ORIGINAL RESEARCH

The use of saffron in depression among nursing students in Indonesia: A quasi-experimental study

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Abstract
Globally, around 17,3% of college students perceived depression. Untreated depression will negatively impact students' quality of life; moreover, it can trigger students to consume drugs and alcohol or commit suicide. This study aimed to evaluate the effect of saffron on students who perceive depression. This is an experimental, un-blinded study. In this study, 71 nursing students who perceived depression symptoms participated. In the saffron (intervention group), 40 nursing students were voluntarily assigned to receive saffron (5 strands of dried saffron petals, brewed in 200 ml warm water, consumed twice daily, morning and night). In comparison, 31 students (control group) drink regular tea for two weeks. Using the DASS 21 Checklist, we assessed the students at baseline and, after two weeks, completed therapy to measure the outcome. Finally, the data were analyzed using Wilcoxon Test statistical analysis. Saffron had a more significant impact on depression levels among the intervention group. The mean stress scores decreased from 15.4 ± 6.1 to 10.8 ± 5.8 for the saffron group (p < .0001), while for the control group, the depression score slightly increased from 13,74 to 14,52. Our findings suggest that saffron is effective in reducing depression levels among nursing students.

Keywords: Depression; nursing care; nursing students; nursing intervention; complementary therapy

Introduction

Research shows that college campuses are where many students struggle with mental illnesses. Globally, studies indicate an increasing number of university students who experience depression. A recent WHO study estimated that 17,3% of university students experience depression and 4,1% have panic attacks (Auerbach et al., 2018). The depression range from mild to severe depression, with prevalence in each field, reported as follows: 21.1% of college students experienced mild depression, 17% had moderate depression, and 3.4% had major depression (Li, Wang, Wu, Han, & Huang, 2021). Depressive symptoms include psychological parameters, physical signs, and behavioural symptoms, including depressed mood, loss of interest in any action, pessimism, fatigue, feelings of worthlessness, reduced ably to think or concentrate, tearfulness, thoughts of suicide or death, and weight loss, sleep, and appetite disorders. The untreated depressive symptoms affect students' quality of life and lead to worse conditions. It has been reported that 18% of students commit suicide, 27% consume alcohol, and 20% have suicidal ideation (Han et al., 2016). Depression can be effectively treated with either pharmacotherapy or psychotherapy. Although effective treatments are available, many students who suffer from depression tend to ignore and keep their condition secret. They did not seek professional help due to the negative stigma of seeking mental health services (Han et al., 2016). They attempt to overcome and cope with their depression-perceived symptoms through negative modes of action such as consuming alcohol, marijuana, smoking, and drug abuse (Nobiling & Maykrantz, 2017). Eventually, those negative actions resulted in a destroyed student's life in the future.

Increasing evidence has shown the efficacy of Internet-based interventions in treating depression (Mak, Chio, Chan, Lui, & Wu, 2017). A meta-analysis study on relieving depression among college students recommended a digital mental health intervention focused on Internet-based Cognitive Behavioral Therapy (Lattie et al., 2019). Were 71 studies conducted on web-based Cognitive Behavioral Therapy via smartphone and offline computer delivery? Those represented interventions were claimed to be effective at producing a beneficial change in the psychological outcomes,

even though some obstacles remain a concern. The concern was the issue of the lack of engagement of users with these programs. Many respondents stopped in the middle of the program due to time-consuming issues, high commitment demand, and technical problems such as screen radiation's negative impact on neurocognitive function and mood deterioration (Juniar et al., 2019). Eventually, they perceive the care available to them as inconvenient (Juniar et al., 2019). It appears to be a vital concern for the sustainable implementation of digital mental health interventions.

Because of the lack of user engagement in digital mental health intervention for college students, and considering the character of students vulnerable to negative stigma, personal therapy that reduces the risk of students being exposed to society because of visiting a therapist is needed. Furthermore, an affordable self-administered treatment that is simple, easy, and quick therapy is necessary to sustain student engagement for better outcomes. Plant extracts, commonly known as herbal, are some of the most attractive sources of new drugs and have shown promising results in treating depression (Marx et al., 2019). Therefore, herbal saffron might be considered an alternative natural therapy for depression (Ghaderi et al., 2020). A meta-analysis of 11 studies revealed the therapeutic effect of saffron as an antidepressant effect (Ghaderi et al., 2020). Other evidence has shown the efficacy of 30 mg/day of saffron administration to depressive patients during six weeks of treatment. The respondents indicated significantly improved depression scores. Another study taking 30 mg/day of saffron for 12 weeks by patients provided a significant mean on reduced Beck Depression Inventory (BDI) score. A survey about saffron as mood supplementation on 56 low-mood adults reported that saffron extract improves subclinical depressive symptoms in healthy individuals and may contribute to increased resilience against the development of stress-related psychiatric disorders (Jackson et al., 2021). Based on many previous studies, they concluded that saffron showed anti-depressive effects.

