


Role of Curcumin in the Management of Schizophrenia: A Narrative Review

Damodharan Dinakaran¹ , Vanteemar S. Sreeraj¹ and Ganesan Venkatasubramanian¹

ABSTRACT

Nutraceutical agents and food supplements are commonly used as treatment adjuncts in neuropsychiatric disorders. Curcumin, a bioactive agent obtained from the rhizome of *Curcuma longa*, with its antioxidant and anti-inflammatory properties, has gained much research attention in the last few decades. In this narrative review, we intend to summarize the evidence available for curcumin as an add-on agent in the management of schizophrenia. We searched PubMed/EBSCO for both human and animal trials utilizing curcumin in the management of schizophrenia. We obtained ten articles (five preclinical and five clinical) from the focused literature search. Clinical research utilizing curcumin in schizophrenia is limited to negative and cognitive symptoms. Available preclinical studies suggest curcumin's utility in ameliorating extrapyramidal and metabolic side effects when given as an adjunct with antipsychotics. Curcumin, as an add-on agent, appears promising to improve the negative and cognitive symptoms of schizophrenia. Notably, curcumin was tolerable and safe in all the randomized human clinical trials. The poor oral bioavailability is, however, a limiting factor in its widespread use.

Key words: curcumin, schizophrenia, psychosis, cognition, adverse effects, antipsychotics

Nutraceuticals and food supplements are commonly used as either stand-alone treatments or as add-on agents with ongoing psychopharmacological management. Different supplementary food agents tried include S-Adenosyl Methionine, l-methyl folate, omega-3-fatty acids, and vitamins like B complex, D, and E.^{1,2} The indications for such use include augmenting drugs for symptom reduction, reducing side effects, and cognitive enhancement. Curcumin is diferuloylmethane, an active ingredient present in the Indian spice turmeric.³ Turmeric is widely used in the cuisines of India and other Asian countries.^{3,4} Curcumin is a nonflavonoid polyphenolic molecule derived from *Curcuma longa*. In traditional medicine, turmeric is commonly used as an anti-inflammatory and antiseptic agent.^{2,4} Its antioxidant property and low toxicity potential are utilized in physical disorders like rheumatoid arthritis, cardiovascular disorders, asthma, and neuropsychiatric disorders like Alzheimer's dementia and Parkinsonism.³⁻⁸ There are no available reports of toxicity in humans following long-standing use of curcumin.² Despite its cost-effectiveness

and favorable tolerability profile, poor absorption and high first-pass metabolism, with overall low bioavailability, have hindered its clinical utility.^{4,6}

Schizophrenia is a severe mental disorder with disturbances in thought, emotion, perception, and behavior.⁹ Genetic, early environmental, and psychological and social factors are conceptualized to play an important role in the development and progression of schizophrenia. Oxidative stress deregulation and related neuroplasticity changes are key contributors in the etiopathogenesis of this neurodevelopmental disorder.^{10,11} The life expectancy of schizophrenia patients is less by 10–15 years in comparison with the general population.¹² Increased substance use, cardiovascular morbidity, sedentary lifestyle, side effects of psychotropic drugs, and suicides contribute to this early mortality.^{13,14} Available antipsychotic drugs are often criticized for targeting preferentially the positive symptoms of schizophrenia, while the functional recovery depends on the improvement in negative and cognitive symptom domains as well.^{15,16} Repurposing the available drugs and utilizing the

¹Dept. of Psychiatry, National Institute of Mental Health And Neurosciences (NIMHANS), Bengaluru, Karnataka, India.

HOW TO CITE THIS ARTICLE: Dinakaran D, Sreeraj VS. and Venkatasubramanian G. The Role of Curcumin in the Management of Schizophrenia: A Narrative Review. *Indian J Psychol Med.* 2022;44(2):107–113.

Address for correspondence: Damodharan Dinakaran, Dept. of Psychiatry, National Institute of Mental Health And Neurosciences (NIMHANS), Hosur Road, Bengaluru 560029, Karnataka, India. E-mail: dina.nimhans@gmail.com

Submitted: 10 Mar. 2021
Accepted: 30 June. 2021
Published Online: 13 Sep. 2021



Copyright © The Author(s) 2021

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits non-Commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

ACCESS THIS ARTICLE ONLINE
Website: journals.sagepub.com/home/szj
DOI: 10.1177/02537176211033331

emerging adjunctive nutraceuticals may be beneficial in better understanding the pathophysiology of this complex disorder as well as in providing potential safe and tolerable treatment options.^{17,18} Such novel pharmacological options could be utilized to reduce the burden of negative and cognitive symptoms of schizophrenia.¹⁹

The role of curcumin in the management of depression and bipolar disorder has been proposed recently.²⁰ Curcumin as an add-on to antidepressant drugs has been convincingly shown to reduce depressive symptoms, compared to placebo add-on. A recent meta-analysis supported the utility of adjunctive curcumin in the management of depression and anxiety disorders.²¹ Notably, curcumin was tolerable and safe in all those randomized human clinical trials. In this narrative review, we aim to discuss the mechanism of action of curcumin, followed by a review of available evidence and its implications for clinical use of curcumin in schizophrenia management.

