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The Ambit of Phytotherapy in Psychotic Care

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Abstract

The rate of psychosis has drastically increased in recent years and the number of prescriptions for psychiatric medications has made an even bigger jump. With the worrisome side effects of the medications, which can pose serious health risks and make medication compliance difficult, coupled with the prohibitive cost for many patients, there is an obvious need for alternative solutions. This review presents the ambit of phytotherapy in psychotic care. Interestingly, the review revealed that, plant-based medicines are rich in phytonutrients of antipsychotic importance and may be effective as stand-alone treatments or supplementary to conventional interventions. Despite the emerging interest in phytotherapy for mental disorders, the majority of the formulations are yet to be clinically certified. However, simply disregarding them for this reason might be consequential and as such, for better and improved mental health, research into phytotherapeutic care for psychosis must remain to be continuously explored as a promising niche.

Keywords: hallucination, mental health, phytonutrient, phytotherapy, psychosis

1. Introduction

Feelings and perceptions like paranoia/hearing voices may be highly discomfoting, worrying, and necessitate people to seek definitive aid. Generally, help have been offered medically, and mental illnesses or psychosis have always been diagnosed for such feelings. Many individuals always assume that psychosis occur in the manner as other ailments exist and may be accurately revealed by medical tests in the same way. However, this is not always the

case and several theories are in place to significantly understand the causatives of mental disorders. The notion that psychosis is a typical symptom of illnesses, possibly caused by some chemical imbalance or infiltrations in the brain, is just one of these theories [1]. While the rate of psychosis has drastically increased in recent years, the number of prescriptions for psychiatric medications has made an even bigger jump [2, 3]. For instance, in the United States, the prescription and use of antidepressant drugs has increased by almost 400% between 1998 and 2008 [4]. With the worrisome side effects of the medications, which can pose serious health risks and make medication compliance difficult, coupled with the prohibitive cost for many patients, there is an obvious need for alternative solutions. Interestingly, in addition to medical and clinical care for psychosis, the significance of phytotherapy has also become well established over the past decade. For instance, phytotherapeutic formulations such as St John's Wort and Kava have potentiated remarkable clinical evidence [5]. Also, the beneficial effects of peppermint aroma from plants on memory and alertness have offered new opportunities for research regarding cognitive decline [6]. Such formulations are direct efforts of the plant-based remedies that have been used by indigenous cultures for thousands of years.

Although, attempts have been previously made on the review of the significance of traditional systems of medicines in the management of mental illnesses [5, 7–11], a comprehensive review on the ambit of herbal remedies and the mechanism of actions of the anti-psychotic bioactive principles is still lacking till date. It is on this background, that, this review was conducted to identify the major psychotic disorders, the broad scope of phytotherapy in psychotic care and the mechanisms of action of anti-psychotic phytonutrients.

2. Major psychotic disorders and classifications

Psychotic disorder forms a diverse group of illness that are serious and often treatable [12]. Psychotic disorders affect the way a person may act or feel (loss of motivation, delusion, social withdrawal from others, depression, intense elation, 'uncontrollable laughter or crying', altered emotions), thinking (confused or disjointed thoughts, superficially-irrelevant thinking, unconsolidated connections between ideas, and incoherence), auditory and visual hallucination [13]. These itemized features make it difficult for the affected individuals to distinguish between what is real and not real. On the other hand, psychosis encompasses conditions that influence the mind where contact with reality has been lost [14].

According to the American Psychiatric Association [15], psychotic disorders can be classified into four basic groups including; non-affective psychotic disorder (e.g. schizophrenia, schizoaffective, schizophreniform, delusional, brief psychotic, shared psychotic, and psychotic disorder NOS), affective psychotic disorder (e.g. bipolar I and II disorder with psychotic features and major depressive disorder with psychotic feature), substance-induced psychotic disorder (e.g. alcohol-induced psychotic disorder and other substance-induced), and psychotic disorder to general medical condition [16, 17].

Schizophrenia is one of the most common and severe psychotic disorders. It is a cluster of disorders characterized by fundamental disturbances of thinking, perception and emotions.

