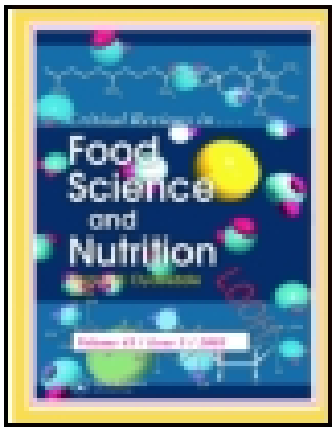

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Efficacy and Safety of Saffron Supplementation: Current Clinical Findings

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Efficacy and Safety of Saffron Supplementation: Current Clinical Findings

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Keywords

Saffron; Clinical Studies; Carotenoids; Antioxidant.

Abstract

Saffron (*Crocus savitus*) is a Middle-Eastern herb with strong antioxidant properties. Its major constituents, safranal, crocin and crocetin, are also antioxidants and bear structural similarities to other well known natural antixodant substances, such as zeaxanthin. Given the role of oxidative stress in many diseases, considerable interest has been shown into the potential role of saffron supplementation as a treatment for a range of diseases. *In vitro* and animal studies have provided evidence that saffron and its constituents may be potent therapies for a range of pathologies, including Alzheimerôs disease, age-related macular degeneration and cardiac ischaemia. Whether these findings translate into clinical efficacy, however, has as of yet been incompletely assessed. This makes assessing the role of saffron supplementation in these diseases difficult. Here, we review the current human clinical evidence supporting saffron supplementation as a treatment for a range of pathologies and the underlying science supporting its use.

Introduction

The spice saffron, derived from the herb *Crocus sativus,* has been used as a dye and to flavour foodstuffs for millennia. Saffron has also been employed in many cultures as a traditional medicine for a range of conditions, including urinary tract infections and to assist with childbirth (Javadi, et al. 2013, Lev and Amar 2008). The spice contains a number of chemical entities, which have been demonstrated to have powerful antioxidant capabilities (Assimopoulou, et al. 2005, Ordoudi, et al. 2009). Recently there has been expanding interest in the potential medicinal applications of many of these molecules. Although much work has been done on the use of saffron-based compounds in cellular and animal models of disease, little is known about the efficacy and safety of these agents *in vivo*. This is a review of the clinical evidence regarding saffron supplementation as a potential treatment, and the science underpinning the role of saffron in these conditions.

Chemistry

Saffron contains over 150 potentially biologically active agents, including a range of carotenoids (Bathaie and Mousavi 2010). These molecules are named for their pigmentary abilities, and are powerful antioxidants. Other carotenoids, including beta-carotene and lutein, have been investigated as treatments for a range of diseases such as age-related macular degeneration (AMD) due to their antioxidant potential (2013). The most well studied components of saffron are crocetin, crocin and safranal, all of which are well characterised (Figure 1). Crocetin, safranal and other phenolic components of saffron have been shown to have significant antioxidant potential by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay (Kanakis, et al. 2007, Karimi, et al. 2010), and collectively the activity of the multiple active compounds in saffron (Figure 2) make

it a powerful antioxidant (Kanakis, Tarantilis, Tajmir-Riahi and Polissiou 2007). Some of these compounds, notably crocetin, are also found in other medicinal herbs such as *Gardenia jasminoides,* and may be responsible for the medicinal properties of these plants (Kuratsune, et al. 2010).

Safranal (2, 6, 6-trimethyl-1, 3-cyclohexadien-1-carboxaldehyde) is thought to be responsible for saffronôs odour (Tarantilis 1997), and is formed via enzymatic hydrolysis of picrocrocin (4-glucopyranosyloxy-2,6,6-trimethyl-1-cyclohexene-1-carboxaldehyde), often during the preparation and drying process that occurs following saffron harvest (Himeno 1987). This reaction can also occur under the influence of acid or base catalysis (Pfander 1982). Picrocrocins are a family of structurally similar glycoside molecules responsible for the bitter taste of saffron.

It is thought that both crocetin (2, 6, 11, 15-tetramethylhexadeca-2, 4, 6, 8, 10, 12, 14-heptaenenedioic acid) and picrocrocins themselves are formed via enzymatic degradation of zeaxanthin (Pfander 1982). There has been considerable recent interest in zeaxanthin as a potential treatment for a range of conditions including AMD (2013), largely as a result of its antioxidant properties.