Mechanism of Action

Oxidative-stress-dependent pathological changes are postulated to underlie the progression of neuropsychiatric disorders.²² The proposed pharmacological actions of curcumin include antioxidant, anti-inflammatory, antimutagenic, antibacterial, antiprotozoal, antiobesity, antidiabetic, hepatoprotective, and procognitive properties.^{3,4,23,24} Curcumin inhibits the production of reactive oxygen species and reduces the production of inflammatory cytokines by inhibiting cyclooxygenase and lipoxygenase enzymes.²⁵ Curcumin is a lipophilic compound with the ability to penetrate the blood-brain barrier and exert its antioxidant, neuroprotective activity.²⁶ Generally, an oral dose of more than 2 g/day is reported to intensify curcumin's antioxidant effects.^{27,28} Curcumin reduces the turnover of monoamines such as dopamine, serotonin, and norepinephrine and thereby prevents the accumulation of free radicals.^{23,25} Curcumin is also implicated as a free radicals scavenger that removes superoxide anion, hydroxyl, and singlet oxygen radicals. Curcumin upregulates the expression of genes related to the enzyme glutathione synthetase, ultimately leading to increased glutathione levels in the

astrocytes and neurons. This enables better scavenging of the free radicals in the neuronal milieu.²⁹ Curcumin improves neuroplasticity and hippocampal neurogenesis through the enhancement of brain-derived neurotrophic factor (BDNF).^{30,31} Curcumin also improves the synthesis of docosahexaenoic acid (DHEA) through the activation of the enzymes involved. In animal models of depression, upregulation of DHEA levels is proposed to be neuroprotective.³²

Anti-obesity effects of curcumin are postulated to be secondary to the suppression of nuclear factor kappa B (NFkB) and suppression of tumor necrosis factor (TNF) expression.^{5,8,33} Curcumin regulates cellular enzymes like protein kinase C (PKC) and inhibits apoptosis.⁵ In animal models of schizophrenia, curcumin protects against mitochondrial dysfunction by removing free radicals.³⁴ Inflammatory insults and oxidative stress since obstetric period cumulatively modulate the expression of neuroplasticity genes and ultimately result in "neuroprogression" of psychiatric disorders like schizophrenia.^{35,36} Deoxy-ribonucleic acid (DNA) methylation secondary to inflammatory insults silences gene expression and impairs neuroplasticity. Given its epigenetic regulatory properties, curcumin is postulated to reduce DNA methylation, histone deacetylation, and associated gene expression deficits.^{35,37-39} Importantly, curcumin inhibits monoamine oxidase A and B (MAO-A and MAO-B) enzymes and shows potent antidepressant action.⁴⁰ Also, in animal models, it reduces the expression of dopamine D1 receptor in the cerebellum and thereby probably reduces antipsychotic-induced depressive features.⁴¹

To summarize, the possible mechanisms of curcumin's action postulated to be useful in neuropsychiatric disorders include (but not limited to) regulation of oxidative stress and inflammation, reduction of monoaminergic and hypothalamo-pituitary-adrenal axis disturbances, addressing mitochondrial dysfunction, and hindering neuroprogression.⁷ The current understanding of the etiopathogenesis of schizophrenia suggests all the above-mentioned mechanisms to be involved in the neuroprogression of the disorder.⁴²⁻⁴⁶ Hence, the role of adjunctive curcumin in the

management of schizophrenia appears as a promising area of interest.

Methodology

The authors (DD and VS) searched PubMed and EBSCO independently with the following search terms (as on April 2021): "Curcumin" "AND" "Schizophrenia," "Psychosis," "Delusional disorder," "Catatonia," "Cognition," "adverse effects," and "antipsychotic." The authors identified 17 manuscripts. Both preclinical (animal studies) and clinical research studies that used curcumin in managing both the symptoms and antipsychotic-related side effects were included for this narrative review. The search was neither restricted to languages nor time. After removing review articles, commentaries or opinion letters, and manuscripts not relevant to psychosis, the total unique manuscripts identified for the final review were "10" (5-human clinical; 5-animal models). The selected studies are reviewed below and summarized in **Tables 1** and **2**. The outcome of the literature review is outlined in **Figure 1**.

Curcumin's Role in the Management of Schizophrenia

An exploratory proof-of-concept study examined the effects of curcumin combined with piperine (from black pepper extract—used to improve the bioavailability of curcumin) as an add-on to the ongoing antipsychotic treatment. Fifteen chronic schizophrenia patients were randomized to receive 1 g vs 4 g of add-on curcumin and piperine compounds.⁴⁷ At the end of 16 weeks, both groups showed significant improvements in total scores and general psychopathology subscale of the Positive and Negative Syndrome Scale (PANSS). Both the doses were tolerated well without much adverse effects.⁴⁷

Another double-blind, randomized controlled trial examined the procognitive effects of curcumin (versus placebo) in stable, medicated schizophrenia patients. Despite a significant increase in the serum BDNF levels, 360 mg/day of a nanoparticle-based curcumin (Theracumin) preparation failed to improve cognitive performance or clinical variables at eight weeks. However, the study

TABLE 1.

