REVIEW

ANTIPSCYHOTIC INDIAN HERBAL FORMULATIONS: AN OVERVIEW

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ABSTRACT

Psychosis is a serious mental disorder characterized by impaired thinking and emotions which indicate that the person experiencing them has lost contact with reality and affects about 1% of the population. It is characterized by a myriad of signs and symptoms which include distortion of thinking and perception, cognitive impairments, motor abnormalities, volition and apathy, difficulties in communication and restricted affective expression. Various allopathic medicines are available in markets which are chlorpromazine, fluphenazin, trifluprомazine, haloperidol, trifluperidol, penfluridol, flupenthixol, clozapine, resperidone. But prolonged exposure to antipsychotic medication has been associated with side effects including extrapyramidal symptoms (EPS) and adverse events, such as tardive dyskinesia, an irreversible motor disorder, diabetes or metabolic problems, weight gain/ obesity, heart problems, strokes, Parkinson's disease, lack of efficacy, cognitive decline or impairment, brain shrinkage, seizures or convulsions, lowered bone mineral density, violence and homicidal ideation, psychosis and delusional thinking, tumours and brain defects which leads to increases mortality. Therefore demand for herbal formulation is increasing. This article enlightens about the various antipsychotic Indian Herbal Formulations that can be used to abolish the drug induced side effects and improve the psychotic symptoms clinically.

KEY WORDS: Extrapyramidal, Psychosis, Negative dimension.

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INTRODUCTION:

Psychosis is a serious mental disorder characterized by impaired thinking and emotions which indicate that the person experiencing them has lost contact with reality and affects about 1% of the population. Impaired thinking, cognitive impairments, difficulties to communicate and restricted affective expression are the signs and symptoms by which psychosis can be characterised. People who are psychotic have delusions or hallucinations. These are referred to as "positive" symptoms; "negative" symptoms like loss of motivation and social withdrawn can also occur. Furthermore, there is impairment in attention, memory, and executive functions, which equally contribute to psychotic disability and refer to cognitive symptoms [1]. These experiences can be frightening and develops gradually over a period of time. This is not common that psychosis starts suddenly. Psychosis generally occurs in three phases. These three phases are early warning signs that usually develops in late adolescence or early adulthood, acute phase is when the symptoms of psychosis begin to emerge, recovery phase. Psychosis is classified into different types which are brief reactive psychosis, organic psychosis, delusional disorders, bipolar disorder, psychotic depression, schizoaffective disorder. On the basis of diagnosis, psychosis can be classified into non-affective and affective psychosis. Non-affective psychotic disorders include schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder due to medical condition, substance-induced psychotic disorder. Affective psychotic disorders co-occur with severe mood disturbances, and include disorders such as bipolar disorder and depression with psychotic features [2]. It is believed that multiple pathological processes can lead to psychosis i.e. involvement of Akt/GSK3 signaling pathway [3].

Antipsychotic medication has been established as a standard of care for persons diagnosed with a psychotic disorder. Antipsychotic agents work as antagonists at dopamine receptors and provide support in treatment of psychotic symptoms. Patients often evidence decreases in positive symptoms with antipsychotic medication treatment. Antipsychotic medication includes chlorpromazine, fluphenazine, trifluprom azine, haloperidol, trifluperidol, penfluridol flupenthixol, clozapine, resperidone [4]. But antipsychotic medication has been associated with side effects including tardive dyskinesia, diabetes, weight gain/ obesity, heart problems, strokes, Parkinson's disease, lack of efficacy, brain shrinkage, seizures or convulsions, lowered bone mineral density, delusional thinking, tumors and brain defects. To overcome these side effects various herbal formulations are being administered nowadays. These herbal formulations are *Euphorbia neriifolia, Randia dumetorum Lam, Aegle marmel, Coccinia grandis, Ocimum americanum, Brassica juncea, Acorus calamus, vitex negundo, Cannabis Indica, morinda citrifolia, Oenothera biennis, Allum Satium, Ginko Biloba, Panax Ginseng, Gotu Kola, Hops, Kava, Lavender, Lemon Balm, Rosemary, Skullcap, St. John Wort Valerian, Ashwagandha, Brahmi, Chamomile, Green Cardamom.* Therefore, the present study has been designed to review the antipsychotic Indian Herbal formulation.

