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Review Article

Protective role of biological potential curcumin in epileptic seizures and memory impairment

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Abstract

Central nervous system disorders are of great concern due to increasing stress and changing living conditions. Epilepsy is one of the most prevalent CNS disorders, and as a number of side effects are associated with the present antiepileptic drug treatments. The effect of curcumin on epileptic seizures, together with its effect on memory retention and the role of monoamines in protection from seizures and memory impairment. The estimations of norepinephrine, dopamine and serotonin in cerebral cortex, cerebellum, hippocampus, pons and hypothalamus made it evident that curcumin exerted a potential antiepileptic and memory retentive effects, with considerable influence on the brain monoamine levels.

1. Introduction

Turmeric, derived from the plant *Curcuma longa*, is a gold-colored spice commonly used in the Indian subcontinent, not only for health care but also for the preservation of food and as a yellow dye for textiles. Curcumin, which gives the yellow color to turmeric, since the time of Ayurveda numerous therapeutic activities have been assigned to turmeric for a wide variety of diseases and conditions, including those of the skin, pulmonary, and gastrointestinal systems, aches, pains, wounds, sprains, and liver disorders. Extensive research within the last half century has proven that most of these activities, once associated with turmeric, are due to curcumin. Curcumin has been shown to exhibit antiviral [1,2], antibacterial [3], anti-fungal [4], antimalarial [5,6], antiparasitic [7-10], anti-AIDS [11], antidepressant [12.13], anti-spasmodic [14], antivenomic [15], antiatherosclerosis [16], contraceptive [17], anticataract [18,19], anti-cyctic fibrosis [20,21], antiepilepsy [22], anti-hyalinen membrane disease (HMD) [23], antihypolipidemic [24], hepatoprotectives [25], effective in lung disease [26], antiosteoprosis [27], antiparkinson [28] and effective in renal diseases [29-31] etc. curcumin also exhibited antioxidant, anti-inflammatory, anticancer activities and thus has a potential against various malignant diseases, diabetes, allergies, arthritis, Alzheimer's disease, and other chronic illnesses. These effects are mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes. Curcumin exhibits activities similar to recently discovered tumor necrosis factor blockers, a vascular endothelial cell growth factor blocker, and human epidermal growth factor receptor blockers. Considering the recent scientific band wagon that multi targeted therapy is better than mono targeted therapy for most diseases [32-40].

Curcumin is one such medicine. Its history goes back over 5000 years, to the heyday of Ayurveda (which means the science of long life). Turmeric derived from the rhizome of the plant *Curcuma longa* has been used by the people of the Indian subcontinent for centuries with no known side effects, not only as a component of food but also to treat a wide variety of ailments. Turmeric is a spice of golden color that is used in cooking in the Indian subcontinent. Because of its color and taste, turmeric was named "Indian saffron" in Europe. Today, India is the primary exporter of turmeric (known as haldi in India). Although its ability to preserve food through its antioxidant mechanism, to give color to food, and to add taste to the food is well known, its health promoting effects are less well recognized or appreciated. It was once considered a cure for jaundice, an appetite suppressant, and a digestive. In Indian and Chinese medicines, turmeric was used as an anti-inflammatory agent to treat gas, colic, toothaches, chest pains, and menstrual difficulties. This spice was also used to help with stomach and liver problems, to heal wounds and lighten scars, and as a cosmetic. Turmeric was mentioned in the writings of Marco Polo concerning his 1280 journey to China and India and it was first introduced to Europe in the 13th century by Arab traders.

