Neuroprotective Effects Of Curcumin

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Abstract: Turmeric, derived from the plant *Curcuma longa*, is a gold-colored Spice that has been used as a traditional medicine. Curcumin (CUR), the principal curcuminoid of turmeric, which gives the yellow color to turmeric, is now recognized as being responsible for most of the therapeutic effects. It has been shown to exhibit antioxidant, anti-inflammatory, antiviral, antibacterial and antifungal as well as anticancer activities. The loss of functional neurons and synapses lead to neurodegenerative diseases. Current treatments for most of these diseases had not succeeded adequate until now. Both of oxidative damage and inflammation have been proved as having roles in age-related neurodegenerative diseases. Antioxidants have been demonstrated to protect neurons against a variety of experimental neurodegenerative conditions. A number of experimental studies indicate that CUR, as an antioxidant protects the brain against various oxidative stressors. CUR is a powerful scavenger of superoxide anions, and it has both neuroprotective and anti-aging effects. CUR can cross the blood-brain barrier (BBB) and reach the brain. Accumulating cell culture and animal model data show that dietary CUR is a strong candidate for use in the prevention or treatment of Neurodegenerative diseases includes Alzheimer's disease, Parkinson's disease and multiple sclerosis. Also CUR showed protection against Ischemic cerebral stroke, epilepsy and depression.

Key words: Curcumin, Neurodegenerative diseases, Antioxidant, Neuroprotective.

INTRODUCTION

Medicines derived from plants have played a pivotal role in the health care of many cultures. Modern medicine has neither held in very high esteem nor encouraged the medicinal use of natural products. CUR ($C_{21}H_{20}O_6$) or diferuloylmethane is a coloring agent derived from the root turmeric or Curcuma longa, belonging to the Zingeberacea family, is widely cultivated in several tropical parts of Asia (Kelloff,1996). Turmeric commonly used as a spice in Indian cooking, a cosmetic agent for skin care and it is a traditional Indian and Chinese medicine. Those people have used turmeric for the treatment of some disease like common cold, fever, skin diseases, stomachaches, liver diseases, chronic inflammations and etc (Aggarwal, 2007). The main components of turmeric include CUR (curcuminI), demethoxycurcumin (curcuminII), and bis-demethoxycurcumin (curcuminIII) together referred to as curcuminoids. CUR is a polyphenol with low molecular weight that is responsible for the bright yellow color of turmeric. It has been identified as the active principle of turmeric, which comprises 2–8% of most turmeric preparations (Srivastava, 2010; Aggarwal, 2007). CUR exhibits antioxidant, anti-inflammatory, antirheumatic antimicrobial and anti cancer activities (Ammon, 1991; Rao, 1995; Ruby, 1995) as well as nephroprotective activity, therapeutic activity against myocardial infarction, skin diseases and cystic fibrosis (Aggarwal, 2003; Limtrakul, 1997; Dikshit, 1995). Some researches have revealed that CUR mediates its anti-inflammatory and antioxidant effects by downregulation of nuclear factor-kB (NF-kB) and modulation of several important molecular targets, including, enzymes COX-2 (cyclooxygenase-2), iNOS (Inducible nitric oxide synthases), and cytokines TNFa(Tumor necrosis factor-alpha), IL-1b (Interleukin-1 beta), IL-6(Interleukin-6) and chemokines (Kunnumakkara, 2008; Hong, 2004; Moon,2008; Kim, 2007). Brain is perhaps the most sensitive organ to oxidative damages (Halliwell, 1992). This organ consumes 20% of the body's oxygen despite accounting for only 2% of the total body weight (Smith, 2008). Oxidative stress , that is due to the highly oxidative intracellular environment of the neurons and glial cells, has been shown to increase with both normal brain ageing as well as with brain injuries (Beal, 1995; Lu, 2004). Administration of CUR significantly reduced the progression of kindling and also attenuated the oxidative stress in mice; therefore it could be a candidate to control development of seizure and oxidative stress during epilepsy (Guangwei, 2010). CUR have been described to ability for scavenge oxygen derived free radicals that it has been implicated its potential as a neuroprotective agent (Sharma, 2009). Cerebral edema, a cause of increased intracranial pressure after acute brain injury, was significantly controlled by pretreatment as well as post treatment with CUR (Thiyagarajan, 2004). Administration of CUR after inducing cerebral ischemia indicated neuroprotection activity against stroke (Longa, 1989). CUR has potential to increase the cholinergic activity of neurons in streptozotocin- induced dementia in rats (Awasthi, 2010). Effects of CUR on the pathophysiology of Alzheimer's disease (AD) have been studied and several groups have shown its ability to inhibit Aβ-plaque formation (Lim, 2001; Perl, 2010; Yang, 2004). Also, CUR has been proposed as a potential candidate to treat Parkinson's disease (PD) (Jagatha, 2008; Zbarsky, 2005).Liu *et al.,* showed that CUR can

inhibit mitochondrial cell death and so it can protect against PD (Liu, 2011). Chronic stress is a risk factor for the onset of Depression that induce neurodegeneration in hippocampal neurons. Ii has shown that CUR administration can increase hippocampal neurogenesis in chronically stressed rats (Gold, 2003; Xua, 2007). Experimental autoimuno encephalomyelitis (EAE) is an animal model for multiple sclerosis (MS) and treatment of EAE rats with CUR reduced clinical severity of EAE (Xie, 2009). According to all of these studies, CUR can act against a wide variety of neurologic diseases. In the study presented here the effect of CUR on some different neurologic diseases were evaluated, that some of this effects showed in table 1 (see table1).

