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REVIEW

Schizophrenia, Curcumin and Minimizing Side Effects of Antipsychotic Drugs: Possible Mechanisms

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Abstract

Schizophrenia is a mental disorder characterized by episodes of psychosis; major symptoms include hallucinations, delusions, and disorganized thinking. More recent theories focus on particular disorders of interneurons, dysfunctions in the immune system, abnormalities in the formation of myelin, and augmented oxidative stress that lead to alterations in brain structure. Decreased dopaminergic activity and increased phospholipid metabolism in the prefrontal cortex might be involved in schizophrenia. Antipsychotic drugs used to treat schizophrenia have many side effects. Alternative therapy such as curcumin (CUR) can reduce the severity of symptoms without significant side effects. CUR has important therapeutic properties such as antioxidant, anti-mutagenic, anti-inflammatory, and antimicrobial functions and protection of the nervous system. Also, the ability of CUR to pass the blood–brain barrier raises new hopes for neuroprotection. CUR can improve and prevent further probable neurological and behavioral disorders in patients with schizophrenia. It decreases the side effects of neuroleptics and retains lipid homeostasis. CUR increases the level of brain-derived neurotrophic factor and improves hyperkinetic movement disorders. CUR may act as an added counteraction mechanism to retain cell integrity and defense against free radical injury. Thus it appears to have therapeutic potential for improvement of schizophrenia. In this study, we review several properties of CUR and its ability to improve schizophrenia and minimize the side effects of antipsychotic drugs, and we explore the underlying mechanisms by which CUR affects schizophrenia and its symptoms.

Keywords Curcumin · Cognitive functions · Schizophrenia · Positive and negative symptoms · Antipsychotics

Abbreviations

CUR	Curcumin
BDNF	Brain-derived neurotrophic factor
CLO	Clozapine
TD	Tardive dyskinesia
EPSE	Extrapyramidal side effects
AMPK	AMP-activated protein kinase
ACC	Acetyl CoA carboxylase
SREBPs	Sterol regulatory element-binding proteins
CREB	CAMP response element-binding protein
DISC1	Disrupted-in-schizophrenia 1
NMDA	N-methyl-D-aspartate
HDAC	Histone deacetylase
PDB	Protein data bank

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Introduction

Schizophrenia as a long-term mental disorder affects about one percent of the world's total population [1]. The main contributory factors in this disease seem to be early environmental and genetic factors, whereas the presence of other mental disorders can play a role as well. Because of all possible combinations of symptoms, it remains to be seen whether schizophrenia is a single disorder or composed of different syndromes. Augmented oxidative stress may be related to the pathophysiology of schizophrenia disease [2]. This condition is related to alterations in brain structures involving loss of gray matter, expanded ventricles [3] and reduction of dendritic spines from pyramidal neurons of

the cortex [4]. Also, decreased dopaminergic activity and increased phospholipid metabolism in the prefrontal cortex might be involved in schizophrenia [5].

The onset of symptoms usually occurs during young adulthood, and approximately 0.3–0.7% of people will experience schizophrenia during their lifetime. Despite the fact that this disorder affects a person's ability to think in an organized manner, it also is associated with chronic behavioral and emotional problems [2]. Schizophrenic patients are likely to have extra comorbidities such as major depression and anxiety. Social problems like long-term unemployment, impoverishment, and homelessness are prevalent. Symptoms may be caused by or worsen with some recreational and prescription drugs [2]. In schizophrenia, considerable functional defectss include negative symptoms (such as loss of volition, insensibility, antisocial behaviors, and affective flattening), positive symptoms (such as hallucinations, delusions, and bizarre behavioral disturbances), and neurocognitive impairments that involve 20–30% of people with schizophrenia who are refractory to current antipsychotic treatment [6]. The positive symptoms of schizophrenia significantly improve with the second generation of atypical antipsychotics such as quetiapine, clozapine (CLO), olanzapine, risperidone, ziprasidone, and aripiprazole [7]. But comprehensive psychosocial consequences in schizophrenia remain moderate after using the agents [6]. Antipsychotics, although the first line of treatment, cause many side effects. There is, therefore, a need for an adjuvant therapy that could be utilized as an alternative therapy to reduce the severity of symptoms. CUR could be considered an alternative treatment because of its extensive beneficial effects on neurodegenerative diseases [8]. CUR (diferuloylmethane) is the yellow plant pigment in Indian saffron. It is extensively utilized in South Asian and Middle East regions as a dietary component [9]. Past studies have shown that CUR has important therapeutic properties such as antioxidant, antimutagenic, anti-inflammatory and antimicrobial functions and protection of the nervous system [10, 11]. The ability of CUR to pass the blood–brain barrier raises new hopes for neuroprotection. Inflammation and oxidative stress around neurons and glial cells are significantly related to brain aging and injury [12]. Limited absorption, fast metabolism, and quick systemic elimination even at high doses of CUR and its metabolites imply the low bioavailability of this agent [13]. To improve the bioavailability of CUR, very different approaches have been utilized. These approaches include the application of adjuvants like piperine, liposomal CUR, CUR nanocapsules, and phospholipid complexes of CUR [14].

