Chapter

Medicinal Plants Used in the Management of Psychosis

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Abstract

Substantial number of studies has been conducted to find alternatives or treatments for psychosis. Psychosis represents a variety of mental disorders characterized by the presence of delusions, hallucinations and grossly disorganized thinking in a clear sensorium. Psychosis is burdensome and difficult to treat given the inability of the typical and atypical antipsychotics to adequately manage it, accompanied by numerous disturbing adverse effects. Therefore, many with chronic mental health problems justifiably feel disappointed by the apparent ineffectiveness of conventional treatment and naturally search for a more holistic approach to treatment and alternative medicines having less or no side-effects. Plants are rich in secondary metabolites which have the ability to interact with the Central nervous system (CNS) to produce effects that can be beneficial for the management of psychosis, these phytochemicals are believed to have minimal adverse effects. A review of some of the medicinal plants used as antipsychotics, indicated that many medicinal plants possess antipsychotic effects that can improve the treatment of psychosis. Apparently, further studies are necessary in order to isolate the active constituents, ascertain their molecular mechanisms and safety, and also to test them in clinical studies for the development of new pharmacotherapies for psychosis.

Keywords: Medicinal plants, Molecular mechanisms, Psychosis, Secondary metabolites, Antipsychotics

1. Introduction

The term "psychosis" denotes a variety of mental disorders: the presence of delusions, various types of hallucinations, usually auditory or visual, but sometimes tactile or olfactory, and grossly disorganized thinking in a clear sensorium. Schizophrenia is an enduring, disabling psychiatric illness affecting about 1% of the population globally. It is characterized by various symptoms classified into positive, negative and cognitive) [1, 2].

Plants provide the essential nutrients and remedy needed by humans, they are healthier compared to animal diets. Over time much benefits have been derived from medicinal plants due to their rich natural phytochemicals that interact favorably with the human body and neurotransmitters to produce effects that are beneficial to man. In this chapter we will look at some medicinal plant used in the pharmacotherapy of psychosis.

2. Management of psychosis

Psychosis is an immense social and economic problem, but the management of psychosis remains insufficient. Basically typical and atypical antipsychotics are used for the treatment of schizophrenia, the typical antipsychotics such as chlorpromazine and haloperidol are only effective in the treatment of positive symptoms, and are accompanied by disturbing adverse effects such as extrapyramidal side-effects [3], the atypical antipsychotic drugs such as risperidone and olanzapine provide some beneficial effects on negative symptoms and cognitive deficits [4], but they are inadequate and mild. Prolonged use also results in increased oxidative load [5] which could lead to cardiovascular disorders, diabetes, and agranulocytosis seen with clozapine, they also cause moderate to severe weight gain [2, 6–8]. The use of medicinal plants as complementary remedies for the treatment of psychosis have become necessary because of their characteristically high chemical diversity, biochemical specificity, and several other properties that make them favorable lead structures for the treatment of various disorders, including psychosis [9], for example, *Alpinia zerumbet* (Pers.) B. L. Burtt (Zingiberaceae) [10], *Lonchocarpus cyanescens* (Schumach and Thonn.) Benth. (Fabaceae) [11] etc., which have been used in the pharmacotherapy of psychosis. Interestingly many of these plants were studied and found to have lesser side effects e.g. catalepsy [12–15] indicating that these plants may not cause extrapyramidal side effects in humans.

Medicinal plants are either used as an alternative or in addition to orthodox medicine [16], users search for a more holistic approach to treatment, others expect that alternative medicines have less or no side-effects, and many with chronic mental health problems justifiably feel disappointed by the apparent ineffectiveness of conventional treatment [17].

3. Review of relevant pathophysiology

Neuropsychiatric Disorders may occur as a result of a number of factors such as genetic predisposition, lifestyle factors such as substance abuse and recently diet is also believed to be a factor [18] due to certain observations that associated incidence of psychotic episodes in neuropsychiatric diseases with poor dietary patterns, such as a lower intake of omega-3 fatty acids, vegetables, fibers, fruits, vitamins and minerals [19], all these are substances that can be obtained naturally supporting the use of natural products in psychosis especially because of the high antioxidant content of these natural products, since oxidative stress is implicated in psychosis.

4. Secondary metabolites in medicinal plants for psychosis

The discovery of effective plant-based medicinal plants for the treatment of psychosis is constrained by a need to conclusively identify relevant active constituents and understand synergies within them and an inability to sufficiently standardize replicable extracts.

A large number of natural phytochemicals are claimed to have beneficial effects on the adequate functioning of the human brain [20]. Essentially, metabolites produce effects on human brain function probably due to the connection between plant, mammalian biochemistry and molecular functioning. Principally, as a result of the numerous molecular signaling pathways that are conserved between taxa and their role in the synthesis of secondary metabolite [21]. Secondly the effects might

be based on the similarities between the prevalent natural herbivores of plants and the nervous systems of humans. Therefore, the phytochemicals whose synthesis has been retained by a process of natural selection and on the basis of their ability to interact with the CNS of herbivorous or symbiotic insects will also interact with the human CNS system via the same mechanisms [22]. Some of the significance of secondary metabolites involve general protective roles (such as antioxidant, ultra violet (UV) light-absorbing, free radical-scavenging and antiproliferative agents) and preservation the plant against microorganisms such as bacteria, fungi, and viruses. More intricate actions involve dictating or modifying the plant's relationship with more complex organisms [23–25]. This is achieved primarily by their role of feeding deterrence, consequently, many phytochemicals are bitter and/or toxic to potential herbivores, with this toxicity often extending to direct interactions with the herbivore's central and peripheral nervous systems [26] identified extracts and constituents from 85 individual medicinal plants that have potential efficacy for treating psychiatric disorder. Accordingly, secondary metabolites often act as agonists or antagonists of neurotransmitter systems [25, 27] or form structural analogs of endogenous hormones [28].

