

The Role of Herbal and Nutraceutical Supplementation in the Amelioration of Schizophrenia and Schizoaffective Symptomology

John B. Holloway

Abstract

Herbal supplements are used increasingly in both developed and undeveloped countries for purposes of prevention, delaying onset, decreasing overall severity, and potential reversal of mental illness. The purpose of this overview is to present the latest empirical findings regarding the efficacy of various herbal and nutraceutical supplements in the prevention, treatment, and delaying onset of symptomology in relation to schizophrenia and other schizoaffective disorders, as well as further to explore their potential role in the future of psychiatry and related health practices. The supplements and their efficacy examined in this literature overview are Omega-3 fatty acids, Curcumin, Folic Acid, B12, B6, vitamin D, N-acetylcysteine, SAM-e, Bocopa Monniera, Ginkgo Biloba, Iron, Glycine, (-)-Stepholidine, Yokukansan, Oregadoku, and Ficus Platyphylla,

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Herbal and nutraceutical supplements are being studied for their effects on symptoms of mental illness. Reductions in mental illness symptomatology have been found with use of particular phytochemicals, adaptogenic herbs, essential fatty acids, and traditional Chinese and Amazonian medicine. Mussarat et al. (2014) state that of the reported 422,000 flowering plants that have been reported around the world, over 50,000 are used medicinally. Further, Mussarat et al. (2014) suggest that 80% of the population of developing countries and 60% of the world population rely on traditional medicine, and over 4.5 billion people within developing countries rely on medicinal plants for their health maintenance. This data presented by Mussarat et al. (2014) displays the wide-reaching breadth of indigenous medicine for traditional health practices and has great implications for the number of psychiatric issues that can be addressed with the phytochemical constituents of these botanicals. Particularly, schizophrenia and schizoaffective disorders have been indicated by the literature to benefit largely from the supplementation of herbs and nutraceuticals. Chen and Hui (2012) note schizophrenia to be a severe psychiatric disorder that negatively impacts a wide-range of cognitive functions such as executive functioning, memory and attention (p. 1166-72). Schizophrenia is characterized by negative symptoms (such as emotional blunting and apathy), positive symptoms (hallucinations and delusions), and mild to severe impairment of cognition.

The ideal treatment would eliminate these negative, positive, and cognitive symptoms. This is important to note, as Brown and Roffman (2014) state that while antipsychotic medications can often aid in reducing positive symptoms, these pharmaceuticals produce little to no response in regard to negative symptoms and cognitive impairment (p. 611-22). In so far as the etiology of schizophrenia is concerned, it is generally accepted that it is multifactorial, with a particular combination of environmental circumstances and biological predisposition playing the major role. Mirsky and Duncan (1986) note, however, that there is much disagreement with respect to the weighting of environmental to biological factors in the etiology of schizophrenia (p. 291-319). Mayer et al. (2011) suggest that researchers are still not positive as to a precise prognosis for those dealing with schizophrenia, but there are certain factors posited negatively to affect prognosis, such as: lack of social support, indolent onset, poor insight and presence of negative symptoms (p. 140-41). While there are many typical and atypical antipsychotic medications for the treatment of schizophrenia, Doruk, Uzun, and Ozsahin (2008) report that many patients show little to no response to these interventions—necessitating an urgent

need for alternative treatments of high efficacy and few adverse effects (p. 223-27). Additionally, research has shown that in individuals with schizophrenia, consumption of essential amino acids, vitamins, and nutritional building blocks to raise levels of neuroprotective chemicals such as endogenous glutathione (by way of precursors like N-acetylcysteine and Alpha Lipoic Acid) can decrease cortical inflammation and help maximize the body's innate compensatory homeostatic healing mechanisms to deal more effectively with states of psychosis. Various studies have displayed a repertoire of supplements, stand-alone or adjunct with traditional pharmaceutical approaches, to be as effective as pharmaceutical treatment, and have fewer side-effects, and some have even been found to make reparations to vital physiological and psychological operations—and be ceased—without relapse or necessitation of alternative interventions.

