efpsa Journal of European Psychology Students

Khalil, S.A. (2022). Saffron as a Treatment for Mild to Moderate Depression: A Revision of Current Literature *Journal of European Psychology Students, 13*(1), 1–6. https://doi.org/10.5334/jeps.529

LITERATURE REVIEW

# Saffron as a Treatment for Mild to Moderate Depression: A Revision of Current Literature

Samera A. Khalil [1]

Mild to moderate depression (MMD) is becoming a health burden due to its increasing prevalence. Current treatment options are not effective in all patients. Hence, researchers have studied herbal options. It has emerged in research that saffron can be used for the treatment of MMD due to its anti-depressant properties. This literature review focussed on the treatment of MMD by comparing saffron to placebo and current antidepressants. Overall, research has shown that saffron reduces depression rating scores, but little is known about its safety and toxicity. Thus, this literature review concluded that there is inconsistent evidence to recommend saffron for the treatment of MMD. Further research is of high clinical need to resolve the growing burden of MMD.

**Keywords**: saffron, crocus sativus, antidepressants, mild depression, moderate depression.

Depression is a mental illness that significantly reduces the quality of life of patients, affecting on average 3.3 out of every 100 people in England (National Health Service [NHS] Digital, 2014). It leads to negative feelings, impacting on patients' social, emotional, and psychological well-being (Wells & Fisher, 2015).

Currently, there are a wide range of options for treating MMD. Although cognitive behaviour therapy (CBT) is considered the gold standard (Beck & Dozois, 2011), it can be a few months before patients have their first CBT appointment and hence, antidepressants are routinely prescribed by GPs (David, Cristea, & Hofmann, 2018). Interestingly, CBT was not recommended by the National Institute for Health and Care Excellence (NICE) approximately ten years ago (NICE, 2018). This reflects that guidelines can change drastically in the light of new robust research (Beck, 2011). Although CBT improves Hamilton Depression (HAM-D) scores of most patients, some argue that CBT does not address the underlying causes of depression and is associated with high rates of non-adherence (Lepping, 2017).

Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) can take four to five weeks to have an effect, and ineffectiveness in 30 to 40% of patients may lead to non-adherence (Rang, Ritter, Flower, & Henderson, 2016). Therefore, treatments for depression are an area of high clinical need because it places a huge burden on the healthcare services, as seen in Figure 1, due to increasing service demands and hospitalization (McCrone, 2008).

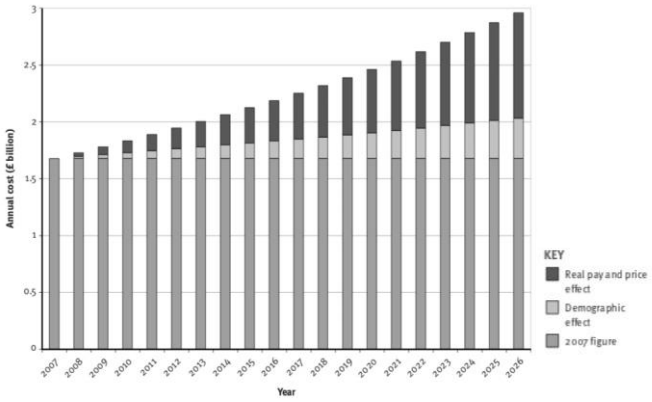
There is a need for a novel treatment that effectively treats MMD with less extensive side effects. Saffron (*crocus sativus*), a herbal medicine, falls into the category of complementary and alternative medicines (CAMs), due to its healing properties (Moazen-Zadeh et al., 2017), and has emerged as a possible emerging treatment for MMD. The study of herbal psychopharmacology, including saffron, has become increasingly significant in clinical investigations (Shafiee, Arekhi, Omranzadeh, & Sahebkar, 2018). The principles of CAMs are similar to that of NHS principles. They are as follows (Novey, 2000):

1. First identify and treat the root causes.
2. Prevention is better than cure.
3. Teach the patients healthier alternatives.
4. Do no harm to the patient.
5. Treat the patient as a whole.
6. CAMs uses the healing power of nature.

1 Hull York Medical School.
Corresponding author: Samera A. Khalil (samera.khalil@nhs.net)

**Figure 1**

*Cost of depression from 2007 and predicted costs until 2026 (McCrone, 2008)*




Note. Depression is an expensive disease and the cost figures are expected to continue rising. In 2007, the overall cost of depression in the UK was £1.7 billion. By 2026, this figure is expected to rise to £3 billion (McCrone, 2008).

