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Review Article

Curcumin as nature's neuroprotector; A multifunctional approach to mental wellness

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Abstract

Curcumin, the primary active component isolated from the herb turmeric (*Curcuma longa*), stands out with its possible disease-treating effects on the mental health issues, notably depression. Depression, a mental condition distinguished by the lasting depressed mood, anhedonia, or cognitive dysfunction, has been widely researched in relation to curcumin's drug effects. Curcumin has anti-inflammatory, antioxidant, neuroprotective, and neurotransmitter-modulating properties, which promise it to be a good candidate for mental health together with therapies being used by the doctors. A few trials that were carried out recently to see the medications in action on major depressive disorder patients. A vivid example was a randomized group trial done by Sanmukhani et al. (2014) that proved the use of curcumin (1000 mg/day) was equally the same as fluoxetine (20 mg/day) at reducing the symptoms of depression during six weeks. In a similar vein, Lopresti et al. conducted a double-blind, placebo-controlled study in 56 patients with MDD, where twice-daily use of curcumin (500 mg) showed a significant improvement in depressive symptoms compared to the control group. These findings have been backed up by meta-analyses of numerous trials which have demonstrated the complete efficiency of curcumin in a way similar to common antidepressants but with little or none of the adverse effects. The mechanisms through which curcumin is active encompass regulation of monoamine neurotransmitters (serotonin, as well as dopamine, and norepinephrine), boosting the synthesis of plasticity marker BDNF, the reduction of inflammatory substances and ROS production, and also the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. However, despite all these amazing findings, some problems such as low bioavailability have led to the development of more advanced methods (e.g., nanoparticles, piperine co-administration) to increase absorption and therapeutic efficacy. In summary, curcumin is expected to be a new way of treating depression in the future, however, a more comprehensive study with larger sections in the future is needed to clinch its clinical utility.

Keywords: Curcumin, Neuroprotective, Depression, Schizophrenia, Anti-inflammatory, Anxiety

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1. Introduction

Mental disorders are one of the most challenging public health issues as they have been consistently reported to be associated with billions of disability-adjusted life years lost worldwide. The global number of Disability-adjusted life-years (DALYs) cause by mental disorders increased from80.8 million (95% uncertainty interval (UI) 59.5–105.9) to 125.3 million (93.0–163.2), and the proportion of Disability-adjusted life-years in the world assigned to mental disorder increase from 3.1% to 4.9%.[1] curcumin is a bioactive molecules found in turmeric (Curcuma longa), has gaining popularity in the scientific community due to its potential therapeutic effects benefit for wide range health conditions including mental disorder such as known for its anti-inflammatory, antioxidant, and neuroprotective characteristics. curcumin has been studied extensively for its potential role in prevention and treatment mental health disorders such as depression, anxiety, and cognitive decline.[2] According to the World Health Organization, nearly 25% of people will experience mental or neurological disorders in their lifetime. Limitations and side effects of conventional treatments have led to an interest in the therapeutic potential of natural compounds in mental health.[3]

Curcumin is a non-flavonoid polyphenolic compound obtained from the root of the plant *Curcuma longa* (turmeric), belonging to family *Zingiberaceae*. It is commonly used in

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Indian and Chinese folk medicine for the treatment of rheumatism, inflammation, asthma, cancer, and wounds.[4]

The major component of turmeric (*Curcuma longa*) is curcumin, which has been utilized for several years in traditional medicine systems, especially those in Asia. Remais Meilong, aka Curcuma poteri, is a luminescent yellow tar compound that has received much attention in the last few years and has anti-inflammatory, antioxidant, and neuroprotective pharmacological properties. Concept of looking into the future for curcumin for mental disorders is based on its multiple mechanisms of action and promising results in pre-clinical and clinical studies. The present review intends to systematically analyze the existing evidence of (curcumin as a multitargeted spice component for treatment of diverse mental disorders in humans, elucidating its chemistry, pharmacology, therapeutic implications, and potential clinical relevance.[5]

