Alternative Therapy of Psychosis: Potential Phytochemicals and Drug Targets in the Management of Schizophrenia

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Schizophrenia is a chronic mental and behavioral disorder characterized by clusters of symptoms including hallucinations, delusions, disorganized thoughts and social withdrawal. It is mainly contributed by defects in dopamine, glutamate, cholinergic and serotonergic pathways, genetic and environmental factors, prenatal infections, oxidative stress, immune system activation and inflammation. Management of schizophrenia is usually carried out with typical and atypical antipsychotics, but it yields modest benefits with a diversity of side effects. Therefore, the current study was designed to determine the phytochemicals as new drug candidates for treatment and management of schizophrenia. These phytochemicals alter and affect neurotransmission, cell signaling pathways, endocannabinoid receptors, neuro-inflammation, activation of immune system and status of oxidative stress. Phytochemicals exhibiting anti-schizophrenic activity are mostly flavonoids, polyphenols, alkaloids, terpenoids, terpenes, polypropanoids, lactones and glycosides. However, well-designed clinical trials are consequently required to investigate potential protective effect and therapeutic benefits of these phytochemicals against schizophrenia.

Keywords: schizophrenia, phytochemicals, oxidative stress, flavonoids, dopamine

INTRODUCTION

Schizophrenia is a major debilitating disease of adults in every society, affecting about 1–1.5% of global population (Howes and Murray, 2014). The incidence of schizophrenia is higher among males than female at a ratio of 1.4 to 1.0 (McGrath et al., 2008). Schizophrenia is the seventh most costly disorders in the world (Ross and Margolis, 2005; McGrath et al., 2008). It is a syndrome involving positive and negative symptoms, and cognitive problems (McCutcheon et al., 2019). Positive symptoms, including hallucinations and delusions are the foremost feature of this syndrome. Negative symptoms include the failure to express emotions and apathy. Cognitive problems
arise before the appearance of psychosis and can act as a better predictor of the disease (Diener and Lewis, 2019). Unlike other degenerative diseases, its onset occurs during early adulthood or late adolescence (An der Heiden and Häfner, 2000). Schizophrenia predominantly occurs during second and third decade of the life, but it can also affect elderly individuals (Nieminen et al., 2003). It increases the risk of other brain disorders such as Parkinson’s disease, autism, Alzheimer’s disease and multiple sclerosis (Brown, 2012).

A complex interaction of genetic, nutritional, microbial and environmental factors contribute to schizophrenia (Eyles, 2021). Several neurotransmitters such as Dopamine, gamma aminobutyric acid (GABA) and glutamate, serotonin and noradrenaline play a significant role in the pathogenesis as well as progression of schizophrenia (Prestwood et al., 2021). Moreover, schizophrenia also results from interplay of neuro-inflammation, oxidative stress, cell signaling pathways and abnormal immune system activation with schizophrenia (Kokkinou et al., 2021).

Typical anti-psychotic drugs show higher affinity, stronger binding and more inhibition of dopamine receptors than the atypical anti-psychotic drugs. However, atypical anti-psychotic drugs are more effective than the typical antipsychotics as their action at dopamine, serotonin and cholinergic receptors. Individual anti-schizophrenic drugs have variable efficacy in different patients (Bahta et al., 2021). Atypical antipsychotics are generally more effective, but have fewer side effects as compared to typical anti-psychotic drugs. General adverse effects of these synthetic drugs include but not limited to hormonal disturbances, vertigo, tardive dyskinesia, obesity, infertility, neuroleptic malignant syndrome, sedation and agitation. For avoiding these drug related problems, there is a great need of more efficacious and safer remedies (Prestwood et al., 2021).

Phytochemicals are of natural origin that offer cost effective, accessible and valuable source of drugs. Herbal therapies have played their beneficial role throughout human history. Humanity is turning towards herbal therapies due to questionable efficacy and toxic health implications of already used pharmacotherapy of schizophrenia (Datta et al., 2021). Moreover, the progress in developing synthetic anti-schizophrenic drugs is still glaringly slow because of diverse factors such as heterogeneity of schizophrenia phenotypes, ambiguous pathophysiology, pathological lesions, complex genetics changes and other risk factors (Yadav, 2021). Therefore, the phytochemicals offer potential and diverse alternatives to allopathic anti-schizophrenic medicines due to their wide array of biological activities such as anti-inflammatory activity, anti-oxidant potential, affecting neurotransmission, and modulating cell signaling pathways (Arnold et al., 2005; Ross and Margolis, 2005; Rapoport et al., 2005).

Pharmacotherapy of schizophrenia is usually carried out with typical and atypical antipsychotics, but these drugs yield only modest benefits with a diversity of side effects. Phytochemicals are diverse chemicals that offer themselves as useful alternative to conventional allopathic treatments. Therefore, the current review was designed to determine the potential of anti-schizophrenic phytochemicals as new drug candidates and the pre-clinical and clinical progress regarding their antipsychotic action.

**Risk Factors of Schizophrenia**

Schizophrenia is a complex disease which remains rudimentary and has involvement of various genetic, nutritional, microbial and environmental factors (Caspi and Moffitt, 2006; Lewis and Sweet, 2009). A person can have several defective genes, but risk factors such as infections, drug abuse and obstetric complications may conclusively lead to illness (Craddock et al., 2005; Winder et al., 2003). Infections like influenza, rubella, cytomegalovirus, Toxoplasma gondii, herpes simplex virus 1 and 2, and polio virus can predispose the vulnerable individuals to schizophrenia (Brown and Susser, 2002). Obstetric complications including low birth weight, premature birth, rhesus incompatibility, resuscitation at birth time, nutritional deficiency of fetus and emergency caesarean delivery have been strongly correlated to the disease (Kyle and Pichard, 2006; St Clair et al., 2005). After maternal infection, there is an increased production of cytokines that adversely affects the immune system culminating in brain damage (Brown and Derkits, 2010). Nutritional factors that can contribute to schizophrenia include continuous intake of high fat and high sugar diets, and deficiency of vitamin D, B9 and B12. Recent studies showed that a high level of maternal IL-8 had caused anatomical problems in fetus (Meyer 2011; Na et al., 2014).