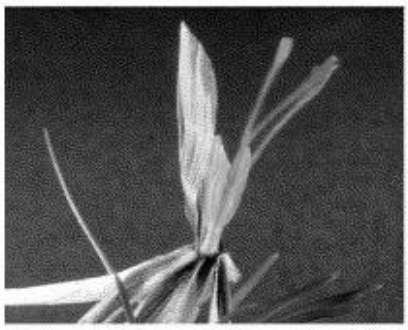
It is important to offer patients a choice in terms of orthodox and non-orthodox treatments. CAMs ensure that patients are at the centre of treatment, just like the NHS principles (Novey, 2000).

For many years, depression has been thought to be caused by an imbalance in neurotransmitters, which are the targets of antidepressants (Katzung, Masters, & Trevor, 2012). However, it has emerged that depression has a more complex pathophysiology, suggesting that this may be the reason for the ineffectiveness of current antidepressants (Hasler, 2010). Although depression is associated with a reduction in the production of monoamines such as serotonin, it has emerged that oxidative stress and antioxidant defense mechanisms are prevalent in depression (Krishnan & Nesler, 2008). Consequently, Saffron and its constituents (Figure 2) have been found to have antioxidant and neuroprotective properties (Liakopoulou-Kyriakides & Kyriakidis, 2002).

Saffron consists of four major compounds: Crocin; Picrocrocin; Crocetin; Safranal. These major components of saffron inhibit the reuptake of dopamine, norepinephrine and serotonin. Saffron works by altering monoamine signaling and thus, increasing the neurotransmitter levels in the brain, reducing symptoms of depression (Gohari, Saeidnia, & Mahmoodabadi, 2013). The purpose of this literature review is to critically analyse research that has investigated the potential of saffron as an alternative therapy for MMD. Due to the extensive side effect profile of current therapies, the emergence of saffron as a potential treatment for MMD seems promising.

**Figure 2**

*Crocus sativus plant (Bouvier, Isner, Dogbo, & Camara, 2005)*



## *Methodology and Search Criteria*

Keywords used when selecting research papers in Summon, PubMed and Google Scholar were: "crocus sativus", "saffron" and "mild to moderate depression". These keywords were chosen so that selected trials remain focused on the main aim of this literature review. Personal bias was avoided by verifying findings in a wide range of sources, which increased confidence in the research findings (Swanson & Halton, 2005). Confirmation bias was avoided by critically analyzing quantitative data in every study and reporting findings (Fforde, 2017). Trials that were not peer-reviewed were excluded from this review. Trials conducted between 2004-2019 satisfied the research analysis. There were no relevant studies found after 2019. However, the extent of the oldest trial's relevance since publication (2004) is an element of debate.

## *Results*

Trials for saffron have been conducted mainly in Asia, where saffron is readily available. B.A. Akhondzadeh et al. (2008) studied the efficacy of saffron petal versus stigma for MMD. This trial lasted six weeks and it was found that both had similar efficacy. There was no statistical difference between both stigma and petal of saffron ($p$ = 0.810). The results of this trial were significant and made an original contribution in providing a way forward for future studies of saffron. They focused on saffron petal instead of stigma because petals are cheaper, more readily available, and just as efficacious as stigma and therefore would be of greater economic interest for research groups and pharmaceutical companies.

Double-blind randomised controlled trials (RCTs) were conducted by Mazidi et al. (2016) and Moshiri et al. (2006). Both RCTs studied the efficacy of saffron

compared to placebo. Mazidi et al. (2016) used Beck's Depression Inventory (BDI) as a primary outcome measure (Beck, 2011), whilst Moshiri et al. (2006) used HAM-D scores (Bech, 2006). Both studies had a 10% drop-out rate, with 36 and 54 patients participating in Moshiri et al. (2006) and Mazidi et al.'s (2016) studies respectively. Mazidi et al. (2016) found a significant difference between saffron and placebo ($p$ = 0.001). Moshiri et al. (2006) observed eight side effects, which were not statistically significant between both groups ($p$ values ranged from 0.400—1.00). Both studies concluded with a high need of larger sample sizes for increasing validity of future studies. The results, however, were of clinical significance, supporting the findings of B.A. Akhondzadeh et al. (2008). The results provided an original contribution in suggesting that saffron is much more effective than placebos in reducing depression.