The onset of schizophrenia is often in young adulthood, and for those affected, the disorder often causes many years of intense suffering [12]. The course, sign and symptoms in affected individual are highly inconsistent, but for a smaller ratio, the disorder causes lifelong disabilities with deterioration in functional capacity [18]. However, an average of 1 in every 7 patients with schizophrenia have been able to recover from the ailment despite the improvement in available treatment options in the recent years [19]. Schizophreniform disorder is basically identical with schizophrenia except that the ailment period is at least 1 month, but full recovery in 6 months is required. Another difference is that decline in functioning is not required in diagnostic criteria of schizophreniform disorder, while decline in social and occupational function is one criteria of schizophrenia. The diagnosis is often provisional and diagnosis may be changed to schizophrenia, should symptoms remain longer than 24 weeks [20]. In schizoaffective disorder on the other hand, the full criteria of both the active phase of schizophrenia and a mood episode should be met. In the same illness period, a 14-day delusional or hallucinational feeling without obvious mood symptoms may be evident. Symptoms meeting criteria for a mood episode should be present for the duration of the disorder [21]. The delusional disorder is often characterized by non-bizarre delusions and mostly last for almost 4 weeks. However, with the exception of the presence of tactile and olfactory hallucinations, other active-phase signs of schizophrenia should not be present, particularly if they are delusional-related. Besides the delusional impacts, normal behavior is always observed and functioning is not markedly impaired [15]. Unlike others, the brief psychotic occurrence is accompanied by sudden onset of psychotic symptoms (disorganized speech, delusions, catatonic behavior, hallucinations,) which persist for at least 24 hours but usually not exceeding 4 weeks. After this, a full remission and return to an optimal level of functioning is normally achieved [22, 23]. Furthermore, a variant of the non-affective psychotic disorders, the shared psychotic ailment, occurs rarely and is normally characterized by delusional experience in one individual when in a close relationship with an established delusional person [24]. Also, with the psychotic disorder NOS, the symptoms of psychosis are evident, but a specific diagnosis of any psychotic disorder cannot be made. There may be inadequate information to make a specific diagnosis, the information is contradictory, or symptoms fail to fulfill full criteria for a specific psychotic disorder. According to Arciniegas [17], diagnosis may be assigned for example if; a postpartum psychosis fails to meet criteria for a specific psychotic ailment, symptoms of psychosis have existed not beyond 4 weeks but yet to be remitted, occurrence of persistent auditory hallucinations void of any other psychotic feature, existence of persistent non-bizarre delusions with episodes of overlapping mood, evidence of uncertainty as to whether symptoms of psychosis are primary or substance use related or of general medical issues [12].

Unlike the non-affective disorders, the bipolar I disorder is an affective type of psychosis, characterized with manic or mixed episodes, usually accompanied with major episodes of depression. Symptoms of psychosis, which have to be hallucinations/delusions, can occur during manic, mixed and severe depressive episodes [25, 26] Typical mood-congruent psychotic symptoms during manic episodes include grandiosity and persecutory delusions linked to some special features of the person. Mood-incongruent psychotic symptoms include persecutory delusions without grandiose themes or delusions of thought insertion, thought broadcasting or being controlled [27]. The bipolar II disorder diagnosis means that person

