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• Systematic Review

A systematic review of randomized controlled trials examining the effectiveness of saffron (*Crocus sativus* L.) on psychological and behavioral outcomes

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ABSTRACT

BACKGROUND: Throughout the past three decades, increased scientific attention has been given to examining saffron's (*Crocus sativus* L.) use as a potential therapeutic or preventive agent for a number of health conditions, including cancer, cardiovascular disease, and depression.

OBJECTIVE: The purpose of this systematic review is to examine and categorize the current state of scientific evidence from randomized controlled trials (RCTs) regarding the efficacy of saffron on psychological/behavioral outcomes.

SEARCH STRATEGY: Electronic and non-electronic systematic searches were conducted to identify all relevant human clinical research on saffron. The search strategy was extensive and was designed according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)." Reference lists of articles that met the inclusion criteria were searched. Only English language studies were reviewed.

INCLUSION CRITERIA: Saffron trials in combination with other substances and saffron safety studies were considered, in accordance with the PRISMA statement. Included studies must have a control group. Included studies must measure a physiological and/or a behavioral outcome.

DATA EXTRACTION AND ANALYSIS: The methodological quality of all included studies was independently evaluated by two reviewers using the Jadad score. Mean scores and *P*-values of measures were compared both inter- and intra-study for each parameter (*i.e.*, depression).

RESULTS: Twelve studies met our inclusion criteria. These studies examined the effects of saffron on psychological/behavioral outcomes of: major depressive disorder ($n = 6$), premenstrual syndrome ($n = 1$), sexual dysfunction and infertility ($n = 4$), and weight loss/snacking behaviors ($n = 1$). The data from these studies support the efficacy of saffron as compared to placebo in improving the following conditions: depressive symptoms (compared to anti-depressants and placebo), premenstrual symptoms, and sexual dysfunction. In addition, saffron use was also effective in reducing excessive snacking behavior.

CONCLUSION: Findings from initial clinical trials suggest that saffron may improve the symptoms and the effects of depression, premenstrual syndrome, sexual dysfunction and infertility, and excessive snacking behaviors. Larger multi-site clinical trials are needed to extend these preliminary findings.

Keywords: *Crocus*; health-related outcomes; systematic review

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1 Introduction

In the age of genomics, nanotechnology, and proteomics, many diseases continue to provide challenges in terms of prevention and treatment, thus prolonging and sustaining the search for new, viable evidence-based solutions. The role of phytotherapy in potentially preventing and treating many of these diseases has been of interest to several scientific and nonscientific communities. Phytotherapy is broadly defined as the use of natural therapeutic agents derived from either plants or crude herbal drugs for medicinal purposes^[1,2].

Although medicinal plants are used for a wide variety of physical ailments, there is often limited research supporting such practices. Saffron is the dried stigma (thread-like parts) of the flower of *Crocus sativus* L., and it has a long history of use as a spice, coloring agent, and medicine. Due to how saffron is grown and harvested, saffron is considered one of the world's most expensive spices^[3]. Apart from its traditional value as a spice and coloring agent, saffron has a long history of medicinal use spanning over 2 500 years^[4,5]. Saffron has been used in traditional medicine for treating numerous diseases including cramps, asthma, menstruation disorders, liver disease, and pain^[6]. These medicinal properties of saffron are likely due to a number of compounds contained within this spice, including crocetin, crocins, and safranal^[3-5,7], which have been found to have strong antioxidant and radical scavenger properties^[5,7] and thus would provide increased protection against a variety of reactive oxygen species and pro-inflammatory cytokines^[7]. In line with this, evidence from recent *in vitro* and *in vivo* research indicates that saffron has potential anticancerogenic (cancer-suppressing), anti-mutagenic (mutation-preventing), antioxidant, antidepressant, and memory-enhancing properties^[5,7-9].

Saffron may also act in a manner similar to antidepressants to improve mood^[10,11]. Specifically, saffron may modulate levels of certain neurotransmitters in the brain, including serotonin, by inhibiting serotonin reuptake, thereby keeping serotonin in the synaptic cleft longer^[10]. This mechanism of action is suggested based on findings from animal studies but additional research is needed to identify the mechanism of action through which saffron may improve mood states^[10].