CUR, in the early stages of the disease, can prevent additional oxidative damages and may result in improving and preventing further probable neurological and behavioral disorders [15]. The role of CUR and its different mechanisms in the improvement of schizophrenia have been shown in preclinical and clinical studies. CUR may be able to decrease the serious side effects associated with prescribing neuroleptics [8, 16]. To this day, a comprehensive review article about CUR and new specific mechanisms of action on schizophrenia has not been published. Thus, the current study aims to review the underlying mechanisms of CUR that affect schizophrenia and its symptoms.

Pathophysiology of Schizophrenia

The accurate pathophysiology of schizophrenia is not well known yet. The dopamine hypothesis and the glutamate hypothesis are two commonly supported hypotheses [17]. More recent theories focus on particular disorders of interneurons, dysfunctions of the immune system, abnormalities in the formation of myelin, and oxidative stress [18–20]. This disorder is characterized by positive and negative symptoms and neurocognitive disorders [21]. In addition to positive and negative symptoms, cognitive damage is a frequent core characteristic of schizophrenia [22] and is associated with the volume diminution of the hippocampus, a region central to learning, memory, and cognitive integration [23].

Cognitive impairments are present in domains of episodic memory, executive function, social cognition and attention [24]. These functions are dependent on the prefrontal cortex and hippocampus [25]. In schizophrenia, neurodevelopmental anomalies in sensitive brain development periods probably lead to hippocampal-prefrontal pathway damages and subsequently cause the appearance of disease symptoms in young adulthood [26]. Depression and schizophrenia are interrelated as indicated by several observations. The most common indicators advanced include depression as intrinsic to the disease, depression as a side effect of antipsychotics, depression as a negative symptom of the disease and depression as a psychological response to the consciousness of suffering from psychosis [27]. In the pre-psychotic stage, negative and cognitive symptoms emerge [28]. The presence of more cognitive and negative symptoms are significantly related to less functional outcomes [29, 30]. Also, motor symptoms like parkinsonism, neurological soft signs, and abnormal involuntary movements due to their high prevalence in schizophrenia have received special attention [31].

Due to the lack of pathognomonic symptoms, schizophrenia is usually diagnosed by exclusion, based on picking up characteristics of psychosis from collateral information and diagnostic interview [32]. Identification of the clinical syndrome is still the basis of diagnosis in psychiatry [33], and the diagnostic criteria constantly rely on family history, clinical features and outcomes [34]. Due to the lack of biological markers to diagnose schizophrenia, long-term attention to patients' symptoms and behaviors is necessary

to verify the diagnosis [33, 35]. The efficiency of these diagnostic categories depends on the temporal stability and the inter-rater reliability [36, 37]. The first line of treatment for schizophrenia is antipsychotic drugs such as clozapine, risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone that usually result in a decrease in positive symptoms whilst they have minimal or no effect on cognitive and negative symptoms [38]. The treatment with antipsychotic drugs also leads to side effects such as metabolic syndrome, weight gain, tardive dyskinesia (TD), and dyslipidemia [39, 40]. Therefore, considering the side effects of antipsychotic drugs and the results of some studies that show the role of CUR in the treatment of schizophrenia, CUR can be proposed as an alternative treatment that will focus on as an effective adjuvant agent in the present review.

