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REVIEW

Neuroprotective expression of turmeric and curcumin

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Abstract

Turmeric (*Curcuma longa*) is extensively used as a spice and a coloring agent in Southeast Asia. Turmeric is used as a traditional remedy for cough, diabetic wounds, hepatic disorders, and rheumatism due to its antiseptic, antibacterial, and anti-inflammatory properties. Since the last few decades, extensive work has been done on turmeric and its constituents to explore its pharmacological actions. Curcumin is the main constituent of turmeric and is well demonstrated for its anti-inflammatory, hypoglycaemic, antioxidant, wound-healing, and antimicrobial activities. The functional neurons of the brain and synapses are lost in neurodegenerative disorders for which there is no permanent cure. Oxidative damage and inflammation play a role in age-related neurological disorders. The antioxidants have the ability to prevent different neurological disorders. Recent studies have shown that both turmeric and curcumin possess neuroprotective and cognitive-enhancing properties that help to prevent neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. Different experimental studies have indicated the antioxidant and anti-ageing properties of turmeric and curcumin. Various studies have shown that curcumin acts as a strong barrier against neurological disorders and, hence, it may be a potential drug candidate for the prevention of neurodegenerative diseases. The aim of this review was to present the current pieces of evidence in the literature regarding the neuroprotective effects of turmeric and curcumin.

1. Introduction

Turmeric is a herbaceous rhizome perennial plant that belongs to the ginger family, Zingiberaceae. Although the origin of turmeric is uncertain, it is thought to be originated from the tropical part of Southeast Asia, most probably India. Now it is also cultivated in Thailand, Indonesia, China, Japan, and Africa. Turmeric is used in food as an active ingredient of curries and mustard (Kim *et al.*, 2014; Yuliani *et al.*, 2019). It is also used as a colouring agent, flavour enhancer and food preservative. It is reported as one of the most investigated medicinal plant species (Jessica Elizabeth *et al.*, 2017). The plant of turmeric is funnel-shaped which is covered with green and white coloured bracts. It has 5 to 5.5 cm long flowers of yellow colour without any fruit. It is reported that different genotypes of turmeric are rich sources of the essential oils (Akbar *et al.*, 2015; Azmi *et al.*, 2016). Due to a wide spectrum of pharmacological activities, turmeric has received much attention worldwide in recent years. Turmeric possesses antioxidant, anti-inflammatory, anticarcinogenic, antimicrobial and antimutagenic properties (Kuwatada *et al.*, 2017). Turmeric is used as a traditional medicine in the Ayurvedic, Unani and Siddha systems of medicine (Selvi *et al.*, 2015). Its medicinal uses encompass the treatment of different diseases like ulcers, skin diseases, parasitic infections, and to improve the immune system. It is also used for the treatment of cold and flu (Siviero *et al.*, 2015). It has antioxidant (Arya *et al.*, 2015; Lim and Han, 2018), anti-inflammatory, antiproliferative (Amalraj *et al.*, 2017), and anti-ageing (Vaughn *et al.*, 2016) properties. It is also reported to have activity against the protozoans (Llurba-Montesino *et al.*, 2015), venoms (Singh *et al.*, 2017) and tumours (Vemuri *et al.*, 2017). The essential oil, as well as alcoholic and aqueous extracts of turmeric, have shown remarkable pesticidal properties besides acting as a mosquito repellent (Dosoky and Setzer, 2018).

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Coagulation of proteins, inflammation and oxidative damage are characteristic features of many neurodegenerative diseases related to ageing. Curcumin was shown to possess the neuroprotective function as an anti-coagulating agent for protein besides having anti-inflammatory and antioxidant properties (Maiti and Dunbar, 2018). The long history of use, low cost, oral safety, pluripotency, and the neuroprotective character make the use of curcumin as a neuroprotective drug of choice in different neurological conditions including neurodegenerative disorders, stroke and ageing (Tamagno *et al.*, 2005). Various studies have shown that turmeric and curcumin ameliorate the symptoms related to dementia (Ahmed and Gilani, 2014; Samy *et al.*, 2016). However, the low absorption, fast metabolic breakdown, and rapid systemic clearance are the factors that limit the bioavailability of curcumin thereby restricting its enormous therapeutic potential (Anand *et al.*, 2007; Yu and Huang, 2012; Prasad *et al.*, 2014; Liu *et al.*, 2016).

