Saffron a Prototype Example for Evidence Based Herbal Medicine

Hajiaghaee R (Ph.D.)[1], Heidari M (M.D.)[2], Akhondzadeh S (Ph.D.)[3]*

1- Pharmacognosy & Pharmaceutics Department of Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, Karaj, Iran
2- Iranian Academic Center for Education, Culture & Research (ACECR), Tehran, Iran
3- Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran
* Corresponding author: Psychiatric Research Center, Roozbeh Hospital, South Kargar Street, Tehran 13337, Iran
Tel: +98-21-88281866, Fax: +98-21-55419113
Email: s.akhond@neda.net

Received: 21 July 2013 **Accepted:** 5 Oct. 2013

Abstract

Evidence-based medicine is now generally perceived to be the dominant operating system in conventional medicine. Evidence-based medicine developed concurrently with the internet and the world wide web. This is no coincidence since evidence-based medicine suggests a personal responsibility for clinicians to keep abreast of research that would be difficult without the information access that the web provides. Over the last two decades, evidence based herbal medicine has been considered as interesting field. One of prototype example of evidence base medicine is saffron. In this paper, we review saffron from evidence point of view.

Keywords: **Alzheimer's disease, Depression, Evidence-based medicine, Saffron**

[Downloaded from jmp.ir on 2026-11-12]

[DOR: 20.1001.1.2717204.2013.12.47.2.7]

Evidence-based medicine (EBM) is now generally perceived to be the dominant operating system in conventional medicine. EBM developed concurrently with the internet and the world wide web. This is no coincidence since EBM suggests a personal responsibility for clinicians to keep abreast of research that would be difficult without the information access that the web provides. The term “evidence-based medicine” first appears in 1991, in a piece by Gordon Guyatt [1]. But EBM came to the attention of a wider audience in 1992 with an article by the Evidence-Based Medicine Working Group [2] that boldly proclaimed EBM as a “new paradigm” in medicine.

It is unsurprising then that some have counseled complementary and alternative medicine practitioners to resist EBM. The concept of EBM has been widely adopted by orthodox Western medicine. Proponents of EBM have argued that Complementary and Alternative Medicine (CAM) modalities ought to be subject to rigorous, controlled trials. However, this does not represent a scientific necessity, but rather is a philosophical demand: promoters of EBM seek to establish their particular epistemology as the primary arbiter of all medical knowledge. This claim is problematic. The methods for obtaining knowledge in a healing art must be coherent with that art’s understanding and theory of illness.

In the last century, western countries have seen a dramatic movement of the population away from the countryside into cities and towns. There has been a shift in the exposure and thus mind set of modern man away from the energetic natural world of nature that they experienced in the countryside into the more physical material world of towns and cities. This has happened in parallel with the development of science and the scientific way, along with a reduction or even discontinuance in the use of the human senses of touch, taste, smell and visual observation as a means of evaluating one's surroundings. There has been a similar shift in the mindset of Medicinal Herb Practitioners where in the practice of their herbal medicine they now focus on the herbal extract as being a liquid extract of a stated quantity of chemical compounds rather than it being a vibrant energetic extract of a living plant containing an 'extract' of the plant's vibrational essence including its chemicals.

As the basis for the practice of herbal medicine becomes more scientific in its approach, the question that needs to be asked is: is the practice direction in order to maximize the healing potential of herbal extracts and is this direction in the best interests of the patient? Or is it more to prove herbal medicines are therapeutically beneficial to governments and pharmaceutical companies?

The efficacy of medicinal herbs does need to be established and toxicity, contraindications and side effects also need to be investigated, and this is best done with clinical research and trials that at this time are being conducted almost exclusively on efficacy and are limited in number most probably because of funding. Very little to no

[Downloaded from jmp.ir on 2026-11-12]

[DOR: 20.1001.1.2717204.2013.12.47.2.7]

attention is being given to the more traditional fresh herbal extracts.

Many herbal medicines are now being supported by scientific evidence and have been shown to exert significant effects in the body, relieve symptoms, treat disease and improve everyday function. Any 'expert' who still states there's no scientific evidence to support the use of herbal medicines hasn't done their homework. One of prototype example is saffron (*Crocus sativus*) for Alzheimer's disease and depression.

Saffron is the world's most expensive spice, derived from the flower of *Crocus sativus*. The *Crocus sativus* is a grass-like and perennial plant that grows 20 to 30 cm high. There is a large squat tuber, surrounded by reticulate and fibrous sheaths. The leaves are erect or splayed, narrow, and have a ciliate margin and keel. Each saffron bears up to four flowers, each with three vivid crimson stigmas [3]. 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 [4, 5].

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 [6]. 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 [7]. 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 [6]. The mechanism of action of antidepressant effects of saffron is not clearly understood. However, reuptake inhibition of monoamines, glutamate antagonism, and possibly improved Brain Derived Neurotrophic factor signaling might be implicated in its mechanism of action [8, 9]. 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 [10]. 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 [11, 12].