Although Vasco de Gama (a Portugeese sailor) during 15th century, after his visit to India, truly introduced spices to the West, it was during the rule of British in India that turmeric was combined with various other spices and renamed "curry powder," as it is called in the West. Epilepsy affects approximately 50 million people of whom about 40 million people lack appropriate treatment and is emerging fast as a hindrance to many lives. On the other hand, the abundant side effects of the existing antiepileptic drugs (AEDs) are of great concern for both patients and physicians. The long term use of traditional medicines for prophylaxis is ruled out in the treatment of epilepsy, since the unpredictability of seizure occurrence limits their therapeutic efficacy. Furthermore, cognitive defects pose a serious threat in epileptic patients and the worsening effects of the existing AEDs are anchoring the cognitive deficits of the epileptic patients. Although extensive research on the neurobiological bases was performed to understand the role of neurochemicals in regulation of epilepsy, studies showing the involvement of brain catecholoamines and indoleamines in seizure reduction are meager. However, a few studies have reported the protective effect of norepinephrine (NE) against electroshock induced GTC seizures, and serotonin (5-HT) against pentylenetetrazole (PTZ) induced absence seizures, throw some light on the role of neurotransmitters in the treatment of seizures, involvement of brain monoamines, mainly the NE and dopamine (DA), in mediating the cognitive tasks in patients with Alzheimer's disease. Additionally, several publications have provided information on seizures and their treatment, although very few attempts have been made to study the effect of drugs on memory after seizure inductement, the role of monoamines in protection from seizure occurrence and memory impairment, and the effect of standard AED treatment on memory. In view of these findings, we have chosen curcumin–the active constituent of C*urcuma longa*–which has been claimed to possess efficacy in the treatment of

Alzheimer's disease , MAO-A & B inhibitory activity enhancement of brain monoamine levels, and rhizomes being cited in the database for Indian medicinal plants in the treatment of epilepsy, for which no reported evidence was available, all these factors had made us to focus on the objectives of the present study, to evaluate: 1) the protective effect of curcumin on the Maximal electro shock (MES) induced seizures; 2) effect on memory retention after seizure induction; and 3) effect on the neurotransmitter levels in various regions of rat brain [40-56].

2. Composition of turmeric

Turmeric contains a wide variety of phytochemicals, including curcumin, demethoxycurcumin, bisdemethoxycurcumin, zingiberene, curcumenol, curcumol, eugenol, tetrahydro curcumin, triethylcurcumin, turmerin, turmerones, and turmeronols. 1) Curcumin, demethoxycurcumin, and bisdemethoxycurcumin have also been isolated from *Curcuma mangga*, 2) *C. longa, C. cassia C. zedoaria*, 3) *Costus speciosus*, 4) *C. xanthorrhiza*, *C. aromatica*, 5) *C. phaeocaulis*, *Etlingera elatior*, 6) and *Zingiber cassumunar* 7) Curcumin is the phytochemical that gives a yellow color to turmeric and is now recognized as being responsible for most of the therapeutic effects. It is estimated that 2–5% of turmeric is curcumin [57,58].

3. Curcumin and its analogues

Curcumin was first isolated from turmeric in 1815, and structure was elucidated in 1910 as diferuloylmethane. Curcumin is hydrophobic in nature and frequently soluble in dimethylsulfoxide, acetone, ethanol, and oils. When exposed to acidic conditions, the color of turmeric/curcumin turns from yellow to deep red, and the form in which it is used routinely for various religious ceremonies. Turmeric contains three different analogues of curcumin (i.e., diferuloylmethane, also called curcumin, demethoxycurcumin, and bisdemothycurcumin. Whether all three analogues exhibit equal activity is not clear. Although in most systems curcumin was found to be most potent, in some systems bisdemethoxycurcumin was found to exhibit higher activity. There are also suggestions that the mixture of all three is more potent than either one alone. When administered orally, curcumin is metabolized into curcumin glucuronide and curcumin sulfonate. However, when administered systemically or intraperitoneally, it is metabolized into tetrahydrocurcumin, hexhyrdrocurcumin, and hexhydrocurcuminol. Tetrahydrocurcumin has been shown to be active in some systems and not in others [57,58].

4. Uses of curcumin

The use of turmeric for health purposes is nothing new. As a folklore medicine, its use has been documented in both Indian and Chinese cultures. The long list of uses include antiseptic, analgesic, anti-inflammatory, antioxidant, antimalarial, insect repellant, and other activities associated to turmeric.[4,20–27]. Perhaps one of the most often prescribed uses is for wound-healing.[28] This activity is well known to people from the Indian subcontinent. Modern research has provided considerable evidence, and the mechanism by which turmeric/curcumin could accelerate wound-healing has been described.[29–36] It is now well recognized that most chronic diseases are the result of disregulated inflammation,[37,38] Turmeric has been traditionally described as an anti-inflammatory agent. Recent scientific evidence has indeed demonstrated that turmeric, and curcumin in particular, exhibits potent anti-inflammatory activities as determined by a wide variety of systems.[39–49] Therefore, it is not too surprising that turmeric displays activities against a variety of diseases. Because curcumin also exhibits potent antioxidant activity, whether the anti-inflammatory activity of curcumin is mediated through its antioxidant mechanism is not clear. Since most well-characterized antioxidants do not exhibit antinflammatory activity, it is unlikely that the anti-inflammatory activity of curcumin is due to its antioxidant activity [40-56].