Dementia is expressed by an array of clinical symptoms that comprises memory deficit, language problems, and behavioural changes leading to the disturbing activities of daily life. Of all dementia disorders, Alzheimer's disease (AD) is considered as the most prevalent type followed by vascular dementia (VD), mixed dementia (MD), and dementia with Lewy bodies (DLB). Dementia is categorized as a global problem in view of the rapidly ageing population around the globe and the disease puts a significant social and economic burden (Robinson *et al.*, 2015). Accumulation of free radicals and acetylcholine (ACh) deficiency in the brains of Alzheimer's patients is considered as an established factor leading to dementia and cognitive problems. The mechanisms involving a disturbance in a balance between the number of free radicals and the antioxidant (AO) defence system along with cholinergic deficit lead to impaired cholinergic neurotransmission (Ovais *et al.*, 2018; Abu Bakar *et al.*, 2020). According to the epidemiologic studies in Southeast Asian countries, the incidence of AD is 4.4 times less in comparison to the West because turmeric is commonly used there as a dietary spice (Mishra and Palanivelu, 2008; Latif *et al.*, 2019). This review attempts to present the neuroprotective role of turmeric in neurodegenerative diseases with a special focus on its therapeutic potential in Alzheimer's and Parkinson's diseases.

2. Chemical constituents of turmeric

Turmeric root or rhizome is commonly used in traditional medicine. A large number of different constituents have been identified in turmeric. Polyphenolic curcuminoids constitute the main group of turmeric's bioactive compounds which include curcumin (diferuloylmethane), bisdemethoxycurcumin, demethoxycurcumin, and cyclocurcumin. The yellow-pigmented curcuminoids contain 85% curcumin, 10% demethoxycurcumin and 5% bisdemethoxycurcumin. Curcumin is a well-studied compound of turmeric. Turmeric also contains sesquiterpenes (turmerone, zingiberone atlantone, germacrone, turmeronol, and bisabolene), proteins, carbohydrates, resins, and caffeic acid (Jurenka, 2009; Dosoky and Setzer, 2018). Additionally, turmeric has been reported to contain a variety of biochemical compounds involved in a variety of biological functions as summarized in Table 1.

3. Curcumin: the most important bioactive compound of turmeric

Curcumin is a widely studied nutraceutical isolated from the rhizomes of turmeric. It was first discovered about two centuries ago by Vogel and Pelletier, the scientists of Harvard College laboratory (Gupta *et al.*, 2012). The active principle of turmeric is curcumin that is a low molecular weight polyphenol with a bright yellow colour. Curcumin is a highly pleiotropic molecule. This polyphenol has been shown to possess anti-inflammatory, hypoglycaemic, antioxidant, wound-healing, and antimicrobial antiangiogenic, antimutagenic, and antiplatelet aggregation activities. Curcumin is also reported to have nephroprotective activity and shown to work as a therapeutic agent against myocardial infarction, cystic fibrosis, atherosclerosis, neurodegenerative diseases, cancer, rheumatoid inflammation, ocular diseases, osteoporosis, hypertension, chronic kidney diseases, diabetes, chronic inflammation, infection and various skin diseases (Maiti and Dunbar, 2018). Some populations having traditional use of a curcumin-rich diet have shown a low incidence of AD and their good cognitive ability has been associated with the use of curry, a routine food that contains turmeric which is a source of curcumin (Nakayama *et al.*, 2014). In vivo experiments on the dementia rat model have shown the efficacy of curcumin for the treatment of memory impairment and proved to be a safeguard against oxidative damage (Yaari *et al.*, 2008; Kumar *et al.*, 2009; Agrawal *et al.*, 2010). Despite its demonstrated safety and efficacy, the use of curcumin in chemopreventive or therapeutic settings has been limited by its short biological half-life and low bioavailability. Low serum and tissue levels of curcumin irrespective of the route of administration, rapid metabolism and elimination are some of the major factors curtailing the bioavailability of curcumin. Different studies have also shown that curcumin was poorly bioavailable on oral administration (Ravindranath and Chandrasekhara, 1980; Perkins *et al.*, 2002; Jamwal,