Throughout the past three decades, over 20 controlled and uncontrolled studies have been published examining saffron's potential to lower the risk of disease and improve health conditions in human participants, in particular with a focus on behavioral and psychological conditions, such as depressive symptoms and mood-related conditions^[10,11]. To date, no systematic review has been conducted on the effects of saffron for either preventing or treating specific health conditions related to psychological and behavioral function. The purpose of our study was to conduct a systematic

and meta-analytic (when the data were available) review to summarize and critically evaluate the evidence from randomized controlled trials (RCTs) that have examined the efficacy or effectiveness of saffron supplementation in regards to outcomes related to psychological and behavioral function.

2 Methods

To ensure the rigor of our systematic review and meta-analysis, we designed and reported our findings using a checklist of items in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" statement^[12].

2.1 Search strategy

To conduct a thorough literature search and to avoid biased retrieval, we used the following four search strategies: (1) Two independent reviewers searched the following electronic databases from inception to October 2014: AMED, CINAHL, the Cochrane Library, EMBASE, MEDLINE, PubMed, and Web of Science. The key terms outlined by Ulbricht and colleagues were used to browse relevant titles and abstracts^[12]. (2) Ancestry searches (*i.e.*, treeing backward) were conducted using the references lists of all located clinical studies that met our inclusion criteria^[13]. (3) We contacted active researchers in the field to retrieve current research. (4) Computerized author database searches were conducted on all authors of retrieved studies that met our inclusion criteria. Only articles published in English were reviewed.

2.2 Inclusion and exclusion criteria

We conducted a systematic review of RCTs that examined the efficacy and effectiveness of saffron for either the prevention or treatment of health conditions in both healthy and diseased populations. Saffron trials in combination with other substances and saffron safety studies were considered^[14,15]. Based on their titles and abstracts, the studies that appeared to meet the criteria were independently considered for inclusion by the co-authors. Only English language studies were included. Disagreements among the co-authors were resolved through discussion. Data, including the details of the study design, quality of the study, participants, intervention, outcomes, and adverse events were independently extracted by two reviewers (HAH and SA) using predefined criteria. Disagreements were resolved by discussion between the two reviewers and by seeking the opinion of the other authors when necessary. The methodological quality of all included studies were independently evaluated by two reviewers using the Jadad score^[16].

3 Results

Our search strategy located 24 human trials that examined the effects of saffron supplementation on psychological

and behavioral outcomes and complied with the inclusion criteria listed above. Five of these studies were excluded because they did not include a control group^[17-21]. Seven studies were excluded because they only examined physiological outcomes^[6,14,22-26]. Thus, 12 published randomized clinical trials^[27-38] were included in our review, which examined the following behavioral/psychological outcomes: major depressive disorder, pre-menstrual syndrome, sexual dysfunction and infertility, and weight loss and snacking behaviors. See Figure 1. Table 1 provides a comprehensive summary of the results for the 12 studies included in our review. Below we review empirical evidence from identified clinical trials on the effects of saffron on each of these health conditions. The studies are categorized by their main outcomes below.

3.1 Depression

Six randomized trials were identified that examined the effects of saffron on symptoms of depression in adults with major depressive disorder ($n = 2$ placebo controlled trials, $n = 4$ antidepressant controlled trials). Hausenblas *et al*^[10] conducted a meta-analysis of the 5 published RCTs (published until April 2013) examining the effects of saffron supplementation on symptoms of depression among participants with major depressive disorder^[10,27-31]. They found a large effect size for saffron supplementation versus placebo in treating depressive symptoms (mean effect size = 1.62, $P < 0.001$, $n = 2$) indicating saffron supplementation significantly reduced depression symptoms compared to placebo^[10]. Hausenblas *et al*^[10] also found a null effect size between

saffron supplementation and the antidepressant groups (mean effect size = -0.15 , study $n = 3$)^[10].

A recent study, by Shahmansouri *et al*^[32], not included in the 2013 meta-analysis by Hausenblas *et al*^[10], examined the effects of saffron supplementation versus fluoxetine in patients with major depressive disorder who had undergone percutaneous coronary intervention^[10,32]. The researchers found that short-term therapy of six weeks with saffron supplementation produced similar improvements in symptoms of depression as the antidepressant medication fluoxetine.