Clinical Studies on Add-on Curcumin in Schizophrenia

Author Year Study Site	Study Design Sample (n)	Study Population	Curcumin Used Dose Duration	Domain Studied	Remarks
Chiu et al. ⁴⁷ 2019 USA	Exploratory Pre/ post-treatment group n = 15	Patients with DSM-IV Schizophrenia with persistent negative symptoms (SANS > 20)	Curcumin+Piperine 1 g/day vs 4 g/day 16 weeks	Positive, negative, and cognitive symptoms	Both groups significantly improved in the total PANSS scores. No adverse effects reported.
Wynn et al. ⁴⁸ 2018 USA	DB-RCT Placebo-controlled n = 36	Patients with DSM-5 Schizophrenia on stable medications, outpatients	Nanocurcumin 360 mg/ day vs placebo Eight weeks	Serum BDNF levels and cognitive symptoms	Curcumin group had significantly increased BDNF levels but no difference in cognitive and other clinical symptoms.
Kucukgoncu et al. ⁴⁹ 2019 USA	DB-RCT Placebo controlled, Pilot n = 12	Patients with DSM-5 Schizophrenia on stable medications, outpatients	Nanocurcumin 180 mg/ day vs placebo Eight weeks	Cognition and inflammatory markers	Add-on curcumin significantly improved working memory and reduced IL-6 levels.
Miodownik et al. ⁵⁰ 2019 Israel	DB-RCT Placebo controlled n = 38	Patients with DSM-IV Schizophrenia with persistent negative symptoms (SANS > 30)	Curcumin 3 g/day vs placebo 24 weeks	Positive, negative, and depressive symptoms	Significant improvement noted in total and negative subscale scores in PANSS at six months. No adverse effects reported.
Hosseinasab et al. ⁵¹ 2021 Iran	DB-RCT Placebo controlled n = 56	Patients with DSM-5 Schizophrenia with predominant negative symptoms	Nanocurcumin 160 mg/ day vs placebo 16 weeks	Negative symptoms	Negative symptoms and general psychopathology scores improved significantly in the study group. No adverse effects reported.

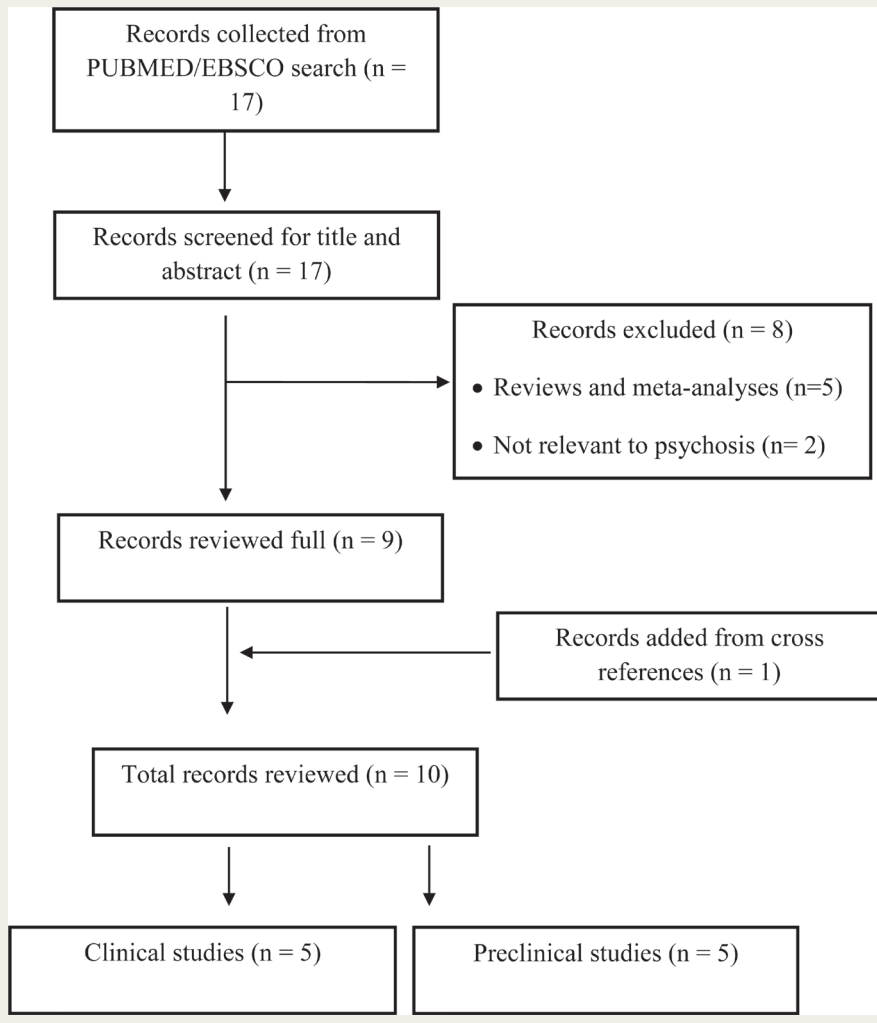
BDNF: brain-derived neurotropic factor, DB-RCT: double blind randomized controlled trial, DSM: Diagnostic and Statistic Manual, IL-6: interleukin-6, PANSS: positive and negative syndrome scale, SANS: Scale for the Assessment of Negative Symptoms.

