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Analysis of the Main Effective Composition of Saffron and its Assistant Application in the Treatment of Depression

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Abstract: Currently, as the number of people suffering from depression gradually increases, different research has been done to find a better therapy for treating depression. Saffron as one of the naturopathic medicines become the focus of research. Scientists have done various clinical trials and confirmed its positive effect in treating depression as well as its potential to assist treatment. However, it still lacks long-term studies to find out its pharmacological mechanism. This essay mainly talks about active ingredients in saffron and their function. Apart from that, this essay describes the methods of extracting and also the toxicity and safety of saffron and its main components. Some research about the anti-depressant effects of saffron are also included in this essay which results in its good efficacy. This research aims to explore novel methods to treat depression and avoid the side effects compared with conventional treatments. The future research will be about its basic pharmacological mechanism so that its therapeutic use can be optimized and also avoid its side effect.

Keywords: Saffron, depression, clinical application.

1. Introduction

Depression is a common disease occurring among the public and is gradually considered a huge threat to global health. The reasons that cause depression are different among different people such as biological factors, psychological factors, environmental factors, societal factors, and even medical factors. Due to various causes, it has different effects after getting treatments which makes it hard to be completely cured as well. Its main symptoms include abnormal psychological and physiological states, such as difficulty in concentrating, loss of interest in life as well as insomnia, and so on characteristics that influence the quality of life. Due to its extremely high rate, depression which requires a lot of treatment has also become a hot topic of concern. Depression can cause changes in neurotransmitters such as serotonin, norepinephrine, and dopamine, which can also cause chronic neuroinflammation, leading to increased inflammatory markers level such as cytokines IL-6 and TNF-α, affecting brain activity and mood regulation [1].

Most depression treatments are based on drugs like Serotonin-Norepinephrine Reuptake Inhibitor(SNRI)or Selective Serotonin Reuptake Inhibitor(SSRI). Although these medicines show great effect, their side effect cannot be ignored which also brings the patients a lot of pain and inconvenience. Conventional drug treatment may cause functional diseases of the digestive system, disorders of the nervous system, and even discontinuation syndrome [2]. Luckily, since naturopathic medicine has had huge success in cancer biology, it become much more popular in other medical

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fields like depression. Some research also shows that natural components like green tea catechins and resveratrol can significantly reduce depressive behaviors which may be, in part, a result of hindering monoamine oxidase (MAO) [3]. These natural components can improve treatment efficiency and reduce side effects to a huge extent. Saffron as one of the most potential antidepressant herbs has gradually appeared in front of people.

Currently, there is established literature on the anti-depression effect of saffron and its important components. Scientists have done a series of in vivo and in vitro experiments to try to understand its mechanism, safety, and side effects. This article aims to show its effective components, toxicity as well as its application potential assessment.

2. Active Ingredient Analysis

Researchers in the field of phytochemistry have identified various active compounds in saffron, which lead to its color, taste, and aroma. The main components are crocins, safranal and picrocrocin. (fig.1) [4].