REVIEW OF LITERATURE:

Psychosis is a severe mental disorder which has lifetime prevalence of 1% throughout the world population [5]. This mental disorder is associated with functional decline, lifelong disability and tremendous suffering. Unlike other neuropsychiatric disorders no abnormality is observed in psychosis, and there are not many biochemical tests that can confirm psychosis. Diagnosis begins with observation of positive symptoms such as delusion, hallucinations, impaired thinking, and later with negative symptoms, including low levels of emotional arousal, mental activity and social drives [6]. The psychotic symptoms also include inappropriate emotional expressions, motivational deficits, and abnormalities in mood and sleep disturbances.

Psychosis develops gradually over a period of time. This is not common that psychosis starts suddenly, it generally occurs in three phases. The first phase of psychosis involves Early Warning Signs that develops in late adolescence or early adulthood. These early warning signs can last for months but each person's experience will differ. These include reduced concentration, motivation, depressed mood, sleep disturbances, anxiety, social withdrawal, irritability. The second phase is the acute phase in which symptoms begin to emerge and are most noticeable. The third phase is the Recovery phase in which some symptoms may linger but most people successfully recover and return to their normal, everyday lives.

There are three symptom dimensions which are the Negative dimension, the Positive dimension and disorganised symptom dimension. The positive dimension was divided into two, delusions and hallucinations. The Disorganized symptoms included anxiety, depression and sleep disturbances.

Psychosis can be classified into various types which includes A) brief reactive psychosis whose symptoms arise suddenly, and last over a shorter period. This type of psychosis will usually make a quick recovery. B) Organic Psychosis that occur as a result of a defects in brain functioning. C) Delusional Disorder which is characterized by one psychotic symptom, delusions. D) Bi-polar Disorder which involves mania) and depression. E) Psychotic Depression which is characterised by severe depression. F) Schizoaffective Disorder which is similar to bipolar and psychotic depression. The only difference is that the symptoms of either psychosis or mood disturbance occurs at the same time but sometimes there is psychosis present but not mood disturbance.

MOLECULAR PATHWAY INVOLVED IN PSYCHOSIS:

Emamian reported that psychosis involves the impairment of AKT/GSK3 signaling pathway.He found that gene variations are associated with differences in cognitive function including executive functioning, and processing speed. Patients with psychosis have reduced AKT_1 protein level in different tissues. Psychotics expressed 68% less AKT_1 level compared to control subjects. This decrease in protein level in the brain was specific only to AKT_1 isoform and not to AKT_2 and not to AKT_2 and AKT_3 levels [3]. A number of studies showed that there is marked decrease in AKT_1 mRNA, protein, and activity levels in the prefrontal cortex and hippocampus, as well as in peripheral blood of individuals with psychosis [7,8]. The activity of major AKT_1 targets such as GSK_3 was also found to be altered in individuals with psychosis (Yang et al firstly reported decreased levels of GSK-3α proteins in lymphocytes of individuals with psychosis. Several studies have reported that chronic administration of antipsychotics phosphorylates GSK-3β at the Ser-9 residue, and inhibits its activity [3]. Other studies also reported that chronic administration of clozapine, risperidone or haloperidol enhanced protein levels of β-catenin and GSK-3 [9]. Atypical antipsychotics were also increase phosphorylation of GSK-3β in the mouse brain [10]. Besides antipsychotics, lithium, and electroconvulsive shocks which are used in antipsychotic treatment have been shown to lead to activation of AKT in rats [11, 12].

Dopamine receptor antagonists as well as chemicals enhancing serotonergic transmission have also been found to increase the expression and inhibitory phosphorylation of GSK-3β and activation of AKT in the mouse brain [10]. The activity of AKT can be modulated by Dopamine D_2 class receptors [13]. The activation of dopamine D_2receptor can inhibit AKT activity through an arrestin-dependent but G protein independent pathway [14].

