

Neuroprotective Medicinal Plants: Focus on *Curcuma longa*

Sana Rehman and Arunabha Ray*

Department of Pharmacology, Hamdard Institute of Medical Sciences and Research (HIMSR), Hamdard University, New Delhi, India

***Corresponding Author:** Arunabha Ray, Professor, Head, Department of Pharmacology, Hamdard Institute of Medical Sciences and Research (HIMSR), Hamdard University, New Delhi, India.

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Abstract

Neuroprotection encompasses mechanisms and strategies targeted at protection of the nervous system from injury and damage, which could result in development of debilitating brain disorders with complex etiopathologies. Most currently available neuroprotective agents have either poorly sustainable effects or undesirable adverse effects and hence the constant search for viable alternatives. Medicinal plants like *Curcuma longa* and its active natural polyphenol, diferuloylmethane (curcumin) are traditionally used in Asian countries (India, China, etc.) and benefits have been shown in neurological/neuropsychiatric diseases like Alzheimer's disease, Parkinsons Disease, Multiple Sclerosis, Traumatic Brain Injury, Epilepsy, Depression, etc. Several complex mechanism like antioxidant, anti-inflammatory, immunomodulatory, antimutagenic, antimicrobial, and anticancer properties have been proposed for curcumin effects. However, pharmacokinetic issues like bioavailability have been one of the major detriments to unanimous and unequivocal acceptance and several strategies and hypothesis have been forwarded in support of this excitingly multipurpose and active molecule. In spite of the long standing belief that *Curcuma longa* effects are primarily due to curcumin, recent evidence indicates that there is need to look beyond this concept. In addition to curcumin (which contributes to 77% of total curcuminoids in the rhizome of *Curcuma longa*), there are other curcuminoids which could also contribute to the observed health effects [14]. It has also been suggested that these curcuminoids may actually interact and have synergistic effects. This review revisits and critically analyses some of the scientific data generated on *Curcuma longa* and curcumin and suggests that alternative hypothesis and strategies are worth exploring to enhance the cause of this very beneficial nutraceutical/phytopharmaceutical agent with specific reference to neuroprotection.

Keywords: Neuroprotective Medicinal Plants; *Curcuma longa*; Alzheimer's Disease; Parkinsons Disease; Multiple Sclerosis; Traumatic Brain Injury; Epilepsy; Depression

Introduction

The nervous system is constituted by neurons and neuroglia - the neurons being responsible for transmission of nerve impulses or signals and glial cells support and ensure neuronal function. The microglia and astrocytes protect neurons from injury/stress and hence their dysfunction could have deleterious effects on neurons. Neuroglial function is also dependent on neuronal signals and optimal function is necessary for prevention of damage. Thus, interactions between neurons and neuroglia are crucial for the maintenance of neuronal homeostasis. Neuroprotection refers to strategies that aim to protect the nervous system from injury and maintain their integrity. The relative preservation of neuronal structure and/or function and reduction in rate of neuronal loss in the event of an insult is central to the

