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A Review on Anti-Depressant Activity of '*Crocus sativus*' (Saffron)

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ABSTRACT

Saffron, *Crocus sativus* (Iridaceae), is a perennial herb, which earned its popularity as both medicine and spice. It is inhabitant of different mountainous regions of Asia minor to Greece, Western Asia, India and Egypt. The benefits of saffron as an antidepressant are well documented. The major bioactive compounds identified are Safranal, Crocin and Picrocrocin, which are responsible for its aroma as well as bitter taste. Almost 150 volatile and non-volatile from the chemical analysis of this plant. The purpose of this study was to conduct a meta-analysis of published randomized controlled trials examining the effect of saffron supplementation on symptoms of depression among participants with MDD (major depressive disorder). The plants and their active compounds can relieve depression through different pathways and hence are considered a new source to produce antidepressant. This review is focus on the medicinal plant and plant based formulations having antidepressant activity in animals and in humans.

INTRODUCTION

Depression is one of the most commonly diagnosed psychological disorders. It is multifactorial, chronic and life threatening disease with globally high prevalence. Approximately 1 in 5 adults report experiencing one episodes of depression in their lifetime, with women being twice as likely to develop depression [1]. According to World Health Organisation, depression will be second leading disease in the developed countries in 2020 [2]. Depression affects not only the patients but also their friends and families. Symptoms of major depression disorder (MDD) include excessive weight loss or gain, sleepiness or insomnia, feeling of worthlessness, anhedonia, difficulty thinking and concentration, persistent sad mood, loss of libido, inadequacy and ugliness and thoughts of suicide or death for 2 weeks period or longer [3,4]. There are two types of mental depression, namely unipolar depression, in which mood swings are always in same direction and is common, non-familial, clearly associated with stressful life events. The second type of bipolar depression shows a familiar pattern, unrelated to external stressful and usually appears in early adult life and much less common and mania over a period of a few week [5]. Recently, internal stressors such as variations in serum level of cholesterol, triglycerides, sugar and coagulation factors have been reported to be involved in developed of depression [6]. Additionally, many patients can not tolerate the side effect associated with some antidepressant medications, do not respond adequately, or develop tolerance through the course of treatment with medication [7]. Currently, certain drugs including lithium salts, stimulants, serotonin inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors are used to treat depression [8]. Due to safety concerns and side effects of many antidepressant medications, herbal psychopharmacology research has increased and herbal remedies are becoming increasingly popular as alternatives to prescribed medicating for the treatment of MDD in last several years [9].

In antidepressant activity, medicinal plants i.e. *Crocus Sativus* (Saffron) is widely used. Saffron (C.S) is a bulbous perennial of the iris family (Iridaceae) treasured for its golden coloured, pungent stigmas, which are dried and used to flavour and colour foods as well as dye. Saffron can be planted from an altitude of sea level to almost 2000m, but it is most preferably adapted to hill sides and mountain valleys, ranging in altitude between 600 and 1700 m [10].