DRUG THERAPY INVOLVED IN PSYCHOSIS:

Antipsychotics are a class of drugs used in the treatment of psychiatric disorders, most notably schizophrenia, but also in disorders such as bipolar disorder, delusional disorder and certain nonpsychotic disorders. The first generation of antipsychotic medication are also known as 'typical antipsychotics' which were first discovered in the 1950s. And, second generation of antipsychotics has known as the 'atypical antipsychotics' which were clinically introduced in the 1970s. Antipsychotics are classified into:

Typical antipsychotics:

Phenothiazines:

a) Aliphatic side chain: chlorpromazine, triflupromazine.
b) Piperidine side chain: thioridazine
c) Piperazine side chain: trifluoperazine, fluphenazine.

Butyrophenones: Haloperidol, Trifluperidol, Penfluperidol.

Thioxanthenes: Flupenthixol

Other heterocyclics: pimozide, loxapine.

Atypical antipsychotics: Clozapine, Risperidone, Olanzapine, Quetaipine, Aripiprazole, Ziprasidone, Amisulpride, Zotepine.

But the clinical use of Typical antipsychotics caused extrapyramidal symptoms (EPS) in patients including parkinsonism, tardive dyskinesia, akathisia and dystonia. Newer generation medications showed some success, but a new list of

concerning side effects have been associated with both generations of the drugs – namely weight gain and associated metabolic effects; prolactin elevation; associated sexual side effects; and QT prolongation. It has been generally thought that the newer generation of antipsychotics are more effective than the typical. Horacek reported that there was no difference, while others have found that atypicals were only somewhat more efficacious [15, 16]. Clozapine, risperidone, amisulpride and olanzapine have higher efficacy. This is particularly true of clozapine [17].

MAJOR SIDE EFFECTS OF ANTI-PSYCHOTICS:

Weight gain and other metabolic effects: In 2009 controlled trials were took up to create a database that was analysed [18].They found that atypical ziprasidone caused least weight gain as compared to two other atypicals, olanzapine and risperidone. Antipsychotics are also known to have other metabolic effects. The use of atypical antipsychotics such as olanzapine, risperidone, clozapine and quetiapine has shown greater association with diabetes than typical antipsychotics [19]. Study in 2008 on atypicals olanzapine showed greater risk for diabetes [20]. Other metabolic effect of antipsychotics is that on lipids and cholesterol. First generation antipsychotics i.e, phenothiazines, cause increases in triglycerides and LDL cholesterol and decreases in HDL cholesterol [21]. Atypical antipsychotics such as olanzapine tend to raise cholesterol and in particular triglycerides, and which are associated with obesity and diabetes. Olanzapine, quetiapine and risperidone has greatest, moderate and minimal propensity to increased cholesterol and lipids, while aripiprazole and ziprasidone have minimal adverse effects on blood lipids [21].

Clozapine markedly increases the triglyceride levels and cholesterol levels after treatment for five years [22]. Haloperidol, olanzapine and risperidone show no significant difference in metabolic adverse effect after the first year of treatment [23].

Extrapyramidal symptoms and Tardive Diskinaesia: These include parkinsonism, acute dystonia, akathisia. These motor side effects are less frequently encountered now because of the introduction and more first-line use of the atypical generation of antipsychotics. Halopridol showed more EPS as compared to the risperidone group but prolatin level is observed to increase with risperidone [24]. Haloperidol showed increased rates/severity of parkinsonism and akithisia when compared to one or more atypical anti-psychotics [25, 26, 27].

Prolactin elevation and associated side effects: Both atypical and typical antipsychotic drugs work by blocking D2 receptors and reducing the increased dopamine transmission which occurs as a feature of psychosis. But they also block D2 receptors on lactotrophs and as such cause elevated release of prolactin. Increased levels of prolactin and hyperprolactinaemia is a frequent side effect of antipsychotic medication and can result in galactorrhoea, gynaecomastia, menstrual irregularities, sexual dysfunction and osteoporosis [28, 29].