concept of neuroprotection. Such strategies depend on the ability of therapy to prevent neuronal cell death by intervening and inhibiting the pathogenic cascade that ultimately results in cell dysfunction and death. Thus, neuroprotection is complex and involves preventing cell death and restoring function to damaged neurons, as well as restoring neuronal numbers. Accordingly, neuroprotective agents aid by salvage, recovery or regeneration of the structure and function of neuronal cells and nervous system. Acute and chronic nervous system damage in response to an insult may lead to acute or delayed neuronal death, apoptotic cell death, neuronal degeneration, injury and loss, and gliosis. Cell death in the CNS following injury can occur in the manner of apoptosis, necrosis or hybrid forms. The effects of neuronal injury depend on factors like the degree of brain maturity or site of the lesion. There is some evidence supporting the hypothesis that neuroprotection may be achievable by drugs, which, though of limited benefit currently, can give the desired effects if used early in disease. Such strategies enable the neuronal system to defend against neuronal degeneration/injury/toxicity due to physiological ageing, acute damage (e.g. stroke or trauma) or chronic neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson's disease etc). Neurodegenerative diseases are characterized by progressive loss (and even death) of structure and function of neurons and have created great burden to the individual and the society. The actual cause of various neurodegenerative diseases still remains a mystery in healthcare. Ageing also plays a very important role in neurodegenerative diseases. Understanding of the neurochemical basis of neurotoxicity can help in the designing of newer agents with favourable efficacy and safety profiles. Diseases like Alzheimer's, Parkinson's, Multiple sclerosis, Epilepsy, ALS etc. require neuroprotection and agents have been designed on the basis of the specific etiopathology involved. For example, in epilepsy, excessive glutamate-mediated neurotransmission, impaired voltage sensitive sodium and calcium channel functioning, impaired GABA-mediated inhibition and alterations in acid base balance, when set in motion, may trigger a cascade of events leading to neuronal damage and cell death. NMDA receptor and non-NMDA receptor mediated excitotoxic injury results in neurodegeneration along an apoptosis-necrosis continuum [1]. Further, neuroprotective strategies that limit secondary tissue loss and/or improve functional outcomes have been identified in multiple animal models of ischemic, hemorrhagic, traumatic and non-traumatic cerebral lesions. Researchers are looking for ways to protect the body after acute events, such as a stroke or nervous system injury, and to help people with conditions that affect the nervous system, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis (MS). Currently available neuroprotective strategies cannot reverse existing damage, but they may protect against further nerve damage and slow down any degeneration of the CNS. The various processes that result in neuronal damage/death include oxidative stress, mitochondrial dysfunction, excitotoxicity, neuroinflammation, iron accumulation, altered brain proteins, etc. Examples of neuroprotective agents include: free radical scavengers/antioxidants, anti-excitotoxic agents, apoptotic inhibitors, anti-inflammatory agents, neurotropic factors, iron chelators, gene therapy, stem cell therapy, etc. Drugs such as amantadine, memantine, donepezil, selegiline, galantamine, and rivastigmine, that are clinically available for the management of neurodegenerative disorders, are only able to provide symptomatic relief and slow the progression of the diseases, in addition to inducing untoward adverse effects. Some other pathways have recently been targeted for developing neuroprotective agents, but success rates in drug development are still not satisfactory, and there is an unmet need and constant search for newer agents and new drug targets.

Medicinal plants have long been recognized as important sources of therapeutic agents. They are of special significance in Indian and Asian traditional systems of medicine, which effectively use such herbal agents for therapeutic benefits. Many phytochemicals have been identified in medicinal plants which can have long-term beneficial effects in health and disease with minimal safety concerns. Many nutraceuticals are now used as dietary supplements with health promoting actions and the constituents of which are primarily medicinal plant products. Historically, many of the very successful modern medicines have been derived from botanical sources, e.g. atropine, morphine, digoxin, tubocurarine, artemisinin, paclitaxel, vincristine, etc. With advances in research, integrative studies on their cellular and molecular mechanisms of action have led to scientific validation of medicinal plant based drugs. Such interactive studies with herbal agents have not only shown them to be efficacious but safer than their conventional counterparts. Further, their complimentary roles in several chronic diseases have been widely speculated. With specific reference to the CNS, neuromodulatory roles of some medicinal plants and their constituents have been consistently reported, and complex mechanisms may be involved in their neuroprotective effects in related

pathophysiological states. A systems biology approach in herbal drug research has further authenticated and established the importance of phytopharmaceuticals and highlighted their therapeutic value in contemporary medicine.

In recent years, a great deal of emphasis has been given to herbs and other natural products used in ethnomedicine around the world for neuroprotection purposes. Several medicinal plant derived products, primarily extracts, have been reported to be used in traditional medicine for neuroprotective, memory enhancing, and anti-ageing purposes. Specifically, plants like *Ginkgo biloba*, *Panax ginseng*, *Bacopa monnieri*, *Curcuma longa*, *Salvia officinalis*, *Hypericum perforatum* and many others have been studied to confirm the traditional claim with special attention given in understanding the mechanism by which they elicit their neuroprotective effects [2,3]. *Curcuma longa* is generally known as turmeric in English (Haldi in India), a perennial herb which belongs to Zingiberaceae family and genus curcuma. The centre of origin of the herb is south Asia and is extensively used as a spice in cuisine of many Asian countries. It has also been used as traditional Chinese and Indian systems (Ayurveda and Siddha) of medicine since very long time.

