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

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**ABSTRACT**

Nutraceuticals and food supplements are commonly used as either stand-alone treatments or as add-on agents with ongoing pharmacological management. Different nutraceutical 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 for treatments like Alzheimer's disease, cardiovascular disorders, asthma, and neuropsychiatric disorders like rheumatoid arthritis, cardiovascular disorders, asthma, and neuropsychiatric disorders like Alzheimer's dementia and Parkinsonism.\(^{3,4}\) Curcumin is a nonflavanoid 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.\(^{3,4}\)

There are no available reports of toxicity in humans following long-standing use of curcumin.\(^{4}\) 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.\(^{13,16}\) Repurposing the available drugs and utilizing the
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. Such novel pharmacological options could be utilized to reduce the burden of negative and cognitive symptoms of schizophrenia.

The role of curcumin in the management of depression and bipolar disorder has been proposed recently. 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. 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. The proposed pharmacological actions of curcumin include antioxidant, anti-inflammatory, antimutagenic, antibacterial, antiproteolysis, antiobsesity, antiangiogenic, hepatoprotective, and procognitive properties. Curcumin inhibits the production of reactive oxygen species and reduces the production of inflammatory cytokines by inhibiting cyclooxygenase and lipoxygenase enzymes. Curcumin is a lipophilic compound with the ability to penetrate the blood-brain barrier and exert its antioxidant, neuroprotective activity. Generally, an oral dose of more than 2 g/day is reported to intensify curcumin's antioxidant effects. Curcumin reduces the turnover of monoamines such as dopamine, serotonin, and noradrenaline and thereby prevents the accumulation of free radicals. 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. Curcumin improves neuroplasticity and hippocampal neurogenesis through the enhancement of brain-derived neurotrophic factor (BDNF). 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.

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. Curcumin regulates cellular enzymes like protein kinase C (PKC) and inhibits apoptosis. In animal models of schizophrenia, curcumin protects against mitochondrial dysfunction by removing free radicals. 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. 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. Importantly, curcumin inhibits monoamine oxidase A and B (MAO-A and MAO-B) enzymes and shows potent antidepressant action. Also, in animal models, it reduces the expression of dopamine D1 receptor in the cerebellum and thereby probably reduces antipsychotic-induced depressive features.

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. The current understanding of the etiopathogenesis of schizophrenia suggests all the above-mentioned mechanisms to be involved in the neuroprogression of the disorder. 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. 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.

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 (Theracurmin) preparation failed to improve cognitive performance or clinical variables at eight weeks. However, the study
Preclinical Studies on Add-on Curcumin in Schizophrenia

| Author/Years | Study Design | Study Population | Curcumin Used | Duration | Domain Studied | Remarks |
|--------------|--------------|------------------|---------------|----------|----------------|---------|
| Chiu et al. 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 18 weeks | Positive, negative, and cognitive symptoms | Both groups significantly improved in the total PANSS scores. No adverse effects reported. |
| Wynn et al. 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. 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. 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. |
| Hosseini et al. 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.

Preclinical Studies on Add-on Curcumin in Schizophrenia

| Author/Years | Study Characteristics | Main Outcomes |
|--------------|-----------------------|--------------|
| Bishnoi et al. 2008 | Male Wistar rats were divided into five groups and given a control, haloperidol (1 mg/kg), curcumin (25 or 50 mg/kg), and clozapine (10 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. 2011 | Male Wistar rats were divided into nine groups and given a control, haloperidol (5 mg/kg), clozapine (10 mg/kg), and 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. 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. 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. 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. |
was underpowered, with a small sample size. 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.

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. 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. 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.