A more recent meta-analysis by Lopresti and Drummond^[11] that included the Shahmansouri *et al*^[32] study confirmed the results of the meta-analysis by Hausenblas *et al*^[10]; in the placebo-comparison trials, saffron had large treatment effects and, when compared with antidepressant medications, had similar antidepressant efficacy^[10,11,32]. A statistical difference in adverse effects could not be calculated across the treatment groups; Lopresti and Drummond^[11] found a minimal frequency of adverse events. An inspection of frequency data indicates increased reports of sedation/drowsiness, headache, dry mouth, constipation and sexual dysfunction with antidepressant treatment compared with saffron^[32]. Compared with placebo treatment, treatment with saffron was associated with a tendency of increased reports of anxiety/nervousness, increased appetite, nausea and headache.

3.2 Sexual dysfunction and infertility

Four studies examined the effects of saffron supplementation on sexual function. Modabbernia *et al*^[33] found that saffron

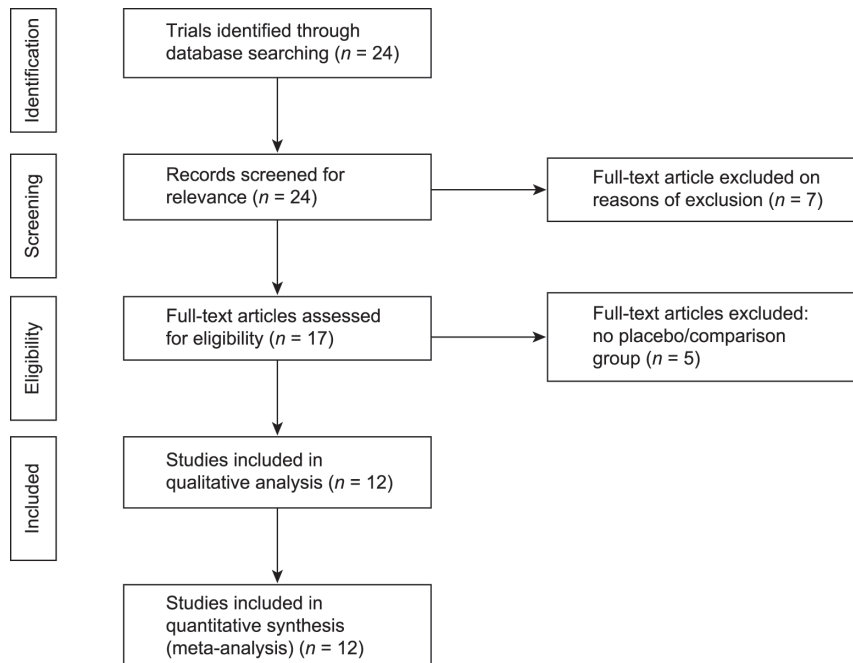


Figure 1 Flow of studies selected through phases of systematic review

Table 1 (to be continued) Summary of the randomized trials on the effectiveness and efficacy for psychological/behavioral outcomes ($n = 12$)

| First author (year) [condition] | Design | Participants | Treatment group | Control/ comparison group | Country | Main outcome | Other outcomes | Main results | Adverse events | Jadad score |
|---|---|--|--|---------------------------|---------|-----------------------------|-----------------|---|---|-------------|
| Agha-Hosseini (2008) ^[37] [PMS] | 8 week double-blind, placebo-controlled, randomized | 50 women (mean age = 34.3 years) with regular menstrual cycles and experience of PMS for ≥ 6 months | Saffron capsule (30 mg/d) for 2 menstrual cycles | Capsule placebo | Iran | Daily Symptom Report of PMS | HDRS | Saffron group had better outcome on PMS and depression than control group | No group differences; no severe adverse effects | 5 |
| Akhondzadeh (2004) ^[31] [depression] | 6 week double-blind randomized | 30 adults with major depression (mean age = 34) | Saffron capsule (30 mg/d) | Imipramine 100 mg/d | Iran | HDRS | None | Saffron and imipramine similarly effective in improving HDRS | More side effects for imipramine | 5 |
| Akhondzadeh (2005) ^[27] [depression] | 6 week double-blind, placebo-controlled | 35 adults with major depression (mean age = 36.3) | Saffron capsule (30 mg/d) {stigma} | Capsule placebo | Iran | HDRS | None | Saffron had better outcome on HDRS | No group differences | 5 |
| Akhondzadeh Basti (2007) ^[28] [depression] | 8 week double-blind randomized | 38 adults with major depression (mean age = 34.8) | Saffron capsule (30 mg/d) | Fluoxetine (20 mg/d) | Iran | HDRS | None | Saffron and fluoxetine similarly effective in improving HDRS | No group differences | 5 |
| Gout (2010) ^[38] [weight loss/snacking] | 8 week double-blind, placebo-controlled randomized | 60 overweight women (mean age = 36.1); BMI = 26.8 | Satiereal saffron (176.5 mg/d) | Placebo | France | Body weight | Snacking events | Satiereal resulted in significant reductions in body weight at 8 weeks compared to placebo (mean weight loss = 0.96 kg); 55% reduction in snacking in Satiereal by 8 weeks compared to 28% in the control | No group differences regarding tolerance and safety | 5 |