In Ayurveda, turmeric has been used for the treatment of various diseases such as liver disease, common cold, throat infections, indigestion and skin sores. *Curcuma longa* constitutes various active chemical compounds such as curcuminoids and terpenoids volatile oils, sugars, proteins and resins. Curcuminoids are a group of pharmacologically active compounds which are commonly found in different species of curcuma longa. The available curcuminoids are curcumin (diferuloylmethane), dimethoxy curcumin and bisdemethoxycurcumin. Studies have revealed that curcumin is one of the most active biomolecules of components of the rhizome and possess 150 different therapeutic actions including strong anticancer properties. The pharmacological roles of curcumin include antioxidant, anti-proliferative, anti-inflammatory and anti-angiogenic effects in animals and humans. However, studies have also shown available that curcumin is very poorly absorbed compound with very low curcumin levels in blood/serum [4]. In a pioneering study, Wahlstrom., *et al.* (1978) orally fed rats 1 g/kg of curcumin and they found that a very small amount of curcumin was present in the blood plasma after 15 hours of treatment that was absorbed from the gut [5]. In another study, Ravindranath., *et al.* treated rats 400 mg of Curcumin orally and analyzed portal and heart blood after 15 - 24 hours of treatment and found that there was no curcumin present in heart blood - though only trace amounts (less than 5 µg/mL) were detected in portal blood [6]. On the other hand, clinical studies have shown that Alzheimer's disease and other neuropsychiatric disorders like, Tardive dyskinesia and Major depression, have been effectively treated with Curcumin [7]. In this review, we critically analyse and revisit the reported pharmacological actions of *Curcuma longa* and curcumin with reference to neurological/neuropsychiatric disorder such as Alzheimer's disease, Tardive dyskinesia, Major depression etc. and the possible mechanisms of action for their proposed neuroprotective effects.

Neuroprotection against Alzheimer's disease

Alzheimer's (AD) is the most widespread form of age-related dementia, with the risk of disease doubling every 5 years after the age of 65 years. Therefore, risk to AD for people living into their eighties increases to 20 - 40% depending on the population. The classical pathology of AD includes neurodegeneration and accumulation of protein aggregates to form two major lesions: neurofibrillary tangles (NFTs) and the senile plaques. The senile plaques is made of abnormal neuronal processes ("dystrophic neurites") and activated glial cells surrounding and penetrating a more central proteinaceous deposit of amyloid fibrils consists of β -amyloid (A β) peptide. Recent studies suggested that curcumin reduced oxidative damage, inflammation, and cognitive deficits in rats receiving CNS infusions of toxic A β [8]. Since curcumin is structurally similar to the amyloid-binding dye Congo red, it has the potential to bind with amyloid and inhibit A β aggregation and thus blocked A β aggregation dose dependently. Also, curcumin has been shown to reduce preformed amyloid *in vitro* and markedly suppress A β accumulation and plaques *in vivo*. Curcumin's *in vivo* capacity to reduce β -amyloid accumulation might be due to either direct binding and inhibition of A β aggregate formation or amyloid formation which has been shown to be restricted by five additional mechanisms: (a) metal chelation [9], (b) the antioxidant vitamin E [10], (c) lowering cholesterol [11] and minimizing the expression of β -secretase enzyme BACE1 by reducing its induction by both (d) pro-inflammatory cytokines [interleukin (IL)-1 β and tumor necrosis factor (TNF- α) [12] and (e) the lipid peroxidation product 4 hydroxynonenal acting on JNK-mediated transcription [13]. Amyloid aggregates can be cleared via phagocytosis by brain macrophages. Curcumin at dose as low as 100 - 500-nM range can stimulate microglial

phagocytosis, and clearance of amyloid *in vitro* and curcumin appears to promote phagocytosis *in vivo*. Finally, one of the prime defences against intraneuronal protein aggregate formation is the heat shock proteins (Hsp) induction that functions as molecular chaperones to block the formation of protein aggregates [14]. Curcumin potentiates *in vitro* and *in vivo* Hsp response to infused (*in vivo*) or applied soluble A β aggregates on neurons in culture [15]. Thus, there are various known ways by which curcumin can limit β -amyloid accumulation and protect against amyloid peptide-mediated toxicity. In the process, curcumin targets at least eight anti-amyloid mechanisms relevant to AD pathogenesis, suggesting that it might be useful in preventing or treating AD. These are summarized in figure 1.

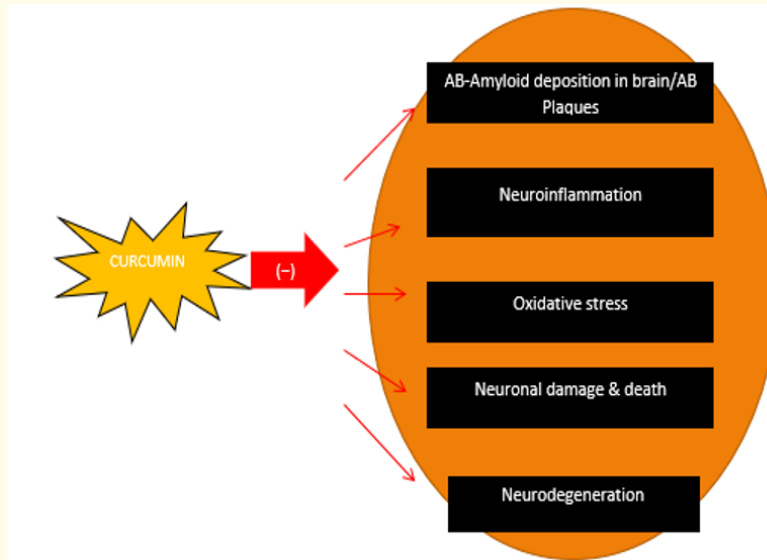


Figure 1: Diagrammatic representation of the neuroprotective action of curcumin in Alzheimer's disease.

