Herbs And Natural Compounds In Neuropharmacology: Biochemical Innovations of Biomolecules Used to Treat Schizophrenia

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Abstract:

Social disengagement, delusions, hallucinations, disordered thinking, and cognitive deficits are all symptoms of schizophrenia, a severe and long-lasting neuropsychiatric disorder. Environmental, neurochemical, and genetic risk factors, including substance addiction, prenatal stress, family history, and neurodevelopmental abnormalities, are all part of the complicated Etiology. Depression, a higher risk of suicide, and trouble interacting with others are common significant side effects of schizophrenia. Cognitive and neuroimaging testing support the diagnosis, which is mostly based on the DSM-5 criteria. Even though antipsychotic medications are still the mainstay of treatment, interest in complementary therapy has grown due to their ineffectiveness un treating negative and cognitive symptoms as well as the side effects they cause. Numerous chemicals produced by plants may have therapeutic relevance in the treatment of schizophrenia, according to recent phytochemical studies. The anti-inflammatory and antioxidant qualities of Gallic acid, Rutin, and Curcumin may help prevent oxidative stress and Neuroinflammation. An antipsychotic with Neuroprotective and anxiolytic properties, cannabidiol (CBD), exhibits promise. Glycine, an NMDA receptor co-agonist, and nicotinic receptor modification may help with cognitive impairments. By influencing the dopaminergic and cholinergic systems, respectively, Apomorphine and Physostigmine control important neurotransmitter pathways. Alstonine, which comes from Picralima nitida, and Apigenin, a flavonoid, exhibit antipsychotic-like characteristics in preclinical studies. Reticulin, another alkaloid that interacts with dopaminergic receptors, is of Neuropharmacological relevance. These phytochemicals may improve well-established therapies through a variety of pathways, such as dopaminergic, glutamatergic, antioxidant, and anti-inflammatory regulation. To demonstrate their effectiveness, safety, and long-term advantages in treating schizophrenia, more clinical trials are required.

Keywords: Schizophrenia, Cognitive, Depression, Phytomolecules, Anti-oxidant, Antiinflammatory, Neuroprotective, anxiolytic ,Cannabidiol, Neuroinflammation.

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1.Introduction:

Psychotic symptoms, such as delusions and hallucinations that profoundly impact emotions, conduct, and most importantly mental processes and content, are hallmarks of schizophrenia. By improving the activities of the human body's organs, the chemicals can significantly lower the incidence of numerous diseases. It has been demonstrated that many traditional medicinal plants and their parts have therapeutic value and can be used to prevent, treat, or cure a variety of human illnesses. They desire greater authority over their own medical treatment .[1,2]. Mental diseases affect at least 700 million people worldwide.[3] .At least 1% of people worldwide suffer from schizophrenia or schizophrenia spectrum and other psychotic disorders, which are among the most severe.[4]. To improve the accuracy and precision of the diagnosis, the word spectrum was introduced to the category of schizophrenia in the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders.[5]. Schizophrenia, other psychotic diseases, and schizotypal (personality) disorder are all included in the spectrum of psychotic disorder. Approximately 76–85% of people with major mental problems in low- and middle-income countries still struggle to receive professional psychiatric therapy; for this reason, traditional healing practices are seen as a promising treatment alternative.[6,7] .
Findings from The Consortium on the Genetics of Schizophrenia (COGS), a multi-site NIMH-sponsored partnership that examines the genetic foundation of 12 primary and numerous subsidiary potential Endophenotypes in individuals with schizophrenia and their family members, are presented in this Special Issue (COGS-1). In order to increase sample ascertainment and, consequently, the power for genetic linkage and association research, the COGS method has been to get Endophenotype data across several geographically dispersed

sites. According to COGS-1, patients with schizophrenia exhibit significant endophenotype deficits. Ave on shown that persons with mental illnesses refrain from getting treatment out of fear of stigmatise [8] . Numerous studies Hiton and its repercussions. They conceal their ailment if they attend a service and it is diagnosed. Because a diagnosis is stigmatised and associated with ideas of danger, incurability, and unpredictability, doctors are reluctant to give them. This makes patients feel as though there is no hope and that there is no use in adhering to advice regarding their lifestyle or how to treat their illness. [9,10,11] .This study revealed the plant materials and biomolecules of natural origin used to treatment and management of schizophrenia at the same time make aware the medical field to discover new lead molecules from plant origin to avoid the unwanted adverse reactions producing by synthetic drugs.

2.Pathophysiology:

Dopamine hypothesis:

The mesolimbic pathway's overactive dopaminergic transmission is linked to pleasant symptoms including delusions and hallucinations. Negative and cognitive symptoms may be exacerbated by decreased dopamine activation in the prefrontal cortex (neocortical pathway) [12] .

Glutamate Dysfunction:

The symptoms are exacerbated by excitatory/inhibitory imbalance caused by NMDA receptor Hypofunction, particularly on Gabaergic interneurons [13].

Neurodevelopmental Abnormalities:

Adolescents altered synaptic pruning and structural brain alterations (more ventricles, less grey matter) might be contributing factors.[14].