Secondary metabolites can be subdivided into many distinct groups base on their chemical structure and synthetic pathways, furthermore, these groups can be broadly categorized in terms of the nature of their ecological roles and also their eventual effects and comparative toxicity in the consuming animal. The phytochemicals are herewith, discussed base on the chemical nature of their alleged active components. The largest and most widespread of phytochemical groups are the alkaloids, phenolic compounds and terpenes.

4.1 Alkaloids

Alkaloids are a structurally diverse group of over 12,000 cyclic nitrogen-containing compounds that are found in over 20% of plant species [29]. The use of alkaloids for medicinal purposes dates as far back as the Stone Age [20].

The alkaloids are known to be the common poisons, neurotoxins, and traditional psychedelics for example atropine, scopolamine, and hyoscyamine, from *Atropa Belladonna* plant and social drugs such as ephedrine, nicotine, opiates, cocaine, and caffeine widely consumed for recreational purposes [30]. Despite their posoinous nature, this group of chemicals also found application in the treatment of Alzheimer's Disease, because of their cholinesterase inhibiting effects e.g. riverstigmine, huperzine, physostigmine, and huperzine [31].

Gentianine is a major alkaloid extracted from *Swertia chirata* Linn (Gentianaceae), it was reported to possess antipsychotic activity in experimental animals by antagonizing amphetamine induced stereotypy [32]. 11-demethoxyreserpiline, 10- demethoxyreserpiline, α-yohimbine and reserpiline are alkaloids isolated from the leaves of *Rauwolfia tetraphylla* and are found to possess atypical antipsychotic-like actions [33]. alstonine an indole alkaloid isolated from *Picralima nitida* Alstonine was found to possess antipsychotic properties [34, 35].

4.2 Phenolic compounds

Phenolic compounds are universally found across the plant kingdom, with approximately 10,000 structures identified to date. Phenolics are synthesized from precursors produced by the phenylpropanoid pathway with the exception of a few notable compounds. Structurally, they share at least one aromatic hydrocarbon ring with one or more hydroxyl groups attached [22].

Phenolic compounds comprise of simple low-molecular weight compounds, such as the coumarins, simple phenylpropanoids, and benzoic acid derivatives, to more complex structures such as flavanoids, tannins and stilbenes [22]. These compounds play an important role in CNS functioning by interacting directly with neurotransmitter systems. In in vivo models, phenolics enhance cognition through antagonistic gamma-aminobutyric acid (GABA) receptor binding, with resultant cholinergic upregulation and exert antidepressant effects via monoamine oxidase inhibition in the brain, sedative, anxiolytic and antipsychotic effects by binding to GABA receptors, [36–38]. Flavonoids are widely distributed throughout the plant kingdom. They are constituents of medicinal plants used as herbal medicines in traditional medical practice, and are now considered valuable therapeutic agents in modern medicines [39, 40]. Many studies have reported that flavones modulate neurotransmission through enhancement of GABA activity in the central nervous system; which led to the hypothesis that they could exert tranquilizing effects in behavioral hyperactivity such as schizophrenia [41, 42]. Undeniably, a number of evidences have implicated the role of altered GABAergic transmission in the pathophysiology of schizophrenia [43, 44]. Morin a flavonoid isolated from plants was found to exhibit antipsychotic effects [45].

4.2.1 Tannins

Tannins are a group of plant secondary metabolites that have the ability to tan or convert animal skin into leather. These compounds are classified as being water soluble phenolics with the ability to precipitate alkaloids, gelatins, and other proteins. High tannin concentrations are found in nearly every part of many plants, such as in the bark, wood, leaves, fruit, roots, plant galls, and seed. Tannins may exert their biological effects in two different ways: as unabsorbables, these are usually complex structures with binding properties which may produce local effects in the gastrointestinal tract (antioxidant, radical scavenging, antimicrobial, antiviral, antimutagenic, and antinutrient effects), or as absorbable, these are usually low molecular weight structures which are easily absorbed, and produce systemic effects in various organs [46]. Gallic acid, a gallotanin found in many plants was reported to demonstrate anti-schizophrenic activity primarily due to its antioxidant and anti-inflammatory effects [47]. A novel tannin composition effective in treating mental diseases such as acute or chronic schizophrenia, was isolated from Rhubarb (Rhe; Rhi zoma) a kind of crude drug known from the past and has been frequently used as a Japanese-Chinese medicine [48].