Neuroprotection against Parkinson's disease (PD)

Parkinson's disease (PD) is another age-related neurodegenerative condition which is the movement disorder in which there is selective vulnerability to the neuro melanin bearing dopaminergic neurons of the pars compacta region of the substantia nigra and their terminals in the striatum but symptoms of PD do not manifest until 60 - 80% neuron loss. PD has been linked with auto-oxidative breakdown of dopamine and metabolism of related semiquinone to superoxide, along with monoamine oxidase formation of hydrogen peroxide [16]. Studies showed dopamine toxicity can be prevented by curcumin *in vivo* [17]. Recently, mitochondrial electron transport defects at complex I and increase in the formation of free radicals have been recognised in PD brain and peripheral sites, whereas oxidative damage to vulnerable dopaminergic neurons and a PD syndrome can be induced in human and animal models by the MPTP toxin [18]. MPTP toxicity is mediated by MPP+, and studies revealed that curcumin can directly inhibit MPP+ toxicity to the PC12 neuronal cell line [19]. Although it is unusual, few genetic cases of PD are linked to mutations in a synaptic protein called α -synuclein that was originally identified from smaller peptides isolated in amyloid-containing fractions of AD brains [20]. The α -synuclein protein is an aggregating, fibril-forming protein, a component of the Lewy body lesions which is a characteristic of PD as well as some cases of AD and several other neurodegenerative conditions. Synuclein aggregates showed evidence of nitration-based oxidative damage [21] which might play a critical role in aggregate formation [22]. Recent studies showed that curcumin can reduce the α -synuclein aggregation [23] and administration to cultured cells with α -synuclein aggregate formation results in lesser aggregates [24]. Thus, these data provide some rationale relevant to curcumin induced neuroprotection suggesting that it might provide protection from PD.

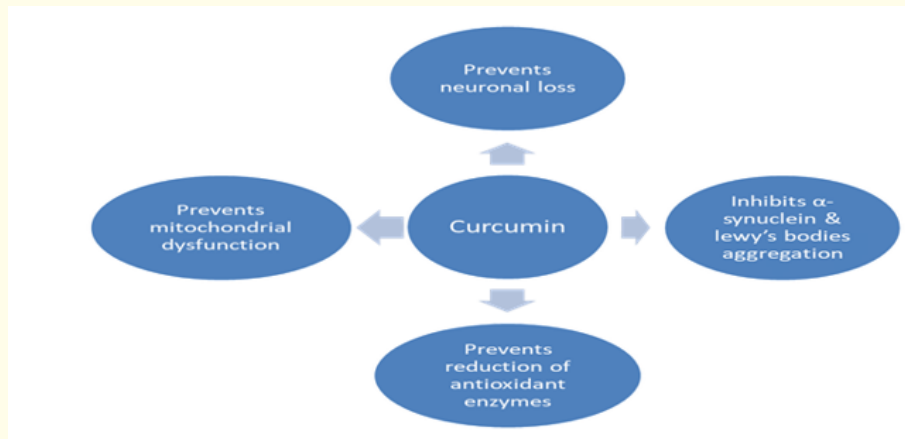


Figure 2: Diagrammatic representation of the neuroprotective effects of curcumin in Parkinson's Disease.

Neuroprotection against epilepsy

Epilepsy is one of the important neurological disorders affecting 50 million of world's total population, requiring long-term antiepileptic drug (AED) therapy [25,26]. Several experimental evidences have shown the protective effect of curcumin in the animal models of seizures. Curcumin is protective against amygdaloid kindled seizures in rat model, iron-induced experimental model of epileptogenesis and electroshock seizures in mice [27]. Many studies suggested the involvement of oxidative stress in pathophysiology of epilepsy [28]. Free radicals are generated in the cellular aerobic metabolism in the development of seizures [29]. Excessive oxidative stress leads to the degeneration of neurons by lipid peroxidation and reduced concentrations of GSH in the epileptic focus [30]. GSH is an endogenous antioxidant which gets converted into oxidized form. This oxidized form of GSH reacts with free radicals and prevent formation of most toxic hydroxyl radical [31]. Malondialdehyde (MDA) is an end product of free radical generation [32] and GSH plays an crucial role in protecting cells against oxidative damage as a free radical scavenger [33]. Curcumin, in a dose dependent manner, reduced MDA and increased GSH levels (the two markers of oxidative stress) in the brain tissue of PTZ -kindled mice [34]. Curcumin provided protection against seizures and cognitive impairment and increases retention latencies, in a pentylenetetrazole-kindled epileptic model in rats [35]. It also reduced the kainic acid-induced hippocampal cell death in mice [36]. All these observations indicate the possible beneficial effects of curcumin in epilepsy.

