Vol.67: e24220004, 2024
https://doi.org/10.1590/1678-4324-2024220004
ISSN 1678-4324 Online Edition

BABT
Brazilian Archives of Biology and Technology

Review - Human and Animal Health

Curcumin in Alzheimer's Disease and Depression: Therapeutic Potential and Mechanisms of Action

Jordan Teixeira Oliveira[1]
https://orcid.org/0000-0003-3126-2700

Simone Pieniz[1*]
https://orcid.org/0000-0002-7403-1577

[1]Universidade Federal de Pelotas, Departamento de Nutrição, Pelotas, Rio Grande do Sul, Brasil.

Editor-in-Chief: Paulo Vitor Farago
Associate Editor: Paulo Vitor Farago

Received: 04-Jan-2022; Accepted: 15-Sep-2023.

*Corresponding author: nutrisimone@yahoo.com.br; Tel.: +5553 3284 3834 (S.P.).

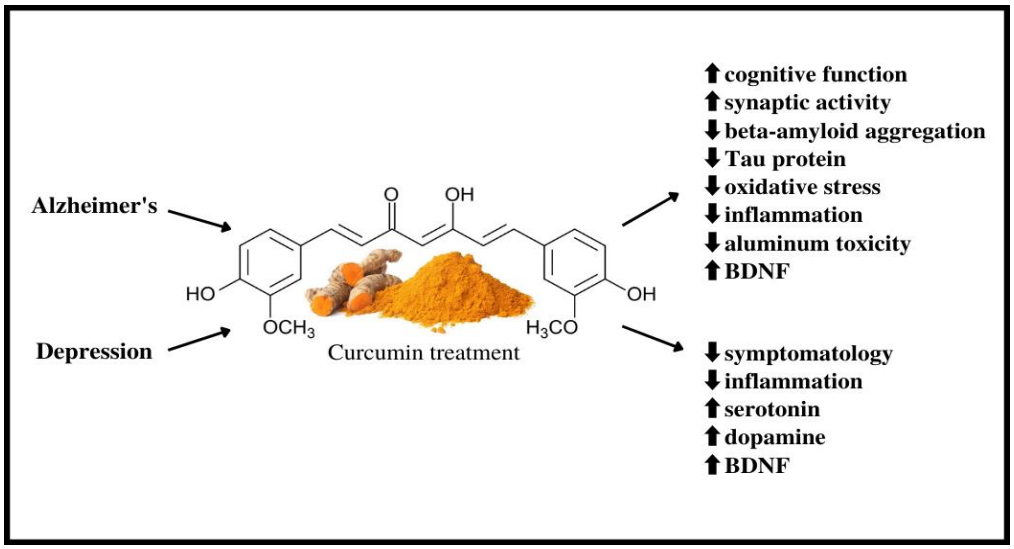
HIGHLIGHTS

- A decrease in BDNF levels is associated with Alzheimer's disease and depression.
- Curcumin supplementation improves BDNF levels in Alzheimer's and depression.
- Curcumin supplementation improves symptomatology in Alzheimer's and depression.
- Curcumin is a powerful anti-inflammatory and antioxidant.

Abstract: Curcumin is a polyphenol present in *Curcuma longa*, a root used in Asian cuisine for thousands of years, and it has several medicinal properties, acting as an antioxidant, anti-inflammatory, anticancer, among others. Polyphenols generally have the ability to restore BDNF (Brain Derived Neurotrophic Factor) levels, which is a very important neurotrophin in controlling neuronal development and survival, when they are impaired, offering a therapeutic effect. The aim of this study was to evaluate the effects of curcumin in Alzheimer's disease and Depression, which has as its main pathogenesis the reduction of BDNF levels, monoamine levels, increased oxidative stress, inflammation, beta-amyloid aggregation, Tau protein accumulation and aluminum neurotoxicity, verifying its therapeutic capacity. Therefore, a literature review was performed in the Scholar Google, ScienceDirect, and PubMed databases. The data analyzed demonstrated that curcumin supplementation is able to restore BDNF levels in Alzheimer's disease and depression, in addition to modulating monoamines and reducing oxidative stress, inflammation, beta-amyloid aggregation, Tau protein accumulation and aluminum neurotoxicity, improving their symptoms.

Keywords: *Curcuma longa*; turmeric; polyphenol; BDNF; Dementia; neurological disease.

GRAPHICAL ABSTRACT



INTRODUCTION

Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophin of the Neurotrophin-3 (NT-3) and Nervous Growth Factor (NGF) family, very important in regulating neuron development and survival [1-4], besides possibly regulating synaptic function and inducing the synthesis of several synaptic proteins [5]. BDNF is a molecule capable of stimulating neurogenesis [6], and a decrease in its levels is associated with several neurocognitive and psychological disorders, such as Alzheimer's disease [7] and depression [8]. However, several factors are capable of upregulating BDNF and, consequently, neurogenesis, such as caloric restriction [9], physical activity [10], enriched environment [11-12], omega 3 fatty acids [13] and polyphenols [14], being curcumin one of the most studied polyphenols with this effect [15-16].

Turmeric (*Curcuma longa*) is a root widely used in Asian cuisine as a spice and has a variety of medicinal properties, such as antioxidant, anti-inflammatory, anti-HIV, antibacterial, anti-tumor [17], BDNF restorative [18], among others. One of the main constituents of turmeric and accounting for most of its benefits is curcumin, a polyphenol with numerous biological effects, but with low water solubility. Therefore, it has low bioavailability due to its low absorption, fast metabolism and rapid systemic elimination [19]. As a result, many researchers have found ways to overcome this problem, such as the association of curcumin with piperine [20], in addition to curcumin-loaded lipid core nanocapsules, which also improves its bioavailability [21].

Due to the scarcity of studies related to the restorative effects of curcumin on BDNF in the intervention of Alzheimer's disease and depression, this study becomes extremely relevant. The following sections will address BDNF, curcumin, curcumin's effects on Alzheimer's disease and depression through their various mechanisms of action. Thus, the present study aimed to evaluate the implications of curcumin in the intervention of Alzheimer's disease and depression and its mechanisms of action, such as in BDNF levels, monoamines, oxidative stress, inflammation, beta-amyloid aggregation, Tau protein accumulation, and aluminum neurotoxicity, to assess its potential as a therapeutic agent.

MATERIAL AND METHODS

Search strategy and data extraction

A literature review was conducted to verify studies that evaluated the effects of curcumin supplementation on neurodegenerative/psychological disorders such as Alzheimer's and depression in animal and human models, and their respective mechanisms of action. Scholar google, ScienceDirect and PubMed electronic databases were consulted up to September 2021. In the search, the following descriptor combinations were used in the English-language databases: “BDNF”, “Neurogenesis”, “Curcumin BDNF”, “Curcumin Bioavailability”, “Curcumin Depression”, “Curcumin Depression BDNF”, “Curcumin Depression Inflammation”, “Curcumin Serotonin Depression”, “Depression BDNF”, “Depression Brain Size”, “Depression mechanism”, “Depression Medication”, “Depression Neurogenesis”, “Polyphenol Depression”, “Polyphenol Bioavailability”, “Alzheimer's”, “Alzheimer's BDNF”, “Alzheimer's Curcumin”, “Curcumin Alzheimer's BDNF”,

“Alzheimer's Inflammation”, “Alzheimer's Oxidation”, "Curcumin Tau protein", "Alzheimer Metals", "Alzheimer Neurogenesis", "Exercise BDNF", "Calorie restriction BDNF ”,“ Omega 3 BDNF ”.

Methodological quality assessment

The selection of articles was performed first by reading the titles found in the three electronic databases, then, the articles were selected according to their abstracts, so that the articles considered most relevant for the complete reading were selected, with a total of 79 being included in the review, as shown in the PRISMA flow diagram (Figure 1) [22]. Consultations were also performed in bibliographies of the selected articles, in order to locate articles not found in the search.

