COMPARATIVE REVIEW OF SYNTHETIC AND NATURAL COMPOUNDS UTILIZED IN THE MANAGEMENT OF PSYCHOSIS

Supported by tetfund

[ǂ1]Bukunola Oluyemisi Adegbesan, [1]Esther Nkechi Ezima, [1]Adefemi Oluwasegun Adefuye, [1]Enitan Omobolanle Adesanya and [2]Samuel Oluwadare Olalekan

[1] Department of Biochemistry, Faculty of Basic Medical Sciences, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Sagamu Campus, Ogun State, Nigeria.

[2] Department of Physiology, Faculty of Basic Medical Sciences, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Sagamu Campus, Ogun State, Nigeria.

[ǂ] *Corresponding author e-mail*: adegbesan.bukunola@oouagoiwoye.edu.ng

Received: June 14, 2023 Accepted: August 21, 2023

Abstract: Neurological diseases remain a major global healthcare challenge resulting from disturbances in the nervous system and impaired brain function due to consumption of diet or exposure to dangerous substances. One of the neurological diseases requiring global attention is psychosis. The challenge of neurodegeneration affects millions of people worldwide with substantial growth in annual estimates of affected persons. Major contributing factors to psychosis promote the generation of reactive oxygen species (ROS), mitochondrial malfunction, and systemic toxicity, especially in the blood and cerebral fluids of psychotic patients. Major symptoms of psychosis include delusions, incarnation syndrome, wildly disorganized thinking, loss of touch with reality, misidentification syndrome, hallucinations, mood disorders, delirium, aggression, anxiety, and agitation. The need to find safe therapy for neurodegenerative diseases such as psychosis influenced this study to suggest some potent, non-deleterious plants as therapy against psychosis with the widely used conventional and non-conventional drugs. Significantly, both conventional and non-conventional anti-psychotics such as clozapine, quetiapine, risperidone, quetiapine, memantine, olanzapine, pimavanserin, aripiprazole, and rivastigmine have been adopted for managing issues of psychosis because they act as serotonin-dopamine antagonists or as partial agonists to dopamine. The usage of antipsychotic medications has been dampened by various hazards or adverse effects such as death, cerebrovascular accidents, worsened motor impairment, nausea, insomnia, agitation, and metabolic and endocrine anomaly which makes their long-term prescription questionable. However, antioxidants like vitamins and nutraceuticals from plants are suggested to be prescribed as therapy against neurological diseases like psychosis based on their increased safety on users, affordability, and non-detrimental side effects. Also, medicinal plants have been adopted in ameliorating psychosis as investigation proved them to have fewer side effects on their users.

Keywords: Natural, synthetic, psychosis, antioxidants, nutraceuticals, neurological

Introduction

Neurological diseases, to which psychosis belongs, stand as one of the major healthcare challenges in the entire world with a significant burden on the healthcare and financial sectors of the society (Makkar *et al*., 2020). Neurological diseases result from disturbances in the central and/or peripheral nervous system due to the consumption of diets that lack specific nutrients (Mandolini *et al*., 2018). Annually, neurological illnesses impact more than 10 million people worldwide, and this estimation is expected to keep growing as time passes (Williams *et al*., 2016). Neurodegenerative processes that come along with aging are strongly observed to impair brain function (Williams *et al*., 2016). Approximately 3.1% of people in Western countries between the ages of 70 and 79 have neurodegenerative disorders (Williams *et al*., 2016). According to Makkar *et al*., (2020), diverse lifestyles, eating customs, and feeding practices are largely to blame for the variation in the occurrence of neurodegenerative disorders among different ethnicities. Psychosis is characterized by delusions, hallucinations, and wildly disorganized thinking, which poses this disorder as an enormous social and financial burden. Among these different psychotic diseases is Schizophrenia; which is a harmful ailment that affects people all over the world (Charlson *et al*., 2018). Psychosis is also widely defined as a loss of touch with reality and is associated with disorders that affect both the content and the process of thought.

The occurrence of psychosis is dependent on the administration or increased secretion of compounds that block the dopamine receptors from binding their actual substrates which invariably affects the rate at which appropriate neurotransmitters are produced and distributed around the body of an individual (Insel, 2010). According to Mandolini *et al*., (2018), the pathophysiology of psychosis is associated with the system of endo-cannabinoids whereas a recent meta-analysis by Minichino *et al*., (2019) reported that there is an increased level of endocannabinoid anandamide in the blood and cerebral fluid of patients diagnosed with psychosis. The immune cells of the peripheral nervous system (PNS) are also involved in a much-increased synthesis (alteration) of the primary cannabinoid 1 receptor (CB1); in a mechanism that directly signals or suggests that psychosis exists (Minichino *et al*., 2019). Minichino *et al*. (2019) noted this increased endocannabinoid tone at every stage of psychosis (from the precursor/risk factor to acute and then to the severe stage). In addition, according to Johnston (2015), aberrant protein misfolding is also linked with neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, and psychotic diseases. The mechanism of psychosis occurrence involves the activation of NF-B, which leads to the production of inflammatory cytokines like interleukin-1 (IL-1), and tumor necrosis factor (TNF) as well as the activation of harmful molecules like cyclooxygenase (COX-2) and inducible nitric oxide synthase (iNOS). These processes will generate reactive oxygen species (ROS) and glutamate-induced oxidative damage leading to mitochondrial malfunction and systemic toxicity (Asadi-Shekaari *et al*., 2012).

Psychosocial stressors frequently cause or exacerbate psychosis symptoms, which are episodic (Gautam and Mathur, 2018). The most frequent underlying cause of late-onset psychosis is still dementia, though. Delusions, incarnation syndrome, misidentification syndrome, and partition delusion are all common

in psychotic individuals. Visual, auditory, and tactile hallucinations are the most frequent types of hallucinations for those connected to psychosis. According to Javadpou *et al*., (2013), mood disorders, primary psychosis, delirium, general medical diseases, and pharmaceuticals can all cause psychosis.

As the issue of neurodegenerative disease gains attention globally, scientists are in search of potent, non-deleterious therapy for controlling its damage to affected persons. Currently, antipsychotics are used to treat agitation, hallucinations, and delusions orchestrated by a specific neurodegenerative illness named psychosis (Rothenberg, 2017). According to Rothenberg (2017), antipsychotics are used to treat agitation in neurodegenerative illnesses as well as psychosis (hallucinations and delusions). The potential benefits of all antipsychotic medications have been balanced against a few important hazards, including death and cerebrovascular accidents; which makes their long-term prescription questionable.