Crocin (a digentobiose of crocetin) and other crocin-like esters are largely responsible for the characteristic colour of saffron (Pfister 1996). The different crocin molecules vary largely in relation to the nature of the attached sugar moieties, with different light absorption properties noted for these (Pfister 1996).

A number of other carotenoid components are also found in saffron, although they constitute a relatively minor component of the total mass of saffron (Pfander 1982, Winterhalter 2001). Some of these, notably zeaxanthin as mentioned above, have been studied as possible future therapies.

However, as they are not thought to form a significant component of saffron or its biological activity, they will not be reviewed in detail here.

Therapeutic Applications

Due to the strong antioxidant potential of many of the chemical constituents of saffron, supplementation therapy has been investigated as a possible treatment for disease processes involving increased oxidative stress. Some of these pathologies, such as ischaemia-reperfusion injuries in cerebral or hepatic tissues, or malignancies, have currently only been investigated in cellular or animal models (Ochiai, et al. 2007, Pan, et al. 2013, Yan, et al. 2010, Zhang, et al. 2013). Those conditions where saffron supplementation has been tested in human clinical trials are detailed below (see Table 1 for summary).

Cognition

Many neurodegenerative processes are thought to involve increased oxidative stress. Of these, the most common condition globally is Alzheimerôs disease, which is believed to involve immune-mediated oxidative damage to CNS tissue, resulting in decreased cognitive function. There is some evidence that saffron extracts may inhibit beta-amyloid aggregation in animal models, a key step in the pathogenesis of Alzheimerôs disease (Papandreou, et al. 2006). Crocin has been shown to be effective in preventing amyloid plaque formation (Ghahghaei, et al. 2013), and *in vitro* also prevented the formation of neurofibrillary tangles, another key histological marker of Alzheimerôs disease (Ebrahim-Habibi, et al. 2010, Papandreou, Kanakis, Polissiou, Efthimiopoulos, Cordopatis, Margarity and Lamari 2006). Safranal also possesses some activity in this regard, although appears less efficacious that crocin (Ebrahim-Habibi, Amininasab, Ebrahim-Habibi, Sabbaghian and Nemat-Gorgani 2010). Saffron supplementation has also been

shown to improve memory in both normal rats and those with scopolamine-induced memory impairment (Pitsikas and Sakellaridis 2006), as well as benefiting memory in streptozocin-induced rat models of diabetic cerebral disease (Tamaddonfard, et al. 2013) and Alzheimerôs disease (Khalili and Hamzeh 2010). This may be related to protection of substantia niagra cells, with recent research showing that saffron treatment may preserve these cells in animal models of Alzheimerôs (Purushothuman, et al. 2013) and Parkinsonôs Disease (Ahmad, et al. 2005). Molecular docking and enzymatic studies have suggested that safranal and crocetin bind acetylcholinesterase with inhibitory effects, which is a similar mechanism to currently used pharmaceuticals (Geromichalos, et al. 2012) for Alzheimerôs disease such as donepezil.

Based on such findings, two small clinical studies have been conducted to assess the efficacy of saffron in Alzheimerôs Disease. Compared to placebo, 30 mg saffron supplementation daily for 16 weeks resulted in improved cognitive function (change in both Alzheimerôs Disease Scale-cognitive subscale (ADAS-cog) and Clinical dementia ratings-scale sums of boxes (CDR-SB) significant, $p<0.0001$ for both) (Akhondzadeh, et al. 2010a). Follow-up of this study comparing saffron (30 mg/day) to donepezil therapy (10 mg/day) for mild to moderate Alzheimerôs disease suggested that saffron was non-inferior for maintaining cognitive function (change in both ADAS-cog and CDR-SB non-significant between groups, $p>0.05$) (Akhondzadeh, et al. 2010b).

There is also evidence that saffron and its constituents may be beneficial in promoting sleep. In barbiturate-treated mice, safranal, crocin and crocetin have been shown to increase the length of non-rapid eye movement (NREM) sleep (Liu, et al. 2012, Masaki, et al. 2012). There is some discrepancy regarding the efficacy of crocin, with different results regarding its hypnotic ability demonstrated in animal models of sleep disorders (Hosseinzadeh and Noraei 2009, Masaki,

Aritake, Tanaka, Shoyama, Huang and Urade 2012). Examination of safranal-treated mice showed increased c-Fos expression in sleep centres including the ventrolateral preoptic nucleus (VLPO) and decreased expression in arousal centres such as the tuberomamillary nuclei (Liu, Xu, Liu, Hong, Urade, Huang and Qu 2012). Saffron may thus affect sleep by both promoting and decreasing arousal, although given the discrepencies in efficacy. Further research is required to clarify this.