Due to the Multidimensional nature of the biological, psychological and environmental factors involved in mental disorders, there is an increasing interest in using multifunctional, natural compounds such as curcumin for an integrative approach to mental health.[6]

Figure 1: Curcumin

2. Discussion

I. Chemistry and Pharmacology of Curcumin:

A. Chemical Structure and Properties:

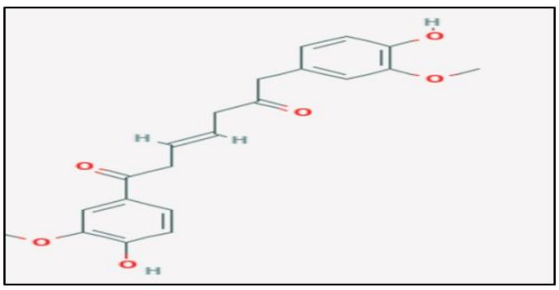

Figure 2: 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione

(1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a polyphenolic compound, and its chemical structure is c21H20o6 It is composed of two aromatic rings and a seven carbon chain, containing two α,β-unsaturated carbonyl moieties. Such a particular structure is likely to underlie the diverse biological activities of curcumin and its ability to interact with multiple cellular targets.[7]
Curcumin has several properties such as:

1. Low solubility in water
2. High lipophilicity
3. pH-depend stability (stable under acidific conditions).
4. There are strong capacities for chelation of metal ions.
5. Potent antioxidant activity due to its phenolic groups and β-diketone moiety.[8]

B. Absorption, Metabolism, and Bioavailability

In its free and non-conjugated forms, curcumin is poorly bioavailable although its therapeutic potential is promising. It is poorly absorbed and quickly metabolized for many reasons.[7]

1. Low aqueous solubility: The hydrophobic property of curcumin affects its solubility in the gastrointestinal fluid, and it also reduces the absorption of curcumin.[7]
2. Rapid metabolism: Curcumin is subject to extensive first-pass metabolism in both liver and intestine upon oral ingestion mainly via glucuronidation and sulfation.[9]
3. Instability at physiological pH: Curcumin in its natural state is the least stable at neutral to alkaline pH and may degrade in the intestinal environment.[10]
4. Rapid systemic clearance: Curcumin and its Subsequent metabolites undergo rapid clearance in the systemic circulation, thereby further restricting its bioavailability.[11]

Thus, improved bioavailability of curcumin has been achieved through different approaches such as:

1. Piperine-treated formulation, the bioenhancer that inhibits glucuronidation
2. Design of nanoparticle-based delivery systems
3. Formulation of liposomal formulations.
4. Administration of curcumin derivatives with modified pharmacokinetic characteristics

These strategies have been found to improve its absorption, improve its systemic availability, and consequently, its therapeutic effects.[12-14]

II. Pharmacological Effects of Curcumin:

1. Anti-inflammatory effects: In particular, curcumin is known to regulate several pathways involved in the initiation of inflammation such as the inhibition of NF-κB activation, suppression of the secretion of the pro-inflammatory cytokines like e.g. TNF-α, IL-1β, IL-6, and reducing the degradation of cyclooxygenase-2 (COX-2) protein.[15]
2. Antioxidant properties: Other than that, curcumin has also been known to function both as a strong

antioxidant and as a catalyst for the antioxidant enzymes like superoxide dismutase (SOD) and catalase.[16]

3. Neuroprotective actions: Curcumin has also been found to inhibit cell death. It can also stimulate neuronal growth, which are both processes related to an increase in the expression of the brain-derived neurotrophic factor (BDNF). Synaptic plasticity and neurogenesis are augmented as well.[17]
4. Modulation of neurotransmitter systems: In an atypical way, ------, curcumin can involve itself in the processes of metabolism and signalling of various neurotransmitters that are accounted for mental retardation such as serotonin, dopamine, and also glutamate.[18]
5. Epigenetic regulation: It has been found that curcumin alters the epigenetic mechanisms such as DNA methylation and histone modification which in long term contribute to the altering of the expression of genes along with neuroplasticity.[19]

III. Curcumin's Relationships and Effects on Mental Health:

A. Depression

Depression is a prevalent and burdensome mental disorder, the core symptoms of which include a low mood, anhedonia, cognitive and somatic manifestations. Preclinical and clinical studies suggested antidepressant effects of curcumin.[20]

1. Preclinical evidence: Animal studies revealed that curcumin possesses antidepressant-like activities in models of depression, such as the forced swim test and tail suspension test. These effects are similar to those of established antidepressant medications[21]
2. Clinical evidence: There have been several randomized controlled trials examining the efficacy of curcumin for treatment of depression.