Table 1 (continuation 1) Summary of the randomized trials on the effectiveness and efficacy for psychological/behavioral outcomes (*n* = 12)

| First author (Year) [condition] | Design | Participants | Treatment group | Control/ comparison group | Country | Main outcome | Other outcomes | Main results | Adverse events | Jadad score |
|--|---|---|--|---------------------------------|---------|--|----------------|---|--|-------------|
| Kashani (2013) ^[36] [depression] | 4 week randomized double-blind placebo-controlled | 34 women with major depression who were stabilized on fluoxetine and had experienced subjective feelings of sexual dysfunction (mean age = 35.35) | Saffron capsule (30 mg/d) [Green Plants of Life Co.] | Placebo | Iran | Female Sexual Function Index | HDRS | Saffron group had improvements in some of the fluoxetine-induced sexual problems (e.g., arousal, lubrication, and pain) compared to the control | No group differences | 5 |
| Modabbernia (2012) ^[33] [sexual function] | 4 week randomized double-blind placebo-controlled | 30 married men with major depression whose depression had been stabilized on fluoxetine and had sexual impairment (mean age = 38.55) | Saffron (30 mg/d) | Placebo | Iran | International Index of Erectile Function scale | None | Saffron is efficacious treatment for fluoxetine-related erectile dysfunction | Frequency of side effects similar in both groups | 5 |
| Moshiri (2006) ^[29] [depression] | 6 week double-blind, placebo controlled, randomized | 36 adults with major depression (mean age = 35.65) | Saffron capsule (30 mg/d) | Placebo capsule | Iran | HDRS | None | Saffron had better improvement on HDRS scores than the control | No group differences | 5 |
| Noorbala (2005) ^[30] [depression] | 6 week double-blind randomized | 38 adults with major depression (mean age = 36.9) | Saffron capsule (30 mg/d) | Capsule of fluoxetine (20 mg/d) | Iran | HDRS | HDRS | Both groups similarly effective in treating depression | No group differences | 5 |

Table 1 (continuation 2) Summary of the randomized trials on the effectiveness and efficacy for psychological/behavioral outcomes (*n* = 12)

| First author (year) [condition] | Design | Participants | Treatment group | Control/ comparison group | Country | Main outcome | Other outcomes | Main results | Adverse events | Jadad score |
|---|---|--|---------------------------|---------------------------|---------|---|--|--|---|-------------|
| Safarinejad (2010) ^[35] [sexual function] | 12 week open label, randomized, crossover study | 307 men with erectile dysfunction (mean age = 46.6) | Saffron (60 mg/d) | Sildenafil (50 mg) | Iran | International Index of Erectile Dysfunction | Several self-report, interview, and objective measures | No beneficial effect of saffron in men with erectile dysfunction | No serious adverse events. Saffron group had significant decreases on several lab parameters. However decreases were not clinically significant | 5 |
| Safarinejad (2011) ^[34] [sexual function] | 26 week double-blind randomized | 230 infertile men (mean age = 28.6) | Saffron capsule (60 mg/d) | Placebo | Iran | Semen analysis (objective) | None | Saffron did not improve semen parameters | No serious adverse events. Saffron group had significant decreases on several lab parameters and vital signs | 5 |
| Shahmansouri (2014) ^[32] [sexual function] | 6 week, randomized double-blind parallel-group | 40 male and female patients (mean age = 52.75) with major depressive disorder who had undergone percutaneous coronary intervention | Saffron capsule (30 mg/d) | Fluoxetine (40 mg/d) | Iran | HDRS | Response and remission rate | No group differences | No significant group difference | 5 |