Schizophrenia has a strong hereditary tendency, showing 10% chance in close relatives of patient. A complex interaction of one or more of 20 genes is responsible for the disease (Harrison and Weinberger, 2005). The genes including neuregulin-1 (NRG1), dysbindin (DTNBP1), disrupted in schizophrenia (DISC1), n-aminoo acid oxidase (DAAO), regulator of G protein signaling-4 (RGS4), catechol-O-methyl transferase (COMT), proline dehydrogenase (PRODH) and G72 are schizophrenia susceptible while several genes affect the glutamatergic transmission pathway in the brain (Craddock et al., 2005; Ross and Margolis, 2005). The effect of various gene expressions on schizophrenia is shown in Figure 1.

There is another phenomenon called endo-phenotypes that is responsible for different clinical symptoms e.g. cognitive defects, neurological abnormalities, impaired emotions and eye movement abnormality (Cannon, 2005; Ross and Margolis, 2005). Different genes control different endo-phenotypes of specific characteristics, inherited in a Mendelian fashion and can cause full schizophrenia if all genes are inherited together (Rapoport et al., 2005; Khandaker et al., 2015).

**Pathophysiology of Schizophrenia**

Etiopathogenicity of schizophrenia is mainly understood based on several hypotheses (Fendri et al., 2006). The dopamine hypothesis remains a mainstay in understanding schizophrenia and is based on the fact that antipsychotics produce their effect by blocking dopamine D2/D3 receptors. It was further validated by the action of those agents which enhance dopamine level (Abidargham, 2004). Hypo-stimulation of D1 receptor in hippocampus causes negative and cognitive symptoms, while hyper-stimulation of dopamine D2 receptor causes positive symptoms in the subcortical regions (Davis et al., 1991).
However, new approaches during recent times have demonstrated a complex interplay among different neurotransmitter circuits (Agren et al., 1991). Another hypothesis indicated that the reduced function of NMDA receptors could produce symptoms of schizophrenia (Moghaddam, 2003; Coyle, 2006). A controlled study showed that antipsychotic drugs positively affected negative symptoms and to lesser extent, cognitive and positive symptoms by increasing the function of NMDA receptors (Coyle, 2006). Moreover, the role of glutamate in schizophrenia was depicted by the discovery of phencyclidine (PCP angel dust) as it induces a psychotic condition by powerful antagonistic action on glutamate receptor i.e. NMDA receptor (Lodge, 1989). The action of dopaminergic neurons may either directly be enhanced by the glutamatergic neurons or indirectly inhibited through the involvement of GABAergic transmission. The interplay of...
different neuronal signals involved in schizophrenia is depicted in Figure 2.

Dopamine, GABA and glutamate are not the only neurotransmitters involved, but serotonin and noradrenaline also play a significant role in the onset of disease. Moreover, many atypical antipsychotics possess adrenergic blocking ability (Hayes and Schulz, 1983). Lysergic acid diethylamide acts as a serotonin agonist on limbic cortex affecting GABAergic neurons that causes a reduction in glutamatergic tone in corticostriatal area resulting in hallucinations (Gellman and Aghajanian, 1991). Newer atypical antipsychotics have better tolerability profile as compared to typical antipsychotics owing to higher affinity for 5HT2A and lower affinity for D2 receptors in comparison to typical antipsychotic drugs (Schotte et al., 1996). Other receptors usually involved are 5HT2C, 5HT6 or 5HT7 and their modulation shows fewer extra pyramidal symptoms (EPS) (Meltzer and Fatemi, 1996).

In recent studies, it was found that atypical anti-psychotic action was partly mediated through their agonistic action at 5HT1A and 5HT2C, and antagonistic action at 5HT6 and 5HT7 (Meltzer, 1999). Some antipsychotics such asphenothiazines, induce less EPS, which shows their effects were partially muscarinic antagonistic in nature. In striatum, dopaminergic terminals have an affinity to affect cholinergic interneurons that eventually affect D2 inhibitory receptors (Pisani et al., 2007). When an antipsychotic agent blocks D2 receptors, it enhances acetylcholine release in striatum. Indeed, it is also now considered that 5HT has no direct involvement in pathophysiology of schizophrenia, but its manipulation with D2 antagonist can produce improved therapeutic effects (Meltzer and Nash, 1991).

**Neurotransmitters and Brain Regions Involved in Schizophrenia**

In addition to several neurotransmitters, there is also huge brain areas implicated in schizophrenia, including brainstem, striatum, limbic cortex, neocortex and basal ganglia (Grace and Gomes, 2019). Imaging studies have revealed the lateral and third ventricle enlargement, loss of some brain volume and, volume deficit in the prefrontal and temporal cortex, para-hippocampus, hippocampus and thalamus (Wright et al., 2000; Sullivan et al., 2003). Other cerebral lesions include cavum septi pellucidum enlargement, and abnormalities in corpus callosum, cerebellar and basal ganglia (Niznikiewicz et al., 2003; Antonova et al., 2004; Honea et al., 2005). Moreover, cyto-architectural abnormalities in the grey matter of entorhinal area, corticolumbic portion, and aberrant neurons in the white matter of prefrontal cortex, para-hippocampus and temporal regions are evident (Arnold et al., 1997; Arnold et al., 2005).

The abnormal dopamine signaling in striatum is responsible for increase of positive and negative symptoms, and decline of cognition in schizophrenia. Striatum mainly associative striatum acts as an integrative hub that moderates communication between limbic and motor regions. In schizophrenia, anomalous dopamine signaling in associative striatum adversely affects integrative functions, connectivity between striatum and cortex disrupting the cortical input from emotional, cognition and motor regions. Dopamine receptors respond differently to dopamine in different regions of striatum. An increased level of D2 receptors was found in associative striatum of schizophrenic patients that was responsible for cognitive deficit and altered neuronal information arriving from various areas of prefrontal cortex (McCutcheon et al., 2019; Simpson et al., 2010).

Summary of various brain regions involved in schizophrenia is shown in Figure 3.

**Oxidative Stress, Inflammation and Immune System Involved in the Schizophrenia**

Recent investigations showed that the oxidative stress and neuro-inflammation played a critical role in the pathogenesis of schizophrenia. Inflammation, oxidative stress and altered expression of proteins collectively lead to schizophrenia. Mitochondrial damage in neurons results in the impairment of mitochondrial respiration and changes in morphology. It also causes a low pH in the brain leading to psychotic symptoms and cognitive defects (Manji et al., 2012; Morris and Maes, 2014). These effects in peripheral tissues work as biomarker of the disease. Oxidative stress is evident both in early onset and chronic schizophrenia (Boskovic et al., 2011). The immune system acts by producing ROS and RNS promoting the release of cytokines that causes neuro-inflammation (Halliwell, 2012). By manipulation of these oxidative stress responses, different new pharmacological treatments can be identified.