Table1: Neuroprotective effects of Curcumin in some brain diseases

Disease		Effects	References
Alzheimer's disease			
In vitro		Protects nerve cells and EC from A beta-induced Cytotoxicity, repairs the neuritic abnormalities induced by Aβ insult	Kim,(2001)
In vitro		Inhibits the peroxidase activity of A beta-heme complex	Atamna,(2006)
In vitro		Inhibited cytotoxicity induced by transfection of Aβ1–42 driven by virus infection	Qin, 2010
Patients		Enhance Aβ uptake by macrophages	Zhang,(2006)
Mice		Inhibits A beta oligomers and fibrils, binds plaques and reduces amyloid^{β}	Yang, (2005)
Mice		Prevents aggregation of new amyloid deposits, Clears and reduces existing plaque	Garcia-Alloza, (2007)
In vitro		Inhibition of amyloid beta (Aβ) oligomerization and fibril formation	Ono,(2004)
Parkinson's disease			
In vitro		Inhibition of oxidative stress and mitochondrial cell death pathway	Liu,(2011)
In vitro		Increases the level of SOD on 6-OHDA- induced Parkinson's disease	Wang, 2009
In vitro		Protection against protein oxidation and preservation of CI activity lost by induces GSH synthesis	Dickinson,2003
Multiple sclerosis			
In vitro		Prevents disruption of the BBB induced by Th17 cells	Kimura, (2008)
Rats		Reduced the clinical severity of EAE by decreases inflammatory cells like Th17 cells, infiltration and differentiation in CSN	Xie, (2009)
Mice		Delays recovery from EAE	Verbeek, (2005)
Depression			
Rats		Increase in cell proliferation in the dentate gyrus, increases serotonin receptor 1A expression in chronically stressed rat	Xua, (2007)
In vitro		Activatives brain-derived neurotrophic factor and its receptor TrkB	Wang, (2010)
Epilepsy			
Rate		Protects against seizures and cognitive impairment increases retention latencies, in a pentylenetetrazole-kindled epileptic model in epileptic rat	Mehla, (2010)
Mice		Attenuates the kainic acid-induced hippocampal cell death	Shin, (2007)
Cerebral Injury			
Rats		Protects rat brain against focal ischemia through upregulation of expression of Nrf2 and HO-1	Yang, (2009)
Rats		Prevents blood–brain barrier damage in focal cerebral ischemic rats	Jiang, (2007)

CUR Is Protective Against AD:

AD is the most common form of progressive neurodegenerative dementia in the elderly population, and after heart disease, cancer and stroke AD is the fourth common cause of death in Western countries (Selkoe, 2001; Brookmeyer, 1998). AD is induced by different causes including genetics, oxidative stress, head trauma, inflammation and environmental factors (Butterfield, 2005; Zhu, 2005). AD is associated with impairment in working memory (Germano, 2005), visuoperception, attention and semantic memory (Bolla, 1992). Oxidative stress and extracellular beta- Amyloid (Aβ) deposits is known to contribute to the etiology of AD (Zhu, 2005; Hardy, 1992). Oxidative damage to lipid and protein can lead to structural and functional disruption of the cell membrane, inactivation of enzymes, and finally caused cell death (Ashok, 1992). Pathological and biochemical clues suggest that the progressive production and subsequent accumulation of Aβ, an increased generation of amyloid precursor protein and senile plaques play a central role in pathogenesis of AD. Some potential therapeutic targets for the treatment of AD are inhibition of the accumulation of Aβ, the formation fibrillar Abeta (fAbeta) from Aβ and the destabilization of preformed fAbeta in the central nervous system (Walsh, 2002; Huang, 2004; Tschape, 2006). CUR can effect against AD through the different mechanisms: It has been shown that CUR has ability to bind Aβ peptides and prevent aggregation of new amyloid deposits in mice and so it can promote disaggregation of existing amyloid deposits (Garcia-Alloza, 2007). Kim *et al.,* reported that CUR and its analogues have protective effects against Aβ toxicity. They showed that CUR and its analogues demethoxycurcumin and bis-demethoxycurcumin can protect PC12 rat pheochromocytoma and normal human umbilical vein endothelial cells from Aβ-induced oxidative stress(Kim, 2001). Furthermore, Qin *et al.,* showed that CUR inhibited cytotoxicity induced by transfection of Aβ1–42 driven by virus infection in primary cultured prefrontal cortical neurons (Qin, 2010). CUR has ability to inhibit Aβ oligomerization and fibril formation in vitro (Ono, 2004). Aβ peptide binds with heme to form a peroxidase. This action plays a major role in the