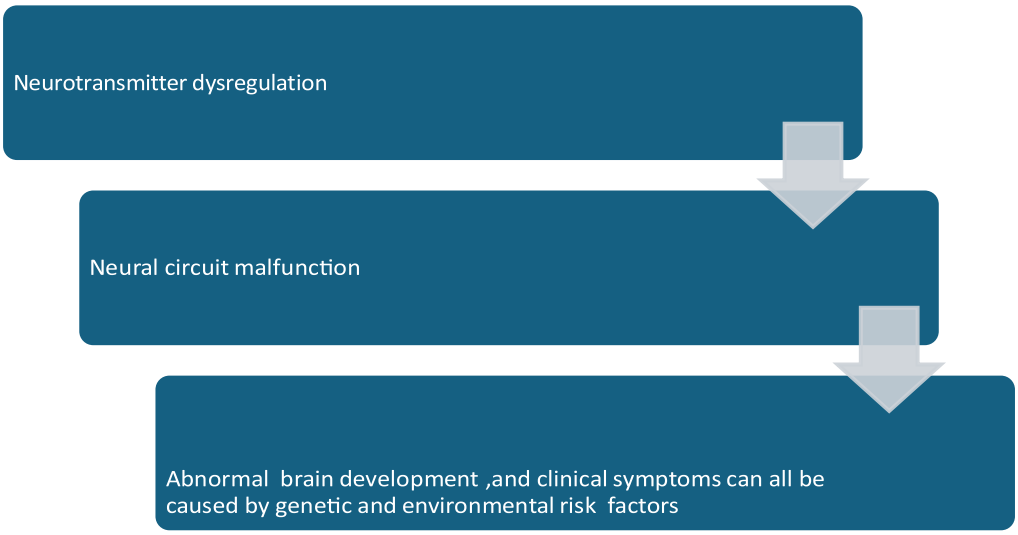
Inflammation and Immune Dysregulation:

Prenatal infections and elevated inflammatory markers (such as CRP and IL-6) have been associated with an increased risk of schizophrenia.[15].

Genetic Factors:

Large-scale genomic research and a number of risk genes (such as DISC1, COMT, and NRG1) demonstrate high heritability.[16].

Flow Chart:[17] .



3.Etiology:

According to twin and family studies, about 80% of the risk for schizophrenia can be attributed to genetic factors [18]. Rare mutations significantly affect risk, but related common genetic variants have less of an effect.[19]. The deletion of chromosome 22q11.2, which raises lifetime risk by 25 times, is one such uncommon mutation.[20].130 genes that are mostly linked to brain differentiation, organisation, and transmission have been shown through genome-wide association studies to raise the risk of schizophrenia. The majority of these genes regulate gene expression rather than being located in coding areas. Interestingly, about 30% of these genes affect the transmission of N-methyl-D-aspartic acid (NMDA) receptors, which in turn affects the presynaptic and postsynaptic components of the glutamatergic synapse. The combined effects of several genes dispersed throughout the genome, each of which contributes little, make schizophrenia a polygenic condition.[21].

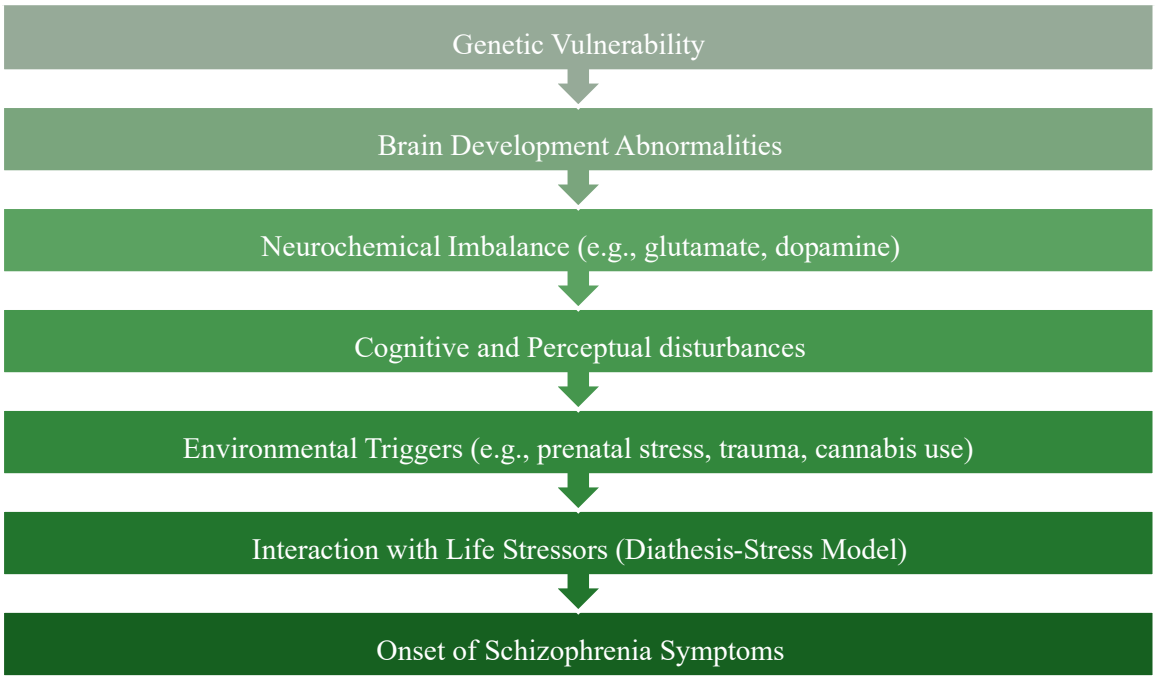


Fig:1.1Flow Chart for Etiology [22] .

4.Complication:

Separating studies based on study characteristics allowed for a more thorough evaluation of the impact of methodological heterogeneity across research. Finding Overall, the pooled odds ratio for the exposure to ocs on the eventual development of schizophrenia was 2.0 (95% CI 1.6–2.4), and there was no discernible heterogeneity of effect between trials. The pooled estimate from the case-control studies and that from the historical cohort studies, however, showed considerable heterogeneity (z) 2.60, $P < 0.01$) when partitioned by study design. The area of tiny studies that found no effect has a gap on the funnel plot. Conclusions The research reveals that both selection and publication biases may have link, even while the finding shows that people exposed to ocs have a twofold increased risk of with developing schizophrenia [23] . Substance abuse: Substance use disorders are most likely to develop in people schizophrenia. Which can: exacerbate symptoms and treatment results [24]. Cardiovascular disease and metabolic syndrome: Numerous antipsychotic drugs raise the risk of metabolic issues such dyslipidaemia diabetes and obesity.[25] . Suicide risk: Suicide claims the lives of up to 10% of people with schizophrenia, particularly young men who are only beginning to suffer from the disorder.[26] . Social and occupational dysfunction: Long deficits in social and professional functioning are prevalent and contribute to low quality of life and disability.[27]. Non-

adherence to treatment: Poor medication adherence can result in relapse and hospitalisation due to cognitive impairment and a lack of understanding.[28] .