1. In a meta-analysis of 6 clinical trials with 377 patients, curcumin significantly reduced depressive symptoms compared to placebo, and the effect was similar to some antidepressant medications.[22]
2. In a study of 60 subjects with major depressive disorder one group received curcumin (1000 mg/day) and the other group received fluoxetine (20 mg/day) and found that curcumin was at least as effective at reducing depressive symptoms over 6 weeks.[23]
3. In another trial, curcumin (500 mg twice daily) reliably improved depressive symptoms in patients diagnosed with major depression, and especially in those with atypical depression.[24]

2.1. Potential Mechanisms

The antidepressant effects of curcumin are believed to be mediated through multiple mechanisms:

1. It modulates monoamine neurotransmission (serotonin, norepinephrine, dopamine)
2. Increase BDNF formation for better neuroplasticity and neurogenesis
3. Decrease in inflammatory response and oxidative stress in the brain
4. Such very regulation of the hypothalamic-pituitary-adrenal (HPA) axis[25]

A. Anxiety Disorders

Anxiety disorders are a category of conditions that involve excessive fears, worries, and associated behaviors. Anxiolytic potential of curcumin has been demonstrated on animal models and human studies.

1. Preclinical evidence: In animal experiments, using curcumin have shown anxiolytic-like effects across different behavioral tests like the elevated plus maze and open field test. These effects are similar to those of some existing anxiolytic medication.[26]
2. Clinical evidence: Clinical studies on curcumin's effects on anxiety disorders are few and far between, but a few positive results have been reported:

1. A multicentre, randomized, double-blind, placebo-controlled clinical trial with 30 obese patients showed that curcumin supplementation (1 g/d for 30 d) significantly decreased anxiety scores as compared to placebo.[27]
2. A separate study in patients with major depression found that curcumin supplementation. Higher levels of depressive symptoms at the same time explaining improvements in anxiety symptoms.[28]

2.3. Proposed mechanisms

The application of curcumin's anxiolytic effect can be found at three levels

1. Affecting the state of neurotransmitters such as GABA and 5 HT.
2. It has an antioxidant response
3. Regulating the HPA axis and stress reactions
4. Improving synaptic plasticity—a healthy and flexible brain[29]

3. A Bipolar Disorder

Bipolar disorder is a complex mood disorder characterized by alternating episodes of mania or hypomania with depression. Little research has been carried on the effects of curcumin in bipolar disorder, but there is some evidence that it may have certain kinds of influence and prove beneficial.[30]

1. Preclinical evidence: Curcumin has been demonstrated to have mood-stabilizing properties in rodent models of bipolar disorder; animal studies showed that escalate both manic-like and depressive symptoms.[31]
2. Clinical evidence. Only limited clinical research on curcumin in bipolar disorder exists, but a few studies have yielded promising results.

3. In patients with bipolar depression, a small open-label investigation demonstrated that the adjunctive use of curcumin (1-2 g/day for 3-6 months) led to improvements in depressive symptoms and general functioning
4. Another case reported a significant improvement in mood symptoms following curcumin supplementation for a rapid-cycling bipolar disorder (RBD) patient.[32-33]

3.1.. Potential mechanisms

Curcumin repurposing in bipolar disorder is believed to be related to improving neurotransirritation of ion systems involved in mood regulation Neuroplastic properties. Protection against neuropathy and promotion new growth of neurones anti-inflammatory effects and antioxidative activities. Regulating mitochondrial function as well as energy metabolism.[34]

