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An Investigation of the Efficacy of Curcumin for Treatment of Alzheimer's Disease

By Parantap Patel

Abstract

Curcumin is the primary curcuminoid found in the rhizome of the turmeric plant (*Curcuma longa*), responsible for the spice's distinctive yellow color. Research conducted within the past two decades suggests that the compound may be an effective treatment for Alzheimer's disease, the most prevalent form of dementia affecting nearly 5.2 million Americans. This paper investigates the efficacy of curcumin as treatment for the pathogenesis and symptoms of Alzheimer's. Research was conducted pertaining to the pathogenesis of Alzheimer's, the *in vitro* applications of curcumin, the chemical properties of curcumin, and the *in vivo* clinical applications of curcumin. The pathogenesis of Alzheimer's is defined by the aggregation of amyloid-beta plaques, dissociation of tau protein, propagation of reactive oxygen species, and neuroinflammation. Alzheimer's is also characterized by symptoms of cognitive decline and memory loss. The physiochemical nature of curcumin enables it to interact with multiple biochemical pathways in the central nervous system (CNS), inhibiting the pathogenesis of the disease. *In vitro* applications of curcumin show much promise to this end. *In vivo* studies of curcumin on living subjects provide mixed results for the substance's efficacy on symptoms and pathogenesis. Furthermore, the complex chemical properties of curcumin make drug development very difficult. Curcumin shows much promise in inhibiting the pathogenesis of Alzheimer's, according to *in vitro* studies. However, the lack of definitive conclusions from *in vivo* applications and difficulty in overcoming curcumin's complex chemical properties for drug development show that the substance cannot yet be designated as an effective treatment for the disease.

Introduction

Alzheimer's disease is the most prevalent form of dementia, affecting nearly 5.2 million Americans and millions of people worldwide. The disease is characterized by cognitive decline and memory loss with the progression of time. At the neurological level, Alzheimer's is characterized by complex biochemical pathway dysfunctions, including the aggregation of amyloid-beta plaques, dissociation of tau protein, propagation of reactive oxygen species, and neuroinflammation. Treating the disease has proven to be difficult by conventional, allopathic therapies which utilize cholinesterase inhibitors.

Curcumin is an organic compound found in the rhizome of the turmeric plant, *Curcuma longa*. It is the phenol compound responsible for the turmeric spice's distinctive yellow color. At equilibrium, the substance exists in keto-enol tautomers. Curcumin is hydrophobic and difficult to dissolve in many neutral solvents. Furthermore, curcumin decomposes according to the pH of solution. It has a relatively small molecular mass of 368.37 daltons.

Research conducted in the field of alternative medicine over the past two decades suggests

that the chemical properties of curcumin may establish it as a candidate for treatment of Alzheimer's disease. Despite the fact that many allopathic therapy routes have been explored by neuroscientists over the years, very few have exhibited major success in effectively treating Alzheimer's. Curcumin may prove to be an effective treatment for Alzheimer's, helping 5.2 million Americans and their caretakers significantly increase quality of life and peace of mind. Millions of Alzheimer's patients and their caretakers around the world would benefit as well. The lack of effective treatment of Alzheimer's disease is a dilemma the medical field faces today that may be resolved by investigating the efficacy of curcumin as a potential treatment.

Although research suggests that curcumin may be an effective treatment for Alzheimer's disease, the lack of substantive *in vivo* evidence and curcumin's complex chemical properties prevent establishing and developing the compound as treatment. However, *in vitro* evidence suggests that curcumin may become a candidate for treatment in the future, because the unique physiochemical properties of the compound provide it with multidimensional abilities to inhibit Alzheimer's pathogenesis at the biochemical level.