As long as cardiovascular risk factors of drug usage should be carefully controlled, antipsychotics have been shown to consistently raise the risk of severe complications and even early death among their users; hence the suggestion of nutraceuticals from food sources that offer nutritional value and health benefits, as natural remedy against neurodegeneration linked with psychosis. These nutraceuticals alongside phytonutrients, herbal molecules, and natural chemicals have played key roles in helping patients deal with neurodegeneration and allow cognition with reduced or no side effects (Johnston, 2015). Terms like Pharma-foods, Medi-foods, Vita-foods, and medical foods have been created as a result of the push to include functional foods (Makkar *et al*., 2020). Due to their origin and healthful alternatives, they are also known as nutraceuticals. Due to their natural state and healthy status, the demand for nutraceuticals in treating neurological illnesses has reportedly increased globally (Makkar *et al*., 2020). Secondary metabolites such as phenolics, flavonoids, tannins, terpenes, and saponins obtained from plant parts have been discovered to help abrogate the deleterious effects of psychosis and improve intellectual ability as indicated by their tendency to confer anti-inflammatory and anti-oxidative effects on the vital body system. This finding on reduced adverse effects following the usage of natural compounds suggests that they would be more suitable for managing neurological disorders such as psychosis. Medicinal plants containing natural compounds are also found to be important because patients with acute or severe psychiatric issues understandably feel dissatisfied by the ineffectiveness of conventional antipsychotic drugs.

This review is based on the comparison of both synthetic and natural compounds used in the management of psychosis and to provide further recommendations on the discovery of non-toxic compounds or substances to manage the neurological disorder with an alternative mechanism of action that produces very little or no side effect. Hence, an attempt has been made in this study to explain a few of these natural compounds (nutraceuticals) from food products that pose therapeutic action and/or prevention against psychotic disorders.

Synthetic interventions against psychosis

In studies of psychosis, it has been shown that dopaminergic dysregulation, reduced functioning of NMDA receptors, reduced hydrolysis of GABA, reduced firing of choline receptors, neuro-inflammation, and enhanced oxidative damage play pathogenic roles (Yadav *et al*., 2018). The management of neurological conditions such as psychosis has involved the usage of both conventional and non-conventional anti-psychotics. Non-conventional antipsychotics like olanzapine and risperidone have some beneficial effects on non-significant abnormalities and deficits in cognition, whereas conventional antipsychotics like haloperidol and chlorpromazine can only effectively treat significant adverse reactions and have unsettling or extrapyramidal side effects.

In addition to the agranulocytosis found with clozapine, prolonged use also causes an increase in oxidative load, which can result in moderate to severe weight gain as well as cardiovascular problems, diabetes, and agranulocytosis (Baldessarini and Tarazi, 2006).

Therefore, the introduction of dopamine D2 receptor antagonists has been adopted as a major means by which psychotic disorders may be managed. However, synthetic compounds as well as traditional antipsychotics can also be adopted in the management of psychosis; although they are linked with some adverse effects alongside significantly aggravated symptoms in substantial proportion which may experience increased symptoms and/or symptoms to other neurodegenerative diseases (Samara *et al*., 2019). Thus, there is an important need to discover and develop novel interventions against psychosis in a manner that a mechanism of action other than non-D2 antagonism will be involved (Samara *et al*., 2019).

According to Cummings *et al*., (2014), the pharmacologic substance pimavanserin is approved for the management of delusions and optical illusions that happen in psychotic patients. Additionally, currently available antipsychotic medications including cannabidiol, olanzapine, quetiapine, and clozapine are crucial for effectively treating the positive symptoms of psychosis while having minimal impact on the negative or cognitive symptoms (Insel, 2010). Also, many of these antipsychotics that work on dopamine have a variety of adverse effects, some of which can be severe for those who are afflicted.

Clinically, treatment of psychosis is governed by the main tenets of geriatric medicine and involves the use of medications including antidepressants that are tricyclic, anticholinergics, cortisone, corticosteroids, opiates, and benzodiazepines. Additionally, the use of acetylcholinesterase inhibitors (AChI) such as rivastigmine, donepezil, or galantamine as the primary therapy for psychosis is advantageous because it may minimize or perhaps completely remove the requirement for the administration of antipsychotics, given their link with adverse side effects (Devanand *et al*., 2012; Rothenberg, 2017).

Memantine, one of many anti-psychotics, is said to have a favorable safety profile but appears to have just a slight advantage in the treatment of psychosis in connection with Alzheimer's disease. Memantine has been linked to a substantial decrease in psychosis, anxiety, nervousness, and violence notwithstanding the flaws of memantine and other AChEIs as inadequate therapies for serious manifestations of psychosis (Wilcock *et al*., 2008).

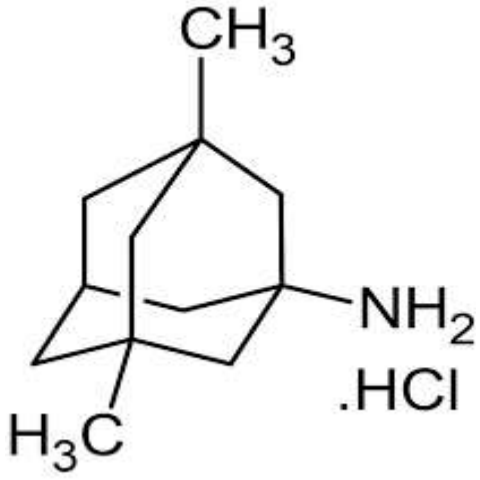

Fig 1: Chemical Structure of memantine (El Nashar *et al*., 2012)

The drug olanzapine (as much as 10 mg per day) has also been shown to be helpful in the management of hallucinations, delusions, nervousness, disturbance in sleep, and false belief in patients with neurodegenerative diseases (Moretti *et al*., 2003). Olanzapine has also been found to be helpful for psychosis, particularly delusions, in observational studies that targeted patients with Parkinson's disease and dementia (PDD); although about 80% of the PDD patients are reported to experience worsening motor impairment and generalized mental health problems after taking olanzapine treatment (Fenelon and Alves, 2010). Therefore, despite the well-documented risk for recurrence of symptoms, careful monitoring and relatively short courses of antipsychotics are advised.