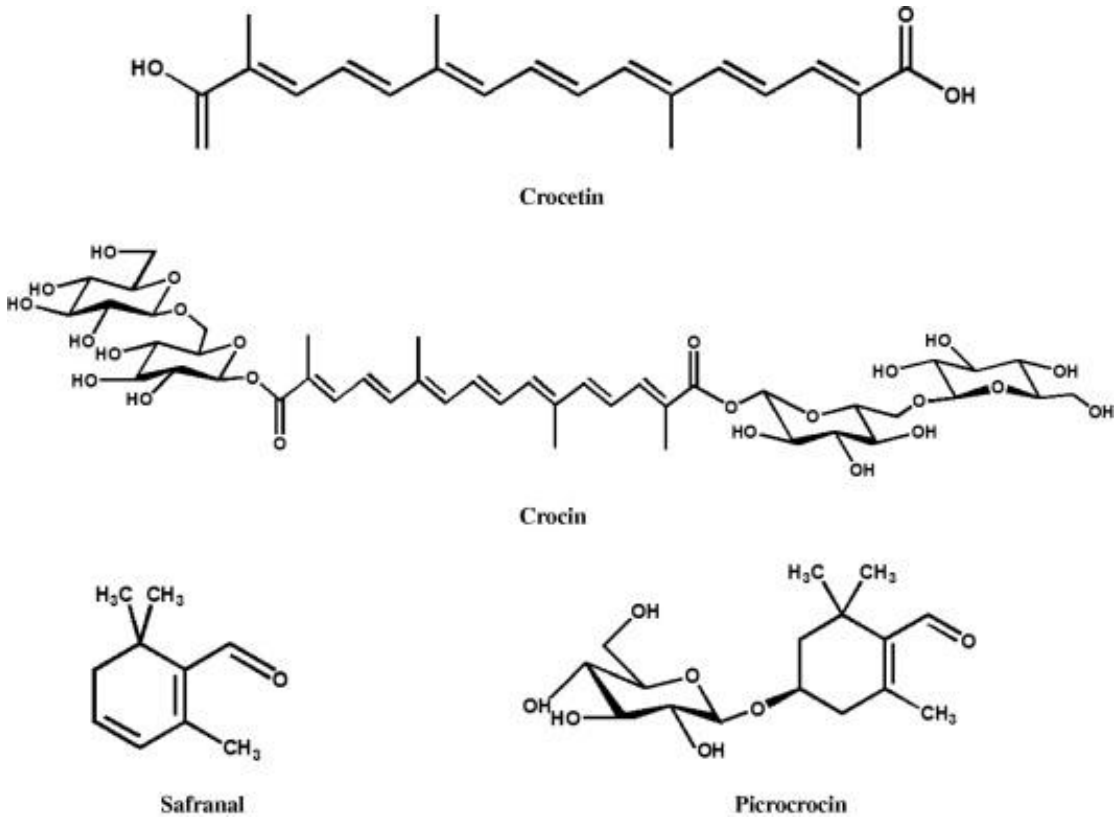

Figure 1: Molecular structures of crocins, safranal and picrocrocin [5].

2.1. Active Ingredients

A range of carotenoid compounds has been identified in saffron such as small amounts of lycopene, α and β carotene, zeaxanthin, phytoene, and phytoene. They are also collectively referred to as oil-soluble pigments. Among them, crocin is a class of hydrophilic carotenoids, which are mono- or disaccharide polyenyl esters of crocetin. D-glucose and d-gentiobiose exist as carbohydrate residues. The crocin family includes various sugar moieties and it has also been tested for six types (Table 1). Crocin is famous for its free radical scavenging and anti-tumor properties, which makes it considered the best choice of water-soluble food additive, though it is also soluble in methanol and ethanol. The

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geographic location may affect the concentration of crocin. For example, Greek saffron had the highest concentration of crocin, followed by India and New Zealand, which possibly caused by different local climates and storage methods. Crocin also has a lot of pharmacological influences on the nervous system which include anxiolytic and anti-depressant effects. That is because crocin markedly countered the inhibition of long-term potentiation caused by ethanol in hippocampal neurons [5].

Table 1: six types of sugar moieties.

Compound	Sugar Moieties	Chemical Formula	Isomer Occurrence in Saffron
Crocetin	R1=R2=OH	$C_{20}H_{24}O_4$	Cis-trans
Crocin 1	R1 = β-D-glucosyl, R2 = H	$C_{26}H_{34}O_9$	Trans
Crocin 2	R1 = β-D-gentiobiosyl, R2 = H	$C_{32}H_{44}O_{14}$	Cis-trans
Crocin 2’	R1 = R2 = β-D-gentiobiosyl	$C_{32}H_{44}O_{14}$	Cis-trans
Crocin 3	R1 = β-D-gentiobiosyl, R2 = β-D-glucosyl	$C_{38}H_{54}O_{19}$	Cis-trans
Crocin 4	R1 = R2 = β-D-gentiobiosyl	$C_{44}H_{64}O_{24}$	Cis-trans
Crocin 5	R1 = β-D-glucosyl, R2 = β-D-gentiobiosyl	$C_{50}H_{24}O_{29}$	Cis-trans