Table 1. Chemical constituents of turmeric and their effect on the brain

Turmeric Compounds	Effect on brain
Alpha linolenic acid (omega-3 fatty acid)	Antioxidant and anti-inflammatory; increases ACh production; increases glucose absorption by cell; anti-AD; energy production and signaling in brain cells (Kaplan *et al*., 2017; Ajith, 2018).
Calebin-A	Antioxidant and anti-inflammatory; neuroprotection (Novaes *et al*., 2017).
Cinnamic acid	Anti-inflammatory (Qabaha *et al*., 2017); neuroprotection (Prorok *et al*., 2019).
Ferulic acid	Antioxidant; AChE inhibition (Kaur *et al*., 2018).
Vanillic acid	Antioxidant; anti-inflammatory (Kaur *et al*., 2018).
Magnesium	Anti-inflammatory; antioxidant; lowers the rate of dementia and vascular dementia (Novaes *et al*., 2017).
Thiamine (vitamin B1)	Deficiency of thiamine causes confusion and memory loss; glucose absorption in brain and nervous system cells (Kaur *et al*., 2018; Nedeljković *et al*., 2018).
Riboflavin (vitamin B2)	Detoxification and excess metal chelation; neuroprotective effects in some neurological conditions (PD, multiple sclerosis, migraine); antioxidant; myelin formation; mitochondrial function; iron metabolism (Nedeljković *et al*., 2018).
Niacin (vitamin B3)	Essential for the production of cell energy; antioxidant; stimulates mitochondria; increases ATP production; neuronal maturation and neuroprotection (Fricker *et al*., 2018).
Pyridoxine (vitamin B6)	Rate-limiting cofactor in the production of neurotransmitters; neuroprotection (Nedeljković *et al*., 2018).
Folic Acid (folate; vitamin B9)	Anti-AD; promotes energy production by mitochondria; memory enhancement and cognitive improvement; anti-inflammatory (Chen *et al*., 2016; Cianciulli *et al*., 2016).
Vitamin C	Antioxidant; enhances the immune system; reduces glutamate-mediated excitotoxicity; neuronal differentiation and maturation; modulation of neurotransmission; increase ATP production (Man Anh *et al*., 2019).
Vitamin E	Neuroprotective; anti-inflammatory; antioxidant; hypocholesterolemic; cognitive enhancement; reduces the progression of AD (Lloret *et al*., 2019).
Quercetin	Antioxidant; anti-inflammatory; protection of mitochondria; elimination of extra iron; inhibition of AD causing TNF-α and COX-2 (Khan *et al.,* 2018).
Resveratrol	Antioxidant; protection against neurodegenerative diseases and assembly of Aβ protein by activating SIRT1 longevity gene (Gomes *et al*., 2018); prevention of brain cell death in hippocampus (Kodali *et al*., 2015); inhibition of inflammatory enzymes (de Sá Coutinho *et al*., 2018); protection of brain cells from injury by stimulating vitagenes; clearance of α-synuclein (Guo *et al*., 2016); protects from metabolic stress (Palomera-Avalos *et al*., 2017).
Turmerones	Blocks Aβ production and aggregation (Maiti and Dunbar, 2018).
Xanthorrhizol	Neuroprotection; antioxidant; anti-inflammatory; anti-Aβ (Lim and Han, 2018).
Zingiberene	anti-Aβ; prevents the formation of advanced glycation end products (AGEs) in brain cells (Lim and Han, 2018).

2018).

4. Neurodegenerative diseases and neuroprotection

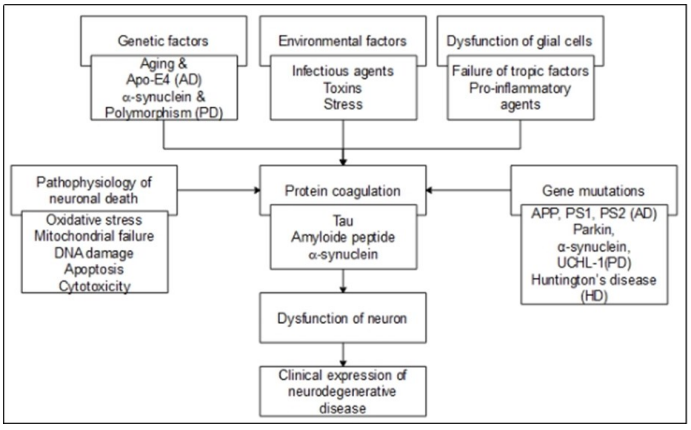

Figure 1. The causes of neurodegeneration including neuronal death gene mutation, genetic factors, environmental factors and dysfunctioning of cells involving protein coagulation and then neuronal death with clinical expression of neurodegenerative diseases.

The etiology of neurodegeneration involves various environmental and genetic factors, genetic mutations, pathophysiological processes of neuronal death, and dysfunction of glial cells (Figure 1). Degeneration of the central nervous system leads to cell death, failure of axon regeneration, demyelination, and in general the structural and functional neuronal deficits. All these conditions partly or completely, single or combined, genetic or attained, are demonstrated in neurological disorders, collectively known as neurodegenerative disorders. These disorders are harmful to the normal functioning of the brain and cause progressive deterioration as they are one of the leading causes of disability and mortality. There are various neurodegenerative disorders but special attention has been given to AD, Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), and Huntington disease (HD) (Hussain *et al*., 2018). Although there are hundreds of neurodegenerative diseases, their classification is quite challenging in view of their overlapping clinical and pathological symptoms. Neurodegenerative diseases may be grouped into a disease of ganglion, cortex, brainstem, cerebellum or spinal cord. Among neurodegenerative diseases, AD is the sixth leading cause of death in the world (McMackin *et al.*, 2019; Weis *et al.*, 2019). Studies have shown that

the increased level of age-dependent neurodegeneration is associated with increased oxidative damage to protein, lipids, and DNA with a decrease in antioxidant levels (Lee *et al.*, 2012; Höhn and Grune, 2013). In neurodegenerative diseases, the modification of oxidative proteins occurs at a low level that accumulates in a variety of cells and tissues (Zhang, 2013).