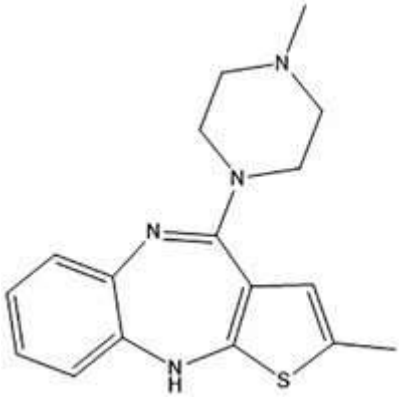

Fig 2: Chemical Structure of Olanzapine (Albayrak *et al*., 2019)

Aripiprazole, an atypical antipsychotic, is recognized based on its pharmacological characteristics, which include partial agonism at the D2 receptor, antagonism against serotonin-dopamine action, targeting of receptors for psychotics, antagonism against 5-HT2A receptor and partial support for dopamine (Horacek *et al*., 2006). A monotherapeutic approach of aripiprazole is evidenced as effective against the deleterious and cognitive symptoms of neurological disorders. However, it is associated with common adverse effects such as nausea, insomnia, and agitation as well as alterations in metabolism and endocrine system (Stip and Tourjman, 2010).

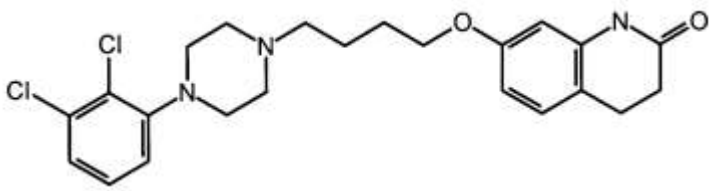

Fig 3: Chemical Structure of Aripiprazole (Tessler and Goldberg, 2006)

Furthermore, another antipsychotic most usually administered to manage the symptoms associated with psychosis is quetiapine because it shares structural similarities with an important anti-psychotic drug named clozapine. Quetiapine is also frequently used against neurodegenerative disorders; although when contrasted with various antipsychotics, quetiapine is associated with reduced cases of serious extrapyramidal adverse reactions and tardive dyskinesia (TD). To control psychosis, specialists advise the administration of quetiapine in the range of 12.5 mg and 150 mg before administering clozapine due to the risk of agranulocytosis and the requirement of blood monitoring (Marsh *et al*., 2004; Goldman and Holden, 2014). According to clinical global impression ratings, the quetiapine-treated PD patients with psychosis performed better overall clinically in the studies that were found (Marsh *et al*., 2004; Goldman and Holden, 2014). According to research, individuals taking quetiapine reported less adverse effects than those on other antipsychotics (Rothenberg, 2017)

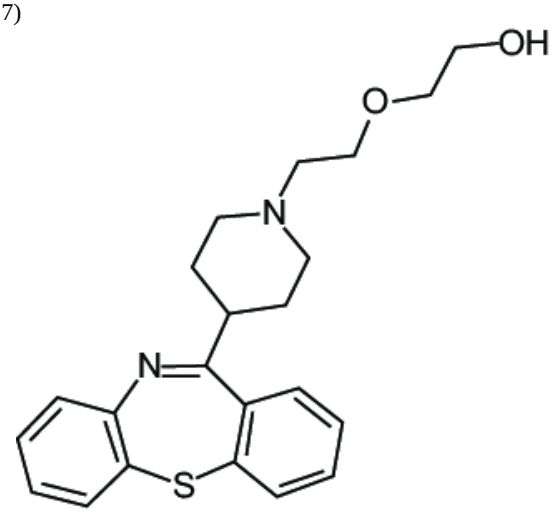

Fig 4: Chemical Structure of Quetiapine (Riedel *et al*., 2007)

In addition, pimavanserin, a promoter of serotonin action which preferentially activates 5-HT2A receptors while bypassing dopaminergic receptors that are often targeted by antipsychotic medications is also a pharmaceutical drug with FDA approval for the management of psychosis. Patients who rightly followed the prescription of the pharmacologic substance pimavanserin reported less severe hallucinations and irrational thoughts with the absence of motor adverse effects that are frequently associated with other antipsychotics which act by blocking dopamine (Cummings *et al*., 2014). Peripheral edema, nausea, and confusion were the most frequent side effects that pimavanserin users reported (Devanand *et al*., 2012; Cummings *et al*., 2014).

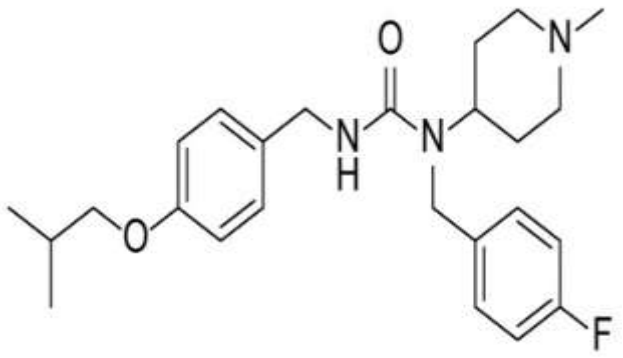

Fig 5: Chemical Structure of pimavanserin (Wu *et al*., 2019)

Potentially secure cannabidiol therapy for psychosis

An important plant product suggested to help manage psychosis is cannabidiol (CBD); which when ingested does not cause intoxication. This CBD is a Phyto cannabinoid component of the cannabis plant (*Cannabis sativa*) which is suggested as a potential antipsychotic agent due to its distinct mode of action linked with cannabinoid receptors. THC, or delta-9-tetrahydrocannabinol, is the basic psychoactive substance in *Cannabis sativa*. The psychoactive substance has been identified to exhibit little or no negative effect on memory and also exhibits anxiogenic, psychotomimetic, amnestic, anxiolytic, antipsychotic, and anticonvulsant properties (Crippa *et al*., 2018). It is reported that the main positive psychotic symptom that antipsychotic medication can eliminate is hyperactivity (Jones *et al*., 2011). Thus, Moreira and Guimaraes (2005) reported that CBD may help to lessen hyper-locomotion brought on by amphetamine and ketamine. Therefore, pharmaceutical substances that might improve this abnormality in the endocannabinoid system may have therapeutic properties against psychosis if the large increase in the endocannabinoid system contributes to the occurrence of psychosis.