Crocetin has also been trialled as a therapy for sleep complaints, although the crocetin for this study was sourced from *Gardenia jasminoides*, not saffron. In a double-blind, placebo-controlled trial of 21 males with mild sleep complaints, crocetin improved both objective (actigraph) and subjective measures of sleep quality ($p=0.025$ for reduction in waking episodes compared to placebo) (Kuratsune, Umigai, Takeno, Kajimoto and Nakano 2010). The success of using crocetin from non-saffron sources suggests that these may offer cheaper alternative means of sourcing some saffron-based compounds for future therapeutic use.

Mood

Saffronôs effects on mood have also been investigated. Both molecular binding studies (Lechtenberg, et al. 2008) and rat models of synaptic transmission(Berger, et al. 2011) have shown that crocetin and other crocetin-based molecules bind NMDA receptors. In rat models these compounds have antagonist activity at these sites, potentially affecting CNS function and mood (Berger, Hensel and Nieber 2011). This has also been investigated in clinical studies. Two small, 6-week trials have compared 30 mg/daily saffron to placebo for the treatment of mild-moderate depression, with significant improvements in the Hamilton depression scale noted with saffron therapy (Akhondzadeh, et al. 2005, Moshiri, et al. 2006). These have been followed by

two other trials comparing saffron to currently used antidepressants. One 6-week study compared the same dose of saffron to imipramine (100 mg/daily) and another 9-week trial compared 30mg/daily saffron to 10 mg/daily fluoxetine. Both trials demonstrated non-inferiority of saffron in treating mild-moderate depression as measured by the Hamilton depression scale (Akhondzadeh Basti, et al. 2007, Akhondzadeh, et al. 2004).

Saffron extract has also been shown to reduce snacking frequency in overweight women compared to placebo over an 8-week period, and this was associated with significant body weight reduction compared to placebo over the same period (0.96 kg weight loss with saffron extract, $p<0.05$ compared to placebo) (Gout, et al. 2010). The mechanism underlying this is unknown, however may to relate to the activity of saffron on the CNS described above (Gout, Bourges and Paineau-Dubreuil 2010).

The effect of saffron in other psychiatric conditions, including anxiety, substance withdrawal and obsessive-compulsive disorder, has as yet been studied only in animal models (Georgiadou, et al. 2012, Hosseinzadeh and Jahanian 2010, Hosseinzadeh and Noraei 2009, Pitsikas, et al. 2008), and awaits further assessment via clinical trials in human patients.

Vision

The effect of saffron on disorders of vision has been studied *in vitro*. In rabbits, topical saffron extract improved retinal blood flow (Xuan, et al. 1999), and in rat models of cataract, saffron protected against cataractogenesis via enhancing levels of natural antioxidants including superoxide disumatase (SOD), glutathione (GSH) and GSH peroxidase in the lens (Makri, et al. 2013). Saffron has also been investigated in degenerative retinal diseases such as Retinitis pigmentosa (RP), with oral saffron supplementation resulting in stabilisation of

electroretinogram (ERG) findings and immunohistochemical evidence of delay in disease progression in rat models (Fernandez-Sanchez, et al. 2012, Maccarone, et al. 2008). Saffron and safranal supplementation have both also been shown to preserve retinal morphology and neuronal integrity in animal models of RP and light-induced retinal damage (Fernandez-Sanchez, Lax, Esquiva, Martin-Nieto, Pinilla and Cuenca 2012, Maccarone, Di Marco and Bisti 2008). It is thought the underlying mechanism of saffron in retinal disease may relate to the prevention of oxidative damage and resultant cellular apoptosis by antioxidants such as saffranal (Fernandez-Sanchez, Lax, Esquiva, Martin-Nieto, Pinilla and Cuenca 2012), possibly by reducing peroxide induced oxidative damage and inhibition of caspase-mediated apoptosis(Ohno, et al. 2012, Yamauchi, et al. 2011). Supplementation with other antioxidants such as Vitamin A in some inherited retinal degenerations, such as Stargardtôs disease, has been associated with accelerated retinal decline in mice models (Radu, et al. 2008). For this reason dietary supplementation (including with saffron) in retinal degeneration is recommended to occur in conjunction with ophthalmological review.