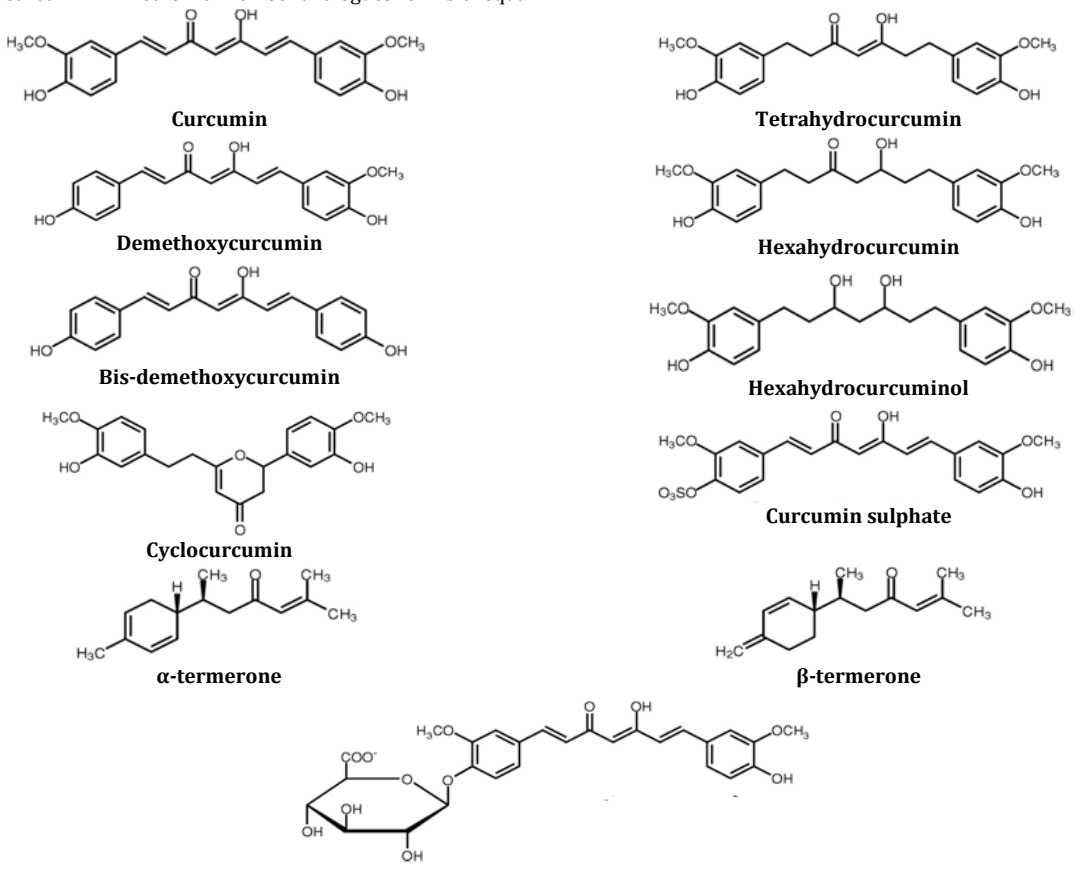

Figure 1. Chemical structures of curcumin and its analogues

5. Disease targets of curcumin

The research has revealed that curcumin has potential against a wide variety of diseases, both malignant and nonmalignant. The potential of curcumin, however, has not been systematically examined through the modern multicenter, randomized, doubleblind, placebo-controlled clinical trial. Its potential in humans is indicated either through preclinical studies, some pilot studies in humans, anecdotal studies in patients, or epidemiological studies. Curcumin has been shown to exhibit activity against numerous inflammatory diseases, including pancreatitis, arthritis, inflammatory bowel disease (IBD), colitis, gastrititis, allergy, and fever, possibly through the downregulation of inflammatory markers, as indicated earlier. The effect of curcumin against various autoimmune diseases has also been demonstrated; they include scleroderma, psoriasis, multiple sclerosis, and diabetes. Again, these effects of curcumin are through the regulation of pro-inflammatory signaling. Although once thought to be distinct, the molecular targets for both the prevention and therapy of cancer are now considered the same. Numerous lines of evidence suggest the potential of curcumin against various types of cancer. First, curcumin has been shown to suppress the proliferation of a wide variety of tumor cells through the down regulation of antiapoptotic gene products, activation of caspases, and induction of tumor suppressor genes such as. Second, curcumin has also been to shown to suppress the invasion of tumors through the down regulation of matrix metalloproteinases (MMPs) and cell surface adhesion molecules. Third, curcumin suppresses the angiogenesis of tumors through the suppression of angiogeneic cytokines. Fourth, the anti-inflammatory effects of curcumin contribute to its antitumor activity as well. Curcumin has also been shown to play a role in diabetes mellitus type II, in which the patient develops a resistance to insulin. Several animal studies have demonstrated that curcumin can overcome insulin resistance. That curcumin prevents myocardial infarction and other cardiovascular diseases has also been demonstrated. The effects of curcumin in cardiovascular diseases are linked to its ability to inhibit platelet aggregation inhibit inflammatory response lower LDL and elevate HDL, inhibit fibrinogen synthesis, and inhibit oxidation of LDL. All of these activities contribute to the cardiovascular effects of curcumin. Because curcumin can suppress amyloid-induced inflammation, curcumin has also been linked to the suppression of Alzheimer's disease [33-56].

Epilepsy affects approximately 50 million people of whom about 40 million people lack appropriate treatment [59] and is emerging fast as a hindrance to many lives. On the other hand, the abundant side effects of the existing antiepileptic drugs (AEDs) are of great concern for both patients and physicians. The long term use of traditional medicines for prophylaxis is ruled out in the treatment of epilepsy, since the unpredictability of seizure occurrence limits their therapeutic efficacy. Furthermore, cognitive defects pose a serious threat in epileptic patients [60] and the worsening effects of the existing AEDs are anchoring the cognitive deficits of the epileptic