CUR and the Side Effects of Antipsychotic Drugs for Schizophrenia Therapy

Antipsychotic drugs are widely used to treat schizophrenia disorder and other related psychiatric diseases. Dopamine (DA) receptors which are widely present throughout the brain**,** are blocked by these drugs. Unfortunately, the long-term use of antipsychotic drugs results in severe extrapyramidal side effects (EPSE) [41]. Moreover, the short-term effects involve parkinsonism and the next emerging tardive dyskinesia [42–44]. Presently available treatments for these diseases are mainly symptomatic and insufficient; they are usually associated with damaging side effects. Due to tardive dyskinesia caused by antipsychotic drugs, researchers seek new drugs with less adverse extrapyramidal side effects [43, 45]. The roles of 5-hydroxytryptamine (serotonin)-1A and 2A/2C receptors in the regulation of dopaminergic neurotransmission in preclinical studies have been suggested [46, 47]. Research is also aimed at finding better therapeutic strategies for schizophrenia and related diseases. Moreover, in the early phases of the disease, the use of antioxidants like CUR as an adjunctive treatment may prevent additional oxidative damages and may result in improving and preventing further probable neurological and behavioral disorders [48]. The first neuroleptic drugs were developed in the early 1950s. The common antipsychotic properties of these drugs are executed via their antagonistic effect on dopaminergic receptors. Haloperidol, the most typical antipsychotic drug, is primarily beneficial in improving the positive signs of schizophrenia [49]. It was between the early 1960s and the 1980s that the "second generation" of neuroleptics expanded. Clozapine was primarily proposed as an innovator drug with more effectiveness than the existing drugs [50]. The mechanism of the action of atypical neuroleptics is different from that of the older drugs. They show fewer EPSE because of their combined effects on serotonergic and dopaminergic receptors. In the past, they were called atypical, because they were thought to not likely induce dyskinetic symptoms in some patients. Nowadays, we know that the symptoms of tardive dyskinesia are induced by atypical neuroleptics. However, the appearance of these symptoms may be delayed [15]. CUR administration reversed oxidative stress-induced tardive dyskinesia in rats and perhaps can be a promising therapeutic choice to improve hyperkinetic movement disorder [48]. Although there is no report about the direct interference of polyphenols with the pathophysiology of schizophrenia, the indirect effects of the natural polyphenols on the side effects of some drugs have been reported in several studies [8]. The role of oxidative stress in the development of haloperidol-induced orofacial tardive dyskinesia was verified by Bishnoi et al. [48], who concluded that the chronic administration of haloperidol enhanced vacuous chewing movements, facial jerking, tongue protrusions, and even an oxidative detriment in all main areas of the rat's brain. CUR dose-dependently eliminated these changes (Table 1). CUR has been suggested as a possible treatment for hyperkinetic movement. Moreover, flavonoid quercetin (3,5,7,3,4-pentahydroxyflavone) reversed haloperidol-induced EPSE, catalepsy, which is commonly related to catatonic schizophrenia in vitro. This physical condition is defined by muscular rigidity, suspension of sensation, fixity of posture, and the lack of contact with surroundings [51]. Furthermore, lipid peroxidation in plasma induced by haloperidol, the first-generation antipsychotic, was decreased by quercetin and resveratrol (3,4,5-trihydroxystilbene) in vivo. Amisulpride, a second-generation antipsychotic, did not affect the amount of lipid peroxidation biomarker thiobarbituric acid reactive species (TBARS) [52]. However, oxidative stress induced by haloperidol could be eliminated in vivo by various polyphenols such as CUR [8]. The ability of counteraction to TD induced by haloperidol established its potential in the pharmacotherapy of schizophrenia in rodents [48]. In patients with treatment-resistant schizophrenia, Clozapine is a last choice treatment, but serious metabolic side effects such as dyslipidemia are often observed as a result of the prescription of atypical antipsychotics [53]. Drug-induced dyslipidemia may be secondary to obesity and hyperorexia. The antipsychotic drugs could also induce direct effects on the lipid metabolism of the peripheral tissues [54]. AMP-activated protein kinase (AMPK) appeared as a key modulator in both lipid homeostasis and hepatic energy metabolism. It inhibited the activity of acetyl CoA carboxylase (ACC) and 3-hydroxy-3-methyl glutaryl CoA reductase and led to the suppression of both cholesterol and fatty acid biosynthesis [55, 56].