Promising results have also been observed in small clinical studies in humans. The most common degenerative retinal condition worldwide is AMD, a disease that is thought to involve immune-mediated oxidative damage to retinal tissue. Saffron supplementation has been shown to delay improve focal ERG (fERG) findings in one small placebo-controlled study of patients with AMD (change in fERG amplitude 0.25 log uV vs -0.003 log uV, $p<0.01$) (Falsini, et al. 2010). Longer-term follow-up of these patients demonstrated ongoing saffron supplementation improved visual acuity and fERG parameters, potentially delaying disease progression (Piccardi,

et al. 2012). These gains appear to be independent of the presence of known óat-riskô genotypes for AMD (Marangoni, et al. 2013).

Reproductive Disease

Herbal remedies, including saffron, have been used in many regions of the world as treatments for disorders of gynaecology and urology. The potential efficacy of saffron in this setting may relate to oxidative-stress mediated mechanisms of disease underlying some of these disorders (Heidary, et al. 2008), and there is some evidence from rat studies that crocin and saffron extract, but not safranal, may have aphrodisiac effects in male animals (Hosseinzadeh, et al. 2008). Saffron supplementation has formally been trialled as therapy for a number of these conditions, including primary dysmenorrhea, premenstrual tension (PMS) and erectile dysfunction (ED).

In primary dysmenorrhea, Saffron supplementation has shown encouraging therapeutic results. In a trial of 180 female patients, a 500 mg combination of saffron, celery seed and anise (SCA) given three times daily for three days for two to three menstrual cycles, was shown to reduce pain with similar efficacy as a commonly used treatment for primary dysmenorrhea (mefenamic acid) compared to placebo (2.9 point reduction in pain scores for SCA, $p<0.001$ and 2.45 point reduction in pain scores for mefenamic acid, $p<0.01$) (Nahid, et al. 2009).

In women with symptoms of PMS, supplementation with 30mg/day saffron for two menstrual cycles resulted in improvement of symptoms as measured by Daily Symptoms Report and Hamilton Depression Rating Scale compared to placebo (difference between two groups on both measures significant, $df = 48$, $p<0.001$ for both) (Agha-Hosseini, et al. 2008). Further investigations of the effect of saffron odour on hormone levels in women demonstrated increased 17-B estradiol and reduced levels of cortisol, as well as reduced stress as measured by State-Trait

Anxiety Inventory (STAI) Scores even after adjusting for phase in the reproductive cycle(Fukui, et al. 2011). Given that cortisol levels are a biomarker of psychological stress, changes in stress levels have been hypothesized to account for some of the improvement in symptoms of PMS (Fukui, Toyoshima and Komaki 2011). It may also account for some of the other improvements in mood following saffron supplementation discussed above.

A number of small trials have also investigated the role of saffron in treating disorders of sexual function in human subjects. Two small, 4-week, placebo-controlled trials of saffron as a treatment for fluoxetine-induced sexual dysfunction in men and women showed that it was of benefit in reducing overall sexual dysfunction in both genders. Men experienced greater erectile function and intercourse satisfaction, whilst women achieved greater arousal and reduced pain with saffron supplements (Kashani, et al. 2013, Modabbernia, et al. 2012). Further follow up of these studies has not been conducted, however research into the role of saffron in other disorders of sexual function, such as ED is detailed below.

In men with ED a pilot study of 200mg/daily saffron supplementation for 10 days showed improved International Index of Erectile Function questionnaire scores (IIEF), (change in score 17.05, $p<0.001$) (Shamsa, et al. 2009). However, a larger scale 12-week trial comparing sildenafil to saffron for ED showed no difference in IIEF scores, or Sexual Encounter Profile questionnaires. Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) scores and Global Efficacy Question outcomes were more effective for sildenafil than saffron (72.4 vs 25.4 for sildenafil vs saffron, positive GEQ response 91.2% vs 4.2% for sildenafil vs saffron, both $p<0.01$) (Safarinejad, et al. 2010). The results of this larger study indicate that saffron is unlikely to be of significant benefit in ED.