4.2.2 Saponins

Saponins are naturally occurring, but functionally and structurally diverse phytochemicals that are broadly distributed in plants. They are a complex and chemically varied group of compounds consisting of triterpenoid or steroidal glycones linked to oligosaccharide moieties. Although there is a scarce documentation on the antipsychotic potential of saponin, polygalasaponins, a saponin isolated from *Polygalae tenuifolia* was reported to possessed antipsychotic effects [49].

4.3 Terpenes

Terpenes are a diverse group of more than 30,000 lipid-soluble compounds. Their structure includes 1 or more 5-carbon isoprene units, Terpenoids are classified base on the number of isoprene units they contain; isoprene, which itself is synthesized and released by plants, comprises 1 unit and is classified as a hemiterpene;

monoterpenes incorporate 2 isoprene units, sesquiterpenes incorporate 3 units, diterpenes comprise 4 units, sesterpenes include 5 units, triterpenes incorporate 6 units, and tetraterpenes 8 units [22]. Some of the recognized antipsychotic terpenoids are myrcene, beta-caryophyllene and limonene. However, these terpenoids do not only have antipsychotic properties but possess anti-depressant effects due to the suppression and activation of the cannabinoid receptor 2 [20].

5. Review of medicinal plants for psychosis

Many medicinal plants are in use both in developed and developing countries for the treatment of psychosis, some of these plants have been studied for their antipsychotic properties whereas most of these plants have no scientific backings for their efficacy. Literature search of the PUBMED and Sciencedirect journals have documented a number of plants studied for their antipsychotic properties in laboratory animals, however, most of the studies carried out are preliminary, and the need for further studies to isolate the active constituents, determine the mechanism of action and conduct clinical trials to verify their efficacy and safety is necessary. **Table 1** gave a list of some of the reviewed antipsychotic plants, their constituents and probable mechanism of action.

6. Efficacy of natural plants in the treatment of psychosis

Many medicinal plants studied for psychosis were found to have efficacy against the positive, negative and cognitive deficit of schizophrenia in laboratory animals, without the disturbing adverse effects seen with conventional antipsychotic drugs. Even those that are thought to act on the dopamine receptors had minimal or no cataleptic tendencies. The tendency for these plants to ameliorate the negative symptoms in schizophrenia, and in some cases also improve psychotic symptoms, may be owing to the ability of most plants to generally exert anti-inflammatory effects [71] and given that inflammation is a risk factor in most neuropsychiatric disorders including schizophrenia [72]. Oxidative stress is also a major factor in psychosis, plants contain diverse constituents which exhibit antioxidant, and neuroprotective effects useful in ameliorating psychotic symptoms [67].

Large number of schizophrenic patients fail to respond adequately to the initial antipsychotic drug treatment necessitating the addition of natural antipsychotic plants to their treatment regimen. As recently reviewed by Hoenders et al. [73] the inclusion of traditional medicine or Ayurvedic herbs to antipsychotics, generally improve the psychopathology of the disease, however, more studies are needed to conclusively support this finding.

7. Molecular mechanisms of antipsychotic action of medicinal plants

Many medicinal plants have been studied for their antipsychotic properties and several mechanisms of action have been proposed for their actions. A number of these plants were believed to act in a similar manner as orthodox medicines but in most cases without the disturbing adverse effects. **Table 1** gave a summary of the probable antipsychotic mechanism of action of the medicinal plants. Various animal models are used to investigate the antipsychotic properties of medicinal plants, some of these models help to determine whether these plants have typical or atypical antipsychotic like effects.

Plant name	Parts used	Constituents and effects	Probable mechanism of action	Author
Albizia zygia (DC.) J.F. Macbr. (Leguminosae)	Roots	The root extract of *Albizia zygia* is used to manage mental disorders in African traditional medicine. Some of the phytochemical constituents are flavonoids, alkaloids, tannins and saponins. The extract exhibited an antipsychotic-like activity in mice with potential to alleviate positive, negative and cognitive symptoms of schizophrenia.	The possible mechanism of action of *Albizia zygia* may be related to enhancement of N-methyl-D-aspartate (NMDA) receptors located on inhibitory GABAergic neurons.	Kumbol, et al. [50]
Alpinia zerumbet	Leaves	The essential oil was extracted from the leaves of *Alpinia zerumbet,* the major constituents are 1,8-cineole and terpinen4-ol which may be responsible for the antipsychotic effects observed from the plant.	The possible mechanism of action might be due to antioxidant effects as well as enhancing NMDA neurotransmission.	de Araújoa et al. [10]
Alstonia scholaris Linn. R.Br. (Apocynaceae)	Leaves	*Alstonia scholaris* is used widely in the treatment of anxiety, depression and other mental illnesses. The plant was found to possess antipsychotic effects.	Mechanism of action may be attributed to dopamine antagonism in the frontal cortical regions of the brain.	Jash & Chowdary. [15]
Bacopa monniera (Linn.) (Scrophularia-ceae)	Whole plant	Triterpenoid, saponins, and bacosides are considered to be the major constituents in the plant. *Bacopa monniera* has been reported to possess antipsychotic, anxiolytic and other medicinal properties.	The antipsychotic properties may be related to its normalization of dopamine and serotonergic neurotransmission and reduction of acetylcholinesterase activity.	Chatterjee et al. [9]
Brassica Oleracea Var. sabellica (Brassicaceae)	Leaf Juice	*Brassica oleracea* possess excellent phytoconstituents such as flavonoids and polyphenols and is widely used as dietary supplements. It has antioxidant and anti-inflammatory properties, and was found to possess antipsychotic properties.	*Brassica oleracea* increase GABA levels resulting in the control of dopaminergic neurotransmission which may be its possible mechanism of action.	Yadav et al. [51]
Cannabis sativa Linn. (Cannabaceae)	Leaves	Cannabidiol one of the major constituent of *Cannabis sativa* leaves possesses atypical antipsychotic-like properties in humans and laboratory animals.	The possible mechanism of *C. sativa* may be due to enhancement of NMDA receptors located on inhibitory GABAergic neurons in the limbic and subcortical brain regions.	Zuardi et al. [52]