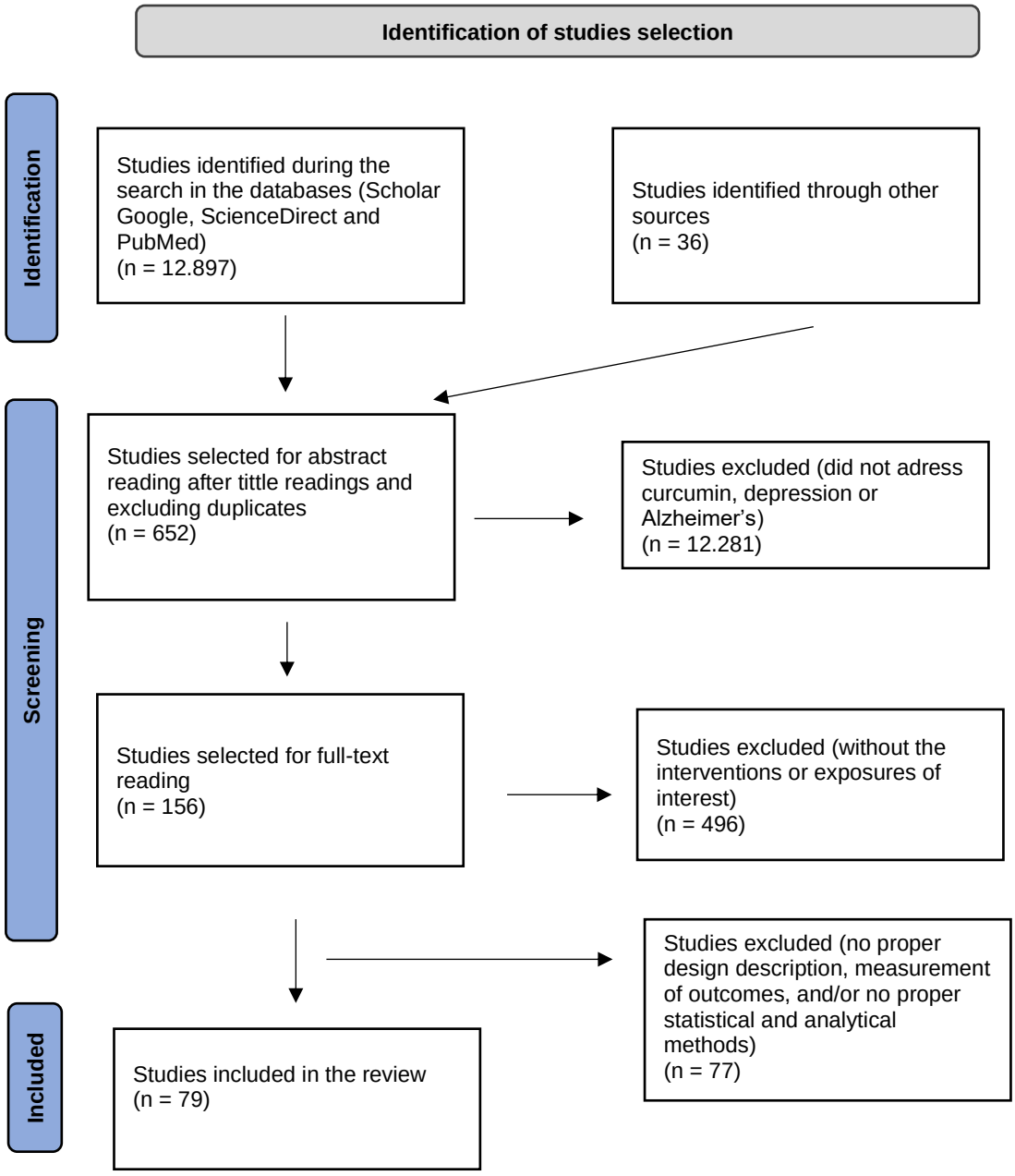


Figure 1. Flow diagram of the literature review [22].

Inclusion and exclusion criteria

The studies included had proper design description, measurement of outcomes and statistical and analytical methods. Studies without the interventions or exposures of interest, or with no proper design description were not included in the review. No restrictions were set on language, publication time, or study design. All data collected was revised by the both authors independently.

RESULTS AND DISCUSSION

Curcumin

Curcumin is the main polyphenol derived from *Curcuma longa L*' rhizome, a plant used as a spice, preservative, yellowish dye and as a medicine in Ayurvedic and Chinese medicine [23-24]. This polyphenol has several medicinal properties as antioxidant, anti-inflammatory, anti-HIV, antibacterial and antitumor effect [17]. In addition, curcumin is also used as a therapeutic agent in inflammatory bowel disease, pancreatitis, arthritis, some types of cancer [24], head trauma [25], anxiety [26], Parkinson's [27], depression [28], Alzheimer's disease [16], as well as acting as BDNF restorer [18].

Most of curcumin' benefits can be attributed to its anti-inflammatory action, obtained by the modulation of the expression and production of enzymes such as cyclooxygenase-2 (COX-2), lipoxygenase and inducible nitric oxide synthase (iNOS), and by the inhibition of inflammatory cytokines, including interleukin (IL) -1, -2, -6, -8 and -12, tumor necrosis factor alpha (TNF-α), monocyte chemotactic protein (MCP), among others [24, 29]. In neurodegenerative and neuropsychological diseases, its role in restoring BDNF levels and, consequently, promoting neurogenesis, it's extremely important and may contribute to the reversal of cognitive and mood disorders [30]. Polyphenols metabolites can activate cellular stress response pathways, leading to upregulation of neuroprotective genes, such as BDNF (Figure 2) [31].

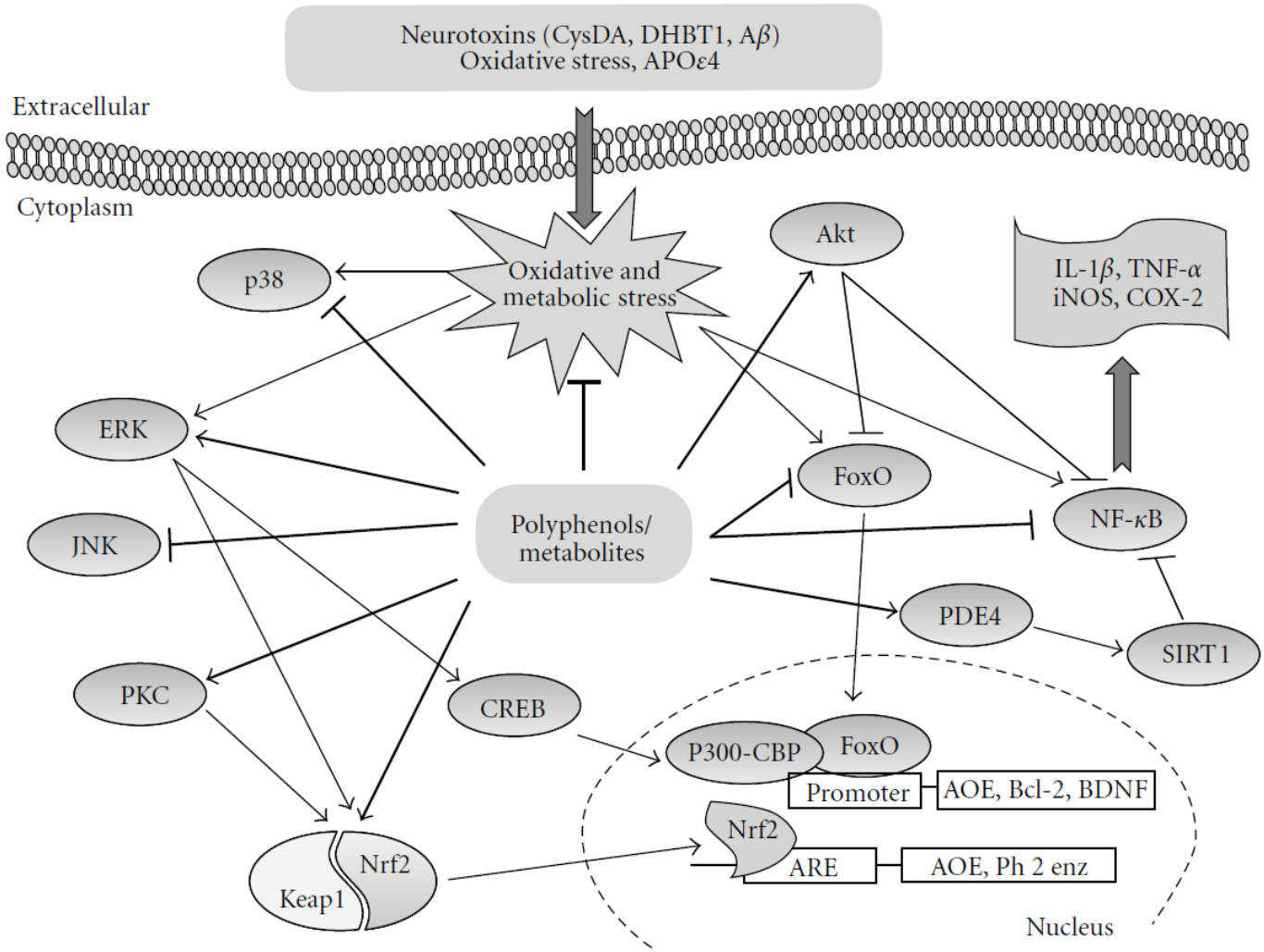


Figure 2. Metabolic routes involved in the biological effects of polyphenols, such as curcumin, mainly in neurological and neuropsychological disorders. They can act in vivo by activating cellular stress response mechanisms leading to upregulation of neuroprotective genes [31].