Neuroprotection against multiple sclerosis

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease directed against CNS myelin and the myelin-forming cells, the oligodendrocytes [37,38]. Earlier studies reported that Th17 cells, which are involved in the production of interleukin-17 (IL-17) and which are essential in the initiation of demyelination in the relapsing-remitting phase of MS [39]. MS is associated with breakdown of the BBB, injury of axons and myelin sheaths and autoimmune attack [40]. Th17 cells cause neuronal apoptosis after migrating across BBB [41]. Several other inflammatory mediators also get stimulated by IL-17 [42]. Curcumin has great potential for the treatment of MS and other Th17 cells mediated autoimmune inflammatory diseases. The BBB endothelial cells (ECS) in MS lesions express IL-17R and IL-22R, while they are undetectable in normal subjects, which are used by Th17 cells to infiltrate the BBB. IL-17 activates the endothelial IL-17R which is followed by increased ROS production. The resultant oxidative stress activates the endothelial contractile machinery by raising the amount of phosphorylated myosin light chain (MLC) and a down-regulation of the tight junction molecule occluding and ZO-1. Phosphorylated MLC interacts with the actin cytoskeleton, leading to a cell contraction that further increases the intercellular space of the

endothelial cell monolayer [41,43]. Curcumin, an NF- κ B inhibitor, is effective in preventing disruption of the BBB induced by Th17 cells through affecting the expression and subcellular localization of ZO-1, inhibiting MLC phosphorylation, and abolishing ROS generation [44] indicating that curcumin could arrest the increase in permeability and reduction of ZO-1 expression was associated with inhibition NF- κ B activation. Also, it prevents the lymphocyte recruitment promoting CNS inflammation across BBB [45,46].

Neuroprotection against Huntington's disease (HD) and other CAG repeat diseases

These disorders have extended C-terminal CAG repeats coding for polyglutamine, which leads to the aggregation of proteins to form at a rate determined by the repeat length. Since curcumin has anti-amyloid binding protein properties, it has a protective effect in HD [47]. Evidence for the protective effect of curcumin in an HD transgenic model has been recently obtained [48], leading to a clinical trial with HD patients. Marie-Charcot Tooth disorder is another example of a similar protein-misfolding neuropathy and curcumin also showed protection against this disorder *in vitro* [49] and *in vivo* in a transgenic model.

Neuroprotection against cerebral ischemia-reperfusion

Stroke is the second largest frequent cause of death after coronary artery disease, and accounts for approximately 12% of deaths, among which more than 50% patients die of cerebral ischemia. Recanalization of occluded arteries via thrombolysis or thrombectomy is a common therapeutic strategy, but this procedure is often associated with cerebral ischemia-reperfusion (I/R) injury. The episode of I/R injury after stroke is often unavoidable and may spark numerous molecular cascades which lead to the breakdown of the blood-brain barrier, thus aggravating brain damage [50]. However, there are still very few effective treatments available which can save ischemic brain tissue. Curcumin has been shown to reduce I/R injury in various organs/tissues, including cardiomyocytes, liver, and lung in various studies [51-53]. Recent studies have proven that curcumin can cross the blood-brain barrier and can have a neuroprotective effect in cerebral I/R injury [54,55]. However, the underlying mechanism for this protection is not yet clear. Since LC3II/LC3I is an active marker of autophagosomes which is adequately raised after I/R injury, but decreased after treatment with curcumin. Thus, these findings suggested that autophagy might be involved in the neuroprotective role of curcumin. The PI3K/Akt/mTOR pathway is an intracellular signalling pathway that is involved in regulating cell migration, survival and proliferation. Previous studies have confirmed that systemic activation of PI3K/Akt/mTOR promotes neuroprotection after central nerve system (CNS) injury, which contributes to augmented recovery in the CNS via maintaining neural metabolism [56,57]. mTOR is a key governor of cell growth and metabolism and raised mTOR activity attenuates autophagy and restores the full complement of lysosomes in the cell [58]. Curcumin augmented the expression of p-Akt and p-mTOR, but decreased the ratio of LC3II/LC3I, thus lessening the autophagy. Thus, curcumin has shown to be neuroprotective in ischaemia-reperfusion injury.