An increased amount of ROS and RNS saturates ability of antioxidants, such as glutathione, which neutralize them to cause oxidative stress (Sies, 2015). Inflammomasomes, after formation, can stimulate the production of IL-18 and IL-1B that adversely affect the microglia, macrophages and astrocytes. Interleukins also interact with the cytokines (Calabrese, 2008). Moreover, there is variable response to anti-schizophrenic treatments in patients. An increase in IL-6 is associated with delayed response as resistance to treatment is associated with an elevated level of both IL-6 receptor and Tumor necrosis factor receptor (TNFR) (Lurie, 2018). Furthermore, stress can increase pro-inflammatory cytokines leading to schizophrenia (Müller and Bechter, 2013). There is evidence that schizophrenic
patients have increased level of peripheral plasma cytokines, prostaglandin E2, IL-1, IL-8, and C reactive protein, indicating elevated immune response in peripheral plasma (Miller et al., 2011). It is now established that the immune changes in peripheral blood are indicative of brain function and behavior in different neuropsychiatric disorders (Dantzer, 2004). Understanding the causes and mechanism of neuro-inflammation associated with schizophrenia presents a potential target for the treatment of disease (Watkins and Andrews, 2016).

The involvement of abnormal immune response in pathogenesis of disease is evident (Feigenson et al., 2014). Traditionally, it is thought that the brain is protected immunologically by blood brain barrier, but recent studies demonstrated a complex interaction between brain, systemic inflammation and immune system, altering the mood and behavior (Khandaker et al., 2015). Moreover, alterations in immune system can profoundly affect neurotransmission involved in the pathogenesis of schizophrenia. It can activate the enzyme indoleamine 2,3-dioxygenase involved in tryptophan and kynurenic acid metabolism that influences glutamatergic and serotonergic neurotransmission through these neuroactive metabolites (Müller and Bechter, 2013).

Cholinergic System as Potential Target
Cholinergic system is a potential target for ameliorating the symptoms of schizophrenia, including negative and cognitive symptoms. This system affects working memory, attention and motivation (Berman et al., 2007). As, Nicotinic acetylcholine receptors (nAChR) belong to family of ligand gated ion channel and its homomeric subtype, nAChR-a7 is found in central and peripheral nervous system. It found to have pivotal role in the pathophysiology of several neurological disorders including psychosis. There is a direct role of nAChR-a7 and muscarinic M1 receptor in schizophrenia symptoms (Ochoa and Lasalde-Domnicci 2007; Raedler et al., 2007). Hence, agents acting on these targets are potential candidate for treating schizophrenia.

Phosphodiesterase Inhibitors for Schizophrenia
Phosphodiesterases (PDE) are the enzymes often targeted for their pharmacological inhibition because PDE inhibitors can potentiate the effect of different physiological processes which are mediated by cGMP or cAMP. These are identified as a new adjunctive therapy for different diseases including schizophrenia (Madeswaran et al., 2012).

Signaling Pathways as Treatment Target for Schizophrenia
It is found that the level of glycogen synthase kinase-3 (GSK-3) is increased while Akt (protein kinase) is reduced in schizophrenic patients (Sahin et al., 2014). Dopamine regulates lithium sensitive signaling cascade that involves GSK3β. Modulation in its increased activity can have impact on long lasting remission of the disease (Duda et al., 2018). A protein kinase, called Akt, is involved in a variety of functions such as neuronal cell size regulation, synaptic plasticity and cell survival, while Akt1 has the most important role in schizophrenia. It is activated by phosphorylation. The GSK-3, regulating the synaptic plasticity, is inactivated after phosphorylating with Akt1. The reduced level of Akt1 also decreases phosphorylation of GSK, thus the activity of GSK-isofom GSK-3β is enhanced in the frontal cortex area of schizophrenic patients. Antipsychotic drugs are expected to increase Akt activity through blockade of D2 receptor activation (Karam et al., 2010). Other molecules such as Wnt, are lipoglycoproteins, which regulate embryonic development by acting as signaling molecules. Dysregulation in the Wnt signaling pathway contributes to various human diseases including schizophrenia. Moreover, reduction of β-catenin, increase in Wnt-1 expression and reduced GSK-3β contribute to multifaceted kinase present in Wnt signaling (Hoseth et al., 2018). Investigations are being carried out on natural and synthetic agents affecting these cascades in order to cope with schizophrenia.

Alteration in Hormonal Balance for Treatment Option of Schizophrenia
The protective role of estrogen against schizophrenia has been demonstrated previously. Recent clinical trials have validated the usefulness of estradiol in the treatment of disease (Gogos et al., 2015). Oxytocin and vasopressin have been implicated in the disease etiology and the antagonistic approach against vasopressin V1A receptors may provide an opportunity for treating schizophrenia (Park et al., 2020).

Current Pharmacological and Non-pharmacological Treatments
Antipsychotic drugs are also called neuroleptics (meaning, taking hold of one’s nerves) and are used to manage acute and chronic schizophrenia symptoms. Generally, first generation (typical) and second generation (atypical) anti-psychotic drugs are used in allopathy (Khandaker et al., 2015). Typical antipsychotics include chlorpromazine, thioridazine, fluphenazine, trifluperidol, flupenthixol, loxapine, triflupromazine, trifluperazine, haloperidol, penfluridol and pimozide. Risperidone, clozapine, ariprazole, olanzapine, ziprasidone, quetiapine and sulpiride are a few examples of atypical antipsychotic drugs. Atypical antipsychotics are generally more effective, but have fewer side effects as compared to typical anti-psychotic drugs [27]. General adverse effects of these synthetic drugs include but not limited to diabetes, dizziness, tardive dyskinesia, weight gain, sexual dysfunction, neuroleptic malignant syndrome, sedation and agitation. For avoiding these drug related problems, more efficacious and safer remedies are needed [36].