cytopathologies of AD. Atamna *et al.,* showed that CUR inhibits the peroxidase activity of Aβ-heme complex (Atamna, 2006). Defects in phagocytosis of Aβ by the macrophages and in clearance of Aβ plaques have been shown in patient with AD. CUR administration was found to enhance Aβ uptake by macrophages of patients with AD (Zhang, 2006). There is association between senile plaques, synaptic loss and abnormal neurite morphology (Perl, 2010), which results in a disruption of synaptic integration in AD. CUR could reverse distorted and curvy neurites located in the surrounding of senile plaques, and repaired the neuritic abnormalities induced by Aβ insult (Kim, 2001). It has demonstrated that AD is associated with reduced cerebral blood flow (CBF) (Wyper, 1995). This declines in CBF due to vascular amyloidosis, oxidative stress and endothelial dysfunction (Ajmani, 2000). Awasthi et al, showed that CUR dose dependently improved CBF in streptozotocin (STZ) induced memory deficit mice (Awasthi, 2010). Thus, it has been hypothesized that there is a association between extensive use of CUR and significantly lower prevalence of AD in the Asian Indian population and that CUR may be considered as an ideal therapeutic agent for the treatment of AD (Ganguli, 2000).

CUR Protects Against PD:

PD is a neurodegenerative disorder characterized by a selective loss of dopaminergic neurons in the nigrostriatal pathway (Jenner, 1996). Some features of this disease include autonomic dysfunction, anxiety, depression, sleep disturbance, and cognitive dysfunction (Samii, 2004). PD is a common disorder, with a mean age at onset of 55 years (Dauer, 2003). It is evaluated that about 90% of PD cases are sporadic and about 10% are familial (Polymeropoulos, 1997). PD is a multifactorial disease involving oxidative stress, mitochondrial dysfunction, protein aggregation and proteasome inhibition (Katzenschlager, 2004). The nigral vulnerability associated with the oxidative stress observed in PD. Increased reactive oxygen species (ROS) generation has been identified within the degenerating substantia nigra (SN) of PD patients (Blum, 2001).

CUR can increase the level of SOD and inhibit activation of NF-kB in 6-OHDA-induced cytotoxicity:

Oxidative stress and mitochondrial dysfunction play important role in PD (Kidd, 2000), and dopamine-rich areas of the brain are particularly vulnerable to oxidative stress, because metabolism of dopamine itself causes to the generation of ROS (Lotharius, 2002). The most important defenses against oxygen radicals are the superoxide dismutase (SOD) enzymes. SOD enzymes catalyze the breakdown of superoxide into hydrogen peroxide and water and so they are central regulators of ROS levels (Landis, 2005). Furthermore, nuclear NF-kB is supposed to be a sensor of oxidative stress and is increased in dopaminergic neurons of patients with PD (Hunot, 1997). Some evidence have indicated that the inhibition of NF-kB activation in astrocytes might be useful in the intervention of PD (Aoki, 2008). Wang *et al.,* investigated the effect of CUR on the mitochondrial membrane potential, ROS generation, and expressions of NF-kB nuclear in MES23.5 cells induced by 6-Hydroxydopamine (6-OHDA) (Wang, 2009). 6-OHDA is a common neurotoxin used for inducing PD models that injures the mitochondria function and increases intracellular ROS level (Ono, 2004). This group indicated when CUR pretreated these results observed: 1. A fall in mitochondrial membrane potential induced by 6-OHDA was blocked and intracellular ROS level was decreased. 2. Increasing in the level of SOD on 6-OHDA-induced cytotoxicity in MES23.5 cells, which inhibited the oxidative stress. 3. The activation of NF-kB by 6-OHDA, was prevented (Crawford, 1992).

CUR induces GSH synthesis and it has effects against GSH depletion:

PD toxins via selective inhibition of mitochondrial complex I (CI) act on dopaminergic neurons in the SN that lead to mitochondrial dysfunction (Schapira, 1990). Glutathione (GSH) depletion significantly contributes to the oxidative load in these neurons. The significant decreased levels of total glutathione (GSH+GSSG) have been observed in the SN of early PD patients (Perry, 1986). GSH is the major nonproteinaceous antioxidant in the brain. GSH depletion occurs sooner than both mitochondrial dysfunction and dopamine loss and it is therefore considered as the earliest triggering factor of neurodegeneration (Jenner, 1993; Bharath, 2002). Mitochondrial dysfunction in dopaminergic cells is due to a selective inhibition of CI activity probably via thiol oxidation of the complex. These data suggested that the early GSH loss in the SN of PD patients could be linked to CI inhibition and subsequent mitochondrial dysfunction, finally leading to neurodegeneration (Beal, 1992; Jha, 2000). It has shown that CUR protects CI against peroxynitrite (PN)-mediated mitochondrial toxicity both in vitro and in vivo with relevance to PD (Mythri, 2007). Jagatha *et al.,* investigated the effect of CUR on GSH depletion in vitro and in vivo using a neuronal culture and mouse model of GSH depletion. They have used buthionine sulfoximine (BSO), an irreversible selective inhibitor of γ-GCL, for GSH depletion in these models (Andersen,1996; Bharath, 2002). They demonstrated that treatment of BSO models with CUR restores the cellular GSH pool, so it protects cells against oxidative stress. These researchers also showed that CUR treatment leads to significant protection against protein oxidation and preservation of CI activity lost due to GSH depletion(Jagatha, 2008). Dickinson *et al.,* observed CUR also induces GSH synthesis in vitro (Dickinson, 2003). GSH is synthesized by a two-step reaction involving the γ-glutamyl cysteine ligase (γ-GCL) and GSH synthetase (Meister, 1988). CUR induces GSH synthesis via upregulation of γ-GCL (Dickinson, 2003).