TABLE 2.

Preclinical Studies on Add-on Curcumin in Schizophrenia

Author/Year	Study Characteristics	Main Outcomes
Bishnoi et al. ²³ 2008	Male Wistar rats were divided into five groups and given a control, haloperidol (1 mg/kg), curcumin (25 or 50 mg/kg) in different combinations for 21 days. Rats were evaluated for orofacial dyskinesia, stereotyped movements, and elevated plus maze test. Free radical scavenging enzyme assays and neurotransmitters estimation were done.	In a dose-dependent fashion (25 or 50 mg), pretreatment with curcumin reduced the haloperidol-induced extrapyramidal movements. Also, curcumin prevented the increase in lipid peroxidation in both cortical and subcortical regions. Changes in dopamine, serotonin, and norepinephrine levels were also prevented by adding curcumin to haloperidol.
Bishnoi et al. ²⁷ 2011	Male Wistar rats were divided into nine groups and given a control, haloperidol (5 mg/kg), clozapine (10 mg/kg), curcumin (25 or 50 mg/kg) with or without piperine (2.5 mg/kg) in different combinations for 21 days. Behavioral assessment for orofacial dyskinesias and locomotor activity levels, inflammatory mediators assessments, and neurotransmitter quantification were done.	In a dose-dependent fashion, curcumin pretreatment reduced the haloperidol-induced orofacial dyskinesias. Curcumin administration also reduced the surge in inflammatory markers associated with haloperidol use. Changes in dopamine, serotonin, and norepinephrine levels were also prevented by adding curcumin to haloperidol. Clozapine use was associated with relatively less lipid peroxidation.
Sookram et al. ⁵⁹ 2011	Male Sprague Dawley rats were divided into four groups and given a control base, haloperidol (2 mg/kg), and curcumin (200 mg/kg), in different combinations for 14 days. Abnormal orofacial movements and levels of locomotor activity were observed.	Concurrent curcumin with haloperidol treatment was observed to reduce abnormal orofacial movements by day 14. However, such co-administration did not prevent the haloperidol-induced hypolocomotion. Striatal tissue evaluation revealed curcumin upregulated the Bcl-XL levels (anti-apoptotic protein)
Parasuraman et al. ²⁸ 2017	Female Sprague Dawley rats were divided into six groups and given a control base, betahistine (10 mg/kg), olanzapine (4 mg/kg), and add-on curcumin (50 or 100 or 200 mg/kg) for 28 days. Weight gain was checked weekly. Behavioral and neurochemical assessments were done.	Add-on curcumin 100 mg and 200 mg/kg dose groups showed significant inhibition of olanzapine-induced weight gain. Add-on curcumin 200 mg/day dose group additionally reduced the olanzapine-induced dyslipidemia as well. Betahistine group too significantly inhibited the weight gain.
Liu et al. ⁵⁶ 2017	Male Sprague Dawley rats were divided into four groups and given a control base, clozapine (15 mg/kg), and curcumin (80 mg/kg), for 28 days. Serum and hepatic lipid levels were measured.	Serum glucose was unchanged in both clozapine alone and clozapine with curcumin groups. Curcumin significantly reduced the clozapine-induced dyslipidemic changes in both serum and hepatic tissue.

FIGURE 1.

Outcome of the Literature Review

and cardiovascular morbidity.⁵² Clozapine is the ultimate treatment option in resistant schizophrenia.⁵³ Though increased appetite, food intake, and sedentary lifestyle may contribute to dyslipidemia, clozapine may affect lipid metabolism through other peripheral mechanisms as well.⁵⁴ Adenosine monophosphate-activated pro-tein kinase (AMPK) is a key regulator in hepatic energy and lipid metabolism. Clozapine and other antipsychotics suppress AMPK activity, thereby ultimately leading to dyslipidemia.⁵⁵ Curcumin, on the other hand, by facilitating AMPK activity, reduces lipogenesis. Recent evidence from animal studies suggests that curcumin mitigated clozapine-induced dyslipidemic changes through AMPK activation⁵⁶ and olanzapine-induced weight gain and dyslipidemia.²⁸ Curcumin as an add-on with antipsychotics appears a promising avenue to be explored to reduce lipid abnormalities.