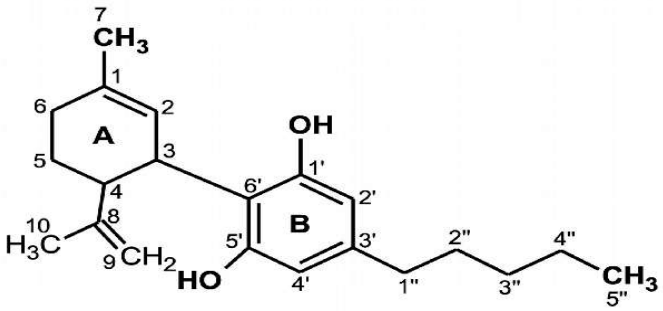

Fig 6: Chemical Structure of cannabidiol (Atalay *et al*., 2019)

Although epidemiological research has found few contrarian effects of cannabis use, it has also found plenty of evidence linking cannabis use to poor activity and/or delivery in cannabis users (Schoeler *et al*., 2017). However, the amount of THC and CBD in cannabis affects how harmful it is to patients with schizophrenia. In contrast to people who use hash-like cannabis which has lower THC and higher CBD, users of cannabis that looks like skunk containing high THC and low CBD levels have a greater probability of going through the onset of psychosis (Schoeler *et al*., 2017).

Importantly, it has been found that CBD has a host of advantages due to its different mechanism of action which involves an interaction with cannabinoid (CB) receptors of the endogenous-cannabinoid system located throughout the body, including the peripheral and central neurological systems. First of all, CBD helps to prevent dopamine receptor antagonism by sufficiently allowing dopamine agonists to bind for neurotransmission to proceed; nevertheless, it may also have negative effects like extrapyramidal symptoms and a rise in prolactin. Second, to boost the efficacy of existing antipsychotics, CBD can be used as monotherapy or as an adjuvant treatment via many molecular routes (Crippa *et al*., 2018).

Cannabidiol's role in the pathophysiology of neurodegeneration

The induction of psychosis, which is linked to anxious symptoms, nervousness, anger, figment, and illusion is also connected with THC activation in the amygdala (Bhattacharyya *et al*., 2010). This enhancement in the amygdala as psychotic symptoms increase raises the possibility that CBD treatment is linked to anxiolysis, a technique for controlling psychotic disorders. Thus, issues directly related to THC-induced psychotic symptoms indicate that the amygdala and striatum may play a key role in the psychotogenic effects of THC (Bhattacharyya *et al*., 2010; Bhattacharyya *et al*., 2012). Neuroimaging investigations, which offer a way to non-invasively investigate the nervous system after CBD action as it augments the striatal activation with less production of psychotic symptoms, have led to research on the antipsychotic potential of CBD (Bhattacharyya *et al*., 2012).

Safety and side effects of cannabidiol

CBD has been demonstrated to be both safe and well-tolerated but there have not been enough reports on severe consequences following CBD administration (Boggs *et al*., 2018). Also, it has been reported that CBD is not harmful to cell lines and poses a non-significant adverse impact on physiological processes such as gastrointestinal transit, psychomotor, pulse, blood pressure, and temperature of the body (Iffland and Grotenhermen, 2017). However, research indicated that CBD may influence cell function and reproduction; therefore, CBD is not completely without side effects (Bergamaschi *et al*., 2011, Iffland and Grotenhermen, 2017). Some of the frequent negative effects linked to CBD usage are diarrhoea, fatigue or drowsiness, changes in appetite, and weight alterations (Bergamaschi *et al*., 2011).

Nutritional supplements against Psychotic disorders

According to Cloutier *et al*., (2016), nutritional supplements are crucial in the treatment of emotional disorders and psychotic illnesses. By increasing the re-uptake of monoamines, decreasing the activity of monoamine oxidase, and inducing neurobiological effects, nutraceuticals significantly increase the therapeutic efficacy of medications (when used as adjuvants) via neuroprotection, provision of synergistic support for the effectiveness of psychiatric medications and reducing their adverse effects (Savitz *et al*., 2016). One of the two primary types of polyunsaturated fatty acids (PUFA) in the human body are the omega-3-fatty acids, derived as alpha-linolenic acid; whereas the other type of PUFA are the omega-6-fatty acids such as arachidonic acid obtained from linoleic acid (Brown and Roffman, 2016).

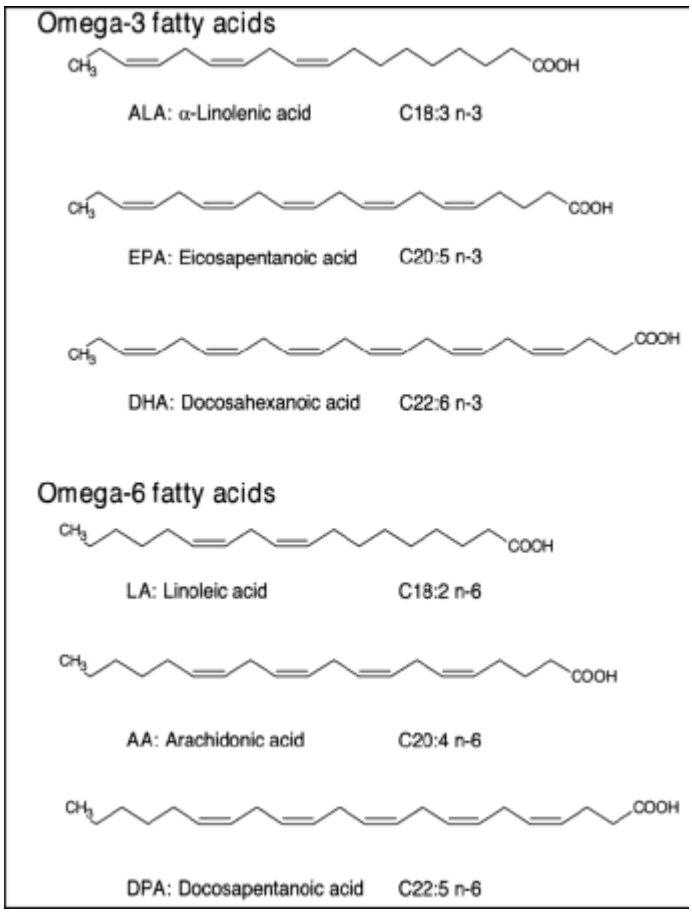

Fig 7: Chemical Structures of omega-3 and omega-6 fatty acids (Kashiwagi and Huang, 2012)

Both omega-3 essential fatty acids namely; docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) found in cold-water fatty fish such as salmon are crucial parts of the phospholipid cell membranes and necessary for human existence (Brown and Roffman, 2016). They are nonetheless categorized as essential fatty acids because the human body cannot generate them and must instead obtain them through diet (Brown and Roffman, 2016). According to molecular research, EPA and DHA help to enhance dopamine neurotransmission, increase serotonin neurotransmission, reduce micro-inflammation reduce oxidative damage, and modulate mitochondrial function. Omega-3 EPA and DHA also guard against toxicity brought on by the start of apoptosis. The initiation of apoptosis and the control of the brain-derived neurotrophic factor (BDNF) gene expression are additional mechanisms by which omega-3 EPA and DHA protect against toxicity (Makkar *et al*., 2020).

