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Original article

A current review for some methodological aspects on using *Crocus sativus* and *Whitania somnifera* sp. extracts in the treatment of schizophrenia

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Abstract

Abstract: Schizophrenia is a severe mental illnes that affects population all around the world which poses a problem for the abilities of the affected person as well as their family members. Aim of the study: This narrative review has as its objective the potential evaluation of treatment with extracts from *Crocus sativus* and *Whitania somnifera* on patients with schizophrenia. Results: The plant extracts *C. sativus* and *W. somnifera* have a very well developed extraction method and beneficial effects in the case of patients with schizophrenia. Conclusion: *Crocus sativus and Whitania somnifera* extracts could be used as an adjuvant treatment for positive and negative simptoms in schizophrenia.

Keywords

Crocus sativus, *Whitania somnifera*, Plant extract.

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Introduction

Schizophrenia is a severe chronic mental illness that affects up to 1% of the global population. It's a complex and multifaceted psychiatric condition that hinders social, occupational, and individual functioning and results in a deterioration in the patients' standard of life. This condition typically appears in late adolescence or early adulthood. Positive symptoms (e.g., hallucinations, delusions, disordered thinking, catatonic behavior), negative symptoms (e.g., social withdrawal, anhedonia, avolition, neglect of hygiene), and cognitive disturbances (e.g., in attention, executive functioning, and memory) are common in schizophrenia [1, 2].

The mechanism and etiology of schizophrenia are still poorly understood. Even so, it is generally recognized as a composite neurodevelopmental disorder influenced by genetic and environmental factors [3, 4]. It has been discovered, in particular, that monozygotic siblings of schizophrenics have a 50–80% probability of contracting the illness. Additionally, aberrant synaptic connections between various brain regions and inadequate brain maturation are also demonstrated [5]. It's interesting to note that more and more studies are arguing that oxidative stress has a role in the pathophysiology of schizophrenia [2, 6].

According to clinical research, first-generation or atypical conventional antipsychotics have some efficacy in reducing positive symptoms but are ineffective in reducing negative symptoms and cognitive deficits in schizophrenia patients. However, many drugs have significant adverse effects that limit their usefulness. Particularly, negative effects on the motor system (Parkinsonism) are linked to the use of conventional neuroleptics (such as chlorpromazine and haloperidol). On the other hand, the usage of atypical antipsychotics (such as clozapine, olanzapine, and risperidone) results in weight gain rather than Parkinsonism. Additionally, 30% of patients are resistant to the therapy mentioned above. Collectively, these findings indicate that new drugs that could reduce the negative symptoms and cognitive deficiencies that are typical of schizophrenia patients are urgently needed [2, 7, 8].

The use of plant extracts and their bioactive elements as potential anti-schizophrenia drugs has recently been recommended as one of the many alternative therapies for the treatment of schizophrenia. In the current investigation, we aim to critically evaluate any potential therapeutic benefit of *Crocus sativus* and *Withania somnifera* extracts and their constituent parts for treating schizophrenia.

Methods

We have conducted searches for Crocus sativus and Withania somnifera extracts and their impact in pacients with schizophrenia. For the most part, information was taken from scientific journals, published between 2005 and 2022 about the different strategies and methods used in makeing extracts with the plants mentioned before. The search keywords used were „withania somnifera biological constituents"; „withania somnifera compounds"; „withania somnifera schizophrenia"; „crocus sativus extract schizophrenia"; „crocus sativus chemical constituents"; „crocus sativus extract".

Results

Crocus sativus L. (Saffron)

Crocus sativus L. (CS) is a perennial herb that belongs to the Liliaceae line of the Iridaceae family and the genus Crocus. Several nations, including Azerbaijan, China, France, Greece, Egypt, India, Iran, Israel, Italy, Mexico, Morocco, Spain, and Turkey, grow this plant. The final output of this plant is the spice saffron. The dried, deep-red stigmas of the CS flower are saffron, in filament form. Each bloom has three stigmata, each of which weighs about 2 mg. To obtain 1 kilogram of spice, 150.000 flowers must be carefully chosen. Saffron has a distinctive hue, flavor, and aroma. There have been many uses for saffron throughout history, from antiquity to the present. It is frequently used as a perfume and as a spice to flavor and color food and beverage preparations. Saffron is still typically consumed by adding it to food or any hot or warm beverage [9, 10].