Safranal is another important component of saffron, which causes the unique aroma of saffron. Safranal (C10H14O) is a cyclical terpenic aldehyde, which is produced from picrocrocin. In an acid environment, picrocrocin creaks down and results in a molecule of water and an aglycone, which subsequently loses a water molecule and ultimately converts to safranal. Safranal has lots of pharmacological effects such as anticonvulsants, reducing withdrawal syndrome, and also anti-tumor effects. Also, some research shows the protective influence of safranal in the Central Nervous System (CNS) that is because it can bind to the BDZ site of the GABAA receptor(This results in increased inhibitory effects in the central nervous) (fig.2) [6].

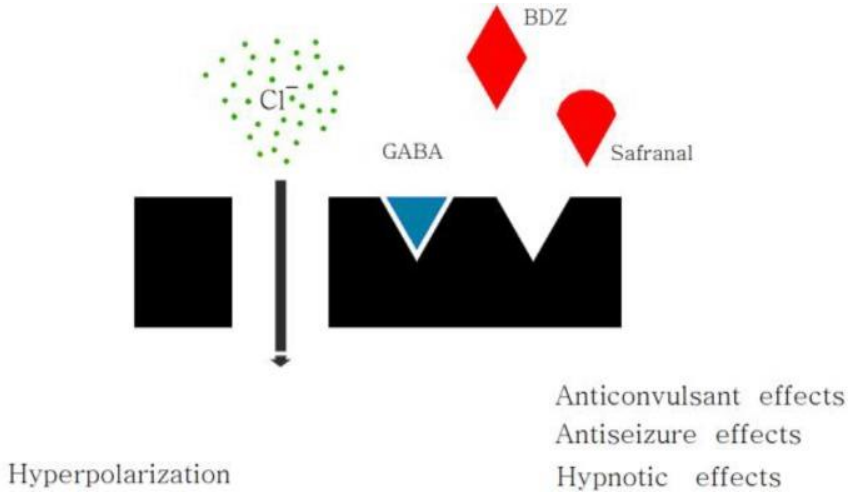

Figure 2: Safranal binds to the BDZ site of the GABAA receptor to make effect [6].

Picrocrocin, the second major saffron apocarotenoid, is an important component of saffron that decides that unique bitter taste of saffron. It also has abundant Biological and Pharmacological Effects like Antioxidant activity, Anti-inflammatory effects, Neuroprotective properties, Anti-tumor activity, and antidepressant effects, even picrocrocin can benefit in Lipid Metabolism aspect. That is because picrocrocin has the capability of picrocrocin to suppress HMGR activity. HMGR is a crucial enzyme in lipid metabolism regulation and serves as the primary pharmacological target for treating

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hypercholesterolemia or hyperlipidemia. Compared with pravastatin, a famous HMGR inhibitor that can decrease enzyme activity in a dose-dependent manner, researchers have confirmed its effect on the regulation of lipid metabolism [7]. Meanwhile, because of the properties of being an antioxidant and anti-inflammatory of picrocrocin researchers are now considering its protentional in some diseases like cardiovascular diseases and metabolic disorders [7].

In summary, there are three major components in saffron crocins, safranal, and picrocrocin. They jointly decided the color, flavor, and scent of saffron and also decided its unique sensory properties and health benefits.

2.2. Extraction

Extraction of bioactive components from plants is a vital step, which could impact the quality of nutraceutical products and health-enhancing foods. In the extraction of saffron, a suitable extraction method may collect the target bioactive up to 5 times compared to conventional methods. In general, traditional extraction includes Soxhlet extraction, vapor or hydro distillation, and maceration or solvent extraction, which may lead to extirpate thermo-liable compounds that is because these methods use a lot of organic hazardous solvents. To overcome these problems, researchers developed new extraction methods to replace these outdated methods which are called ‘Green Methods’.

These green methods have higher safety and efficiency and they are eco-friendly, fast, and accurate. Emulsion liquid membranes (ELMs), enzyme-assisted extraction (EAE), supercritical fluid extraction (SFE), ultrasound-assisted extraction (UAE) or sonication, microwave-assisted extraction (MAE), and pulsed electric field (PEF) extraction are good samples of green methods, which will be described in detail below.