PMS: premenstrual syndrome; HDRS: Hamilton Depression Rating Scale; BMI: body mass index. Participants refer number of participants who completed the trial.

supplementation (30 mg/d for 4 weeks) was efficacious in treating fluoxetine-related erectile dysfunction. Of importance, the side effect profile of saffron was comparable to placebo. Nine side effects were recorded during the study, and the frequency of the side effects did not differ between the two treatment groups. This finding is important because most pharmacotherapies for selective serotonin reuptake inhibitor (SSRI)-induced sexual impairment are associated with significant and potentially dangerous side effects, and some may even reverse the beneficial effects of SSRIs on mood. Conversely, saffron's antidepressant effects are an additional advantage to its aphrodisiac effect, which makes it a potentially useful adjunct to SSRIs in the treatment of depression. However, in a larger-scale RCT, no group differences were evidenced in sexual function parameters in 260 infertile men with idiopathic oligoasthenoteratozoospermia who had taken 60 mg/d of saffron compared to placebo for 26 weeks^[34]. Using an open label, randomized, fixed-dose, crossover study, Safarinejad *et al*^[35] compared saffron (60 mg/d) to sildenafil (50 mg/d) in 307 men with erectile dysfunction. They found no beneficial effect of saffron administration for 12 weeks (30 mg/d) in men with erectile dysfunction.

In a randomized double-blind, placebo-controlled study, Kashani *et al*^[36] examined 38 women with major depression who were stabilized on fluoxetine 40 mg/d for a minimum of 6 weeks and had experienced subjective feelings of sexual dysfunction; these patients were randomly assigned to take a saffron (30 mg/d) or a placebo capsule for four weeks. At the end of the fourth week, participants reported significant improvements in sexual function as indicated by a self-report questionnaire, the Female Sexual Function Index. The authors concluded that saffron may safely and effectively improve sexual function including sexual arousal, lubrication, and pain in women reporting fluoxetine-related sexual problems. However, there were no reported changes in desire, satisfaction, or orgasm. The frequency of reported adverse effects was similar between the two groups.

3.3 Premenstrual syndrome

One RCT examined the effects of saffron supplementation on premenstrual syndrome. Agha-Hosseini *et al*^[37] found that women with regular menstrual cycles experiencing premenstrual syndrome who took 30 mg/d of saffron supplementation for eight weeks reported relief in premenstrual symptoms and depression levels compared to placebo.

3.4 Weight management/snacking

In an eight-week randomized, placebo-controlled, double-blind study, Gout *et al*^[38] examined the effects of saffron supplementation (176.5 mg/d) on snacking behaviors and weight loss. Caloric intake and exercise were left unrestricted during the study. They found that healthy, mildly overweight women (mean body mass index = 26.8)

who took saffron for eight weeks lost significantly more weight (0.997 kg vs 0 kg) and had a reduction in snacking compared to placebo. Specifically, snacking decreased by 55% in the saffron group as compared to 28% in the placebo group. The authors concluded that saffron produced a satiating effect contributing to a reduction in snacking and an increase in weight loss.

4 Discussion

The purpose of our study was to systematically review controlled trials examining the effectiveness of *Crocus sativus* L., commonly known as saffron, on psychological and behavioral health outcomes in human participants. The psychological and behavioral outcomes examined were depression, sexual dysfunction, premenstrual syndrome, and weight management/snacking. Most of the studies found that saffron supplementation had a positive effect on these health outcomes^[10,11,32,36], although there were limited studies on premenstrual syndrome and snacking behavior^[37,38]. None of the studies found that saffron supplementation either worsened the condition or had negative effects. Of all outcomes evaluated, the strongest evidence exists to support the efficacy of saffron for improving symptoms of major depressive disorder. Specifically, saffron was found to be more effective than placebo^[10,11,33,34,36-38] and have effects similar to imipramine and fluoxetine in reducing symptoms of depression^[28,32] in clinical trials evaluating its use in the treatment of major depressive disorder. Larger RCTs are needed to extend these preliminary findings before firm conclusions can be made regarding the efficacy of saffron for preventing and treating health conditions. More detailed scientific findings and implications for future research directions are described below.