CUR protects against α-synuclein-induced cell death:

Studies of familial PD have documented several genes associate with PD; these genes include α-synuclein (Lotharius, 2002), parkin (Kitada, 1998), PTEN-induced novel kinase 1 (PINK1) (Valente, 2004), DJ-1 (Bonifati, 2003), and the leucine-rich repeat kinase 2 (LRRK2) (Paisan-Ruiz, 2004). The most potent cause of autosomal dominant PD is α-synuclein mutations (Mata, 2006). α-Synuclein was as the first genetically identified PD-associated protein (Forno, 1996). α-Synuclein (A30P, A53T and E46K) mutations cause rare familial PD (Lotharius, 2002; Kruger, 1998; Zarranz, 2004). Another cause of genetic PD is genetic duplication or triplication at the α-synuclein locus leading to over-expression of α-synuclein protein (Singleton, 2003). Variation in levels of α-synuclein expression inherited by promoter variants maybe contribute to the risk of developing PD (Pals, 2004; Farrer, 2001). In vitro expression of A53T α-synuclein increased intracellular ROS levels, mitochondrial dysfunction and finally caused cell death (Smith, 2005; Petrucelli, 2002). Liu *et al.,* found that CUR protects against mutant A53T α-synuclein-induced cell death using PC12 cells inducibly expressing A53T α-synuclein. CUR decreased mutant α-synuclein-induced intracellular ROS levels, mitochondrial depolarization, cytochrome c release, and caspase-9 as well as caspase-3 activation. These results indicate that CUR via inhibition of oxidative stress and mitochondrial cell death pathway, protected against A53T α-synuclein-induced cell death, that it suggests CUR may be a candidate neuroprotective agent for A53T-linked PD intervention (Zhaohui, 2011).

CUR Exerts Neuroprotective Effects Against MS:

MS is an inflammatory demyelization disease of the central nervous system (CNS) and the most common neurodegenerative disease of young adults (Coffman, 2006). In general MS is considered as an autoimmune disease directed against CNS myelin and the myelin-producing cells, the oligodendrocytes (Noseworthy, 2000; Yan, 2008). Most studies in patient with MS symptoms and also in the animal model for MS (EAE), suggest that Th17 cells which are characterized by the production of interleukin-17(IL-17) are important in the initiation of demyelination in the relapsing-remitting phase of MS (Tzartos, 2008; Mc Farland, 2007). MS is associated with breakdown of the BBB, autoimmune attack, injury of axons and myelin sheaths (Charil, 2007; Steinman, 2001). Th17 cells migrate across BBB induce neurons apoptosis (Kebir, 2007). Many other inflammatory mediators were activated by IL-17 (Miljkovic, 2005). CUR has great potential for the treatment of MS and other Th17 cells mediated autoimmune inflammatory diseases . The treatment of EAE rats with CUR significantly reduced the clinical severity of this model and had a dramatic reduction in the number of inflammatory cells infiltration in the spinal cord (Xie, 2009).

CUR prevents disruption of the BBB induced by Th17 cells:

It is firmly established that disruption of the BBB and the trafficking of autoreactive T-cells from the systemic compartment into the CNS play an important role in early events of the development of MS lesions (Kebir, 2007). The BBB plays an important role in the homeostatic regulation of the brain microenvironment and maintains the immune-privileged status of the brain by restricting the entry of lymphocytes (Banks, 2006; Maes, 2008). Th17 cells have emerged as critical autoimmune effectors in multifocal perivascular infiltration of mononuclear cells with a relative breakdown in BBB integrity (Maes, 2007; Kim, 2006; Engelhardt, 2005; Aloisi, 2000). Indeed, a significant number of IL-17 and IL-22 expressing CD4+CD45RO+ memory lymphocytes upon their migration across BBB expressed IL-17+and IL-22+ markers, which confirmed the ability of Th17 cells to cross the BBB in vitro and in vivo. 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 oxidative stress activates the endothelial contractile machinery by increasing the amount of phosphorylated myosin light chain (MLC) and accompanied with 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 per se increases the intercellular space of the endothelial cell monolayer (Kebir, 2007; Huppert, 2010).CUR, an NF-kB 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 (Kimura,2008).The treatment of CUR was accompanied by up-regulation of ZO-1 proteins and alteration in junctional localization of ZO-1 proteins (Ma, 2004), indicating that CUR blocked the increase in permeability and the decrease of ZO-1 expression was associated with inhibiting NF-kB activation. CUR abolished both PMA and thapsigargin-induced ROS generation (Balasubramanyam, 2003; Chan, 2005).