Literature Review

Omega 3 fatty acids

Omega-3 fatty acids, or n-3 polyunsaturated fatty acids (PUFAs), are amassing significant attention in the literature on alternative avenues for the treatment of psychotic disorders. Omega-3 PUFAs supply a wide range of neurochemical activities via their modulation of the reuptake, degradation, synthesis and receptor binding actions of noradrenaline, dopamine and serotonin. Omega-3s also possess anti-inflammatory and anti-apoptotic effects in addition to their significant activity in increasing neurogenesis and cell membrane fluidity. According to one study led by Amminger (2015), it has been found that intervention with omega-3 fatty acids may reduce the risk of pathogenesis with respect to psychotic disorders as well as a reduced risk of psychiatric morbidity. This study noted that the individuals in the omega-3 group no longer displayed severe functional impairment, nor did they experience dramatic psychotic symptoms upon a 6.7 year follow-up of this randomized, double-blind, placebo-controlled trial (Amminger, Schäfer, Schlögelhofer, Klier, & McGorry, 2015). Research indicates that many developed countries, such as America, are deficient in essential vitamins, minerals, and omega-3 fatty acids. Those suffering from mental illness are exceptionally deficient in Omega-3s. Research also posits the brains of schizophrenic persons to have profound abnormalities in myelin sheaths and oligodendrocytes, and suggests that Omega-3 fatty acids are essential for the reparation and maintenance of these. The eicosapentaenoic acid (EPA) found in Omega-3s is noted to aid in the maintenance of a balanced mood and improving blood circulation. Two grams of EPA adjunct with one's normal antipsychotic regimen

effectively decreased overall symptoms of schizophrenia in those suffering (Ibrahim & El-Sayed, 2013).

Curcumin and Glycine

Curcumin, a common household spice, is a polyphenol with an active medicinal component being turmeric, or *curcuma longa*. Studies show that it possesses significant antidepressant properties in both rodents and humans without adverse effects. A 6 week placebo-controlled study found that chronic supplementation of curcumin (1,000 mg daily) produced significant antidepressant behavioral responses in depressed participants as measured by reduction of 17-item Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale scores. Furthermore, this same study found curcumin to decrease levels of inflammatory cytokines interleukin 1 β and tumor necrosis factor α level, and it was found to increase brain-derived neurotrophic factor (BDNF) levels in plasma concentrations while decreasing concentrations of salivary cortisol as compared to placebo (Lopresti, Maes, Maker, Hood, & Drummond, 2014). Another study, carried out by Hishikawa et al. (2012), examined three patients with Alzheimer's disease (AD) and found curcumin to facilitate the recovery of cognitive decline and Psychological Symptoms of Dementia (BPSD). After 12 weeks of treatment there was a significant decrease in the acuity of symptoms and the burden on caregivers. Within one year of treatment with curcumin, participants with AD began to recognize their families once again (p. 499-504). Curcumin has been found to exhibit antioxidant, anti-inflammatory, and anti-cancer properties. Additionally, it is known to act as a neuroprotective agent in neurological disorders and can cross the blood-brain barrier with significant bioavailability. Multiple studies have found it effective in the amelioration of motor symptoms in Parkinson's disease as well (Mythri & Bharath, 2012). Furthermore, in addition to its neuroprotective properties, it has been found to modulate oxidative-stress induced apoptosis and neuroinflammation (Rinwa, Kumar, & Garg, 2013). Lastly, a study found that curcumin extract was able to significantly restore depleted glutathione levels and recover oxidative damage after 72-hour sleep deprivation in mice (Kumar & Singh, 2008).