Several non-pharmacological treatments are currently used for the management of schizophrenia. Aromatherapy and aroma massage are helpful in ameliorating depressive symptoms of schizophrenia [54]. Acupuncture activates different brain
| Chemical Class | Phytochemical | Source | Assay/Test | Animal/Cell Type | Doses | Method | Mechanism | Result | References |
|----------------|---------------|--------|------------|------------------|-------|--------|-----------|--------|------------|
| Alkaloids      | Arecoline     | Areca catechu | Y-maze Behavioral test | cuprizone induced mouse model | 0, 2.5, or 5 mg/kg/Day | Recorded spontaneous alternation behavior | Preventing white matter injury, prevented memory impairment | Attenuated spatial working memory impairment, increased the expression of myelin basic protein in the frontal cortex | Xu, Adilijiang, Wang, You, Lin, Li and He (2019) |
|                | Stepholidine  | Stephania intermedia | Paw test Pre-pulse inhibition | Male Wistar rats | 4–16 mg/kg | Determined limb retraction time and D1 receptor agonist and D2 receptor antagonist | Reverse apomorphine induced disruption | Ellenbroek, ZHANG and JIN (2006) |
|                | Galantamine   | Galanthus caucasicus | Dopamine receptor agonism by apomorphine, NMDA antagonism by MK-801, muscarinic receptor antagonism by scopolamine | Wistar rats | 0.3, 1.0 and 3.0 mg/kg | Apomorphine agonism, NMDA and Ach antagonist models | Increase in cholinergic activity | Pre-pulse inhibition was improved | Hohnadel et al. (2007) |
|                | Corymine      | Hunter zeylancia | 2 electrode voltage clamp technique | cDNA clones of NR1a and NR2b OF Xenopus | 100 µM | Potentiating effect of corymine was induced in presence of glycine | Potentiation on NMDA response | Potentiates the NMDA induced currents and can be used for schizophrenia | Leewanich et al. (2005) |
|                | Reticuline    | Ocotea duckei | Amphetamine induced hyper-motility | Swiss albino mice | 50–100 mg/kg | Number of steps recorded | Dopamine antagonist activity | Reduced hyper-motility | Morais, Barbosa-Filho and Almeida (1998) |
| Geissoschizine methyl ether | Uncariae ramulus | Cell based Calcium imaging analysis | Human cell line and mouse brain tissue | Inhibited dopamine induced calcium response | Partial agonist/antagonist at D2, partial antagonist at SHT receptors | Inhibited calcium induced serotonin current | Costa-Campos, Lara, Nunes and Elisabetsky (1998) |
| Psychollatine  | Psychotria umbellata | Male adult mice | a) Apomorphine induced climbing b)MK-801 induced hyperactivity | Climbing behavior and locomotion determined | 100 mg/kg | | | | Costa-Campos, Lara, Nunes and Elisabetsky (1998) |
| Alstonine      | Picralima nitida | Male albino mice Male Wistar rats | a) Apomorphine induced stereotypy, b) haloperidol induced catatonia | Determined behavioral score and catatonic time | 0.5 to 2 mg/kg | | | | Costa-Campos, Lara, Nunes and Elisabetsky (1998) |
| Physostigmine  | Physostigma venenosum | Conditioned emotional response | Male Wistar rats | Pre-exposure and conditioning | 0.5 mg/kg | | | Reverse the cognitive impairment in schizophrenia | Barak and Weiner (2010) |

(Continued on following page)
| Chemical Class | Phytochemical | Source | Assay/Test | Animal/Cell Type | Doses | Method | Mechanism | Result | References |
|----------------|--------------|--------|------------|-----------------|-------|--------|-----------|--------|------------|
| Amino acid and derivatives | Leucine | Cucurbita pepo | Apomorphine induced stereotypy, Haloperidol induced catalepsy | Wistar rats | 0.7 mg/kg | Stereotypy, catalepsy | Anti-dopaminergic effect | Decreased stereotypy, potentiated catalepsy | Suresh and Raju (2013) |
| Betaine | Beta vulgaris | | Apomorphine induced stereotypy. Haloperidol induced catalepsy | Male ICR mice | O, 30, 100 mg/kg | Modulation of NMDA R glycine site | Attenuated ketamine induced disruption in PPI, improved novel recognition | Lin et al. (2016) |
| Bioflavonoids/Polyphenols | Quercetin-3-rutoside | Fagopyrum esculentum | PCR-RFLP method | Human brain | 10 µmol | Hetero-plasmic sequence variation determined | Anti-dopaminergic effect | Reduced oxidative stress | Marchbanks et al. (2003) |
| Scopoletin | Morinda citrifolia | a) Apomorphine induced Cage climbing, b) Amphetamine induced stereotypy | Male ICR mice | 0.1 mg/kg | Climb and stereotypy determined | Anti-dopaminergic effect | Quench the superoxide production | Pandy and VjeePallam (2017) |
| Quercitin | Lonchocarpus cyanescens | Novel object recognition (NOR) | Balb-C mice | 25 and 50 mg/kg | Memory impairment model by ketamine used | Antioxidant potential | Improves cognitive deficit | Mert, Turgut, Arslanbas, Gungor and Kara (2019); Moore and Martin (1957); Pereira et al. (2011) |
| Myricitrin | Eugenia uniflora | Apomorphine induced stereotypy, catalepsy and paw test | Swiss albino mice Wistar rats | 5.10 and 30 mg/kg | Stereotypy, climbing, limbs retraction and catalepsy noted | Nitric oxide and Protein kinase C inhibitor | Blocked stereotypy, climbing, impaired retraction time of limbs, increased catalepsy | Young et al. (2008); Calabrese et al. (2017) |
| Cannabinoids | Cannabidiol | Cannabis sativa L | Apomorphine induced stereotypy | Male Wistar rats | 15–480 mg/kg | Stereotypy and prolactin secretion were measured | Blockade of serotonin reuptake or increased GABAergic activity regulations of SIRT1 and downstream BDNF expression in the hippocampus | Attenuated the stereotypy and increase in prolactin | Zuardi et al. (1991) |
| Carotenoids | Crocin | Crocus sativus L | MK-801 induced Rotarod test, open field test | Neonatal Sprague Dawley rats | 25,50 mg/kg | Balance, motor coordination and locomotion | Neuroprotective efficacy, might be useful for schizophrenia | Sun, Zhao, Xie and Wan (2020) |
| Cholesterols | Hydroxytyrosol | Olea europaea | Prenatal restraint stress model | Sprague dawley rats | 10 and 50 mg/kg/day | Spontaneous alteration performance, Morris water maze test performed | Antioxidant, anti-inflammatory and brain protecting | Improves cognitive functions and Might be used for schizophrenia | Young et al. (2008); Calabrese et al. (2017) |
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| Chemical Class | Phytochemical | Source | Assay/Test | Animal/Cell Type | Doses | Method | Mechanism | Result | References |
|---------------|--------------|--------|------------|------------------|-------|--------|-----------|--------|------------|
| Glycosides    | Bacosides A and B | *Bacopa monnieri* | Novel object recognition test | Rat | Step-through Passive-Avoidance Task | receptor-ERK signaling | might be beneficial for schizophrenia | Wetchateng and Piyabhan (2014) |
|               | sulfuraphane  | *Brassica oleracea* | Locomotor activity, Pre-pulse inhibition | Male mice | 30 mg/kg | Hyper-locomotion and PPI deficits were examined | Increasing VGLUT2 density to normal level | Increase in Discrimination Ratio score | Shirai et al. (2012) |
| Hypericin     | Hypericum perfolatum | | | | | | | Might be used for schizophrenia | Butterweck et al. (2002); Mizuno et al. (2008); Mizuno et al. (2010) |
| Emodin        | *Rheum rhubarbarum* | | Acoustic startle response, Methamphetamine induced hyper-locomotion | Sprague dawley rats | 50 mg/kg | Startle response and locomotor activity | Targets ErbB signaling alters dopamine and serotonin metabolism | Attenuated PCP-induced hyper-locomotion and PPI deficits | |
| carotinoids   | *Nerium oleander* | | | NMRI male albino mice | | | | Might be used for schizophrenia | Zhang (2004) |
| Polygalasaponins | *Polygala tenuifolia* | | a) Female TO mice | 25–500mg/kg | Animal’s movements, behavioral patterns and hyperactivity measured | Dopamine and serotonin antagonist activity | Might be used for schizophrenia Reduction in climbing, stereotypy and hyperactivity | Chung et al. (2002) |
|               | | | b) Male lister hooded rats | | | | | |
| Diosmin       | *Scrophularia nodosa* | | Apomorphine induced stereotypy, catalepsy | Swiss male mice | 25, 50, 100 mg/kg | Stereotypy scoring, cataleptic behavior | Enhancement of GABAergic neurotransmission Interaction with NMDA receptor | Attenuated stereotyped behavior, devoid of cat Good docking score | Eneri et al. (2020); Bagchi and Somashekhar (2014) |
| Picriside II, | *Picrorhiza scrophulariiflora* | In vitro studies | | | Docking studies | | | |
| Polyphenols   | *Resveratrol* | *Vitis vinifer* | a) Apomorphine induced stereotypy | Swiss albino mice | 200 and 400 mg/kg | Stereotypy and grooming determined | D1 receptor antagonistic effect | Decreased climbing and swim induced grooming | Magaji et al. (2017) |
|               | | | b) Swim induced grooming | Wistar rats albino mice | 50–400 mg/kg (i.p) | Stereotypy was measured, Spontaneous motor activity was measured | | Suppressed stereotyped behavior, Reduction in spontaneous motor activity | Sonibare et al. (2012) |
| Kaempferol    | *Loranthus cyanescens* | | a) Amphetamine induced-stereotype | | | | | |
| Rutin         | *Morinda citrifolia* | | a) Apomorphine induced stereotypy | Male ICR mice | 0.1 mg/kg | Climbing and stereotypy determined | Inhibition of D2 receptors | Reduction in climbing and stereotypy | Pandy and VijeePallam, (2017) |
|               | | | b) Open field test | | | | | |