patients. Although extensive research on the neurobiological bases was performed to understand the role of neurochemicals in regulation of epilepsy, studies showing the involvement of brain catecholoamines and indoleamines in seizure reduction are meager. However, a few studies have reported the protective effect of norepinephrine (NE) against electroshock induced GTC seizures, and serotonin (5-HT) against pentylenetetrazole (PTZ) induced absence seizures [61], throw some light on the role of neurotransmitters in the treatment of seizures, involvement of brain monoamines, mainly the NE and dopamine (DA), in mediating the cognitive tasks in patients with Alzheimer's disease. Additionally, several publications have provided information on seizures and their treatment, although very few attempts have been made to study the effect of drugs on memory after seizure inductement, the role of monoamines in protection from seizure occurrence and memory impairment, and the effect of standard AED treatment on memory. In view of these findings, we have chosen curcumin–the active constituent of C*urcuma longa*-which has been claimed to possess effi cacy in the treatment of Alzheimer's disease [62], MAO-A & B inhibitory activity [63] enhancement of brain monoamine levels, and rhizomes being cited in the database for Indian medicinal plants in the treatment of epilepsy [64], for which no reported evidence was available, all these factors had made us to focus on the objectives of the present study, to evaluate: 1) the protective effect of curcumin on the MES induced seizures; 2) effect on memory retention after seizure induction; and 3) effect on the neurotransmitter levels in various regions of rat brain. Epilepsy is a serious and common neurological disease. Nearly 70% of patients with epilepsy achieve seizure control with antiepileptic drugs. Pharmacological treatment of seizures has primarily involved modulation of voltage-gated ion channels, enhancement of GABAergic inhibition, and reduction of glutamatergic excitation [65]. Phytochemical and pharmacological studies have been done on anticonvulsant plants, and an increasing number of patients use herbal medicines as a supplement to or substitute for prescription drugs. Such treatments are considered to be gentle and safe alternatives to synthetic drugs [66]. Curcumin, the major component of the spice turmeric, can reduce oxidative and inflammatory damage [67]. Several studies have shown that curcumin has anticonvulsant effects against seizures induced by kainic acid (KA) [68] and $FeCl_3$ [69] in rats. We have previously shown that high doses (100 and 300 mg/kg, i.p.), but not low doses (10 and 30 mg/kg), of curcumin inhibited amygdala-kindled seizures in rats [70,71]. The aim of this study was to test the effects of curcumin on pilocarpine-induced seizures in rats, to confirm its anticonvulsant effects in an additional typical seizure model. Seizures can induce the generation of epoxide and free radicals, and this has been suggested to contribute to the recurrence of seizures [72]. Lipid peroxidation, resulting from an increase in free radicals, causes cellular membrane damage, which can also increase the recurrence of seizures [73]. Therefore, we also investigated the generation of epoxide and free radicals in the hippocampus during pilocarpine-induced seizures and its modulation by curcumin treatment.