5.RISK FACTOR:

Fig:1.2Risk factor of schizophrenia

6.Treatment:

- Antipsychotic Medication:
- Fgas, or first-generation antipsychotics, include chlorpromazine and haloperidol.
- Second-generation antipsychotics (sgas), such as clozapine, olanzapine, and Risperidone are particularly useful in instances that are resistant to treatment.
- For schizophrenia that is resistant to therapy, clozapine is still the recommended medication
- Psychosocial Interventions
- CBT, or cognitive behavioural therapy
  Family counselling
  Supported programs for job and skill development
- Cognitive Remediation: Focused treatment meant to address cognitive impairments.
- Assertive Community Treatment
- A collaborative strategy that offers strong community support.
- Electroconvulsive Therapy (ECT): Used, especially for catatonic schizophrenia, when individuals do not react to treatment. [29].

7.Common Symptoms:

Fig 1.3 Common symptoms for Schizophernia.

8.Diagnosis:

Using standardised criteria like the DSM-5 or ICD-11, a clinical evaluation is used to diagnose schizophrenia. Delusions, hallucinations, disordered speech, severely disordered or catatonic behaviour, and negative symptoms (such reduced emotional expressiveness) are the main characteristics needed for diagnosis. There must be consistent indications of disruption for at least six months, and at least two of these symptoms must be present for a sizable amount of time over the course of a month. Crucially, before confirming a diagnosis, other reasons including substance abuse or other mental illnesses must be checked out.

Clinical interviews (such as the Structured Clinical Interview for DSM-5 Disorders — SCID5) and symptom rating scales (like the Positive and Negative Syndrome Scale — PANSS) are commonly used to support diagnosis [30] .

Role of phytochemicals and their functions:

Rutin:

Families: Polygonaceae(Fagopyrum esculentum),Rutaceae (citrus species),Fabaceae (sophora japonica) ,Capparaceae(Capparis spinosa),Moraceae(Morus alba).

Biological sources: Fagopyrum esculentum (Buckwheat), Citrus species (like orange),Sophora japonica (Japanese pagoda tree) ,Capparis Spinosa (caper plant), Morus Alba (White Mulberry) .[31].

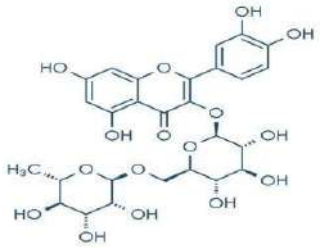
Flavonoid with anti-inflammatory, neuroprotective, and antioxidant qualities. Inflammation and oxidative stress are thought to be important factors in the development of schizophrenia and the intensity of its symptoms. According to certain preclinical research, rutin may be beneficial by lowering oxidative damage and modifying neurotransmitter systems that are dysregulated in schizophrenia, such as glutamate and dopamine.[32].

Rutin Chemical Structure:

Rutin (sometimes termed Ruto side or quercetin-3-rutinoside) is a flavonoid glycoside. It is composed of routinise, a disaccharide (sugar) that is a mixture of rhamnose and glucose, and the flavanol quercetin.

Formula for the chemical: C27H30O16

Weight in molecules: ~610.52 g/mol [32,33]



rutin

Method of preparation of rutin to schziophernia:

Preparation of Rutin Extract: Plants such as buckwheat and Sophora japonica, which are Japanese pagoda trees. The extraction technique extraction of solvents (with ethanol, methanol, and water).Occasionally followed by chromatographic purification.[34].

Formulation For Improved Delivery: Because rutin has a low bioavailability (it doesn't absorb well when taken regularly) ,researchers occasionally make it in a different way. Rutin nanoparticles are used in nano formulations to get past the blood-brain barrier. Rutin-loaded liposomes or microspheres are used for encapsulation.[35].

Administration In Schizophrenia Models:

Rutin is typically administered in vivo (in animal research) by: Gavage by mouth (into the stomach).Injection intraperitoneally (into the bodily cavity).The dosage of the rutin in rat models varies between 10 and 100 mg/kg body weight each day. Used to simulate schizophrenia in models generated by ketamine and phencyclidine (PCP). [36] .

Concentration of rutin used in schziophernia:

Rutin Against Ketamine -Induced Schizophrenia in Rats Model: Rats given ketamine to produce schizophrenia. The dose of rutin:60 mg/kg and 30 mg/kg, taken orally once a day. Time frame: 14 days and Results: Rutin restored oxidative stress and behavioural impairment.[36].

Rutin-Loaded Nanoparticles for Schizophrenia in Model: Ketamine-induced schizophrenia like symptoms in rats. Dosage of Rutin (in nanoparticles): Intraperitoneally (I.P.) at doses of 10 mg/kg, 20 mg/kg, and 40 mg/kg. It lasts for seven days. Results: Compared to free rutin, rutin nanoparticles were more effective.[37].

Rutin in PCP -Induced Schizophrenia Model: Rats given PCP (phencyclidine) to simulate schizophrenia. Rutin Dosage: The intraperitoneal dose is 25 mg/kg.Time frame: 10 days.
Results: Less oxidative damage and better memory.[38].

Curcumin:

Biological source : Curuma Longa L.(Commonly known as turmeric) Family:
Zingiberaceae [39].

The primary active ingredient in turmeric (Curcuma longa) is curcumin. Its potent neuroprotective, anti-inflammatory, and antioxidant qualities have made it a popular choice for treating conditions like schizophrenia. Glutamate/dopamine imbalance, neuroinflammation, and oxidative stress are important pathogenic variables in schizophrenia. Research indicates that curcumin could be beneficial by: lowering neuronal oxidative damage. Lowering the inflammatory cytokines that cause inflammation in the brain, such as TNF-α and IL-6.Enhancing mental processes like focus and memory.

