity of these effects is not yet determined (44).

Resveratrol also proves effective in stopping $A\beta_{1\text{-}42}$ from crossing the blood-brain barrier (BBB), a packed layer of cells lining the blood vessels in the brain, defending the brain from harmful substances (45), and preventing BBB impairment. In these studies, following the intracerebroventricular injection of Resveratrol into an animal model, neurodegeneration in the hippocampus was significantly reduced, coinciding with a decrease in SIRT1 acetylation, a significant protein that establishes

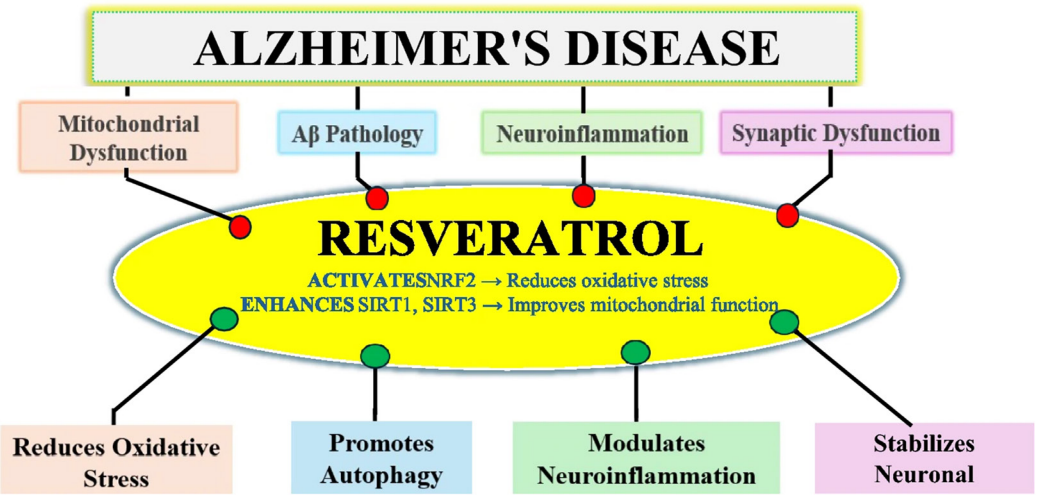

Figure 3. *Resveratrol 's antioxidant effects against AD: Resveratrol modulates key signaling pathways in AD, such as SIRT1, and facilitates pathologies to downregulate AD, including promoting autophagy, reducing oxidative stress, and modulating neuroinflammation (61).*

Resveratrol as effective in inhibiting the hallmarks of AD (46). In another study, mice were administered Resveratrol for 45 days, resulting in decreased Aβ toxicity, implying that Resveratrol can inhibit Aβ formation and safeguard against oxidative stress.

A study comprehensively reviewed randomized controlled trials on Resveratrol treatment in AD patients using publicly available databases. The meta-analysis included five trials with a total of 271 AD patients; approximately half received Resveratrol or a placebo. The Resveratrol treatment in comparison to the placebo trials showed significant improvements in AD Cooperative Study – Activities of Daily Living scores, cerebrospinal fluid Aβ40 levels, and plasma Aβ40 levels. However, there were no significant differences observed in the groups. Network pharmacology analysis showed that the main pathway affected beneficially by Resveratrol was the PI3K signaling pathway, an intracellular signaling pathway critical for regulating diverse cell functions such as metabolism and protein synthesis (47). An in vivo model of aluminum-induced neuroinflammation and an in vitro aluminum-stimulated cultured PC-12 cells showed that in Resveratrol and curcumin-treated rats, there was a significant attenuation of inflammatory markers and a decrease in amyloidogenic mediators (18).

Curcumin and Resveratrol have a myriad of positive effects on combatting early stages of AD disease independently. However, there exists little evidence from clinical studies or in vivo and vitro studies on the synergetic effects of Curcumin and Resveratrol that corroborates the pre-clinical studies' hypothesis on the dual treatment's benefits. Pre-clinical studies have shown that Resveratrol and Curcumin have the potential to be therapeutic treatments for AD as they target different pathways and have anti-amyloidogenic, antioxidant, and neuroprotective effects. Resveratrol targets autophagy pathways whilst Curcumin augments regenerative activity, enhancing the utility of Resveratrol and Curcumin as dual treatments.

VITAMIN D3

Vitamin D3 (Cholecalciferol) is an important compound that is a subgroup of the fat-soluble Vitamin Vitamin D, which is present naturally in foods and exists as a dietary supplement that is produced endogenously as the sun's ultraviolet rays strike the skin, generating Vitamin D synthesis (48). Vitamin D3 is classified with medications in Vitamin D analogs and is crucial for the maintenance of healthy bones, muscles, nerves, and for supporting the immune system (49). Vitamin D3 is used more often medically than Vitamin D2, as it is pharmaceutically more potent and has been proven to be 87% more beneficial for increasing blood levels (50). Vitamin D levels are crucial to maintain in the body to have a healthy physiologic range of calcium and phosphorus levels that ultimately support metabolic functions, transcription regulation, and bone metabolism (51).

