



CROCUS SATIVUS IN NEUROPSYCHIATRIC DISORDERS - A REVIEW

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ABSTRACT

Neuropsychiatric illnesses have been emerging as global concern and are quite prevailing in the community. The COVID-19 pandemic psycho-social impacts such as fear of infection, loss of loved ones, social stigmatisation, financial deterioration are prompting and associated with increased risk or worsening the sequelae of neuropsychiatric illnesses especially depression & anxiety. In conventional system of Medicine, drugs for such disorders have their own limitations & trouble-some side effects on their long term usage, therefore drugs from herbal source can be considered. Several drugs have been described by Unani scholars for treating neuropsychiatric disorders. *Zafran* (*Crocus sativus*) has been used in Unani system of medicine against several diseases including, cardiovascular disorders, depression, digestive ailments, migraine and insomnia. Its properties such as *Mufarrehat* (Exhilarant), *Muqawwi Dimagh* (Brain tonic), *Muqawwi Aasa'b* (Nervine tonic) are mentioned in Unani classical literature and validates its efficacy in such disorders. Several pre-clinical & clinical studies have been conducted and exhibit encouraging effects of *Crocus sativus*, e.g, anti-depressant, anti-anxiety, neuro-protective.

KEYWORDS: *Crocus sativus*, Unani, Brain tonic, neuropsychiatry.

INTRODUCTION

Psychiatric disorders are among the most common human illnesses and are characterized by disturbances in emotion, cognition, motivation & socialization.^[1] As per report of WHO, one in every 8 people, or 970 million people around the world were living with mental disorders, anxiety and depressive disorders were the most common. In 2020, the number of people living with depression and vision rose significantly because of the COVID-19 pandemic. Over 30% of patients hospitalized with COVID-19 may exhibit cognitive impairment, depression, and anxiety that persist for months after discharge.^[2] In addition to the pandemic-related psychological stress, multiple biological mechanisms have been proposed to understand the neuropsychiatric symptoms observed with COVID-19. The pathogenesis of neuropsychiatric disorders is complex and multiple mechanisms are involved. Dysfunction of monoamine neurotransmitter systems, and abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis, neuro-inflammation are some possible mechanisms. Genetic predisposition, developmental & environmental factor also contribute to neuropsychiatric disorder susceptibility.

BOTANICAL DESCRIPTION

Classification

Crocus sativus are the dehydrated stigmas of the flower *Crocus sativus* Linnaeus, a member of the family of *Iridaceae*. Saffron was first grown in Iran, other producing countries are Spain, Greece, Italy, Morocco, Egypt, Israel, New Zealand, Australia, Pakistan, and India.

Chemical constituents

There are about 150 volatile and non-volatile compounds present in stigmas of *Crocus sativus*, categorized into volatile & non-volatile compounds. The volatiles consist of more than 34 components that are terpenes, terpene alcohols and their esters and crocin, crocetin, picrocrocetin and flavonoids (quercetin and kaempferol) are non-volatile compounds. Apart from these, anthocyanins, vitamins such as riboflavin and thiamine, proteins, starch, amino acids, mineral matter and gums are also present. Studies of saffron stigma reveals crocetin, crocin, picrocrocetin and safranal as most bio-active components. The physical properties of saffron stigma are due to these bio-active compounds. The apocarotenoids, including crocetin and crocin are responsible for the red pigmentation of saffron stigmas, picrocrocetin (a colourless glycoside) is responsible for the bitter flavour of saffron, and safranal (a volatile oil) is

responsible for characteristic aroma of saffron (Sui et al., 2013) (Bathaie & Mousavi, 2010; Sohaei et al., 2020).^[3,22] *Crocus sativus* has been used in the management of various disorders, including cardiovascular diseases (CVDs), immune disorders, diabetes, cancer, metabolic syndrome (Met S), neurodegenerative diseases, and sexual dysfunction. Saffron extract and its active compounds are known to modulate serotonin, dopamine, norepinephrine, glutamate, and GABA-A neurotransmitters.^[14]