Furthermore, sterol regulatory element-binding proteins (SREBPs), the main transcriptional regulators of lipogenesis, can be inactivated by AMPK, and subsequently

Table 1 Characteristics of studies investigating the effects of curcumin on schizophrenia and minimizing side effects of antipsychotic drugs

Study and year	Participants	Study design	Conclusion
Mahendra Bishnoi et al. [48]	Male wistar rats (180–220g;10–12 rats/group)	haloperidol was diluted with distilled water	Administration of haloperidol
			increased vacuous
		Curcumin was dissolved in	chewing movements,
		carboxymethyl cellulose (CMC)	tongue protrusions, facial jerking
		haloperidol and/or curcumin	which was does- dependently
		was/were administered intraperi-toneally	inhibited by curcumin
		and per-orally respectively in a	
		constant volume of 0/5 ml per 100 g	
		of body weight of rats	Haloperidol resulted increased
			dopamine receptor sensitivity
		Animals divided in 5 groups:	and decrease retention time on
		1_ received CMC	elevated plus maze paradigm
		2_received haloperidol(1 mg/kg) + CMC	pretreatment with curcumin reversed
		3_received haloperidol(1 mg/kg) + 25 mg/kg curcumin	these behavioral changes
		4_received haloperidol(1 mg/kg) + 50 mg/kg curcumin	
		5_received 50 mg/kg curcumin	Haloperidol induced oxidative
			damage in all major regions of
		They were administered once daily for a 21 days	brain which was attenuated by curcumin
			haloperidol decrease turnover
			of dopamine, serotonin and norepi-nephrine
			in both cortical and subcortical regions which
			was again does_dependently reversed by
			treatment with curcumin
Woodburry-Farina [57]	Patients with schizophrenia	There are two groups:	Both groups improved in neuro-cognitive index
		1_ 1 g/d curcumin (n = 7)	
		2_4g/d curcumin (n = 8)	
		12 weeks	
Wynn et al. [58]	Patients with schizophrenia	Intervention group:	
	Sexes eligible for study	360 mg/d Curcumin (n = 17)	increased brain_drived_neuro-trophic
	Age: 18 to 65 years	Compared with placebo group (n = 19)	
		8 weeks	
Kucukgoncu et al. [59]	Patients with schizophrenia	Intervention group:	
	9 males, 3 females	180 mg/d curcumin (n = 6)	Improve working memory
	Mean age = 41.33	Placebo group (n = 6)	Reduce IL_6 levels
	(5 to 51 years)	8 weeks	
Chiu et al. [60]	Patients with schizophrenia	n = 17 Randomized in two groups	Both groups improved in cognition
		1_1g/d Supercurcumin TM	
		2–4g/d Supercurcumin TM	
		16 Weeks	

Table 1 (continued)

Study and year	Participants	Study design	Conclusion
Miodownik et al. [61]	Patients with chronic schizophrenia	Intervention group:	Reduced negative symptoms
	18_60 years old	3000 mg/day Curcumin	
	were hospitalized for	(1000 mg capsule for 3 daily	
	over 2 years and	oral administrations with meals)	
	continued receiving their	%95 curcumin and %5 piperine (n = 20)o	
	regular antipsychotic	compared with placebo group (n = 18)	
	25men, 13 women	24 weeks	
Hosseininasab [62]	Patients with chronic schizophrenia	Intervention group:	
		160 mg/day nanocurcumin soft gel	Improved negative subscale
		capsule (n = 28)	Improved positive subscale
		compared with placebo group (n = 28)	Improve in working memory and motor speed
		16 weeks	