CUR inhibit proinflammatory cytokines and chemokines:

Th17 cells transmigrate efficiently across BBB to promote CNS inflammation through lymphocyte recruitment (Balasubramanyam, 2003). IL-17 induces production of CXC chemokines, such as CXCL1, CXCL2 and CXCL8/IL-8 and receptors CXCR1, CXCR2 in the recruitment of circulating lymphocytes and monocytes

to the CNS during EAE and MS (Carlson, 2008). Transfers of encephalitogenic CD4 positive Th17 cells are sufficient to induce CXCL1 and CXCL2 transcription in the spinal cords of naive, syngeneic recipients. In EAE mice and rats, CUR decreased obviously inflammatory cells, especially Th17 cells, infiltration and differentiation in CSN (Xie, 2009; Natarajan, 2002). CUR reduced the mRNA and protein expression of CXCL1 and CXCL2 by downregulated NF-kB activation correlated with CXC production (Bachmeier, 2008). CUR blocks cytokines mediated NF-kB activation through inhibition of IkBα kinase and AKT, down-regulates the expression of the NF-κB-regulated gene products such as IL-17, IL-1β, TNF-α, IL-6, IL-8, MIP-1, PGE2, C-reactive protein, CXCR-4, and others induced by inflammatory stimuli (Gertsch, 2003; Oono, 2002; Shogi, 2003)

CUR inhibit Th17 differentiation:

The Th17 differentiation of naive T cells is initiated by TGF-β and IL-6. TGF-β1, TGF-β2, and TGF-β3 are the three isoforms that have been identified in mammals. Among these three isoforms, TGF-β1 is predominantly expressed in the immune system and is believed to be an important pleiotropic cytokine with potent immunoregulatory properties. TGF-β1 induces Foxp3-positive regulatory T cells (iTregs) in the presence of IL-2, while in the presence of IL-6, induces pathogenic IL-17 producing Th17 cells (Yoshimura, 2010).

CUR blocks multiple sites of the TGF-β signaling cascade (Hu, 2010). CUR inhibits the activity of the transcription factor c-jun and also has NF-kB inhibitory activity, and it is possible that CUR limits essential transcription factor availability, which subsequently leads to reduced TGF-βR mRNA expression (Gaedeke, 2004). Activation of STAT3 is required for differentiation of Th17 cell lineage, which is activated by IL-6 and IL-21, and induces expression of RORγt that is served as the master switch of differentiation of Th17 cell (Wei, 2007; Ichiyama, 2008; Manel, 2008; Zhou, 2008). STAT3 plays a critical role in the induction of the orphan nuclear receptor, RORγt, which directs Th17 cell differentiation by inducing the IL-23 receptor (Chaudhry, 2009). Xie *et al.,* examined the production and activity of STAT3, and its consequent transducer production of RORγt. The results showed CUR inhibits the production of STAT3 and phosphorylation of STAT3 transcription factors in activated rat lymphocytes and Jurkat T cells. Correspondingly, its consequent transducer-production of RORγt obvious decreased in vivo and in vitro. Thus, the blockade of IL-6 and IL-21 activated STAT3 signal pathway by CUR resulted in inhibition of proliferation and differentiation of Th17 cells in EAE. CUR inhibited IL-6-induced STAT3 phosphorylation and consequent STAT3 nuclear translocation. CUR inhibits differentiation and development of Th17 cells depends on down-regulating expression of IL-6, IL-21, RORγt signaling and inhibition STAT3-phosphorylation in EAE rat (Xie, 2009). These studies suggest that CUR maybe is a good candidate in the treatment of MS and other Th17- mediate inflammatory diseases (Bharti, 2003).

CUR Offers Protection Against Depression:

Depression is a multifaceted psychological disorder that has been estimated to affect up to 21% of the world population (Schechter, 2005). Depression is characterized by a pervasive low mood, loss of interest in usual activities and diminished ability to experience pleasure (Eley, 1999).

There are four main types of classical antidepressants in clinical practice, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and serotonin-noradrenergic reuptake inhibitors (SNRIs). However, the therapeutic benefits of these drugs are associated with several undesirable side effects (Nemeroff, 2007). CUR is commonly used to treat the symptoms of mental stress, hypochondriac pain and mania (Gold, 2003; Ying, 2007). Thus, it is valuable to develop more selective therapeutic tools with fewer side effects. Since accumulating evidence supports that herbal medicines could serve as effective treatment for psychiatric diseases (Linde, 2005). A large number of clinical observations have suggested that stress can act as a precipitating factor in the onset of affective illness, especially major depression (Bidzinska, 1984).

Chronic stress can induce depressive disorders, and animal stress models are widely used in pre-clinical antidepressant evaluation (Garcia, 2002).