Traditional uses

In Unani system of medicine, *Zafran* or saffron has been used for medicinal purposes and its description has been mentioned in Unani classical literature. *Ibn Sina* in his book "*Al Qanoon Fitt Tibb*" describe its properties as anti-inflammatory (*Muhallil*), Hypnotic (*Munawwim*), aphrodisiac, diuretic (*Mudir baul*), Cardio-tonic (*Muqawwi Qalb*), Hepatonic (*Muqawwi jigar*).^[24] *Zafran* is also used as Brain tonic (*Muqawwi Dimagh*), Nervine tonic (*Muqawwi aasa'b*), Mufarreh (*Exhilirant*), emmengoque (*Mudir haiz*)^[25] and it is indicated in treatment of migraine (*Shaqiqqa*), insomnia (Seh'r), palpitation (*Khafqan*), gout & arthritis (*Niqris/waja ul Mafasil*).^[25]

In conventional system of medicine, several group of medications e.g. SSRI, TCA, NDMA antagonist etc are effective and being used for treating the neuropsychiatric disorders. However, sometimes patients may not respond well due to inadequate clinical response, patients cannot tolerate the side effects of medications such as dry mouth, nausea, excessive sleepiness, male sexual dysfunction, somnolence, headache, dizziness, anorexia, diarrhoea etc which eventually leads to treatment failure. Hence, use of herbal drugs from alternative system of medicine with potent action and lesser side effects should be encouraged.

POTENTIAL THERAPEUTIC USES

1) Depression & Anxiety

Depression is, by definition, a mood disorder. A depressed mood, loss of interest or pleasure, feeling worthless, trouble sleeping, especially early morning awakening (i.e., terminal insomnia) and multiple awakenings at night, are some symptoms of depression. Almost all depressed patients complain about reduced energy, difficulty finishing tasks, are impaired & less motivated at school and work. *Melancholia* is one of the oldest terms used in psychiatry, dating back to *Hippocrates* in the 4th century to describe the dark mood of depression and still use refer to a depression characterized by severe anhedonia, early morning awakening, weight loss, and profound feelings of guilt (often over trivial events).^[26] Several studies have demonstrated that antidepressant effects of saffron has been attributed to its several mechanisms of action such as inhibiting reuptake of monoamines, N-methyl-D-aspartate (NMDA) receptor antagonism and γ -aminobutyric acid agonism, and facilitating Brain-

Derived Neurotrophic Factor (BDNF) signaling.^[6,27] Hosseinzadeh et al. demonstrated the antidepressant effect of saffron in mice by forced swimming test and it was linked to underlying mechanism of activation of dopaminergic, noradrenergic, and serotonergic systems (Hosseinzadeh et al., 2004).^[8] Wang et al. also reported the therapeutic effects of saffron on depression. The aqueous ethanol extract of saffron was fractionated, based on the polarity at which the petroleum ether fraction and dichloromethane fraction showed dose-dependent antidepressant effects in a behavioural model of depression (Wang et al., 2010).^[8]

The efficacy of the co-administration of a hydro-alcoholic extract of saffron (40 or 80 mg) and fluoxetine (30 mg/day) was also investigated in a double-blind, randomized clinical trial for 6 weeks. The results revealed that a dose of saffron of 80 mg plus fluoxetine was more effective to treat mild to moderate depressive disorders than that of saffron of 40 mg and fluoxetine.^[6] Furthermore, a correlation between depression and deficiency of folic acid, vitamin B12 and B6 has been reported. Deficiency of these vitamins results in an increase in homocysteine and is associated with deficiencies of neurotransmitters (serotonin, dopamine, noradrenaline, and γ -aminobutyric acid (GABA) (Bottiglieri et al., 2000, Holford, 2003).^[9] It has been proposed that homocysteine exerts its effect via a glutamate receptor, called as N-methyl-D-aspartic acid receptor (NMDA) (Lipton et al 1997- Li J et al., 2013) and saffron has reported antagonistic activities on NMDA receptors (Hosseinzadeh et al., 2002 Lechtenberg et al., 2008). In a clinical trial of 40 patients with severe depression were treated with *C. sativus* and fluoxetine for 4 weeks, experienced significantly improved mood clinical findings (Beck Depression Rating Scale). Result also showed that improvement of depression status is correlated with the decrease in serum homocysteine level. (Gholamali et al., 2018). The findings of these studies were in accordance with previous reported antidepressant effects of *C. sativus* stigmas (Akhondzadeh et al., 2004, 2005; Noorbala et al., 2005).^[9]