Considering the efficacy of saffron as an anti-depressive agent and the extent to which saffron is a safe treatment for depression, this study aims to understand the potential effects of using saffron as an alternative therapy to treat depressive symptoms among college students. The mechanism of the antidepressant effect of saffron is by inhibiting synaptic serotonin reuptake (Hosseini, Razavi, & Hosseinzadeh, 2018). Doses of up to 1.5 g/day of saffron capsules are considered safe, and toxic effects have been reported at 5 g (Ghaderi et al., 2020). With a concern for the feasibility and affordability of the saffron preparation, particularly for students, this study modifies the saffron shape from capsules to saffron-brewed drinks or similar saffron tea. There is little evidence that saffron supplements in the form of brewed beverages are effective for treating depression in college students, so this study aimed to evaluate the antidepressant effect of saffron in the form of brewed drinks on college students with depression.

Method
This is a pre- and post-experimental study within two study groups (saffron and control). This study design is selected to assess the effectiveness of saffron in reducing depressive symptoms among nursing college students. The study was conducted in one of the nursing schools in Yogyakarta in July – August 2022. The study targeted nursing college students who perceived any depression symptoms. Students who perceived any depression symptoms are interested in participating and meet the inclusion criteria are voluntarily recruited in this study. The inclusion criteria were as follows: nursing students perceived any depression symptoms or struggled with depression symptoms (depressed mood, sad, unmotivated, anxiety) and could follow and complete the treatment. The exclusion criteria were as follow: being pregnant, presence of any unstable medical condition that might interfere with completing two weeks of treatment.

At the beginning of the study, the recruitment was conducted by sending an announcement about the research aim and potential benefit for students with mental health issues through social media platforms (what's application group) spread evenly on campus. Students who feel interested in this study and meet the inclusion criteria are welcome to join this study. Eligible students were screened by completing the depression Questionnaire. The depression is assessed using DASS 21 questionnaire. Questionnaire validation has been carried out in previous studies on 105 college students. The results of this study reported that DASS-21 could be utilized as a valid and reliable instrument for measuring depression, anxiety and stress in college students. The depression, anxiety, and stress scales show good internal consistency. The Cronbach alpha coefficients scores are 0.85, 0.84, and 0.84, while the Spearman-Brown coefficients scores are 0.84, 0.83, and 0.85. Confirmatory factor analysis showed that the CFI and TLI values were higher than 0.90, and the RMSEA and SRMR values were less than 0.08, with factor loadings ranging from 0.49 – 0.75 for each DASS-21 item (12). Based on DASS 21 scores, participants were categorized as belonging to one of four

groups: scores 0-9 represent minimal depression, scores 10-13 represent mild depression, scores 14-20 represent moderate depression, scores 21-27 represent severe depression and >28 represent incredibly severe depression.

After completing the assessment using DASS 21, 71 college students with mild-extremely severe depression were recruited in this study. They were divided into two groups (saffron group n=40 and control group n=31) and underwent treatment for two weeks. The Saffron group received saffron, whereas the control group only drank tea. The researcher collected informed consent from all participants before their treatment. Next, participants were informed of the technical process, the treatment's length, and the benefit of participating in this study. In the saffron group, each participant received 1 cup of saffron equal to 1 gr of dried petal saffron brought home for further consumption. The protocol guideline of the study was available on an accessible video shared with all participants. The protocol of the treatment for the saffron group was: each day, and the participant had to consume the saffron (twice a day, morning and evening) at home, as prepared as a brewed drink. To produce a saffron-brewed drink, participants can soak five strands of dried saffron in 200 ml cup of warm water for 5-10 minutes or until the water turns yellow.

Furthermore, the saffron-brewed drink is ready to drink. While they drink, they have to send a recorded video presenting their process of drinking saffron. The video was sent and uploaded on google drive twice daily (morning and evening) as a research validation method. For the control group, participants had to drink tea twice daily (morning and evening) and report their activity through the What's Application group. General information such as demographic, academic, and interpersonal variables was recorded. The primary outcome (depression scale) was assessed using DASS 21 questionnaire. The researcher distributed a valid questionnaire to respondents through Google Forms. We sent the Google form link to the WhatsApp group with a member of the respondents. To ensure every respondent fills out the questionnaires, the research team follows up with all respondents privately. The questionnaires were filled out before and after two weeks of intervention to measure the efficacy of treatments. The collected data were entered into the Statistical Package for Social Sciences (version 25, IBM Corporation). The descriptive data were presented in mean and standard deviation, absolute numbers, and percentages. Chi-Square, Fisher Exact, Wilcoxon, and Mann-Whitney tests were used for inferential data. The $p < 0.05$ was considered a statistically significant level.

Results

The following is the detail of the finding. This study included 71 participants at a baseline until two weeks follow-up. There are 40 participants in the saffron group and 31 in the control group. The table presents the characteristic of the participant at a baseline, consisting of demographic characteristics, the presence of academic stressors, interpersonal stressors, and general stressors. There were no significant differences between participants' demographic data in the two study groups (P>0,05). The majority of the participant in both groups were female (saffron 77,5% while control 90,3%) and came from Yogyakarta (saffron 62,5%, control 38,7%). Among the saffron group, participants who live within a family and live with friends are equal (50%), whereas, in a control group, most students were living with friends (67,7%). Within academic stressors, an issue with the thesis was the primary stressor perceived by participants in the saffron group (42,9%), while control groups struggled with general academic load (54,8%). Most of the participants in both groups have problems with friends (saffron 62,5%, control 41,9%) and struggle to deal with their failure (saffron 40,0%, power 48,4%) **(Table 1)**.