Neuroprotection against HIV-1 induced neurological complications

The human immunodeficiency virus type 1 (HIV-1) pandemic has claimed over 20 million lives, with 38.6 million people worldwide currently infected (2009 AIDS Epidemic Update by UNAIDS/WHO, www.unaids.org) and will continue to contribute to human morbidity and mortality since there is no vaccine available for this virus. Neurological disorders associated with HIV such as neurocognitive disorders are common neurological complications in the patients chronically infected HIV-1. Microglial overstimulation and neuroinflammation are involved in the pathogenesis of HIV-1-associated neurologic disorders. Microglia are the primary inflammatory cells in the central nervous system (CNS). Over stimulated microglial cells can lead to the overproduction of several pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) and chemokines, which are thought to contribute to HIV-1-associated neurological disorders [59]. Studies have also suggested that gp120 plays a crucial role in HIV-1-associated nervous system impairment. Also, neuronal voltage-gated potassium (Kv) channels are involved in HIV-1-associated neuronal injury [60]. Curcumin exerted a powerful inhibitory effect against HIV-1 gp120-induced neuronal damage by decreasing the generation of ROS and inflammatory mediators (TNF- α , MCP-1) in HIV-1-gp120-stimulated microglia, and provided protection to cortical neurons against HIV-1-mediated apoptosis,

necessarily through inhibition of HIV-1 gp120-induced elevation of the delayed rectification and transient outward K^+ current [61]. Thus, curcumin has a great potential in the neurodegenerative disorders associated with HIV. This is summarized in figure 3.

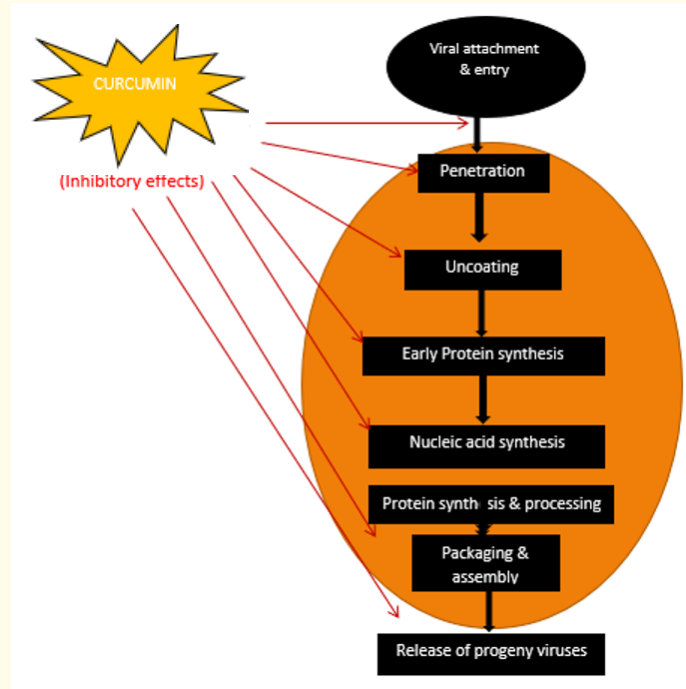


Figure 3: Diagrammatic representation of the neuroprotective effects of curcumin in HIV.

Neuroprotection against traumatic brain injury

Traumatic brain injury (TBI) is described as a brain damage which results from any external mechanical force. TBI contributes to considerable mortality and morbidity, with many people having functional impairments such as motor and sensory dysfunctions and even cognitive deficits. A yearly estimation of 10 million individuals worldwide diagnosed with TBI showed that it is a complex disorder comprises of both primary and secondary brain injuries. Tissue loss and cell death contributes to the primary injury and the inflammatory response from stimulated microglia as well as recruited neutrophils and macrophages, and reactive oxygen species (ROS) from blood metabolites contributes to secondary brain damage and subsequently, to progressive damage. As inflammatory reaction and oxidative stress are identified as the important mechanisms of TBI-induced secondary injury, augmenting antioxidant response and decreasing inflammation would be expected alleviate TBI-induced secondary brain damage. Nuclear factor erythroid 2 related factor 2 (Nrf2), a basic leucine zipper (bZIP) protein, is an essential regulator of endogenous defense against oxidative stress in the brain. Under physiological conditions, Nrf2 is mainly present in the cytoplasm. In response to oxidative stress, Nrf-2 shifts into the nucleus, heterodimerizes with the proteins, followed by binding with specific DNA sites, antioxidant response elements (ARE) or electrophile response elements (EpRE) to trigger the transcription process of cytoprotective genes in the nucleus. Emerging evidence from the studies revealed that Nrf2 plays a key protective role in brain injury and neurodegenerative diseases, since Nrf2 deletion worsens TBI-induced acute oxidative damage and subsequent neurological deficits in mice. However, insufficient Nrf2 activation in humans is associated with the chronic neurodegenerative diseases. Additionally, Nrf2 activation ameliorates TBI induced damage. Curcumin treatment resulted in decreased ipsilateral cortex