Adjusting dopamine and glutamate, two neurotransmitters that are dysregulated in schizophrenia. Preventing synaptic dysfunction and neurodegeneration.

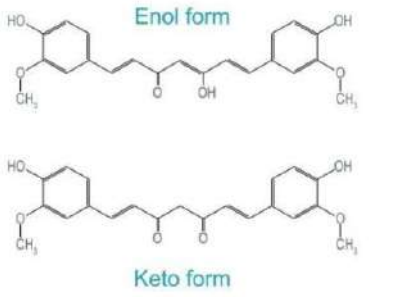
When used with antipsychotic drugs, curcumin can improve therapeutic outcomes, particularly for negative symptoms (such as apathy or lack of emotion) and cognitive symptoms, according to some animal research and clinical trials.[40,41,42] .

Chemical Structure of Curcumin;

It is the primary bioactive component of curcuma longa, or turmeric.

Two aromatic (benzene) rings connected by a seven-carbon chain make up its linear diarylheptanoid structure.

Formula Chemical: $C_{21}H_{20}O_6$ Molecular Weight: about 368.38 g/mol [43].



Method of preparation of curcumin to schziophernia:

The active ingredient in turmeric, or curcuma longa, curcumin, has been researched for its antioxidant, anti-inflammatory, and neuroprotective qualities, all of which may help cure schizophrenia. Since the body does not absorb natural curcumin well, it is frequently manufactured in more soluble forms for use in studies. Getting ready for schizophrenia research frequently entails: Using curcumin-pipevine combos (black pepper pipevine enhances curcumin absorption), solid lipid nanoparticles, liposomes, or nanoparticles. Usually, oral administration is employed, perhaps in the form of powdered curcumin, capsules, or standardized extracts. [44].

Concentration of curcumin used in schziophernia:

Dosage of curcumin: 360 mg daily. Optimized Curcumin Formulation by Long Vida® Duration: Eight weeks. As a result, the unpleasant symptoms of schizophrenia are lessened.[45].

Dosage:500 mg twice daily for a total of 1000 mg is the dosage.

Boosting bioavailability with curcumin and pipevine.

Duration: 12 weeks. Inflammatory markers, which are frequently increased in individuals with schizophrenia, drop as a result.[46].

Dosage:160 mg of nanocurcumin per day is the dosage. Nano micelle structure (to enhance absorption).

Duration: sixteen weeks . Patients with chronic schizophrenia therefore performed better cognitively and showed reduced levels of inflammatory markers.[47] .

Gallic acid:

Biological source: Commonly found in a variety of plants, especially in fruits ,nuts and tea, including: Phyllanthus emblica(Indian gooseberry),Terminalia Cebula and Terminalia bellerica,Quercus infectoria(oak galls),Camellia sinensis(tea).

Families: phyllanthaceae (Phyllanthus emblica) ,Combretaceae (terminalia species), Fagaceae (Quercus infectoria), Theacea (camellia sinesis).[48].

A naturally occurring phenolic chemical, gallic acid (3,4,5-trihydroxybenzoic acid) is present in a variety of foods and plants, such as strawberries, gallnuts, and green tea.

It may be helpful in the treatment of neuropsychiatric disorders like schizophrenia due to its strong anti-inflammatory, neuroprotective, and antioxidant qualities.

Schizophrenia, neuronal damage and cognitive dysfunction are primarily caused by neuroinflammation and oxidative stress.

Gallic acid may be beneficial for: scavenging of free radicals (because of the hydroxyl groups).

Inflammation in the brain can be reduced by lowering pro-inflammatory cytokines such as TNF-α and IL-6.

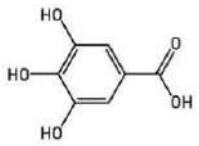
Protecting neurons from oxidative damage and death.

Enhancing cognitive, behavioural, and memory abilities in animal models of schizophrenia.[49].

Chemical structure of Gallic acid:

The compound is known as 3,4,5-trihydroxybenzoic acid.

$C_7H_6O_5$ is the chemical formula. An explanation of the structure: The benzene ring received one carboxylic acid group (-COOH) at position 1 and three hydroxyl groups (-OH) at locations 3, 4, and 5. [50] .



Gallic Acid

Method of preparation of gallic acid to schziophernia:

Acid is a naturally occurring polyphenol found in many different plants, such as berries, tea, and grapes. Because oxidative stress and inflammation are linked to the ethology of schizophrenia, its antioxidant, anti-inflammatory, and neuroprotective properties are advantageous. Because gallic acid has a low bioavailability, researchers often prepare it carefully by putting it into nanoparticles or suspending it in carriers like carboxymethylcellulose (CMC) Typical Preparation Method: For oral administration in Gallic animal research, gallic acid powder is typically dissolved or suspended in a small portion of CMC solution (0.5%–1%). Lipid-based carriers or nanoparticles are sometimes used to increase bioavailability. Route: intraperitoneal (I.P.) injection or oral (gavage). [51].

Concentration of gallic acid used in schziophernia:

Animal Study (Rat Model of Schizophrenia-Like Symptoms):

Gallic acid Dosage: 30 mg/kg per day.

Technique: Oral Dispensation

Duration:14Days

Effect: As oxidative stress dropped in a ketamine-induced schizophrenia model, cognitive impairments improved.[52].

Another animal study:

Gallic acid dose (20–40 mg/kg)

Mimic: psychosis brought on by apomorphine (used to mimic schizophrenia)

Impact: Abnormal behaviour and reduced oxidative stress. [53] .

Cannabidiol:

Biological source: Extracted primarily from cannabis sativa L.(industrial hemp and marijuana varieties).

Family: Cannabaceae[54] .

One of the non-psychoactive compounds found in cannabis sativa is cannabidiol. Studies suggest that CBD may have antipsychotic qualities, which could make it a viable treatment for schizophrenia.