The term neuroprotection means the ability to defend the central nervous system from an acute neural injury such as stroke or trauma, and chronic neurodegenerative disorders like AD and PD. In this respect, herbal medicines may play a valuable role in the prevention of neurodegenerative diseases with a healthy lifestyle including good physical activity and dietary habits. The medicinal use of plant organs like roots, stem, leaves, flowers, fruits, and seeds in herbal medicine is a complementary and alternative method of treatment. The plant products contain a complex mixture of phytochemicals compounds (Nour *et al.*, 2014; Fazel Nabavi *et al.*, 2016; Spagnuolo *et al.*, 2016).

5. Potential therapeutic targets in neurodegenerative disorders

The neurodegenerative disorders constitute the most common forms of dementia but the identification of suitable therapeutic targets is restricted due to a variety of aetiologies involved. Except for the inherited AD and VD, the underlying aetiologies are still unidentified for most dementia disorders. However, multiple pathologies leading to potential therapeutic targets include amyloid-beta (Aβ) and abnormal tau proteins for AD, angiogenic and ischemic lesions for VD, and α-synucleinopathy for LBD, primarily cholinergic neurotransmitter defects, inflammatory pathways, oxidative stress, apoptosis, and diminished neuroplasticity (Kumar and Singh, 2015; Zhou *et al.*, 2016). Other therapeutic targets include the cholinesterase inhibitors (ChEIs) which act as anti-AChE thereby enhancing the cholinergic neurotransmission by increasing the ACh level at the synaptic junction; secretase inhibitors including β-secretase and γ-secretase which prevent the deposition of the amyloid plaques in brain by restricting the synthesis of $A\beta_{1-42}$ fragment from amyloid precursor protein (APP); anti-inflammatory drugs including cyclooxygenase (COX) inhibitors which act by decreasing the neurotoxic COX level thereby reducing the inflammation of brain tissue, and antioxidants including the drugs which combat the free radicals which are considered as one of the main factors that oxidatively injure the brain tissue (Natarajan *et al.*, 2013).

6. Turmeric and neurological disorders

Neurological disorders are defined as the disorders of the peripheral and central nervous system including the brain, spinal cord, nerves, autonomic nervous system, and neuromuscular junction, muscles leading to AD, PD, epilepsy, migraine, and brain tumours (Khan *et al.*, 2018). The use of turmeric in medicine is due to its chemical composition. Turmeric contains almost 235 compounds among which curcuminoids are the most bioactive compounds containing curcumin. A study on turmeric consumption and cognitive function in Asian people showed that the elderly Asians who use curry (once a month or more) containing turmeric had a superior cognitive function as compared to those who rarely consume curry (less than one in six months). They have higher Mini-Mental State Examination (MMSE), which proves their superior cognitive function (Ng *et al.*, 2006; Suryanarayana *et al.*, 2007; Yao and Xue, 2014). Turmeric was found effective for behavioural and psychological symptoms of dementia (BPSD) treatment including hallucination, apathy, delusions, agitation, anxiety, and depression. In a clinical study on turmeric administration, a decrease in the acuity of symptoms was observed (Huang *et al.*, 2012).

There are many molecular targets like transcription factors, kinases, inflammatory cytokinases, antioxidants and growth factors which are modulated and communicated by curcumin. All these actions of curcumin are due to its neuroprotective activity. Various pathways in different types of cells of the nervous system like neurons, astrocytes, and microglia (Lavoie *et al.*, 2009; Maiti and Dunbar, 2018) have explained this supportive effect of curcumin. The curcumin was observed to possess a neuroprotective function in the primary cell culture of different areas of the nervous system, for instance, in cortical (Wang *et al.*, 2012), mesencephalic (Ortiz-Ortiz *et al.*, 2010), spinal cord (Jiang *et al.*, 2011), and hippocampal regions (Ye and Zhang, 2012), due to its antioxidant, anti-inflammatory and anti-protein coagulating properties. Curcumin was reported to reduce the expression of *interleukin-1* alpha (IL-1α), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α) in the neurodegenerative disorder due to which the neuro-inflammation decreased (Darvesh *et al.*, 2012; Hatami *et al.*, 2019). The brain cells have high oxygen demand due to which they are more sensitive to oxidative damage. The oxidation of unsaturated fatty acid 4- hydroxy-2,3-nonenal, acrolein, malondialdehyde (MDA) and other compounds as an end product have a negative impact on human health (Ayala *et al*., 2014). The glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) are endogenous antioxidant enzymes which protect the cells against oxidative damage due to a high content of unsaturated fatty acids in the brain (Kim *et al.*, 2015). The antioxidant defense system of the brain is weaker as compared to other body

parts. So the oxidative stress rapidly leads to the hippocampus degeneration, which is the major memory processing region. Such degeneration may lead to the pathogenesis of neurodegenerative diseases including dementia (Liu *et al.*, 2017). The organometal trimethyltin (TMT) has a harmful effect on the brain by enhancing the formation of reactive oxygen species (ROS) in the hippocampus region. TMT also enhances the expression of presenilin, APP, and c-fos (a transcription factor) in the limbic system, which are linked to the pathophysiology of AD. The ethanolic turmeric extract reduces the TMT-induced oxidative stress by decreasing the level of plasma and brain MDA and increases the levels of SOD, glutathione (GHS), CAT, and GPx enzymes in the brain (Yuliani *et al.*, 2019). Curcumin was shown to improve the survival of cortical neurons deprived of oxygen and glucose and concomitant cell injury in an in vitro study. Moreover, the results of this study also suggested a decrease in the volume of infarct and oxidative stress following the focal cerebral ischemia in rats (Li *et al.*, 2017). Figure 2 summarizes the neuroprotective effects of curcumin.