Curcumin extract was found to lessen some of the serious side effects associated with use of neuroleptics to schizophrenic patients (Trebatická & Ďuračková, 2015). Curcumin was able to reverse oxidative damage induced by haloperidol. Chronic administration of haloperidol was found to decrease the turnover of dopamine, serotonin and norepinephrine, which was dose-dependently reversed through utilization of curcumin.

The results of this study suggest curcumin as a potential aid in orofacial dyskinesia, a hyperkinetic disorder of high-incidence and unfortunate irreversibility during the treatment of schizophrenia with haloperidol (Bishnoi, Chopra, & Kulkarni, 2008). High doses of glycine, an endogenously produced amino acid, have been found effective at 30 grams per day to reduce social withdrawal, emotional flatness, and states of apathy in schizophrenia—these being symptoms usually unresponsive to traditional antipsychotic medication. Additionally, clinical trials revealed that glycine given at 60 grams per day could be administered to schizophrenic patients with no adverse effects, as well as a twofold increase of glycine levels in the cerebrospinal fluid (CSF) (Ibrahim & El-Sayed, 2013).

B vitamins

The B vitamins folic acid, B12, and B6 play a pertinent role in neuronal function. Deficiencies in these have been indicated in increased risk of psychiatric disease and dementia (Mitchell, Conus, & Kaput, 2014). Deficiencies in Cobalamin, an important nutrient that is not synthesized endogenously and supplied in non-vegetarian diets, has been reported with a range of psychiatric disorders, and a case-report found dietary cobalamin deficiency to present solely as a schizoaffective disorder without neurological manifestations (Dhananjaya, Manjunatha, Manjunatha, & Kumar, 2015). The most common of psychiatric symptoms found to be reported in the literature on vitamin B12 deficiencies are depression, mania, impaired cognition, dementia, delirium, psychotic symptoms, OCD, and states of confusion. Vitamin B12 deficiency is indicated to be causative of subacute combined degeneration (SCD) where there is a demyelination of the lateral and dorsal spinal cord. Symptoms of SCD manifest in the way of psychosis, dementia, and severe depression. Nevertheless, these symptoms can be prevented with B12 supplementation (Naik & Dsouza, 2015). Even further, deficiencies in B12 have been linked to a proliferation of vascular risk factors and increase homocysteine and the load of cognitive decline in neuropsychiatric illnesses (Issac, Soundarya, Christopher, & Chandra, 2015). B Vitamins and a broad-spectrum multivitamin were also found to significantly improve levels of stress and anxiety associated with natural disasters while achieving a large effect size in the study (Kaplan, Rucklidge, Romijn, & Dolph, 2015). Vitamin B6 was found to reduce extrapyramidal side-effects of typical antipsychotics. The same study found N-acetylcysteine (NAC) to be effective against the negative symptoms of schizophrenia, as well as akathisia and abnormal movements in schizophrenia (Himmerich & Erbguth, 2014).

N-acetylcysteine (NAC)

NAC has proven to hold a significant role in the aid of pathophysiological processes associated with psychiatric and neurological disorders. A systemic review by Deepmala et al. (2015) has found favorable evidence regarding NAC supplementation for disorders such as autism, Alzheimer's disease, bipolar disorder, depression, OCD tendencies, and schizophrenia. NAC's action of lowering levels of glutamate is indicated to be a key factor in its role of the amelioration of OCD and various grooming disorders (Racz, Sweet, & Sohoni, 2015). Another study found that in individuals with chronic schizophrenia (SZ), adjunctive NAC—when compared to placebo—has therapeutic potential for overall functioning and a decrease in positive symptoms of schizophrenia (Rapado-Castro et al., 2015). Several lines of research and empirical evidence have indicated that a large component of the pathogenesis of schizophrenia is a deficit in brain glutathione (GSH) levels by result of impaired GSH synthesis. A study supplemented individuals suffering from schizophrenia with a GSH precursor, NAC, which significantly reduced clinical severity and negative symptoms. This same study concluded that polyphenol, curcumin, and the flavonoid quercetin were able significantly to increase levels of GSH and, in turn, reduce the overall clinical severity of schizoaffective disorders (Lavoie et al., 2009).

