e-ISSN:2321-6182
p-ISSN:2347-2332

RESEARCH AND REVIEWS: JOURNAL OF PHARMACOGNSOY AND PHYTOCHEMISTRY

Curcumin as an Antidepressant: A Review.

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Review Article

Received: 19/01/2014
Revised: 26/02/2014
Accepted: 07/03/2014

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Keywords: curcumin, anti-depressant, CNS disorders

ABSTRACT

Curcumin, commonly called diferuloyl methane, is a hydrophobic polyphone derived from the rhizome (turmeric) of the herb *Curcuma longa.* Turmeric has been used traditionally for many ailments because of its wide spectrum of pharmacological activities. Curcumin has been identified as the active principle of turmeric, which is useful in clinical setting because of its safety profile. Depression is the most common psychiatric disorder carrying high burden in terms of treatment costs and is currently ranked fourth in terms of global disease burden by the World Health Organization. Antidepressant therapy includes drugs having plenty of side effects which counterbalance the therapeutic benefit. Thus, it is worthwhile to look for antidepressant from plants with proven advantage and favorable benefit to risk ratio. So, there are tremendous researches going on curcumin to reveal the mechanism of action for its antidepressant effect. The present review summarizes the possible mechanisms involved in its antidepressant effect.

INTRODUCTION

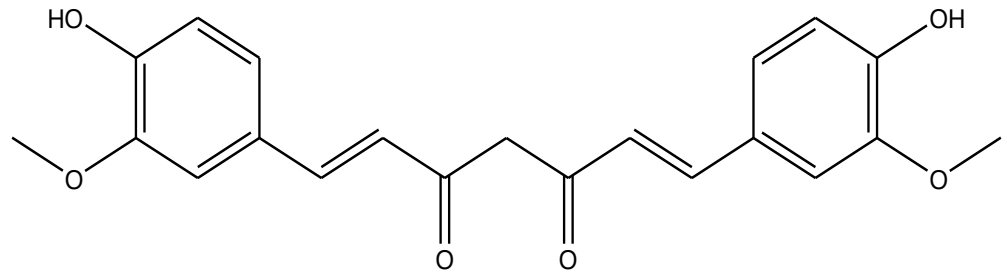
Curcumin, the principal curcuminoid present in the "Golden Herb"-Turmeric, is obtained from the dried as well as fresh rhizomes of *Curcuma longa* L. (Family: Zingiberaceae). Turmeric has been widely used for centuries in indigenous medicine for the treatment of a variety of inflammatory conditions and other diseases[1]. It has been used in the Indian and Chinese systems of medicines to treat wounds and sprains, and gastrointestinal, pulmonary, and liver disorders[2]. Curcumin was first isolated almost two centuries ago and its structure was determined in 1910[2]. Curcumin can exist in several tautomeric forms, including a 1,3-diketo form and two equivalent enol forms. The enol form is more energetically stable in the solid phase and in solution[3]. Many pharmacological studies have been conducted to describe multiple biological actions of curcumin. There has been an exponential increase in the trend of research involved in exploring the efficacy of curcumin in animal models of major depression during last few years. Curcumin does not produce any harmful effect on human body even at high dose of 1000-2000 mg/day.

Depression is a mental disorder characterized by episodes of all-encompassing low mood accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities. It is the most common psychiatric disorder and carries a high burden in terms of treatment costs, effect on families and carriers and loss of workplace productivity and is currently ranked fourth in terms of global disease burden by the World Health Organization (WHO)[4]. There are two types of mental depression, namely unipolar depression, in which mood swings are always in the same direction and is common (about 75% of cases) non familial , clearly associated with stressful life events and accompanied by symptoms of anxiety and agitation. The second type is bipolar depression (about 25% of cases) sometimes also called as endogenous depression, shows a familiar pattern, unrelated to external stresses and usually appears in early adult life, results in oscillating depression and mania over a period of a few weeks. Major theories responsible for depression are monoamine theory, biochemical theory, neuroendocrine mechanisms, neuroplasticity and trophic effects and electroconvulsive therapy[5]. Although a number of synthetic drugs are being used as the standard treatment for clinically depressed patients, they have adverse effects that can compromise the therapeutic treatment, these common adverse effect include dry mouth, fatigue, gastrointestinal or respiratory problems, anxiety, agitation, drowsiness and cardiac arrhythmias. These conditions create an opportunity for alternative treatment of depression by use of medicinal plants [6].