SCIENTIFIC CLASSIFICATION:-

Kingdom:- Plantae

Division:- Magnoliophyta

Class:- Liliopsida

Order:- Asparagales

Family:- Iridaceae

Genus:- Crocus

Species:- *C. sativus*

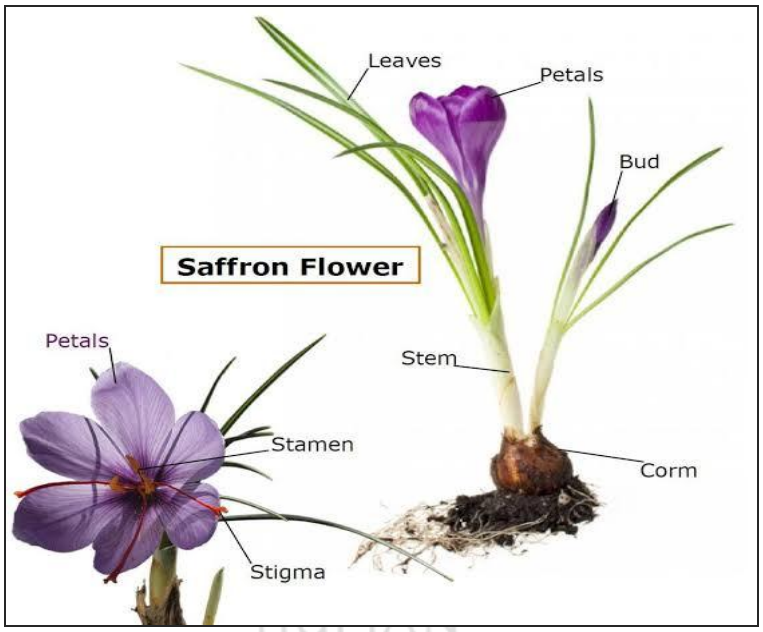

Figure No. 1: Saffron Flower

The main aroma factor in saffron is Safranal, which comprises of about 60% of the volatile components of saffron [11]. Saffron extract or its active constituents have shown different activities on the Central Nervous System such as antidepressant [12,13], anticonvulsants [14] and sedative. Various and high quality of final products are due to harvest process involved [15]. Saffron has been famous as both medicine and spice in some culture. The stigma of saffron has been used as medicine over 3600 year ago [16]. Also, saffron has been used in coloring tunics in the region of spain and by the Babylonian culture around 2400 BC [17]. Each of flowers has three red colored stigmas and one stigma of saffron weighs approximately 2 mg. Applying 1kg of this valuable spice is made from 150,000 flowers that must be carefully picked [18]. Recently, approximately 150 volatile and non-volatile compounds have been detected from the chemical analysis of *Crocus Sativum* Linn. However, fewer than so constituents have been identified so far as the phytochemicals of *Crocus Sativum.* The major constituents of saffron are crocin, picrocrocin and safranal [19]. Many clinical studies focused more on the antidepressant effect of

saffron. The aim of this article is to review the finding of the studies on antidepressant effects and mechanisms of action of *C. sativus* plant and biological compound of these plants responsible for the antidepressant action.

Figure No. 2: Benefits of Saffron

HISTORY OF SAFFRON:-

Human cultivations and use of saffron spans more than 3500 years [20,21] and extends across cultures, continents and civilization. Saffron, a spice derived from the dried stigmas of the saffron crocus (*Crocus Sativus*), has through history remained among the world's most costly substances. With its bitter taste, hay like fragrance and slight metallic notes, the apocarotenoid rich saffron has been used as a seasoning, fragrance, dye, beauty treatment and medicine [22]. Generally, the history of drug uses and especially those derivating from plants is very similar.

Figure No. 3: Saffron Flower and petals

Drugs were used for specific healing purposes and, later on, for treating many types of diseases, taking into consideration that the diseases at those times were very specific and widely spread. The wild precursor of domesticated saffron crocus was likely *Crocus cartwrightianus*, which originated in Crete or Central Asia [23]; *C. pallasii* and *C. thomasii* are other possible sources [24,25]. It is believed that saffron originated in Iran (Persian) [26]. However, Greece and Mesopotamia [27] have also been suggested as the possible region of origin of this plant. The saffron crocus is now a triploid that is 'self-incompatible' and male sterile; it undergoes aberrant meiosis and is hence incapable of independent sexual reproduction all propagation is by vegetative multiplication via manual "divide and set'' of a starter clone or by interspecific hybridisation [28,24]. If *C. Sativus* is a mutant form of C.cartwrightianus, then it may have emerged via plant breeding, which would have selected for elongated stigmas, in late Bronze Age Crete [29]. Humans may have bred *C. cartwrightianus* specimens by screening for specimens with abnormally long stigmas. Dezani, in his treatise regarding pharmacology [30,31] explains that in Nuremberg, between 1449 and 1495, three persons were condemned to pyre for the crime of adulteration saffron. However, the 1895 Genoa edition of Villavecchias Dizionario di Merciologia reports; nowadays it is only used in pharmacy to produce laudanum. The resulting saffron crocus was documented in a 7th century BC Assyrian botanical reference compiled under Ashurbanipal. The *C. sativus* clone was slowly propagated throughout much of Eurasia, later reaching parts of North Africa, North America and Oceania. Global production on a by mass basis is now dominated by Iran, which accounts for some 90% of the annual harvest [32]. Studies have shown the beneficial effects of saffron in depression, premenstrual syndrome and Alzheimer's diseases [33].