Through its effects on dopamine/glutamate transmission, suppression of anandamide breakdown, and modulation of the endocannabinoid system, CBD is believed to affect important pathways in schizophrenia.

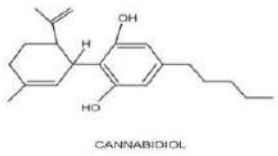
Unlike THC, CBD may help reduce hallucinations and psychotic symptoms.[55] .

Chemical Structure for Cannabidiol:

2-[(1R,6R)3-methyl-6-cyclohex-2-en-1-yl (prop-1-en-2-yl) is the chemical's name.1,3-diol-5pentylbenzene

$C_{21}H_{30}O_2$ is the chemical formula.

Each mole has a weight of 314.46 grams. [56].



CANNABIDIOL

Method of preparation of cannabidiol to schizophrenia:

CBD is one of Cannabis saliva's key non-psychoactive components. Its potential as a therapy for schizophrenia, namely positive symptoms and cognitive impairments, has been the subject of numerous clinical trials. It has anti-psychotic, anxiolytic, and neuroprotective properties.

Preparing for use:

Dissolved in an oil, such as olive oil, sesame oil, or medium-chain triglyceride (MCT) oil for oral delivery. Sometimes a combination of ethanol, Cremophor, and saline is used for experimental injections.

Route: clinical studies using oral solutions, oral capsules, and sublingual oils. In animal studies, intraperitoneal (I.P.) injections are occasionally used.[57] .

Concentration of cannabidiol used in schizophrenia:

800 mg of oral CBD per day is the dosage.

Design: A double-blind, randomized controlled study that contrasts CBD with amisulpride, an antipsychotic.CBD had less adverse effects and reduced psychotic symptoms just as well as amisulpride.[58].

The recommended daily dosage for oral CBD is 1000 mg (500 mg twice a day).

Design: A placebo-controlled, randomized study to support antipsychotic drugs.

Finding: Positive symptoms and overall clinical impressions were much enhanced by CBD when compared to a placebo[59].

Physostigmine:

Biological source: Derived from the seeds of physostigmine venenosum balf.(commonly called the Calabar bean). Family: Fabaceae (Leguminosae family).

The alkaloid physostigmine is found naturally in Calabar beans (Physostigmine Veneno sum). It is mainly referred to as a reversible acetylcholinesterase inhibitor, which implies that it raises acetylcholine levels in the brain by blocking the enzyme that breaks it down.

In relation to schizophrenia: Complex neurotransmitter imbalances are a hallmark of schizophrenia; acetylcholine may also be involved, especially in cognitive symptoms (such memory issues and attention difficulties), while dopamine and glutamate are the main culprits. Physostigmine temporarily alleviates cognitive abnormalities in schizophrenia, especially those related to memory and attention. It is not a commonly utilized treatment, despite experimental research showing the role of the cholinergic system in symptoms of schizophrenia.

Physostigmine challenge tests were utilized in several early studies in the 1980s and 1990s to examine how the brain functions in individuals with schizophrenia.

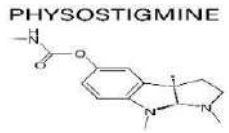
Important:

Physostigmine can intensify pleasurable effects like hallucinations, even while it improves cognition.

It is not recommended for long-term use due to the dangers of bradycardia, seizures, and cholinergic toxicity.[61,62].

Chemical Structure of Physostigmine:

Trimethylpyrroloindol-5-yl N-methylcarbamate (3as,8ar)-1,2,3,3a,8,8a-hexahydro-1,3a,8$C_{15}H_{21}N_3O_2$ is the formula for molecules. Its structure is characterized by a carbamate group joined to a pyrroloindoline core.[63].



Method of preparation of physostigmine to schziophernia:

Natural Extraction:
Traditional Preparation Involves: They grind the Calabar beans. Use a nonpolar solvent, like petroleum ether, to defatted the powder. Use an acidic aqueous solution (diluted sulfuric acid, for instance) for extraction. Ammonia or sodium carbonate can be used as the basis for the aqueous extract. The alkaloid is released into an organic solvent, such as chloroform. Crystallization is used to achieve purification. Chemical Synthesis (Laboratory Method): Studies have also led to the development [64] .

Physostigmine in treatment of Schizophrenia: Artificial pathways, A generic synthetic outline includes: Creating a technology that is inefficient. They add the methylcarbamate group. One of the final steps in the pyrroloindoline structure's creation is ring closure. By preventing its breakdown, physostigmine, a cholinesterase inhibitor, mainly raises acetylcholine levels in the brain.

In cases of schizophrenia:

Justification: Dopaminergic, glutamatergic, and cholinergic system dysfunction are thought to be the main causes of schizophrenia.
Clinical Use: Physostigmine has been used in an experimental setting (not as a standard treatment).Sometimes, acute psychosis is confused with reverse anticholinergic delirium.

Enhance cognitive function in individuals with schizophrenia, especially those who have negative symptoms and cognitive impairments.
Mechanism: By raising acetylcholine, it may momentarily enhance memory, focus, and certain symptoms.[65,66].

Concentration of physostigmine used in schizophernia:

Mania and tardive dyskinesia, it did not find any good outcomes in three patients with schizophrenia. Regretfully, the study did not specify the specific dosages given to these patients.[67].

Alstonine :

Biological source: Isolated mainly from Alstonia Boonie De Wild and other species of alstonia.

Family: Apocynaceae [68] .

The primary source of the indole alkaloid Alstonine is Picralima nitida. Studies on animal models have shown that alstonine has antipsychotic-like qualities, which may help treat schizophrenia. Studies have shown that Alstonine can reduce stereotyped behaviours, alter dopamine and serotonin levels in the brain, and lessen psychotic symptoms without having some of the motor adverse effects of antipsychotics. [69] .