CUR increases serotonin receptor 1A mRNA expression:

Stress-induced damage to hippocampal neurons may contribute to the phathophysiology of depression. Chronic stress is associated with structural and functional changes in the hippocampus, including atrophy of apical dendrites of CA3 pyramidal neurons (Campbell, 2004). Chronic unpredictable stress decreases neurogenesis in the adult hippocampus, which may contribute to this hippocampal atrophy (Li, 2004; Joels, 2004; Beauquis, 2006). More researches on depression have been focused on 5-hydroxytryptamine (5-HT, serotonin) and its specific receptors (Bockaert, 2008; Dawson, 2008; Jensen, 2008). 5-HT1A receptor is the best-characterized subtype of currently known 5-HT receptor subtypes and its affinity to 5-HT is higher than that of other 5-HT receptor subtypes (Uphouse, 1997). The serotonin receptor 1A (5-HT1A receptor) is specific antagonists decreased cell proliferation in the adult dentate gyrus. 5-HT1A receptors therefore represent attractive target for studying the pathophysiology of depression and the actions of antidepressant treatment

(Radley, 2002). It has shown that chronic administration of CUR can reverse the decreased serotonin level caused by stress and the antidepressant effect of CUR in the forced swimming test is highly related to 5-HT receptor subtypes, such as 5-HT1A (Wang, 2008). CUR administration increased hippocampal neurogenesis in chronically stressed rats. CUR significantly prevented the stress-induced decrease in 5-HT1A mRNA in the hippocampus, the molecule implicated in neurogenesis (Rutherford, 1997; Santarelli, 2003; Henn, 2004). Furthermore, CUR induced increase in cell proliferation in the dentate gyrus of stressed rats. It is possible that 5-HT, through activity at 5- HT1A receptors, is a potent stimulator of cell proliferation and subsequent neurogenesis in the hippocampus following CUR administration (Xua, 2007).

CUR activatives brain-derived neurotrophic factor and its receptor TrkB:

There is compelling evidence indicating that neurotrophins play an important role in the survival of mammalian nervous system (Lindsay, 1994). Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, promotes the development of immature neurons, regulates the survival and function of adult neurons, cell survival during stressful conditions such as depression and post-traumatic stress disorders (Duman, 2006; Kuipers, 2006). Depression and repeated stress exposure will lead to a reduction in hippocampal BDNF (Nibuya, 1995). The BDNF knockout mice are insensitive to some antidepressants in the behavioral tests (Sairanen, 2005). Previous studies have observed that local infusion of BDNF into the midbrain, dentate gyrus, or CA3 area of the hippocampus produces antidepressant-like effects in behavioral animal models of depression (Siuciak, 1994; Shirayama, 2002; Reagan, 2007). BDNF exerts its biological function through binding to its receptor, tropomyosin-related kinase B (TrkB), which initiates multiple signaling cascades (Klein, 1991; Jiang, 2005). It has reported that CUR produces widespread increase in BDNF levels in the brains of stressed rats (Xu, 2005). Pretreatment of CUR reverses the down-regulated expression of BDNF and phosphorylated- TrkB induced by glutamate in the primary cultured cortical neurons (Wang, 2005). CUR could evoke a dose- and time-dependent increase in BDNF protein in the cortical culture, which activates TrkB phosphorylation and hence promotes neuronal survival (Rui, 2010). CUR treatment, via up-regulation of 5-HT1A receptor mRNA and BDNF, may reverse or protect hippocampal neurons from further damage in response to chronic stress or other environmental insults (Xua, 2007). Also, the antidepressant effects of CUR were evaluated in two behavioral models, the forced swim task and the OB rat model of depression. Chronic administration of CUR resulted in a dose-dependent reduction of the immobile time in the forced swim test. CUR treatment also reversed the increased activity in the open field test and the deficit in step-down passive avoidance learning deficit displayed by OB rats (Janscar, 1983; Xu, 2005).

Protective Effects of CUR on Epilepsy:

Epilepsy is one of the leading neurological disorders affecting 50 million of world's total population, requiring long-term antiepileptic drug (AED) therapy (Lowenstein, 2008; Prilipko, 2006). Despite treatment with AED, epilepsy remains refractory in one third of patient (Maertns, 1995). Generation of ROS in the brain is considered as one of the leading causes of generalized epilepsy associated with recurrent seizures (Sudha, 2001). Clinical reports suggest that not only epilepsy but therapeutic drugs used in the treatment of epilepsy also exert negative effect on cognition which affects quality of life of epileptic patients (Rajkumar, 1994). CUR has been reported to act as a free radical scavenger and an antioxidant,thus inhibiting lipid peroxidation and oxidative DNA damage (Shukla, 2003). Furthermore, Both experimental and epidemiological evidence have shown beneficial influence of CUR on seizures, oxidative stress and cognitive impairment (Frautschy, 2001; Morimoto, 2004).

CUR Offers Protection Against Experimental Animal Model For Epileptogenesis:

Pentylenetetrazole (PTZ) kindling is widely accepted as an experimental animal model for epileptogenesis. In this model repeated injection of sub-convulsive dose of PTZ causes gradual development of seizure culminating to generalised-tonic–clonic seizures (Cavazos, 1990). Kindled seizures have been shown to cause a neuronal loss in limbic systems CA1, CA3, dentate gyrus of hippocampus, amygdala and entorhinal cortex (Pitkanen, 2002; Jogender, 2010). Administration of CUR dose dependently protected against kindling as indicated by decreased seizure score and attenuated the oxidative stress in mice. Therefore it could be a promising candidate to control both development of seizure and oxidative stress during epilepsy (Agarwal, 2010). PTZ caused a significant decrease in retention latency in the passive avoidance task and a significant increase in the retention transfer latency in elevated plus maze test which indicate impairment of memory of rats. In the groups that were administered CUR, the rats exhibited significantly increased retention latencies in the passive avoidance paradigm and significantly shorter retention transfer latencies in the elevated plus maze as compared to the animals administered PTZ alone(Shin, 2007). Furthermore, CUR showed protection against kainic acid-induced (Peng, 2009) and amygdaloid seizures (Jyoti, 2009). Also, CUR prevented seizures in the iron-induced experimental model of epileptogenesis (Bharal, 2008) and electroshock induced seizures (Torbati, 1992).