A meta-analysis was recently conducted by Yang, Fu, Luo, Du, and Qui (2018). This further added weight to Moshiri et al. (2006) and Mazidi et al.'s (2016) findings through analysing the effects of saffron stigma versus placebo in treating MMD. Saffron led to more improvements in depression compared to placebo ($p$ = 0.001). Results of this meta-analysis were more robust compared to a meta-analysis conducted by Hausenblas et al. (2013) because it involved fewer studies. Although CBT is the first in line treatment for depression, saffron's efficacy in this meta-analysis reflects that it can be used as an alternative first line treatment because CBT is associated with high rates of non-adherence (Lepping et al. 2017). Participants in this meta-analysis were of a similar mean age (37.1 years). Therefore, it was not possible to analyse the efficacy of saffron in different age populations. Although seven significant studies were included in this analysis, the sample size in each study ranged from 30-66, which is very small compared to the general clinical population. To address the research gap of small sample sizes, more recently, Lopresti et al. (2019) made a unique contribution to this research area by studying 160 participants and found that saffron was more effective at reducing depressive symptoms compared to placebo ($p$ = 0.001). These recent findings are consistent with previous research and add weight to the potential of saffron for the treatment of MMD. However, despite the larger sample size, 160 participants is still a small figure when compared to the general population. But it is important to note that in this trial, depressive symptoms improved only according to the clinician-rated scale, not the self-rated scale. It is important to interpret results with caution because it is worth considering whether the clinicians over-estimated the effects or whether participants under-estimated their improvements. Nonetheless, Lopresti et al. (2019) demonstrated the importance of addressing gaps in research through employing a higher sample size. Going forward, it would be helpful for researchers to assess the efficacy of saffron versus placebo over a longer period (e.g., six months) instead of a few weeks.

Five double blind RCTs have studied the efficacy of saffron compared to antidepressants. Four trials compared saffron to the SSRI Fluoxetine. Noorbala et al. (2005), Shahmansouri et al. (2014), and B.A. Akhondzadeh et al. (2007) found that saffron had similar therapeutic efficacy to Fluoxetine. There was no significant difference between both groups ($p$ = 0.710, $p$ = 0.620, $p$ = 0.270, respectively). In all three studies, saffron had a faster onset (one week), whereas Fluoxetine took three or more weeks to show a therapeutic effect. Future studies could potentially test different doses of saffron so that its therapeutic efficacy at different doses can be determined.

In contrast, Sahraian et al. (2016) found that saffron was not effective in displaying antidepressant effects when compared to Fluoxetine. This is a noteworthy finding since the majority of the trials have found that saffron was effective in treating depression. The results collected by Sahraian et al. (2016) could be considered anomalous and they could be explained by the following methodological issues: they conducted the shortest trial compared to other studies (four weeks), they also had the smallest sample size (30 patients), they had the highest patient drop-out rate (25%), and they did not specify which extract of saffron was used.

S. Akhondzadeh et al. (2004) compared saffron to the tricyclic antidepressant Imipramine in 30 patients. There was no statistical significance between both treatment groups ($p$ = 0.090). Although the study sample was small, there was no drop-out: 100% of the participants completed the study, increasing its validity. However, there was no placebo group for comparison and one dose of each treatment modality was tested. Nonetheless, this trial still holds clinical relevance because it shows that saffron does still have a significant effect compared to Imipramine at a particular dose. It is important to note that this is the oldest trial that was conducted and currently, Imipramine would be a second in line treatment, prescribed by a psychiatrist instead of a GP, if SSRIs are ineffective. Hence, whether this trial would still hold relevance today is an element of debate. Table 1 summarises trials comparing saffron to antidepressants.

**Table 1**

*Double-blind RCTs to study the efficacy of saffron compared to antidepressants*

| | Noorbala et al. (2005) | Shahmansouri et al. (2014) | B.A. Akhondzadeh et al. (2007) | Sahraian et al. (2016) | S. Akhondzadeh et al. (2004) |
|---|---|---|---|---|---|
| Study duration | Six weeks | Six weeks | Eight weeks | Four weeks | Six weeks |
| No. of patients recruited initially | 40 | 40 | 40 | 40 | 30 |
| Drop-out rate (%) | 5% | 20% | 0% | 25% | 0% |
| No. of patients till endpoint | 38 | 32 | 40 | 30 | 30 |
| Patient age range | Mean: 36.9 | Range: 20-65 | Range: 18-55 | Range: 18-65 | Range: 18-55 |
| Saffron extract; Dose (mg/day) | Stigma; 30 mg/day | Stigma; 15 mg/day | Petal; 15mg/day | Not specified | Stigma; 30 mg/day |
| Primary outcome measure | HAMD | HAMD | HAMD | BDI | HAMD |
| Significance between both groups (*p* values) | 0.710 | 0.620 | 0.270 | 0.560 | 0.090 |