Background

Alzheimer's disease is the most prevalent form of dementia that affects individuals above the age of 65. It is a terminal disease, and to date, no cures for this neurodegenerative disease have been discovered. It is characterized by memory loss and cognitive decline. Initially, patients develop forgetfulness of short-term memories, such as deadlines and minor responsibilities. Later, patients develop severe cognitive decline and loss of long-term memory, forgetting their identities and the identities of their loved ones. As the disease progresses, cognitive decline and personality changes develop in the patient. The average life expectancy of a patient after diagnosis is between 6 to 8 years. At the neurological level, biochemical dysfunctions in the brain cause neurodegeneration and pathogenesis of the disease. Four biochemical factors are attributed to the development of Alzheimer's disease: amyloid beta plaques and fibrils, tau protein, oxidative stress, and neuroinflammation. Amyloid beta is the main protein component of amyloid plaques, aggregations of misfolded, naturally-occurring proteins in the body. These plaques are toxic and insoluble, and they have been implicated in numerous neurodegenerative conditions. Tau protein is found in the neurons of the central nervous system (CNS) and is responsible for stabilizing microtubules in the cell bodies. However, tau protein can become detrimental to CNS functioning when it becomes defective and fails to stabilize microtubules. Oxidative stress, which damages all cellular components, occurs when reactive oxygen species propagate free radicals in the CNS. Neuroinflammation results when insult or injury triggers inflammatory responses in the CNS.

Conventional, allopathic treatments only treat the symptoms of Alzheimer's, including memory loss and general cognitive decline. The most widely used medications are cholinesterase inhibitors, such as Exelon and Aricept. This group of drugs works by inhibiting the breakdown of acetylcholine, the neurotransmitter in the brain associated with learning and memory. However, cholinesterase inhibitors slow down the progression of the disease for only 6 to 12 months. Outside of this group of drugs, very little effective allopathic treatment exists.

Curcumin is the primary curcuminoid found in the rhizome of the turmeric plant, *Curcuma longa*. The rhizome of the turmeric plant has long been heralded in India and South Asia to hold anti-bacterial, anti-inflammatory, and anti-cancer properties. The rhizome of *Curcuma longa* contains three other curcuminoids, as well: demethoxycurcumin, bisdemethoxycurcumin, and cyclocurcumin. The International Union for Pure and Applied Chemistry name for curcumin is 1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione, also known

simply as diferuloylmethane. At equilibrium, the substance exists in keto-enol tautomers, due to the presence of intramolecular hydrogen atoms that transfer at the beta-diketone chain. The keto-enol isomers also have numerous cis and trans isomer forms. The relative concentrations of these cis-trans isomers vary with polarity of solvent, pH, temperature, and substitution of the compound's aromatic rings. In acidic and neutral solutions, curcumin acts as a proton donor, present in di-keto form. In basic solutions, curcumin acts as an electron donor, present in enolate form. Curcumin degrades in basic environments rapidly via hydrolysis. Furthermore, curcumin is prone to photodegradation, especially by ultraviolet light.

Research has been conducted in the past two decades pertaining to curcumin and its clinical applications. The majority of this body of research can be divided into two types of studies: in vivo and in vitro.

Clinical Applications of Curcumin in Alzheimer's

Very few in vivo clinical studies have been conducted investigating the efficacy of curcumin in treating Alzheimer's disease. The clinical studies performed have tested for symptom alleviation and pathology inhibition. However, these studies use varying methods and provide varying results, proving it difficult to designate curcumin as an effective treatment for Alzheimer's.

Hishikawa et al. (2012) presents data from three Alzheimer's patients that were studied over the span of one year, concluding that daily turmeric treatment along with routine Alzheimer's therapy significantly increases the quality of life for patients. All three patients had cognitive decline and severe behavioral and psychological symptoms of dementia (BPSD). Case 1 was an 83-year-old female with progressive dementia, who presented symptoms at the age of 76. She was medicated with donepezil 10 mg, an acetylcholinesterase inhibitor, and traditional Japanese medicine, Yokukansan, before this study was conducted. Her cognitive functions were evaluated at a very low 1/30 using the Mini-Mental State Examination (MMSE), and brain magnetic resonance imaging (MRI) showed bilateral temporal atrophy. The patient was placed on a 764 mg per day turmeric treatment (100 mg per day of curcumin). After 12 weeks, the effectiveness of the treatment was measured by the Japanese version of the Neuropsychiatric Inventory-brief Questionnaire (NPI-Q). The researchers found that

“...her agitation, apathy, anxiety, and irritability were relieved. She began to tell about the need to urinate. Furthermore, she came to join in the laughter watching TV comedy program, began to sing some songs and do knitting, which she used to do. After taking turmeric for more than 1 year, she came to recognize her family, and seem to remind her late husband and she lives a peaceful life without a significant BPSD” (500).