has had at least one hypomanic, but no manic or mixed episodes, and one major depressive episode. Bipolar II disorder may also include psychotic symptoms during the severe depressive episodes. Bipolar I disorder leads to hospitalizations, need for treatment, and decline in daily functioning more often compared with bipolar II disorder [28, 29]. Similarly, the major depressive disorder with psychotic features is diagnosed when the criteria for major depressive disorder episode are met and delusions or hallucinations occur within the episode. Mood-congruent delusions or hallucinations are consistent with the depressive themes (delusions of guilt, delusions of deserved punishment, nihilistic delusions etc.). Mood-incongruent delusions or hallucinations do not have any apparent relationship to depressive themes (persecutory delusions, delusions of thought insertion, delusions of control etc.) [30]. For the substance-induced psychotic disorders, the victim is characterized by prominent hallucinations or delusions that are judged to be due to the direct physiological effects of a substance (drug of abuse, a medication, or a toxin exposure). Substance-induced psychotic disorders are distinguished from the substance-induced delirium (clear consciousness), from substance intoxication or withdrawal with perceptual disturbances (more persistent, clinically relevant symptoms, and the individual is void of insight) and from primary psychotic disorders [31]. The onset of substance use typically precedes the onset of psychotic symptoms, and the symptoms should disappear within 1 month after the substance use has ceased. Psychotic symptoms may occur during withdrawal or intoxication of these substances: cannabis, inhalants, hypnotics, hallucinogens, amphetamine, opioids, cocaine, alcohol, anxiolytics, phencyclidine and sedatives [32]. Some medications (e.g. antiparkinsonian medications, corticosteroids, anticholinergic agents, antimalarial medications and chemotherapeutic agents) can also trigger symptoms of psychosis. The clinical picture of psychosis varies depending on the substance [12]. For the one resulting from a general medical condition, the victim feels hallucinated or deluded. These symptoms can be judged to result from the direct physiological impacts of a general medical condition, and they are not explained by any other mental disorder [33]. Clear temporal association should be found between the general medical issue and the onset of psychotic disturbance. Additionally, there must be literature evidence on the particular medical condition causing psychotic symptoms [34]. Examples of general medical conditions that can cause psychotic symptoms include temporal lobe epilepsy, brain lesions and tumors, central nervous system infections and any severe medical condition requiring treatment in intensive care unit [34, 35]. Delirium is a condition characterized by disturbance of consciousness and cognition which may have psychotic symptoms as an associated feature [36, 37]. The etiology of delirium varies, including substance-induced delirium and delirium due to underlying general medical issues. Irrespective of the cause, associated challenges emanate within the shortest time possible and usually not consistent during the course of the day [37–39].

3. Conventional treatment and management options

Many of the drugs that have been introduced for the treatment of psychotic disorders are known to interfere with the normal physiological actions of several of the brain neurotransmitters and their receptors. The major brain neurotransmitters that have been implicated in

psychiatric disorders are: neuropeptides, epinephrine, norepinephrine, dopamine, acetylcholinesterase, 5-hydroxytryptamine, and Gamma-aminobutyric acid (GABA). In the hospital, many psychotic patients that are not confined to the bed and medication may be given and/or administered at a central point rather than having a 'drug round'. In psychiatric units, patient's compliance may be a problem and it is often necessary to ensure that drug is taken [40, 41]. Occasionally, a patients' paranoia may extend to the drugs they are given. They may think the staff members attending to them are trying to poison them [42].

Traditionally, antipsychotic drugs are classified as typical (classical) or atypical. The typical antipsychotic drugs are generally those that have been use for many years and common examples include; chlorpromazine, flupentixol, fluphenazine, haloperidol, and thioridazine [43]. The atypical antipsychotic drugs on the other hand, are more recent additions to the repertoire of drugs available. These drugs (e.g. amisulpride, clozapine, olanzapine, quetiapine, risperidone, zotepine) produce fewer adverse effects (e.g. tremor) on the motor system and may also help patients who do not respond to typical antipsychotic drugs [44].

4. Mechanism of action of antipsychotic drugs

Almost all antipsychotic drugs have many different pharmacological actions that it is very difficult to relate any one action to a therapeutic effect [45, 46]. Effective antipsychotic drugs share the ability to inhibit the physiological actions of dopamine D₂ receptors in the brain [47]. Collectively, the drugs are quite useful in controlling the states of agitation observed/found in acute schizophrenia, mania and some other forms of delirium and in paranoia. Their exact mode of action in these conditions remains unknown but most of them block the action of dopamine on D₂ receptors in the mesolimbic system of the brain and this seems crucial to their sedative and antipsychotic properties [48]. These drugs also inhibit the action of dopamine on chemoreceptor trigger zone of the brain and are thus antiemetic. Furthermore, drugs such as haloperidol prevent the action of the dopaminergic nerves that run from the substantia nigra to the corpus striatum. Disruption of physiological action of this system causes Parkinsonism and these drugs may cause various disorders of movement and posture [49].