(Continued on following page)
| Chemical Class | Phytochemical | Source | Assay/Test | Animal/Cell Type | Doses | Method | Mechanism | Result | References |
|----------------|--------------|--------|------------|------------------|-------|--------|-----------|--------|------------|
| Curcumin       | Curcuma longa| Assay based on tietze method | Mice | 10 and 50 µM | Oxidized and reduced GSH level determined | Antioxidant action | Increased GSL and GSH level in astrocytes and neurons | Lavoie et al. (2009) |
| Genistein      | Genista tinctoria L | Locomotor activity, forced swim test, active avoidance | rats | 50 mg/kg | Hyperactivity, immobility, avoidance | Anti-dopaminergic activity due to increased estrogen | Hyperactivity, enhanced immobility and decreased avoidance | Kalpana, Raju and Merugu (2014) |
| Gallic acid    | Camellia sinensis | Ketamine-induced psychosis | Swiss albino mice | 50, 100 and 200 mg/kg | Stereotopy, locomotor activity | Enhancement of NMDA receptor function | Stereotopy improved and locomotor activity increased | Yadav et al. (2018a) |
| Morin          | Allium cepa  | Open field, apomorphine-induced stereotypy, ketamine-induced stereotypy | Male Swiss mice | 50 and 100 mg/kg | Locomotor activity, stereotypy | Might be enhancement of GABA activity | Decreased stereotypy and locomotion | Ben-Azu et al. (2018) |
| Polypropanoid  | Alpha (α)—asarone | Apomorphine-induced stereotypy | Swiss albino mice | 30 and 50 mg/kg | Climbing time and climbing behavior determined | Anti-dopaminergic property | Decrease in the cage climbing time and climbing behavior | Pandy and Vijeepallam (2016) |
| Sesquiterpene  | Tutin | Coriaria ruscifolia | Mouse spinal cord neurons Molecular docking | 1, 3, 5 and 8 mg/kg | Inhibit GABA A receptor | Inhibition of GluN2B-containing NMDARs | Might be useful or schizophrenia | Fuentealba et al. (2007) |
| Steroids       | Anaferine, Beta-Stitostrol, Withaferin A, Withanolide A, Withanolide B and Withanolide D | Withania somnifera | Molecular docking | | | | | |
| Sterol         | Stigmastanol | Akebia quinata | Ketamine induced stereotypy | Swiss albino mice | 50 mg/kg | Stereotopy and hyperlocomotion measured | Antioxidant action and increase in GABA and decrease in dopamine and acetylcholine | Decrease in stereotypy and locomotion | Yadav et al. (2018b) |
| Terpenoid      | 1,8-cineole | Hyptis martusai | Haloperidol-induced catalepsy, and ketamine-induced hyperkinesia | Female Swiss mice | 50 mg/kg | Catelepsy and hyperkinesia | Possible modulation of dopaminergic and glutamatergic systems | | |
| Xanthone/ Polyphenol | α-mangostin | Garcinia mangostana L | Pre-pulse inhibition (PPI) test, open field test (OFT), forced swim test (FST) | Sprague Dawley dams and offspring | 20 mg/kg | Sensorimotor gating, locomotor activity and depressive behavior determine | Antioxidant, %PPI, locomotor hyperactivity and depressive like behavior were reversed | | |
| Magniferin     | Magnifera indica | Open field test | Swiss mice, Wistar rat | 50 mg/kg | Locomotor behavioral changes | Antioxidant, anti-inflammatory effect | Overcome grooming and stereotype | |
regions involved in controlling emotions of schizophrenic patients [42]. For improvement of constant negative symptoms, loving kindness mediation (LKM) has been proved useful [39]. Yoga and aerobic exercises are also very helpful for the psychiatric symptoms of schizophrenia [49].