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 and cardiovascular morbidity. Clozapine is the ultimate treatment option in resistant schizophrenia. Though increased appetite, food intake, and sedentary lifestyle may contribute to dyslipidemia, clozapine may affect lipid metabolism through other peripheral mechanisms as well. Adenosine monophosphate-activated protein kinase (AMPK) is a key regulator in hepatic energy and lipid metabolism. Clozapine and other antipsychotics suppress AMPK activity, thereby ultimately leading to dyslipidemia. 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 activation and olanzapine-induced weight gain and dyslipidemia. 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. Animal studies suggested that curcumin pretreatment protected haloperidol-exposed rats from developing tardive extrapyramidal movements. Curcumin prevented the antipsychotic-associated increase in lipid peroxidation and reduction in levels of antioxidant enzymes such as catalase, superoxide dismutase, and glutathione. 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. Clozapine, however, produced less oxidative stress compared to haloperidol. This protective effect of curcumin is also attributed to its antiapoptotic property. Concurrent curcumin administration...
with haloperidol is shown to upregulate the antiapoptotic protein Bcl-XL in the striatal region, thereby reducing apoptosis.19

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 procoative 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.20–49 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.48–50 Importantly, two double-blind, placebo-controlled trials reported add-on curcumin’s efficacy in reducing the negative symptoms of schizophrenia.31,33

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.42 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 olanzapine48 and clozapine.46 Such positive metabolic changes are postulated to be secondary to the regulation of hepatic energy and lipid metabolism through AMPK activity.54 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 to tardive orofacial movements.25,21,54 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.

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References
1. Andrade C. A Critical examination of studies on curcumin for depression. J Clin Psychiatry 2014; 75. DOI: 10.4088/JCP.14f0948.
2. Bhat A, Mahalakshmi AM, Ray B, et al. Benefits of curcumin in brain disorders. Biofactors 2019; 45. DOI: 10.1002/biof.1533.
3. 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.
4. Kunnunakkara 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.
5. Aggarwal BB. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. Annu Rev of Nutr 2010; 30: 173–199.
6. Anand P, Kunnunakkara AB, Newman RA, et al. Bioavailability of curcumin: Problems and promises. Mol Pharm 2007; 4. DOI: 10.1021/mp070013f.
7. Lopresti AL. Curcumin for neuropsychiatric disorders: A review of in vitro, animal and human studies. J Psychopharmacol 2017; 31. DOI: 10.1177/02698811668883.
8. Mantzorou M, Pavlidou E, Vasiou 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.
9. American Psychiatric Publishing. Diagnostic and statistical manual of mental disorders: DSM-5™. 5th ed.
10. Mahadik SP and Mukherjee S. Free radical pathology and antioxidant defense in schizophrenia: A review. Schizophr Res 1996; 19. DOI: 10.1016/0920-9645(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: 10.1080/24750573.2017.1292343.

12. Hjorthøj C, Munk-Olsen T, and Leweke FM. Neuroprotective and antioxidant effects of curcumin and its combination with piperine (bioavailability enhancer) against haloperidol-associated neurotoxicity: Cellular and neurochemical evidence. Neurotoxicity Res 2011; 20: 215–225.

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-Deregowska 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 Pharmacotherapeut 2015; 16. DOI: 10.1517/14656566.2015.1032248.

18. Cho M, Lee TY, Kwak YB, et al. Adjuvant use of anti-inflammatory drugs for schizophrenia: A meta-analytic investigation of randomized controlled trials. 2019; 53. DOI: 10.1177/0004867419853028.

19. Căpătâiu OO, Miciuța IV, and Fadgyas-Stânculete M. Current perspectives in treating negative symptoms of schizophrenia: A narrative review. Exp Ther Med 2021; 21. DOI: 10.3892/etm.2021.9707.

20. Brichte 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, Gabbiadini A, et al. Curcumin for depression: a meta-analysis. CRC Crit Rev Food Sci Nutr 2019; 60. DOI: 10.1080/10408398.2019.1653260.

22. Trebatka 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 J-N, Mei X, Zhang Z-G, et al. Curcumin intervention for cognitive function in different types of people: A systematic review and meta-analysis. Phyrother Res 2019; 33. DOI: 10.1002/pr.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.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.pnpb.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.pnpb.2013.07.009.

34. Naszaretz 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 Pharm Rep 2015; 1: DOI: 10.1007/ s40495-015-0018-x.

38. Remely M, Lovreci 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: 10.3109/15622495.2015.1062552.
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 antipsychotic treatment in patients with chronic schizophrenia: A randomized, double-blind, placebo-controlled study. Clin Neuropharmacol 2019; 42. DOI: 10.1097/WNF.0000000000000344.

51. Hosseini-Nasab 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.