Vitamin D (VD) and Iron

Seven research studies examining patients with psychosis all indicated insufficient levels of vitamin D (VD). A mini-analyses of these studies found that there was a medium-level effect size for VD in schizophrenia as opposed to the healthy controls, in addition to a trend for overall lower VD levels in comparison to other forms of psychosis (Belvederi et al., 2013). A study examining a Finnish cohort group of over 9,000 people examined supplementation of vitamin D at levels of 2,000 IU per day in the first year of life and noted a 77% decrease in the risk of developing schizophrenia in males compared to those receiving less than 2,000 IU per day. It is hypothesized by the researchers that vitamin D supplementation early in life is pertinent in pro-differentiating signals in the critical periods of brain development, as well as recovery from brain damage after injury (Brown & Roffman, 2014). There are many other vitamin and mineral deficiencies that are posited to play a role in the pathogenesis of schizophrenia. Research has suggested maternal iron-deficiency to induce fetal hypoxia as a result of the high oxygen demand on the part of the growing fetus.

Fetal hypoxia has a plethora of research showing consistent implications as a risk factor for the development of schizophrenia; specifically, it may predispose the child to an expression of schizophrenia in adulthood (Ibrahim & El-Sayed, 2013).

S-Adenosyl methionine (SAM-E)

An increasingly common over-the-counter supplement as an aid for the treatment of depression, SAM-E, was found (over a randomly-assigned, 8 week, placebo-controlled, and double-blind fashion study) significantly to reduce symptoms of psychosis such as aggressive behavior. Strous et al. (2009) report that SAM-E's predominant function is as a methyl group donor for catecholamines, membrane phospholipids, fatty acids, choline carnitine, creatinine, nucleic acids, and porphyrins. A crucial function of SAM-E, as noted by Strous et al. (2009), is myelination of certain phospholipids to promote fluidity and microviscosity of cell membranes. Furthermore, it was posited that the metabolism of SAM-E is crucial for the maintenance of myelin—myelin being essential for facilitating efficient signal conduction between neurons, among many other physiological roles. As for SAM-E's relationship to schizophrenia, Strous et al. (2009) hypothesized that by way of its methyl donor activity, SAM-E would affect catechol-*O*-methyltransferase (COMT) enzyme expression, in turn diminishing aggressive behavior in individuals with schizophrenia who possess the low activity COMT polymorphism—possession of which is noted to be somewhat common. SAM-E was found to improve overall quality of life, and in females the research has shown it to improve depressive symptoms as well (Strous et al., 2009).

Bacopa Monniera

The herbal extract of Bacopa Monniera was found to have significant neuroleptic effects with a reduction of dopamine concentration in the frontal cortex. There was a significant reduction of conditioned avoidance response and reduction of amphetamine-induced stereotype. The results of this study reveal that Bacopa Monniera may hold significant potential for the amelioration of the positive symptoms of schizophrenia (Jash & Chowdary, 2014). The herb Ficus Platyphylla (FP) was shown to have neuroleptic-like properties and significantly reduce locomotor activity. The study was able to reverse an apomorphine-induced prepulse inhibition deficit and hyperactivity by utilizing a co-administration of clozapine or FP. Even further, FP was able to inhibit the retrieval of a conditioned avoidance reaction in individuals with schizophrenia (Chindo et al, 2015).