Phytochemicals and Their Role in Schizophrenia

About 80% of the total population of Asia and Africa are dependent on natural therapeutics. Mainstream antipsychotic drugs are associated with several adverse effects. Therefore, several phytochemicals have been investigated for neuroprotection and anti-psychotic action in cell culture and animal models of CNS disorders. The vast majority of studies have demonstrated that the anti-psychotic and neuroprotective action of phytochemicals is due to their antioxidant action [19]. As pathophysiology of schizophrenia clearly depicts oxidative burden in brain, so the natural antioxidants in the form of extracts or individual phytochemicals are effective for treatment of schizophrenia. These phytochemicals have gained attention due to their therapeutic value, less adverse effects, better safety profile and high efficacy (Gao and Snyder 2013; Choudhury et al., 2014). Several phytochemicals investigated in pre-clinical and clinical studies are shown in Table 1 and 2.

Phytochemicals showing efficacy against schizophrenia belong to different phytochemical classes such as alkaloids, tannins, glycosides, phenolic acids, flavonoids, terpenes, terpenoids and essential oils. Theses phytochemical classes are summarized in Figure 4.

Alkaloids

Alkaloids are present in all plant parts, especially in flowers (Girdhar et al., 2015). These are mainly useful in treating several neurodegenerative disorders. These phytochemicals are effective against schizophrenia via affecting acetylcholine concentration, increasing GABA, antagonizing NMDA receptors, anti-oxidant action, anti-amyloid activity and, preventing neuro-inflammation (Dey and Mukherjee, 2018). Several alkaloids have now been investigated for treatment of schizophrenia. Arecoline, a pyridine alkaloid, has shown a capacity for muscarinic receptors as cholinergic agonist and can improve cognitive symptoms in schizophrenic patients. It also exerts antioxidant action and prevents demyelination of the cerebral white matter to attenuate memory impairment (Xu et al., 2019). Stepholidine, a protoberberine alkaloid, has a special feature of combined D1 agonist and D2 antagonist effect, and is useful in improving memory deficit in schizophrenia (Ellenbroek et al., 2006). Apomorphine, including apomorphine, reportedly caused amelioration of schizophrenic symptoms in patients by potently antagonizing dopamine at its receptor site (Smith et al., 1977; Fletcher et al., 1996). Isoquinoline alkaloids have also been investigated against schizophrenia. Galantamine increases the NMDA current in the rat cortical neurons. It also enhanced the effects of Ach by positive modulation of nAChR that decreased the attentional impairment and, increased short term memory and attention (Moriguchi et al., 2005; Schubert et al., 2006). A combination of galantamine and memantine was effective to enhance cognition in schizophrenic patients (Koola et al., 2014). Reticuline has also demonstrated antipsychotic activity through anti-dopaminergic actions (Morais et al., 1998).

Nicotine, a pyidine alkaloid, was effective in schizophrenic patients to improve attention deficit through action as an alpha nicotinic receptor agonist (Levin et al., 1998). Some indole alkaloids, such as corymine, potentiated the NMDA current and showed efficacy against schizophrenia, while alstonine showed anti-schizophrenic effect by modulating the dopamine uptake and NMDA receptor. These alkaloids also reduced behavioral problems of schizophrenic patients (Costa-Campos et al., 1998). The ameliorating effect of geissoschizine methyl ether against schizophrenia also occurred through modulation of dopamine receptors as well as partial antagonistic effect against NMDA receptors.

Glycosides

In glycosides, a sugar moiety is attached to non sugar molecule through glycosidic linkage. Glycosides are present in plants as secondary metabolites and are their “offense and defence” components (Shadkami and Jones, 2012; Wang et al., 2016). A study on use of bacoside A and B isolated from Bacopa monnieri has shown an improvement in cognitive defects in schizophrenic model by increasing vesicular glutamate transporter 2 in cingulate gyrus region (Wetchateng and Piyabhan, 2014). Isothiocyanates, such as sulforaphane, exhibited antipsychotic activity through activation of Nrf2 pathway, detoxification of phase 2 enzymes and, antioxidant action by enhancing electrophilic response elements (Shirai et al., 2012). Hypericin is nephthodianthrone and exhibits antioxidant properties. It inhibits D3/D4 receptors and is a candidate drug for the management of schizophrenia (Butterweck et al., 2002; Saranya et al., 2019). Emordin Targets ErbB signaling and alters dopamine and serotonin metabolism to exhibit ameliorating effects against schizophrenia symptoms (Mizuno et al., 2008; Mizuno et al., 2010). Polyagalasaponin, a saponin glycoside, has anti-schizophrenic activity due to its dopamine and serotonin antagonist activities (Chung et al., 2002). It is also found that iridoid glycosides and cardenolides were effective in treating psychotic symptoms that required further investigation. Beta sitosterol also inhibited the GluN2B-containing NMDA receptors as demonstrated by docking studies. Picroside II also showed in vitro potential of antipsychotic activity (Bagchi and Somashekar 2014; Kumar and Patnaik 2016).