Management of Extrapyramidal Adverse Effects

The imbalance between production and detoxification of free radicals putatively contributes to the development of antipsychotic-associated tardive extrapyramidal syndromes.^{57,58} Animal studies suggested that curcumin pretreatment protected haloperidol-exposed rats from developing tardive extrapyramidal movements.²³ Curcumin prevented the antipsychotic-associated increase in lipid peroxidation and reduction in levels of antioxidant enzymes such as catalase, superoxide dismutase, and glutathione.²³ Chronic administration of antipsychotics reduced the levels of monoamines such as dopamine, serotonin, and norepinephrine. Simultaneously, antipsychotics also increased oxidative stress parameters, TNF-alpha levels, caspase-3 activity, and NFkB activity in the striatal region. In animal models, pretreatment with curcumin (25–50 mg/kg—intraperitoneal) attenuated the negative oxidative effects of clozapine and haloperidol administration and prevented tardive movements.²⁷ Clozapine, however, produced less oxidative stress compared to haloperidol.²⁷ This protective effect of curcumin is also attributed to its antiapoptotic property. Concurrent curcumin administration

was underpowered, with a small sample size.⁴⁸ Another pilot study examined a lower dose of add-on curcumin (180 mg/day) in chronic stable schizophrenia patients. Curcumin significantly reduced pro-inflammatory cytokine (IL-6) levels and improved working memory performance at 12 weeks.⁴⁹

Curcumin's effects on positive, negative, and depressive symptoms were explored, as an add-on to ongoing antipsychotic treatment, in a double-blind, randomized controlled trial.⁵⁰ At the end of six months, compared to placebo, curcumin significantly reduced negative symptoms and total scores on PANSS. Curcumin dose (3 g/day) was tolerated well by all the patients.

A double-blind randomized placebo-controlled study observed the effects of nanocurcumin soft gel capsules (160 mg/day) given for 16 weeks as an

add-on to the ongoing antipsychotic drug regimen on the negative symptoms of chronic stable schizophrenia patients.⁵¹ The nanocurcumin group showed significant improvements in negative symptoms, positive symptoms, general psychopathology scores, and total PANSS scores. Importantly, there were no significant differences in adverse effects between the groups, and none of the participants left the study citing adverse events.⁵¹

Preclinical Studies

Management of Metabolic Adverse Effects

Metabolic disturbances are common even in drug naïve schizophrenia. Treatment with second-generation antipsychotics further accentuates lipid derangements

with haloperidol is shown to upregulate the antiapoptotic protein Bcl-XL in the striatal region, thereby reducing apoptosis.⁵⁹

It is important to note that human clinical studies and translation of such evidence in managing several antipsychotic-related adverse effects are still pending. However, adjunctive curcumin appears a potential option in the management of antipsychotic-induced metabolic and extrapyramidal side effects.

Discussion

Curcumin's antioxidant, anti-inflammatory, and procognitive properties appear to be useful in managing neuropsychiatric disorders, especially schizophrenia.⁷ Curcumin's effects on monoamines turnover, monoamine oxidase enzyme inhibition, neurosteroid modulation, and upregulation of key neuroplastic markers like BDNF promise to be beneficial in hindering the detrimental neuroprogression in schizophrenia.^{32,49} Preliminary evidence for curcumin's role in schizophrenia was suggested by the exploratory study by Chiu et al.,⁴⁷ where participants in both groups (1 g vs 4 g) showed significant improvement in total PANSS scores. Further studies demonstrated its efficacy in reducing inflammatory markers and improving neuroplasticity markers and cognition in schizophrenia.^{48,49} Importantly, two double-blind, placebo-controlled trials reported add-on curcumin's efficacy in reducing the negative symptoms of schizophrenia.^{50,51}

Four out of five clinical studies reviewed utilized double-blind, randomized controlled designs with active placebo arms. One preliminary study utilized pre-post design in the same treatment group. All five studies recruited patients who were on stable antipsychotic medications. Three studies recruited patients with predominantly negative symptoms. The reviewed studies differed in duration of add-on curcumin treatment (8–24 weeks). Doses (160 mg/day–4 g/day) and preparations of curcumin differed across the studies. Nanocurcumin capsules were used in three studies.^{48,49,51} One study used a combination of curcumin and piperine.⁴⁷ All the doses were tolerated well, and none of the participants withdrew from these studies owing to intolerable

adverse effects. Reportedly, three other clinical trials exploring the potential use of curcumin in schizophrenia are underway.⁴

Further, preclinical studies support curcumin's role in ameliorating the metabolic side effects of antipsychotics such as olanzapine²⁸ and clozapine.⁵⁶ Such positive metabolic changes are postulated to be secondary to the regulation of hepatic energy and lipid metabolism through AMPK activity.⁵⁶ Also, pretreatment with curcumin prevented the development of tardive extrapyramidal syndromes. In both haloperidol and clozapine exposed rats, pretreatment with curcumin successfully prevented the development of tardive orofacial movements.^{23,27,59} Curcumin's antioxidant, free radical scavenging, and antiapoptotic properties are postulated to underlie this preventive mechanism.⁵⁹

To summarize, the evidence regarding curcumin's efficacy in reducing the positive symptoms of schizophrenia is limited. But it has the potential to ameliorate negative symptoms and cognitive deficits. Preclinical studies also reported curcumin's beneficial effects in preventing and reducing extrapyramidal and metabolic side effects.