Note. Males and females were recruited in all trials. There was a wide age range of patients recruited in the trials. However, the sample sizes in all trials are small, which is a major limitation. Adverse effects in all studies were milder for saffron than for antidepressants, with the most common side effects of anxiety and increased appetite. There was a higher rate of adverse effects with antidepressants. The primary outcome measure was changes in HAM-D scores, except for Sahraian et al., who used BDI scores as a measure. Although both depression scales have been widely researched and extensively used, BDI has been criticized for not including vegetative symptoms of depression (LaRue, 2013). They are both self-reported too, which adds an element of bias (Hilsenroth et al., 2004). Therefore, these self-reported assessments should be used cautiously.

## *Discussion*

Recently, research has shown that saffron has the same effect in reducing symptoms of major depressive disorder when compared to Sertraline, an SSRI (Ahmedpanah et al., 2019). Thus, the purpose of this literature review was to evaluate whether saffron has potential as an alternative treatment for MMD. MMD is a major health concern because current treatments are only partially effective, which places a huge burden on the NHS (Independent Mental Health Task Force, 2016). It is important to note that definitions and diagnostic criteria for MMD vary across different diagnostic manuals and within different versions of the same diagnostic manuals, which could lead to possible limitations in treatments (Mitchell et al., 2011). Results from clinical trials indicate that using saffron petal and stigma as a treatment shows greater short-term therapeutic efficacy than placebo and similar short-term efficacy to pharmacological antidepressants. Only Sahraian et al. (2016) found no efficacy for saffron, but this trial had many methodological issues, with no other trial supporting its findings. HAM-D scores or BDI scores were used as primary outcome measures in all trials, except Lopresti et al.'s (2019), which used the Montgomery-Asberg

Depression Rating Scale (MADRS). Self-reported rating scales do not address the underlying pathophysiology of MMD and Lopresti et al. (2019) addressed this gap by using MADRS, which is a clinician-rated depression scale.

Although results from these clinical trials look promising, a great depth of further research is required. Sample sizes in the studies were small with frequent drop-outs, reflecting the need for larger sample sizes to increase validity of evidence. The clinical trials only tested one dose each (ranging from 15-30 mg per day) of saffron, the studies were short term (ranging from four-twelve weeks), and there was no follow-up. It should also be noted that the saffron capsules in Moshiri et al.'s (2006) trial contained lactose. Lactose allergies were not accounted for in the study, possibly contributing to side effects, and only one dose of saffron was used (it was also not specified which part of saffron each dose contained). Further robust clinical trials are warranted to address these gaps so that we can learn more about the safety, toxicity, adverse effects, and exact mechanism of action of saffron. Thus, this review has demonstrated that currently, it is not possible for saffron to be integrated into mainstream healthcare because patient safety would be at risk, since little is known about its pharmacokinetics (Singer & Adams, 2014).

It is important to note that these trials have been conducted in Asia, rather than the UK. It is impossible to apply these findings directly to the UK, because the demographics are different. Furthermore, there is a reducing stigma of mental health in the UK, compared to Asia (Lauber & Rossler, 2007). This could affect the results obtained because depression is seen as a huge social stigma in Asia (Lauber & Rossler, 2007).

### *Conclusion and Recommendations*

Novel treatments for MMD are an area of high clinical need because current treatments are only partially effective (Feldman, 2017). Saffron is not currently recommended by NICE because it is driven by systematic reviews and a robust evidence base, which saffron lacks (Lopresti & Drummond, 2014). Saffron petal would be practical to integrate into mainstream healthcare for treatment of MMD because it is easily obtainable and cheaper than stigma (Sarris & Mischoulon, 2017). Despite this, it can be questioned whether the NHS has money to fund research in this area when other issues, such as high service demand for emergency care, are more pressing (Pope et al., 2017). Introduction of new therapies does not come from the NHS, but from other private companies, so this raises the question of whether the NHS would give saffron any priority (Mossialos et al., 2018). Nonetheless, there is a strong need for large-scale robust RCTs and systematic reviews to be conducted in the UK to relieve the burden of MMD on the NHS

## Acknowledgements

The author would like to express their gratitude to Attiya Khalil for her generous contribution to this literature review.