In addition to maintaining homeostatic biological functions, Vitamin D may serve as a potential serum biomarker for neurodegenerative conditions. As such, patients with AD and Parkinson's disease have been found to exhibit low Vitamin D levels in serum (24). This is supported by many epidemiological studies that have shown that Vitamin D deficiency is linked to AD and other dementias. A study has found that the genomic Vitamin D receptor has already been changed to a non-genomic signaling pathway through the formation of a complex with p53, a protein that repairs DNA, and an altered state of p53 has been present in the brain and peripheral tissues of patients with AD (52). However, the next study by the same group of researchers assessing Vitamin D's impact on mice and humans revealed that a mouse model of AD exhibited significantly lower levels of serum Vitamin D. This suggests that a Vitamin D deficiency is potentially a consequence rather than a cause of AD. Ultimately, studies and experiments reflect that there should be caution against the long-term use of Vitamin D in AD patients (53). But Vitamin D has had beneficial effects on AD in other studies and experiments. New findings indicate that Vitamin D, 1,25-$(OH)_2D_3$, treatment induces a significant increase in LRP1 expression in both in vivo and in vitro models (54), consistent with the overall presence of Vitamin D receptors (VDR) in the brain – VDR deficiency or inhibition is a possible risk factor for AD. This shows that Vitamin D and LRP1 have a close relationship and, if used as a dual treatment, could benefit Aβ clearance (55).

Another study investigated the impact of Vitamin D deficiency and supplementation on AD pathology, where AD mice were given intraperitoneal Vitamin D3 injections, and showed that Vitamin D deficiency increased Aβ plaque deposition and increased GABA-positive reactive astrocytes. GABA is critical in regulating neuronal signaling in the hippocampus (78). These in vivo findings on reactive astrogliosis in AD suggest that maintaining optimal levels of Vitamin D may slow disease progression via reduction of aberrant glial

activation (57). In another study, male AD mice given Vitamin D showed that early high supplementation of Vitamin D improved working memory and neurogenesis, while normal supplementation improved neurogenesis at late stages. Vitamin D deficiency elevated Aβ plaque when it was early and reduced neurogenesis when it was late. Notably, this research found sex-specific effects as the supplementation of Vitamin D benefited males at early stages but females at later stages in terms of cognition. Together, these findings demonstrate that Vitamin D enhances neurogenesis and cognition in AD in a time- and gender-specific manner and mandate sex and disease-stage-specific supplementation approaches (58).

Vitamin D3 and Curcumin have been proven by studies to have beneficial synergistic effects on AD. In an in vitro study, primary cortical neuronal cultures were set and exposed to $A\beta_{1-42}$ for around 72 hours. As a result, treatments that had Aβ resulted in an increase in lipid peroxidation products. By contrast, lipid peroxidation products were reduced in the presence of Vitamin D3 and curcumin. Furthermore, the dual treatment of Vitamin D3 and Curcumin upregulated NGF levels. These findings combined present the dual treatment of Curcumin and Vitamin D3 as an optimistic natural therapy for treating AD (59). Ultimately, it is important to note that there exist some studies on the dual treatment of Vitamin D3 and Curcumin for AD, present as clinical trials, in vivo, or in vitro studies Although these research have established Vitamin D3 and Curcumin as promising therapeutic agents for AD, it nonetheless requires further research and consistent proof in the form of in vivo or in vitro studies or clinical trials to prove its efficacy.

CONCLUSION

AD is a global health crisis that affects 55 million people and has a treatment cost of hundreds of billions of dollars. One of the biggest challenges in the treatment of AD is the poor ability of many drugs to cross the BBB, which is primarily caused by the poor solubility and bioavailability of these treatments (60). Moreover, the current pharmacological therapies have shown only modest efficacy and severe side effects, making it an urgent need to develop new therapeutic approaches that are more effective and less toxic. Natural compounds like Curcumin have shown potent anti-inflammatory, antioxidant, and anti-amyloid effects in the context of AD, thus offering it as a viable treatment option. Although individual compounds such as Curcumin have promise in inhibiting Aβ plaques, their bioavailability is a noticeable factor in their inability to treat AD. However, when synergized with other compounds, otherwise inhibited benefits can be present as a tangible therapeutic treatment for AD patients. Notably, these results are primarily in a preliminary state and need further clinical trials to validate its efficacy. As seen in Table 1, the importance of this research is based on the transition from single-molecule therapy to a synergistic approach with nutraceutical compounds, like Curcumin, targeting the vicious cycle of Aβ plaques, tau protein tangles, and neuroinflammation.