In addition, the administration of vitamins is also essential in the management of psychosis. Although these vitamins are also essential organic substances that the human body is unable to produce in sufficient quantities, they must be supplied from diet. For instance, the study by Graham *et al*., (2015) reported that vitamin D can protect against psychiatric conditions and psychosis. This is based on the premise that calcium homeostasis, bone metabolism, and other metabolic processes are all affected by vitamin D content in cells (Graham *et al*., 2015).

In both developing and adult brains, vitamin D plays crucial roles in the production of neurotransmitters, neuro-protection, and neurotransmission (Shivakumar *et al*., 2015; Berridge, 2018). Also, vitamin D lowers oxidative inflammation and damage (brought about by the generation of free radicals and ROS) following an increase in BDNF (Shivakumar *et al*., 2015).

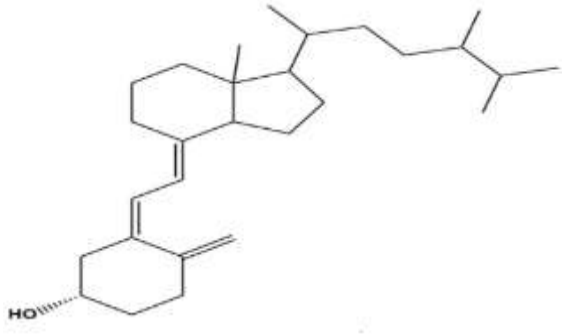

Figure 8: Structure of vitamin D_3 (Cholecalciferol) **(**Wu *et al*., 2012)

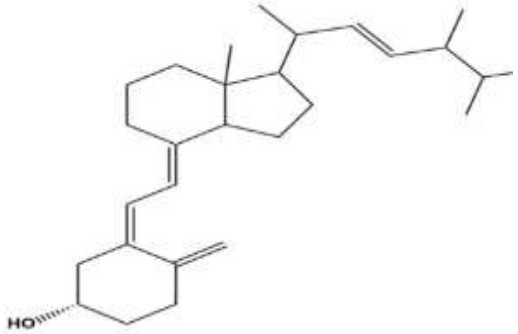

Fig 9: **Structure of vitamin D_2** (Ergocalciferol) **(**Wu *et al*., 2012)

The process of transforming vitamin D into its active form is carried out by an enzyme called 1-alpha hydroxylase which can be found in the substantia nigra, hippocampus, thalamus, hypothalamus, amygdala, prefrontal gyrus, and cingulate gyrus. The enzyme 1-alpha hydroxylase shows an inverse association with total intra-cranial volume, total cortical gray matter, and cerebral white matter volumes, for its effective role in controlling CNS behavior (Graham *et al*., 2015). In essence, Shivakumar *et al*., 2015) reported that vitamin D is essential for the survival of hippocampus cells based on its neuroprotective function.

The Use of Medicinal Plants to Treat Psychosis

According to Otimenyin and Lor (2021), psychosis is a group of psychological diseases where delusions, false speech, anxiety, and severely disorganized thinking are prevalent. Due to the standard and atypical antipsychotics' inadequate management and their various unsettling side effects, psychosis is burdensome and challenging to treat (Otimenyin and Lor, 2021). As a result, many people with long-term mental health issues are understandably discouraged by the apparent inefficacy of the treatment adopted and naturally look for other medications with fewer or no side effects and a more holistic approach to care. Plants are abundant in secondary metabolites such as phenolics, flavonoids, tannins, terpenes, and saponins which may confer modulatory impact on

the CNS to create helpful therapy in the management of psychosis. Based on this therapeutic help offered by secondary metabolites of plants on psychosis, their usage culminates in high safety and few or no unfavorable consequences (Otimenyin and Lor, 2021).

Medicinal plants have been used to manage and treat psychosis in both developed and developing nations. For their potential as antipsychotics, some of these medicinal herbs have been researched. Many medicinal plants have antipsychotic properties that can help treat psychosis, according to a review of some of the drugs used as antipsychotics. As medicinal plants are utilized for managing and treating psychosis, it has been found that these herbs are effective against the detrimental and intellectual disabilities of psychosis either in vitro or in vivo without having disturbing side effects as implicated in conventional antipsychotic medications (Aricioglu *et al*., 2016).

Albizia zygia

In African traditional medicine, *Albizia zygia* root extract is used to treat mental illnesses including insanity (Noté *et al*., 2016). Alkaloids, tannins, saponins, and flavonoids are a few of the phytochemical components. *Albizia zygia*'s potential mode of action is connected with the stimulation of N-methyl-D-aspartate (NMDA) receptors located on the inhibitory gamma amino butyric acid (GABAergic) nerve cells (Kumbol *et al*., 2018). Recently, several substances, including the new zygiaosides A and B of the oleanane-type saponin family, were identified from *Albizia zygia* roots (Noté *et al*., 2016). The *Albizia zygia* root extract may be used to treat the noticeable symptoms of neurodegeneration because it has been shown to have antipsychotic-like effects in rats. Additionally, results from a study on psychotic diseases showed that an extract of *Albizia zygia* considerably reduced apomorphine-induced climbing behavior as well as ketamine-induced hyperlocomotion, immobility, and deficits in object recognition (Yadav *et al*., 2017).

Alpinia zerumbet

Important physiological and pharmacological actions of *Alpinia zerumbet* include antioxidative, anticancer, anti-inflammatory, and antianxiety properties. *Alpinia zerumbet* is a plant that is used as therapy in phytomedicine to treat neuro-psychiatric behaviors like stress, depression, and anxiety (de Arajoa *et al*., 2011). In a study, mice were given *Alpinia zerumbet* essential oil, and it was discovered that the extract containing dosages of 100 mg/kg and 200 mg/kg body weight reduced hyperlocomotion due to ketamine administration.