Ginkgo Biloba (Egb)

Ginkgo Biloba (Egb) extract has been suggested to possess anti-oxidant and anti-inflammatory mechanisms of action. Furthermore, Egb has been shown to increase cerebral blood flow and possess antiplatelet effects that have been attributed to terpene and flavone lactones as well (Diamond & Bailey, 2013). Egb is indicated by the literature to be a significant adjunct aid to the pharmacological treatment of schizophrenia, as its primary pharmacodynamics component is an antioxidant. Egb is believed to provide a favorable adjunctive treatment for schizophrenia with clozapine, as it significantly decreases the negative symptoms of individuals with schizophrenia. The researchers suggest this may be due to the antioxidant action of Egb or the effect it holds on the serotonergic pathway. Even further, Egb administration displayed the capability of normalizing levels of serotonin in the brain (Doruk, Uzun, & Ozsahin, 2008). Another study examining the adjunctive impact of Egb treatment with a prescription antipsychotic found a statistically significant moderate improvement with respect to the total and negative symptoms of schizophrenia. The research selection criteria involved 466 cases on ginkgo with 362 cases on placebo—utilizing the Scale for the Assessment of Negative Symptoms (SANS), the Scale for the Assessment of Positive Symptoms (SAPS), the Brief Psychiatric Rating Scale (BPRS) to measure the positive, negative and total symptoms. This same study explored the role of antioxidants in schizophrenia's pathogenesis, indicating oxidative damage may hold a causative role in the progression of schizophrenia (Singh, Singh, & Chan, 2010).

Traditional Chinese Medicine (CM)

In 2011, research found that concomitant use of antipsychotics and traditional Chinese medicine (CM) in patients with schizophrenia held a significantly higher chance of improved outcomes than those who solely used prescription antipsychotics—61.1% in the adjunctive treatment group with CM versus 34.3% improvement rates in those only utilizing antipsychotics, indicating a potential herb-drug interaction (Z. Zhang et al., 2011). A double-blind, placebo-controlled clinical trial looking to improve cognitive impairments in patients with schizophrenia found that treatments were generally well tolerated, with no reported unwanted side-effects (Z. Chen et al., 2008).

(-)-Stepholidine (SPD)

An active ingredient of the Chinese herb *Stephania*, known as (–)-Stepholidine (SPD), is the first compound found to hold a dual function as a dopamine D1 receptor agonist and a D2 antagonist (Fu et al., 2007). This has led to an increase in research being done on the potential antipsychotic properties of SPD. One study investigating these properties in two animal models for schizophrenia found antipsychotic-like effects in the prepulse inhibition paradigm and in the PAW test. Additionally, the PAW test suggested SPD to be of atypical character with a relatively small potency for inducing extrapyramidal side-effects (Ellenbroek, Zhang, & Jin, 2006). It is suggested that schizophrenia is associated with excessive stimulation of striatal D2 dopamine receptors, too little stimulation of the medial prefrontal cortex D1 dopamine receptors, and neuronal apoptosis. With that said, research has found SPD to hold anti-apoptotic mechanisms in addition to its functions with respect to the D1 and D2 receptors, making it a promising candidate to hold therapeutic action against schizophrenia (L. Zhang, Zhou, & Xiang, 2005). In the way of adjunct treatment, co-administration of SPD with a typical antipsychotic drug was found significantly to enhance the therapeutic effects as well as markedly reduce conditions induced by typical antipsychotics such as tardive dyskinesia. SPD as a stand-alone treatment displayed therapeutic value without significant extrapyramidal side-effects, and it was able to reduce the negative symptoms of schizophrenia. This was confirmed utilizing animal models of schizophrenia wherein SPD improved cognitive function, social interaction, and inhibited hyperactivity in schizophrenic animals (Mo, Guo, & Yang, 2007).