QTc prolongation: Antipsychotic drugs are also reported with ECG alterations, ventricular arrhythmia and sudden cardiac death. They block action on cardiac potassium channels and extend the cardiac QTc interval, a risk factor for torsade de pointes (TdP), a potentially fatal condition [30]. Droperidol and thioridazine also caused QTc prolongation in a dose-dependent way. Clozapine therapy also causes Tachycardia and other cardiovascular problems [31]. It is also linked with a risk of pulmonary thromboembolism. Antipsychotics such as clozapine, olanzapine, quetiapine and risperidone which are antagonistic at postsynaptic adrenergic alpha1 receptors causes postural hypotension [32, 33].

Other miscellaneous side effects of antipsychotics: Clozapine and other antipsychotics are known to lower the seizure threshold in patients with epilepsy. Another fatal side effect of all anti-psychotics is neuroleptic malignant syndrome. This is a syndrome. Symptoms include fever, diaphoresis, rigidity, confusion, fluctuating consciousness, fluctuating blood pressure, tachycardia, leucocytosis and altered liver function tests. Constipation can be severe and can lead to serious consequence such as paralytic ileus, bowel occlusion and death [34]. Ischemic cholitis may also result Sedation [35], hypersalivation [36], fever, nausea, may also occur. Less common reported side effect of clozapine include Colitis, Heat Stroke, Hepatic Failure, Pancreatitis, Pericardial effusion, Pneumonia, Thrombocytopenia, and Ocular pigmentation [33].

HERBAL FORMULATIONS:

Today number of Herbal formulations are being used in psychosis. These are *Euphorbia neriifolia, Randia dumetorum Lam, Aegle marmelos, Coccinia grandis, Ocimum americanu, Brassica juncea, Acorus calamus, vitex negundo, Cannabis Indica, morinda citrifolia, Oenothera biennis, Allum Satium, Ginko Biloba, Panax Ginseng, Gotu Kola, Hops, Kava, Lavender, Lemon Balm, Rosemary, Skullcap, St. John Wort, Valerian, Ashwagandha, BrahmiChamomile, Green Cardamom.*

Acorus gramineus. Family: Araceae. Its common name is Japanese Sweet Flag. It is used as insecticidal and antifungicidal [37, 38].

Aegle marmelos. Family: Rutaceae. Its common name is Bael. It is used as Analgesic, anti-inflammatory, anti-pyretic, anti-cancer, anti-oxidant, anti-ulcer, anti-diabetic, anti-thyroid, anti-viral, anti-bacterial, and anti-fungal [39, 40].

Allium cepa. Family: Liliaceae. It is commonly known as Onion. It is used as anti-hypercholestrolemic, hypoglycemic, anti-platelets, anti-oxidant, anti-cancer, and antimicrobial [41].

Areca catechu. Family: Arecaceae. It is commonly called as Betel nut. It is being used as anti psychotic, anti-microbial, anthelmintic, and anti-oxidant [42].

Bacopa. Family: Plantaginaceae. It is commonly known as Brahmi. It is used as as ayurvedic medicine to enhace cognitive ability. It also exhibits neuroprotective properties.

Cannabis sativa. Family: Cannabaceae. It is commonly known as Marijuana. It is used as anti- epileptic, anti- pyretic, anti- parasitic and anti-emetic [43].

Catunargaom Spinosa. Family: Rubiaceae. It is commonly known as Mountain pomegranate. It is known for its anti-bacterial, anti-fungal, anti psychotic and anti-viral activity.

Chrysanthellum indicum Linn. Family: Compositae. Its common name is Rariyar kasa (Kontagora), Dunkufe (Zaria). It is used as anti-tumor, anti-amoebic, diuretic, hypoglycemic, and anti-oxidant [44].

Crocus sativus. Family: Iridaceae. It is very commonly known as Saffron. It is used as memory enhancer, anti-depression, anti-inflammatory, anti-tumor, and radical-scavenging [45, 46].

Coccinia grandis. Family: Cucurbitaceae. Its common name is Scarlet and Parval. It is used as anti-diabetic, analgesic, anti-pyretic, anti-inflammatory, hepatoprotective, antituberculosis, anti-malarial, anti-bacterial, anti-oxidant, anti-cancer, and anti-ulcer [47].