Additionally, the in-vitro antioxidant properties of *Alpinia zerumbet* essential oil caused a reduction in lipid peroxidation levels, raised glutathione levels, and stopped oxidative stress-induced drop in nitrate levels. As a result, these antipsychotic effects were attributed to both 1,8-cineole and terpinene-4-ol compounds identified as the main essential oils in the leaf of *Alpinia zerumbet.* The potential mechanism of action of these essential oils is related to amelioration of oxidative damage and enhancement of NMDA neurotransmission (de Arajoa *et al*., 2011).

Alstonia scholaris

The leaves of the *Alstonia scholaris* plant, which belongs to the Apocynaceae family, are frequently used to treat mental diseases like anxiety and depression. Additionally, it has been reported that the plant possesses anti-psychotic effects, with a mechanism of action related to dopamine antagonistic actions in the frontal-cortical parts of the brain (Jash and Chowdary, 2014).

Bacopa monnieri

It has been claimed that the entire *Bacopa monnieri* (Scrophulariaceae) plant possesses antipsychotic, anxiolytic, and other therapeutic qualities. Its principal ingredients include triterpenoids, saponins, and bacosides. The restoration of dopaminergic and serotonergic neurotransmission and the reduction in degradation of acetylcholinester by acetylcholinesterase enzyme may be associated with the antipsychotic effects of *Bacopa monnieri* (Chatterjee *et al*., 2012).

Brassica oleracea

The juice from *Brassica oleracea* (Brassicaceae) leaf contains phytoconstituents such as flavonoids and polyphenols that allow it to serve as a popular dietary supplement. The leaf juice possesses antipsychotic, anti-inflammatory, and antioxidant qualities. According to Yadav *et al*., (2017), the mechanism of action of *Brassica oleracea* in treating psychosis is associated with an increase in gamma amino butyric acid (GABA) levels that help to regulate dopaminergic neurotransmission.

Cannabis sativa

Cannabis sativa leaves contain a cannabinoid called cannabidiol, which has been found to have atypical antipsychotic-like effects in both people and experimental animals. According to Zuardi *et al*., (2006), an increase in NMDA receptors on inhibitory GABAergic neurons in the limbic and subcortical brain areas may be the likely mechanism of action by which *Cannabis sativa* demonstrates its atypical antipsychotic-like features in humans and experimental animals.

Panax quinquefolium

Panax quinquefolium is a plant that is currently farmed and utilized throughout the world (Zhu *et al*., 2004). Ginseng is a key component found in *Panax quinquefolium* Linn's (Araliaceae) leaves known to have various pharmacological effects. Ketamine-induced negative and cognitive dysfunctions have been reported to be successfully treated with *Panax quinquefolium* leaf extract. The stabilization of dopamine and serotonergic neurotransmission and the decrease in acetylcholinesterase activity may be associated with antipsychotic characteristics (Chatterjee *et al*., 2015). In long-term research, *Panax quinquefolium* reduced the forced swim tests ketamine-enhanced immobility and had no extrapyramidal side effects when used to treat catalepsy using the bar and wood block tests. These behavioral effects of *Panax quinquefolium* were examined alongside those of the common medications clozapine and haloperidol. After continuous use, it was discovered that *Panax quinquefolium* decreased levels of dopamine (DA), 5-hydroxytryptamine (5-HT), and nitrate. Additionally, *Panax quinquefolium* extract increased hippocampus glutamate levels while decreasing acetylcholinesterase activity (Chatterjee *et al*., 2012). Thus, *Panax quinquefolium* has been shown that *Panax quinquefolium* contains antipsychotic-like qualities helpful in managing psychological symptoms of psychosis (Chatterjee *et al*., 2012).

Morinda citrifolia

The evergreen *Morinda citrifolia* tree can be found in both forested and open coastal habitats at sea level. Scopoletin, rutin, and quercetin are the three main components found in the fruits of *Morinda citrifolia* Linn (Rubiaceae). There are numerous uses for the plant in CNS diseases. Mice's apomorphine-induced cage-climbing behavior and climbing duration were significantly reduced in a dose-dependent way in a study that showed the antidopaminergic action of the extract of *Morinda citrifolia* (Amos *et al*., 2005). Fruit juice from *Morinda citrifolia* was discovered to

have antipsychotic characteristics, with its antidopaminergic activity being suggested as a possible mechanism of action (Pandy *et al*., 2012).

Conclusion and Recommendation

The global burden of neurodegeneration with varying disturbances on the nervous system requires urgent attention. This study reports the use or incorporation of vitamins and potent nutraceuticals from plants as a safer mode of managing psychosis. Medicinal plants such as *Albizia zygia, Alpinia zerumbet, Alstonia scholaris, Bacopa monnieri, Brassica oleracea, Cannabis sativa, Morinda citrifolia, and Panax quinquefolium* contain nutraceuticals that are suggested to be more effective against psychosis compared to the recently used conventional and non-conventional anti-psychotics. These plants contain compounds that will help to efficiently ameliorate the observed impairment in brain functioning due to psychological stress, delusions, hallucinations, and wildly disorganized thinking that characterize psychosis. Importantly, the usage of medicinal plants poses very little or no side effects on their users as compared to the cases of death, cerebrovascular accidents, agranulocytosis, increase in oxidative load, moderate or severe weight gain, diabetes, and endocrine disorder. Thus, medicinal plants possess a variety of compounds with antioxidant and neuro-protective properties which help reduce psychotic symptoms with fewer or no side effects compared to other conventional or manufactured drugs. Further research is required to extract the active components of the plant parts via High-performance liquid chromatography (HPLC) and/or Gas chromatography-mass spectroscopy (GC-MS). There should also be the determination of the dosage, mechanism of action of each plant extract, and safety via pre-clinical and clinical studies using biochemical and molecular assays with the incorporation of behavioral studies developing safe, affordable, readily available pharmacotherapies for managing psychosis**.**

Acknowledgments

The authors wish to acknowledge the support of Prof Joseph Olagunju of the Department of Biochemistry, Lagos State University College of Medicine, Nigeria, and Prof. Oladipo Ademuyiwa of Federal University of Agriculture Abeokuta, Ogun State Nigeria for their expertise in medicinal plant functions and usage.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this work.

References

Albayrak, M., Kadioglu, Y., Yaman, M.E., Senol, O. and Oral, E., 2019. Determination of olanzapine for therapeutic drug monitoring in schizophrenia patients by LC/MS method. *Biomedical Chromatography*, *33*(4): e4468.