The conventional extraction methods like Soxhlet, maceration, and distillation have simple operations with a lower cost which is best suited for small-scale industries, but it is lengthy and needs significant amounts of solvents which makes it not eco-friendly, also it is unsuitable for heat-sensitive ingredients as it can produce byproducts and degrade some bioactive compounds so that it is low efficiency. So, it is only suitable for initial extraction of bioactive, oils, essential oils etc. By contrast, green methods have more advantages [8].

1) Emulsion liquid membrane extraction: it can rapidly extract with high efficiency and selectivity, and also it can scale up and use toxic organic solvents. Its membrane components can be recycled which makes it eco-friendly. But the emulsion is unstable which may cause leakage and swelling. All in all, it plays a crucial role in the efficient extraction of bioactive compounds.

2) Microwave-assisted extraction: this method has high selectivity and can produce extracts of superior quality. This method offers greater cost efficiency when compared to conventional extraction techniques. The short extraction time brings a higher extraction rate. Although it is economically feasible for scale-up, the difficult operation and expensive equipment make it hard to be popular. The using organic solvents also make it not eco-friendly.

3) Ultrasound-assisted extraction: this method is easy to use because of simple technique. It has fast extraction speed and an economic-clean method. Meanwhile, it is suitable for thermo-sensitive bioactive and the feature of least interaction with bioactive makes it easy to couple with other extraction routes. However, it is hard to scale up for industrial uses, which means it cannot be the main extraction method in the industry.

4) High hydrostatic pressure extraction: This method avoids the use of heating and enhances mass transfer efficiency. It is versatile, allowing for the extraction of highly polar, mildly polar, and non-polar compounds by utilizing various diluents. However, the drawbacks of this low-energy technique include the high cost of equipment and the challenge of maintaining a consistent processing pressure.

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5) Supercritical fluid extraction: this method has enhanced mass transfer and is eco-friendly. The capacity to recycle the supercritical fluid brings it higher operation space. It has high cost and complicated thermodynamics but it is suitable for volatile compounds like safranal.

6) Enzyme-assisted extraction: this method uses water as an alternative to conventional chemical solvents which makes it environmentally friendly. It is suitable for isolating bound components from the plant matrix and it has a high rate of extraction. But expensive price and sensitivity of enzymes mean that scaling up this process for industrial applications poses significant challenges.

7) Pulsed electric field extraction: it has high efficiency in a short extraction time and its low energy consumption makes it easy to scale up in industry. It is eco-friendly but the highly accurate control of processing parameters it requires and the high cost of maintenance make it hard to be widely used in industry.

Thus, though more and more green methods are being invented, there are still lots of advantages and difficulties that need to be overcome. The novel methods still need to be continuously improved.

3. Toxicity

Researchers have done a lot of experiments in animal models and get basic data about the toxicity and safety of saffron and its main components. Meanwhile, the safe and toxic doses of saffron are also researched in Clinical studies.

3.1. Data in Animal Models

LD_{50} (Lethal Dose, 50%) is a standard measurement used in toxicology which represents the dose required to kill 50% of a test population. Based on the LD50 values in acute toxicity tests, the chemical agents can be classified with different toxicity levels: super toxic (<1 mg kg−1), extremely toxic (<5 mg kg−1), highly toxic (1–50 mg kg−1), moderately toxic (50–500 mg kg−1), slightly toxic (500–5000 mg kg−1), practically nontoxic (5000–15,000 mg kg−1), and relatively harmless (>15,000 mg kg−1). Several reports show the LD_{50} in experiments of saffron.

3.1.1. Saffron Extract

1)Acute toxicity

In the Oral Administration experiment, the LD_{50} of saffron aqueous extract was determined to be 4,120 ± 556 mg/kg, in BALB/c mice which was classifying it as slightly toxic. It resulted in an LD50 value of 1.6 g kg−1 when Intraperitoneal (IP) was exposed to saffron stigma extract in mice. For IP administration of saffron petal extract in mice, the LD50 was 6 g kg−1, which indicates moderate toxicity.