5. Phytotherapy and the conventional therapies for psychosis

5.1. Conventional therapy

Contrary to phytotherapy that involves the use of medicinal plants, conventional therapy for psychosis is majorly by the use of medications. Others include cognitive therapy treatment, counseling, family or support group, the use of mood stabilizers etc. Cognitive therapy centers on identifying different patterns of thought (perception about situation) that brings about undesirable action or feelings. In some countries of the world particularly United Kingdom and United States, this kind of therapy is embraced (sometimes in combination with medications) as the most effective way of treating psychosis or psychosis-related disorder such as schizophrenia,

depression and or substance abuse. Additionally, family or support group form of psychosis therapy deals with the informal measure of treatment by a way of caring or providing support to people or family members suffering from the menace geared towards knowing how they fare on the various treatment or medications being exposed to and perhaps discussion on whether there is need for a change if medication is presenting havoc than alleviating the situation.

5.2. Medications as a form of therapy for psychosis

The discovery of chlorpromazine in the mid-1900s (1953) for the treatment of psychosis or related ailments led to the emergence of other conventional or typical antipsychotics such as perphenazine (marketed in 1957), trifluoperazine (1958), fluphenazine (1960), haloperidol (1966), thiothixene (1968), loxapine (1978), flupentixol (1983) usually referred as the first line or first generation antipsychotics [45]. These traditional agents aside exhibiting different level of potencies such as low (e.g. chlorpromazine), intermediate (perphenazine), high (haloperidol) are embraced and adopted for short or long-term use against acute or chronic psychotic disorders (schizophrenia, schizoaffective and or delusional disorders, psychotic-depressive ailments, dementia etc.). Antipsychotics or neuroleptics (derived from the combination of neuron and 'lepsis' to mean 'take hold of nervous system') ordinarily acts by blocking the Dopamine D₂ receptors (protein) domicile in the limbic system and striatum, thus, producing adverse effects such as the development of extrapyramidal side effects (EPSs), hyperprolactemia (elevated level of prolactin in the blood), neuroleptic malignant with Tardive dyskinesia, sexual dysfunction, restlessness, stiffness and shaking of the joints etc. among common names or features of these effects [50, 51]. Moreover, the coming of the newer or modern or second generation antipsychotic drugs (**Table 1**) otherwise referred to as atypical antipsychotics have in a way in recent times in clinical medicine replaced the use of first generation (FG) counterpart owing to their ability to lower some of the side effects known with FG. They exert these actions by proffering less affinity for D₂ receptor,

Antipsychotics	Brand name	Year of first market
Clozapine	Clozaril	1991
Olanzapine	Zyprexa	1996
Quetiapine	Seroquel	1998
Risperidone	Risperdal	2004
Ziprasidone	Zeldox	2009
Aripiprazole	Abilify	2013
Asenapine	Saphris	2009
Iloperidone*	Zomaril	2009
Blonanserin	Lonasen	2009
Lurasidone*	Latuda	2010

*Not yet approved by Food, Drug and Administration (FDA, US).

Table 1. Modern antipsychotics.

higher affinities for other neuroreceptors such as serotonin (e.g. 5-HT_{1A}, 5-HT_{2A} etc.) and nor-epinephrine (α 1, α 2 subtypes) as well as regulate glutamate receptor-mediated functions and behaviors among others [51, 52]. However, it is interesting to note that with issues relating to pharmacological effect, efficacy, safety, tolerability, cost effectiveness and adverse effects, it is important to weigh the pros and cons between both sides in terms of the above enumerated factors. In fact, there are reports that these newer generation drugs are more expensive, although the benefits they rendered outweighs the financial implications and are of less consequence as highlighted by clinicians and policy makers [51]. Similarly, despite revelations of side effects such as weight gain attributed to some modern class of antipsychotics such as Clozapine and Olanzapine but evidence as to why this is so is still unclear. Above all, in a review by Gardner and others [45] at comparing the superiority between typical and atypical antipsychotics taking into consideration above factors, they affirm the supremacy of the atypical antipsychotics over the old ones as evidenced in a number of cited reports (though accompanied with limitations) but still, generated huge number of prescriptions and acceptance globally [53–55].