Amos, S., Abbah, J., Chindo, B., Edmond, I., Binda, L., Adzu, B., Buhari, S., Odutola, A.A., Wambebe, C. and Gamaniel, K., 2005. Neuropharmacological effects of the aqueous extract of Nauclea latifolia root bark in rats and mice. *Journal of Ethnopharmacology*, *97*(1):53-57.

Aricioglu, F., Ozkartal, C.S., Unal, G., Dursun, S., Cetin, M. and Müller, N., 2016. Neuroinflammation in schizophrenia: a critical review and the future. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology*, *26*(4):429-437.

Asadi-Shekaari, M., Kalantaripour, T.P., Nejad, F.A., Namazian, E. and Eslami, A., 2012. The anticonvulsant and neuroprotective effects of walnuts on the neurons of rat brain cortex. *Avicenna Journal of Medical Biotechnology*, *4*(3):.155.

Atalay, S., Jarocka-Karpowicz, I. and Skrzydlewska, E., 2019. Antioxidative and anti-inflammatory properties of cannabidiol. *Antioxidants*, *9*(1):21.

Baldessarini, R.J. and Tarazi, F.I., 2006. Pharmacotherapy of psychosis and mania. *Goodman and Gilman's the pharmacological basis of therapeutics*, *11*:461-500.

Bergamaschi, M., Helena Costa Queiroz, R., Waldo Zuardi, A. and Crippa, A.S., 2011. Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Current drug safety*, *6*(4):237-249.

Berridge, M.J., 2018. Vitamin D deficiency: infertility and neurodevelopmental diseases (attention deficit hyperactivity disorder, autism, and schizophrenia). *American Journal of Physiology Cell Physiology*, *314*(2): C135-C151.

Bhattacharyya, S., Crippa, J.A., Allen, P., Martin-Santos, R., Borgwardt, S., Fusar-Poli, P., Rubia, K., Kambeitz, J., O'Carroll, C., Seal, M.L. and Giampietro, V., 2012. Induction of psychosis by δ9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. *Archives of General Psychiatry*, *69*(1):27-36.

Bhattacharyya, S., Morrison, P.D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., Nosarti, C., O'Carroll, C.M., Seal, M., Allen, P. and Mehta, M.A., 2010. Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology*, *35*(3):764-774.

Boggs, D.L., Surti, T., Gupta, A., Gupta, S., Niciu, M., Pittman, B., Schnakenberg Martin, A.M. Thurnauer, H., Davies, A., D'Souza, D.C. and Ranganathan, M., 2018. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo-controlled trial. *Psychopharmacology*, *235*:1923-1932.

Brown, H.E. and Roffman, J.L., 2016. Emerging treatments in schizophrenia: highlights from recent supplementation and prevention trials. *Harvard Review of Psychiatry*, *24*(2): e1-e7.

Charlson, F.J., Ferrari, A.J., Santomauro, D.F., Diminic, S., Stockings, E., Scott, J.G., McGrath, J.J. and Whiteford, H.A., 2018. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. *Schizophrenia Bulletin*, *44*(6):1195-1203.

Chatterjee, M., Singh, S., Kumari, R., Verma, A.K. and Palit, G., 2012. Evaluation of the antipsychotic potential of Panax quinquefolium in ketamine-induced experimental psychosis model in mice. *Neurochemical research*, *37*:759-770.

Chatterjee, M., Verma, R., Kumari, R., Singh, S., Verma, A.K., Dwivedi, A.K. and Palit, G., 2015. The antipsychotic activity of standardized Bacopa extract against ketamine-induced experimental psychosis in mice: evidence for the involvement of dopaminergic, serotonergic, and cholinergic systems. *Pharmaceutical Biology*, *53*(12):1850-1860.

Cloutier, M., Aigbogun, M.S., Guerin, A., Nitulescu, R., Ramanakumar, A.V., Kamat, S.A., DeLucia, M., Duffy, R., Legacy, S.N., Henderson, C. and Francois, C., 2016. The economic burden of schizophrenia in the United States in 2013. *The Journal of Clinical Psychiatry*, *77*(6):5379.

Crippa, J.A., Guimarães, F.S., Campos, A.C. and Zuardi, A.W., 2018. Translational investigation of the therapeutic potential of cannabidiol (CBD): toward a new age. *Frontiers in immunology*, *9*: 2009.

Cummings, J., Isaacson, S., Mills, R., Williams, H., Chi-Burris, K., Corbett, A., Dhall, R. and Ballard, C., 2014. Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo- controlled phase 3 trial. *The Lancet*, *383*(9916):533-540.

Devanand, D.P., Mintzer, J., Schultz, S.K., Andrews, H.F., Sultzer, D.L., de la Pena, D., Gupta, S., Colon, S., Schimming, C., Pelton, G.H. and Levin, B., 2012. Relapse risk after discontinuation of risperidone in Alzheimer's disease. *New England Journal of Medicine*, *367*(16):1497-1507.

El Nashar, R.M., El-Tantawy, A.S. and Hassan, S.S., 2012. Potentiometric membrane sensors for the selective determination of memantine hydrochloride in pharmaceutical preparations. *Int. J. Electrochem. Sci*, *7*:10802-10817.

Gautam, A. and Mathur, R., 2018. Influence of mindfulness on decision making and psychological flexibility among aircrew. *Journal of Psychosocial Research*, *13*(1):199-207.

Goldman, J.G. and Holden, S., 2014. Treatment of psychosis and dementia in Parkinson's disease. *Current treatment options in neurology*, *16*:1-18.

Graham, K.A., Keefe, R.S., Lieberman, J.A., Calikoglu, A.S., Lansing, K.M. and Perkins, D.O., 2015. Relationship of low vitamin D status with positive, negative and cognitive symptom domains in people with first-episode schizophrenia. *Early intervention in psychiatry*, *9*(5):397-405.

Horacek, J., Bubenikova-Valesova, V., Kopecek, M., Palenicek, T., Dockery, C., Mohr, P. and Höschl, C., 2006. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. *CNS drugs*, *20*:389-409.

Iffland, K. and Grotenhermen, F., 2017. An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies. *Cannabis and cannabinoid research*, *2*(1):139-154.

Insel, T.R., 2010. Rethinking schizophrenia. *Nature*, *468*(7321):187-193.

Jash, R. and Chowdary, K.A., 2014. Ethanolic extracts of Alstonia Scholaris and Bacopa Monnieri possess neuroleptic activity due to the anti-dopaminergic effect. *Pharmacognosy research*, *6*(1):46.