Curcumin, an active ingredient of turmeric with antioxidant and anti-inflammatory properties has recently been reported to have anticonvulsant effects in several animal models of epilepsy. This study aimed to investigate the effects of curcumin on the pilocarpine rat model of status epilepticus. The effect of intraperitoneal administration of curcumin (30, 100, and 300 mg/kg) on pilocarpine-induced seizures in rats was tested. The correlation between seizure activity and hippocampal levels of nitric oxide synthase and free radicals was quantified. Whether curcumin treatment modulated these parameters was also investigated. Curcumin significantly increased seizure threshold at doses of 100 and 300 mg/kg. Rats with pilocarpineinduced seizures showed significantly elevated levels of malonaldehyde, nitric oxide synthase, and lactate dehydrogenase, but decreased levels of superoxide dismutase and glutathione compared with normal control rats. At doses of 100 and 300 mg/kg, curcumin reversed the effects of pilocarpine-induced seizures on nitric oxide synthase, lactate dehydrogenase, glutathione, and superoxide dismutase. However, curcumin did not restore the elevated malonaldehyde levels. Curcumin has anticonvulsant activity in the pilocarpine rat model of seizures, and that modulation of free radicals and nitric oxide synthase may be involved in this effect [74].

5.1 Epileptic behaviors

All the rats in the control group exhibited generalized limbic seizures after pilocarpine administration, at a latency of minutes. Pretreatment with curcumin significantly delayed the onset of seizures at doses of 300 mg/kg and 100 mg/kg compared with control. The 30 mg/kg dose of curcumin had no significant effect. Similarly, the mean seizure severity score was significantly reduced compared with control at curcumin doses of 300 mg/kg and 100 mg/kg, but not at 30 mg/kg. Pretreatment with curcumin at 300 and 100 mg/kg also decreased the occurrence of pilocarpine-induced

status epilepticus. Several rats died before the onset of status epilepticus (2/15 rats treated with 300 mg/kg, 2/15 rats treated with 100 mg/kg, 4/15 rats treated with 30 mg/kg. In the remaining rats, curcumin significantly delayed the onset of status epilepticus at doses of 300 mg/kg and 100 mg/kg minutes, compared with control. Curcumin at 30 mg/kg did not delay the onset of status epilepticus compared with control.

5.2 Biochemical analysis

Pilocarpine-induced seizures significantly increased malonaldehyde (MDA) content, and treatment with curcumin did not normalize this effect. Animals treated with pilocarpine showed an elevation in lactate dehydrogenase (LDH) activity that was restored by curcumin at 100 or 300 mg/kg. Pilocarpine also caused an increase in NOS activity, and curcumin at 100 and 300 mg/kg prevented this effect. Both glutathione (GSH) and superoxide dismutase (SOD) levels were decreased in pilocarpine-treated rats. GSH content was restored to near normal in animals treated with curcumin at 100 and 300 mg/kg. Curcumin at 30 mg/kg failed to restore SOD activity, but the 100 and 300 mg/kg doses significantly increased it towards normal levels.