Datura metel. Family: Solanaceae. It is commonly called as Thorn apple. It is used for its analgesic activity, anti anxiety, anti-spasmodic, antitussive, and bronchodilator activity [48]. ***Delonix regia***. Family: Fabaceae. It is commonly named as Gulmohar. It is used for wound healing, hepatoprotective, anti-inflammatory, anti-bacterial, and anti-malarial [49].

Euphorbia neriifolia. Family: Euphorbiaceae. It is used as Anti-anxiety, anticonvulsant, anti-oxidant, anti-inflammatory, analgesic, anti-diabetic and hepatoprotective [50].

Elettaria cardamomum. Family: Zingiberaceae. Its common name is Green cardamomum. It is used ase used to deal with schizophrenia as they are good for the nervous system.

Ginkgo Biloba. Family: Ginkgoaceae. Its commonly known as Oriental plum tree, Hill apricot, Maidenhair tree, Kew tree, Silver apricot, Silver plume, Silver fruit. It is used as anti-oxidant and treat cerebral hemorrage.

Gliricidia sepium. Family: Leguminosae. It is commonly called as Gliricidia. It is used as anti-bacterial, anti-fungal, anti-oxidant [51].

Humulus lupuluds. Family: Cannabaceae. It is commonly known as Hops. It is often used as a sedative, promote sleep.

Hypericum perforatum. Family: Hypericaceae. It is commonly known as St. John's Wort. It is used as a mild tranquilizer and as a treatment for depression, insomnia and as a muscle relaxer. It is also used to treat minor burns, wounds, skin inflammation and treat nerve pain. ***Ipomoea reniformis***. Family: Convolvulaceae. Its common name is Undirkana or Mushakparni. It is used as anti-diabetic, anti-inflammatory, anti-epileptic, anti-oxidant, anxiolytic, neuroprotective and anti-microbial [52].

Litsea polyantha. Family: Lauraceae. It is commonly named as Barkukuchita. It is used as anti-inflammatory, anti-diarrheal, anti-oxidant, anti-depressant, anti-bacterial, anti-fungal, anti-HIV, anti-thrombotic.

Lavendula officinalis. Family: Lamiaceae. It is commonly known as Lavender. It is used as anti depressant. It is used in treatment of nervous tension, restlessness, depression, and insomnia.

Lonchocarpus cyanescens. Family: Fabaceae. Its common name is Indigo vine. It is used as anti psychotic, anti-oxidant, anti-anxiety, and anti-inflammatory [53].

Morus alba. Family: Moraceae. It is commonly called as White mulberry. It is used as anti microbial, anti-oxidant, anti-HIV, neuroprotective, anti psychotic and anti-stress [54].

Morinda citrifolia. Family: Rubiaceae. It is commonly known as Noni. It is used as analgesic, anti-inflammatory, anti-oxidant, anti-tumor, hepatoprotective, anti-fungal, anxiolytic, and antiepileptic [55].

Melissa officinalis. Family: Lamiaceae. It is commonly known as Lemon Balm. It is used to relieve anxiety and insomnia. It is also used as aroma therapy for Alzheimer's disease. ***Matricaria recutita***. Family: Asteraceae. It is commonly known as Chamomile. It has soothing and calming properties. It also promotes restful sleep and is thus useful useful for those suffering from psychosis.

Ocotea duckei. Family: Lauraceae. It is commonly called as Sweet weed. It is used as anti mycobacterial, anti-leishmanial, and anti-depressant.

Ocimum sanctum. Family: Lamiaceae. It is common name as Tulsi. It is used as analgesic, anti-inflammatory, anti-ulcer, anti-anxiety, anti-asthmatic, anti-fertility, anti-cancer, anticonvulsant, anti-diabetic, anti-hyperlipidemic, and anti-oxidant [56].

Oenothera biennis. Family: Onagraceae. It is commonly known as Evening Promise Oil. It is used as anxiolytic and to reduce hyperactivity in children. It can also be used in reducing psychosis symptoms.

Ocimum basilicum. Family: Lamiaceae. Its commonly known as Basil. It is used as antioxidant and also promote brain functionality to improve the symptoms of psychosis. ***Panax Ginseng***. Family: Araliaceae. It is commonly known as American Ginseng. It is used as anti-sterility, anti-proliferative, memory enhancing, anti-inflammatory and anti-diabetic [57].