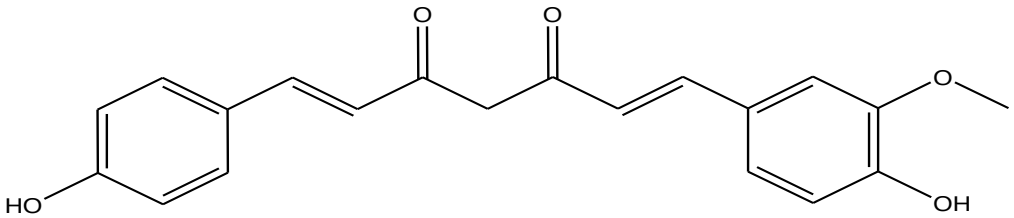
e-ISSN:2321-6182
p-ISSN:2347-2332

Curcumin

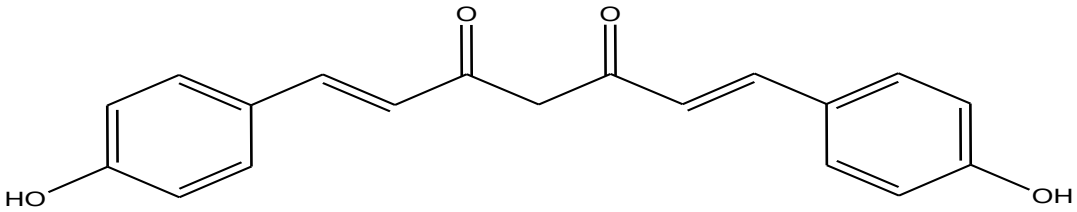
All Curcuminoids are often referred to simply as "curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl0-1,6-heptadiene-3,5-dione] even though turmeric contains a variety of different curcuminoids[7]. Commercial curcumin typically contains three major curcuminoids: curcumin (~77%), demethoxycurcumin (~17%) and bis-demethoxycurcumin (~3%). The bioactive degradation products may contribute to the pharmacological effects of curcumin[8].



Curcumin



Demethoxycurcumin



Bis-demethoxycurcumin

Pharmacological activity

Studies have demonstrated that curcumin possesses antioxidant[9], anti-inflammatory[1][10,11], anticarcinogenic[12], antimicrobial[13,14,15], hepatoprotective[14], hypoglycemic[16,17,18], thrombosuppressive[19] and antiarthritic[20] activities.

Pharmacokinetics

Over the years, a number of studies have tried addressing the pharmacokinetics of curcumin that is poorly absorbed from intestine after oral administration of different doses of 3H-curcumin in rats[21]. It was shown that oral consumption of curcumin in rats resulted in approximately 75% being excreted in the feces and only traces appeared in the urine[22], whereas intra-peritoneal (i.p) administration accounted for similar levels of fecal excretion of curcumin, with only 11% found in bile[23] suggesting poor absorption of curcumin from the intestine. Numerous studies have suggested presence of different metabolites of curcumin. It has been shown to be bio-transformed to dihydrocurcumin and tetrahydrocurcumin.Subsequently, these products are converted to monoglucuronide conjugates[24]. In another study, it was reported that the main biliary metabolites of curcumin are glucuronide conjugates of tetrahydrocurcumin (THC) and hexahydrocurcumin[23].

Safety Profile of Curcumin

Several clinical reports state that curcumin even at a high dose of 1000-2000 mg/day does not produce any harmful effects of human body. Thus, curcumin has the potential for the development of modern medicine for treatment of various diseases [25].