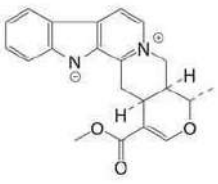
Chemical Structure of Alstonine:

Alstonine, which has the molecular formula $C_{21}H_{20}N_2O_3$, is an indole alkaloid. Among its components are: A five-membered pyrrole ring with nitrogen joined to a six membered benzene ring forms the bicyclic structure known as an indole core.

It has an oxygenated side chain in addition to the several substituents found in monoterpene indole alkaloids.

Explain the chemical structure: an indole ring system.

A side chain with an oxygen atom. Numerous naturally occurring bioactive alkaloids have a fused ring structure in common. [70].



Alstonine

Method of preparation of Alstonine to schizophrenia:

Studies on animals have shown that alstonine has antipsychotic properties.
It has a similar effect to atypical antipsychotics like clozapine on the dopamine and serotonin systems of the brain.
Alstonine lowers positive indicators like hyperactivity and has a reduced risk of extrapyramidal side effects, in contrast to earlier conventional antipsychotics.
Mechanisms observed:
The decrease in amphetamine-induced hyperlocomotion (a model of positive sensations), Alterations in dopamine metabolism in the prefrontal cortex and striatum.
Serotonin receptors may be involved. [71] .

Concentration of Alstonine used in schizophrenia:

The antipsychotic potential of alstonine was regularly assessed in animal experiments using the following dosages:
Dosage: Mice or rats received intraperitoneal (I.p.) Doses of 1–10 mg/kg.
At dosages between 5 mg/kg and 10 mg/kg, effective antipsychotic-like effects (such as decreased amphetamine-induced hyperlocomotion and the lack of catalepsy) were shown[71]

Reticuline:

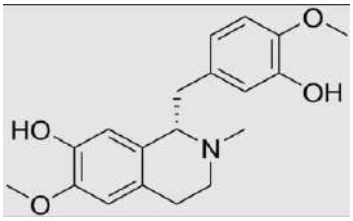
Biological source: Papaver somniferum (opium poppy), Sanguinaria canadensis,Eschscholzia Californica (California poppy), Annona Squamosa.

Families: Papaveraceae (Papaver somniferum, sanguinaria canadensis), Ranunculaceae (occasionally in related species),Annonaceae(Annona squamosa) [72].
The benzylisoquinoline alkaloid reticuline is found in a number of medicinal plants, including the opium poppy, Papaver somniferum.
Scientists have investigated it's neuropharmacological effects, despite the fact that it is not a traditional antipsychotic. These effects include
Interaction of the dopaminergic system (crucial in schizophrenia) Possible hypnotic, sedative, and anxiolytic (anti-anxiety) effects: It may affect neuronal pathways linked to psychosis, according to some research. [73,74] .

Chemical structure of Reticuline:

(1S)-1-[(3-hydroxy-4-methoxyphenyl)methyl] is the IUPAC designation .-6-methoxytwo methyl's are present.Tetrahydroisoquinolin-7-ol -1,2,3,4-

A molecule's formula is $C_{19}H_{23}NO_4$.[75] .



Method of preparation of reticulin treating schizophernia:

Method of preparation of reticuline: Manufacturing of Chemo enzymes

The chemoenzymatic synthesis of reticuline is described in the paper.[76] .

Reticuline in schizophrenia treatment:

Pharmacological Research

Reticuline's demonstration of dopaminergic antagonism raises the possibility that it has antipsychotic properties.[77] .

Concentration of reticuline used in schizophernia:

It has been demonstrated that reticuline, a benzylisoquinoline alkaloid, blocks dopamine receptors; this mechanism is common to many antipsychotic medications. When reticuline was administered intraperitoneally to animal models at a dose of 50 mg/kg in a preclinical trial by Melo et al. (1980), the findings were comparable to those of conventional antipsychotics, suggesting that it might be helpful in treating the symptoms of schizophrenia. However, no clinical studies on humans have been carried out to verify its effectiveness or establish a safe dosage. [78] .

Phytochemicals in non – clinical studies:[79] .

Chemical Class	Phytochemical	Source	Mechanism	Result	References

Alkaloids	Reticuline	Ocotea duckei	Dopamine Antagonist Activity	Reduced hypermotility	Morais Barbosa-Filho and Almeida (1998) Ueda et al. (2011)
	Alstonine	Picralima nitida	Modulating the DA uptake and serotonin receptors	Reduction in behavioral Score diminished catatonic time	Costa –campos, Lara, Nunes and Elisabet sky (1998)
	Physostigmine	Physostigmine venenosum	Induced latent inhibition disruption	Reverse the cognitive impairment in schizophrenia	Barak and Weiner (2010)
Cannabinoids	Cannabidiol	Cannabis sativa L	Blockade of serotonin reuptake or increased gabaergic activity	Attenuated the stereotypy and increase in prolactin	Zanardi et al. (1991)
Polyphenols	Rutin	Marinda citrifolia	Inhibition of D2 receptors	Reduction in climbing and stereotypy	Pandy and vijeepallam (2017)
	Curcumin	Curcuma Lona	Antioxidant action	Increased GSL and GSH level in astrocytes and neurons	Lavoie et al. (2009)

	Gallic acid	Camellia sinensis	Enhancement of NMDA receptor function	Stereotypy improved and locomotor activity increased	Yadav et al. (2018)

Apomorphine:

Biological sources: Nymphaea caerulea, Annona species.

Families: Nymphaeaceae (Nymphaea caerulea),Annonaceae (Annona species). [80] .

Apomorphine, a non-selective dopamine receptor agonist, was used in an experiment to examine the function of the dopaminergic system in schizophrenia. Its findings have shed new light on the dopamine theory of schizophrenia, which maintains that a major contributing factor to the illness is disturbance of dopamine neurotransmission.

Apomorphine and psychotic symptoms:

Results: Contrary to the hypothesis that apomorphine would make symptoms worse (due to dopaminergic effects), some patients experienced no worsening of symptoms, and in chronic individuals, some symptom relief was noted [81].