Based upon the hypothesized role of oxidative damage in the pathogenesis of male infertility (Sanocka, et al. 1997), trials have also investigated the potential role of saffron in this condition. One small non-controlled trial in men with idiopathic infertility suggested that 50 mg saffron 3 times a week for 3 months improved sperm morphology and motility (change in percentage of sperm with normal morphology 7.4%, $p<0.001$) (Heidary, Vahhabi, Reza Nejadi, Delfan, Birjandi, Kaviani and Givrad 2008). A larger, randomised, placebo-controlled trial of 60 mg/daily saffron for 6 months in a similar patient group showed no difference in sperm count, morphology or motility between treatment groups ($p=0.1$ for difference between treatment groups for all parameters) (Safarinejad, et al. 2011). Taken in conjunction with the outcomes seen for saffron in ED, these results suggest that the role of saffron in treating disorders of reproduction in males is limited at best. It also highlights the need for preliminary results reported in smaller studies to be confirmed by larger, more rigorously designed trials.

Cardiovascular

Saffron has been investigated as a therapy for a range of cardiovascular disorders, including ischemia-reperfusion injuries (Joukar, et al. 2013) and arrhythmias such as atrial fibrillation (Khori, et al. 2012). In rat models, saffron decreased activity and tissue levels of biomarkers associated with myocardial infarction including creatine phosphokinase-MB (CK-MB) and lactate dehydrogenase (LDH) (Bharti, et al. 2012, Joukar, et al. 2010, Mehdizadeh, et al. 2013, Razavi, et al. 2013). It is thought this is due to both increased levels of antioxidants such as GSH and suppression of activation of inflammatory and apoptotic pathways including nuclear factor kappa-B (NFəB) and caspase mediated cell death (Bharti, Golechha, Kumari, Siddiqui and Arya 2012, Razavi, Hosseinzadeh, Movassaghi, Imenshahidi and Abnous 2013). There is some

evidence that Crocetin related inhibition of NFəB has been associated with decreased expression of endothelial vascular cellular adhesion molecules (VCAMs) involved in lipoprotein uptake (Zheng, et al. 2005). Thus far, this evidence supporting the use of saffron in the treatment of ischaemic cardiac disease and arrhythmic disorders has not been tested in human trials.

Animal studies have also suggested that saffron, as well as select saffron constituents such as crocin, are effective in reducing serum cholesterol and triglycerides in models of both Diabetes mellitus related and diet-induced hyperlipidaemia (Asdaq and Inamdar 2010, He, et al. 2007, Samarghandian, et al. 2013, Sheng, et al. 2006, Shirali, et al. 2013). Although the exact mechanism of action in treating hyperlipidaemia is unknown, there is some evidence that crocin and crocetin may reduce gastrointestinal cholesterol and fat absorption by acting as an inhibitor of pancreatic lipase (Lee, et al. 2005, Sheng, Qian, Zheng and Xi 2006). Both crocin and crocetin also appear to impair oxidation and endothelial uptake of modified lipid particles, potentially preventing atherosclerosis (He, et al. 2005, He, Qian, Wen, Tang, Xu and Zhou 2007, Zheng, et al. 2006). Similar pathways to those seen in the retina are partly implicated, with increased activity of SOD and other antioxidants noted in rabbit models of atherosclerosis (Zheng, Qian, Sheng and Wen 2006). Interestingly, one of the proposed mechanisms by which saffron prevented vascular endothelial dysfunction was through upregulation of nitric oxide (NO) synthesis (Tang, et al. 2006). This is also the suggested mechanism of action of saffron on the AV node in atrial fibrillation, suggesting that this may be a common mode of action for saffron in cardiovascular disorders (Khori, Alizadeh, Yazdi, Rakhshan, Mirabbasi, Changizi, Mazandarani and Nayebpour 2012).

A single, short duration trial has investigated saffron in lipid metabolism and arterial disease. Oral consumption of 50 mg saffron dissolved in 100 mL milk daily for 6 weeks was undertaken in 10 healthy participants and to 10 patients with coronary artery disease, and these results were compared to 10 control patients consuming milk only. Both intervention groups experienced a significant reduction in lipoprotein oxidation susceptibility (reduction from 66.4 to 38.3 units in healthy participants, from 76.0 to 48.8 in patients with CAD, $p<0.001$ for both), whereas the control patients did not (Verma and Bordia 1998). Although promising, no further clinical studies are yet reported on saffron in coronary artery disease, and further investigation is required.