downstream lipogenic genes are inhibited [63]. In the allosteric regulation of multiple lipid biosynthetic pathways, hepatic SREBPs are important. Several studies have indicated that CLO can stimulate the SREBP pathway and can increase downstream lipogenesis, whilst CUR has hypolipidemic properties. A research has been conducted to analyze the protective effects of CUR versus lipid disturbance induced by CLO via the expression of the key components in the metabolism of hepatic lipid. The results indicated that a four-week treatment with CLO (15 mg/kg/day) significantly increased the serum lipid levels and led to the accumulation of lipids in the liver [64]. The suppressed activity of AMPK and the elevated SREBP-dependent lipid synthesis might be related to dyslipidemia induced by antipsychotics, while the concomitant treatment with CUR (80 mg/kg/day) diminished the CLO-stimulated dyslipidemia [64, 65]. Moreover, studies have indicated that CUR is probably a novel AMPK agonist [64]. It can retain lipid homeostasis by directly binding to AMPK, increasing AMPK phosphorylation, and reducing CLO-stimulated SREBP overexpression. CUR regulates the downstream SREBP-targeted genes attributed to cholesterol metabolism and fatty acid synthesis, including HMG-CoA reductase (HMGCR) and fatty acid synthase (FAS). It implies that the adjunctive usage of CUR might be a promising preventive method for lipogenesis induced by drugs [64].

CUR's effective treatment of multiple drug-induced side effects of schizophrenia, including hyperglycemia and dyslipidemia has attracted much attention. Studies have demonstrated that CUR, by regulating the SREBP pathway, can alleviate obesity and decrease lipogenesis in mouse models fed with a high fat diet [66]. Although in vivo and in vitro studies have indicated the modulatory effects of CUR on SREBP-dependent lipid synthesis [66, 67], the mechanisms of CUR in terms of restoring SREBP over-activation are not fully understood. The main objective of some studies was the evaluation of the effects of CUR on metabolic disorders induced by CLO. Moreover, for further explanation of the potential mechanisms, the AMPK-SREBP signaling pathway was examined [64]. An essential instigator of metabolic disorders is dysregulated lipid metabolism. Some animal studies indicated that atypical antipsychotic drug-induced dyslipidemia resulted from the stimulation of appetite and weight gain, is likely mediated via the antagonistic functions of hypothalamic serotonin 5HT2C and histamine H1 receptors [68]. CUR mitigated obesity and the accumulation of periphery lipid, and ameliorated insulin sensitivity in high fat diet mice [66, 69]. CUR also had an inhibitory effect on hepatic fat accumulation and hyperlipidemia in rats fed with a high fructose diet [70]. Researchers have found recently that, through AMPK-SREBP signaling, CUR reduced renal lipid accumulation in type 1 diabetes induced by streptozotocin in rats [65]. Furthermore, through the regulation of the AMPK-SREBP pathway, CUR partly restored disorders of lipid metabolism induced by CLO. Other investigations of cancer cells and primary white adipocytes indicated that CUR induced the activation of AMPK [71–73]. Using molecular modeling, Zhen Liu et al. further advanced the idea that CUR shares usual binding features with the selective AMPK allosteric ligand, PF-249 [64, 74], which could create hydrogen bonds with residues Asn111 and Arg83 and could create p-p stacking interactions with residue Hie109 at

the allosteric modulatory site of AMPK (PDB: 5T5T) [74]. In previous studies and other in vitro and in vivo studies, the agonist effect of CUR on AMPK was documented [66]. Similarly, CUR can have direct interaction with AMPK and consequently modulate the SREBP-dependent lipid formation. It is remarkable that although CUR reduces metabolic disorders induced by CLO, it does not affect body weight gain. This scenario might be involved in the variant mechanisms of CLO in lipid metabolism and body weight growth. Dyslipidemia induced by the drug may occur owing to the hepatic AMPK-SREBP pathway which can be modulated by CUR, while weight loss stimulated by CLO in male rats is likely due to the interferences of the sedative effect of CLO on ingestion or its energy expenditure effect in which CUR may not play a role [64]. In sum, it appears that there is a successful interaction of CUR with CLO-stimulated dyslipidemia, indicating that the use of CUR as an adjunctive treatment is promising in the prevention of AAPD-induced lipid disorder. Furthermore, the beneficial effects of CUR on lipid profile and the involvement of the AMPK-SREBP pathway in the AAPD-stimulated hyperlipidemia were shown in previous studies. Thus, as a novel AMPK agonist, CUR might bind to AMPK directly, interestingly shedding extra light on the complex pharmacological functions of CUR [64].