5.3. Phytotherapy in psychotic care

Herbal medicine or phytotherapy according to World Health Organization (WHO) means herbal (medicinal plant) product containing the active components of plant parts or materials or both combined. In recent times, the use of medicinal plants in complementary and alternative medicine has continued to receive wider publicity in many quarters of the world. In fact 80% of the entire global population makes use of one form of traditional medicine in the prevention, diagnosis and treatment of numerous diseases facing them while also being incorporated within their national healthcare system. Psychosis, a mental condition resulting in the ability of an individual to witness distorted or total loss of contact with reality is considered among the neuropsychiatric disorders according to WHO with 13–49% of individual worldwide being affected by them at a particular stage within their life time [13]. Many medicinal plants and orthodox medicines are embraced and used in the management of this derangement [13, 45, 56], despite the numerous adverse effects including but not limited to restlessness, sexual dysfunction, extrapyramidal (EPSs) such as tardive dyskinesia (persistent tongue, mouth and jaw movement), malignant syndrome etc. attributed to these chemical moieties [51]. Interestingly, it is worthy of mention that out of several medicinal plants with reported antipsychotic effect [13, 11], very few, such as Lemon balm (*Melissa officinalis*), Yokukansan (TJ-54), Ginkgo (*Ginkgo biloba*), Valerian (*Valeriana officinalis*), St John's wort (*Hypericum perforatum*), Kava-kava (*Piper methysticum*) have been developed as agents with reported use for phytotherapy while being functioning as antidote against prominent psychiatric ailments (depressive, somatic, psychotic, anxiety, sleep) [5, 57] with the latter four agents among the first 10 best-selling herbal formulations in the US [13] and Africa in the management of neurological diseases [58], although, there are reports of agent like St John's wort inducing psychosis [59, 60]. In fact, despite their wide usage and preference over conventional antipsychotic drugs with varying adverse effects [61], psychiatric patients have continued to adopt herbal therapy for the management of psychosis [11]. The respective list of selected medicinal plants commonly used in psychotic care and the most prominently implicated phytonutrients of antipsychotic significance are presented in **Tables 2** and **3**.

Family	Species	Parts	Folkloric usage	Scientific validation	Toxicity	Phytonutrients
Alliaceae	<i>Agapanthus campanulatus</i> F.M. Leighton	Root	Decoction of the root is taken orally [62]	Extract exhibited serotonin, noradrenalin, and dopamine transporter inhibitors [63, 64].	No record	Flavonoid [64]
Amaryllidaceae	<i>Boophane disticha</i> (L.f.) herb	Leaves and bulbs	Decoctions of bulb scales given to sedate violent, psychotic patients [65]	Affinity to the serotonin transporter protein [66]; It also inhibited serotonin, noradrenalin and dopamine transporters [64]	No record	Alkaloids (buphanidrine and buphanamine) [64]
Anacardiaceae	<i>Spondias mombin</i> L.	Leaves	Leaves extract is used traditionally [67]	The aqueous extract prolonged the sleeping time and decreased the stereotyped behavior [67]	Non-toxic [67]	Tannins, anthraquinones, flavonoids, glycosides. Phenols, saponins, phlobatannins and alkaloids [67]
Apocynaceae	<i>Rauvolfia vomitoria</i> Afzel.	Root	The root is ground into powder and taken with pap or decoctions orally taken [68]	Decreased locomotor behavior [69]	Non-toxic [70]	Beta-carboline alkaloid, alstonine [69]
Apocynaceae	<i>Rauvolfia tetraphylla</i> L.	Leaves	No record	Significant affinity for 5-HT _{2A} and DA-D ₂ receptors [71]	Non-toxic [71]	11demethoxyreserpiline (3) and 10-demethoxyreserpiline (4), α -yohimbine (5) and reserpiline [71]
Asclepiadaceae	<i>Gomphocarpus physocarpus</i> E. Mey	Leaves	Powdered leaf is used to sedate psychotic patient [65]	The extract inhibited monoamine oxidase [72]	No record	Carbohydrates, cardiac glycosides, steroids/terpenoids, alkaloids and phenols [73]
Asclepiadaceae	<i>Xysmalobium undulatum</i> (L.) Aiton.f.	Root	Roots administered [74]	Extracts exhibited SSRI activity [64]	No toxicity [75]	Flavonoid (xysmalorin and uzarin) [64]
Euphorbiaceae	<i>Securinega virosa</i> (Roxb ex. Willd) Baill.	Leaves and root	Decoction of the leaves and roots [76]	The extract exhibited significant effect on D ₁ receptor by inhibiting grooming and climbing behaviors in rats [76].	Non-toxic [77]	Alkaloids, saponin, flavonoid, and tannin [76]