PHARMACOLOGICAL ACTION OF SAFFRON:-

Saffron (*C. Sativus*) is an extortionate conventional spice. The active components present in the saffron shown a number of useful pharmacological actions like antidepressant, anticonvulsant, anti-inflammatory, antitumor, radial scavenger effects and learning and memory improving effect [34]. According, to Srivastava *et al* two active components of saffron crocin and safranal have shown antidepressant activity [35].

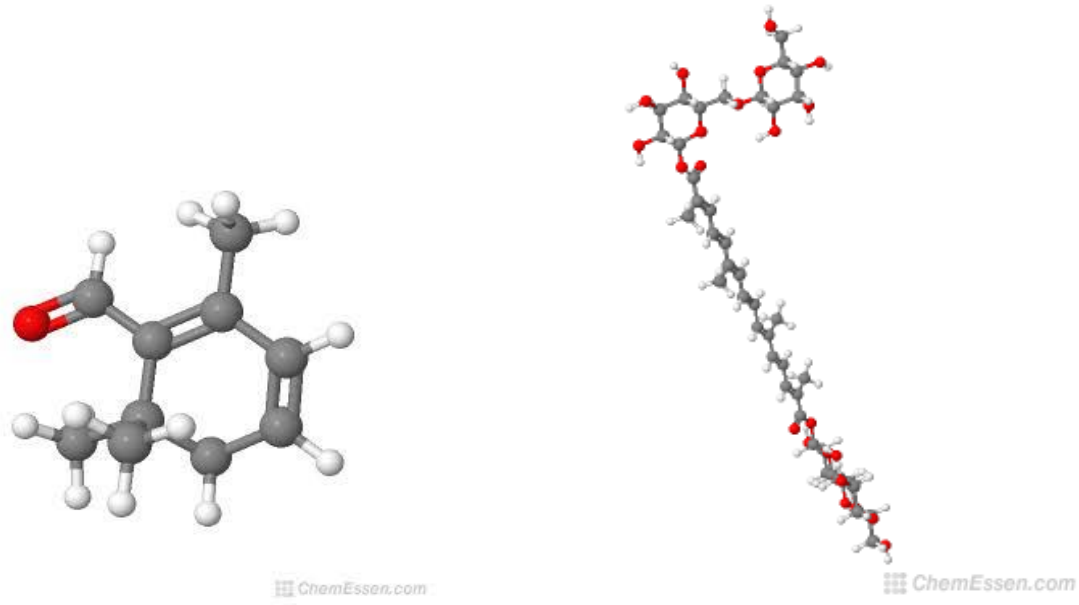

Figure No. 4: Chemical Structure of Safranal and Crocin

This is also proved by study carried out by Hosseinzadeh *et al* related to the result of aqueous and ethanolic extracts of *C. sativus*. *L. stigma* and their chemical components such as saffranal and crocin, for out forced swimming test in mice. The result which are acquired exhibit that the aqueous and ethanolic extracts of stigma (0.2-0.8/kg), Safranal (0.15-0.5 ml/kg) and crocin (50-600 mg/kg) reduce the immobility time of mice and the swimming time maximum by a considerable amount [36] of dopamine, noradrenaline and serotonin reuptake by crocin and safranal would be possible mechanism of antidepressant effect [38]. According, to Hausenblas *et al* saffron exhibit antidepressant activity by adjusting the levels of certain chemicals in the brain including serotonin (a mood elevating neurotransmitter), and helpful to relieve depression effect in a patients which are suffering from the physiological condition of depression [37].