Potency of Curcumin in CNS Disorders

Curcumin has also demonstrated neuroprotective effects in animal models of Alzheimer's disease[26], Parkinson's disease[27], schizophrenia[28], drug addiction[29], Prion's infection[30], stroke[31], aluminum neurotoxicity[32], epilepsy[33], and diabetic neuropathy[34].

e-ISSN:2321-6182
p-ISSN:2347-2332

Curcumin as an Antidepressant

Epidemiological studies have revealed that people consuming curcumin in daily life have sharper brain functions and higher cognitive abilities. Curcumin possesses some interesting properties that justify its use in major depression. These include: [35]

- Curcumin is an inhibitor of monoamine oxidase (MAO) enzyme
- Curcumin modulates the level of various neurotransmitters
- Curcumin promotes hippocampal neurogenesis

Monoaminergic neurotransmitter system[36]

Curcumin would have an influence on depressive-like behaviors. Curcumin reversed the OB-induced behavioral abnormalities such as hyperactivity in the open field, as well as deficits in stepdown passive avoidance. In addition, OB-induced low levels of serotonin (5-HT), noradrenaline (NA), high 5-hydroxyindoleacetic acid (5-HIAA) and 4-dihydroxyphenylacetic acid (DOPAC) in the hippocampus were completely reversed by curcumin administration. A slight decrease in 5-HT, NA and dopamine (DA) levels found in the frontal cortex of OB rats was reversed by curcumin treatment. Thus, the antidepressant effects may be mediated by actions in the central monoaminergic neurotransmitter systems.

Curcumin reverses the effects of chronic stress on behavior, the HPA axis, BDNF expression and phosphorylation of CREB[37]

Curcumin may also alleviate stress-induced depressive-like behaviors and hypothalamic–pituitary–adrenal (HPA) axis dysfunction. Subjecting animals to the chronic stress several physiological effects, such as an abnormal adrenal gland weight to body weight (AG/B) ratio and increased thickness of the adrenal cortex as well as elevated serum corticosterone levels and reduced glucocorticoid receptor (GR) mRNA expression was observed which were reversed by curcumin administration (5 or 10 mg/kg, p.o.). In addition, the chronic stress procedure induced a down-regulation of brain-derived neurotrophic factor (BDNF) protein levels and reduced the ratio of phosphorylated cAMP response element-binding protein (pCREB) to CREB levels (pCREB/CREB) in the hippocampus and frontal cortex of stressed rats. Furthermore, these stress-induced decreases in BDNF and pCREB/CREB were also blocked by chronic curcumin administration. The results provide evidence that the behavioral effects of curcumin in chronically stressed animals may be related to their modulating effects on the HPA axis and neurotrophin factor expressions.

Serotonergic receptor-coupled AC-cAMP pathway[38]

Serotonergic receptors take their physiologic effects by affecting adenylyl cyclase (AC) catalytic activity and cyclic adenosine monophosphate (cAMP) concentration. AC-cAMP second messenger pathway has been suggested to play an important role in depression. Curcumin produced beneficial effects on the stressed rats by effectively improving CUMS-induced low sucrose consumption and reducing serum corticosterone levels in rats. Moreover, curcumin enhanced AC activity and cAMP levels in platelet and various brain regions, and upregulated mRNA expressions of AC subtypes AC 2, AC 8 and cAMP response element binding protein (CREB) in the hippocampus, cortex and hypothalamus of the CUMS rats. Curcumin also attenuated CUMS-induced reductions of 5-hydroxytryptamine (5-HT) levels and high expressions of central 5-HT1A/1B/7 receptors in rats. Thus, the antidepressant effect of curcumin might be attributed to its improvement of AC-cAMP pathway as well as CREB via suppressing central 5-HT1A/1B/7 receptors in the CUMS rats.

Glutamate release in nerve terminals from rat prefrontal cortex[39]

The effect of curcumin on endogenous glutamate release in nerve terminals of rat prefrontal cortex and the underlying mechanisms was investigated in this study. Curcumin inhibited evoked glutamate release from rat prefrontocortical synaptosomes by the suppression of presynaptic Ca^{+2} channels. Additionally, the inhibitory effect of curcumin on evoked glutamate release was completely abolished by the clinically effective antidepressant fluoxetine suggesting a common intracellular mechanism of curcumin and fluoxetine to inhibit glutamate release from rat prefrontal cortex nerve terminals.