Yokukansan (TJ-54)

The medicinal herb Yokukansan (TJ-54) was found by Miyaoka et al. (2013) to induce displays of highly significant improvement with respect to all measures of psychotic symptomology in the patients involved in the clinical research. Miyaoka et al. (2013) state that the hooks of TJ-54 contain indol and oxyindole alkaloids that protect against glutamate-induced neuronal death. *Angelica radix*, another component of TJ-54, is known for the effects it has on particular serotonin receptors. Considering that previous research has displayed schizophrenia to commonly present dysfunction of serotonin, glutamate, and dopamine receptors, TJ-54 seems to have the pharmacological properties necessary to be a viable treatment option for individuals with schizophrenia. The research by Miyaoka et al. (2013) showed that TJ-54 was very well-tolerated by the patients, and there were no observed adverse effects. This study concluded that TJ-54 seems to be

an efficacious alternative treatment for very-late-onset schizophrenia and related forms of psychosis (Miyaoaka et al., 2013b). A double-blind, placebo-controlled, randomized trial examining the effects of TJ-54 on treatment-resistant schizophrenia found the TJ-54 group to display statistically significant improvements in the PANSS excitement/hostility measures, with no significant side-effects reported (Miyaoaka et al., 2013a).

Orengedoku

Another study, adding to TJ-54 the medicinal supplement orengedoku, resulted in the same efficacy as the atypical antipsychotic aripiprazole in the management of aggressiveness and impulses to aggressive behavior, as well as improvement of tardive dystonia (by 80%). With reductions in irritability, impulsivity, and aggression, these two supplements taken together may be a combination worth exploring further. The individual in whom the aggressive impulses were measured had been on olanzapine, which was unsuccessful in abating his anger and even induced somnolence, unlike the combination of TJ-54 and orengedoku, which improved his symptoms (Okamoto et al., 2013).

Lonchocarpus cyanescens (LC)

A medicinal plant known as *lonchocarpus cyanescens* (LC) has been used in traditional medicine for the treatment of psychotic disorders, and the research on its antipsychotic-like efficacy explored why this may be such a potentially vital addition in the amelioration of psychotic disorders. A preliminary phytochemical screening of LC suggested the presence of constituents with anti-psychotic properties, such as: alkaloids, cardiac glycosides, cyanogenetic glycosides, flavonoids, steroids, saponins, anthraquinones, and tannins. Ethanolic and aqueous extracts of LC were able to suppress stereotyped behavior induced by amphetamines in rats and further produced a significant reduction in spontaneous motor activity in the open field test. The research is indicative of LC containing phytochemically-active antipsychotic constituents that may be efficacious in the management of varying forms of psychoses (Sonibare, Umukoro, & Shonibare, 2012).

Discussion

There is no blanket strategy for therapeutic approaches to schizophrenia, but a significant number of studies have indicated the clinical potential of adjunctive therapies with antipsychotics (or stand-alone) utilizing supplementation of antioxidants, B vitamins, anti-inflammatory, and neuro-

protective nutrients, as well as dietary-restrictive practices (Arroll, Wilder & Neil, 2014). It is very important to note that due to lack of regulation by the FDA, using herbal and nutraceutical supplementation can have contraindications with any preexisting treatment regimen one may be prescribed. Furthermore, using these supplements in place of one's prescribed treatment regimen without consulting one's doctor can be very dangerous and is not recommended.

While much of the research regarding the aforementioned supplements indicates there may be less risk associated with their use when compared to traditional antipsychotics, one should still consult their mental health practitioner or doctor before making any adjustments to one's treatment protocol. Moreover, dosages for a majority of herbal supplements have not been standardized, so one should proceed with caution and only after speaking with a mental health professional. These herbs and nutraceuticals can play a vital role for many people in recovery from and the staving off mental illness, especially considering the high rate of nutritional deficiencies in the population at large. Research by Fryar-Williams and Strobel (2015) indicates that schizophrenia and schizoaffective disorders are significantly correlated with nutritional and biochemical biomarkers identified as deficiencies in vitamins D, B6, and folate, as well as oxidative stress. Brown and Roffman (2014) note that specific vitamin levels at various critical periods of prenatal development play a very crucial role in determining whether or not an individual will develop schizophrenia. Doruk et al. (2008) hypothesize that excessive free radicals and their consequent damage play a significant role in the symptomology of schizophrenia. Doruk et al. (2008) also suggest that these highly destructive and active free radicals are products of the excess metabolism for the neurotransmitter dopamine and can cause membrane damage in addition to overall cognitive dysfunction. Disturbances in amino acid metabolism have been implicated in the pathogenesis of schizophrenia as well.