Neuroendocrine Effects and Dopamine function:

Growth hormone and prolactin, two hormones generated by apomorphine, were used to evaluate the sensitivity of the dopamine receptor. Poor dopaminergic receptor activity has been linked to schizophrenia, according to research .[82].

Brain Imaging Studies:

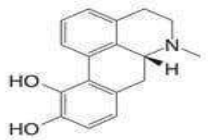
By controlling frontal-temporal activity and bringing it closer to typical control patterns, apomorphine may "normalize" aberrant brain activity in schizophrenia, according to PET scans. [83] .

Receptor binding studies:

Results: Postmortem investigations using radiolabelled apomorphine showed that the brains of individuals with schizophrenia have different patterns of dopamine receptor binding. [84].

Chemical structure of Apomorphine:

The apomorphine's chemical makeup. A molecule's formula is $C_{17}H_{17}NO_2$.Each mole has a weight of 267.32 grams. Tetrahydro (6ar)-6-methyl-5,6,6a,7--4H-dibenzo[de, g] is the IUPAC designation for it.Diol quinoline (10,11-). Comprising two continuous hydroxyl groups on a benzene ring, the catechol group is part of the tetracyclic aporphine structure of apomorphine and is necessary for dopaminergic action. [85] .



Apomorphine

Method of preparation of apomorphine treating schizophernia:

Method of preparation of Apomorphine:Apomorphine is a semi-synthetic substance that is created by rearranging morphine in an acidic manner; it is not derived directly from natural sources.

General Synthesis Method:

First drug: morphine,Reagents: Hydrochloric acid, concentrated phosphoric acid, and heat. Method: When acid and morphine are heated together, a process of dehydration and rearrangement occurs. The intermediate is cyclized to create apomorphine.

The compound is often transformed into a hydrochloride salt for use in medicine after purification Apomorphine in treating schizophrenia: The effects of apomorphine on the dopaminergic circuitry linked to schizophrenia have been investigated. It primarily targets D1 and D2 dopamine and functions as a non-selective agonist. .[86] . Schizophrenia patients received 0.75 mg of apomorphine subcutaneously. The findings demonstrated no discernible improvement in psychotic symptoms or tardive dyskinesia . Lastly, apomorphine showed no clinically significant antipsychotic effects. [87] .

Research: Individuals with acute and chronic schizophrenia participated in a double-blind, placebo-controlled study. In acute situations, apomorphine decreased anxiety, but it had no antipsychotic effects. Conclusion: Apomorphine's use as a therapy for schizophrenia is not supported by any evidence.[88] .

Concentration of apomorphine used in schizophernia:

A subcutaneous injection of 0.75 mg was given.

By monitoring their behavioural and neuroendocrine reactions, the goal is to evaluate central dopaminergic activity in individuals with schizophrenia.[89] .

Glycine:

Biological source: Botanical genus : Glycine ,Key species: Glycine max(soybean) Family: Fabaceae (Leguminosae) [90].

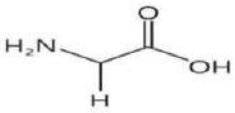
The function of glycine in schizophrenia:

Glycine is a co-agonist at the NMDA receptor, which needs both glycine and glutamate to work properly. NMDA Receptor Modulation is the term used for this. The hypofunction of this receptor is associated with negative and cognitive symptoms of schizophrenia. Adjunctive Therapy: Glycine has been demonstrated to lessen unpleasant symptoms and cognitive deficits when taken as a supplement to antipsychotics, particularly clozapine or traditional antipsychotics .[91] .

Chemical structure of glycine:

The chemical formula is NH_2CH_2COOH.

The IUPAC name for it is amino ethanoic acid.[92] .



Method of preparation of glycine treating schizophernia:

Strecker synthesis:Glycine is produced by hydrolysing aminoacetonitrile following its interaction with formaldehyde, ammonia, and hydrogen cyanide.

Glycine can be expressed as follows: $CH2O + NH3 + HCN \rightarrow NH2CH2CN \rightarrow NH2CH2COOH$.

Protein hydrolysis:

Gelatine or other proteins can be hydrolysed with an acid or enzyme to provide glycine and other amino acids.

In contrast, pharmaceutical-grade glycine is sold commercially and is taken orally for clinical trials in dosages between 15 and 60 grams daily.[93] .

Concentration of glycine used in schizophernia:

Clinical trials have used high-dose glycine as an adjuvant treatment for schizophrenia, primarily to reduce negative and cognitive symptoms.

Normal Range of Doses: 0.4–0.8 g/kg per day is the dosage.

For a 70-kilogram adult, this corresponds to 28 to 56 grams daily.

Method: Oral (diluted with water or juice).

Form: Powdered glycine of pharmaceutical quality.[94] .

Apigenin:

Biological source: Parsley (Petroselinum crispum) , Celery (Apium graveolens), Chamomile (Matricaria chamomilla).

Families:Apiaceae(Petroselinum crispum, Apium graveolens), Asteraceae(Matricaria chamomilla) [95,96,97] . The flavonoid apigenin is found naturally in a variety of plants, such as parsley, celery, and chamomile. It may be useful in treating neuropsychiatric conditions like schizophrenia because of its well-known neuroprotective, anti-inflammatory, and antioxidant qualities.

Potential cause of schizophrenia

Apigenin may reduce some symptoms of schizophrenia through the following mechanisms, per research on its effects.

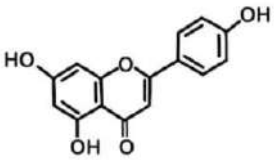
The neuroinflammatory response is altered.

A rise in synaptogenesis

Impact the GABA ergic and NMDA receptor pathways.

Avoiding damage from oxidation .[98] .

Chemical structure of Apigenin:4′,5,7-trihydroxyflavone is the IUPAC name for this molecule, which has the chemical formula $C_{15}H_{10}O_5$ with a molecular weight of 270.24 g .[99] .