Possible Mechanisms

Increasing Brain-Derived Neurotrophic Factor

The peripheral BDNF levels decrease in schizophrenia whilst BDNF levels do not associate with illness severity [75]. CUR up-regulates the pro-survival extracellular signal-regulated kinase (ERK) pathway and leads to the elevation of hippocampal BDNF [76, 77]. The properties of anti-inflammation, anti-oxidation, neuroprotection, and neurocognition, have been offered for CUR in preclinical studies [78]. Also, increased levels of BDNF by CUR have been shown [78–80]. In schizophrenia, neurocognitive symptoms, low levels of BDNF, and the effect of CUR on these phenomena have been reported [81].

Although still the accurate mechanism through which CUR can enhance levels of BDNF is not known, there may be a role for increased expression of the BDNF gene by phosphorylated cAMP response element-binding protein (CREB) (Fig. 1) [82]. Likewise, alterations of CREB have been indicated in schizophrenia [83], and CUR could potentially increase the expression of BDNF by reversing these CREB alterations [58] (Table 1).

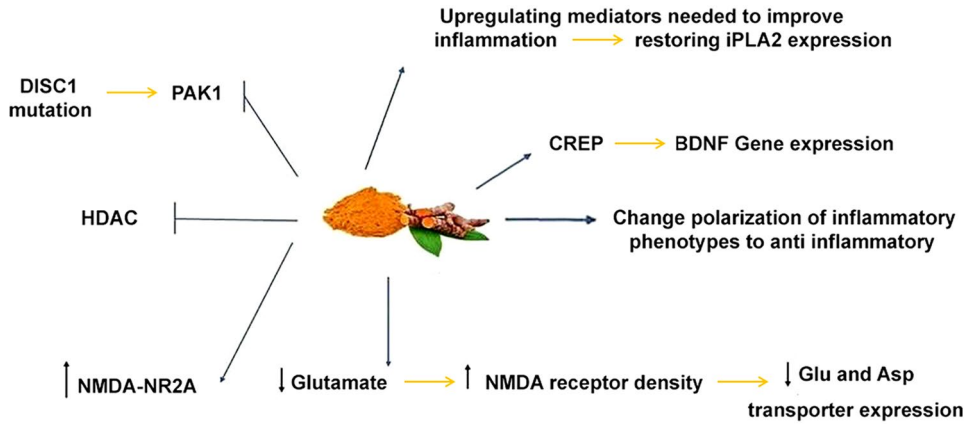

Fig. 1 Some mechanisms of curcumin involved in schizophrenia. Curcumin phosphorylates CREB (cAMP response element-binding protein) and increases expression of the BDNF gene (brain derived neurotrophic factor). Curcumin blocks abnormal activation of PAK1(P21-activated kinase1) that is occurred by DISC1 (disrupted-in-schizophrenia1). Curcumin inhibits HDAC (histone deacetylase) and regulates the expression of non-coding miRNA. Curcumin decreases glutamate cumulation and increases the density of NMDA (N-methyl-D-aspartate) receptors and reduces expression of glutamate/aspartate transporters in the cerebral cortex. IPLA2 (Ca 2 + -independent phospholipase A2) expression is restored by upregulating mediators needed to improve inflammation via intake of CUR. Curcumin has been proposed as an interesting compound in managing of psychosis episodes in schizophrenia disease because of its property in resurrecting the polarization of inflammatory phenotypes to anti-inflammatory mode. The neuroprotection property of CUR is significantly related to the extended activity of NMDA-NR2A level

Restoration of imPLA2 Expression

It seems that phospholipase A_2 (PLA2) plays a role in schizophrenia, both as a player in enhanced phospholipid metabolism and decreased dopaminergic activity in the prefrontal cortex [84]. If PLA2 is injected intra-cerebro ventricularly in rats, it inhibits apomorphine-induced motions, indicating that PLA2 represses the function of dopaminergic postsynaptic receptors [5]. Furthermore, in schizophrenic brains, mRNA and protein expression of secretory PLA_2 (sPLA2), cytosolic PLA_2 (cPLA2), and cyclooxygenase (COX) increase in addition to the enhancement of cytokines and pro-inflammatory markers [83]. Elevated flexibility of fatty acid chains in brain membranes from the prefrontal cortex of patients with schizophrenia has been evidenced, which implies that the activity of PLA2 increases [85]. In the initial stage of schizophrenia, the brain's PLA2 activity can increase, which is related to structural changes in the left prefrontal cortex and thalamus; however, in recurrent episodes of the disease extensive relations are found between PLA2 activity and structural alterations in the left hemisphere and cerebellum [86].