Plant name	Parts used	Constituents and effects	Probable mechanism of action	Author
Crassocephalum bauchiense (Hutch.) Milne-Redh (Asteraceae)	Leaves	*Crassocephalum bauchiense* is a medicinal herb effective in the cases of cerebral deficit, anxiety, epilepsy, cerebral malaria, neuropathic pain, and behavioral disturbances in mentally retarded children. The plant contains alkaloid that was found to possess promising antipsychotic properties.	The antipsychotic properties are possibly mediated via the GABAergic neurotransmission as well as blockade of dopamine D-2 receptors	Taıwe et al. [53]
Crinum Giganteum (Amarylli-daceae)	Bulb	alkaloids, saponins and tannins were found to be some of the major constituents of *Crinum giganteum,* the plant is used traditionally for various medicinal purposes including psychiatric illnesses. The extract of *C. giganteum* was found to possess antipsychotic effects in laboratory animals	The possible mechanism of action of Crinum giganteum may be limited to dopamine D_1 antagonism.	Amos et al. [54]
Desmodium adscendens (Sw.) DC (Fabaceae)	Whole plant	The major constituent in *Desmodium adscendens* is alkaloid, it is a medicinal herb with several uses including psychosis. The extract was found to possess antipsychotic effects against apomorphine induced climbing and stereotypic behavior.	The possible mechanism of action may be due to dopamine receptor antagonism	Amoateng et al. [13]
Embelia ribes Burm.f (Myrsinaceae)	Ber-ries	Embelin was isolated from Embelia ribes and found to be responsible for the antipsychotic effect of the plant. Embelin reversed apomorphine induced stereotypic behavior, confirming its antipsychotic potential.	Embelin action may be due dopamine antagonism and decreased level of neurotransmitters such as dopamine, serotonin and noradrenaline as well as antioxidant effects.	Durg et al. [55]
Guiera senegalensis J. F. Gmel (Combretacea)	*Stem bark*	*Guiera senegalensis* is rich in tannin and known to possess varying medicinal effects. The extracts attenuated amphetamine-induced stereotyped behavior in mice suggesting that the plant possess antipsychotic properties that can be useful as a safe alternative.	The effect of the extract amphetamine-induced stereotyped behavior in mice suggest anti-dopaminergic actions on the limbic system	Amos et al. [56]

Plant name	Parts used	Constituents and effects	Probable mechanism of action	Author
Lonchocarpus cyanescens (Schumach and Thonn.) Benth. (Fabaceae)	Leaves	*Lonchocarpus cyanescens* is reputed for its used in traditional medicine for the treatment of Psychosis. Studies have shown that *Lonchocarpus cyanescens* contains various active principles such as quercetin, kaempferol, loncocarpin, and rhamnetin which may be responsible for its antipsychotic activity. *Lonchocarpus cyanescens* was found to possess antipsychotic properties.	The probable mechanism of action of *Lonchocarpus cyanescens* might be due to antidopaminergic effects.	Arowona et al. [57]
Maytenus obtufisolia Mart. (Celastraceae)	Roots	Triterpenes has been identified in *Maytenus obtufisolia*, it is known that terpenes have pharmacological actions on animal behavior. Findings revealed the antipsychotic effects of *M. obtufisolia*	The probable mechanism of action of *Maytenus obtufisolia* might be via a central dopaminergic action	de Sousa & de Almeida. [58]
Morinda citrifolia Linn (Rubiaceae)	Fruits	scopoletin, rutin and quercetin are the major constituents of *Morinda citrifolia*. The plant has so many Uses for CNS disorders. The fruit juice was found to possess antipsychotic properties.	The probable mechanism of antipsychotic effect of *M. citrifolia* extract is attributed to antidopaminergic activity.	Pandy et al. [59]
Nauclea laltifolia Smith (Rubiaceae)	Root bark	Saponins are present in abundance in the extract and might contribute in part for the observed CNS effects. The extract demonstrated antipsychotic effects by attenuating apomorphine induced stereotypic behavior	The effect of the extract against apomorphine is suggestive of possible interference with central dopaminergic neurotransmission.	Amos et al. [60]
Newbouldia laevis Seem. (Bignoniaceae)	Stem bark	*Newbouldia laevis* is a medicinal plant used in the treatment of various ailments. The plant contains alkaloids and saponins which might be responsible for its neuroleptic effects. The extract of *N. laevis* was found to possess antipsychotic effects.	The probable mechanism of action might be due to dopamine D_1 and D_2 antagonism.	Amos, et al. [61]