2)Subacute toxicity

Subacute toxicity refers to the toxic effects of a substance when it is continuedly used over a period, typically 28–30 days. In Doses (up to 100 mg/kg) experiments, rats and mice didn't observe significant adverse effects, that with normal liver and kidney function tests. In High Doses (600–1000 mg/kg) experiments, Mild histopathological changes in the liver and kidneys, such as mild inflammation and hepatocellular. Therefore, the saffron extract has a slight toxicity but in high doses, may cause mild organ stress [9].

3.1.2. Crocin

1)Acute Toxicity

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Study shows that both Oral and IP Administration with 3 g/kg will not result in mortality after 24 and 48 hours of treatment in mice. It has been confirmed that the tolerated dose of 3 g kg−1 of crocin has very low toxicity in acute ingestion or IP treatment.

2)Subacute toxicity

When we did the experiments with 15–180 mg/kg body weight of Crocin per day, there didn't have any adverse effects on organ histology, body weight, or hematological parameters in rats. Even high doses of crocin can improve antioxidant enzyme activity, which shows its protective effects instead of toxicity.

In conclusion, crocin has good tolerance even with high doses [9].

3.1.3. Safranal

1) Acute Toxicity

In Intraperitoneal Administration, LD_{50} values for safranal have differences between different types of rats. To Male BALB/c mice, it was 1.48 ml/kg. To Female BALB/c mice, it was 1.88 ml/kg. To Male Wistar rats it was 1.50 ml/kg. In Oral Administration, LD_{50} values for safranal was 21.42 ml/kg Male BALB/c mice. In Female BALB/c mice which was 11.42 ml/kg. To Male Wistar rats it was 5.53 ml/kg. These data show that safranal has moderate toxicity. Meanwhile, compared with Oral Administration, the Intraperitoneal Administration has higher toxicity.

2) Subacute toxicity

With administration of Low Doses (50–100 mg/kg), no significant toxicity was observed in rats and mice. To the High Doses (200–300 mg/kg), Mild to moderate toxicity which includes slight hepatotoxic effects (elevated liver enzymes) and histopathological changes in the liver was found in rats and mice. In conclusion, Safranal shows subacute toxicity to some extent and also has mild hepatotoxicity in higher doses [10].

3.1.4. Picrocrocin

1)Acute Toxicity

There isn't any date of LD_{50} value for picrocrocin, but studies also show that compared to safranal, picrocrocin has lower toxicity, even in the slightly toxic or practically non-toxic category.

2)Subacute toxicity

There is limited data available on the subacute toxicity of picrocrocin, but it seems to have a low subacute toxicity profile, as its concentrations in saffron extracts have not shown adverse effects at moderate doses [11]. So, there still needs some experiments to confirm the safety and toxicity of picrocrocin.

3.2. Safe and Toxic Doses of Saffron in Clinical Studies

Saffron is always used as a kind of food additive and didn't find any complications. Some research report that a dose of approximately 20 g may be lethal, more than 5 g day−1 may cause side effects, and lower than 5 g day−1 is considered to be safe. According to the research, doses of more than 10 g day−1 will lead to a series of adverse reactions, which include Nausea, uterine hemorrhage, blood in urine, bleeding of the gastrointestinal lining, and episodes of vertigo and lightheadedness. However, little research directly reports the safety of saffron because saffron can also elevate sodium, blood urea nitrogen, and creatinine, which are not clinically important [12].

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4. Evaluation of the Potential for Application in Depression

Saffron and its main components are considered to have a positive influence on the treatment of depression. There are also some in vivo and in vitro experiments to make sure its effect in the treatment of depression.