Case 2 was an 84-year-old female, who presented with symptoms of disorientation, forgetfulness, hallucination, and agitation, among several others. The symptoms had developed several years prior to presentation. Apart from a history of hypertension and little alcohol usage, her medical history was unremarkable. Her MMSE score was 0/30, and brain MRI revealed moderate bilateral temporal atrophy with mild ventricular dilation. The patient used Yokukansan and atypical antipsychotics. The patient's BPSD did not improve with these medications. The 764 mg per day turmeric treatment was administered. After 12 weeks, the NPI-Q showed relief from BPSD. The researchers found that

“her BPSD, which were hallucination, delusion, depression, agitation, apathy, anxiety, and irritability, were relieved. She stopped urinating outside the front door. She came to put on her clothes properly, and distinguish her family from staffs of the care center” (501).

Case 3 was a 79-year-old male whose BPSD was depression, apathy, agitation, anxiety, euphoria, irritability, and aberrant eating behavior. The patient had been taking donepezil 5 mg for 3

years before this study. Apart from a history of hypertension (treated with losartan potassium), the patient had no remarkable medical history. His MMSE score was 12/30, and brain MRI showed mild bilateral temporal atrophy and mild ischemic changes in deep white matter. Turmeric was administered at 764 mg per day. After 12 weeks, his BPSD was relieved significantly. In addition, a post-study MMSE saw his score increase to 17/30. All three patients have been taking the turmeric treatment for over a year with significant improvement in BPSD and no side effects. Using the evidence accumulated from these three cases, the researchers claim that the turmeric treatment is very effective in relieving BPSD of Alzheimer's. Furthermore, they claim that the "turmeric treatment in AD is safer than other pharmacological treatments and useful for patients, and that it can possibly reduce the doses of antipsychotics required for the treatment of BPSD" (502).

The case studies presented by Hishikawa et al. provide evidence that curcumin can be used in conjunction with conventional therapies to significantly benefit the quality of life for patients. Symptoms of Alzheimer's were significantly alleviated via the curcumin treatment, as shown by MMSE and NPI-Q test scores and behavioral changes. As a case study, this paper provides invaluable in-depth data about the effect of curcumin on Alzheimer's over an extended period of time.

Larger-sample clinical trials disagree with the findings of Hishikawa et al. The very first study that tested the efficacy of curcumin in treating Alzheimer's was conducted by Baum et al. (2008). The study was double-blind, randomized, and placebo-controlled, consisting of 34 possible or probable ethnic Chinese Alzheimer's disease (AD) patients, above the age of 50. The patients were given 0, 1, or 4 grams of curcumin in capsule or powder form over a 6-month period, concurrently with standard 120 mg of ginkgo leaf extract. The patients were allowed to continue all of their standard AD medications, as well. The study measured levels of beta amyloids in blood serum and MMSE scores to determine the effectiveness of the curcumin treatment. Furthermore, the study recorded incidents of adverse effects to treatment and levels of curcumin absorption in the body.

The study found that amyloid-beta levels in blood serum increased with curcumin treatment, suggesting that the compound was able to disaggregate amyloid-beta deposits in the AD brain, successfully treating Alzheimer's at the biochemical level. However, Baum et al. shows that curcumin does not successfully treat Alzheimer's symptoms. The MMSE results did not prove conclusive, as both patients on the placebo and on the curcumin treatment experienced no significant cognitive decline. Therefore, it was not possible to test changes in cognitive decline due to treatment. It is possible that this was due to poor sample selection. However, it is more likely that curcumin simply held no effect on symptoms of the disease. Furthermore, the researchers provide data showing that curcumin in capsule form is absorbed better by the body than curcumin in powder form. In the study, 17 adverse effects cases were documented in patients, including edema, respiratory tract infection, and gastrointestinal complaints.