Plant name	Parts used	Constituents and effects	Probable mechanism of action	Author
Ocimum sanctum (Lamiaceae)	Leaves	*Ocimum sanctum* have been reported for their pharmacological actions including anti-oxidant, anti-stress, and anticonvulsant. The plant contains flavonoids, essential oil, Caffeic acid and vitamins. *Ocimum sanctum* leaves possesses anti-psychotic like property.	The Probable mechanism of action include antioxidant action and enhancement of NMDA neurotransmission as well as neuroprotection.	Sharma et al. [62]
Panax quinquefolium Linn (Araliaceae)	Leaves	The plant's major compound is ginseng which is known to possess numerous pharmacological effects. *Panax quinquefolium* extract was effective against negative and cognitive dysfunctions induced by ketamine	The antipsychotic properties may be related to its normalization of dopamine and serotonergic neurotransmission and reduction of acetylcholinesterase activity.	Chatterjee et al [14]
Picralima nitida Stampf Th. et H.Dur. (Apocynaceae)	Fruits	alstonine an indole alkaloid isolated from *Picralima nitida* a plant commonly used by traditional psychiatrist as part of the treatment of psychosis. Alstonine was found to possess antipsychotic properties experimental profile comparable with that of clozapine and is compatible with the alleged effects in mental patients.	Alstonine indirectly modulates DA receptors, specifically by modulating DA uptake, it also decreases glutamate uptake in acute hippocampal slices. Alstonine also increases serotonergic transmission and increases intraneuronal dopamine catabolism.	Linck et al. [34, 35]
Piper guineense Schum & Thonn (Piperaceae)	Fruits	*Piper guineense* is a medicinal plant used in the Southern States of Nigeria to treat fever, mental disorders and febrile convulsions. β-sesquiphellandren is an essential oil isolated from the plant and was found to possess antipsychotic effects.	The antipsychotic activity may be mediated through augmentation of GABA at the GABAA–benzodiazepine receptor complex pathway, or inhibition of dopamine neurotransmission at dopamine D1/D2 receptors	Oyemitan et al. [63]
Polygala tenuifolia Willdenow (Polygalaceae)	Roots	*Polygala tenuifolia Willdenow* has been prescribed for hundreds of years to treat psychotic illnesses in Korean traditional medicine. Studies have found polygasaponin to be the major constituent responsible for its antipsychotic effect.	polygalasaponin molecular mechanism of action is dopamine (D_2) and serotonin ($5HT_2$) receptor antagonism	Chung et al. [49]

Plant name	Parts used	Constituents and effects	Probable mechanism of action	Author
Rauwolfia tetraphylla L. (Syn. *R. canescens*/*R. heterophylla*/ *R. hirsuta*; (Apocynaceae)	Leaves	11-demethoxyreserpiline, 10- demethoxyreserpiline, α-yohimbine and reserpiline are alkaloids isolated from the leaves of *Rauwolfia tetraphylla* and are found to possess atypical antipsychotic-like actions	The mechanism of action of the plant is due to the blockade of dopamine (D_2) and serotonin ($5HT_2$) receptor.	Gupta et al. [33]
Rhodiola rosea Linn. (Crassulaceae)		The extracts of *R. rosea* are used in traditional medicine for various conditions related to nervous system function. Studies has shown that the extract has beneficial antipsychotic properties.	The probable antipsychotic mechanism of *R. rosea* is due to reversal of prepulse inhibition deficits in laboratory rodents.	Coors et al. [64]
Saururus cernuus Linn. (Sauru-ruraceae)		*Saururus cernuus* has been used in folk medicine as a sedative and to treat other illnesses. Manassantin A. a neolignoid isolated from *Saururus cernuus* was found to demonstrate neuroleptic activity	The antipsychotic effect of *Saururus cernuus* may be due to weak antagonism of dopamine receptors.	Rao et al. [65]
Securinega virosa (Roxb ex. Willd) Baill.	Root Bark	Securinega virosa has been described as "cure all" in Africa traditional medicine because of its use widely in the treatment of many illnesses. The plant contains saponins, flavonoids, alkaloids and tannins, and was found to possess antipsycotic activity	The probable mechanism of action may be due to dopamine D_1 and D_2 antagonism.	Magaji et al. [66]
Spinacia oleracea Linn Chenopo-diaceae	Seeds	*Spinacia oleracea* is reported to have beneficial effect against several neurodegenerative disorders. Phytoconstituents such as ascorbic acid, apigenin, astragalin, caffeic, lutein, β-carotene, ferulic acid, kampeferol, rutin, querecetin were isolated from the plant. The seed extract of *Spinacia oleracea* showed antipsychotic activity.	*Spinacia oleracea's* protective effect in schizophrenia may be associated with its regulating effect on dopamine, GABA, acetylcholinesterase, glutathione, malondialdehyde levels	Yadav [67]
Spondias mombin Linn. (Anacar-diaceae)	Leaves	*Spondias mombin* is a medicinal plant widely use in the treatment of various ailments including mental illness. The extract contains tannins, flavonoids and saponins as its major constituents. *S. mombin* possess typical antipsychotic-like effects.	The antipsychotic mechanism of *S. mombin* may be due to dopaminergic receptor antagonism.	Ayoka et al. [68]