CUR Decreases Malondialdehyde And Increase Glutathione Levels:

Increasing data from experimental and clinical reports suggest the involvement of oxidative stress in pathophysiology of epilepsy (Agarwal, 2010). Free radicals are normal products of cellular aerobic metabolism involved in the development of seizures (Jyoti, 2009). Excessive oxidative stress contributes to neuronal degeneration through lipid peroxidation and decreased GSH concentrations in the epileptic focus (Sejima, 1997). GSH is an endogenous antioxidant which gets converted to oxidized form. This oxidized form of GSH reacts with free radicals and prevent generation of most toxic hydroxyl radical(Jesberger, 1991; Schulz, 2000). Malondialdehyde (MDA) is an end product of free radical generation (Gupta, 2003) and GSH plays an important role in protecting cells against oxidative damage as a free radical scavenger (Liu, 1997). Repeated PTZ administration has significantly increased the free radical generation as indicated by increased MDA and decreased the GSH level in the rat brain. CUR administration with dose dependent manner, significantly decreases MDA and increases GSH levels (two oxidative stress markers) in the brain tissue of PTZ -kindled mice (Ono, 2000).

CUR is Protective Against The Cognitive Impairment And Oxidative Stress Induced By Conventional AED:

Cognitive impairment is an important comorbidity of chronic epilepsy (Elger, 2004). The evidence shows an association between persistent epilepsy and cognitive impairment (Dodrill, 2004). Apart from the epilepsy disease itself producing cognitive impairment, the conventional anticonvulsant drugs can also produce cognitive deficits. Though all the conventional AED have been shown to affect cognitive function (Park, 2008). Studies have shown that phenobarbitone induces behavioral and cognitive deficits including alterations in attention vigilance, reaction time and short-term memory (Meador, 1995). Phenytoin is a commonly and effectively used AED, effective against all types of partial and tonic–clonic seizures (Leppik, 2008) have been shown to have harmful effects on the immature brain, (Namara, 2006). When CUR was administered along with phenobarbitone, Phenytoin and carbamazepine, produced significant reversal of the effect of these drugs in elevated plus maze test. Co-administration of CUR did not cause significant change in the serum concentrations of Phenytoin, phenobarbitone and carbamazepine, suggests that CUR did not prevent cognitive impairment by decreasing the serum concentrations of this drugs, thus implicating the possibility of other mechanisms being responsible for this beneficial effect (Reeta, 2009; Reeta, 2010). Oxidative stress has been reported to affect the synaptic plasticity and cognition (Keller, 2005). Phenobarbitone, Phenytoin and carbamazepine have been reported to cause an imbalance between the oxidative and antioxidant status. Thus, oxidative stress induced by AED may also contribute to the induction of cognitive impairment in rats (Reeta, 2009; Aycicek, 2007). When CUR was administered along with phenobarbitone, Phenytoin and carbamazepine, CUR is effective in preventing Phenytoin- phenobarbitone- and carbamazepine-induced oxidative stress and cognitive impairment (Reeta, 2009; Reeta, 2010).

Neuroprotective Effects of CUR against Ischemic Cerebral Stroke:

Stroke is the third leading cause of morbidity and human death in developed countries (Rogers., 1997). Complete occlusion of the middle cerebral artery (MCA) occurs in 10%-15% of stroke patients (Hacke, 1995). A variety of mechanisms are involved in ischemic brain injury (Cheng, 2004). The brain has low levels of endogenous antioxidants like GSH and Vitamins E and C (Kehrer, 1994). Compared with other tissues, the brain is particularly vulnerable to oxidative damage because of its high oxygen consumption rate, abundant lipid content, and relative paucity of antioxidant enzymes (Miquel, 1992). Involvement of oxidative stress in neuronal loss after stroke is well established. Undesirable byproducts, such as components of ROS (superoxide, hydroxyl radical, hydrogen peroxide and peroxynitrite radical), continuously result from physiological process supporting life of all cells, have been found to be elevated after ischemic reperfusion (IR) injury and play an important role in the neuronal loss after cerebral ischemia (Imaizumi, 1986 Oliver, 1990). CUR possesses many therapeutic properties including anti-oxidant activities (Dutta, 2005; Suryanarayana, 2007; Antonio, 2008). Several studies have indicated that CUR has protective effects against cerebral ischemia in rats and gerbils (Thiyagarajan, 2004; Ghoneim, 2002; Wang, 2005). CUR is a powerful scavenger of superoxide anions, hydroxyl radicals, nitrogen dioxide and hydrogen donor, and exhibits antioxidant activity directly and indirectly (Lim, 2005; Biswas, 2005). Apoptosis or related phenomena are possibly involved in secondary cell death in cerebral ischemia. Cerebral ischemia can induce the activation of caspases including caspase-3, the up-regulation and activation of which have been found to precede neuronal death. CUR can reduce neuronal loss of the ischemic brain tissue, and inhibit expression of the activated caspase-3, a key executor of apoptosis (Ashe, 2003; Q, 2006).