The University of California, Los Angeles (UCLA) clinical trial conducted in 2012 by Ringman et al. also finds curcumin to be ineffective treatment for Alzheimer's symptoms. Furthermore, the researchers argue that curcumin is also ineffective treatment for Alzheimer's at the biochemical level. This study used 36 patients that were identified as having mild to moderate probable Alzheimer's according to the criteria set by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The patients had an average Mini-Mental Status examination score of 22.5 and an average age of 73.5 years. Thirty patients completed the study; one patient from the placebo group withdrew, and five subjects withdrew from the curcumin group. It was ensured that the dosage of acetylcholinesterase inhibiting drugs had been steady for one month prior to the conduct of the study in the patient sample. Patients were also screened for

“significant systemic illness or recent history of gastrointestinal bleeding. Exclusionary medications included aspirin at doses greater than 325 mg/day, use of non-steroidal anti-inflammatory drugs more than three times a week, coumadin, heparin, ginkgo biloba, and antioxidant supplements” (44).

The study was conducted with a placebo and was double-blind. Patients were given 2 grams, 4 grams, or 0 grams of Curcumin C3 Complex for 24 weeks. Curcumin C3 Complex consists of 70-80% curcumin, 15-25% demethoxycurcumin, and 2.5-6.5% bisdemethoxycurcumin.

The results were measured using a variety of methods. At weeks 4, 12, 24, 36, and 48, subjects and caregivers were interviewed. Furthermore, lab tests were conducted, including blood count, lipid profile, chemistry panel, thyroid, and thyroxine levels. At the 24 and 48 week marks, the Alzheimer’s Disease Assessment Scale, cognitive sub-portion (ADAS-Cog) was administered. Furthermore, the Neuropsychiatric Inventory and the Alzheimer’s Disease Cooperative Study Activities of Daily Living tests were run. The MMSE was also given at weeks 4, 12, 24, 36, and 48. Cerebrospinal fluid (CSF) was collected at the beginning of the study and at week 24. Both A-beta and tau protein were measured from the blood and CSF samples. Pharmacokinetic analyses were also performed to quantify the effect of the drug on the body.

Despite the extensive biochemical data collected, the clinical efficacy of curcumin against AD was not demonstrated in the study. No significant improvement was shown in the curcumin group compared to the placebo group, according to the results from the MMSE and the ADAS-Cog. Blood plasma analysis also showed no significant presence of curcumin, likely due to high gastrointestinal metabolism. No significant differences were found in the CSF analyzed, as well. Some patients actually presented adverse effects in clinic. Four patients of the curcumin group experienced GI side effects and had to withdraw before the completion of the trial.

In vivo data provides the most accurate representation of a treatment’s efficacy on a disease, because the treatment is tested within the organism as a whole. Because in vivo clinical studies about the efficacy of curcumin in treating Alzheimer’s provide contradicting results, the compound curcumin cannot yet be designated as treatment.

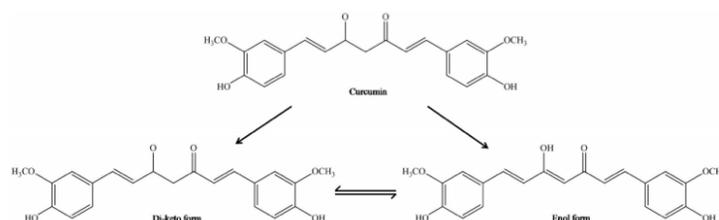


Figure 1. Curcumin exists in the two tautomers depicted above at equilibrium (340).

Chemical Properties of Curcumin

Curcumin possesses unique chemical properties that make it a viable drug for treating Alzheimer’s disease. Lee et al. (2013), for example, claims that “the presence of enolate in solution is found to be important in the radical-scavenging ability of curcumin” (340). However, according to Lee et al. (2013), the versatile chemical properties exhibited by curcumin may pose problems for drug development.

