Evidence Based Herbal Medicine and Mental Health

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Abstract

Many cultures have developed folk herbal remedies for various symptoms of mental illness. An evidence base now is being developed for some of these "alternative" herbal remedies. There has been an increase in the number and proportion of clinical trials of complementary medicine, which suggests a trend toward an evidence-based approach. This review presents the scientific information regarding herbal medicine with evidence based approaches for saffron.

Keywords: ***Crocus sativus*, Evidence Based Herbal Medicine, Mental health**

Introduction

Complementary medicine are interventions that are not widely taught in medical schools and are not part of the usual arsenal of treatments and medications recommended and prescribed by physicians and available in hospitals. Use of Complementary medicine is dependent, not on dissatisfaction with conventional medicine as it is most commonly used in association with conventional medicine, but on philosophical orientations towards health and life [1]. A vast quantity of information of varying quality exists in the media and on the internet. There are concerns, however, that the media and internet provide too rosy a picture of complementary medicine and downplay adverse reactions to complementary medicine, which can be dangerous and potentially fatal. These factors suggest that significant improvements need to be made to knowledge translation mechanisms for the public, healthcare professionals, and policy makers. The response of the medical and scientific community has been an increasing interest in complementary medicine issues [1]. There has been an increase in the number and proportion of clinical trials of complementary medicine, which suggests a trend toward an evidence-based approach. One of main branches of complementary medicine, is herbal medicine. Herbal medicine has seen a growth in scientifically referenced texts in the past twenty years. However, herbal medicines are interventions that are not widely taught in medical schools and are not part of the usual arsenal of treatments and medications recommended and prescribed by physicians and available in hospitals. Nevertheless, many people using herbal medicines find the health care alternatives are more congruent with their own values, beliefs and philosophical orientations toward health and life. Similarly, it seems likely that many people feel that herbal medicines are empowering by allowing them to treat themselves without seeing a physician. The danger is that, many people believe that herbal medicines have no toxicity problems or even side effects. In addition, they are not aware of many possible interactions of herbal medicine with concurrent prescribed medications [1].

Herbal medicines include a range of pharmacologically active compounds: in some cases it is not well understood which ingredients are important for a therapeutic effect. The supporters of herbal medicine believe that isolated ingredients in the majority of cases have weaker clinical effects than whole plant extract, a claim that would obviously require proof in each case. Generalizations about the efficacy of herbal medicines are clearly not possible. Each one needs systematic research including a variety of animal studies and also randomized clinical trials. Indeed, clinical trials of herbal medicines are feasible much in the same way as for other drugs [1]. Numerous randomized clinical trials of herbal medicines have been published and systematic review and meta-analyses of these studies have been available. Many of today's synthetic drugs originated from the plant kingdom, and only about two centuries ago the major pharmacopoeias were

dominated by herbal drugs. It has been reported that most patients with a mental disorder sought herbal medicine treatment for somatic problems rather than for their mental and emotional symptoms and the best example is somatic symptoms of depression [1].

Physicians need to understand the biochemical and evidential bases for the use of herbs and nutrients to diagnose and treat patients safely and effectively, to avoid interactions with standard medications, and to provide patients with the benefits of alternative treatments [1]. This review will present saffron as example for evidence based herbal medicine.

Saffron (*Crocus sativus*)

Saffron is the world's most expensive spice, derived from the flower of *Crocus sativus*. Each saffron crocus grows to 20 – 30 cm and bears up to four flowers, each with three vivid crimson stigmas [1]. Indeed, it is a Persian herb with a history as long as the Persian Empire itself. Iran, the world's largest producer of saffron has been investing in research into saffron's potential medicinal uses.

Depression

To date, five published randomized controlled trials have been published about effects of saffron on depression. The first evidence-based study on this subject was published in 2004 showing that saffron was as efficacious as imipramine in the short-term treatment of mild to moderate depression in adults [2]. Importantly, saffron was more tolerable than imipramine (which often causes anticholinergic side effects). Subsequently, saffron was compared to placebo in a six-week randomized controlled trial of 40 adult patients with mild to moderate depression. Saffron resulted in about 12-point reduction on Hamilton depression rating scale (HDRS) compared with only five points seen with the placebo. Tolerability profile of saffron was similar to the placebo [3]. Later, several studies provided evidence for antidepressant effects of different *Crocus sativus* L. constituents compared with both placebo and fluoxetine. Both petal and stigma of *Crocus sativus* L. have shown beneficial effects for treatment of depression [3, 4]. The mechanism of action of antidepressant effects of saffron is not clearly understood. However, reuptake inhibition of monoamines, NMDA antagonism, and possibly improved BDNF signaling might be implicated in its mechanism of action [5, 6]. In summary, saffron extract with a dose of 20 mg twice daily, seems to be as efficacious and tolerable as fluoxetine for short-term treatment of mild to moderate depression [7]. Long-term studies for comparison of relapse rates are still lacking. Interestingly, saffron does not cause sexual side effects generally associated with fluoxetine use; indeed it can prevent or treat some aspects of fluoxetine induced sexual impairment [8].

Anxiety and sleep problems

Published studies on anti-anxiety effects of saffron are limited to animal experiments [9, 10]. Activation of GABA-A receptors might explain the anxiolytic effects of saffron [11].