Johnston, G.A., 2015. Flavonoid nutraceuticals and ionotropic receptors for the inhibitory neurotransmitter GABA. *Neurochemistry International*, *89*:120-125.

Kashiwagi, S. and Huang, P.L., 2012. Dietary Supplements and Cardiovascular Disease: What is the Evidence and What Should We Recommend? *Cardiovascular Risk Factors*:978-953.

Kumbol, V.W.A., Abotsi, W.K.M., Ekuadzi, E. and Woode, E., 2018. Albizia zygia root extract exhibits antipsychotic-like properties in murine models of schizophrenia. *Biomedicine & Pharmacotherapy*, *106*:831-841.

Makkar, R., Behl, T., Bungau, S., Zengin, G., Mehta, V., Kumar, A., Uddin, M.S., Ashraf, G.M., Abdel- Daim, M.M., Arora, S. and Oancea, R., 2020. Nutraceuticals in neurological disorders. *International journal of molecular sciences*, *21*(12):4424.

Mandolini, G.M., Lazzaretti, M., Pigoni, A., Oldani, L., Delvecchio, G. and Brambilla, P., 2018. Pharmacological properties of cannabidiol in the treatment of psychiatric disorders: a critical overview. *Epidemiology and psychiatric sciences*, *27*(4):327-335.

Marsh, L., Williams, J.R., Rocco, M., Grill, S., Munro, C. and Dawson, T.M., 2004. Psychiatric comorbidities in patients with Parkinson's disease and psychosis. *Neurology*, *63*(2):293-300.

Minichino, A., Senior, M., Brondino, N., Zhang, S.H., Godlewska, B.R., Burnet, P.W., Cipriani, A. and Lennox, B.R., 2019. Measuring disturbance of the endocannabinoid system in psychosis: a systematic review and meta-analysis. *JAMA psychiatry*, *76*(9):914-923.

Moretti, R., Torre, P., Antonello, R.M., Cazzato, G., Griggio, S. and Bava, A., 2003. Olanzapine as a treatment of neuropsychiatric disorders of Alzheimer's disease and other dementias: a 24-month follow-up of 68 patients. *American Journal of Alzheimer's Disease & Other Dementias®*, *18*(4):205-214.

Noté, O.P., Simo, L., Mbing, J.N., Guillaume, D., Aouazou, S.A., Muller, C.D., Pegnyemb, D.E. and Lobstein, A., 2016. Two new triterpenoid saponins from the roots of Albizia zygia (DC.) JF Macbr. *Phytochemistry Letters*, *18*:128-135.

Pandy, V., Narasingam, M. and Mohamed, Z., 2012. Antipsychotic-like activity of Noni (Morinda citrifolia Linn.) in mice. *BMC complementary and alternative medicine*, *12*:1-9.

Riedel, M., Müller, N., Strassnig, M., Spellmann, I., Severus, E. and Möller, H.J., 2007. Quetiapine in the treatment of schizophrenia and related disorders. *Neuropsychiatric disease and treatment*, *3(2):219-235.*

Rothenberg, K.G., 2017. Assessment and Management of Psychiatric Symptoms in Neurodegenerative Disorders. *Neuro-Geriatrics: A Clinical Manual*:367-388.

Samara, M.T., Nikolakopoulou, A., Salanti, G. and Leucht, S., 2019. How many patients with schizophrenia do not respond to antipsychotic drugs in the short term? An analysis based on individual patient data from randomized controlled trials. *Schizophrenia Bulletin*, *45*(3):639-646.

Savitz, A.J., Xu, H., Gopal, S., Nuamah, I., Ravenstijn, P., Janik,

A., Schotte, A., Hough, D. and Fleischhacker, W.W., 2016. Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, noninferiority study. *International Journal of Neuropsychopharmacology*, *19*(7): pyw018.

Schoeler, T., Petros, N., Di Forti, M., Klamerus, E., Foglia, E., Murray, R. and Bhattacharyya, S., 2017. Effect of continued cannabis use on medication adherence in the first two years following onset of psychosis. *Psychiatry Research*, *255*:36-41.

Shivakumar, V., Kalmady, S.V., Amaresha, A.C., Jose, D., Narayanaswamy, J.C., Agarwal, S.M., Joseph, B., Venkatasubramanian, G., Ravi, V., Keshavan, M.S. and Gangadhar, B.N., 2015. Serum vitamin D and hippocampal gray matter volume in schizophrenia. *Psychiatry Research: Neuroimaging*, *233*(2):175-179.

Stip, E. and Tourjman, V., 2010. Aripiprazole in schizophrenia and schizoaffective disorder: A review. *Clinical Therapeutics*, *32*: S3-S20.

Tessler, L. and Goldberg, I., 2006. Crystal structures of aripiprazole, a new antipsychotic drug, and of its inclusion compounds with methanol, ethanol, and water. *Journal of inclusion phenomena and macrocyclic chemistry*, *55*:255-261.

Wilcock, G.K., Ballard, C.G., Cooper, J.A. and Loft, H., 2008. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *Journal of Clinical Psychiatry*, *69*(3):341-348.

Williams, R.J., Mohanakumar, K.P. and Beart, P.M., 2016. Neuro-nutraceuticals: Further insights into their promise for brain health. *Neurochemistry International*, *95*:1-3.

Wu, C., Zhou, Q., Song, D., Li, H., Bao, C., Liu, X., Bao, X. and Chen, G., 2019. An improved process for the preparation of pimavanserin tartrate. *Journal of Chemical Research*, *43*(11-12):480-485.

Wu, Z., Liu, D. and Deng, F., 2022. The role of vitamin D in the immune system and inflammatory bowel disease. *Journal of Inflammation Research*:3167-3185.

Yadav, M., Parle, M. and Dhingra, M.S., 2017. Protective effect of Brassica oleracea juice against Ketamine-induced stereotypic behaviors in mice. *J Med Plants*, *5*:200-4.

Yadav, M., Parle, M., Sharma, N., Jindal, D.K., Bhidhasra, A., Dhingra, M.S., Kumar, A. and Dhingra, S., 2018. Protective effects of Spinacia oleracea seeds extract in an experimental model of schizophrenia: Possible behavior, biochemical, neurochemical and cellular alterations. *Biomedicine & Pharmacotherapy*, *105*:1015-1025.

Zuardi, A.W., Crippa, J.A.S., Hallak, J.E., Moreira, F.A. and Guimarães, F.S., 2006. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Brazilian journal of medical and biological research*, *39*:421-429.