Solvents are necessary in drug development, because they hold the drug’s active ingredient in solution, enabling it to exhibit its physiochemical properties. The solvent used to dissolve curcumin plays a large role in the relative concentrations of the enolate and di-keto forms (Figure 1). Curcumin is hydrophobic by nature, proving difficult to dissolve in water and neutral solvents. However, basic solutions provide better solubility for the compound. Curcumin is

most soluble in organic solvents “such as ethanol, methanol, isopropanol, acetone and dimethylsulfoxide (DMSO) and has moderate solubility in hexane, cyclohexane, tetrahydrofuran and dioxane” (340). Absorption spectrophotometry reveals ideal solvents for curcumin. Curcumin’s maximum absorption ranges from 408 to 434 nanometers. In polar solvents, the maximum absorption lies at 420 nanometers, being red-shifted; in nonpolar solvents, absorption is blue-shifted. The di-keto form of curcumin is in higher concentration in nonpolar solvents, perhaps contributing to the blue-shift. The enolate form is in the majority in polar solvents. In acidic and neutral solutions, curcumin acts as a proton donor, present in di-keto form. In basic solutions, curcumin acts as an electron donor, present in enolate form. Lee et al. states that “the amount of keto-enol-enolate of the heptadienone moiety in equilibrium plays a crucial role in the physicochemical properties and anti-oxidant activities of curcumin” (340).

Furthermore, a chemical’s stability in the body is a fundamental aspect of pharmacology. Lee et al. agrees, claiming that the “stability of curcumin is crucial to [maintaining] its physiological activities” (341). Curcumin decomposes depending on pH, as seen in Figure 2, a factor that varies greatly in the environment of the human body and is difficult to control. A study by Tonnesen and Karlsen (1985) shows that at a pH of 1.23, curcumin’s half-life is 6600 hours, which progressively decreases as pH is increased. In acidic environments, curcumin degrades slower, with less than 20 percent of the substance degraded after one hour. Literature about the decomposition of curcumin in basic environments presents varying results, but most research agrees that in basic environments, like those found in the body, curcumin degrades rapidly via hydrolysis, forming ferulic acid and feruloylmethane according to second-order kinetics. This is a major disadvantage in therapy, as curcumin itself, the active ingredient, is no longer present after hydrolysis in the body’s basic environment.

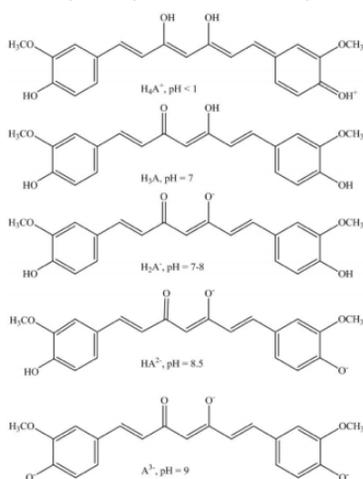


Figure 2. The physical structure of curcumin varies at different pH levels (Lee et al., 2013, 342).

Curcumin is also prone to photodegradation, especially by ultraviolet light. This is not a concern in the physiological processes of the body, as photodegradation is not a factor to consider in the internal environment of the body. However, the external environment in which the drug is produced and manufactured must factor this chemical property of curcumin into drug development. The Tonnesen and Karlsen study also shows that curcumin’s photo-stability is dependent on the solvent used, listing common solvents that are used in drug development and the half-life of curcumin with respect to photodegradation in the solvents. In methanol, the half-life is 92.7 hours, in ethyl acetate, 15.1 hours, in acetonitrile, 6.3 hours, and in chloroform, 2.7 hours. According to Lee et al., “the absorption of curcumin in water [has] no apparent effect on curcumin photo-stability” (343). Furthermore, Souza et al. (1997) shows that curcumin exposed to air and light is more prone to photo-degradation,

in comparison to just light.

Despite the fact that curcumin has been found to treat Alzheimer’s, the inherent complexity of the compound’s chemical properties proves very difficult to overcome in drug development and delivery. This major disadvantage is likely to stall the designation of the compound as potential treatment for Alzheimer’s.

Curcumin’s Effect on Pathogenesis of Alzheimer’s

The pathogenesis of Alzheimer’s at the biochemical level is defined by multiple dysfunctions,

including amyloid-beta plaque aggregation, tau protein dissociation, oxidative stress via reactive oxygen species, and neuroinflammation. In vitro evidence shows that curcumin possesses multidimensional properties that inhibit these pathways of pathogenesis. Furthermore, innovative curcumin nanoparticles and curcumin analogues have been developed and studied to show that minor modifications to the compound result in augmented inhibitory properties.