Family	Species	Parts	Folkloric usage	Scientific validation	Toxicity	Phytonutrients
Fabaceae	<i>Afzelia Africana</i> Smith	Stem bark	Fresh stembark of <i>Lophira alata</i> and <i>A. africana</i> are powdered together. The powder is then infused in water for 2 h and given to the patient to drink and bath [78]	The extract reduced the locomotive activity, rearing and sniffing in rats [78]	Non-toxic [79]	Alkaloids, tannins, saponins, flavonoids, triterpenoid, phytosterols and glycosides [79]
Fabaceae	<i>Amblygonocarpus andongensis</i>	Stem bark	Aqueous extract of the stem bark is taken orally [80]	The extract reduced the psychotic behavior characterized by anorexia and agitation in rats [81]	Mildly toxic and has reducing effects on weight [80]	No record
Fabaceae	<i>Arachis hypogaea</i> L	Leaves and stem	Aqueous extract of the leaves taken orally [82]	It has sedative effect [83]	No records	Linalool [83]
Fabaceae	<i>Lonchocarpus cyanescens</i> (Schumach and Thonn.) Benth.	Leaves	It is used in combination with another recipe of plant origin [84]	The extract inhibited stereotype behavior and spontaneous motor activity [84]	No records	Alkaloids, anthraquinones, cardiac glycosides, cyanogenetic glycosides, flavonoids, saponins, steroids and tannins [84]
Lamiaceae	<i>Ocimum sanctum</i> L.	Leaves	Extract from the leaves is taken orally [85]	Attenuation of locomotory activity and dopamine levels [85]	Non-toxic [86]	Eugenol, cardinene, cubenol, borneol, linolenic acid, oleic acid, palmitric acid, steric acid, vallinin, vicenin, vitexin, vllinin acid, orientin, circineol, gallic acid, vitamin A, vitamin C, phosphorus and iron [87]
Lamiaceae	<i>Mentha aquatica</i> L.	Leaves	Mixed with leaves of <i>Tagetes minuta</i> L. burned and the smoke is inhaled [88]	Leaf extracts exhibited SSRI activity and MAO-B inhibitory activity [63, 89]	No record	Flavones and flavanone derivatives [90]
Liliaceae	<i>Allium cepa</i> Linn	Bulb	Paste [91].	Onion paste inhibited dopaminergic neurotransmission and possibly blocks dopamine D2 receptor [91]	Non-toxic [92]	Phenolic acid, flavonoids, anthocyanin, sterols, vitamins, pectin and peptides [91].

Family	Species	Parts	Folkloric usage	Scientific validation	Toxicity	Phytonutrients
Ochnaceae	<i>Lophira alata</i> Banks ex. Gaertn.f.	Stem bark	Fresh stembark is powdered with <i>Azelia africana</i> stembark. It is then infused in water for 2 h and given to the patient to drink and bath [78].	The extract reduced locomotive activity and rearing in rats [78]	Non-toxic [79]	Alkaloids, tannins, saponins, flavonoids, triterpenoid, phytosterols and glycosides [79]
Piperaceae	<i>Piper guineense</i> Schum & Thonn	Fruit	No record	Significant reduction on rearing, locomotor activity and dips in mice [93]	Non-toxic [94]	β -Sesquiphellandrene, limonene, linalool [93]
Rutaceae	<i>Ruta graveolens</i> L.	Leaves	Decoction of the leaves and oil extract are used [95]	It exhibited MAO inhibitory activity [89]	No toxicity [96]	Furocoumarins, furoquinolines and acridone alkaloids [89].
Solanaceae	<i>Datura stramonium</i> L.	Leaves and seeds	Information not provided [65, 97]	The seeds and leaves of <i>D. stramonium</i> are used to sedate psychotic patients [98]	Toxic [97]	Alkaloids, tannins, saponins and cardiac glycosides [97]