Toxicity

The safety of any potential supplementation therapy needs carefully evaluation to ensure that the potential adverse effects of therapy are well understood. Although saffron has been used as a foodstuff without complication for many centuries, much of the reported toxicity data for saffron is anecdotal at best. Doses up to 1.5g/daily are considered relatively safe, and harmful effects are reportedly encountered with doses >5g/day, with doses of 20g/daily considered a lethal dose (Schmidt, et al. 2007). There have been reports that doses of >10g/day have previously been used as an abortifactant, and that such doses may cause haematuria, as well as genitourinary and gastrointestinal bleeding (Schmidt, Betti and Hensel 2007). It is important to note that many reported adverse events may be due to consumption of ómeadow saffronô (*Cochicum autumnale)*, found commonly in Europe, which has a different botanical, biochemical and toxicity profile to *Crocus savitus* (Babu, et al. 2012, Schmidt, Betti and Hensel 2007).

Few studies have directly evaluated the safety of saffron, however. In healthy volunteers, supplementation with the saffron constituent crocin at dosages of 20 mg/daily over a period of 1 month did not produce any clinically evident adverse events compared to placebo, although decreases in serum amylase, mixed white blood cells and PTT were noted (Mohamadpour, et al. 2013). However, further placebo controlled-studies of dosages of saffron up to 400 mg daily for 1 week have not shown any differences in PT, APTT, fibrinogen, Factor VII and protein C or S levels (Ayatollahi, et al. 2013).

Similar placebo controlled studies in healthy male volunteers showed that supplementation with 100 mg daily for 6 weeks produced an increased serum IgG and IgM compared to placebo at week 3, but these levels returned to baseline at the end of 6 weeks. It also transiently reduced platelet counts and altered the percentage of monocytes and basophils compared to baseline, however these levels returned to baseline after 6 weeks (Kianbakht and Ghazavi 2011).

As a plant material, it is conceivable that saffron may produce allergies, and asthma, rhinoconjunctivitis and contact dermatitis have been reported in sensitised saffron workers (Feo, et al. 1997, Martinez, et al. 2007). A single case of anaphylaxis to saffron particles has been reported (Wuthrich, et al. 1997). These allergies may mechanistically involve IgE mediated reactivity to lipid transfer proteins (Gomez-Gomez, et al. 2010). Given the rarity of reports of adverse reactions and the considerable volume of saffron harvested and consumed each year, the overall allergenic potential of saffron is considered low, and this is supported by data from finger prick allergy tests (Lucas, et al. 2001, Moneret-Vautrin, et al. 2002).

Conclusions

Saffron, and its constituents such as crocetin and crocin, are effective in reducing damage mediated by reactive-oxygen species. Animal studies have suggested that these substances may be efficacious in treating a range of conditions, and possible molecular mechanisms have been identified for its potential efficacy in some human diseases. There is evidence from clinical trials that this research translates into measurable clinical benefits, such as in the treatment of depression or primary dysmenorrhea. Although promising results have been obtained from many of the clinical studies, the small size and short follow-up of many of these trials limits the conclusions that can be drawn from them. The use of saffron as a treatment is therefore a promising area of medicinal development that requires further research, and clinical trials are underway in a number of areas to further evaluate the role of saffron as a therapeutic agent.

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Table 1. Summary of published data relating to the use of saffron in clinical settings and the possible mechanisms underpinning its action.

Application	Constituents Tested	Subjects & Efficacy	Proposed Mechanism	Reference
Cognition				
• Alzheimerôs Disease	Saffron Safranal Crocin	Small human studies. Improved cognitive function. Rat models. Improved memory.	Decreased neurofibrillary tangle and amyloid plaque formation. Possible acetylcholinesterase inhibitor activity.	Ghahghaei et al. (2013) Geromichalos et al. (2012) Akhondzadeh et al. (2010). Papendreou et al. (2006)
• Sleep	Crocetin Safranal Crocin	Small human trial. Improved sleep quality. Mice models. Increased sleep time but no change in REM sleep time.	Decreased activity at CNS arousal centres and increased function of sleep centres.	Kuratsune et al. (2010). Liu et al. (2012).
Mood				
• Depression	Saffron	Small human studies. Improvement in depression scores.	Inhibition of NMDA-based CNS signal transmission.	Akhondzadeh et al. (2007) and Akhondzadeh et al. (2004). Berger et al. (2011)
• Snacking Frequency	Saffron	Rat Models. Small human trial. Weight loss.		Gout et al.