6. Discussion

We have demonstrated that pretreatment with curcumin at doses of 100 and 300 mg/kg significantly delayed the onset of pilocarpine-induced limbic seizures and status epilepticus. These doses of curcumin also counteracted pilocarpine-induced changes in hippocampal Nitric oxide synthase (NOS), SOD, and LDH activity and GSH content. Taken together, these results indicate that the anticonvulsant properties of curcumin may at least in part be mediated by the central nitric oxide system and free radical production. Recent research has shown that curcumin exerted anticonvulsant effect against acute generalized seizures induced by MES [75], KA [68], and $FeCl_3$ [69], and delayed the development of amygdala kindling [70]. These findings suggest that curcumin has anticonvulsant activity in a range of models. The mechanisms underlying the potential anticonvulsant effects of curcumin are not yet fully understood. Previous research has indicated that curcumin has antioxidant and anti-inflammatory activity. Epidemiological studies showed that curcumin also had antioxidant effects after the injury of central nervous system [76]. Curcumin was reported to be several times more potent than vitamin E as a free radical scavenger, and effective against nitric oxide-based radicals [77]. Oxidative stress is known to play a role in epileptogenesis. Free radicals such as oxygen, superoxide, and nitrite, are generated during epileptogenesis [78]. In lead-induced neurotoxicity in rats, curcumin (100 mg/kg, p.o.) has been shown to significantly decrease lipid peroxidation, and increase the levels of reduced glutathione and activity of superoxide dismutase and catalase [79]. Thus, curcumin is an effective antioxidant, and this action may be responsible for its anticonvulsive activity. An increase in MDA has been observed in the brain of rats with seizures induced by $FeCl_3$ [80] and N-methyl-D-aspartate (NMDA) [81]. The MDA level in the hippocampus was also significantly increased after pilocarpine-induced seizures. However, administration of curcumin could not reverse this effect. Recent research has shown that curcumin may trigger intracellular signaling responsible for modulation of NMDA receptor function [82] and expression of brain-derived neurotrophic factor [83]. Our previous research has indicated that curcumin modulates the influx of calcium mediated by 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) and kainate in cultured hippocampal neurons from rats.19 Thus, it is likely that the suppression of pilocarpine-induced seizures and status epilepticus is associated with modulation of neuronal excitability. Curcumin has anticonvulsant potential in the pilocarpine model of temporal lobe seizures. Curcumin is abundant, inexpensive, and relatively safe in humans. It can cross the blood-brain barrier and directly exert its effect on the brain [84].

Effects on various phases of GTC seizures

Treatment with curcumin at doses of 5 mg/kg and 10 mg/kg exhibited a percentage protection of 50 and 66, respectively. Whereas, PHT treated rats showed a 100% protection against the MES induced seizures by inhibiting HLTE. Neither of the 2 doses of curcumin nor the PHT treated rats had shown any significant changes in the duration of tonic flexion and clonic convulsions, but a significant reduction was observed in the time taken for the righting reflex in curcumin 10 mg/kg and PHT treated rats, respectively.

Effect on the performance in conditioned avoidance response after induction of seizures

Rats that received MES (epileptic control) exhibited a signifi cant decrease in memory retention when compared to the control animals (not exposed to MES). Whereas, a significant increase in the retention of memory was observed in both the dose levels of curcumin. PHT treated rats also had showed a significant performance impairment in the conditioned avoidance response.

Effect on Dopamine, Norepinephrine and Serotonin levels in different regions of rat brain: The monoamine levels.

Effect on brain Dopamine

A significant decrease in the DA levels were observed in cortex, pons, hippocampus and hypothalamus in rats exposed to MES. Rats treated with curcumin 5 and 10 mg/kg showed a significant increased in DA levels in cortex, pons, hippocampus and hypothalamus. PHT treated rats showed a significant increase in cortex, hippocampus and hypothalamus. Whereas, no significant change was observed in the cerebellum when compared to epileptic control (MES) rats.

Effect on brain Norepinephrine

A significant decrease in the NE levels of the hippocampus and hypothalamus was observed in rats exposed to MES. Curcumin at 5 and 10 mg/kg showed a significant increase in the NE levels of cortex, hippocampus, hypothalamus and pons, respectively, while PHT treated rats showed a significant increase in NE levels of the cortex, pons and hippocampus. No significant changes were observed in the NE levels of cerebellum when compared to epileptic control (MES) rats. Values of curcumin (5 & 10 mg/kg) PHT treatments were compared with control individually for each phase.

Effect on brain Serotonin

A significant decrease in brain serotonin levels were observed in cerebellum, hippocampus and hypothalamus of epileptic control rats (MES). Curcumin treatment at 5 mg/kg showed an increase in the levels of 5-HT in cerebellum, hippocampus and hypothalamus.