Plant name	Parts used	Constituents and effects	Probable mechanism of action	Author
Swertia chirata Linn Gentianaceae)	Leaves	Gentianine is a major alkaloid isolated from *Swertia chirata* and was found to possess antipsychotic properties by antagonizing amphetamine induced stereotypy.	It probable mechanism of action might be due to dopamine antagonism.	Bhattacharya et al. [32]
Synedrella nodiflora (Linn.) Gaertn (family Asteraceae)		The extract of the whole plant has demonstrated anticonvulsant, sedative, in vitro antioxidant and free radical scavenging properties as well as antinociceptive properties in acute and neuropathic pain. *Synedrella nodiflora* also possess antipsychotic properties.	The probably mechanism of the antipsychotic properties of *Synedrella nodiflora* might be due to central dopamine receptor antagonism.	Amoateng et al. [69]
Terminalia macroptera Guill. & Perr. (Combreta-ceae)	Leaves and roots	The plant contains Flavonoids, saponins and tannins in abundance which may be responsible in part for the observed activities. *T. macroptera* has been used traditionally for the treatment of hallucinations, and has also being found to possess antipsychotic properties in the ketamine-induced psychosis model.	*T. macroptera* possible mechanism of action may be due to enhancement of NMDA receptors located on inhibitory GABAergic neurons in the limbic and subcortical brain regions and also its antioxidant properties.	Ior et al. [12]
Viscum album Linn. (Lorantha-ceae)		*Viscum album* is claimed in traditional medical practice, to be useful in the treatment of psychosis and insomnia. Some of the major constituents of the extract are flavonoids and tannins. *V. album* was found to possess antipsychotic properties.	The mechanism of action of *Viscum album* maybe due to dopamine antagonism.	Guptaa et al. [70]

Table 1.
Some medicinal plants, their constituents, effects and probable mechanisms of action.

Dopaminergic deregulation, hypofunction of NMDA receptors and GABAergic activity, diminished cholinergic firing, neuroinflammation and increased oxidative stress has been demonstrated to play a pathophysiological role in schizophrenia [67].

The dopamine and amphetamine animal models are basically used to study the typical antipsychotic effects of drugs, their action are similar to the conventional antipsychotics such as haloperidol, chlorpromazine, fluphenazine and thioridazine. The stereotypic behavior observed in animals following the administration of apomorphine a dopaminergic agonist, are attributed to stimulation of D_1 and D_2 receptors [74, 75]. Mesolimbic and nigrostriatal dopaminergic pathways play key roles in the mediation of locomotor activity and stereotyped behavior. Animal models used for assessing antipsychotic drugs are established on the neurochemical hypothesis of schizophrenia, which involve largely the neurotransmitters dopamine and glutamate [76]. The antagonism of dopamine D_2 receptors in the mesolimbic-mesocortical system is thought to be the basis of the therapeutic actions of the antipsychotic drugs, especially those active against hallucinations and delusions [77]. The dopamine-based models usually employ apomorphine, a direct agonist, or amphetamine, a drug that increases the release of this neurotransmitter and blocks its re-uptake.

The term atypical refers to the reduced propensity of the of an agent to cause undesirable motor side effects, but it is also used to describe agents with a different pharmacological profile from the typical antipsychotics; several of these newer antipsychotics improve the negative as well as the positive symptoms [78]. The atypical antipsychotics are categorized base on their pharmacological properties. These include serotonin–dopamine antagonists, multi-acting receptor- Targeted antipsychotics, and dopamine partial agonists. [79]. Examples include clozapine, quetiapine, risperidone, amisulpride, sertindole, zotepine and aripiprazole. The dopamine dysregulation with hyperfunction of the mesolimbic dopamine system was the original tenet theory underlying the basis of schizophrenia [80] and the earliest animal models were established on the basis of pharmacological manipulation in an endeavor to simulate this feature [81], which respond to agents that affect primarily the dopaminergic system, but does not demonstrate the negative or cognitive symptoms seen in schizophrenia [82]. In contrast, a widely used animal model of schizophrenia involves the acute or repeated administration of sub-anesthetic doses of ketamine [83]. In rodents, N-methyl-Daspartic acid receptor (NMDAR) blockade induces hyperactivity, stereotypy, deficits in prepulse inhibition [84], social interaction and memory (Becker and Grecksch [85]), which models the positive, negative and cognitive symptoms of schizophrenia, respectively [9]. Furthermore, studies have revealed that reactive oxygen species have a significant role in the pathogenesis of many illnesses, particularly neurological and psychiatric illnesses. [86] Oxidative stress may be a common pathogenic mechanism underlying many major psychiatric disorders as the brain is relatively susceptible to oxidative damage [87]. Previous study confirmed that oxidative stress damage occurs in patients with schizophrenia and one possible therapeutic solution is to use antioxidants [88]. Reports from some of the medicinal plants studied that delineate some of the animal models used and their molecular mechanism of action are highlighted.