Curcumin's low absorption, rapid metabolism and rapid excretion [19] makes its bioavailability very low. When administered orally at a dose of 1 g/kg, its fecal excretion is around 75% [32], achieving very low plasma concentrations, in both rat and human studies [33, 34]. However, the association with piperine, an alkaloid derived from black pepper (*Pipernigrum L*) and long pepper (*Piperlongum L*), is capable of increasing the bioavailability of some drugs by inhibiting intestinal [35] and hepatic glucuronidation [20, 35, 36]. The administration of 20mg/kg of piperine with 2g/kg of curcumin in rats increases its bioavailability by 154% compared to administration of 2g/kg of curcumin alone. In humans, administration of 20mg of piperine with 2g of curcumin increased its bioavailability by 2000% compared to administration of 2g of curcumin alone. Piperine is capable of increasing absorption, plasma concentration, and bioavailability of curcumin in both rats and humans without significant side effects [20]. Piperine is a non-specific drug metabolism inhibitor, with low discrimination between different forms of cytochrome P-450. In rats, orally administered piperine strongly inhibits the hepatic activity of aryl hydrocarbon hydroxylase (AHH) and UDP-glucuronyl transferase, with a potent inhibitory effect on pharmacological metabolism [37]. Moreover, another way to overcome its low bioavailability is through the use of curcumin-loaded lipid-core nanocapsules. Considering the fact that curcumin is a liposoluble compound, this formulation is able to stabilize it and improve its absorption and biological activities [16].

Alzheimer's disease: pathophysiology

Alzheimer's disease is a neurodegenerative disease characterized by gradual memory degradation due to neuron damage and/or disruption. When neurons begin to malfunction and die, various symptoms start to appear, such as memory loss, difficulty in planning or problem solving, mood and personality changes, confusion about time or place, problems understanding visual images and spatial relations, problems writing or pronouncing words, difficulty walking, swallowing, among other symptoms [38].

Also according to the Alzheimer's Association [38], the disease is the most common form of dementia and it is associated with the accumulation of beta-amyloid plaques and abnormal amounts of Tau protein in the brain. Beta-amyloid accumulation is believed to be responsible for interfering with neuronal communication at synapses and contributing to cell death. Tau protein blocks the transport of nutrients and other essential molecules into neurons and contributes to neuronal death. Patients with advanced Alzheimer's have considerable brain shrinkage due to cell loss and debris from dead and dying neurons. The brain changes caused by the disease may begin about 20 years before symptoms manifestation.

There is evidence of the involvement of BDNF in the pathogenesis of Alzheimer's disease [39-40], as it plays an important role in synaptic plasticity, differentiation and neuronal survival. In the early stages of Alzheimer's disease, BDNF plasma levels are elevated, possibly due to a compensatory repair mechanism in the early stages of neurodegeneration, which could contribute to the degradation of beta-amyloid plaques. In the disease progression, BDNF levels are increasingly reduced due to the constant accumulation of beta-amyloid, and this decrease contributes to the progressive degeneration of specific brain regions and to disease severity [39]. Postmortem hippocampal analyzes of organ donors with Alzheimer's disease demonstrated a reduction in BDNF, but not NGF or NT-3 levels, suggesting the possibility that decreased BDNF expression may contribute to the progression and cell death in Alzheimer's disease [7].

Weinstein and coauthors [41] evaluated plasma BDNF concentrations from 2131 participants, and monitored them for 10 years to examine any association with dementia and Alzheimer's disease. During the study, 140 participants developed dementia, of which 117 had Alzheimer's disease, showing a strong correlation between lower BDNF levels and the risk of developing these diseases. Each quintile increase in BDNF plasma concentration was associated with a 23% reduction in the risk of developing dementia and Alzheimer's disease. These associations were significant among female participants, participants older than 80 years, and those with college degree. The study concluded that higher plasma BDNF levels may protect against future development of dementia and Alzheimer's disease, and it may be an active participant in the pathogenesis of these diseases, not just an incidental risk factor. Therefore, this data demonstrates the importance of BDNF in the biology and prevention of these pathologies.

A study by Nagahara and coauthors [42] demonstrated that BDNF infusion in older rats reversed cognitive decline, improved age-related disorders (by gene expression) and restored cell signaling. In older primates, BDNF improved age-related cognitive impairment and reversed neuronal atrophy. Evidence suggests that the use of strategies to stimulate the restoration of BDNF plasma levels could be used in the prevention and treatment of Alzheimer's disease [39]. Among the most effective non-drug strategies for potentially treating the disease are omega 3 fatty acids supplementation [43], intermittent fasting and calorie restriction [44], physical activity [45] and polyphenol ingestion/supplementation [46], in particular curcumin [15].

Curcumin effects on cognition

To verify the effects of curcumin on cognition and mood in elderly people, Cox and coauthors [47] recruited 60 healthy adults aged 60-85 in a randomized, double-blind, placebo-controlled trial. The solid lipid curcumin (400 mg as Longvida®) supplementation was tested acutely (1 and 3h after a single dose), chronically (after 4 weeks) and acute-on-chronic (1 and 3h after single dose following chronic treatment) on cognitive function, mood and blood biomarkers. The acute treatment (1h) demonstrated a significant improvement in performance on sustained attention and working memory tasks, when compared with placebo supplementation. The chronic treatment demonstrated a significant improvement on working memory, mood and psychological stress resilience, while the acute-on-chronic treatment also had a significant effect on alertness and contentedness. A significant reduction in total and LDL cholesterol were also observed after the treatment with curcumin, with no alterations in hematological safety measures. These results indicate a possible applicability of curcumin supplementation in Alzheimer's patients, due the significant improvement on cognitive functions, however, more studies with this specific population are needed.

Curcumin and inhibition of beta-amyloid plaque aggregation

As previously described, it is believed that one of the major causes of Alzheimer's disease is the accumulation of beta-amyloid plaques in the brain, leading to several cellular changes that leads to synaptic dysfunction. Many studies have shown positive effects of curcumin supplementation in counteracting the deleterious effects of beta-amyloid plaques [16, 48].

To evaluate curcumin's inhibitory effects on beta-amyloid plaque aggregation, Yang and coauthors [48] used groups of APPsw Tg2576 transgenic mice bred on 500ppm of curcumin or safflower oil diets, aged until their 22 months of age. Prior to slaughter, a mice from the 500ppm curcumin diet was injected with 200µl of curcumin/PBS within 5 minutes. Two other mice were injected with PBS alone, one without dietary curcumin as a control and the other with dietary curcumin. Then, these mice were brain analyzed and it was observed that the amyloid plaques were dyed with a yellowish fluorescence color of curcumin, as well as of thioflavin, proving that curcumin can cross the blood-brain barrier. After hours of exposure to light, the yellow/orange curcumin fluorescence gradually changed to yellow/green. Animals not treated with curcumin showed no fluorescence. To evaluate beta-amyloid aggregation, the ELISA (Enzyme-Linked Immunosorbent Assay) protocol and N-terminal antibody (6E10) were used for capture and detection. The aggregation of amyloid plaques was significantly reduced with curcumin, with an approximate IC_{50} of 0.81 M ($p < 0.001$).

In the same study [48], it was found that in vitro, increasing doses of curcumin (0-8µM) were able to disaggregate pre-aggregated beta-amyloid. The present study also compared the beta-amyloid anti-aggregating effect of curcumin with non-steroidal anti-inflammatory drugs. Beta-amyloid40 (50µg/ml concentration) was incubated with naproxen (0-32µM), ibuprofen (0-32µM) or curcumin (0-8µM) for 6 days at 37ºC. Beta-amyloid aggregation was verified with the 6E10/6E10 ELISA. Curcumin exhibited dose-dependent beta-amyloid antiaggregating effects, superior to the effects of naproxen and ibuprofen, which were only effective at high doses.