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 [13, 14]. Among several constituent of saffron, crocin showed

[Downloaded from jmp.ir on 2026-11-12]

[DOR: 20.1001.1.2717204.2013.12.47.2.7]

the highest neuroprotective activity in one study. The neuroprotective activity of crocin is probably secondary to enhancement of glutathione synthesis through increasing expression of gamma-glutamylcysteinyl synthase. In a hemi-parkinsonian mouse model, crocetin pretreatment preserved levels of GSH, dopamine, and activity of antioxidant enzymes, and protected neurons of substantia nigra [15].

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 [16, 17]. 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 [18, 19]. Saffron showed similar protective effects on recognition and spatial memory in chronic stress and hypoperfusion models of memory impairment [20, 21].

In an animal model of Alzheimer's Disease (AD) induced by intraventricular injection of streptozocin, Khalili et al. showed that administration of crocin resulted in significantly better results in passive avoidance test [22]. 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 [23]. 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 [24]. 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) [25, 26] and to inhibit acetylcholinesterases (similar to donepezil) [27]. 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 [28, 29].

References

1. Guyatt, G. Evidence-based Medicine. *ACP J. Club.* 1991; 114 (supp. l2): A16.

2. Evidence-Based Medicine Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. *J. Am. Med. Assoc.* 1992; 268 (17): 2420 - 5.

3. Akhondzadeh S. Herbal medicine in the treatment of psychiatric and neurological Disorders. In: L'Abate L. Low Cost Approaches to Promote Physical and Mental Health: Theory Research and Practice. New York. 2007, pp: 119 - 38.

4. Akhondzadeh S and Abbasi SH. Herbal medicine in the treatment of Alzheimer's disease. *Am. J. Alzheimers Dis. Other Demen.* 2006; 21 (2): 113 - 8.

[Downloaded from jmp.ir on 2026-11-12]

[DOR: 20.1001.1.2717204.2013.12.47.2.7]

5. Agha-Hosseini M, Kashani L, Aleyaseen A, Ghoreishi A, Rahmanpour H, Zarrinara AR and Akhondzadeh S. *Crocus sativus* L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo controlled trial. *BJOG.* 2008; 115 (4): 515 - 9.

6. Akhondzadeh S, Fallah-Pour H, Afkham K, Jamshidi AH and Khalighi-Cigaroudi F. Comparison of *Crocus sativus* L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial [ISRCTN45683816]. *BMC Comp. Alt. Med.* 2004; 4: 12.

7. Akhondzadeh S, Tamacebi-pour N, Noorbala AA, Amini H, Fallah Pour H, Jamshidi AH and Khani M. *Crocus sativus* L. in the treatment of mild to moderate depression: A double-blind, randomized and placebo controlled trial. *Phytother. Res.* 2005; 19: 25 - 9.

8. Berger F, Hensel A, Nieber K. Saffron extract and trans-crocetin inhibit glutamatergic synaptic transmission in rat cortical brain slices. *Neuroscience* 2011; 180: 238 - 47.

9. Shimizu Y, Inoue E, Motegi J, Nonaka K, Noguchi T, Shoji M and Sudoh K. Pharmacological studies of Noukassei, a crude drug containing red ginseng, polygala root, saffron, antelope horn and agarwood - Antidepressant-like effect in the mouse forced swimming test. *Jap. Pharmacol. Therapeutics* 2011; 39 (6): 587 - 94.

10. Akhondzadeh Basti A, Moshiri E, Noorbala AA, Jamshidi AH, Abbasi SH and Akhondzadeh S. Comparison of petal of *Crocus sativus* L. and fluoxetine in the treatment of depressed outpatients: a pilot double-blind randomized trial. *Prog Neuropsychopharmacol. Biol. Psychiatry* 2007; 31: 439 - 42.

11. Modabbernia A, Sohrabi H, Nasehi AA, Raisi F, Saroukhani S, Jamshidi A, Tabrizi M, Ashrafi M and Akhondzadeh S. Effect of saffron on fluoxetine-induced sexual impairment in men: randomized double-blind placebo controlled trial. *Psychopharmacol.* 2012; 223 (4): 381 - 8.

12. Kashani L, Raisi F, Saroukhani S, Sohrabi H, Modabbernia A, Nasehi AA, Jamshidi A, Ashrafi M, Mansouri P, Ghaeli P and Akhondzadeh S. Saffron for treatment of fluoxetine-induced sexual dysfunction in women: randomized double-blind placebocontrolled study. *Hum Psychopharmacol.* 2013; 28 (1): 54 - 60.

13. Premkumar K, S.K. Abraham, S.T. Santhiya and A. Ramesh. Protective effects of saffron (*Crocus sativus* Linn.) on genotoxins-induced oxidative stress in Swiss albino mice. *Phytother Res.* 2003; 17 (6): 614 - 7.

14. Hosseinzadeh H and Sadeghnia HR. Safranal, a constituent of *Crocus sativus* (saffron), attenuated cerebral ischemia induced oxidative damage in rat hippocampus. *J. Pharm. Pharm. Sci.* 2005; 8 (3): 394 - 9.