7.1 *Morinda citrifolia* Linn (Rubiaceae)

Morinda citrifolia (noni) is an evergreen tree that grows in open coastline areas at sea level and in forest regions. Four doses (1, 3, 5, 10 g/kg) of the fruit extract of noni were administered prior to apomorphine/ amphetamine administration and observed for climbing behavior and stereotypy. The extract significantly decreased

the apomorphine-induced cage climbing behavior and climbing time in mice in a dose dependent manner. Demonstrating the antidopaminergic effect of the plant. The plant was found to be rich in rutin and scopoletin which might have played a role in the antipsychotic mechanism [60].

7.2 *Securinega virosa* (Roxb ex. Willd) Baill

Securinega virosa is a medicinal plant commonly used in Africa in the management of epilepsy and other mental illnesses. The antipsychotic prospect of the residual aqueous fraction of the plant was assessed by means of the apomorphine induced stereotypic climbing behavior model and the swim induced grooming model, all in mice. The effect of the fraction on haloperidol-induced catalepsy was also assessed. The fraction inhibited the grooming behavior and attenuated the climbing behavior of the mice. These action of *S. virosa* extract was associated to its involvement with the dopamine D1 receptor. Therefore, the study confirmed the antipsychotic potential of *S. virosa* in traditional medicine [66]. The observed effects were ascribed to the presence of alkaloid, saponin, flavonoid and tannin in the leaves.

7.3 *Picralima nitida* Stampf Th. et H. Dur.

Picralima nitida is the only species of the genus Picralima and it is related to Hunteria and Pleiocarpa. it belongs to the apocynaceae family. *P. nitida* has widely varied applications in West Africa folk medicine. The indole alkaloid alstonine was identified as the major component of the fruit rind of *P. nitida*, a plant-based treatment administered to psychotic patients in Nigeria [34]. Alstonine was given prior to apomorphine/ amphetamine administration and observed for climbing behavior and stereotypy, the effect of the alkaloid on haloperidol-induced catalepsy was also assessed [89]. Further studies of alstonine showed a clear antipsychotic profile in rodents, closer to atypical than to typical antipsychotics. Apparently, apomorphine induced stereotypy and amphetamine-induced lethality were significantly reduced by alstonine, suggesting a decrease in mesolimbic dopamine, alstonine reversed haloperidol-induced catalepsy, indicating that nigrostriatal dopamine transmission is not lessened [89]. Alstonine was found to reduce negative symptoms, through a mechanism involving $5HT2_{A,C}$ receptors, and reverses interaction deficits induced by MK801 [90]. Further studies by Linck et al. [35] indicated that alstonine indirectly modified DA receptors, precisely by modifying DA uptake. This unique mechanism for DA transmission modulation backs the antipsychotic-like effects of alstonine and is attuned with its behavioral profile in mice and apparent effects in patients. These findings may signify an innovation in the antipsychotic development field [35].

7.4 *Panax quinquefolium* Linn

Panax quinquefolium is a native plant of North America, but is now cultivated widely and used in many countries. The plant contains dammarane type ginsenosides as the major biologically active constituents particularly Rb1, Rd. and Re ginsenoside saponins [91] which are responsible for most of its bioactive properties. A graded dose study with *P. quinquefolium* revealed differential effects against the ketamine induced hyperactivity in the Digiscan animal activity monitor, and blocked ketamine induced memory impairment in the passive avoidance paradigm. In the chronic studies, *P. quinquefolium* attenuated the ketamine-enhanced immobility in the forced swim test and did not produce extra-pyramidal side effects

in bar test and wood block test of catalepsy. These behavioral effects were compared with standard drugs haloperidol and clozapine. *P. quinquefolium* was also found to reduced DA and 5-HT content after prolonged treatment. Furthermore, *P. quinquefolium* extract reduced acetylcholinesterase activity and nitrate levels, conversely it increased glutamate levels in hippocampus. Ultimately, the study revealed that *P. quinquefolium* possess antipsychotic like properties, which may be beneficial in predominant negative and cognitive symptoms of schizophrenia [9].

7.5 *Spinacia oleracea* Linn

Spinacia oleracea commonly known as spinach is endowed with a number of medicinal properties [92]. Ethnopharmacological studies proposed that *Spinacia oleracea* seeds have promising antioxidant, neuroprotective, anti-epileptic, anti-alzheimer and anti-inflammatory effects [93–95]. The study evaluated the protective effects of *Spinacia oleracea* seed extract in an experimental model of ketamine-induced schizophrenia in mice. Ketamine was used to induce stereotyped psychotic symptoms in mice. Behavioral studies (locomotor activity, stereotypy, immobility duration and memory retention) were carried out followed by biochemical, neurochemical and cellular alterations in the brain. Chronic treatment with *Spinacia oleracea* seed extract significantly attenuated stereotyped behavioral symptoms in mice. Biochemical estimations revealed that the extract reduced lipid peroxidation and restored total brain proteins. Likewise, *Spinacia oleracea* remarkably reduced dopamine levels, acetylcholinesterase activity & inflammatory surge serum tumor necrosis factor (TNF-α) and increased the levels of GABA and reduced glutathione in mice. The results of the study indicated that the extract could ameliorate ketamine-induced psychotic symptoms in mice, signifying a protective effect in the treatment of schizophrenia. Moreover, its protective effect in schizophrenia may be associated with its regulating effect on dopamine, GABA, acetylcholinesterase enzymes, glutathione and malondialdehyde levels [67].