Curcumin in the restoration of cognitive and synaptic deficit caused by beta-amyloid

One of the characteristics of Alzheimer's disease is the cognitive and synaptic deficit, interfering with ordinary activities. To simulate the effects of Alzheimer's disease, rats were injected with beta-amyloid (2nmol) for 2 weeks, experiencing memory and learning decline, with decreased spontaneous Y-maze alternation. To evaluate the effects of curcumin, the animals were treated with 50mg/kg/day of curcumin (Cur 50) or 2.5mg/kg/day of curcumin loaded lipid-core nanocapsules (Cur-LNC 2.5) for 10 days. Curcumin-treated animals (Cur 50 and Cur-LNC 2.5) increased spontaneous alternation of behavior, significantly attenuating the damage caused by beta-amyloid injection without increasing the number of maze entries, indicating that the improvement was not due to motivational, exploratory or locomotor effects. In the object recognition test, animals injected with beta-amyloid were unable to distinguish between familiar and new objects, whereas those receiving curcumin treatment, Cur 50 and Cur-LNC 2.5, had both improved short-term and long-term memory, being able to distinguish between new and familiar objects. A lower dose of free curcumin (10mg/kg/day) had no effect on behavioral tests against beta-amyloid toxicity [16].

In the same study [16], to assess synaptic integrity, synaptophysin (presynaptic marker) was analyzed. Its levels were significantly reduced after beta-amyloid injection, indicating synaptic dysfunction. The animals treated with Cur 50 and Cur-LNC 2.5 did not had a reduction in synaptophysin levels, indicating preservation of synaptic activity, consistent with the results found in the behavioral tests.

Curcumin in Tau protein suppression

One of the mechanisms involved in the neurotoxic effects produced by beta-amyloid plaques is caused by hyperphosphorylation of Tau protein, which generates neurofibrillary tangles. This is a limiting factor for beta-amyloid-induced cell death, and an intervention that reduces the levels of this protein is extremely important [49]. To evaluate the effects of curcumin in the treatment of Tau protein hyperphosphorylation, Ma and coauthors [50] analyzed aged transgenic mice that overexpress human Tau protein, compared to an unmutated group (wild type C57B1/6J), both with pathological levels of Tau protein and with neuronal loss. One group received a control diet and the other a diet containing brain-permeable beta-amyloid and curcumin. Curcumin-treated rats had a suppression of soluble dimers levels of the Tau protein (without changing insoluble Tau), correcting cognitive, synaptic, and heat shock protein deficits (HSP70, HSP90, and HSC70 without elevation of their mRNAs), which are closely linked to Tau protein removal, even after the formation of their tangles. Heat shock protein kinases were affected differently, reducing Fyn without reducing Akt (protein kinase B). From these results, it is concluded that curcumin has a significant effect on reducing Tau protein and its beta-amyloid-induced tangles, improving behavioral/cognitive and synaptic functions [50].

Curcumin in the control of oxidative stress and inflammatory response

Oxidative stress and the inflammatory process are very important factors in the pathogenesis of Alzheimer's disease. Protein oxidation by reactive oxygen species and nitrogen reactive species can generate unstable products, such as protein hydroperoxides, which generate even more free radicals. Some of these oxidized proteins can accumulate and contribute to the development and to the damage generated by various diseases. Patients with Alzheimer's disease have greater susceptibility to oxidative stress and lipid peroxidation, presenting neuronal changes in various antioxidant enzymes. In the progression of the disease there is an accumulation of lipofuscin, an aggregate of lipids and peroxidized proteins, in the lysosomes of aged cells and brain cells, contributing to the severity of the pathology. Therefore, it is important to use antioxidants to control excessive reactive oxygen species and protein/lipid peroxidation [51-52].

Exacerbated inflammation is a hallmark of Alzheimer's disease through increased expression of inflammatory cytokines and activation of microglia. Aggarwal and coauthors [53] found that curcumin down-regulates the expression of NF-kB-regulated genetic products, such as COX-2, TNF, 5-LOX, IL-1, IL-6, IL-8, MIP-1α, adhesion molecules, C-reactive protein (CRP), CXCR-4, among others, besides down-regulating their own activation by inhibiting AKT and IκBα. This modulation of the inflammatory response provides benefits in numerous pathologies, including neurodegenerative diseases such as Alzheimer's disease.

Curcumin has a much higher antioxidant activity than vitamin E, with the ability to protect the brain against lipid peroxidation and oxidative stress. Divided into three groups, APPSw transgenic mice were treated with low doses of curcumin (160 ppm), high doses of curcumin (5000 ppm), or no treatment, for 6 months, before being sacrificed. Oxidative damage was evaluated using Western blot analysis, where carbonyl groups of oxidized proteins were derived with 2,4-dinitrophenylhydrazine and detected using an anti-deoxyribonucleoprotein antibody. Untreated mice had a 10.7-fold increase in oxidized proteins. Animals treated with high doses of curcumin had a reduction in protein oxidation by 46.3%, while animals treated with low doses of curcumin had a 61.5% reduction, when compared to untreated animals [54].

In the same study, to verify its inhibitory effect on the inflammatory process generated by beta-amyloid, Lim and coauthors [54] evaluated levels of IL-1beta (interleukin-1beta) in APPSw transgenic mice, because they are related to Alzheimer's disease, involved in the inflammatory response, and also because their elevation is associated with cognitive loss in rodents. Its levels were measured in the hippocampus, entorhinal cortex, piriform cortex and residual cortex. The low-dose curcumin group showed a 61.8% reduction in IL-1beta expression, while the high-dose group showed a 57% reduction, when compared to the untreated group.

In a study by Bala and coauthors [55], it was found that chronic administration of curcumin in 6 and 24 month old rats significantly reduced cerebral lipid peroxidation, while SOD, GPx and Na(+)/K(+)-ATPase levels were significantly increased in many brain regions. In the 24-month-old rats it was also seen a significant decrease in intraneuronal lipofuscin deposits, in all the four brain regions. This study showcases curcumin’s ability not only to decrease lipid peroxidation due its own antioxidant power, but also to increase endogenous antioxidant enzymes, of which are associated with neuroprotection and anti-aging.

Curcumin and aluminum

Aluminum is a neurotoxic metal capable of increasing the permeability of the blood-brain barrier, negatively affecting the central nervous system. Epidemiological, neuropathological and biochemical studies

have suggested a possible association of aluminum neurotoxicity in the pathogenesis of Alzheimer's disease, promoting insoluble beta-amyloid accumulation and hyperphosphorylated Tau protein aggregation, as well as enhancing the oxidative effect generated by various transition metals [56].

Thus, to verify the protective effects of curcumin on cognitive dysfunction and oxidative damage exerted by aluminum, Kumar and coauthors [57] administered 100 mg/kg of aluminum chloride to rats, daily, for 6 weeks. Rodents were treated with curcumin (30mg/kg or 60mg/kg) for 6 months and, on the twenty-first and forty-second study days, memory and locomotor capacity were evaluated. The non-curcumin-treated group experienced significant memory retention loss and increased oxidative stress, as well as increased aluminum levels and acetylcholinesterase activity. Curcumin-treated groups (30mg/kg and 60mg/kg) displayed a significant improvement in memory retention, decreased oxidative damage, decreased acetylcholinesterase activity and aluminum concentrations, especially in the 60mg/kg treated group, showing neuroprotective effect against cognitive dysfunction and oxidative stress induced by aluminum.

Curcumin in the restoration of BDNF levels

There is evidence that the progression of neurodegenerative diseases, such as Alzheimer's, are mainly linked to synaptic degeneration, and therapies that act on this mechanism through BDNF up-regulation are able to improve the symptomatology and the survival rates of these diseases [58]. To verify the BDNF restorative effects of curcumin, Zhang and coauthors [15] treated rats with beta-amyloid 1-42. Beta-amyloid treated rats experienced significant cognitive deficits in behavioral tests (Y-maze, open field, and Morris water maze). Rodents were divided into several groups, some received single doses of 50, 100 or 200mg/kg of curcumin, while others received chronic treatment for 5 consecutive days at the same doses (50, 100 or 200mg/kg, once a day). Acute treatment rats showed no improvement in both cognitive and locomotor testing compared to the curcumin-free group, but chronically treated rats showed significant improvement in both aspects, especially in the 100mg/kg and 200mg/kg groups. To verify the mechanism involved in the positive effects seen in the chronic treatment with curcumin, the expression of BDNF, GSK3β, ERK, JNK and p38 were verified, and their respective phosphorylated forms in the hippocampus were also analyzed. There was a significant increase in ERK and GSK3β phosphorylation and BDNF expression in the 100 and 200mg/kg treated groups, with no change in the 50mg/kg treated group. Following injection with lentivirus-shBDNF, curcumin's cognitive improvements were blocked, proving that the mechanism involved in curcumin's benefits were obtained by the restoration of BDNF levels. To verify if the improvement in the spatial memory exerted by curcumin occurred by the activation of ERK or GSK3β phosphorylation, their respective inhibitors were used. Inhibition of ERK, but not GSK3 blocked the cognitive benefits of curcumin. It is concluded that the cognitive benefits exerted by curcumin in Alzheimer's mainly occurs by activation of signaling pathway ERK-BDNF.