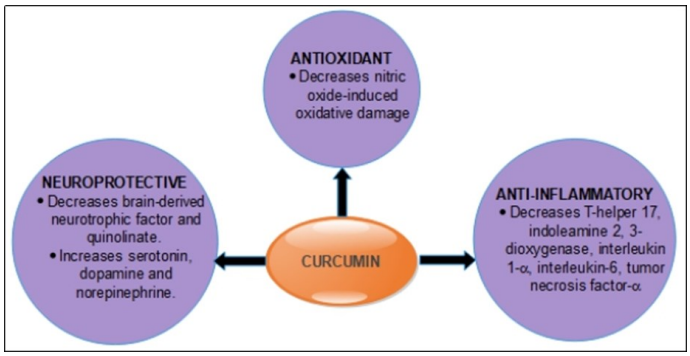

Figure 2. Neuroprotective effects of curcumin

7. Role as antioxidant

An antioxidant is a molecule, which, in a concentration lower than its oxidizable substrate, has the ability to substantially retard or delay the substrate oxidation (Galano, 2015). Antioxidants inhibit the catalysis of ROS generation by removing and scavenging the ROS and ROS precursors. Various studies have indicated that brain tissue in dementia patients are exposed to oxidative stress (Liu *et al.*, 2017; Khan *et al.*, 2018). High oxygen demand, terminal neuronal differentiation, and weak antioxidant mechanisms make the central nervous system (CNS) more prone to oxidative stress, which in turn triggers various neurodegenerative disorders (Kim *et al.*, 2015). Several studies have indicated the efficacy of various antioxidants to prevent cognitive decline (Wong *et al.*, 2018), as the treatment options for mild cognitive impairment (MCI) and AD (Mecocci *et al.*, 2004; Cristina Polidori and Nelles, 2014). Age-associated increase in oxidative stress is considered as one of the significant risk factors for cognitive decline (Konar *et al.*, 2016) and is widely thought to be a significant feature in the complexity of AD pathogenicity (Shen *et al.*, 2018). Consequently, there is a growing interest to explore the role of antioxidants in preventing or retarding the initiation of cognitive decline. Generally, an imbalance between the ROS production and the physiological antioxidant defence system is termed as oxidative stress resulting in a shift in the redox state linked to an increased production of ROS which ultimately leads to increased oxidation of lipids, DNA, protein, neurons, and apo E4, all of which are the risk factors for cognitive ageing (Lacour *et al.*, 2017; Legdeur *et al.*, 2018).

7.1 Animal studies in mice

Naik *et al.* (2011) studied the antioxidant activity of curcumin at a dosage of 200 mg/kg in Wistar strain rats and reported a correlation of its antioxidant activity with hepatoprotective, anti-inflammatory and cardioprotective effects. Banji *et al.* (2014) have described that curcumin improved cognition by suppressing the mitochondrial dysfunction and apoptosis induced by D-galactose in rat brains thereby increasing the antioxidant content in neuronal mitochondria. Ciftci *et al.* (2015) have reported the curcumin-mediated prevention of formaldehyde-induced neurotoxicity in rats. Cui *et al.* (2016) have shown that curcumin ameliorated the dopamine-induced neuronal oxidative damage by decreasing the ROS production and increasing the levels of GSH in rat brain cells. Saha *et al.* (2016) reported that curcumin prevented pentylenetetrazole (PTZ)-induce neurotoxicity via decreasing the ROS and nitric oxide (NO) levels and increasing the levels of GSH and antioxidant enzymes. Samy *et al.* (2016) have shown that curcumin treatment led to the prevention of AD in streptozotocin (STZ)-induced Alzheimer's dementia in rats by modulating apoptosis and oxidative stress. Sankar *et al.* (2016) reported that curcumin prevented the arsenic-induced neurotoxicity and oxidative damage by decreasing lipid peroxygenase (LPO) levels and increasing the levels of GSH and antioxidant enzymes. Waseem and Parvez (2016) reported the preventive effect of curcumin in response to the neurotoxicity and mitochondrial dysfunction induced by oxaliplatin. Sharma *et al.* (2014) have shown that curcumin attenuated the fluoride-induced neurotoxicity and prevented the neurodegeneration by decreasing the level of LPO in the hippocampal region. Nazari *et al.* (2014) reported a neuroprotective effect of highly bioavailable curcumin on sodium nitroprusside-induced oxidative stress model by decreasing oxidative stress.