Method of preparation of apigenin treating schizophernia:

Extraction Method (Natural source preparation): Among the sources include chamomile (Matricaria chamomilla), parsley (Petroselinum crispum), and others.

Method:Hydrolysis is the following stage after solvent extraction with ethanol or methanol.

Further purification by column chromatography or recrystallization.
Lecithin was complexed to improve bioavailability. [100] .

Chemical Synthesis:

Use in schizophrenia research: Apigenin is made and given orally in animal models of schizophrenia. [98] .

Method: Synthesis of anisaldehyde and phenolglucinol.
Procedures for methylation, iodine/DMSO cyclization, and demethylation .[101] .

Concentration of apigenin used in schizophernia:
Apigenin's potential as a treatment for schizophrenia has been investigated in preclinical studies using animal models. The weight of the animals and the study design determine the concentration used. Frequently Employed Concentration: Five, ten, and twenty milligrams per kilogram of body weight are the dosages. Route: oral or intraperitoneal (Ip.), Frequency: Daily.Studies typically run between seven and fourteen days.[98] .

Nicotine:

Biological source: Nicotiana tabacum , Nicotiana rustica.

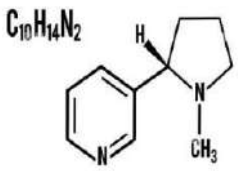
Family: Solanaceae [102] .

Self -medication Hypothesis: Nicotine may improve working memory, reduce unpleasant symptoms, and help people with schizophrenia focus better.
Nicotine enhances dopaminergic and cholinergic neurotransmission, although it decreases in schizophrenia.
Cognitive Enhancement: Nicotinic acetylcholine receptors (nAchrs), specifically the α7 and β2 subtypes, are activated by nicotine, which may lessen cognitive abnormalities in schizophrenia.
Interaction with Antipsychotic Medication: Nicotine may lessen the extrapyramidal adverse effects of antipsychotic drugs, per some research.

Additionally, it might affect cytochrome P450 enzymes, changing how drugs are metabolized.[103].

Chemical structure of Nicotine: Tobacco plants are the main source of nicotine, a naturally occurring alkaloid. Its agonistic activity targets nicotinic acetylcholine receptors (nachrs). Chemical specifics:(S)-3-(1-methylpyrrolidin-2-yl) pyridine is its IUPAC name.

$C_{10}H_{14}N_2$ is the chemical formula.
Each mole has a weight of 162.23 grams.[104] .



Method of preparation of nicotine treating schizophrenia :

Method of preparation of Nicotine: For usage in research and medicine, nicotine is mostly chemically produced in labs or extracted from tobacco leaves.
Extraction Technique (From Natural Sources)
Approach: Tobacco leaves, Nicotiana tabacum, are ground into a powder after being dried.
The extraction procedure uses either acidified water or ethanol.
By raising the Ph to an alkaline level, nicotine is extracted as a free base.
The product was refined using distillation or chromatography.
Synthetic Method: General Reaction: (S)-nicotine can be created by combining the pyridine and pyrrolidine rings.
A technique example. Through a sequence of alkylation and cyclization processes, 2,3,6trimethylpyridine is transformed into nicotine. [105] .

Nicotine in schizophrenia treatment: Nicotine is being researched for its effects on cognitive function and sensory gating, both of which are compromised in schizophrenia, even though it is not expressly approved to treat the disorder.
The system: Impacts the α7 and β2 nicotinic acetylcholine receptors. Enhances focus, working memory, and sensory gating.

The research's main focus: Nicotine patches, inhalers, or agonists of the nicotinic receptor (such as DMXB-A). Addressing unpleasant symptoms and cognitive impairments is the aim. [106] .

Concentration of nicotine used in schizophernia:

Transdermal Nicotine Patches : Either 7 mg, 14 mg, or 21 mg should be taken daily.It is frequently used for one to four weeks in research trials.The goal is to evaluate gains in cognitive function, particularly in working memory and sensory gating.[107].Nasal Spray or Inhalation: Several times a day, nasal spray delivers approximately 1 mg of nicotine per dose used to provide nicotine's immediate effects on behaviour and brain activity under regulated settings.[108].Oral Nicotine Agonists(e.g., DMXB-A):75–150 mg was taken twice a day. Instead of nicotine, the therapy targets α7 nicotinic acetylcholine receptors. Suggests the possibility of treating unpleasant sensations and cognitive impairments.[109] .

Tabulate: phytochemicals in clinical studies:[79]

CHEMICAL CLASS	PHYTOCHEMICAL	SOURCE	MECHANISM	RESULT	REFERENCES
Alkaloids	Apomorphine	Nymphae caerulea	Potent effect on presynaptic dopamine receptor in addition to its postsynaptic stimulation	Decrease in psychotic symptoms in chronic patients	Smith et al. (1977); Fletcher, firth et al.
Alkaloids	Nicotine	Nicotiana tabacum	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	Potentiate NMDA transmission	Improvement in negative symptoms	Leider ran et al.(1996)
Flavonoid/ polyphenols	Apigenin	Perilla fruitiscenscens	Restore function of NMDA receptor by modulating hskca3 channel	Schizophrenic symptoms decreased	Hannan et al. (2021)

CONCLUSION:

Delusions, hallucinations, cognitive impairments, and social disengagement are symptoms of schizophrenia, a complex mental illness brought on by genetic, neurochemical, and environmental causes. Depression, substance misuse, and suicide are prevalent issues. Antipsychotics and psychological assistance are part of the treatment, and a clinical examination is the basis for the diagnosis. Many phytochemicals have demonstrated potential in altering neurotransmitter systems and reducing oxidative stress levels, such as rutin, curcumin, cannabidiol, physostigmine, glycine, nicotine, reticuline, apomorphine, gallic acid, alstonine, and apigenin. These chemical compounds might be useful supplements to conventional therapies, yielding better outcomes with fewer adverse effects. To prove their clinical effectiveness and safety, more study is required.

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