Although the results of our review are encouraging, with most studies displaying a positive effect of saffron on health conditions related to psychological and behavioral function, limitations exist in confirming saffron's therapeutic efficacy. For example, trial lengths have frequently been short (4 to 6 weeks), sample sizes were relatively small ($n = 30 - 40$), and potential biases existed due to certain Iranian research groups conducting most of the human clinical trials within a topic area (*e.g.*, depression). Iran is one of the greatest producers of saffron with nearly 90% of saffron being produced there^[4]. Most of the research regarding this exotic spice has thus come from Iran. Sarris *et al*^[39] encouraged institutions in other countries to validate their research, as saffron appears to be a promising medicinal plant, in particular for depressive symptoms.

Our systematic review had several limitations. Though our search strategy involved both electronic and non-electronic studies, we may not have identified all the available trials involving saffron. As noted above, most trials were of



short duration with relatively small sample sizes. These factors prevent us from drawing firm conclusions about the effects of saffron on health outcomes related to psychological and behavioral function. Other limitations of the studies included in this review include a lack of long-term follow-up, use of single self-report outcome measures, reliance on self-report measures, and lack of moderator analysis. The small sample sizes most likely precluded the examination of important moderator variables (e.g., gender, age). Of importance, most study outcomes were assessed with self-report measures (e.g., Hamilton Depression Rating Scale). Future studies need more objective measures (see Safarinejad *et al*^[34,35] for an exception — they used sexual function analysis and found no group differences).

Our review highlights several areas that require further research. One of the most challenging aspects of evaluating saffron's efficacy in human clinical trials is the variation in doses prescribed to participants in these studies. The human trials that have examined specific health benefits included pure saffron doses ranging from 20 to 400 mg/d, with some supplements containing additional compounds with putative synergistic effects^[13]. For future studies, researchers are encouraged to move beyond fixed doses of saffron because it is plausible that a dose-response may exist. For example, Shamsa *et al*^[21] used 200 mg/d of saffron tablet and found an improvement of 17.05 on the International Index of Erectile Function Scale at 10 d for men with sexual dysfunction. In comparison, Modabbernia *et al*^[33] used 30 mg/d of saffron and found an improvement of 5.5 on the International Index of Erectile Function Scale at 14 d for men with sexual dysfunction. Further research is needed to examine if a dose-plateau exists in regards to saffron's effectiveness.

In all of the trials included in this review ($n = 12$), among a total of 928 participants, there were no significant differences in adverse events between saffron and placebo, supporting the safety of saffron (Table 1). A full list of adverse events is available from the first author. The adverse events reported were mild to moderate, and there were no serious adverse events reported. The most commonly observed adverse effects across all trials were anxiety, appetite fluctuation (increased and decreased), sedation, nausea, headache, and hypomania. Although findings of most studies conducted to date support the safety of saffron, longer-term trials are needed to more fully evaluate the safety of saffron for human consumption.

In summary, saffron has widespread traditional uses. It has demonstrated efficacy in treating the symptoms of mild-to-moderate depression; however, a limited number of high-quality clinical trials exist currently. Studies to date support its role in the treatment of depressive symptoms. Larger scale RCTs are needed to better understand saffron's potential role and mechanisms of action in the treatment

of depression. Data regarding safety, effectiveness, and mechanisms of action from longer-term trials are needed before saffron can be widely recommended for the potential treatment of depression and other health conditions.

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6 Declaration of conflict of interest

Drs. Anton and Hausenblas serve as scientific advisors and as consultants for the company ReBody, LLC., which is an affiliate of Reserve Life Organics, LLC d/b/a Reserveage Organics, the developer and marketer of a product in which saffron is used. Neither author has received personal financial gain from sales of this product. All findings and views expressed in this paper are those of the authors and do not necessarily reflect the views of the Reserve Life Organics, LLC, d/b/a Reserveage Organics that funded this trial.

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