15. Ahmad A.S., M.A. Ansari, M. Ahmad, S. Saleem, S. Yousuf, M. N. Hoda and F. Islam. 2005. Neuroprotection by crocetin in a hemi-parkinsonian rat model. *Pharmacol Biochem. Behav.* 2005; 81 (4): 805 - 13.

16. Zhang Y, Shoyama Y, Sugiura M, Saito H. Effects of *Crocus sativus* L. on the ethanolinduced impairment of passive

[Downloaded from jmp.ir on 2026-11-12]

[DOR: 20.1001.1.2717204.2013.12.47.2.7]

avoidance performances in mice. *Biol. Pharm. Bull.* 1994; 17 (2): 217 - 21.

17. Abe K, Saito H. Effects of saffron extract and its constituent crocin on learning behaviour and long-term potentiation. *Phytother. Res.* 2000; 14 (3): 149 - 52.

18. Pitsikas N, Sakellaridis N. *Crocus sativus* L. extracts antagonize memory impairments in different behavioural tasks in the rat. *Behav. Brain Res.* 2006; 173 (1): 112 - 5.

19. Pitsikas N, Zisopoulou S, Tarantilis PA, Kanakis CD, Polissiou MG and Sakellaridis N. Effects of the active constituents of *Crocus sativus* L., crocins on recognition and spatial rats' memory. *Behav. Brain Res.* 2007; 183 (2): 141 - 6.

20. Ghadrdoost, B, Vafaei AA, Rashidy-Pour A, Hajisoltani R, Bandegi AR, Motamedi F, Haghighi S, Sameni HR and Pahlvan S. Protective effects of saffron extract and its active constituent crocin against oxidative stress and spatial learning and memory deficits induced by chronic stress in rats. *Eur. J. Pharmacol.* 2011; 667 (1 -3): 222 - 9.

21. Hosseinzadeh H, Sadeghnia HR, Ghaeni FA, Motamedshariaty VS and Mohajeri SA. Effects of saffron (*Crocus sativus* L.) and its active constituent, crocin, on recognition and spatial memory after chronic cerebral hypoperfusion in rats. *Phytother. Res.* 2012; 26 (3): 381 - 6.

22. Khalili M and Hamzeh F. Effects of active constituents of *Crocus sativus* L., crocin on streptozocin-induced model of sporadic Alzheimer's disease in male rats. *Iran Biomed. J.* 2010; 14: (1 - 2): 59 - 65.

23. Akhondzadeh S, Sabet MS, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, Hejazi SSH, Yousefi MH, Alimardani R, Jamshidi A, Zare F and Moradi A. Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. *J. Clin. Pharm. Ther.* 2010; 35: 581 - 8.

24. Akhondzadeh S, Shafiee Sabet M, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, Hejazi SSH, Yousefi MH, Alimardani R, Jamshidi A, Rezazadeh SA, Yousefi A, Zare F, Moradi A and Vossoughi A. A 22-week, multicenter, randomized, double blind controlled trial of *Crocus sativus* in the treatment of mild-to-moderate Alzheimer's disease. *Psychopharmacology (Berl)* 2010; 207: 637 - 43.

25. Lechtenberg M, Schepmann D, Niehues M, Hellenbrand N, Wunsch B and Hensel A. Quality and functionality of saffron: quality control, species assortment and affinity of extract and isolated saffron compounds to NMDA and sigma1 (sigma-1) receptors. *Planta Med.* 2008; 74 (7): 764 - 72.

26. Ohno Y, Nakanishi T, Umigai N, Tsuruma K, Shimazawa M and Hara H. Oral administration of crocetin prevents inner retinal damage induced by N-methyl-d-aspartate in mice. *Eur. J. Pharmacol.* 2012; 690 (1 - 3): 84 - 9.

27. Geromichalos GD, Lamari FN, Papandreou MA, Trafalis DT, Margarity M, Papageorgiou A and Sinakos Z. Saffron as a source of novel acetylcholinesterase inhibitors: molecular docking and in vitro enzymatic studies. *J.*

[Downloaded from jmp.ir on 2026-11-12]

[DOR: 20.1001.1.2717204.2013.12.47.2.7]

Agric. Food Chem. 2012; 60 (24): 6131 - 8.

28. Akhondzadeh S. Hippocampal synaptic plasticity and cognition. *J. Clin. Pharm. Ther.* 1999; 24 (4): 241 - 8.

29. Nam KN, Park YM, Jung HJ, Lee JY, Min BD, Park SU, Jung WS, Cho KH, Park JH, Kang L, Hong JW and Lee EH. Antiinflammatory effects of crocin and crocetin in rat brain microglial cells. *Eur. J. Pharmacol.* 2010; 648 (1 - 3): 110 - 6.

[Downloaded from jmp.ir on 2026-11-12]

[DOR: 20.1001.1.2717204.2013.12.47.2.7]