The author would also like to express their appreciation towards the editors and reviewers at JEPS for their perceptive feedback on this manuscript.

## Competing Interests

The author declares that they have no competing interests in publishing this article.

## References

**Ahmadpanah, M., Ramezanshams, F., Ghaleiha, A., Akhondzadeh, S., Bahmani, D. S., & Brand, S. (2019).** Crocus Sativus L.(saffron) versus sertraline on symptoms of depression among older people with major depressive disorders–a double-blind, randomized intervention study. *Psychiatry Research, 282*, 112613. DOI: https://doi.org/10.1016/j.psychres.2019.112613.

**Akhondzadeh, B. A., Ghoreishi, S. A., Noorbala, A. A., Akhondzadeh, S. H., Rezazadeh, S. (2008)**. Petal and Stigma of Crocus sativus L. in the Treatment of Depression: A Pilot Double-blind Randomized Trial. *Journal of Medicinal Plants, 1*(1), 29-36. DOI: https://dx.doi.org/10.4103%2FJPBS.JPBS_83_18.

**Akhondzadeh, B. A., Moshiri, E., Noorbala, A. A., Jamshidi, A. H., Abbasi, S. H., Akhondzadeh, S. (2007).** Comparison of petal of Crocus sativus L. and fluoxetine in the treatment of depressed outpatients: A pilot double-blind randomized trial. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 31*(2), 439-42. DOI: https://doi.org/10.1016/j.pnpbp.2006.11.010.

**Akhondzadeh, S., Fallah-Pour, H., Afkham, K., Jamshidi, A. H., Khalighi-Cigaroudi F. (2004).** Comparison of Crocus sativus L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial. *Biomed Central Complementary and Alternative Medicine, 4*(12), 1-5. DOI: 10.1186/1472-6882-4-12.

**Bech, P. (2006).** Rating scales in depression: limitations and pitfalls. *Dialogues in Clinical Neuroscience, 8*(2), 207-215. DOI: https://dx.doi.org/10.31887%2FDCNS.2006.8.2%2Fpbech.

**Beck, A., Dozois, D. (2011).** Cognitive therapy: current status and future directions. *Annual Review of Medicine*, *62,* 397-409. DOI: 10.1146/annurev-med-052209-100032.

**Beck, J. S. (2011).** *Cognitive behaviour therapy: basics and beyond*. Guilford, UK: Guilford Press.

**Bouvier, F., Isner, J. C., Dogbo, O., Camara, B. (2005).** Oxidative tailoring of carotenoids: a prospect towards novel functions in plants. *Trends in Plant Science, 10*(4), 187-94. DOI: 10.1016/j.tplants.2005.02.007.

**David, D., Cristea, I., Hofmann, SG. (2018).** Why Cognitive Behavioral Therapy Is the Current Gold Standard of Psychotherapy. *Frontiers in Psychiatry, 9*, 1-3. DOI: 10.3389/fpsyt.2018.00004.

**Feldman, E. (2017).** Saffron and depression: what do we know and where do we go? *Integrative Medicine Alert*, 20, 85-90.

**Fforde, A. (2017).** Confirmation bias: methodological causes and a palliative response. *Quality & Quantity*, 51, 2319-35. DOI: 10.1007/s11135-016-0389-z.

**Gohari, A. R., Saeidnia, S., Mahmoodabadi, M. K. (2013).** An overview on

saffron, phytochemicals, and medicinal properties. *Pharmacognosy Reviews, 7*(13), 61-66. DOI: 10.4103/0973-7847.112850.

**Hasler, G. (2010).** Pathophysiology of depression: do we have any solid evidence of interest to clinicians? *Official Journal of the World Psychiatric Association (WPA)*, *9*(3), 155-61. DOI: 10.1002/j.2051-5545.2010.tb00298.x.

**Hausenblas, H. A., Dubyak, S., Jean, P., Dubyak, A., Douglas, S., Anton, S. D. (2013)**. Saffron (Crocus sativus L.) and major depressive disorder: a meta-analysis of randomized clinical trials (2013). *Journal of Integrated Medicine, 11*(6), 377-383. DOI: https://doi.org/10.3736/jintegrmed2013056.

