



PRACTICE POINTS

- The stigmas of saffron are rich in bioactive compounds that exhibit a broad range of pharmacological actions and clinical applications.1
- Primary clinical applications include anxiety, mild-to-moderate depression, and insomnia.²⁻⁵
- Secondary clinical applications include age-related macular degeneration,⁶⁻⁹ asthma,^{10,11} hypertension,¹² dyslipidaemia,¹³ type 2 diabetes mellitus (T2DM),14 and blood glucose control15
- Supplemental saffron is well-tolerated and has a good safety profile¹⁶

OVERVIEW

- Saffron is a deep yellow-coloured, aromatic spice derived from the stigmas of the flowers of Crocus sativus L. a plant native to Europe, the Middle East and North Africa.
- It has been traditionally used as an antidepressant, hypnotic, anti-inflammatory, hepatoprotective, bronchodilator, and aphrodisiac.

Culinary vs. medicinal saffron: what's the difference?

Quality: Medicinal saffron is typically a higher grade, with strict standards on concentration of bioactive compounds to ensure efficacy.

Purity: Medicinal saffron is more rigorously tested for contaminants or adulterants.

Efficacy: Culinary saffron is poorly absorbed. Medicinal saffron has been formulated to enhance absorption to enable its therapeutic action in the body.

SAFFRON & ITS MAIN BIOACTIVE COMPOUNDS

- The stigmas of saffron are rich in bioactive phytochemical compounds, with the most studied being crocin and crocetin (carotenoids), safranal (terpene) and picrocrocin (glycoside).¹
- Crocin and crocetin are derived from zeaxanthin and give saffron its deep yellow colour, whilst picrocrotin and safranal • give saffron its unique taste and aroma, respectively.1



- Anti-inflammatory Antihypertensive
- Antioxidant
- Analgesic
 - (antinociceptive)
- Anticonvulsant
- Antidepressant
- Antihyperglycemic
- - Antimicrobial
 - Anxiolytic
 - Cardioprotective
- Hepatoprotective
- Neuroprotective
- Ocular protective

Figure 1: The main bioactive compounds in saffron and their pharmacological actions.¹⁷

ACTIONS & BENEFITS

Mechanisms of action of crocetin, crocin and safranal on sleep, stress & mood.

Inhibits reuptake of serotonin, dopamine and noradrenalin

- Inhibits the reuptake of serotonin, increasing its availability in the brain, by a mechanism which is not yet fully understood¹⁸
- Modulates the production of dopamine and noradrenalin, contributing to enhanced mood and motivation¹⁸

Increases GABA receptor activity

 Enhances gamma aminobutyric acid (GABA) activity through its action as a GABA_A receptor agonist. GABA is the brain's main inhibitory neurotransmitter and is responsible for producing a calming, anxiolytic effect¹⁸

Stimulates endogenous melatonin production

 affron[®] a standardised extract of saffron, increases the availability of tryptophan, enhancing its conversion to melatonin via serotonin, positively influencing sleep quality²⁰

Modulates HPA activity

 Modulates activity of the hypothalamic-pituitaryadrenal (HPA) axis by decreasing cortisol levels¹⁹

Increases BDNF expression

 Increases the expression of brain-derived neurotrophic factor (BDNF), a molecule that plays a key role in learning, memory and mood regulation. Levels of BDNF are often reduced in individuals with depression¹⁸

Reduces NMDA receptor activity

 Inhibits N-methyl-D-aspartate (NMDA) receptor activity, conferring a neuroprotective effect.
Overactivation of NMDA receptors has been linked to neuroinflammation, which is associated with anxiety and depression¹⁸

Anti-inflammatory and antioxidant

 Depression is linked to inflammation and oxidative stress. Saffron reduces neuroinflammation and protects neurons from oxidative stress²¹

These actions have been observed when all three constituents are present and may result from either a single factor or a combination of factors.





ABSORPTION AND BIOAVAILABILITY



The bioactive compounds in saffron are unstable which impacts their intestinal absorption and bioavailability. Factors such as processing, heat and exposure to air affect their stability.²² Picrocrocin for example, rapidly breaks down to safranal on exposure to air,23 and crocin also exhibits low stability in the digestive tract.²⁴ As a result, the available bioactive compounds from unformulated saffron are greatly reduced. To overcome this, a specialised extraction technology has been developed, which uniquely concentrates and stabilises the bioactive compounds in a natural way, improving their absorption and bioavailability.²⁵



Standardised, premium grade saffron

Aff®ON Cool-Tech technology concentrates, preserves and stabilises bioactive compounds known as Lepticrosalides®

Standardised to ≥3.5% Lepticrosalides[®] including crocin and safranal

Enhanced absorbtion

Clinically trialled



Figure 2: The bioavailability and absorption of crocetin from unformulated saffron vs affron®. Oral crocin needs to be hydrolysed and converted crocetin, the active form of crocin in the body, before being absorbed. Crocetin from affron® is more rapidly absorbed and is detected in the plasma one hour after administration.²

AFFRON®: A SUMMARY OF CLINICAL EVIDENCE

Sleep

RANDOMISED CONTROLLED TRIAL	OUTCOMES
Healthy adults (n=55) with self-reported sleep complaints, 14 mg twice daily for 28 days. $^{\scriptscriptstyle 5}$	Improved sleep quality compared to placebo.
Healthy adults (n=120) with unsatisfactory sleep, 14 mg or 28 mg 1 hour before bedtime for 28 days. ³	Both doses showed greater improvements in sleep quality and mood after awakening compared to placebo. affron [®] use was associated with higher evening melatonin.