8. Turmeric and Alzheimer's disease

Alzheimer's disease is a widespread disease especially in industrialized western countries. The disease rate is higher in the US and European countries than in Asia (Zhang *et al.*, 2018). In AD, two major lesions are formed: senile plaques and neurofibrillary tangles (NFT). In senile plaques, dystrophic neurites and activated glial cells are likely to be more central protein deposits of amyloid fibrils that are made up of Aβ peptide (Luchena *et al.*, 2018; Ziegler-Waldkirch and Meyer-Luehmann, 2018). Turmeric contains different compounds including curcumin, tetrahydrocurcumin, bisdemethoxycurcumin, and demethoxycurcumin, which act as anti-amyloidogenic by preventing the Aβ protein formation, the pathological root cause of AD (Zhang *et al.*, 2010; Randino *et al.*, 2016). It is stated that a low dose of turmeric (160 ppm) can reduce pro-inflammatory cytokine levels which are linked to the neuroinflammatory cascades involved in the neuritic plaque pathogenicity (Lim *et al.*, 2001). In AD, the faulty phagocytosis occurs due to which Aβ plaques cannot be cleared effectively. Curcumin triggers the phagocytosis due to which the Aβ plaques are cleared *in vitro* and enhance the induction of heat shock protein (HSP) in reaction to the addition of soluble Aβ aggregates to neuronal cell cultures. It also reduces the strength of Aβ amassing and prevents the formation of Aβ fibrils in these cells (Cline *et al.*, 2018; Maiti and Dunbar, 2018). It was suggested that the regulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-$_K$B) activity-associated transcription factors, that is, cytokines and enzymes, was responsible for the therapeutic potential of curcumin in AD (Lee *et al.*, 2013). Epidemiological studies of turmeric show its nonsteroidal anti-inflammatory property, which is linked with reducing the risk of AD (He *et al*., 2015). Thus, it may be concluded that turmeric increases the neurocognitive function in Alzheimer's patients.

The major active component of turmeric, the curcumin has some interesting properties. It regulates the level of dopamine, norepinephrine, and serotonin in the brain and inhibits the enzyme monoamine oxidase (MAO) A and B, which decompose serotonin and dopamine (Kulkarni *et al.*, 2008; Wang *et al.*, 2014). The role of serotonin is in the neuro-vegetative function of the body such as sleep, appetite, learning and memory, behaviour, mood, muscle contraction, cardiovascular function and regulation of endocrine, while dopamine is involved in emotion, pleasure and regulating locomotion. A neurotransmitter, norepinephrine, is involved inattentiveness, sleeping, dreaming, emotion and learning. Turmeric modifies the dysfunction of these neurotransmitters and significantly reduces behavioural symptoms of AD (Zhao *et al.*, 1989; Cole *et al.*, 2004). It is suggested by a clinical study that curcumin decreases the oxidative damage and removes the stimulus for Aβ formation. It also reduces the inflammation in microglial cells of the brain by reducing the cytokines level which is pro-inflammatory signalling molecules and by preventing the formation of Aβ, thereby decreasing the Aβ plaques. It generates an enzyme which reduces the risk of Aβ production and lowers the oxidation of those fats and proteins which are dangerous. It triggers the macrophage cells of the brain to clear the Aβ plaques which are already present. It inhibits Aβ aggregation and reverses the neurodegeneration due to Aβ production and also inhibits the Aβ mediated neurotoxicity. It also blocks the cholesterol formation that is also a factor involved in the formation of Aβ (Tang and Taghibiglou, 2017).

In an *in-vitro* study, it was shown that curcumin has the ability to reduce the number of plaques in the brain by impending Aβ plaques formation (Ahmed and Gilani, 2014). The higher concentration of curcumin at the molecular level binds to Aβ to block self-assembly. As curcumin is lipophilic in nature, it easily crosses the blood-brain barrier (BBB) and then binds to the Aβ plaques. Curcumin has metal chelating property as it has the ability to bind with the metal ions and improve the Aβ degradation and decreases the oxidative stress (Maiti and Dunbar, 2018; Reddy *et al.*, 2018). It binds with iron, copper with high affinity rather than zinc thereby acting as a protector against AD, and may protect against iron-mediated damage (Tang and Taghibiglou, 2017). A decreased serum Aβ level along with a reduction in Aβ burden in the brain, that was more prominent in the regions of neocortex and hippocampus, resulted after the administration of curcumin to an AD mouse model (Farooqui *et al.*, 2018; Wang *et al.*, 2012). These studies highlight the promising role of turmeric and curcumin in the inhibition of Aβ plaques formation and, hence, their ability to improve the neurodegenerative disease condition.