By presumably upregulating mediators required for injury recovery, dietary treatment with a curcumin (diferuloylmethane) derivative restores iPLA2 expression and mitigates the consequences of fluid percussion injury, and Ca^{2+}-independent PLA_2 (iPLA2) expression is probably restored by upregulating the mediators needed to improve inflammation via the intake of dietary supplementation which contains a CUR (diferuloylmethane) derivative (Fig. 1). PLA2 is also involved in spinal cord injury [87]. Four hours after the injury, the following events typically happen: the increase of total PLA2 activity and cPLA2α (one of cPLA2 isoforms) protein expression, and the upregulation of sPLA2-IIE (one of sPLA2 forms) and sPLA2-IIA (one of sPLA2 forms). This could lead to the creation of secondary mediators which lead to the loss of oligodendrocytes and the development of the damage [88]. Within 30 min after spinal cord impairment, cPLA2 knockdown decreases motor defects and cell loss, indicating an effect of neuroprotection [89].

Blockage of PAK1

A recent study [90] investigated the specific role of the GTPase RAC (GTP-dependent transducer) and its effector PAK1 in schizophrenia. Schizophrenia can be caused by a loss-of-function mutation of a disrupted-in-schizophrenia 1 (DISC1) gene. The DISC1 mutation activates the RAC-PAK1 signaling pathway [91]. DISC1 interacts with TRIO, a RAC activator and normally blocks the TRIO-RAC-PAK1 pathway in mammals. Thus, DISC1 could be a tumor suppressor that could block the oncogenic kinase PAK1. It is presumed that PAK1 is unusually activated in the schizophrenic brain with DISC1 mutation and that in principle, anti-PAK1 drugs could inhibit schizophrenia as well [92]. Thus, suppression of PAK1 has been suggested as a therapeutic approach in schizophrenia. CUR blocks PAK1 (Fig. 1) while does not affect normal cell growth [92].

Protection Against Free Radical Damage

Recently, after mitochondrial transplantation in ischemia animal models, functional improvement and cellular viability have been shown in several studies. Mitochondrial disorder, as a major participant in different basic cell processes, has frequently been demonstrated in schizophrenia [91]. Moreover, the symptoms of mental diseases likely increase in patients with mitochondrial dysfunction [93, 94]. In the brain and blood cells of schizophrenic patients, alterations in the mitochondrial oxidative phosphorylation system (OXPHOS) have been discovered. Therefore, schizophrenia might be associated with mitochondrial dysfunctions. Ben-Shachar provided an overview of mitochondrial disorders remarked in schizophrenia [95].

Iron oxide magnetic nanoparticles (Including Fe_2O_3 and Fe_3O_4) may affect usual physiological stimuli and cause oxidative stress in cells [96]. Moreover, exposure to iron oxide magnetic nanoparticles has been associated with notable toxic effects such as the formation of apoptotic bodies, inflammation, generation of ROS, and impaired mitochondrial function [97–100]. The investigations indicated that the effective treatment with CUR decreased or precluded Fe_3O_4 magnetic-induced oxidative stress and mitochondrial disorder. The results showed that CUR might act as an added counteraction mechanism to retain cell integrity and defense against free radical injury [101, 102]. CUR, because of its lipophilic nature, can enter the central nervous system (CNS) [103, 104], and displays an extensive range of biological functions containing potent anti-inflammation [105], anti-apoptosis [106], anti-neurotoxic [107, 108], antioxidant activities [106, 109], powerful antioxidant activity [110], preservation of mitochondrial integration [76, 111], and anti-carcinogenic [112]. Additionally, Barzegar and Moosavi-Movahedi [113] and Singh et al. [110] demonstrated that CUR, via scavenging ROS, decreased oxidative stress. Thus, it seems that the use of CUR as an adjuvant therapy can potentially prevent mitochondrial disorder and oxidative stress in schizophrenic animal models that probably involve various mechanisms [114].