Amyloid-beta peptides play a large role in the formation of plaques and amyloid fibrils. Amyloid-beta “is a non-toxic soluble monomer present in plasma and cerebrospinal fluid and is also secreted by cells in culture” (Lee et al., 2013, 345). Amyloid fibrils created from amyloid-beta are not always responsible for dementia, as they can be found in healthy brains, as well. Amyloid-beta found intraneuronally resulting in mild cognitive impairment is an early indicator of AD. With time, these peptides misfold and form extracellular plaques. It is believed that amyloid-beta loses its physiological intent over time or gains pathological qualities, resulting in Alzheimer’s. Genetic factors, such as the Arctic mutation on the Amyloid-beta Precursor Protein (APP) portion of chromosome 21, result in increased amyloid-beta peptide deposition in the brain.

Evidence shows that curcumin is able to reduce the formation of amyloid-beta plaques. A transgenic mice study conducted by Lim et al. (2001) concluded that low doses of curcumin reduce amyloid plaques. Mice treated with low doses of curcumin exhibited a 39.2% reduction in insoluble amyloids and a 43% reduction in soluble amyloids. Furthermore, curcumin reduced amyloid plaque burdens in low-dosed mice by 43.6%. Matthew et al. (2012) proposed an innovative method for curcumin delivery in the body using curcumin encapsulated-poly-lactic-co-glycolic acid (PLGA) nanoparticles. According to the study, the curcumin nanoparticles were able to totally disintegrate amyloid aggregates over 48 hours. The study also established that all the anti-amyloid activity exhibited by the nanoparticles was due solely to curcumin and not PLGA. Furthermore, Zhang et al. (2010) shows that curcumin reduces A-beta levels by attenuating APP maturation. The ratio of mature APP to immature was decreased by 67 percent in the presence of curcumin.

Tau protein also plays a large role in the development of neurofibrillary tangles, another hallmark of Alzheimer’s.

“This protein is a neuronal microtubule-associated protein and functions primarily to stabilize microtubules (MT) through interactions with tubulin and subsequent incorporation into MT assembly, as it is found in abundance in the axons of neurons” (Lee et al., 2013, 346).

Phosphorylated tau protein dissociates from microtubules, enhancing fibrillization. Microtubules are unstabilized and cause dysfunction in neuron cytoskeletons. Hyperphosphorylation results in large neurofibrillary tangle formations. Lee et al. finds that “in healthy brains, only 2 to 3 residues of tau are phosphorylated while the phosphorylated tau level in AD patients is significantly higher at 9 phosphates per molecule of tau” (346).

In vitro studies also suggest that curcumin may be effective against tau protein dissociation and subsequent fibrillation. Chen et al. designed new curcumin analogues to allow intermolecular hydrogen bonding and other electrostatic attractions. The study finds that curcumin-derived compounds significantly depolymerize tau aggregates. A water-soluble sugar conjugate of curcumin designed by Dolai et al., exhibiting one thousand-fold more potency in depolymerizing tau aggregates than unmodified curcumin and significantly higher-fold potency than the Congo red control.

Improper disposal of reactive oxygen species leading to oxidative stress is an important component of the neurodegeneration found in Alzheimer’s. According to Lee et al. (2013), “oxidative stress is characterized by the overproduction of ROS, O₂⁻ and H₂O₂ that arises as a result

of imbalanced equilibrium between pro-oxidant and anti-oxidant homeostasis” (347). Reactive oxygen species attack lipids, carbohydrates, enzymes, and DNA. The body has complex systems that protest against these species, such as enzymatic defenses that inhibit formation of OH⁻ by metabolizing peroxides, the ability to trap free radicals, such as reduced CoQ and melatonin, and other anti-oxidant systems. Neurons are prime targets for oxidative damage because they have a high amount of easily oxidized fatty acids, low amounts of anti-oxidants, high usage of oxygen, high lipid peroxidation metal content, and inability to replicate damaged neurons. The Alzheimer’s brain experience higher levels of oxidative stress than the normal brain does, because the body’s anti-oxidant systems cannot cope with the increase in free reactive oxygen species present in the CNS.