Table 2. Medicinal plants list of plant with antipsychotic potential, their ethnopharmacology, toxicity and mechanism of actions.

Active compound	Mechanism of action	References
Ursolic acid (terpene)	Activation of dopamine D ₁ and D ₂ receptors	[99]
Reserpiline(alkaloid)	inhibition binding to DA-D2 and 5-HT2A receptors	[71]
α -Yohimbine (alkaloid)	inhibition binding to DA-D2 and 5-HT2A receptors	[71]
Methylaplysinopsin (alkaloid)	Inhibition of monoamine oxidase (MAO) and displacement serotonin from its receptors	[100]
Polygalasaponins (saponin)	Affinity for dopamine and serotonin receptors	[101]
Yuanzhi-1 (triterpenoid saponin)	Uptake of inhibitor that block dopamine, norepinephrine and serotonin transporters	[102]
Geranial, neral and 6-methyl-5-hepten-2-one, citronellal, geranyl-acetate, β -caryophyllene and β -caryophyllene-oxide, and 1,8 cineole (terpene)	Nicotinic and muscarinic cholinergic receptor binding properties in human brain tissue, acetylcholinesterase inhibitory properties and inhibition of enzyme GABA transaminase, leading to increased GABA activity	[103, 104]
Tropane (alkaloid)	Muscarinic acetylcholinesterase receptor antagonist	[105]
Purine (alkaloid)	Receptor interactions, specifically involving DA D1 receptor signaling	[106]

Active compound	Mechanism of action	References
Isoquinoline (alkaloid)	Opioid receptor binding	[107]
Pyridine (alkaloid)	Agonist nicotinic acetylcholinesterase receptor binding	[108]
Physostigmine (alkaloid)	Cholinesterase inhibitor and direct agonistic nicotinic acetylcholinesterase receptor binding	[109]
Pilocarpine (alkaloid)	Muscarinic acetylcholinesterase receptor agonist	[105]
Reserpine (alkaloid)	Irreversible blockage of norepinephrine and dopamine	[110]
β -Sesquiphellandrene (terpene)	Inhibition of dopamine neurotransmission at D1/D2 receptors	[93]
Buphanidrine and buphanamine (alkaloids)	Affinity to the serotonin transporter (SERT) protein	[66]
Xysmalorin and uzarin (flavanoids)	Affinity for SERT in the binding assay.	[64]
Atropine (alkaloid)	CNS depressants and competitively antagonize muscarinic cholinergic receptors.	[111]
Scopolamine (alkaloid)	CNS depressants and competitively antagonize muscarinic cholinergic receptors.	[111]
Agathisflavone and amentoflavone (flavanoid)	Affinity for GABAA-benzodiazepine receptor	[110]

Table 3. Psychoprotective bioactive metabolites.