Hoppe and coauthors [16] evaluated the effects of treatment with free curcumin (50mg/kg/day) and curcumin-loaded lipid-core nanocapsules (2.5mg/kg/day) on beta-amilóide1-42 (2nmol) injected rats that had significant cognitive (memory and learning) impairment, with a large reduction in BDNF expression, which is critical for neuronal survival and activity, neurotransmitter release modulation and neuronal plasticity, in addition to mediating long-term memory enhancement and fixation. Both free curcumin-treatment and curcumin-loaded lipid-core nanocapsules treatment were found to block beta-amyloid-induced reduction of BDNF levels in the rats, by restoring them to basal levels.

Depression: pathophysiology

Depression is a mood disorder characterized by sadness and constant loss of interest, which leads to an increased risk of low productivity and absenteeism at work, reflecting in the lower wage rates and higher unemployment rates among people with this disorder, besides having a suicide-related mortality risk 20 times higher than the general population. Severe symptoms of depression are associated with a significantly increased risk of all-cause mortality [59].

The mechanism involved in this disease is thought to be far beyond a simple imbalance of neurotransmitter levels, and antidepressants also act on the activation of the 3',5'-cyclic adenosine monophosphate (cAMP) monophosphate system in some brain regions, including the increased brain expression and function of the transcription factor cyclic adenosine monophosphate response element-binding protein (Figure 3). When activated, the cAMP system leads to regulation of some specific target genes, including increased BDNF expression in some neuronal populations in the hippocampus and cerebral cortex [60]. Antidepressant treatment increases synaptic levels of norepinephrine and serotonin via blocking the reuptake or degradation of these monoamines. This results in the activation of intracellular signal

transduction cascades, one of which is the cAMP-cAMP response element binding protein (CREB) cascade. A target gene for antidepressant treatment and the cAMP-CREB cascade is BDNF, which contributes to the cellular processes underlying neuronal plasticity and cell survival [61].

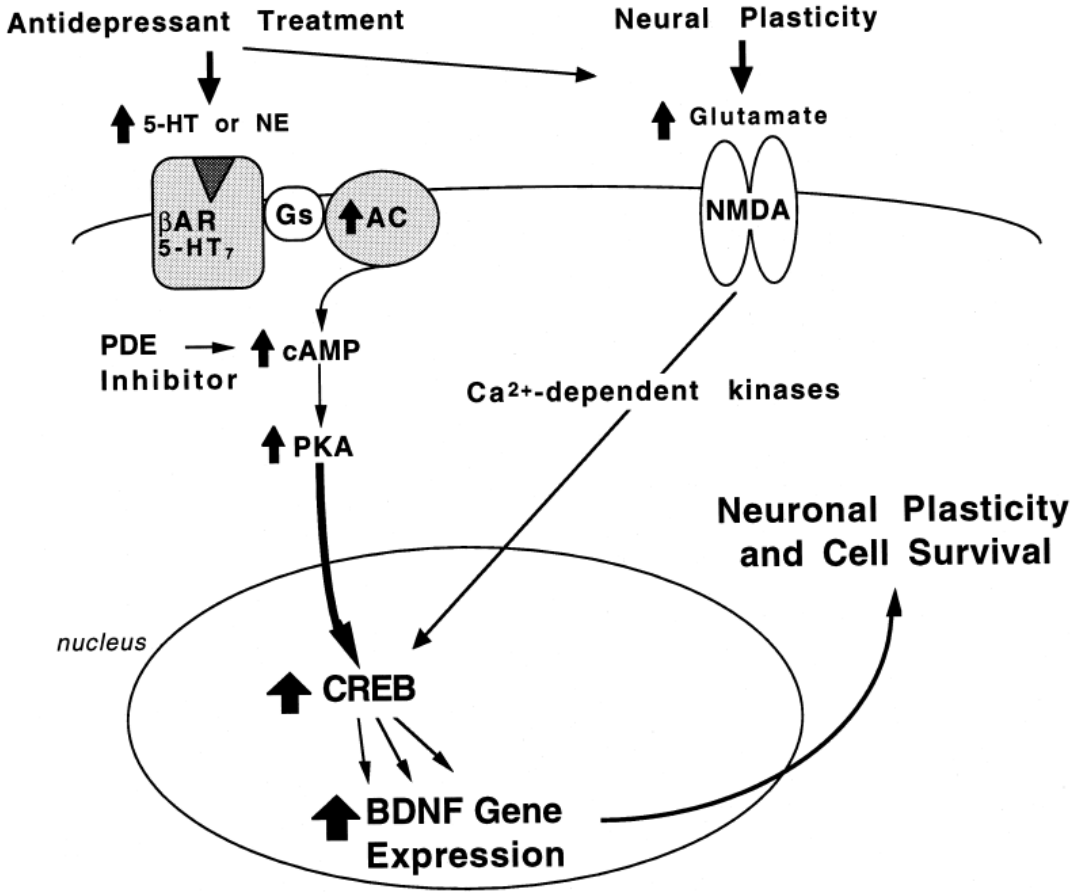


Figure 3. Influence of antidepressant treatment on the cyclic adenosine monophosphate (cAMP)-CREB cascade, increasing BDNF levels [61].

A meta-analysis by Koolschijn and coauthors [62] analyzed brain volume abnormalities in patients with depression. For this, magnetic resonance images were evaluated in 64 studies in a total of 2418 patients with depression and 1974 resonances of healthy subjects. Patients with depression showed large reductions in the frontal regions. In the hippocampus, putamen and caudate nucleus, the volume reductions were moderate.

A study by Sheline and coauthors [63] evaluated hippocampal volume of individuals with a history of depression but who are currently in remission, using volumetric magnetic resonance imaging, compared with normal subjects. Individuals with a history of depression had significantly lower left and right hippocampal volume, and the degree of volumetric reduction correlated with the total duration period of depression.

Frodl and coauthors [64] evaluated the hippocampal size of 60 patients with depression, compared with 60 control subjects, measured by high resolution magnetic resonance imaging. The 120 study subjects were genotyped for BDNF Val66Met polymorphism. Patients with depression had significantly lower hippocampal volume than the control group, but in patients with depression and control subjects carrying the Met-BDNF allele, they had significantly smaller hippocampi than patients with depression and control subjects carrying the homozygous Val-BDNF allele. These results suggest that individuals with Met-BDNF allele have a higher risk of developing smaller hippocampi and may be more susceptible to the development of depression.

There is evidence that neuronal plasticity is the key in treating and recovering from depression. Antidepressant and electroshock/electroconvulsive therapy treatments act on the expression of several molecules, mainly in BDNF and its TrkB receptor, consequently increasing neurogenesis. Response to antidepressant treatment is slow and may take several weeks, possibly due to the need for brain reorganization and physical growth in response to BDNF signaling [65-66].

Curcumin and reduction of depression symptoms

To compare curcumin's antidepressant effects with those of fluoxetine, 60 patients diagnosed with depression were divided into 3 groups and assessed using the Hamilton Depression Rating Scale. The first group received 20mg of fluoxetine, the second received 1000mg of curcumin and the third group received the combination of both. The 3 groups were compared with demographic data and initial clinical characteristics. After 6 weeks of treatment, the group treated with the combination of curcumin and fluoxetine had a 77.8% response to treatment, whereas the group treated with fluoxetine alone had a response of 64.7%, and the curcumin only group had a response of 62.5%. The overall efficacy of the treatments was 70.5% in fluoxetine-treated patients, 75% in curcumin-treated patients and 83.3% in the combined treatment group, with 'excellent' or 'good' efficacy [67]. Similar results were found by Kanchanatawan and coauthors [68], where they tested curcumin supplementation (500-1500mg/day) as monotherapy or as an adjunctive treatment for depression, or placebo, for 12 weeks in Thai patients. The Montgomery-Asberg Depression Rating Scale and the Hamilton Anxiety Rating Scale were used to measure the score of depression and anxiety at baseline and 2, 4, 8, 12, and 16 weeks later. Curcumin treatment was significantly more efficacious than placebo at 12 and 16 weeks, with a more pronounced effect in males. No significant changes in blood parameters or adverse effects were seeing.