3.2. Schizophrenia

Schizophrenia is a serious mental illness that is marked by disturbances in thinking, perception, and behaviour. Research on the effects of curcumin in schizophrenia is not extensive, although some evidence suggests possible gains — especially in handling cognitive symptoms and negative symptoms.[35]

3.1.1. Preclinical Evidence

The antipsychotic-like effects of curcumin and its ability to improve cognitive deficits in rodent models of schizophrenia have been demonstrated in animal studies.[36]
2. Clinical Medical Research Evidence:

Curcumin in schizophrenia clinical studies are limited, but some have found interesting outcomes:

1. A randomized blind trial in 66 patients with chronic schizophrenia found that adjunctive curcumin (3 g/day for 8 weeks) significantly improved cognitive function and negative symptoms compared to placebo.
2. Yet another study found that curcumin supplementation (360 mg/day for 8 weeks) was able to reduce oxidative stress markers among schizophrenia patients in some measure.[37-38]

3.2. Proposed mechanism

Curcumin in the treatment of schizophrenia potential benefit may be due to the following reasons
1. Modulating dopaminergic and glutamatergic transmission.
2. Neuroprotective effects, enhancement of neuroplasticity.
3. Anti-inflammatory, antioxidant actions.
4. Regulation of neuronal mitochondrial function.[39]

4. The Mechanisms of Curcumin's Effect

Curcumin has had good therapeutic results in a wide range of mental disorders largely because it's multiple effects. These involve large numbers of cells and molecular pathways responsible for the mechanism behind some these diseases.
A. Anti-inflammatory Mechanisms:
Chronic inflammation has been increasingly recognized as a contributing factor in the pathogenesis of various mental disorders. Curcumin exhibits potent anti-inflammatory effects through several mechanisms.[40]

1. NF-κB inhibition: Curcumin suppresses the activation of nuclear factor kappa B (NF-κB), a key transcription factor involved in the regulation of inflammatory genes. This inhibition leads to decreased production of pro-inflammatory cytokines and enzymes.[41]
2. Cytokine modulation: Also the biosynthetic production of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-a), interleukin-1 beta (IL-1b), and interleukin-6 (IL-6) are decreased along with their secretion. Anti-inflammatory cytokines such as 0 produce an increase.[42]
3. cox-2 and LOX inhibitor: curcumin halts the action of lipoxygenase (LOX) enzymes and cyclooxygenase-2(COX-2) that are involved in the synthesizing pro-inflammatory eicosanoids.[43]
4. Modulation of microglial: activation Curcumin has been found to inhibit microglial activation in the brain and thereby lower the release of Il-1beta (inflammatory mediators).[44]

4.1 Antioxidant Mechanisms

Oxidative stress is an important factor in the pathogenesis of mental diseases. The anti-oxidant properties of curcumin are main factors that make its neuroprotective effect a reality, operating via various routes:

1. Curcumin captures free radicals Curcumin can absorb direct hull.[45]
2. Antioxidant enzyme induction: Curcumin improves the expression and activity of antioxidant enzymes such as superoxide dismutase (SOD) which is also referred to as SOD1 or SOD2 for its chances catalase and glutathione peroxidase (GPx).

1. Free radical scavenging: Curcumin acts as a direct scavenger of reactive oxygen species (ROS) and reactive nitrogen species (RNS), neutralizing harmful free radicals.
2. Antioxidant enzyme induction: Curcumin enhances the expression and activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx).
3. Nrf2 activates: curcumin activate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathways, which controls the expression of several antioxidant and detoxifying enzymes.
4. Curcumin can chelate metal ions such as iron and copper those are involved in the generation of reactive oxygen species, 4 Metal.[46]

4.2. Neuroprotective Mechanisms

Curcumin has neuroprotective effects that may benefit its potential in mental disorders.