Mood and anxiety

RANDOMISED CONTROLLED TRIAL	OUTCOMES
Healthy adults (n=128) with self-reported low mood, 28 mg daily for 4 weeks. ²⁶	Improved mood and reduced symptoms associated with stress and anxiety compared to placebo. Mild sleep improvement was also reported.
Teenagers 12 - 16 years (n=68), with mild-to-moderate anxiety or depressive symptoms, 14 mg twice daily for 8 weeks. ²	Improved symptoms of anxiety and depression compared to placebo, based on self-reports.
Menopausal symptoms in adult perimenopausal females (n=82), 14 mg twice daily for 12 weeks. ²⁷	Greater improvements in psychological symptoms including occasional anxiety, low mood and negative thoughts, compared to placebo.
Adults (n=139) with persistent depression taking antidepressant medication, 14 mg twice daily for 8 weeks. ⁴	Adjunctive administration was associated with a greater improvement in depressive symptoms compared to placebo, based on clinician-rated reports but not patient self-reports. 3

INTERACTIONS & SAFETY



Medication-Saffron Interactions

MEDICATION	NATURE AND MECHANISM OF INTERACTION	EVIDENCE	LIKELIHOOD OF INTERACTION	SEVERITY OF OUTCOME	RECOMMENDATION
Antihypertensives	Saffron exhibits a very low antihypertensive effect and therefore may modestly increase the drug effect. ¹⁸	Meta-analysis	Possible	Low	Monitor the patient for signs of hypotension.
Antidepressants (SSRIs, tricyclic antidepressants)	Saffron exhibits antidepressant activity, similar to SSRI and tricyclic antidepressants and therefore may have an additive drug effect. ^{4,18}	Animal studies Lower quality human studies Randomised controlled trial	Possible	Moderate	Use with caution and monitor the patient for signs of serotonin syndrome.
Anxiolytics (benzodiazepines)	Saffron exhibits anxiolytic activity, similar to diazepam, and therefore may have an additive drug effect. ²⁸	Lower quality human study	Possible	Moderate	Use with caution and monitor the patient.
CYP1A2 substrates	May increase or decrease the drug effect. ²⁹	Lower quality human study	Possible	Variable (depending on drug and dose)	Use with caution and monitor the patient.
Hypoglycaemics	Saffron may lower blood glucose levels and therefore may have an additive drug effect. ¹⁵	Meta-analysis	Possible	Moderate	Monitor the patient for signs of hypoglycaemia.
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Safet	y	Side effects	F	Pregnancy an	d breastfeeding

Clinical studies report that saffron is safe to use at the doses and duration that are used in the studies.^{16,27}

Side effects

Clinical studies report that oral saffron is generally well-tolerated. Reported adverse effects include mild gastrointestinal symptoms which are not significantly different to placebo.16

Pregnancy and breastfeeding

Research indicates that saffron may induce uterine contractions,³¹ therefore it is not recommended to be used during pregnancy. There is insufficient evidence supporting the use of standardised extracts in breastfeeding.





Saffron and antidepressant medication

A randomised, double-blind, placebo-controlled study investigating the effects of affron® as an addon to antidepressant (SSRI and SNRI) medication for the treatment of persistent depressive symptoms in adults, found that saffron enhanced the effects of the antidepressant medication.⁴

PRESCRIBING GUIDE

Clinical evidence-based dosage guide for the prescribing of saffron supplements

CONDITION	LEVEL OF EVIDENCE	DOSAGE AND DURATION		
Age-related macular degeneration	В	Saffron extract:	20 mg/day for 3-12 months ⁶⁻⁹	
Alzheimer's disease (mild to moderate)	С	Saffron extract:	15 mg twice daily for 16 weeks ³¹	
Anxiety	В	Saffron extract: affron®:	30 mg/day for 4-12 weeks ³⁵ 14 mg twice daily for 8 weeks ²	
Asthma (allergic)	В	Saffron extract:	100 mg/day ^{10,11}	
Attention deficit hyperactivity disorder (ADHD)	В	Saffron extract:	15 mg twice daily, alongside conventional treatment for ADHD (methylphenidate 30 mg/day) ³²⁻³⁴	
Blood glucose control	A/B	Saffron extract:	15-200 mg/day for 8-12 weeks 15	
Depression (mild to moderate including mood support in perimenopause and mood disorder associated with irritable bowel syndrome)	В	Saffron extract: affron®:	30 mg/day for 4-12 weeks ^{27,35-37} 14 mg twice daily for 8-12 weeks ^{3,4}	
Hypertension	A/B	Saffron extract:	≥100 mg/day for 12 weeks ¹²	
Metabolic syndrome & obesity	С	Saffron extract:	30 mg/day ⁴⁰	
Premenstrual dysphoric disorder	В	Saffron extract:	15 mg twice daily for 2 weeks during the luteal phase of the menstrual cycle ⁴⁴	
Post-exercise muscle soreness	С	Saffron extract:	30 mg/day ⁴¹	
Primary open-angle glaucoma	В	Saffron extract:	20 mg/day for \ge 6 months ⁴²	
Rheumatoid arthritis	С	Saffron extract:	100 mg/day for 12 weeks ⁴³	
Sleep disturbance/dysfunction	В	Saffron extract: affron®:	30 mg/day ^{38,39} 14-28 mg daily, 1 hour before bed for 4 weeks ^{3,5}	

Evidence levels:

A: Meta-analysis and/or systematic review B: High quality clinical trial C: Good quality clinical trial

References

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