Asadi and coauthors [69] conducted a double-blind, placebo-controlled clinical trial to test the effects of curcumin supplementation in nano-curcumin form, on depression and anxiety symptoms in diabetic patients with peripheral neuropathy. Eighty diabetic patients were randomly allocated to the intervention group (n = 40), which received 80mg of nano-curcumin, or in the control group (n = 40), which received 80mg of placebo, for 8 weeks, in capsules. The depression, anxiety and stress levels were measured by the Depression, Anxiety, Stress Scale (DASS-21-items) questionnaire before and after the intervention. After the 8 weeks of intervention, it was observed that the nano-curcumin supplementation led to a significant decrease in both depression and anxiety symptoms (from 16.7 [3.1] to 15.3 [2.6] and 22.4 [4.03] to 20.6 [3.4], respectively), compared with placebo (17.5 [3.2] to 17.3 [3.1]; p = .02 and 21.9 [3.5] to 21.2 [3.5]; p = .009, respectively). No significant difference in the stress score were seen. This study reinforces curcumin potential on treating depression and also anxiety symptoms.

To verify the efficacy of antidepressant treatment in rats, immobility time in forced swimming test is used as one of the main parameters. Zhang and coauthors [70] used rats with chronic, moderate, stress-induced depressive behavior (CUMS) to test the effects of curcumin supplementation. Exposure to CUMS for 6 weeks significantly increased the immobility time of rats compared to those not exposed to stress. Animals treated with 40mg/kg/day of curcumin experienced a significant reduction in immobility time and an increased swimming time in the forced swimming test, suggesting that curcumin exerted an antidepressant effect.

Also, to verify the effects of curcumin on immobility time in the forced swimming test, Wang and coauthors [71] used placebo, curcumin (2.5, 5 or 10mg/kg) or fluoxetine (10, 20 or 30mg/kg) in mice. Both curcumin-treated rodents (5 and 10mg/kg) and fluoxetine-treated rodents (20 and 30mg/kg) experienced a significant reduction in immobility time when compared to the placebo group. The reduction was most significant in curcumin-treated mice.

In an open field activity test, Zhang and coauthors [70] exposed rats to CUMS for 6 weeks, resulting in depressive-like symptoms, with a significant reduction in crossings and exploratory behavior, when compared to the control group. Rats that received chronic administration of curcumin (40mg/kg/day) before de CUMS exposure had no decrease in crossings and exploratory behavior, indicating that curcumin can also be used to prevent depressive symptoms.

Curcumin and the inflammatory response

Because inflammation plays a very important role in the development of depression and curcumin is one of the most powerful natural anti-inflammatories in existence, Jiang and coauthors [72] analyzed its effects on rats with chronic mild stress-induced depression (water and food deprivation for 24h, noise exposure for 3h, cage tilt (45°) for 7h, night lighting, dirty cage for 24h, and forced swimming at 4ºC for 6 minutes) for 21 days. RT-PCR and ELISA were used to verify TNF-α and IL-6 expression, and western blotting method to verify NF-κB modulation. Chronic stress-induced depression significantly elevated all inflammatory factors compared to the control group. Curcumin (10mg/kg/day) was able to significantly prevent elevation of TNF-α and IL-6 levels and inhibit the increase of the expression of TNF-α and IL-6 mRNA in stressed rats. Chronic curcumin treatment was also able to inhibit phosphorylation of NF-κB (p65) in the prefrontal cortex and hippocampus. Moreover, curcumin-treated rats also showed improvement on behavioral tests (open field and preferably sucrose), indicating improvement in depression symptoms.

Curcumin in the modulation of monoamines

Considering the monoaminergic theories of depression, Kulkarni and coauthors [73] conducted a study to investigate the involvement of curcumin in the catecholamine and serotoninergic system. Behavioral (forced swimming), biochemical and neurochemical tests were used to measure treatment efficacy in the study rats. After curcumin (10-80mg/kg) supplementation, dose-dependent improvement on behavioral tests was observed, with reduced immobility time on the forced swimming test, as well as increased serotonin and dopamine levels, with inhibition of monoamine oxidase enzymes (MAO-A and MAO-B). When used in combination with other antidepressants (fluoxetine, venlafaxine and bupropion), curcumin at a dose of 20mg/kg was able to increase their efficacy in the anti-immobility effect, resulting in a higher elevation of serotonin levels. When curcumin (20 and 40mg/kg) was co-administered with piperine (bioavailability enhancer) at a dose of 2.5mg/kg, its pharmacological effects were intensified. Therefore, it is concluded that curcumin has antidepressant effects both isolated and in combination with other antidepressants, exerting influence on the serotoninergic and dopaminergic system.

Curcumin on BDNF levels

Depression is a multifactorial disease, however, it is believed that one of the main pillars of its pathogenesis is due to the reduction of BDNF expression. To verify the effects and mechanisms of curcumin in the animal model of depression, Zhang and coauthors [74] divided mice into a control group, curcumin-treated group (40mg/kg), curcumin and SL327-treated (ERK cascade inhibitor), fluoxetine-treated and SL327-treated for 21 days. Both curcumin-treated and fluoxetine-treated rodents had an improvement in depression symptoms (reduced immobility time and increased swimming time in the forced swimming test), showing a significant antidepressant effect. Curcumin treatment also significantly increased BDNF levels, as did fluoxetine treatment, when compared with the control group. Animals treated with the curcumin-SL327 combination had no improvement in depressive symptoms, as well as no significant increase in BDNF levels, indicating that the ERK-CREB-BDNF cascade is the key factor involved in curcumin antidepressant effects.

Also to verify the effects of curcumin on BDNF levels, Huang and coauthors [75] injected corticosterone (30mg/kg) into rats for 3 weeks, inducing depressive symptoms (significant reduction in sucrose consumption and increased forced swim immobility), and significantly reducing BDNF levels in the prefrontal cortex and in the hippocampus. Rats treated with curcumin (20mg/kg) prior to corticosterone injections had a suppression of depressive effects and presented no decrease in BDNF levels.

Xu and coauthors [18] used curcumin in the treatment of stress-induced depression and hypothalamic-pituitary-adrenal axis (HPA) dysfunction, at doses of 2.5, 5 and 10mg/kg. Rats were exposed to a chronic stress protocol for 20 days, resulting in test box performance deficits and various physiological effects, such as abnormal adrenal weight to body weight ratio, increased adrenal cortex thickness, increased plasma concentrations of corticosterone, reduced glucocorticoid mRNA receptor expression, down-regulation of BDNF expression, and reduced CREB phosphorylation. Chronic curcumin treatment at doses of 5 and 10mg/kg were able to reverse all negative physiological and performance changes caused by stress induction in the animals. The behavioral improvement generated by curcumin was attributed to the restoration of neurotrophin levels, especially BDNF, and by the normalization of the HPA axis.

In order to verify the effects of curcumin in combination with conventional antidepressants, Yu and coauthors [76] recruited 108 subjects with depression in a randomized, double-blind, placebo-controlled study. Subjects received 2 capsules of 500mg of curcumin or placebo per day, along with their usual escitalopram medication (5-15mg), for 6 weeks. Depression levels were measured using the Hamilton Depression Rating Scale and the Montgomery-Asberg Depression Rating Scale. After chronic curcumin supplementation, subjects had a significant reduction in depressive symptoms, with a reduction in the Hamilton Depression scale and the Montgomery-Asberg scale. Curcumin supplementation was also able to elevate plasma BDNF levels and reduce inflammatory cytokines TNF-α and IL-1β, and salivary cortisol concentrations, when compared to the placebo group. These results suggest that supplementation with curcumin is able to improve the action of selective serotonin reuptake inhibitor class of antidepressants, such as escitalopram, mainly by increasing BDNF levels, inhibiting proinflammatory cytokines and reducing cortisol secretion. Therefore, there is strong evidence of curcumin potential as a therapeutic agent in the neuropsychological and neurodegenerative context, especially when used in more bioavailable and high-quality formulations [16, 20, 47, 77-79].