1. BDNF upregulation Curcumin: Increasing the expression of brain derived neurotrophic factor (BDNF), a key protein related to neuronal survival, synaptic plasticity and neurogenesis.[47]
2. Neurogenesis promotion: There are studies that curcumin is able to increase the formation of new neurons in the adult hippocampus, which may explain some of its antidepressant and cognitive enhancing effects.[48]
3. Synaptic plasticity enhancement: It has been found that curcumin modulates synaptic plasticity through altering the expression of synaptic proteins and neurotransmitter receptors.[49]
4. Mitochondrial function regulation: Curcumin improves mitochondrial function and energy metabolism in neurons and this is important for neuronal health and function.[50]

4.3. Modulation of Neurotransmitters and Hormone

Curcumin's effect on mental health is also through influence on various neurotransmitter systems and neuroendocrine pathways, such as modulation of neurotransmitters and hormones.

1. Serotonin: Curcumin has been shown to influence serotonin receptor expression and function as well as serotonin metabolism, indicating that curcumin can modulate serotonergic neurotransmission.
2. Dopamine: has been shown that curcumin can affect dopaminergic signalling and this may be responsible for its possible mood-enhancing and schizophrenia-modulating properties
3. Glutamate: Curcumin has been found to affect glutamatergic neurotransmission and protect against excitotoxicity invoked by glutamate
4. GABA: Some studies suggest curcumin to enhance the GABAergic signalling at the basis of its anxiolytic effects.
5. HPA axis regulation: The ability of curcumin to modulate the hypothalamic-pituitary-adrenal axis and cortisol levels within stress responses has been shown to be effective.[51-52]

5. Clinical Evidence and Trials

Ever-rising interest in curcumin's potential therapeutic promise for mental health and, hence, the copious clinical trials enabled some understanding into this issue. This section highlights the human studies that are most relevant for evaluating the benefits of curcumin in treating various mental health problems.

5.1. Depression

A number of clinical trials have studied the efficacy of curcumin for patients with major depressive disorder:

1. A randomized, controlled trial by Sanmukhani et al. (2014) was conducted to compare curcumin (1000 mg/day) with fluoxetine (20 mg/day) and their respective combinations in 60 patients diagnosed with major depression. Curcumin was found as effective as fluoxetine in alleviating depressive symptoms during the 6 weeks of treatment.[53]
2. A randomized, double-blind, placebo-controlled study by Lopresti et al. reported that twice-daily curcumin (500 mg) was more effective in treating depressive symptoms in 56 subjects suffering from major depressive disorder.[54]

6. Conclusion

Curcumin is a polyphenolic compound derived from turmeric (Curcuma longa), is a potent therapeutic agent for numerous mental functional benefits because of its diverse array of pharmacological properties. These principles of curcumin therapy in patients with the above are superior in preventive defense—such as fast inflammatory response, cell resuscitation through the antioxidant effect, metal-recycling mechanism and fully balanced neurotransmitter functions. The experiments with animals have proved that cholestrolin intake leads to a several times increase of the production of serotonin which, in its turn, leads to the reliefs of depression and anxious states.

In the case of some clinical trials, significant amount and quality of studies showed curcumin to be effective especially for depression but also possibly for mania or bipolar disorder. Under normal conditions, patients with low serotonin levels, which can be responsible for mood swings, are prescribed antidepressants to cope with their illness. Analysed comprising two groups of people, not yet diagnosed with depression, of which the first group was consuming curcumin (1%–5%) while the second one was not, the first group was shown to display a considerable reduction in the development of depressive symptoms.

On the other hand, curcumin's lower absorption in the organism is a major weakness, but numerous aids have been developed to tackle this problem, for example, the addition of piperine to the former compounds, the nanoparticle-shape design. By doing so, these studies had the possibility to decrease in vitro activity besides increasing encapsulation of curcumin together with diffusion of the compounds across the outer membrane.

Curcumin has shown plenty of potential in the prevention and cure of mental illness through the form of the natural routes, although it is supported only by the data to a lesser extent. Therefore, future multistep clinical research trials need to be supported by these three aspects aimed at confirming them: their efficacy, safety, and the ideal dose necessary for treatment. In sum, the former is curcumin, whose natural factor treatment makes it bio-friendly—hence, it is a promising potential mainstream therapeutic agent.

7. Source of Funding

None.

8. Conflict of Interest

None.

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