injury, infiltration of neutrophils, and activation of microglial cells-thus improving neuron survival against TBI-induced apoptosis and degeneration. Curcumin exhibited neuroprotective effects by improving the nuclear translocation of Nrf-2 and upregulating antioxidant enzymes in the Nrf2- ARE pathway, e.g. heme oxygenase-1 (HO-1), NADPH quinone oxidoreductase- 1 (NQO-1), GCLC and GCLM, suggesting that curcumin effects were partly through the Nrf2 regulated antioxidant response [62]. These evidences from the previous studies showed that post-injury treatment with curcumin indeed played a neuroprotective role in TBI, at least partly through the Nrf2 signaling pathway, suggesting the therapeutic potential of curcumin in TBI.

Neuroprotection against depression

Depression is a neuropsychiatric disorder which has been estimated to affect up to 21% of the world population [63] and it is characterized by persistently depressed mood, loss of interest in usual activities and diminished ability to experience pleasure [64]. The available classical antidepressant drugs are linked with numerous undesirable side effects [65]. Therefore, it is essential to invent more selective therapeutic tools with improved safety profiles. It has been observed that variety of immune parameters such as mitogen response, natural killer cell activity and T-cell subpopulations were involved in depression. Studies have showed that aqueous extract of *Curcuma longa* dose dependently reduced the duration of immobility in tail suspension test and forced swimming test in rats and which was comparable to the standard (comparator) drug fluoxetine [5]. It also exhibited to have immunostimulatory activity [66]. It has been seen that chronic stress is accompanied with structural and functional changes in the hippocampus, including atrophy of apical dendrites of CA3 pyramidal neurons [67]. Chronic unpredictable stress decreases neurogenesis in the adult hippocampus resulting in hippocampal atrophy [68]. Much research on depression has been in relation to 5-hydroxytryptamine (5-HT, serotonin) and its specific receptors [69]. 5-HT1A receptors serve as interesting target for studying the pathophysiology of depression and for the mechanism of actions of antidepressant drugs [70,71]. Studies have shown that long term administration of curcumin can reverse the reduced levels of serotonin during stress. Administration of curcumin raised the hippocampal neurogenesis in chronically stressed rats. It leads to prevention of the stress-induced reduction in 5-HT1A mRNA in the hippocampus [72]. Neurotrophins play an essential role in the survival of mammalian nervous system. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family and helps in the development of the immature neurons. It regulates the survival and function of adult neurons and cell survival during conditions of stress such as depression and post-traumatic stress disorders. Depression and repeated stress exposure resulted into a reduction in hippocampal BDNF. BDNF exhibits its biological function through binding to its receptor, tropomyosin-related kinase B (TrkB), which triggers various signaling cascades. It has been seen that curcumin exhibits appreciable rise the levels of BDNF in the brains of stressed rats. Also, curcumin pre-treatment reverses the down regulated expression of BDNF and phosphorylated- TrkB induced by glutamate in the primary cultured cortical neurons [73]- thus causing its antidepressant effect.

Table 1: Neuroprotective effects of Curcumin in some neurological and neuropsychiatric disorders.

Disease	Effects of curcumin
Alzheimer’s Disease	<p><i>In vitro</i></p> <ul style="list-style-type: none"> • Inhibit Aβ aggregation and arrest Aβ aggregation • Decrease preformed amyloid • Activate microglial phagocytosis, and clearance of Amyloid. <p><i>In vivo</i></p> <ul style="list-style-type: none"> • Markedly decrease Aβ accumulation and plaques • Metal chelation • Antioxidant vitamin E • Lowering cholesterol and decreasing expression of the β-secretase enzyme BACE1 by decreasing its induction • Lowering pro- inflammatory cytokines (IL-1β and TNF-α), lipid peroxidation product 4-hydroxynon-enal acting on JNK-mediated transcription • Stimulate microglial phagocytosis • Induction of heat shock proteins (HSPs).