Polyphehols

Polyphehols are plant secondary metabolites that have demonstrated neuroprotective and anti-schizophrenic activity. Several studies have indicated that these are useful against neurologic and psychotic disorders (Wu et al., 2009). Kaempferol has demonstrated neuroprotective effects against schizophrenia due to its anti-inflammatory, antioxidant and anti-apoptotic effects (El-Kott et al., 2020). Baicalin is reported to ameliorate negative symptoms and cognitive dysfunction in psychosis. This psychotic effect may be attributed to its anti-
| Chemical Class | Phytochemical | Source | Assessments | Dose | Study Design | Mechanism | Result | References |
|---------------|---------------|--------|-------------|------|-------------|-----------|--------|------------|
| Alkaloids     | Apomorphine   | *Nymphea caerulea* | Interview using NHSI (new haven schizophrenia index) | 1.5 to 6 mg | Randomized double blind placebo study | Potent effect on presynaptic dopamine receptors in addition to its postsynaptic stimulation | Decrease in psychotic symptoms in chronic patients | Smith et al. (1977); Fletcher, Frith et al. (1996) |
| Reserpine     | Rauolfa serpentina | | Seven-point behavioral rating scale | 1–8 mg/day | Controlled study of 8 months | Depressor of hypothalamus and facilitator of synaptic transmission | Marked improvement in behavior occurred | Cowden et al. (1955) |
| Nicotine      | Nicotiana tabacum | | Profile of mood states (POMS) and continuous performance test (CPT) | 7 mg/day | N/A | Alpha 7 nicotinic receptor agonist | Attentional function is increased | (Levin, Conners, Silva, Hinton, Meck, March and Rose 1998) |
| Amino acid and derivatives | Glycine | *Glycine max* | PANSS and Scale for assessing Negative Symptoms (SANS) | 0.14 to 0.8 g/kg/day | Open label trial | Potentiate NMDA transmission | Improvement in negative symptoms | Lederman et al. (1996) |
| Sarcosine     | *Arachis hypogaea* | | Positive and Negative Syndrome Scale total score | 1–2 g/day for six weeks | Double blind randomized clinical trial | Glycin 1 transport inhibitor, increases N-methyl-D-aspartate transmission | Reduced positive and negative syndromes in anti-psychotic naïve patients | Lane et al. (2008) |
| Cannabinoids  | Tetrahydrocannabinol | *Cannabis ruderalis* | Clinical global impression, brief psychiatric rating scale | 2.5 to 10 mg twice a day | Clinical case study | Affecting endocannabinoid receptors | Refractory schizophrenia symptoms improved | Schwarcz et al. (2009) |
| Cannabidiol   | *Cannabis sativa* | | Positive and negative symptoms, Global assessment of functioning scale | 1000 mg/day for six weeks | Double blind randomized clinical trial | As adjunct therapy | Reduced positive symptoms and improved cognitive performance | Philip McGuirePsych. et al. (2018) |
| Flavonoids/ Polyphenols | Luteolin | *Salvia rosmarinus* | N/A | N/A | N/A | Modifier of NMDA function | Schizophrenic symptoms decreased | Hannan et al. (2021) |
| Apigenin      | *Perilla frutescens* | N/A | N/A | N/A | N/A | Restore function of NMDA receptor by modulating hSKCa3 channel | Schizophrenic symptoms decreased | Hannan et al. (2021) |
| Phenolic acid and derivatives | Sodium benzoate | *Styrax benzoin* | Assessment of positive and negative symptoms, and clinical global impression in treatment refractory schizophrenia | 0.5 g twice a day for 12 weeks | Double blind randomized clinical trial | As adjunct therapy | Lack of efficacy in patients with early psychosis | Scott et al. (2020) |
| Sodium benzoate | *Styrax benzoin* | | Clinical Global Impression (CGI), assessment of negative symptoms | 1 g/day for six weeks | Double blind randomized clinical trial | o-aminic acid oxidase inhibitor | Improvement of clinical symptoms and recognition | Lane et al. (2013) |

(Continued on following page)
prolyl-oligopeptidase, anti-inflammatory and antioxidant actions (Miao et al., 2020; Tarragó et al., 2008).

Quercitin, a bioflavonoid, has potential to improve symptoms of schizophrenia due to its free radical scavenging activity (Mert et al., 2019). Myricitrin is an inhibitor of nitric oxide and Protein Kinase C. Its anti-schizophrenic effect is attributed to antioxidant action (Amanzadeh et al., 2019). Scopoletin and rutin are useful for alleviation of positive symptoms of schizophrenia due to the inhibitory interaction with D2 receptor (Pandy and VijeePallam 2017). Xanthones, such as α-mangostin and magniferin, have also been studied for anti-schizophrenic activity. α-mangostin is an antioxidant and has anti-inflammatory properties. It also inhibited phosphodiesterases and 5HT2A receptors, and was shown to be effective in rodent models of schizophrenia. Magniferin improved cognition by its antioxidant mechanism, preserving mitochondrial functions, anti-inflammatory activity and, reduction of dopamine (Lotter 2018; Lum et al., 2020). Hydroxytyrosol is a cholesterol which showed neuroprotection for multiple neurological and psychological diseases. It decreased oxidative stress by activation of Nrf2 pathway and enhanced the mitochondrial functions. It restored the learning ability and memory in prenatal stressed animal and human offspring, when administered during pregnancy, showing its vitality.

TABLE 2 | (Continued) Antipsychotic potential of phytochemicals in clinical studies.

| Chemical Class | Phytochemical | Source | Assessments | Dose | Study Design | Mechanism | Result | References |
|----------------|---------------|--------|-------------|------|--------------|-----------|--------|------------|
| Polyphenols    | Resveratrol   | Vitis vinifera | positive and negative symptoms scale and extrapyramidal symptoms scale | 200 mg/day for eight weeks add-on therapy | Double blind randomized clinical trial | Managed negative symptoms and increased efficacy of risperidone | Samaei et al. (2020) |
| Sesquiterpenoids | Caryophyllene | Cannabis sativa | N/A | 25 to about 100 mg add-on therapy | Clinical trials (application N° EP13763464.8A) | CB2-selective phytocannabinoid | Might improve schizophrenia symptoms | Anavi-goffer and Gertsch (2015) |

FIGURE 4 | Phytochemical classes effective against Schizophrenia.
for preserving neurogenesis and cognitive functions in off springs (Chen and Wei, 2021).

Curcumin is known for its several beneficial effects on the nervous system attributed to its ability to raise the level of reduced glutathione (Lavoie et al., 2009; Miodownik et al., 2019). Curcumin exerted add-on effects of regular antipsychotic drugs in chronic schizophrenic patients. Such treatments have shown improvement in negative symptoms of schizophrenia. Curcumin regulates the gene expressions involved in inflammation and modulates NMDA activity, which are associated with symptoms of schizophrenia. Morin also exhibited anti-psychotic like effects, without exerting extrapyramidal side effect, by enhancing GABA activity (Ben-Azu et al., 2018). Gallic acid also plays protective role against psychotic like behaviour through enhancement of NMDA receptor (Yadav et al., 2018b). Nobiletin, a flavonoid, improves hypo-functioning of NMDA receptors by acting on extracellular signal-regulated kinases (ERK) signaling and ameliorates cognitive symptoms of schizophrenia (Nakajima et al., 2007).

Diosmin, a flavone, enhances GABA transmission to treat symptoms of schizophrenia (Eneji et al., 2020). Naringin is a flavonoid that acts on Wnt/β catenin and Akt/GSK-3β pathways to exert anti-schizophrenic effect (George et al., 2020). It is also found that genistein, an isoflavone, had exhibited therapeutic effects against different symptoms of schizophrenia by acting on estrogen receptor and affecting dopamine pathway (Kalpana et al., 2014). Furthermore, both apigenin and luteolin have demonstrated considerable potential to improve the symptoms of schizophrenia (Zhao and So, 2018).