7.6 *Terminalia macroptera* Linn

Terminalia macroptera Guill. & Perr. (Combretaceae) is a medicinal plant used commonly in Africa. Ethnomedicinal report from Mali mentions the decoction of leaves of *T. macroptera* in treatment of epilepsy [96], and anxiolytic effects of *T. macroptera* has also been reported by [97]. The study was carried out to investigate the antipsychotic effects of *T. macroptera* in an experimental model of ketamine-induced psychosis in mice. Ketamine and apomorphine were used to induce stereotyped psychotic behavioral symptoms in mice. Behavioral studies (stereotype behavior, locomotor activity, immobility duration and memory retention) were carried out to investigate the protective effect of the ethyl acetate fraction of *T. macroptera* on ketamine-induced psychotic symptoms, repeated treatment with the ethyl acetate fraction for 7 consecutive days significantly attenuated stereotyped behavioral symptoms, immobility duration and memory deficit in mice. The study revealed that *T. macroptera* could ameliorate psychotic symptoms indicating protective effects in psychosis. Agent that ameliorate ketamine induced psychotic symptoms are generally thought to act in a similar manner as atypical antipsychotics [12].

7.7 *Crassocephalum bauchiense* (Hutch.) Milne-Redh

Crassocephalum bauchiense is a medicinal plant with diverse medicinal uses. The leaves decoction of *C. bauchiense* is effective in the treatment of epilepsy, cerebral

malaria, cerebral deficit, anxiety and behavioral disturbances in mentally retarded children. Likewise, an aqueous extract of the whole plant is useful in the treatment of insomnia, psychosis and other central nervous system disorders, [98, 99]. The antipsychotic effects of *C. bauchiense* extracts were evaluated using the apomorphine animal model of psychosis. The ability of the leaves extracts of *C. bauchiense* to modify the duration of akinesia was observed in the catalepsy test. Furthermore, gamma-aminobutyric acid concentrations in the brain of treated mice were also estimated. The aqueous extract and the alkaloid fraction of *C. bauchiense* attenuated the apomorphine-induced stereotypy and fighting, and had significant fall of the body temperature. In biochemical experiments, the concentration of the inhibitory amino acid, gamma-aminobutyric acid, was significantly increased in the brain of animals treated with the aqueous extract of *C. bauchiense.* The results revealed that the antipsychotic and sedative properties of *C. bauchiense* are possibly mediated via the blockade of dopamine D-2 receptors and GABAergic activation [54].

7.8 *Alpinia zerumbet* (Pers.) Burtt. et Smith

Alpinia zerumbet has important physiological and pharmacological functions, such as antioxidative [100], anticancer [101], anti-inflammatory [102], and anti-anxiety [103]. In phytotherapy, *A. zerumbet* is used to treat neuropsychiatric symptoms such as depression, stress and anxiety, but it is only recently that the central nervous system (CNS) effects of the essential oil from the plant leaves have been studied [10]. The essential oil of *A. zerumbet* (50, 100 and 200 mg/kg i.p.) was administered once to mice to evaluate antipsychotic activity assessed by ketamine-induced hyperlocomotion, hypnotic activity induced by sodium pentobarbital, antioxidant effects (determination of lipid peroxidation and GSH levels), as well as variations in nitric oxide levels (determination of nitrite content). The result revealed that the extract at doses of 100 and 200 mg/kg prevented ketamine hyperlocomotion, and at a dose of 200 mg/kg decreased sleep latency, while all doses increased sleeping time. The in-vitro antioxidant capacity of the oil caused a reduction in lipid peroxidation and increase in glutathione levels. The extract also prevented the decrease in nitrite content caused by oxidative stress. The findings indicate antipsychotic and antioxidant effects of the essential oil of *A. zerumbet* that may have promising efficacy for the treatment of schizophrenia [10].

7.9 *Albizia zygia* (DC.) J.F. Macbr. (Leguminosae)

Albizia zygia is one such plant with numerous medicinal uses. A decoction of the roots is used for the treatment of insanity [104]. Several compounds including two novel oleanane-type saponins, zygiaosides A and B, were lately isolated from the roots of *A. zygia* [105].

A. zygia effects were assessed against apomorphine-induced cage climbing, ketamine induced hyperlocomotion, −enhanced immobility, −impaired social interaction as well as novel object recognition. The propensity of the extract to induce catalepsy and to attenuate haloperidol-induced catalepsy were also investigated. Findings revealed that *A. zygia* extract significantly attenuated apomorphine-induced climbing behavior as well as ketamine-induced hyperlocomotion, immobility and object recognition deficits. Furthermore, the extract had no cataleptic effect. The root extract of *A. zygia* therefore exhibited antipsychotic-like activity in mice with potential to alleviate positive, negative and cognitive symptoms of schizophrenia [51].

8. Conclusions

Plants have been the mainstay for the treatment of diseases all over the world before the development of conventional medicines. The interest in the therapeutic uses of plants have been revived due to obvious reasons such as their safety, availability, and affordability as well as their efficacy. Research on medicinal plant have provided evidences for their use, and further studies in order to isolate the active constituents and also to test them in clinical studies is important for the development of new pharmacotherapies for psychosis.

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Conflict of interest

The authors declare no conflict of interest.

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