				(2010).
Vision • Cataract • Age-Related Macular Degeneration	Saffron Saffron Safranal	Rabbit models. Decreased rate of cataract formation. Small human trials. Improvement in retinal electrophysiology and vision. Rat models. Improved retinal electrophysiology.	Increased GSH, GSH peroxidase and SOD levels. Inhibition of caspases and decreased oxidative damage.	Makri et al. (2013) Falsini et al. (2010) Ohno et al. (2012) Yamuchi et al. (2011)
Reproductive Disease • Primary Dysmenorrhea • Premenstrual Tension • Erectile Dysfunction • Male Infertility	Saffron in a combination therapy Saffron Saffron Saffron	Human Study. Reduction in pain scores. Small human trial. Symptomatic Improvement. Human Studies. Not effective as therapy. Human Studies. Not effective as therapy.		Nahid et al. (2009) Agha-Hosseini et al. (2008) Safarinejad et al. (2010) Safarinejad et al. (2011)
Cardiac Disease • Arrhythmia	Saffron Extract	Rabbit models. Increased AV	Increased endogenous nitric	Khori et al. (2012)

• Ischaemic Injury • Coronary Artery Disease • Hyperlipidaemia	Saffron Crocetin Crocin Crocetin Saffron Crocin Crocetin	node refractoriness. Rat Models. Decreased blood and tissue levels of biomarkers of ischaemia (creatine kinase, troponin) Rabbit Models. Decreased progression of atherosclerosis. Small human trial. Decreased lipoprotein oxidation susceptibility. Rat Models. Decreased serum lipid and triglyceride levels.	oxide synthesis. Increased GSH and antioxidant levels; decreased caspase and nuclear factor kappa-beta (NF-KB) activity Increased endogenous nitric oxide synthesis. Increased SOD function. Decreased lipoprotein oxidation and uptake. Decrease pancreatic lipase function.	 Ravazi et al. (2013) Bharti et al. (2012) He at al. (2007) Zheng et al. (2006) Tang et al. (2006) Verma et al. (1998) Sheng et al. (2006) Lee et al. (2005)