Chemistry of CS

We can mention the stamens, perianth, and stigma as the chemical components of the plant. They contain the following:

- A total of 46 components were found in stamen of which 8 compounds were in a higher percentage 4-hydroxydihydro-2-(3H)-furanone (22.01%), hexadecanoic acid (12.09%), tyrosol (7.52%), benzeneacetic acid (5.23%), linolenic acid (4.96%), linoleic acid (3.86%), 1-docosene (3.85%), and vitamin E (3.63%) [11].
- For perianth a total of 50 compounds were found, from which 4 compounds were in a hihger percentage 4-hydroxydihydro-2(3H)-furanone (22.12%), hexadecanoic acid (18.14%), linolenic acid (7.73%) and stigmasterol (4.20%) [11].
- And for stigma 34 components of which 6 compunds were in higher percentage 1,3,3-trimethyl-2-vinyl-1-cyclohexene (22.36%), diisooctyl phthalate (14.77%),

hexadecanoic acid (9.48%), cis-9,cis-12-octadecadienoic acid (7.49%), 4-hydroxy3,5,5-trimethyl-2-cyclohexen-1 -one (4.74%) and stigmasterol (3.31%) [11].

The effect of CS extracts and different compunds in schizophrenia and depression

Norbala et al. created the pills from Novin Zaferan Co. in Mashhad, Iran, which donated the saffron utilized in this study, and the Department of Cultivation and Development at the Institute of Medicinal Plants in Tehran, Iran, recognized it. Stigma is the component of Crocus sativus that is used as an addition and a herbal remedy. The extract from the stigma was made as follows: In three steps of percolation, 120 g of dried and ground stigmas were combined with 1800 ml of 80% ethanol. The ethanolic extract was then dried by evaporation at a temperature between 35 and 40 °C. Each capsule contained lactose as a filler, magnesium stearate as a lubricant, dried saffron extract (15 mg), and sodium starch glycolate as a disintegrant [12, 13].

In this modest preliminary double-blind and randomized study, Norbala and his team compared the efficacy of saffron at a similar dosage to that of fluoxetine in the treatment of mild to moderate depression. The results showed no statistically important difference between the two substances [13].

The Fadai et al. clinical research, in which aqueous extract (SAE) and crocin were made using the procedure outlined in their prior investigations [14, 15, 16], it's the only one to recognize the impact of CS extract on patients with schizophrenia. Crocin or SAE were put into identical capsules. Each crocin capsule has 15 mg dried crocin, and each saffron capsule included 15 mg dried SAE. Vehicle-filled placebo capsules were also used [14, 15, 16]. In the case of using Crocus sativus extract in combination with the antipsychotic olanzapine, it had a beneficial effect in the case of metabolic syndrome (including hyperglycemia, triglyceridemia, decrease in HDL and cardio metabolic risk) [17, 18, 19].

Withania somnifera (WS)

There are 23 species in the Withania genus (Solanaceae), the majority of which are found in North Africa, the Canary Islands, Southern Europe, and Asia [20, 21, 22, 23, 24]. Two of the recognized species, Withania somnifera (L.) Dunal and Withania coagulans (Stocks) Dunal, are of enormous economic significance and are also primarily grown because of their broad use in natural medicine [8]. The majority of both species are grown in subtropical areas of India. W. somnifera, however, even has a bigger economic impact [25, 26]. Withania adpressa Cors. is also an endemic species in Morocco and Algeria [27], despite the fact that the morphological form and phytochemical makeup of these plants might vary depending on their geographic distribution [22, 28].