Curcumin at doses of 5 mg and 10 mg/kg/p.o. exhibited a significant protection against the MES-induced GTC seizures, this might be due to the observed increase in the NE and DA levels in various parts of the brain substantiating reports that drug treatment which increases brain monoamine levels by inhibiting MAO tends to raise the seizure *threshold* [61], as Curcuma longa has been reported to increase the brain monoamine levels by inhibiting MAO-A and B in mice brain [63]. On the other hand, low concentrations of DA in cerebellum had been reported to show an inhibitory effect on glutamate, causing blockade of calcium channels, indicating a possible mechanism involved in the antiepileptic effect of curcumin, i.e. a decreased influx of calcium ions into the neuronal cells, thereby inhibiting neurotransmitter re-uptake. This could be effective in the treatment of CNS disorders as epileptic depolarizations in single motor cortical and hippocampal neurons and focal epileptic discharges in neuronal cortical preparations have been reported to be decreased by calcium channel blockers. As theoretical considerations suggest that calcium channel blockers posses anticonvulsant activity, the protective effect of curcumin against MES induced convulsions might be due to the decreased calcium influx, resulting in a decrease in NE mediated glutamate inhibition. At both the dose levels of curcumin, a good memory retentive effect in seizure induced animals was observed when compared to the epileptic control and PHT

treated rats. This increase in memory retention can be interpreted to the increased NE and DA concentrations in brain regions as drugs like L-Dopa have shown an improvement in cognitive test of patients of Alzheimer's disease by increasing DA levels. Other possible mechanism for the memory retentive effect of curcumin can be attributed to the MAO-B inhibitory activity of curcumin [85], as selegelline a MAO-B inhibitor has demonstrated mild but significant improvement in cognitive tasks in a double blind placebo controlled trial in addition to its capacity to increase brain NE and DA concentrations [86] and in the treatment of Alzheimer's disease. Pathological abnormalities in serotonergic and noradrenergic innervations are known to exist in addition to cholinergic innervations in the brain of Alzheimer's patients. This also indicates the rationality of a combination therapy of cholinergic and monoaminergic drugs in Alzheimer's disease, as forebrain dopaminergic system is related to cognitive functions. However the role of NE and DA on memory retention is also controversial as psycho stimulants such as methyl phenidate and amphetamine, which are known to increase cerebral catecholamine turnover, have proven to be of little value in Alzheimer's disease [86]. Our studies and the data obtained allowed us to substantiate the use of curcumin in protection from GTC seizures and enhancing memory. Of particular interest are the effects of curcumin on the brain monoaminergic system, since it has been suggested that monoamines are of great clinical significance in the treatment of seizures and memory disorders [87-89].

7. Conclusion

The results of the presented study, that the brain monoamines (NE, DA & 5 HT) play an important role in protection from epilepsy and memory impairment. The effect of curcumin on chemically-induced absence seizures and the effect on the threshold for generalized and localized seizures have to be interpreted for understanding the anti-epileptic activity of curcumin, and the role of monoamines in chemically-induced seizures are to be performed for meaningful extrapolations of anti-epileptic activity of curcumin [90-93]. The curcumin has enormous potential for a variety of diseases. Serum levels of curcumin tend to be low, which might be responsible for its pharmacological safety and has low bioavailability. Second, the tissue concentration of curcumin and how it compares to what is seen in cell culture conditions are not known. Some agents such as piperine (black pepper) can enhance the bioavailability of curcumin through suppression of its glucuronidation occurring primarily in the liver and in the intestine. Third, whether there are components of turmeric other than curcumin that have beneficial effects either alone or in combination with curcumin needs to be determined. For instance, numerous activities have been assigned to turmeric oil. Fourth, what effect do other spices have on the pharmacology and the biology of curcumin needs to be determined. Fifth, structural analogues of curcumin that are more bioavailable and efficacious are needed. However, this might compromise the safety of curcumin. Sixth, well-controlled large clinical trials are required to determine the potential of curcumin both in the prevention and therapy of a disease. All of these studies should further add to the usefulness of curcumin. Overall, the biological safety, combined with its cost and efficacy, and thousands of years of experimentation. Curcumin may thus be a good supplement to or substitute for antiepileptic drugs. Further studies focusing on the mechanism of its antiepileptic effects should be conducted.

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