Animal studies also demonstrated improvement of non-rapid eye movement (non-REM) sleep following safranal and crocin administration in mice [12, 13]. Safranal enhanced non-REM sleep probably by activation of the sleep center in the ventrolateral preoptic nucleus and the inhibition of the histaminergic tuberomammillary nuclei [12].

Reproductive and sexual problems

The only clinical trial on the effect of saffron on premenstrual syndrome showed that use of saffron 15 mg twice daily for two menstrual cycles was significantly more effective than placebo in improvement of depression and premenstrual daily symptoms [14]. In an open label study, saffron odor reduced cortisol levels and anxiety, and increased estrogen levels in both follicular and luteal phases [15]. A clinical trial compared the effect of placebo, mefenamic acid, and an herbal drug (composed of saffron, celery seed, and anise) on primary dysmenorrhea in young women. After two or three cycles, patients in the herbal drug group reported significantly lower pain scores than patients in other groups [16].

Traditionally, saffron was thought to improve sexual functioning. From an evidence-based point of view, *Crocus sativus* L. and its constituents improved all components of sexual function in male rats [17]. Administration of high dose of saffron (200 mg/day) for ten days to 20 patients with erectile dysfunction, significantly improved nocturnal penile tumescence as well as score on the international index of erectile function (IIEF) questionnaire [18]. In a recent study, saffron 15 mg twice daily was used to treat fluoxetine-induced sexual dysfunction in male patients with major depression. The authors found significant improvement in the erectile function and intercourse satisfaction (but not desire and orgasmic function) domains of IIEF in the saffron group. Sixty percent of patients in the saffron group compared with only 7% of patients in the placebo group achieved normal erectile function at the end of the study [8]. In a parallel safety study on the same patients, saffron did not affect liver, kidney, and blood tests. Moreover, frequency of adverse events in the saffron group was similar to that of the placebo [19]. In a similar study which was carried out on women with fluoxetine-associated sexual dysfunction, saffron resulted in improvement of arousal, pain and lubrication domains while it did not affect satisfaction, orgasm, and desire (under review).

Neurotoxicity and Alzheimer's disease

Several constituents of saffron including safranal, crocin, crocetin, and carotenoids have shown neuroprotective properties in animal models of ischemic, oxidative, traumatic, and inflammatory brain injury. Among several constituent of saffron, crocin showed the highest neuroprotective activity in one study. The neuroprotective activity of crocin is probably secondary to enhancement of glutathione (GSH) synthesis through increasing expression of gamma-glutamylcysteinyl synthase (gamma-GCS). In

a hemi-parkinsonian mouse model, crocetin pretreatment preserved levels of GSH, dopamine, and activity of antioxidant enzymes, and protected neurons of substantia nigra [21].

Crocus sativus L. is increasingly being studied as a memory enhancer. Saffron can attenuate the deleterious effect of ethanol on memory registration and retrieval, and prevent ethanol-induced inhibition of hippocampal long-term potentiation [23, 24]. Crocin seems to be involved in spatial memory and recognition and blocked scopolamine-induced performance deficits in the step-through passive avoidance and radial water maze tests [25, 26]. Saffron showed similar protective effects on recognition and spatial memory in chronic stress and hypoperfusion models of memory impairment [27, 28].

In an animal model of AD induced by intraventricular injection of streptozocin, Khalili et al. showed that administration of crocin resulted in significantly better results in passive avoidance test [29]. In a 16-week placebo-controlled study, 46 patients with mild to moderate AD were assigned to saffron 15 mg twice daily or placebo. At the end of the trial, saffron was associated with a significantly better outcome on cognitive function than placebo. Importantly, tolerability of saffron was similar to placebo [30]. In a 22-week donepezil-controlled study, saffron 15 mg twice daily was compared to donepezil 5 mg twice daily. Saffron was as efficacious as donepezil, but was associated with lower frequency of side effects than donepezil [31]. The mechanism of action of cognitive enhancement by saffron merits further consideration. Saffron seems to both antagonize glutamatergic activity on NMDA receptors (similar to memantine) [5,32,33] and to inhibit acetylcholinesterases (similar to donepezil) [34]. AD is associated with inflammatory activation in the brain as shown by several studies. Saffron (particularly its crocin and crocetin constituents) effectively inhibited glial activation induced by interferon and amyloid beta, and reduced levels of several inflammatory markers in the rat brain [37].

Adverse effects and toxicity

In a double-blind, placebo-controlled study, three groups of volunteers received placebo, 200 mg/day, or 400 mg/day saffron tablets for one week. High dose saffron reduced systolic blood pressure and mean arterial pressures significantly. Moreover, saffron slightly reduced or increased some hematological and biochemical parameters (hemoglobin, hematocrit, platelets, sodium, blood urea nitrogen and creatinine). None of the mentioned changes had clinical significance [39]. It should be emphasized that with the doses used in the clinical setting (usually less than 100 and often less than 60 mg/day) saffron is generally no less tolerable than placebo. A case of proven anaphylaxis following eating rice cooked with saffron has been reported. The authors recommended that saffron should be regarded as an allergen when investigating the causes of allergies.

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