Chemestry of Withania somnifera

We describe some of the most significant withanolides isolated from Withania spp. despite the fact that they have been extensively reported by several research, taking into account their abundance, bioactive effects, and representative structures, respectively. Misra et al. [29] reported withanolide A, withanolide B, 27-hydroxy withanolide B, withanolide D, withaferin A, 16β-acetoxy-6α, 7α-epoxy-5α-hydroxy-1-oxowitha-2, 17 (20), 24-trienolide, 5, 7α-epoxy-6α, 20α-dihydroxy-1-oxowitha-2, 24- dienolide along with common steroids, β-sitosterol and sitosterol, and their glucosides in W. somnifera. Withanoside I to VII, numbered from withanoside I to 7, were isolated by Matsuda et al. [30] from the roots of W. somnifera, with class VI being the most prevalent. Similar to this, Bessalle and Lavie [31] isolated from dried leaves of W. somnifera two chlorinated withanolides, withanolide C and 4-deoxyphysalolactone [28].

The effect of *Withania somnifera* extract in schizophrenia

To get the best withanolides and aglycone concentrations devoid of impurities, Chengappa et al. employed a breveted method [32]. The WS 250 mg and a number of inactive substances were present in the tablets produced as a consequence of this method and employed in the aforementioned investigation. The trial subjects first took 2 tablets daily for a total of 500 mg throughout the first week. Additionally, they got 4 tablets, totaling 1000 mg/day, twice daily throughout the second week of the trial. According to Chengappa et al.'s findings, the PANSS scale score at the conclusion of the therapies was favorable, improving, but only in the event of an adjuvant therapy [33].

The method of extraction, the dosage of WS, the test duration of 12 weeks, and other factors were the same as those used in Chengappa and his team's experiment given by Gannon et al. At the beginning of the second week of therapy, the dosage is also increased. Their studies aims were similar to one others in wich patients with schizophrenia are monitored for symptoms of depression and anxiety. Additionally, the adjuvant WS pill therapy was good for the PANSS readings.

Discussion

It is worth mentioning that the scientific community is increasingly addressing the issue of plant extracts to obtain new treatments for neurodegenerative diseases. Although many of the studies addressed present unique processing methods of CS and WS extracts, it must be taken into ac-

count that the number of clinical researches on these extracts are very limited. In the case of depression and anxiety in the case of schizophrenia, the replications carried out by researchers are valuable and the way of working to obtain pills with WS is meticulous. However, this type of pill can be used strictly in adjunctive therapy, for depression and anxiety in the case of patients with schizophrenia.

Interesting is the abundance of scientific materials in animal models, a good example of animal models is that of Gupta and her team on anxiety induced in mice and treated with WS extract, diazepam or a combination thereof, which reduced anxiety behaviors and social isolation in mice [38]. Moreover, similar effects have been observed in traditional Chinese medicine, where local herbal preparations help patients with schizophrenia in the negative or positive symptoms they may present. This aspect is however only within adjunctive treatments [35]. Also a study carried out by the same team made a comparison only between the plant extract and antipsychotic and the participants with antipsychotic had positive and negative symptoms and a better state of health than by the herbal treatment only group [34].

The clinical study conducted by Norbala and his team is a promising one, although the data of this nature are very limited and must be viewed in the context of the study conducted by him. But what is worth mentioning is that similar results were obtained in animal models such as the mouse [36], on the plant extract Olax subscoripiodea being a shrub of African origin. Another laboratory study on mice showed the anxiolytic and antidepressant effect of the plant Maerua angolensis [37]. Thus, we can mention that the importance of plant extracts for treating depression and anxiety can be promising for finding new ways to treat depression in patients with schizophrenia.

Conclusions

Although there are notable clinical studies for the capabilities of *Crocus sativus* L. and *Withania somnifera* plant extracts, future studies are needed to form a more complete picture of the importance of plant extracts in the treatment of schizophrenia. The plant extracts could be used as adjuvant therapy for patients with schizophrenia in the context of depression and anxiety simptomsbut also the possibility of other positive or negative symptoms in schizophrenia.

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