CONCLUSION

In summary, the data presented suggests that curcumin is able to prevent and improve the symptoms of Alzheimer's disease through the improvement of cognitive and memory deficit by restoring BDNF levels,

reducing oxidative stress, inflammation, beta-amyloid aggregation, Tau protein accumulation and aluminum neurotoxicity. In Depression, curcumin treatment was also able to improve its symptoms by restoring BDNF levels, modulating monoamines and reducing inflammation.

This study helps to clarify the various mechanisms of action of curcumin in the neurodegenerative/neuropsychological diseases, Alzheimer's disease and depression, suggesting it as a potential therapeutic agent without any significant side effects. However, further long-term clinical studies are needed to better elucidate its efficacy and safety.

Funding: The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest: The author declares that there is no conflict of interest concerning this manuscript.

REFERENCES

1. Levi-Montalcini R. The nerve growth factor 35 years later. Science 1987;237:1154-62.
2. Davies A. The role of neurotrophins in the developing nervous system. J Neurobiol 1994;25:1334-48.
3. Lewin G, Barde Y. Physiology of the neurotrophins. Annu Rev Neurosci 1996;19:289–317. Doi: 10.1146/annurev.ne.19.030196.001445.
4. Bramham C, Massaoudi E. BDNF function in adult synaptic plasticity: The synaptic consolidation hypothesis. Prog Neurobiol 2005;76:99-125.
5. Schratt GM, Nigh EA, Chen WG, Hu L, Greenberg ME. BDNF Regulates the Translation of a Select Group of mRNAs by a Mammalian Target of Rapamycin–Phosphatidylinositol 3-Kinase-Dependent Pathway during Neuronal Development. J Neurosci 2004;24:7366-77.
6. Scharfman H, Goodman J, Macleod A, Phani S, Antonelli C, Croll S. Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Exp Neurol 2005;192:348-56.
7. Phillips HS, Hains JM, Amanini M, Laramee GR, Johnson AS, Winslow JW. BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. Neuron 1991;7:695-702.
8. Shimizu E, Hashimoto K, Okamura N, Koike K, Naoya K, Kumakiri C, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry 2003;54:70–5.
9. Lee J, Seroogy K, Mattson M. Dietary restriction enhances neurotrophin expression and neurogenesis in the hippocampus of adult mice. J Neurochem 2002;80:539-47.
10. Neeper SA, Gómez-Panilla F, Choi J, Cotman CW. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. Brain Res 1996;726:49-56.
11. Abdul T, Mohammed K, Henriksson B, Persson H, Winblad B, Lindefors N. Increased expression of brain-derived neurotrophic factor mRNA in rat hippocampus is associated with improved spatial memory and enriched environment. Neurosci Lett 1992;138:153-6.
12. Kempermann G, Kuhn H, Gage F. More hippocampal neurons in adult mice living in an enriched environment. Nature 1997;386:493-5.
13. Ying A, Gomez-Pinilla F. Dietary Omega-3 Fatty Acids Normalize BDNF Levels, Reduce Oxidative Damage, and Counteract Learning Disability after Traumatic Brain Injury in Rats. J Neurotrauma 2004;21:1457-67.
14. Dias GP, Cavegn N, Nix A, Bevilaqua MCN, Stangl D, Zainuddin MAS, et al. The Role of Dietary Polyphenols on Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavioural Effects on Depression and Anxiety. Oxid Med Cell Longev 2012;2012.
15. Zhang L, Fang Y, Xu Y, Lian Y, Xie N, Wu T, et al. Curcumin Improves Amyloid β-Peptide (1-42) Induced Spatial Memory Deficits through BDNF-ERK Signaling Pathway. PloS One 2015;10:e0131525.
16. Hoppe JB, Coradini K, Frozza RL, Oliveira CM, Meneghetti AB, Bernardi A, et al. Free and nanoencapsulated curcumin suppress b-amyloid-induced cognitive impairments in rats: Involvement of BDNF and Akt/GSK-3b signaling pathway. Neurobiol Learn Mem 2013;106:134-44.
17. Araújo CC, Leon LL. Biological Activities of Curcuma longa L. Mem Inst Oswaldo Cruz 2001;96:723-8.
18. Xu Y, Ku B, Tie L, Yao H, Jiang W, Ma X, et al. Curcumin reverses the effects of chronic stress on behavior, the HPA axis, BDNF expression and phosphorylation of CREB. Brain Res 2006;1122:56-64.
19. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of Curcumin: Problems and Promises. Mol Pharm 2007;4:807-18.
20. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of Piperine on the Pharmacokinetics of Curcumin in Animals and Human Volunteers. Planta Med 1998;64:353-6.
21. Zanotto-Filho A, Coradini K, Braganhol E, Schroder R, Oliveira CM, Simões-Pires A, et al. Curcumin-loaded lipid-core nanocapsules as a strategy to improve pharmacological efficacy of curcumin in glioma treatment. Eur J Pharm Biopharm 2013;83:156-67.
22. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:71.
23. Cousins M, Adelberg J, Chenb F. Antioxidant capacity of fresh and dried rhizomes from four clones of turmeric (Curcuma longa L.) grown in vitro. Ind Crop Prod 2007;25:129-35.
24. Jurenka J. Anti-inflammatory Properties of Curcumin, a Major Constituent of Curcuma longa: A Review of Preclinical and Clinical Research. Altern Med Rev 2009;14:141-53.