Curcumin possesses strong anti-oxidant properties that inhibit the propagation of reactive oxygen species. Lee et al. explains that curcumin’s anti-oxidant property is thought to originate from its phenol moiety. Curcumin mitigates oxidative damages in a time and dose-dependent manner. Furthermore, it mitigates oxidative damage indirectly by enhancing levels of heme oxygenase-1 in brain cells which is responsible for protecting the brain from oxidative stress and increasing nontoxic heme. Curcumin activates HO-1 in the CNS, responsible for neutralizing oxidative stress. Scapagnini et al. (2006) found that 15 mM concentration of curcumin incubated for 6 hours with cells resulted in a 70% higher recovery rate after oxidative damage than incubated control cells. The transgenic mice study conducted by Lim et al. (2001) also concluded that curcumin significantly reduces oxidative damage in the CNS. Four mice brain regions were analyzed post-mortem to show that mice treated with high doses of curcumin had a 46.3% lower level of oxidized proteins than untreated mice. Furthermore, mice treated with low doses of curcumin exhibited a 61.5% reduction in oxidized proteins compared to untreated mice. According to the PLGA nanoparticle study conducted by Matthew et al. (2012), curcumin exhibits 80% free-radical scavenging activity, a very high percentage.

Neuroinflammation is also characteristic of the Alzheimer’s brain. Lee et al. (2013) defines inflammation as

“...a complex cellular response to stress, injury and infection where the depositions of insoluble materials in the periphery are the classic trigger for inflammation. Likewise, in the neuron, the presence of insoluble senile plaques, A-beta and [neurofibrillary tangle] NFT is the stimulant for inflammatory response. The neuroinflammation is characterized by the activation of microglia, astrocytes, macrophages and lymphocytes, which over express mediators such as cytokines, chemokines, prostaglandins, acute proteins, neurotransmitters and [radical oxygen species/radical nitrogen species] ROS/RNS” (348).

In the process of neuroinflammation, microglia cells are the first responders, secreting reactive oxygen species, reactive nitrogen species, and cytokines at the insulted site for neuroprotective homeostasis. However, in aging brains, the microglial signals dysfunction and continuously release ROS, RNS, and cytokines. Astrocytes that work in conjunction with microglia to repair and provide nutrients to the CNS also begin produce proinflammatory compounds, augmenting inflammation.

Curcumin also exhibits anti-inflammatory properties, according to in vitro evidence. A study conducted by Yang, Zhou, Zhang, and Feng (2014) using mice showed that curcumin is a potent anti-inflammatory agent. Mice were induced for intracerebral hemorrhage and then treated with a 100 mg/kg dose for 3 days following the stroke. Treated mice exhibited significantly lower inflammatory marker concentrations than those untreated. Untreated mice exhibited about 85 picograms per milligram concentration of inflammatory marker tumor necrosis factor-alpha (TNF-alpha) in the body, while treated mice exhibited a concentration of about 50 picograms per milligram. Inflammatory markers IL-1beta and IL-6 also provided similar

results.

The in vitro body of literature pertaining to curcumin and its effects on the biochemical pathogenesis of Alzheimer's suggests that curcumin is a very effective inhibitor for the four major biochemical pathways through which Alzheimer's develops in the brain. The successes of in vitro studies provide promise that curcumin can be considered a candidate for treatment of Alzheimer's in the future, after the literature advances further.

Conclusion

The efficacy of curcumin in treating the symptoms and inhibiting the pathogenesis of Alzheimer's disease in a clinical setting is severely limited, possibly due to the complex chemical properties exhibited by both the compound and the environment of the human body. The complex chemical properties of the substance also make it challenging to develop and deliver curcumin treatment to the central nervous system. However, the in vitro successes in literature show that curcumin possesses unique physiochemical properties that provide it with multidimensional abilities to treat Alzheimer's at the biochemical level. This body of literature may accumulate into an effective clinical treatment in the near future. Emphasis should be placed in large-scale in vivo clinical trials and in drug design and development research to provide substantive clinical data and to overcome curcumin's complex chemical properties, respectively.

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