**Hilsenroth, M., Hersen, M., Goldstein, G., Segal, D., Beers, S., Haynes, S. (2004).** Comprehensive handbook of psychological assessment: personality assessment. New Jersey, USA: John Wiley & Sons.

**Independent Mental Health Task Force. (2016).** *The five year forward view for mental health.* Retrieved August 15, 2020 from https://www.england.nhs.uk/wp-content/uploads/2016/02/Mental-Health-Taskforce-FYFV-final.pdf.

**Katzung, B., Masters, S., Trevor, A. (2012).** *Basic and Clinical Pharmacology.* New York, USA: McGraw Hill.

**Krishnan, V., Nestler, E. J. (2008).** The molecular neurobiology of depression. *Nature 455,* 894-902. DOI: 10.1038/nature07455.

**LaRue, A. (2013)**. *Aging and Neuropsychological Assessment*. New York, USA: Springer US.

**Lauber, C., Rossler, W. (2007).** Stigma towards people with mental illness in developing countries in Asia. *International Review of Psychiatry, 19*(2), 157-178. DOI: https://doi.org/10.1080/09540260701278903.

**Lepping, P., Whittington, R., Sambhi, R. S., Lane, S., Poole, R., Leucht, S., Cuijpers, P., McCabe, R., Waheed, W. (2017).** Clinical relevance of findings in trials of CBT for depression. *European Psychiatry, 45,* 207-11. DOI: 10.1016/j.eurpsy.2017.07.003.

**Liakopoulou-Kyriakides, M., Kyriakidis, D. A. (2002)**. Studies in Natural Products Chemistry. London, UK: Elsevier.

**Lopresti, A. L., Drummond, P. D. (2014).** Saffron (Crocus sativus) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. *Human Psychopharmacology: Clinical and Experimental, 29*(6), 517-27. DOI: 10.1002/hup.2434.

**Lopresti, A. L., Smith, S. J., Hood, S. D., & Drummond, P. D. (2019).** Efficacy of a standardised saffron extract (affron®) as an add-on to antidepressant medication for the treatment of persistent depressive symptoms in adults: A randomised, double-blind, placebo-controlled study. *Journal of Psychopharmacology, 33*(11), 1415-1427. DOI: https://doi.org/10.1177/0269881119867703.

**Mazidi, M., Shemshian, M., Mousavi, S. H., Norouzy, A., Kermani, T., Moghiman, T., Sadeghi, A., Mokhber, N., Ghayour-Mobarhan, M., Ferns, G. A. A. (2016).** A double-blind, randomized and placebo-controlled trial of Saffron (Crocus sativus L.) in the treatment of anxiety and depression. *Journal of Complementary and Integrative Medicine, 13*(2):195. DOI: https://doi.org/10.1515/jcim-2015-0043.

**McCrone, P., Dhanasiri, S., Patel, A., Knapp, M., Lawton-Smith, S. (2008).** *Paying the price: the cost of mental health care in England to 2026*. Retrieved August 15, 2020 from https://www.kingsfund.org.uk/sites/default/files/Paying-the-Price-the-cost-of-mental-health-care-England-2026-McCrone-Dhanasiri-Patel-Knapp-Lawton-Smith-Kings-Fund-May-2008_0.pdf.

**Mitchell, A. J., Chan, M., Bhatti, H., Halton, M., Grassi, L., Johansen, C., Meader, N. (2011).** Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *The Lancet Oncology, 12*(2):160-74. DOI: https://doi.org/10.1016/s1470-2045(11)70002-x.

**Moazen-Zadeh, E., Abbasi, S. H., Safi-Aghdam, H., Shahmansouri, N., Akhondzadeh, A. B., Hajhossein, A., Salehiomran, A., Forghan, S. (2017).** Effects of Saffron on Cognition, Anxiety, and Depression in Patients Undergoing Coronary Artery Bypass Grafting: A Randomized Double-Blind Placebo-Controlled Trial. *The Journal of Alternative and Complementary Medicine, 24*(4):361-68. DOI: 10.1089/acm.2017.0173.

**Moshiri, E., Basti, A. A., Noorbala, A. A., Jamshidi, A. H., Abbasi, S. H., Akhondzadeh, S. (2006)**. Crocus sativus L. (petal) in the treatment of mild-to-moderate depression: A double-blind, randomized and placebo-controlled trial. *Phytomedicine, 13*(9), 607-11. DOI: https://doi.org/10.1016/j.phymed.2006.08.006.