25. Wu A, Ying Z, Gomez-Pinilla F. Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. Exp Neurol 2006;197:309-17.
26. Abu-Taweel G, Ajarem J, Ahmad M. Protective Effect of Curcumin on Anxiety, Learning Behavior, Neuromuscular Activities, Brain Neurotransmitters and Oxidative Stress Enzymes in Cadmium Intoxicated Mice. J Behav Brain Sci 2013;3:74-84.
27. Mythri B, Bharath M. Curcumin: A Potential Neuroprotective Agent in Parkinson's Disease. Curr. Pharm. Des. 2012;18:91-9.
28. Sanmukhani J, Anovadiya A, Tripathi C. Evaluation of antidepressant like activity of curcumin and its combination with fluoxetine and imipramine: an acute and chronic study. Acta Pol Pharm 2011;68:769-75.
29. Abe Y, Hashimoto S, Horie T. Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. Pharmacol Res 1999;39:41-7.
30. Kulkarni SK, Bhutani MK, Bishnoi M. Antidepressant activity of curcumin: involvement of serotonin and dopamine system. Psychopharmacology 2008;201:435-42.
31. Vauzour D. Dietary Polyphenols as Modulators of Brain Functions: Biological Actions and Molecular Mechanisms Underpinning Their Beneficial Effects. Oxid Med Cell Longev 2012;2012:914273.
32. Wahlstrom B, Blennow G. A study on the fate of curcumin in the rat. Acta Pharmacol Toxicol 1978;43:86-92.
33. Yang KY, Lin LC, Tseng TY, Wang SC, Tsai TH. Oral bioavailability of curcumin in rat and the herbal analysis from Curcuma longa by LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 2007;853:183–9.
34. Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, et al. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin Cancer Res 2004;10:6847–54.
35. Reen RK, Jamwal DS, Taneja SC, Koul JL, Dubey RK, Wiebel FJ, et al. Impairment of UDP-glucose dehydrogenase and glucuronidation activities in liver and small intestine of rat and guinea pig in vitro by piperine. Biochem Pharmacol. 1993;46:229-38.
36. Atal C, Dubey R, Singh J. Biochemical basis of enhanced drug bioavailability by piperine: evidence that piperine is a potent inhibitor of drug metabolism. J Pharmacol Exp Ther 1985;232:258-62.
37. Singh J, Dubey R, Atal C. Piperine-mediated inhibition of glucuronidation activity in isolated epithelial cells of the guinea-pig small intestine: evidence that piperine lowers the endogenous UDP-glucuronic acid content. J Pharmacol Exp Ther 1986;236:488-93.
38. Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers Dement 2015;11:332-84.
39. Laske C, Stransky E, Leyhe T. Stage-dependent BDNF serum concentrations in Alzheimer's disease. J Neural Transm 2006;113:1217-122.
40. Ng TKS, Ho CSH, Tam WWS, Kua EH, Ho RCM. Decreased Serum Brain-Derived Neurotrophic Factor (BDNF) Levels in Patients with Alzheimer's Disease (AD): A Systematic Review and Meta-Analysis. Int J Mol Sci 2019;20:257.
41. Weinstein G, Beiser AS, Choi SH, Preis SR, Chen TC, Vorgas D, et al. Serum Brain-Derived Neurotrophic Factor and the Risk for Dementia: The Framingham Heart Study. JAMA Neurol 2014;71:55–61.
42. Nagahara AH, Merrill DA, Coppola G, Tsukada S, Schroeder BE, Shaked GM, et al. Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. Nat Med 2009;15:331–7.
43. Hjortha E, Zhua M, Toro VC, Vedin I, Palmblad J, Cederholm T, et al. Omega-3 Fatty Acids Enhance Phagocytosis of Alzheimer's Disease-Related Amyloid-42 by Human Microglia and Decrease Inflammatory Markers. J Alzheimers Dis 2013;35:697-713.
44. Halagappa VKM, Guo Z, Pearson M, Matsuoka Y, Cutler RG, Laferla FM, Mattson MP. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. Neurobiol Dis 2007;23:212-20.
45. Radak Z, Hart N, Sarga L, Koltai E, Atalay M, Ohno H, et al. Exercise Plays a Preventive Role Against Alzheimer's Disease. J Alzheimers Dis 2010;20:777-83.
46. Malar D, Devi K. Dietary Polyphenols for Treatment of Alzheimer's Disease– Future Research and Development. Curr Pharm Biotechnol 2014;15:330-42.
47. Cox KHM, Pipingas A, Scholey AB. Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. J Psychopharmacol 2015;29:642–51.
48. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, et al. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 2005;280:5892–901.
49. Park SY, Kim HS, Cho EK, Kwon BY, Phark S, Hwang KW, et al. Curcumin protected PC12 cells against beta-amyloid-induced toxicity through the inhibition of oxidative damage and tau hyperphosphorylation. Food Chem Toxicol 2008;46:2881–7.
50. Ma QL, Zuo X, Yang F, Ubeda OJ, Gant DJ, Alaverdyan M, et al. Curcumin Suppresses Soluble Tau Dimers and Corrects Molecular Chaperone, Synaptic, and Behavioral Deficits in Aged Human Tau Transgenic Mice. J Biol Chem 2013;288:4056-65.
51. Stadtman ER. Protein oxidation and aging. Science 1992;257:1220-25.
52. Devasagayam TPA, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS, Lele RD. Free Radicals and Antioxidants in Human Health: Current Status and Future Prospects. J Assoc Physicians India 2004;52:794-804.
53. Aggarwal B, Harikumar K. Potential Therapeutic Effects of Curcumin, the Anti-Inflammatory Agent, Against Neurodegenerative, Cardiovascular, Pulmonary, Metabolic, Autoimmune and Neoplastic Diseases. Internat J Biochem Cell Biol 2010;41:40-59.
54. Lim GP, Chu T, Yang F, Beech W, Frautschy AS, Cole GM. The Curry Spice Curcumin Reduces Oxidative Damage and Amyloid Pathology in an Alzheimer Transgenic Mouse. J Neurosci 2001;21:8370-7.
55. Bala K, Tripathy BC, Sharma D. Neuroprotective and anti-ageing effects of curcumin in aged rat brain regions. Biogerontology 2006;7:81-9.

56. Sethi P, Jyoti A, Hussain E, Sharma D. Curcumin attenuates aluminium-induced functional neurotoxicity in rats. Pharmacol Biochem Behav 2009;93:31-9.
57. Kumar A, Dogra S, Prakash A. Protective effect of curcumin (*Curcuma longa*), against aluminium toxicity: Possible behavioral and biochemical alterations in rats. Behav Brain Res 2009;205:384-90.
58. Lu B, Nagappan G, Guan X, Nathan PJ, Wren P. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. Nat Rev Neurosci 2013;14:401-16.
59. Lépine JP, Briley M. The increasing burden of depression. Neuropsychiatr Dis Treat 2011;7:3-7.
60. Duman R, Heninger G, Nestler E. A Molecular and Cellular Theory of Depression. Arch Gen Psychiatry 1997;54:560-97.
61. Duman R, Malberg J, Nakagawa S, D'Sa C. Neuronal Plasticity and Survival in Mood Disorders. Biol Psychiatry 2000;48:732-9.
62. Koolschijn PCMP, Haren NEM, Lensvelt-Mulders GJLM, Pol HEH, Kahn RS. Brain Volume Abnormalities in Major Depressive Disorder: A Meta-Analysis of Magnetic Resonance Imaging Studies. Hum Brain Mapp 2009;30:3719-35.
63. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A 1996;93:3908–13.
64. Frodl T, Schüle C, Schmitt G, Born C, Baghai T, Zill P. Association of the Brain-Derived Neurotrophic Factor Val66Met Polymorphism With Reduced Hippocampal Volumes in Major Depression. Arch Gen Psychiatry 2007;64:410–6.
65. Castrén E. Is mood chemistry? Nat Rev Neurosci 2005;6:241–6.
66. Castrén E, Rantamäki T. The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. Dev Neurobiol 2010;70:289-97.
67. Sanmukhani J, Satodia V, Trivedi J, Patel T, Tiwari D, Panchal B, et al. Efficacy and Safety of Curcumin in Major Depressive Disorder: A Randomized Controlled Trial. Phytother Res 2014;28:579-85.
68. Kanchanatawan B, Tangwongchai S, Sughondhabhirom A, Suppapitiporn S, Hemrunrojn S, Carvalho AF, et al. Add-on Treatment with Curcumin Has Antidepressive Effects in Thai Patients with Major Depression: Results of a Randomized Double-Blind Placebo-Controlled Study. Neurotox Res 2018;33:621–33.
69. Asadi S, Gholami MS, Siassi F, Qorbani M, Sotoudeh G. Beneficial effects of nano-curcumin supplement on depression and anxiety in diabetic patients with peripheral neuropathy: A randomized, double-blind, placebo-controlled clinical trial. Phytother Res 2020;34:896-903.
70. Zhang L, Luo J, Zhang M, Yao W, Ma X, Yu SY. Effects of curcumin on chronic, unpredictable, mild, stress-induced depressive-like 14 behavior and structural plasticity in the lateral amygdala of rats. Int J Neuro Psychopharmacol 2014;17:793-806.
71. Wang R, Xu Y, Wu HL, Li YB, Li YH, Guo JB, et al. The antidepressant effects of curcumin in the forced swimming test involve 5-HT1 and 5-HT2 receptors. Eur J Pharmacol 2008;578:43-50.
72. Jiang H, Wang Z, Wang Y, Xie K, Zhang Q, Luan Q, et al. Antidepressant-like effects of curcumin in chronic mild stress of rats: Involvement of its anti-inflammatory action. Prog Neuropsychopharmacol Biol Psychiatry. 2013;47:33-9.
73. Kulkarni S, Dhir A, Akula K. Potentials of Curcumin as an Antidepressant. Sci World J 2009;9:1233-41.
74. Zhang L, Xu T, Wang S, Yu L, Liu D, Zhan R, et al. Curcumin produces antidepressant effects via activating MAPK/ERK-dependent brain-derived neurotrophic factor expression in the amygdala of mice. Behav Brain Res 2012;235:67-72.
75. Huang Z, Zhong XM, Li ZY, Feng CR, Pan AJ, Mao QQ. Curcumin reverses corticosterone-induced depressive-like behavior and decrease in brain BDNF levels in rats. Neurosci Lett 2011;493:145-8.
76. Yu JJ, Pei LB, Zhang Y, Wen ZY, Yang JL. Chronic Supplementation of Curcumin Enhances the Efficacy of Antidepressants in Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. J Clin Psychopharmacol 2015;35:406-10.
77. Rudnik L, Lyra A, Barboza F, Klein T, Kanunfre C, Farago P. PEG-PCL Nanocapsules Containing Curcumin: Validation of HPLC Method for Analyzing Drug-loading Efficiency, Stability Testing and Cytotoxicity on NIH-3T3 Cell Line. Braz Arch Biol Technol 2020:63:e20200234.
78. Kebede B, Forsido S, Tola Y, Astatkie T. Effects of Variety and Curing and Drying Methods on Quality Attributes of Turmeric (Curcuma domestica) Powder. Braz Arch Biol Technol 2021:64: e21200697.
79. Cas M, Ghidoni R. Dietary Curcumin: Correlation between Bioavailability and Health Potential. Nutrients 2019:11:2147.