8.1 Animal studies in mice

Dohare *et al.* (2008) studied the neuroprotective activity of Curcuma oil (250 mg/kg) in Sprague-Dawley male rats and reported that Curcuma oil promoted the suppression of increasing intracellular concentration of Ca^{2+} that is considered as an important player in different signalling pathways. They also reported that the curcuma oil caused a decrease in ROS generation leading to the prevention of brain neutrophils and NO metabolites infiltration following ischemia in the brain. The neuroprotective activity of curcumin in Sprague-Dawley male rats at a dosage of 300 mg/kg was also reported by Dohare *et al.* (2008) also reported that curcumin-induced selective inhibition of neuronal cytotoxicity. Also, they

stated that curcumin treatment significantly attenuated the increased volumes of brain infarct and edema following ischemia in rats. Zhang *et al.* (2008) investigated the neuroprotective activity of curcuminoids (1-10 μmol) in newborn Sprague-Dawley rats and revealed that curcuminoids significantly suppressed the NO production by LPS-activated microglia in rat brain. Jayanarayanan *et al.* (2013) described the neuroprotective activity of curcumin in STZ-induced Wistar male rats at a dosage of 60 mg/kg and reported the beneficial effect of curcumin supplementation to STZ -induced diabetic rats thereby reducing the alterations in glutamatergic receptors, imbalanced glutamate metabolism, and oxidative stress. Eckert *et al.* (2013) reported the effect of curcumin on mitochondrial dysfunction in brain of male Senescence Accelerated *Mouse* Prone-Strain 8 (SAMP8) and Senescence Accelerated *Mouse* Resistant-Strain 1 (SAMR1) at a dosage of 500 mg/kg and observed a significant decrease in mitochondrial dysfunction and energy production in the brain cells of SAMP8 mice. Chen *et al.* (2014) studied the neuroprotective activity of curcumin at a dosage of 500 nmol/L in Sprague-Dawley female rats (pregnant for 14.5 days) and reported that the neuroprotective effect of curcumin was through upregulation of wnt3a and β-catenin expression in the control experimental group receiving curcumin at a dose of 500 nmol/L. Gazal *et al.* (2014) described that pretreatment of a ketamine-induced model of mania in female adult Wistar rats with curcumin led to the prevention of ketamine-induced behavioral and prooxidant effects. Ahmed and Gilani (2009) studied the anti-AD effects of curcuminoids and its individual components at a dosage range of 3-10 mg/kg in Sprague-Dawley male rats and reported their memory enhancing capacity in addition to the dose-dependent inhibitory effect in frontal cortex and hippocampus as well as *ex vivo* acetylcholinesterase assay. Ahmed *et al.* (2010) described that the anti-AD effect of curcuminoids and its individual components at a dosage range of 3-10 mg/kg in Aβ peptide-infused Sprague-Dawley male rats was due to the curcuminoids-mediated increased expression of synaptophysin. These data suggest the importance of diet supplemented with curcumin as a preventive measure and treatment option for AD that may decrease Aβ and plaque burden in addition to lowering the oxidative stress in the brain.

8.2 Clinical trials using curcumin for AD therapy

Some investigations regarding the preclinical trials to test the efficacy of curcumin in humans along with the pharmacokinetics and safety have been reported in the literature. The oral administration of curcumin in twenty-five patients of neurodegenerative diseases at a dose range of 500-8000 mg (1.36-2.17 mmol/day) for a period of three months was reported to have no noticeable toxicity (Hsieh, 2001). In another preclinical study, the oral administration of curcumin in 24 healthy volunteers at a single dose ranging from 500 to 12000 mg (1.36-32.6 mmol) resulted in dose-independent minimal toxicity in 30% volunteers. This study concluded that curcumin could be safely administered to patients at a single dose of 12 grams, and up to 8 grams per day for a period of three months (Lao *et al.*, 2006). Baum *et al.* (2008) performed a double-blind, randomized, placebo-controlled study on 34 AD patients. The participants were randomly assigned for oral administration of curcumin at two different doses from 1 or 4 g or placebo at a dose of 4 g. The study revealed that there was no improvement in the Mini-Mental State Examination (MMSE) score that assesses the mental status after curcumin treatment. Moreover, there was no effect of curcumin treatment on the level of serum $A\beta_{40}$. However, curcumin treatment was found in association with an increase in vitamin E level, without any adverse side effects. It was concluded that the increase in the level of vitamin E might be in response to the antioxidant activity of curcuminoids leading to a decrease in the need for antioxidant vitamin E. Lopresti *et al.* (2014) conducted a randomized, double-blind, and placebo-controlled study on human subjects aged 18 to 65 and reported a more significant effect of curcumin than placebo on the improvement of several mood-related symptoms. It may be inferred from these studies that there is a need to open a clinical trial of curcumin against AD based on a large number of patients.