Hippocampal BDNF[40]

The antidepressant potential of curcumin in a non-induced model of depression was investigated for involvement of brain derived neurotrophic factor (BDNF) in hippocampus. Adult male Wistar Kyoto (WKY) rats, a putative model of depression, were injected acu|y or chronically (10 d) with 50, 100, and 200 mg/kg curcumin and open field locomotor activity (OFLA) and forced swim test (FST) were measured 1 h after acute and 18–20 h after last chronic injection. Results showed a dose-dependent reduction of immobility in the FST by curcumin in both

acute and chronic studies, without any significant effect on OFLA. Chronic administration of curcumin resulted in a dose-dependent increase in hippocampal BDNF. This data provides evidence for an antidepressant-like effect of curcumin, possibly through increased neurotrophic activity in the WKY model of depression.

NMDA GluN2B receptors[41]

In this study attempts were made to investigate the effects of curcumin on depressive-like behavior with a focus upon the possible contribution of N-methyl-D-aspartate (NMDA) subtype glutamate receptors in this antidepressant-like effect of curcumin. Animals were pretreated with specific receptor antagonists as well as to a partial NMDA receptor agonist prior to administration of curcumin to observe the effects on depressive behavior as measured by immobility scores in the forced swim test. Pre-treatment with NMDA receptor antagonist, blocked the anti-immobility effect of curcumin, suggesting the involvement of the glutamate-NMDA receptors. Furthermore, pre-treatment with NMDA receptor agonist potentiated the anti-immobility effect of a sub-effective dose of curcumin in the forced swimming test. These results suggest that curcumin shows antidepressant-like effects in mice and the activation of GluN2B-containing NMDARs. Therefore, the antidepressant-like effect of curcumin in the forced swim test may be mediated, at least in part, by the glutamatergic system.

MAPK/ERK-dependent brain-derived neurotrophic factor expression in the amygdala of mice[42]

There is little information regarding the site and mechanisms of curcumin in promoting antidepressant effects. In one such study attempts were made to explore the mechanisms underlying the antidepressant-like action of curcumin by measuring the contents of brain derived neurotrophic factor (BDNF) in the amygdala of animal model of depression. The treatment with curcumin (40 mg/kg, i.p.) significantly reduced depressive-like behaviors of mice in the forced swim test. Chronic administration of curcumin increased BDNF protein levels in the amygdala and this enhancement was suppressed by pretreatment with the extracellular signal-regulated kinase (ERK) inhibitor. Additionally, the increased levels of ERK phosphoryation in the amygdala by curcumin were blocked by the ERK inhibitor, and inhibition of this kinase prevented the antidepressant effects of curcumin. All of these effects of curcumin were identical to that observed with the clinical antidepressant, fluoxetine. These results suggest that the antidepressant-like effects of curcumin in the forced swim test are mediated, at least in part, by an ERK-regulated increase of BDNF expression in the amygdala of mice.

Antidepressant-like effects of curcumin due to its anti-inflammatory action[43]

Inflammation may contribute to the pathophysiology of depression based on the current study aimed to explore the immunomodulatory effects of curcumin in an animal model of chronic mild stress (CMS). Rats were subjected to CMS to induce depressive-like behavior. The body weight, sucrose preference and locomotor activity were evaluated. Both RT-PCR and ELISA were used to determine the expression of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in the prefrontal cortex and hippocampus. Chronic treatment with curcumin significantly reversed the CMS-induced behavioral abnormalities (reduced sucrose preference and decreased locomotor activity) in stressed rats. Additionally, curcumin effectively inhibited cytokine gene expression at both the mRNA and the protein level and reduced the activation of NF-κB. The study revealed that curcumin exerted antidepressant-like effects in CMS rats, partially due to its anti-inflammatory aptitude.

CONCLUSION

Curcumin possesses wide-ranging of pharmacological properties. Many of these activities can be attributed to its potent antioxidant capacity. The effect of curcumin in CNS is more prominent. Curcumin has a potential for antidepressant action. Curcumin is known to modulate the neurotransmitter levels in brain and increases the neurotrophic factors enhancing neuronal survival. Tremendous researches are going on curcumin to find out the possible mechanism for its antidepressant action. Positive results obtained in experimental studies on curcumin as an antidepressant emphasizes its testing of efficacy in humans in order to advance the antidepressant therapy.

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