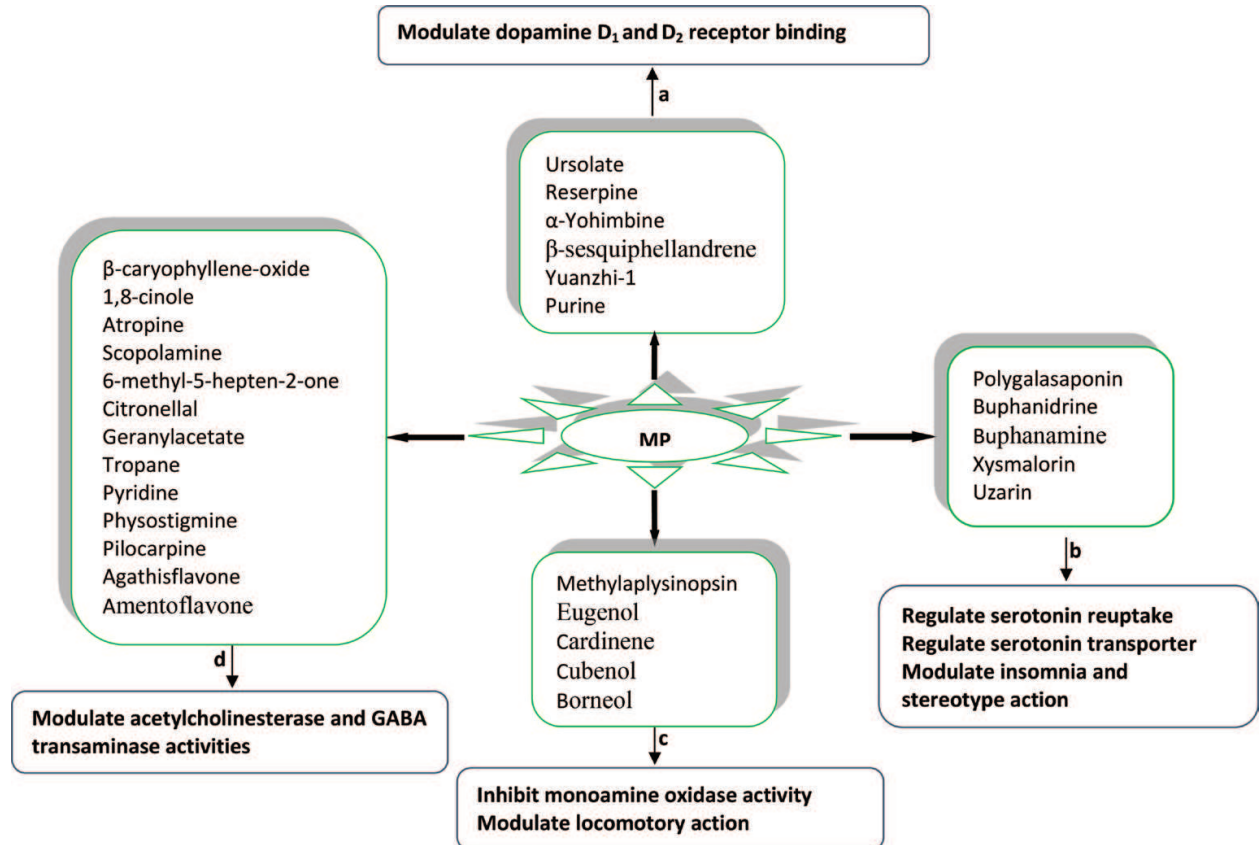


Figure 1. A unified mechanism of actions of antipsychotic phytonutrients. MP, medicinal plants.

Taken together, a unified mechanism of actions of the antipsychotic phytonutrients could be proposed as presented in **Figure 1**. This may be conceptualized to potentiate either (a) modulatory role on dopamine D₁ and D₂ receptors, (b) regulation of serotonin reuptake/transporters, (c) inhibitory effect on the specific activity of monoamine oxidase, or (d) regulation of the specific activities of acetylcholinesterase and Gama-aminobutyric acid transaminase. Plants endowed with these metabolites (**Figure 1**) may unilaterally or synergistically be employed with other conventional antipsychotic therapies to achieve optimal results in alleviating the ill episodes of the different forms (depression, hallucination, schizophrenia, etc.) of psychosis related disorders.

6. Conclusion

Conclusively, considering the potential benefits of medicinal plants in antipsychotic care, it may be evidently suggested that, there is a need for an inclusive integrative approach to manage and treat psychosis. One of such strategies may be to embrace traditional systems of medicine with the use of medicinal plants. This is mainly due to the plants being endowed with antipsychotic phytonutrients and demonstrating significant results in the management of mental health disorders. However, embracing herbal formulations in combination with conventional pharmaceuticals may provide better outcome with a view to targeting different aspects of mental being alertness. Although this concept may be controversial, research into phytotherapeutic care for psychosis is a promising niche for further studies.

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