PHARMACOKINETICS ASPECTS OF CROCIN AND CROCETIN:-

Other than the investigation of the biological activities of crocetin and crocin, it is also important to determine the pharmacokinetic aspects of the compounds such as its absorption, distribution, metabolism and excretion in the body. Also, the review of the pharmacokinetic profile of those compounds in human body remains inadequate. A study was conducted by Umigai *et al* [39]. On 10 healthy human volunteers with a single dose of crocetin orally administered at three doses (7.5, 15, 22.5) in the 1 week interval to investigate the pharmacokinetic profile of plasma crocetin by using RP-HPLC. In pharmacokinetics study, one of the factors affecting the bioavailability of a compound is its solubility and absorption through the gastrointestinal tract. The research carried

out by Vi *et al* [40] using HPLC observed that crocin remained undetected in the serum of tested rats, regardless of gender, following single or repeated doses of oral administration. Crocin also was excreted mainly in faeces. Besides. Following repeated oral doses of crocin, no accumulation of crocin was found in the serum [41]. However, a recent study by Zhang *et al* [41] showed that orally administered crocin could be absorbed through gastrointestinal tract with poorer bioavailability as compared to its metabolite, crocetin, using ultra spectroscopy. This may be due to high lipophilicity, which renders lower aqueous solubility of crocetin in the gastrointestinal tract [41]. Moreover, as suggested from the same study, the absorption of crocetin was saturated following an increased dose of oral administration [42]. Also, to exert its pharmacological activity as an antidepressant, the compound should be able to cross the blood-brain-barrier (BBB). In the study by Lautenschlager *et al* [42] using *in vitro* models of porcine brain capillary endothelial cells and bloods cerebrospinal fluid barrier, it was observed that the penetration across BBB occurs at a quite slow rate with a constant velocity. However, a more recent study by Kanakis *et al* [43] stated that the interaction of crocetin with human serum albumin showed a weak ligand protein interaction. So, the less bound ligand to the plasma protein trends to get easily distributed, suggesting that crocetin is well distributed into the body tissue [39]. In the aspect of metabolism, crocetin was reported to be in intact as well as conjugated forms in the plasma of the tested rats. This was due to the partial metabolism of orally administered crocetin, which occurred in the intestinal mucosa before or during absorption or both and also in the liver of tested mice [44]. However, to the best of our knowledge, no literature was found to investigate the major route of excretion for crocetin.

APPLICATIONS OF SAFFRON:-

Saffron and its constituents are known for a quite large number of possible uses and actions. The pharmacological properties of saffron components, like safranal, crocin and crocetin are due to their chemical structure. The most important pharmaco-active properties of saffron were reported in studies based on *in-vitro* experiments that appeared in the Chemical Abstracts between 1925 and 1999. Saffron has been proposed as one of the modifiers of the gastrointestinal chemical function. Through this action it may stimulate appetite and prevent gastrointestinal atonia [45]. Picrocrocin seems to have a sedative effect on spasms and lumbar pains [46]. The ability to transport oxygen makes crocetin useful therapeutic candidate in various situations, such as atherosclerosis, alveolar hypoxia, haemorrhages, fermentations and cell reproduction, arthritis, tumours, etc [47].

➢ Saffron as dyes:- Dyes and colored garments (principal pigment of saffron is alpha-crocin, a water soluble carotenoid). Saffron has been used as a histological stain, i.e, as a dye for connective tissue [48].

➢ Saffron as food:- It performs the function of a spice, adding its faint, delicate aroma, pleasing flavour, and magnificent yellow color to enhance palatability [49].

➢ Saffron as perfume:- A pleasantly odoriferous compound, safranal, develops during the drying process, probably by enzymes or thermal dissociation of the bitter compound, picrocrocin [50].

CONCLUSION:-

In summary, saffron and especially crocin and safranal components possess significant pharmacological properties, including antidepressant, hypolipidaemic, anticancer, anti-Alzheimer that may applied to a wide spectrum of diseases such as atheromatosis, diabetes and various type of cancer. There is a great need of new, pharmacokinetic and bioavailability studies in conjugation with clinical trials that will establish the role of saffron as a novel therapeutic approach. Research required to get a good quality data regarding saffron mechanism of action. Further research is recommended to increase our understanding about the role and actions of saffron in major depression.

AUTHOR CONTRIBUTION:-

The manuscript is conceptualised and data acquisition done by Saurabh Bodkhe & Vaibhav Bharad. Critically reviewed the content and revised it.

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