**Mossialos, E., McGuire, A., Anderson, M., Pitchforth, E., James, A., Horton, R. (2018).** The future of the NHS: no longer the envy of the world? *The Lancet, 391*(10125), 1001-03. DOI: https://doi.org/10.1016/s0140-6736(18)30574-9.

**National Institute for Health and Care Excellence. (2009)**. *Depression in adults: recognition and management.* Retrieved August 15, 2020 from https://www.nice.org.uk/guidance/cg90.

**NHS Digital. (2014).** *Adult psychiatric morbidity survey: survey of mental health and wellbeing.* Retrieved August 15, 2020 from http://webarchive.nationalarchives.gov.uk/20180328140249/http://digital.nhs.uk/catalogue/PUB21748.

**Noorbala, A., Akhondzadeh, S., Tahmacebi-Pour, N., Jamshidi, A. H. (2005).** Hydro-alcoholic extract of Crocus sativus L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. *Journal of Ethnopharmacology, 97*(2), 281-84. DOI: https://doi.org/10.1016/j.jep.2004.11.004.

**Novey, D. (2000).** Clinician's complete reference to complementary/alternative medicine. New York, USA: Mosby.

**Pope, C., Turnbull, J., Jones, J., Prichard, J., Rowsell, A., Halford, S. (2017).** Has the NHS 111 urgent care telephone service been a success? Case study and secondary data analysis in England. *BMJ Open, 7*(5), 1-8. DOI: https://doi.org/10.1136/bmjopen-2016-014815.

**Rang, H., Ritter, J., Flower, R., Henderson, J. (2016)**. Rang and Dale's Pharmacology. London, UK: Elsevier.

**Sahraian, A., Jelodar, S., Javid, Z., Mowla, A., Ahmadzadeh, L. (2016).** Study the effects of saffron on depression and lipid profiles: A double blind comparative study. *Asian Journal of Psychiatry, 22,* 174-76. DOI: https://doi.org/10.1016/j.ajp.2015.10.012.

**Sarris, J., Mischoulon, D. (2017).** Treatments for comorbid anxiety and mood disorders. *Evidence-Based Herbal and Nutritional Treatments for Anxiety in Psychiatric Disorders, 6,* 103-19. DOI: 10.1007/978-3-319-42307-4_6.

**Shafiee, M., Arekhi, S., Omranzadeh, A., Sahebkar, A. (2018)**. Saffron in the treatment of depression, anxiety and other mental disorders: Current evidence and potential mechanisms of action. *Journal of Affective Disorders, 227,* 330-37. DOI: 10.1016/j.jad.2017.11.020.

**Shahmansouri, N., Farokhnia, M., Abbasi, S. H., Kassaian, S. E., Noorbala, A. A., Gougol, A., Yekehtaz, H., Forghani, S., Mahmoodian, M., Saroukhani, S., Arjmandi-Beglar, A., Akhondzadeh, S. (2014)**. A randomized, double-blind, clinical trial comparing the efficacy and safety of Crocus sativus L. with fluoxetine for improving mild to moderate depression in post percutaneous coronary intervention patients. *Journal of Affective Disorders, 155,* 216-22. DOI: 10.1016/j.jad.2013.11.003.

**Singer, J., Adams, J. (2014).** Integrating complementary and alternative medicine into mainstream healthcare services: the perspectives of health service managers. *BMC Complementary and Alternative Medicine, 14*(167), 1-11. DOI: https://doi.org/10.1186/1472-6882-14-167.

**Swanson, R. A., Holton, E. F. (2005).** Research in Organizations: Foundations and Methods in Inquiry. San Francisco, USA: Berrett-Koehler Publishers.

**Wells, A., Fisher, P. (2015)**. Treating Depression: MCT, CBT, and Third Wave Therapies. Manchester, UK: Wiley.

**Yang, X. Y., Fu, X. Y., Luo, Q. H., Du, L., Qui, H. T. (2018).** Comparative efficacy and safety of Crocus sativus L. for treating mild to moderate major depressive disorder in adults: a meta-analysis of randomized controlled trials. *Neuropsychiatric Disease and Treatment, 14,* 1297-305. DOI: https://doi.org/10.2147/NDT.S157550