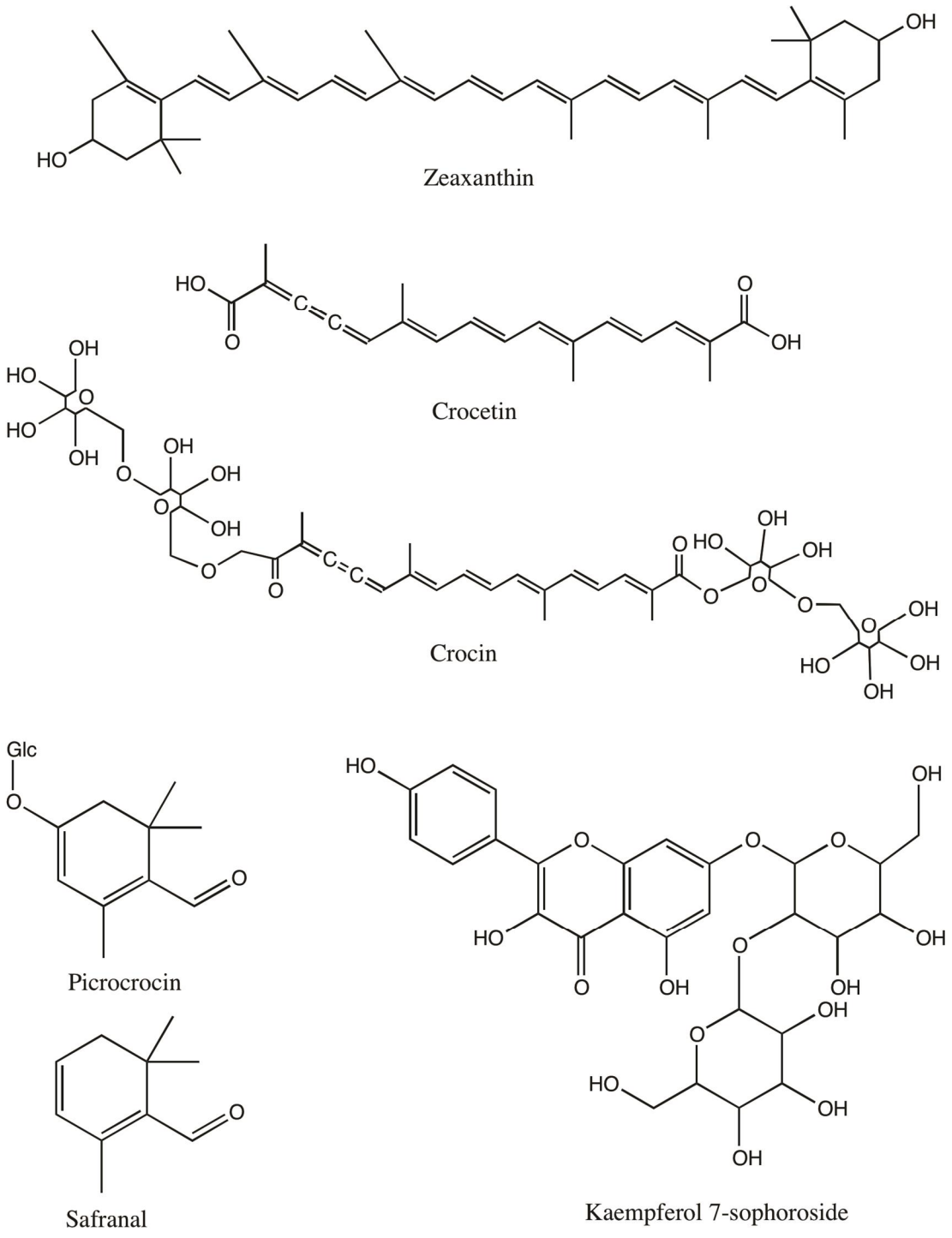

Figure 1. Structure of significant chemical constituents of saffron with known therapeutic activity.

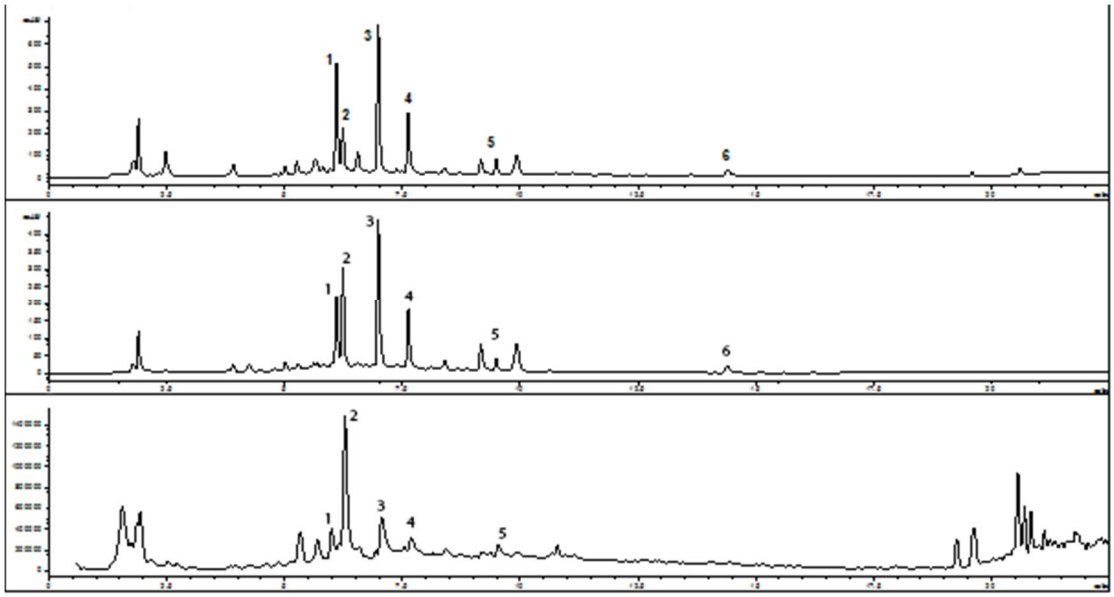

Figure 2. Ultraviolet-visible light spectrograph and mass spectrograph data for saffron. From top to bottom 210 nm, 280 m, and mass spectrography Total Ion Content profiles for saffron. Peaks associated with major constituents are numbered as follows: 1) Kaempferol diglycoside, 2) picrocrocin, 3) Ŭ-crocin, 4) crocin, 5) mixed crocins 6) safranal.