Alterations in hypothalamic-pituitary-adrenocortical (HPA) system have been observed in depression, which results in HPA hyperactivity and elevated cortisol levels (Pariante and Lightman, 2008). Ghadroost et al. demonstrated that *crocin* significantly decreased plasma levels of corticosterone in rats being exposed to chronic restraint stress.^[8]

2) Anxiety & Post-traumatic stress disorders

Anxiety is a diffuse, unpleasant, vague sense of apprehension, usually accompanied by autonomic symptoms.^[26] *Yeung et al., 2018* narrate that mild to moderate anxiety symptoms can be relieved by using saffron extracts.^[10] *Pitsikas & Tarantilis*, demonstrated that the anxiolytic properties of *crocin* are mediated by their agonistic action on the GABAA-benzodiazepine

receptor.^[15] Result of a pre-clinical study reveals anxiolytic activity of *Safranal* in a dose-dependent manner as it increased the percentage of time spent in the open arms. *Safranal* showed a hypnotic effect without induction of motor incoordination or muscle relaxation activity (H. Hosseinzadeh, N. B. Noraei.;2008).^[29]

3) Sleep disturbances

Disturbed sleep is associated with various medical illnesses and can lead to day-time sleepiness, fatigue, poor concentration, thereby the quality of life. *Crocine* and *Safranal*, have been found to reinforce sleep onset, promotes deep sleep, reduces nocturnal awakening, and improves sleep rhythm (Lopresti et al., 2020; Milajerdi et al., 2018; Takeda, 2020).^[22] It has been shown that saffron consumption leads to significant improvement in Pittsburgh Sleep Quality Index (PSQI) scores (Ghaderi et al., 2020).^[22] Zhang et al., (1994) reported that an alcoholic extract of *C. sativus* decreased the motor activity and prolonged the sleeping time induced by hexo-barbital. This study suggests that the ethanolic extract possesses a sedative effect, which is probably responsible for the anticonvulsant effect of the extracts.^[13]

4) Obsessive compulsive disorder

Obsessive compulsive disorders comprises diverse group of symptoms, includes unwanted urges, repetitive thoughts or impulses that leads to anxiety and depression and it also interfere with personal and social life of a person. OCD have four major pattern symptoms: cleansing, checking, forbidden thoughts, ordering. It may be also be found in association with medical conditions.^[26] In a double-blind randomized trial of capsule of *Crocus sativus* stigma vs. fluvoxamine for 10 weeks in the treatment of mild to moderate OCD, *Crocus sativus* was demonstrated to be as safe and effective as fluvoxamin.^[30]

5) ADHD

ADHD is a neuropsychiatric condition affecting pre-schoolers, children, adolescents, and adults around the world. It is characterized by hyperactivity and impulsivity, attention deficit, memory and thinking deficits, specific learning disabilities etc. A double blind randomized trial of *Crocus sativus* versus methylphenidate was conducted in children diagnosed with *ADHD*. *Crocus sativus* was shown to be as effective as the pharmaceutical agent methylphenidate.^[18]

6) Others

Crocine exerts a protective effect against endogenous A β -induced neurotoxicity (Alzheimer disease), which was found to be mediated by reducing apoptosis of neuron, stabilizing mitochondrial function.^[28] In experiments with mice using maximal electroshock seizure (MES) and pentylenetetrazole (PTZ) tests have demonstrated that the aqueous and ethanolic extracts of saffron possess anticonvulsant activity (Hosseinzadeh and Khosrava, 2002).^[13] *Crocine* has a protective effect on ethanol-

induced impairment of learning and memory.^[12] *Safranal* & *crocine* are major bioactive compounds responsible for the neuroprotective potency of *C. sativus* L. through Monoamine oxidase (MAO) inhibitory properties (Hosseinzadeh & Talebzadeh, 2005) and inhibition of neuronal reuptake of dopamine, serotonin (5-HT), and norepinephrine (Leone et al., 2018).^[22]

CONCLUSION

Neuropsychiatric illnesses are quite prevalent and are also associated with medical conditions. A large panel of medications that have been used in successfully treating these disorders are currently available but in compliance with medication, troublesome side effects or inadequate clinical response are some limitations. The *Unani* system of medicine has been enriched with drugs for treating neurological conditions and *Zafran* (*Crocus sativus*) is one of them and could be proposed as a natural solution to combat the situation. Furthermore, clinical studies are needed to investigate the effectiveness of the plant pharmacological active constituents.

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