Future Directions

Clinical trials evaluating curcumin's efficacy against specific domains of psychopathology such as positive, negative, and cognitive symptoms are the need of the hour. Efforts to overcome the pharmacokinetic limitations of the compound are underway. Curcumin dose range, acceptability, and safety of the formulations are to be established for each indication.

Conclusion

Preclinical and clinical trials reported curcumin's potential role in the management of schizophrenia. Clinical research utilizing curcumin in schizophrenia is limited to negative and cognitive symptoms. Preclinical studies reported its utility in ameliorating extrapyramidal and metabolic side effects when given adjunct with antipsychotics. The poor oral bioavailability is a limiting factor in its widespread use. Newer drug delivery models based on nanoparticles, phospholipids, and liposomes appear promising to improve the bioavailability.

Acknowledgments

GV acknowledges the support of Department of Biotechnology (DBT)—Wellcome Trust India Alliance (IA/CRC/19/1/610005) and Department of Biotechnology, Government of India (BT/HRD-NBA-NWB/38/2019-20(6)).

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Damodharan Dinakaran  <https://orcid.org/0000-0002-7359-8168>

References

- Andrade C. A Critical examination of studies on curcumin for depression. *J Clin Psychiatry* 2014; 75. DOI: 10.4088/JCP.14f09489.
- Bhat A, Mahalakshmi AM, Ray B, et al. Benefits of curcumin in brain disorders. *Biofactors* 2019; 45. DOI: 10.1002/biof.1533.
- Aggarwal BB and Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *The Int J of Biochem Cell Biol* 2009; 41: 40–59.
- Kunnumakkara AB, Bordoloi D, Padmavathi G, et al. Curcumin, the golden nutraceutical: Multitargeting for multiple chronic diseases. *Br J Pharmacol* 2017; 174. DOI: 10.1111/bph.13621.
- Aggarwal BB. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. *Annu Rev of Nutr* 2010; 30: 173–199.
- Anand P, Kunnumakkara AB, Newman RA, et al. Bioavailability of curcumin: Problems and promises. *Mol Pharm* 2007; 4. DOI: 10.1021/mp700113r.
- Lopresti AL. Curcumin for neuropsychiatric disorders: A review of in vitro, animal and human studies. *J Psychopharmacol* 2017; 31. DOI: 10.1177/0269881116686883.
- Mantzorou M, Pavlidou E, Vasios G, et al. Effects of curcumin consumption on human chronic diseases: A narrative review of the most recent clinical data. *Phytother Res* 2018; 32. DOI: 10.1002/ptr.6037.
- American Psychiatric Publishing. *Diagnostic and statistical manual of mental disorders: DSM-5™*. 5th ed.