Anti-Inflammatory Properties

Neuro-inflammation in research on the neurobiology of inflammation has been uncovered as a potential target in the improvement of schizophrenic patients [115]. CUR has been proposed as an interesting lead compound in managing psychosis episodes in schizophrenia disease because of its property in terms of resurrecting the polarization of inflammatory phenotypes to anti-inflammatory mode. In summary, it retains a good balance in the polarization phenomenon by CUR as an epigenetic modulator between the pro- and anti-inflammatory phenotypes of cytokines at the neuro-immune interfacing in schizophrenia [116].

NMDA System Modulation

It has been demonstrated that deviant signaling of N-methyl-D-aspartate (NMDA)-glutamate relates to the negative, positive and cognitive damages in schizophrenia [117]. Prior evidence indicates that the NMDA system is targeted by CUR-mediated neuroprotection and regulation of neuroinflammation [116]. The main determinant in relapse of schizophrenia is stress. The latest research showed the buffering effects of CUR against the harmful effects of stress [118]. Curcumin reversed the negative alterations in the dendritic morphology of CA3 pyramidal neurons in the hippocampus in the restraint stress paradigm in rodents and protected against NMDA-NR-2B overexpression in the presence of corticosterone in the hippocampal neurons [118]. In addition, CUR could protect hippocampal neurons versus the upregulation of NMDA-NR-2B (subunit of NMDA receptor) in the attendance of corticosterone [118]. In primary retinal and hippocampal neuronal cultures with whole-cell patch-clamp, NMDA-induced cell death was protected by CUR treatment via decreasing the NMDA-induced [Ca (2 +)] (i) current. In fact, the kinetics were dose- and time-dependent. Additionally, there was a strong correlation between enhanced NMDA-NR2A activity and curcumin neuroprotection [119]. Greater cardio-metabolic risks in schizophrenic patients carried the reduction of life expectancy in comparison to the general population [120]. Medications targeting the cross-talks of metabolic pathways and neural plasticity have encountered marginal progression in the treatment of the general well-being of schizophrenic patients. For example, blood sugar control was discovered to affect the cognitive outcome in patients with schizophrenia [116]. The protective effects of CUR on NMDA neurotoxicity were reported in a streptozotocin-caused diabetes model [121]. CUR inverted glutamate accumulation and the augmented density of NMDA receptors and reduced expression of glutamate/aspartate transporter in the cerebral cortex. In preclinical and clinical studies, there is developing evidence about the helpful effects of CUR in metabolic syndrome [122]. Therefore, curcumin's neuroprotective properties are combined with its positive effects in reducing the detrimental effects of metabolic syndrome on the central nervous system, which are frequently linked to the use of current antipsychotic medications in schizophrenia. When considered collectively, curcumin's pharmacological profile varies in how it affects NMDA-R subunit sensitivity: interaction between NR-1 and NR-2 at the allosteric site [123]. Thus, in schizophrenic disease, it released the vulnerable brains from the destructive outcomes of neuroinflammation through modulating the cytokine network. Finally, CUR's multifaceted CNS pharmacology in interaction with pivotal targets in the brain and the periphery in schizophrenia provides it with a therapeutic potential [116].

Conclusion

The current review has defined several key properties of CUR, particularly its anti-inflammatory, antioxidant, anti-mutagenic, and antimicrobial functions and protection of the nervous system. CUR reduces psychotic symptom severity and improves lipid profile. CUR, as a novel AMPK agonist, may have useful pharmacological functions. CUR inhibits HDAC and blocks PAK1 while not affecting normal cell growth. Therefore, this phytochemical agent can be considered an appropriate candidate for the improvement of Schizophrenia. However, further research is required to confirm these effects of CUR in schizophrenia due to the lack of randomized controlled trials. Therefore, it is suggested to conduct clinical trials in humans to confirm these influences.

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Declarations

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