Recently, however, some research is beginning to view schizophrenia as a neurodevelopmental disorder, being a product of our experiences that took place in the first years of our life, our prime developmental period (Ibrahim & El-sayed, 2013). Russinova, Wewiorski, and Cash (2002) examined the use of alternative health practices in individuals with severe mental illness and noted that herbs and nutritional supplements were the second highest methods used in the treatment of schizophrenia—the first being spiritual practice—when compared to yoga, guided imagery, chiropractic, and massage therapy. It is important to highlight the results of this research by Russinova et al. (2002), as supplementation and pharma-

ceuticals are not the end-all approach to the amelioration of the symptoms of schizophrenia—psychosocial and spiritual domains of treatment have displayed much clinical significance. A study by Mohr, Brandt, Borrás, Gilliéron, & Huguelet (2006) revealed that spiritual practice was able to instill hope, meaning and purpose in 71% of 115 individuals suffering from schizophrenia. Even further, spirituality decreased psychotic and general symptoms in 54% of the sample size, increased social integration in 28%, and decreased the risk of suicide attempts in 33% of the individuals in this study. Going back to the research by Russinova et al. (2002), herbs and nutraceuticals were able to provide a wide array of significant improvements in those with schizophrenia, such as increased energy levels, enhanced overall perception of health, and reduced levels of pain. Furthermore, these supplements were generally found useful in increasing emotional stability and alleviating anxiety, in addition to decreasing social isolation and being causative of a perceived overall increase in sense of well-being.

Stepping aside from the herbs and nutraceuticals empirically suggested to be therapeutic candidates for schizophrenia and other psychiatric illness, there are thousands of potential herbal remedies that have yet to be discovered and properly researched. The Amazon and the people therein utilize many psychoactive plants to alleviate the symptoms of—and potentially cure—a variety of psychiatric conditions. Research carried out by Mckenna, Ruiz, Hoye, Roth, and Shoemaker (2010) examined 128 Amazonian ethnobotanical compounds that were collected in the Loreto province of Iquitos, Peru. From these 128 plant species, 228 fractions were screened using 31 radioreceptor assays and a subset were screened utilizing functional assays at adrenergic, muscarinic, and serotonin receptors. Mckenna et al. (2010) found that 40% of the botanical samples possessed potential therapeutic CNS activity for the diminution of cognitive deficits associated with schizophrenia and dementia via significant inhibition of radioligand binding activity and both antagonistic and agonistic functions with respect to muscarinic, adrenergic, and serotonergic receptors *in vitro*.

This study is only skimming the surface with respect to potentially clinically significant herbal compounds. More extensive research with these compounds, and all other botanicals with promising CNS activity, needs to be carried forth to expand our ethnomedicinal catalogue and possibly discover novel phytochemical properties with therapeutic and clinical potential. Similar to the promising botanicals within the Amazon, Mussarat et al. (2014) examined the traditional uses of plants of the Dera Ismail Khan District in north-west Pakistan, indicating this area to be one

of the country's richest in terms of biodiversity while simultaneously having had very few ethnobotanical studies carried out within its parameters. Going forward, there should come a time where it is widely acknowledged that the current pharmacologic treatment repertoire is simply lacking in pertinent areas where treatments are increasingly necessitated by growing rates of chronic illness and other health crises. These unexplored lands rich in biodiversity, but neglected by empirical research, should be preserved and explored in the reasonable hope that the unexamined botanical species therein may fill the void of viable treatment options made manifestly apparent by the growing rates of those suffering without cure. The earth is by no means lacking in medicine; however, funding for ethnobotanical research is a different story.

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