- Arlington, VA: American Psychiatric Publishing, 2013, p. xliv, 947-948, 947.
10. Mahadik SP and Mukherjee S. Free radical pathology and antioxidant defense in schizophrenia: A review. *Schizophr Res* 1996; 19. DOI: 10.1016/0920-9964(95)00049-6.
 11. Gunes M, Altindag A, Bulut M, et al. Oxidative metabolism may be associated with negative symptoms in schizophrenia. *Psychiatry and Clin Psychopharmacol* 2017; 27. DOI: 10.1080/24750573.2017.1293243.
 12. Hjorthøj C, Stürup AE, McGrath JJ, et al. Years of potential life lost and life expectancy in schizophrenia: A systematic review and meta-analysis. *Lancet Psychiatry* 2017; 4. DOI: 10.1016/S2215-0366(17)30078-0.
 13. Laursen T, Munk-Olsen T, and Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Current Opin in Psychiatry* 2012; 25. DOI: 10.1097/YCO.0b013e32835035ca.
 14. Piotrowski P, M Gondek T, Królicka-Dereęowska A, et al. Causes of mortality in schizophrenia: An updated review of European studies. *Psychiatr Danub* 2017; 29: 108–120.
 15. Harvey PD and Rosenthal JB. Cognitive and functional deficits in people with schizophrenia: Evidence for accelerated or exaggerated aging? *Schizophrenia Res* 2018; 196. DOI: <https://doi.org/10.1016/j.schres.2017.05.009>.
 16. Lahera G, Gálvez JL, Sánchez P, et al. Functional recovery in patients with schizophrenia: Recommendations from a panel of experts. *BMC Psychiatry* 2018; 18. DOI: 10.1186/s12888-018-1755-2.
 17. Bumb JM, Enning F, and Leweke FM. Drug repurposing and emerging adjunctive treatments for schizophrenia. *Expert Opin on Pharmacother* 2015; 16. DOI: 10.1517/14656566.2015.1032248.
 18. Cho M, Lee TY, Kwak YB, et al. Adjunctive use of anti-inflammatory drugs for schizophrenia: A meta-analytic investigation of randomized controlled trials. 2019; 53. DOI: 10.1177/0004867419835028.
 19. Căpățină OO, Micluția IV, and Fadgyas-Stănculete M. Current perspectives in treating negative symptoms of schizophrenia: A narrative review (Review). *Exp Ther Med* 2021; 21. DOI: 10.3892/etm.2021.9707.
 20. Brietzke E, Mansur RB, Zugman A, et al. Is there a role for curcumin in the treatment of bipolar disorder? *Med Hypotheses* 2013; 80. DOI: 10.1016/j.mehy.2013.02.001.
 21. Fusar-Poli L, Vozza L, Gabbadini A, et al. Curcumin for depression: a meta-analysis. *CRC Crit Rev Food Sci Nutr* 2019; 60. DOI: 10.1080/10408398.2019.1653260.
 22. Trebaticka J and Durackova Z. Psychiatric disorders and polyphenols: Can they be helpful in therapy? *Oxid Med Cell Longev* 2015; 2015. DOI: 10.1155/2015/248529.
 23. Bishnoi M, Chopra K, and Kulkarni SK. Protective effect of Curcumin, the active principle of turmeric (*Curcuma longa*) in haloperidol-induced orofacial dyskinesia and associated behavioural, biochemical and neurochemical changes in rat brain. *Pharmacol Biochem Behav* 2008; 88. DOI: 10.1016/j.pbb.2007.10.009.
 24. Zhu L-N, Mei X, Zhang Z-G, et al. Curcumin intervention for cognitive function in different types of people: A systematic review and meta-analysis. *Phytother Res* 2019; 33. DOI: 10.1002/ptr.6257.
 25. Gazal M, Valente MR, Acosta BA, et al. Neuroprotective and antioxidant effects of curcumin in a ketamine-induced model of mania in rats. *Eur J Pharmacol* 2014; 724. DOI: 10.1016/j.ejphar.2013.12.028.
 26. Rao M. Nitric oxide scavenging by curcuminoids. *J Pharm Pharmacol* 1997; 49: 105–107.
 27. Bishnoi M, Chopra K, Rongzhu L, et al. Protective effect of curcumin and its combination with piperine (bioavailability enhancer) against haloperidol-associated neurotoxicity: Cellular and neurochemical evidence. *Neurotoxicity Res* 2011; 20: 215–225.
 28. Parasuraman S, Zhen KM, Banik U, et al. Ameliorative effect of curcumin on olanzapine-induced obesity in Sprague-Dawley rats. *Pharmacognosy Res* 2017; 9. DOI: 10.4103/pr.pr_8_17.
 29. Lavoie S, Chen Y, Dalton TP, et al. Curcumin, quercetin, and tBHQ modulate glutathione levels in astrocytes and neurons: Importance of the glutamate cysteine ligase modifier subunit. *J Neurochem* 2009; 108. DOI: 10.1111/j.1471-4159.2009.05908.x.
 30. Xu Y, Ku B, Cui L, et al. Curcumin reverses impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats. *Brain Res* 2007; 1162. DOI: <https://doi.org/10.1016/j.brainres.2007.05.071>.
 31. Wang R, Li YH, Xu Y, et al. Curcumin produces neuroprotective effects via activating brain-derived neurotrophic factor/TrkB-dependent MAPK and PI-3K cascades in rodent cortical neurons. *Prog Neuropsychopharmacol Biol Psychiatry* 2010; 34. DOI: 10.1016/j.pnpbbp.2009.10.016.
 32. Wu A, Noble EE, Tyagi E, et al. Curcumin boosts DHA in the brain: Implications for the prevention of anxiety disorders. *Biochim Biophys Acta* 2015; 1852. DOI: 10.1016/j.bbadis.2014.12.005.
 33. Jiang H, Wang Z, Wang Y, et al. Antidepressant-like effects of curcumin in chronic mild stress of rats: Involvement of its anti-inflammatory action. *Prog Neuropsychopharmacol Biol Psychiatry* 2013; 47. DOI: 10.1016/j.pnpbbp.2013.07.009.
 34. Naserzadeh P, Hafez AA, Abdorahim M, et al. Curcumin loading potentiates the neuroprotective efficacy of Fe₃O₄ magnetic nanoparticles in cerebellum cells of schizophrenic rats. *Biomed Pharmacother* 2018; 108. DOI: 10.1016/j.biopha.2018.09.106.
 35. Robertson OD, Coronado NG, Sethi R, et al. Putative neuroprotective pharmacotherapies to target the staged progression of mental illness. *Early Interv Psychiatry* 2019; 13. DOI: 10.1111/eip.12775.
 36. Goldsmith D, Rapaport M, and Miller B. A meta-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression. *Molecular Psychiatry* 2016; 21: 1696–1709.
 37. Boyanapalli SS and Kong AT. “Curcumin, the King of Spices”: Epigenetic regulatory mechanisms in the prevention of cancer, neurological, and inflammatory diseases. *Curr Pharmacol Rep* 2015; 1. DOI: 10.1007/s40495-015-0018-x.
 38. Remely M, Lovrecic L, de la Garza AL, et al. Therapeutic perspectives of epigenetically active nutrients. *Br J Pharmacol* 2015; 172. DOI: 10.1111/bph.12854.
 39. Badmaev V, Cernovsky Z, Bureau Y, et al. Targeting epigenetics signaling with curcumin: A transformative drug lead in treatment of schizophrenia? *J Clin Epigenetics* 2017; 3: 32.
 40. Kulkarni S, Dhir A, and Akula KK. Potentials of curcumin as an antidepressant. *TheScientificWorldJournal* 2009; 9: 1233–1241.
 41. Kumar TP, Antony S, Gireesh G, et al. Curcumin modulates dopaminergic receptor, CREB and phospholipase C gene expression in the cerebral cortex and cerebellum of streptozotocin induced diabetic rats. *J Biomed Sci* 2010; 17: 43.
 42. Davis J, Moylan S, Harvey BH, et al. Neuroprogression in schizophrenia: Pathways underpinning clinical staging and therapeutic corollaries. *Aust N Z J Psychiatry* 2014; 48. DOI: 10.1177/0004867414533012.
 43. Noto C, Maes M, Ota VK, et al. High predictive value of immune-inflammatory biomarkers for schizophrenia diagnosis and association with treatment resistance. *The World J Biological Psychiatry* 2015; 16. DOI: 10.3109/15622975.2015.1062552.