**Terpenes and Terpenoids**

Tutin is a sesquiterpene that inhibited glycnergic activity and blocked GABA-A receptors. Moreover, 1,8 cineole is a monoterpenoid that acts on dopamine and glutamate pathways. Caryophylline is a sesquiterpene isolated from essential oils that acts as phytocannabinoid and is being effectively investigated in clinical research of schizophrenia (Kucerova et al., 2014).

**Cannabinoids**

Cannabinoids belong to terpenoid class and are helpful in the treatment of neurodegenerative diseases. Results of a meta-analysis have concluded that the patients of schizophrenia have increased amount of endocannabinoid anandamide in their blood, cerebrospinal fluids and cannabinoids 1 receptors (CB1) present on immune cells (Davies and Bhattacharyya, 2019). Three randomized trials have reported the reduction in disease positive symptom and improved cognition by using cannabidiol (White, 2019).

Cannabidiol is a cannabinoid that blocks the serotonin uptake and increases GABAergic activity to exert anti-schizophrenic effect. This effect was also evident in schizophrenic patients who used cannabis (Morgan and Curran, 2008). Moreover, cannabidiol had also shown a clear advantage in clinical studies over other antipsychotics as it did not exhibit any movement like problems associated with the use of other antipsychotics (García-Gutiérrez et al., 2020).

Another cannabinoid, tetrahydrocannabinol, also improved the symptoms of schizophrenia due to its effect on the endocannabinoid receptors (Schwarz et al., 2009). On the other hand in some reports suggested that the 9-tetrahydrocannabinol administration had increased the symptoms of psychosis. But researchers reported that tetrahydrocannabinol might have dose dependent effect. As at low doses, it improved the symptoms of psychosis while it inflicted disruption to brain circuits causing worsening of psychotic symptoms at large doses.

**Phytosterols**

Phytosterols and oxyphytosterols (oxidation products of phytosterol) are naturally synthesized by several plants. Exposure of these natural agents is growing due to increased intake of plant food enriched with phytosterol and oxyphytosterol (jie et al., 2020).

Stigmasterol is a phytosterol present in vegetables, legumes, nuts, herbs and seeds. It is shown to inhibit ketamine induced biochemical, histopathological and behavioral alterations in mice to exhibit antipsychotic potential. It manages psychosis by ameliorating inflammation and oxidative stress, and by altering dopaminergic, acetylcholinergic and GABAergic neurotransmission (Yadav et al., 2018a).

**Carotenoids**

Saffron (Crocus sativus L.) and its active constituents such as crocins and safranal have shown high potential for treatment of various central nervous system disorders such as anxiety, depression and memory deficit (Pitsikas, 2015). Crocin is a carotenoid that showed effectiveness as antipsychotic drug by regulating Brain-derived neurotrophic factor (BDNF) in hippocampus (Sun et al., 2020). There are increasing preclinical evidences that crocins reversed the ketamine induced memory deficit, hypermotility and social isolation at 15–50 mg/kg dosage in rats (Georgiadou et al., 2014). It is also found that crocins had inhibited the apomorphine induced deficit in novel object recognition task associated with dopaminergic dysfunction in rats (Pitsikas and Tarantilis, 2017). Based on better safety profile and the preclinical evidences of efficacy against psychosis, there is strong need for controlled clinical studies of these agents against schizophrenia (Pitsikas, 2021).

**Other Phytochemicals**

Alpha asarone belongs to polypropenoid class of essential oils and exerts anti-schizophrenic activity due to antagonism of dopamine D2 and/or D1 receptors (Pandy and Vijepallam, 2016). Glycine is an amino acid which improved the negative symptoms of schizophrenia in an open trial on human. This effect is attributed to its potentiating effect on NMDA receptors (Leiderman et al., 1996). It is found effective against treatment resistant schizophrenia, negative symptoms and cognitive problems when given as adjuvant to other medical therapies (Heresco-Levy et al., 2004). Leucine is also
an amino acid that improved schizophrenic symptoms by acting on
dopaminergic receptors (Suresh and Raju, 2013).

Kava is a known herb for several brain disorders and its activity
was reported due to its constituent kavapyrone. Kavapyrone is a
potential candidate for treating schizophrenia as it increases GABA-A
receptor density and blocks glutamate release (Kumari et al., 2011).
Withaferin A, Withanolide A, Withanolide B and Withanolide D are
steroidal lactones which have shown positive effects on NMDA
receptors through docking studies and can be useful in
schizophrenia after further evaluation (Kumar and Patnaik, 2016).
The effect of various phytochemicals on positive, negative and
cognitive symptoms is summarized in Figure 5.

CONCLUSION

Schizophrenia is a multifactorial disease of complex etiology and
pathogenesis that necessitates multiple targeted drug candidates
for the improvement of positive and negative symptoms, and
cognitive impairment. Natural drugs such as phytochemicals
have demonstrated the therapeutic potential in the
management of schizophrenia through modulation of
oxidative stress, neuro-inflammation, immune system
alterations and downstream signaling pathways, which are the
hallmarks of disease. Alkaloids, glycosides, terpenes, terpenoids,
polyphenols, flavonoids, poly-propanoids, steroidal lactones and
amino acids are among the major classes of phytochemicals that
have shown anti-schizophrenic activity in preclinical
investigations. Apomorphine, luteolin, apigenin, caryophyllene,
cannabinoids, baicalin and reserpine are among the
phytochemicals that have demonstrated the anti-schizophrenic
potential in human studies.

Therefore, it is reasonable to propose that the phytochemicals
might be promising candidates for developing new agents with
protective and therapeutic benefits against schizophrenia.
Moreover, additional preclinical and clinical research is
required for establishing pharmacokinetic and toxicity studies
of phytochemicals, and their best possible combinations to
minimize undesirable adverse effects. Unfortunately, in spite of
abundant neuroprotective potential of the phytochemicals
against schizophrenia, long-term studies of these agents
against schizophrenia have not been carried out to address the
effects of these agents to retard the progression of disease.
Furthermore, the exact doses and combinations of
phytochemicals should be investigated in clinical research to
demonstrate the efficacy and safety in schizophrenic patients.

AUTHOR CONTRIBUTIONS

QA, and AS collected the data. AS, QA, and MA all contributed in
article writing.
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