Table 1. *Dual treatments of AD and their specific biological targets, benefits, and downsides.*

Dual Treatment	Specific Biological Target	Benefit	Downside
Curcumin and Piperine	UGT and Cytochrome P450	Increases bioavailability significantly; inhibits aggregation of Aβ fibrils; non-genotoxic	Limited clinical trials; potential gastrointestinal side effects at higher dosages
Curcumin and Berberine	Acetylcholinesterase & AMPK pathway	Inhibits acetylcholinesterase; improves spatial memory and lowers neuroinflammation	Significantly limited research and clinical trials, especially on the AD-related synergy of this pair
Curcumin and Resveratrol	PI3K and Autophagy pathways	Targets autophagy and regeneration; protects the blood-brain barrier	The Resveratrol compound suffers from poor bioavailability and presents inconsistent results in animal models and clinical trials
Curcumin and Vitamin D3	LRP1 and VDR receptors	Upregulates Nerve Growth Factor (NGF); reduces Aβ plaques and reactive astrogliosis	Little evidence in research and clinical trials; Efficacy might be sex- and disease-stage specific; potential risks with long-term high use

Based on the currently available literature, the synergized effects of Curcumin and Piperine appear to be the most viable and promising option for establishing an effective AD treatment. It is important to acknowledge that the majority of this literature corroborating Curcumin dual treatment is preliminary. Although Curcumin has a high affinity for Aβ plaques and potent anti-inflammatory properties, the success of Curcumin has been notoriously hindered by the rapid rate of metabolism of the compound by the liver and intestines, thus metabolizing its benefits. However, preliminary literature shows Piperine has the potential to inhibit the enzymes responsible for the metabolism of Curcumin in the body, allowing it to increase bioavailability by 2000% and have a stronger inhibitory effect in the body. In Boonrueng *et al*, 2022, macrophage-based studies, research shows it reduced proinflammatory mediators more effectively when synergized with another natural compound than as a monotherapy, showing no notable CNS side effects (18).

It is important to note that there are downsides to the different treatments. Vitamin D supplements caused an increase in Aβ deposition and exacerbated AD. Mechanistically, Vitamin D supplementation did not restore the genomic VDR/RXR complex but increased the assembly of the non-genomic VDR/p53 complex in AD brains. A study found that those taking Vitamin D3 supplements for more than 146 days per year were 1.8 times more likely to develop dementia than those who did not. Additionally, a lot of treatments are heavily dependent on the severity of the AD pathology, and thus the age of the mice used in the study, and also significantly rely on the specific pathology that exists in the mice. Acknowledging these disparities allows for the understanding that treatments will react differently in each case and model study, and may provide different results in humans.

There exist some limitations with dual treatment studies for AD, hindering them from being considered as mainstream emerging treatments. For starters, many lack human clinical trial data, and the bulk of research done on the synergetic effects is examined in vitro or in vivo studies. The literature utilized in this study cannot also validate disease treatment mechanisms of the dual treatments in humans. Therefore, the promotion of dual treatments is primarily through examining their potential in human AD. Second, in studies done with clinical trials, a number have had inconsistent results. Notably, this might be due to a short study period of fewer than four years. Furthermore, some had specific outcomes based on physiological characteristics. In Vitamin D3, research found sex-specific outcomes where the drug worked better in men in the early stages of the disease but was more effective in women in the later stages. Still, with longer-term studies and more clinical trials done that identify a specific dosage window for optimal therapeutic effects, many researchers stress that there is promise in these dual treatments to be translated from the laboratory to a clinical setting.

However, the advantages of these treatments are supported by their ability to modulate specific molecular targets while still maintaining a high safety profile even at higher doses. It's important to acknowledge that, under preliminary literature, these treatments can potentially produce measurable clinical outcomes. A meta-analysis of five clinical trials revealed that Resveratrol significantly improved ADAS-ADL scores and altered cerebrospinal fluid and plasma Aβ40 levels. This suggests that polyphenols can have a tangible impact on functional cognitive markers in human subjects. And, in AD mouse models, Piperine ameliorated oxidative-nitrosative stress and cognitive deficits. The synergy between Curcumin and Vitamin D3 demonstrated a 5.76-fold decrease in HMGB-1 mRNA expression in inflammatory models, a much higher reduction than Curcumin achieved alone.

The integration of these bioactive synergies offers a potential frontier for AD treatment. By leveraging the anti-amyloidogenic, anti-inflammatory, and neuroprotective properties of these pairings promoted by precursory studies, researchers can potentially interrupt the progression of AD at a molecular level. Curcumin and Piperine serve as a dual treatment with the most potential according to preliminary research. With in vivo and in vitro evidence on its direct contribution to preventing Aβ aggregation and its positive synergetic effects, Piperine and Curcumin's dual treatment potential outweighs the drawbacks. However, most of these studies provide a provisional conclusion that requires more studies to validate the findings of this review paper. To translate this therapeutic potential into standard clinical practice, the medical community should prioritize longer, well-designed clinical studies with AD patients to establish consistent dosing protocols in a precise therapeutic window and long-term safety profiles in human populations.

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CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work

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