44. Müller N. Neuroprogression in schizophrenia and psychotic disorders: The possible role of inflammation. *Neuroprogression in Psychiatric Disorders*. Karger Publishers, 2017, pp. 1–9.
45. Anderson G, Berk M, Dodd S, et al. Immuno-inflammatory, oxidative and nitrosative stress, and neuroprogressive pathways in the etiology, course and treatment of schizophrenia. *Prog Neuro-Psychopharmacol Biol Psychiatry* 2013; 42: 1–4.
46. Rajasekaran A, Venkatasubramanian G, Berk M, et al. Mitochondrial dysfunction in schizophrenia: pathways, mechanisms and implications. *Neurosci Biobehav Rev* 2015; 48: 10–21.
47. Chiu S, Woodbury-Farina M, Terpstra K, et al. Exploratory study of curcumin isolated from turmeric *Curcuma longa*, the putative histone deacetylase inhibitor, as added-on strategy to antipsychotics in treating negative symptoms and neuro-cognitive deficits in schizophrenia. *Adv Res J Multidisciplinary Discoveries* 2019; 40: 06–15.
48. Wynn JK, Green MF, Hellemann G, et al. The effects of curcumin on brain-derived neurotrophic factor and cognition in schizophrenia: A randomized controlled study. *Schizophr Res* 2018; 195. DOI: 10.1016/j.schres.2017.09.046.
49. Kucukgoncu S, Guloksuz S and Tek C. Effects of curcumin on cognitive functioning and inflammatory state in schizophrenia: A double-blind, placebo-controlled pilot trial. *J Clin Psychopharmacol* 2019; 39. DOI: 10.1097/jcp.0000000000001012.
50. Miodownik C, Lerner V, Kudkaeva N, et al. Curcumin as add-on to anti-psychotic treatment in patients with chronic schizophrenia: A randomized, double-blind, placebo-controlled study. *Clin Neuropharmacol* 2019; 42. DOI: 10.1097/WNF.000000000000344.
51. Hosseininasab M, Zarghami M, Mazhari S, et al. Nanocurcumin as an add-on to antipsychotic drugs for treatment of negative symptoms in patients with chronic schizophrenia: A randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2021; 41. DOI: 10.1097/JCP.0000000000001324.
52. Vancampfort D, Wampers M, Mitchell AJ, et al. A meta-analysis of cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia versus general population controls. *World Psychiatry* 2013; 12: 240–250.
53. Kane JM and Correll CU. The role of clozapine in treatment-resistant schizophrenia. *JAMA Psychiatry* 2016; 73: 187–188.
54. Vantaggiato C, Panzeri E, Citterio A, et al. Antipsychotics promote metabolic disorders disrupting cellular lipid metabolism and trafficking. *Trends in Endocrinol Metab* 2019; 30: 189–210.
55. Kim MK, Kim SH, Yu HS, et al. The effect of clozapine on the AMPK-ACC-CPT1 pathway in the rat frontal cortex. *Int J Neuropsychopharmacol* 2012; 15: 907–917.
56. Liu Z, Cui C, Xu P, et al. Curcumin activates AMPK pathway and regulates lipid metabolism in rats following prolonged clozapine exposure. *Front Neurosci* 2017; 11. DOI: 10.3389/fnins.2017.00558.
57. Zhu Y, Krause M, Huhn M, et al. Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: A systematic review with pairwise and network meta-analyses. *Lancet Psychiatry* 2017; 4. DOI: 10.1016/S2215-0366(17)30270-5.
58. Aquino CCH and Lang AE. Tardive dyskinesia syndromes: current concepts. *Parkinsonism Related Disorders* 2014; 20: S113–S117.
59. Sookram C, Tan M, Daya R, et al. Curcumin prevents haloperidol-induced development of abnormal oro-facial movements: Possible implications of Bcl-XL in its mechanism of action. *Synapse* 2011; 65. DOI: 10.1002/syn.20905.