Passiflora incarnata. Familly: Passifloraceae. It is commonly called as Passion flower. It has been used as antitussive, anti-inflammatory, anti-asthmatic, anti-anxiety, anticonvulsant, analgesic, anti-psychotic and aphrodisiac [58].

Piper retrofractum. Family: Piperaceae. Its common name is Long Cavya. It is used as mosquito larvicidal, anti-microbial, aphrodisiac, anti-hypertensive, anti-psychotic and anti-fungal [59].

Pepper methysticum. Family: Piperaceae. Its common name is Kava. It is used as a natural relaxant and sleep aid. It is usually reserved for times of particularly high anxiety [60].

Randia dumetorum. Family: Rubiaceae. It is commonly called as Emetic nut. It is used as antipsychotic, analgesic, anti-inflammatory, antiallergic, and antibacterial [60].

Rauwolfia tetraphylla. Family: Apocynaceae. Its common name is Devil pepper. It is used as anti-bacterial, anti-diabetic, anti-viral, anti-psychotic and aphrodisiac [61].

Rhodiola rosea. Family: Crassulaceae. Its common name is Golden root. It is used as anti-psychotic, anti-depression and anti-anxiety.

Rosmarinus officinalis. Family: Lamiaceae. It is commonly known as Rosemary. It shows an anti-seizure activity. It causes an increase in GABA. It is used in treating psychotic symptoms [62, 63].

Scutallaria latriflora. Family: Lamiaceae. It is commonly known as Skullcap. It is used as for its calming effect on the body, insomnia, anticonvulsant effects, and to lessen the symptoms of alcohol withdrawal [62, 63].

Saccharum spontaneum. Family: Poaceae. It is commonly named as Sugar cane. It is used as anti-bacterial, anti-fungal, cytotoxic, and anti-oxidant [62, 63].

Securinega virosa. Family: Euphorbiaceae. Its common name is Bushweed. It is used as anti-diabetic, anti-oxidant, anti-rheumatism, anti-diarrheal, and anti-epileptic [62, 63].

Solanum nigrum. Family: Solanaceae. Its common name is Black nightshade. It is used for treatment of psychosis, anticonvulsant, anti-cancer, anti-microbial, anti-ulcerogenic, and anti-inflammatory [64].

Terminalia bellerica. Family: Combretaceae. Its common name is Bahera. It is used as anti-psychotic. It is also used as analgesic, anti-inflammatory, anti-cancer, anti-depressant, anti-diabetic, anti-ulcer, anti-fertility, anti-hypertensive, anti-microbial, and anti-oxidant [65].

Vitex negundo. Family: Verbenaceae. Its common name is Monk Pepper. It is used as anti-inflammatory, analgesic, as an effective anxiolytic agent, anticonvulsant, anti-oxidant, anti-gonorrhoeic, anti-arthritic [66].

Valeriana officinalis. Family: Valerianeceae. It is commonly known as Valerian. It is a sleep aid, used for treatment of insomnia. It is effective in anxiety, depression and nervous irritability [67].

Withania somnifera. Family: Solanaceae. It is commonly known as Ashwagandha. It is a calming herb useful for depression, anxiety, and other psychiatric disorders [68].

CONCLUSION:

Antipsychotics medications have many side effects such as weight gain/ obesity, death or increased mortality, heart problems, strokes, Parkinson's disease, lack of efficacy, cognitive decline or impairment, brain shrinkage, seizures or convulsions, lowered bone mineral density, violence and homicidal ideation, psychosis and delusional thinking, tumors and brain defects. To overcome these side effects herbal formulation are being used nowadays. There has been growing interest in the therapeutic use of plants because of their safety, economical, and effective use. In this review, some plants have been mentioned, which are previously explored by the various researchers for their antipsychotic activity. Collectively, behavioural studies of plants have created a unique opportunity for the development of new pharmacotherapies for psychosis. Some dietary supplements such as antioxidant vitamins, EPA omega-3 fish oils also helps to improve symptoms of psychosis. Therefore, better results can be achieved by herbal therapy along with dietary supplements. On the other hand, our health also depends on our lifestyle choice.

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