9. Therapeutic role in Parkinson's disease

Parkinson's disease is another prevalent age-related neurodegenerative condition. It is associated with selective exposure to the neuromelanin containing dopaminergic neurons pars compacta region of the substantia nigra of the midbrain and their terminals in the striatum. In PD, the death of dopaminergic neurons occurs in this region and the symptoms of PD can't be recognized until 60–80% of neurons are lost. Among the age-related neurodegenerative disorders, PD is strongly associated with an increased rate of oxidative damage. It is also linked with the auto-oxidative breakdown of dopamine and metabolism of semiquinone to superoxides (Blesa *et al.*, 2015; Magalingam *et al.*, 2015; Maiti *et al.*, 2017). Turmeric has antioxidant and anti-inflammatory properties which help in PD as the studies show that turmeric is helpful in preventing the chronic inflammation that causes the neurodegeneration and brain cell malfunctioning. Many conditions are included in association with metabolic disorders like diabetes, high cholesterol level, insulin resistance, hypertension,

fatty liver, and psychological stress (Hewlings and Kalman, 2017; Abdel-Salam, 2019). Turmeric contains resveratrol, quercetin and vitamin C which can assist to conduct heme oxygenase-1 (HO-1) production. Curcumin enhances the response against heat shock and also stimulates the vitagenes HO-1 and Hsp-70. Due to this effect of curcumin, the body enhances the production of its own antioxidants which help to defend the brain against free radical damage. According to some reports, excessive HO-1 can deposit iron in those cells which are damaged in PD, however, animal studies show that only the protective amounts are induced by curcumin. In vitro studies have shown that curcumin enhances the body's effective natural antioxidant enzyme, superoxide dismutase (Mazzio *et al.*, 2011; Kim *et al.*, 2016; Yang *et al.*, 2017; Abdel-Salam, 2019).

A low dose of curcumin was reported to inhibit the toxicity of dopamine *in vivo* (Luo *et al.*, 1999; Maiti *et al.*, 2017). The oxidative damage to selective dopaminergic neuron and consequent PD can be produced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) toxins in human and animal models showing the defect in complex I of mitochondrial electron transport chain as well as an increase in the production of free radicals in brain and peripherals region are also identified (Mehlhorn and Cole, 1985; Dias *et al.*, 2013; Subramaniam and Chesselet, 2013). The toxicity of MPTP is mediated by MPP^+, and toxicity of MPP^+ to the neuronal cell line PC12 is inhibited by curcumin and cyclocurcumin (Chakraborty *et al.*, 2017). The aggregation of fibre-forming protein, that is, α-synuclein is a major part of LB lesions that is the characteristics of PD as well as AD, and other neurological disorders (Melki, 2015).

The clinical application of curcumin is strongly supported in PD through several studies. According to Song *et al.* (2016), curcumin is a promising applicant for PD as it improves the neuro functions of substantia nigra neurons by regulating intracellular expressions of SOD, NGF, GSH, and Hsp70. Gadad *et al.* (2012) showed that curcumin inhibited additional fibrillization of α-synuclein by binding with the α-synuclein oligomer. Phom *et al.* (2014) reported that curcumin refreshes the consumed dopamine level in early PD while its effect is limited as a therapeutic agent in the later stages. Curcumin was shown to reverse the decrease in the levels of dopamine and its metabolite 3, 4-dihydroxyphenylacetic levels induced by hydroxydopamine (6-OHDA) in the striatum. Furthermore, curcumin was able to restore the concentration of tyrosine hydroxylase-positive neurons along with a decrease in the concentration of iron-positive cells in comparison with the control group treated with 6-OHDA. Curcumin was reported to attenuate the neurotoxin-triggered loss of striatal dopamine axons at the same dose for seven days following post 6-OHDA injection. The neuroprotective activity of curcumin has been attributed to the inhibition of astroglial and microglial reaction, as indicated by a decreased levels of glial fibrillary acidic protein and immunoreactivity of ionized calcium-binding adapter molecule 1, in addition to maintaining the level of superoxide dismutase 1 (Kujawska and Jodynis-Liebert, 2018).

10. Conclusion

Turmeric is extensively used as a spice and a colouring agent in Southeast Asia. It is also used in traditional systems of medicine since ancient times. Turmeric and its compounds have different medicinal applications. Curcumin that is the main constituent of turmeric is a pleiotropic molecule having antioxidant and anti-inflammatory properties. Due to these properties, turmeric and curcumin are reported as neuroprotective agents in the neurodegenerative disease especially AD and PD. As currently available drug therapies for neurodegenerative diseases including AD and PD have proven little efficacy with many side effects, the nutraceutical approach using a safe and economical compound such as curcumin may open a new avenue for the management and treatment of these diseases. However, the limited bioavailability of curcumin is one of the major barriers to such a nutraceutical approach for the treatment of neurodegenerative diseases involves. This issue can be solved by different strategies involving chemical modification or co-administration of curcumin with those compounds that may facilitate its absorption. Although there are some promising reports regarding the efficacy of curcumin in neurodegenerative diseases, the clinical trials have not provided conclusive evidence regarding the treatment of such diseases by administering curcumin. In order to establish the efficacy of curcumin in neurodegenerative disorders like AD and PD, it is imperative to conduct well-designed large-scale clinical trials and preventive interventions.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this review paper.

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