CUR Protects Against Ischemia by Inhibits ROS Production:

In cerebral ischemia, the mitochondrial dysfunction and consequent production of ROS due to up-regulation of iNOS, a cascade of events is initiated leading to death (Sreejayan, 1996). Normally there is a balance between the ROS production and the endogenous scavenging system which detoxifies the ROS (Sims, 2000).

During cerebral ischemia xanthine dehydrogenase an enzyme which involved in purine metabolism is irreversibly converted to xanthine oxidase by sulfhydryl cleavage. Xanthine dehydrogenase/xanthine oxidase (XD/XO) conversion, leading to production of ROS (Lin, 1994). Among the ROS, O2 •− was believed to be directly toxic to neurons since it initiates a free radical (FR)-mediated chain reaction causing additional CNS damage (Kondo, 1997). CUR has inhibitory effects on XD/XO conversion and resultant O2 •− production (Ghoneim, 2002).

CUR Promotes The Expression of Nrf2 and HO-1 After MCAO:

Nuclear factor erythroid 2-related factor 2(Nrf2), is a basic leucine zipper transcription factor that binds and activates the antioxidant response element (ARE) in the promoters of many antioxidant and detoxification genes (Kobayashi, 2005). Nrf2 regulates a set of antioxidant/ detoxification genes acting in synergy to remove ROS/ RNS. Nrf2 controls the coordinated expression of important antioxidant and detoxification genes (Phase II genes) (Shih, 2003; Ishii, 2000). Phase II genes, including heme oxygenase-1 (HO-1), glutathione S-transferases (GSTs) and NAD (P) H quinine oxidoreductase, work in synergy to constitute a pleiotropic cellular defense that scavenges ROS and reactive nitrogen species (RNS) (Satoh, 2006; Lee, 2003). HO-1, along with other phase II enzymes, serves as a defense system against oxidative stress. Transcription of HO-1 is activated by Nrf2 in neurons, and an increase in HO-1 protein leads to degradation of heme molecules, producing biliverdin and bilirubin. The accumulation of bilirubin, a potent antioxidant molecule, is responsible for the neuroprotective effects of HO-1 (Motterlini, 2002; Jain, 2006). Nrf2 and HO-1 were up-regulated in cerebral ischemia. Systemic administration of CUR to cerebral ischemic rats significantly increased the expression of Nrf2 in nucleus and HO-1 in cytoplasm of both neurons and astrocytes. These results may indicate that the upregulation of Nrf2/ARE pathway after ischemia by administration of CUR is a potential mechanism for its neuroprotection (Yang, 2009).

CUR Protects Blood–Brain Barrier Against Ischemia:

The BBB, formed by tight interendothelial cell connections, the basal lamina, and astrocyte end-feet, protects the brain from the entrance of potentially harmful substances present in the blood and maintains the homeostasis of the CNS. Regulation of BBB permeability is a necessary part of normal physiology. After stroke insult, excessive increase in vascular permeability leads to disruption of the vasogenic edema (Squire, 2003). Disruption of BBB has been reported after MCAO (Belayev, 1996). Nitric oxide (NO), a free radical that can act both as a signaling molecule and a neurotoxin, produced endogenously by a family of nitric oxide synthase (NOS),is involved in the pathogenesis of cerebral ischemia (Luo, 2005; Zhu, 2002). NO contributes to ischemia- and inflammation-induced disruption of BBB (Tan, 2004). NO rapidly reacts with superoxide anion (O2U−) to form a reactive oxide species, peroxynitrite anion (ONOO−) (Dawson, 2004). This peroxynitrite is a potentially toxic anion that can directly hydroxylate and nitrate the aromatic residues of amino acids and nucleotides in cytosol and nucleus (Beckman, 1992; Moreno, 1992). iNOS is expressed in astrocytes whose end-feet form an essential functional component of blood–brain barrier following cerebral ischemia (Khan, 2005). The iNOS-derived NO contributes to peroxynitrite formation and blood–brain barrier breakdown (Winkler, 2001). CUR significantly reduced iNOS expression in a dose-dependent manner in the cultured astrocytes (Jiang, 2007). furthermore, CUR -treatment would have decreased peroxynitrite formation by inhibiting xanthine oxidase and iNOS and also prevents ONOO−-induced brain capillaries endothelial cells damage (Thiyagarajan, 2004). Also, CUR reduce water content of the brain in ipsilateral hemisphere after focal cerebral ischemia and improved vasogenic edema of the brain suggesting that CUR protects BBB by reducing endothelial cells damage (Yang, 2009; Jiang, 2007).

According to these reports CUR, which has got antioxidant and anti-inflammatory effects, can be a good candidate for treatment of different central nervous system disease such as Alzheimer's disease, Parkinson's disease, Multiple sclerosis, stroke, epilepsy and depression.

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