Parkinson's Disease	<p><i>In vitro</i></p> <ul style="list-style-type: none"> Decrease the aggregation of α-synuclein, and administration to cultured cells with α-synuclein aggregate formation results in fewer aggregates. Inhibition of oxidative stress and mitochondrial cell death pathway. <p><i>In vivo</i></p> <ul style="list-style-type: none"> Inhibit dopamine toxicity. Directly inhibit MPP+ toxicity to the PC12 neuronal cell line.
Epilepsy	<p><i>In animals</i></p> <ul style="list-style-type: none"> Significantly reduces MDA and increases GSH levels (two oxidative stress markers) in the brain tissue in rats Improves cognitive impairment Increases retention latencies Attenuates the kainic acid-induced hippocampal cell death in mice.
Huntington's Disease	<i>In vitro/vivo</i> - provide protection by its anti-amyloid-binding protein properties.
Multiple Sclerosis	<p><i>In vitro</i></p> <p>Prevents disruption of the BBB induced by Th17 cells Kimura, (2008)</p> <p><i>In vivo</i></p> <ul style="list-style-type: none"> Reduced the clinical severity of EAE by decreases inflammatory cells like Th17 cells, infiltration and differentiation in CSN in rats. Delays recovery from EAE in mice.
Cerebral Ischemia-Reperfusion	<p><i>In vivo</i></p> <ul style="list-style-type: none"> Enhanced the expression of p-Akt and p-mTOR but reduced the ratio of LC3II/LC3I, thus attenuating autophagy in rats.
HIV-1-associated neurological disorders	<p><i>In vivo</i></p> <ul style="list-style-type: none"> Inhibits HIV-1 gp120-induced neuronal damage. Reduces the production of ROS and inflammatory mediators (TNF-α, MCP-1) in HIV-1-gp120-stimulated microglia Protects cortical neurons against HIV-1-mediated apoptosis Inhibit HIV-1 gp120-induced elevation of the delayed rectification and transient outward K⁺ current.
Depression	<p><i>In vitro</i></p> <ul style="list-style-type: none"> Activates brain-derived neurotrophic factor and its receptor TrkB <p><i>In vivo</i></p> <ul style="list-style-type: none"> Increases serotonin receptor 1A expression in chronically stressed rat. Increased hippocampal neurogenesis in chronically stressed rats. Significantly prevented the stress-induced decrease in 5-HT1A mRNA in the hippocampus.

Conclusion and Perspectives

Curcuma longa (Turmeric) is a medicinal plant which is effectively used as a food spice and nutraceutical in Asian countries. Curcumin is the most prevalent curcuminoid moiety of the rhizome and is a naturally occurring and highly lipophilic polyphenolic substance. Cur-

cumin can cross blood-brain barrier and produces neuroprotective effects is a variety of brain disorders and complex mechanisms are proposed. Initially, curcumin happened to offer great potential as a therapeutic agent for therapeutic development from a natural product (turmeric) that is classified as a “generally recognized as safe” GRAS material by FDA, a designation that possibly could make things easy for developers to bypass some regulatory requirements for its approval as a therapeutic agent [74]. Though traditional medicinal evidence is historically sound, there is dearth of recent studies and clinical trials which show that any form of curcumin, or its closely related analogues, have potential of a good drug candidate. Studies have mentioned that majority of the results from *in vitro* studies in cell lines which are less reliable due to the interference in assay readouts. Further, studies have questioned the medicinal value of curcumin due to its poor bioavailability [75,76]. However, in India, researchers have explored and critically examined the data and refuted these claims that challenged the medicinal value of curcumin, a substance that gives the age-old Indian spice turmeric (*Curcuma longa*) its hallmark bright yellow colour. While the issues of poor bioavailability and fast metabolism were duly acknowledged, the ability of curcumin to function as an immunomodulator and ability to cross the blood brain barrier confirmed its potential to serve as an adjunct drug to treat inflammatory and neurological diseases and provide long-term protection. In this direction, various efforts have been made to improve the bioavailability of curcumin by altering the physico-chemical characteristics. The use of adjuvants that can block the metabolic pathway of curcumin is also a common strategy for improving the bioavailability of curcumin. Concomitant administration of phytochemical bioenhancers like piperine along with curcumin produced much higher concentrations [77]. Other available promising approaches to increase the bioavailability of curcumin in humans include the use of nanoparticles [78], liposomes [79], complexes of phospholipid [80] and structural analogues [75]. Meriva is a patented curcumin phytosome complex with soy phosphatidylcholine that has better bioavailability than curcumin [80]. Thus, alternative/complimentary approaches like addition of adjuvants and use of nanoparticles along with curcumin will add to its strength in terms of bioavailability could re-establish the therapeutic status of both *Curcuma longa* and curcumin. It has also been speculated that other curcuminoids of *Curcuma longa* (alone or in combination with curcumin) might be responsible for pharmacological actions and therapeutic effects. All these aspects would require further scientific evaluation.

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