4.1. Clinical Trials

The anti-depressant efficacy of saffron has been widely researched. Mazidi, et al. did a 12-week study with 60 patients who took saffron capsules 100 mg/day and finally found it has a similar effect in reducing depression compared with a placebo. Still, Mazidi, et al., studied 40 patients over 6 weeks with saffron 60 mg/day and found saffron got a higher score than placebo on the Hamilton Depression Rating Scale. Akhondzadeh, et al. conducted research in 2005, with 40 patients who took saffron 60 mg/day over 6 weeks and got the same result as Mazidi et al. that saffron performed better than placebo. Sahraian, et al. compared patients with saffron (30 mg per day) combined with fluoxetine (20 mg per day) with patients who used placebo plus fluoxetine over 4 weeks and got the result that both of the groups had a good effect on depression, without an obvious difference. Lopresti and Drummond conducted 12 weeks of research with 123 patients and finally found that low or high-dose curcumin (250/500 mg bid), and a combination of minimal dose curcumin with saffron (15 mg bid) were successful in alleviating depressive and anxiety symptoms in individuals diagnosed with major depressive disorder. Noorbala et al. researched 40 mild to moderate depression patients over 8 weeks and the result showed that saffron sativus 30mg/day has the same effect as fluoxetine 20 mg/day in treatment [13]. Therefore, the data from clinical trials shows that saffron and its main components have a great effect in treating depression without any side effects as well.

4.2. Saffron's Potential Mechanisms for Exerting Antidepressant Effects

Researchers have made some supposes about the potential mechanisms for exerting antidepressant effects of saffron, including Anti-inflammatory effects, Antioxidant effects, and Neuroprotective effects.

4.2.1. Anti-inflammatory Effects

Recent years have established a connection between inflammation, immune dysfunction, and the etiology of depression and anxiety disorders. Meanwhile, the Anti-inflammatory effects of saffron and its main components are supported by huge amounts of reports. Saffron demonstrates significant potential in reducing elevated serum levels of both enzyme-based and non-enzyme-based inflammatory agents. Furthermore, it exhibits anti-inflammatory effects in a rabbit model of osteoarthritis by suppressing the activation of the nuclear factor kappa B (NF-κB) pathway induced by interleukin (IL)-1β. This mechanism underlies its anti-inflammatory properties [14].

4.2.2. Antioxidant Effects

Depressive disorders have been linked to heightened oxidative stress and diminished antioxidant defenses. Extensive research has highlighted the antioxidant properties of saffron and its active compounds. In a study on hyperlipidemic rats, saffron and crocin were shown to lower serum MDA level, glutathione peroxidase (GSHPx), overall glutathione (GSH), and oxidized form of glutathione (GSSG). Additionally, they enhanced superoxide dismutase (SOD), catalase (CAT), ferric reducing ability/antioxidant capacity (FRAP), and total thiol (SH) levels in Liver parenchyma while reducing substances reactive to thiobarbituric acid (TBARS) [15].

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4.2.3. Neuroprotective Effects

Brain-derived neurotrophic factor (BDNF) plays a significant role in the pathophysiology of depression. Research examining the antidepressant potential of crocin in rats revealed that crocin exhibits antidepressant-like effects by enhancing the levels of cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), BDNF, and VGF within the hippocampus. Additionally, in an in vitro research, crocin demonstrated protective effects on PC12 cells against the severe neurotoxicity induced by acrylamide. This protection was achieved through the regulation of apoptosis-related proteins, specifically by reducing Bcl-2 expression, increasing Bax expression, and mitigating cell apoptosis [16].

5. Conclusion

Saffron demonstrates high potential as a natural treatment for depression, which is confirmed by many research and studies. Its main components include crocins, safranal, and picrocrocin all have relevant effects in treating or assisting in treating depression. That may be because of its anti-inflammatory effects, Antioxidant effects and Neuroprotective effects.

The clinical trials also show that in the management of mild to moderate depression, saffron and its main components are as effective as some traditional drugs like fluoxetine and imipramine, with lower side effects. Moreover, saffron also shows the value in assisting therapy, that it can enhance the effect in treatment outcomes.

However, there is still some difficulty in developing saffron as a novel naturopathic medicine. Initially, most of the research are short-team like 4-6 weeks with a small sample size, which means generalizability of findings is limited. Apart from that, the missing data in long-term experiments lead to the inexact mechanisms of saffron's antidepressant effects which brings challenges for clinical use.

In conclusion, although saffron provides a new and safe choice as an alternative or complementary treatment, it still needs more long-term research and stricter standardization to absolutely make sure its clinical utility.

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