The participant distribution of the depression category is shown in the table **(Table 2)**. At the baseline, more than half of the participants in both groups recorded scores suggesting that they had at least mild depression (saffron 53%, control 55%). Throughout the two-week follow-up period, more than half of all participants (65%) in the saffron group were no longer suffering from depression (standard), only 15% had moderate depression, and nobody had a suggestive score of highly severe depression. In the control group, the number of respondents with mild depression was the highest (40%), and 6% suffered highly severe depression.

The depression score of the saffron group was 11.67, while the control group was 10.72. We analyzed using the Mann-Whitney test and obtained a p-value of more than 0.005 results. It illustrates that the mental health conditions of the intervention and control groups at baseline (baseline conditions) were similar (equal). After two weeks of treatment with saffron administration, there was a significant difference in the depression score. The mean depression score of the intervention group was significantly lower than the control group. In the saffron group, the depression score was 8.35, while the control group scored 14.52 **(Table 3)**.

The mean of students' depression scores at baseline and after two weeks of saffron treatment is shown in Table 4. In a saffron group, a reduction in the depression scores from the baseline showed significant differences by the end of the study ($p < .01$). Between the baseline and week 2, the mean of depression scores decreased from 13 (4.2) to 8.35 (6.17) for the saffron group ($p < .000$). It was revealed that there is a significant difference between depression score at the beginning of the study and the end of study within saffron group. In contrast, the mean depression score in the control group slightly increases at the end of the study. At the beginning of the study, the mean depression score was 13.74. After two weeks, the depression score rose to 14.52 **(Table 4)**.

Table 1. Comparison between groups' characteristics

Variables	Intervention (n=40)		Control (n=31)		p
	f	(%)	F	(%)	
Gender					
Male	9	(22,5)	3	(9,7)	0,15[a]
Female	31	(77,5)	28	(90,3)	
Residence					
Living with family	20	(50,0)	10	(32,3)	0,22[a]
Living with friends	20	(50,0)	21	(67,7)	
City of Origin					
West Java	0	(0,0)	3	(9,7)	0,02[b]*
Middle Java	5	(12,5)	8	(25,8)	
Yogyakarta	25	(62,5)	12	(38,7)	
Outside Java	10	(25,0)	8	(25,8)	
Academic Stressor					
Thesis issue	17	(42,5)	6	(19,4)	0,04[b]*
Financial issue	9	(22,45)	3	(9,7)	
Coursework load	3	(7,5)	5	(16,1)	
General academic load	11	(27,5)	17	(54,8)	
Interpersonal Stressor					
Problem with friends	25	(62,5)	13	(41,9)	0,07[a]
Problem with family	9	(22,5)	11	(35,5)	
Problem with partner	6	(15,9)	7	(22,6)	
General Stressor					
Dealt with failure	16	(40,0)	15	(48,4)	0,70[a]
Dealt with loss	13	(32,5)	5	(16,1)	
Break up with a partner	4	(10,0)	5	(16,1)	
Physical health issue	7	(17,5)	6	(19,4)	
TOTAL	40	(100,0)	31	(100,0)	71

[a] Chi-Square
[b] Fisher Exact
*Significantly different

Table 2. The score of depression symptoms after a two-week study

Severity Group	Control (n=31)				Intervention (n=40)			
	Baseline		Two weeks		Baseline		Two weeks	
	f	(%)	f	%	f	%	f	%
Minimal Depression	0	0	5	16	0	0	26	65
Mild Depression	17	55	6	19	21	53	6	15
Moderate depression	13	42	17	55	16	40	7	18
Severe Depression	1	3	1	3	2	5	1	3
Extremely Severe Depression	0	0	2	6	1	3	0	0
TOTAL	31	100	31	100	40	100	40	100

Table 3. The mean score of depression among groups after a two-week study

Depression	Intervention (n=40)	Control (n=31)	Mann Whitney Test	p
	Mean ± (SD)	Mean ± (SD)		
Depression pre	13.55 (4.2)	13.74 (3.5)	-5.35[a]	0.59
Depression post	8.35 (6.2)	14.52 (6.7)	-3.75[a]	0,00*
Total	40 (100)	31 (100)		

*Significantly different

Table 4. Comparison of depression mean score after a two-week study

Depression	Pre	Post	Wilcoxon Test	p
	Mean+SD)	Mean+(SD)		
Saffron Group	13,55(4,2)	8,35(6,17)	-4,39	0,000*
Control Group	13,74(3,5)	14,52(6,7)	-0,448	0,64
Total	40 (100)	40 (100)		

*Significant

Discussion

Depression is a psychiatric problem faced by many college students (Ramón-Arbués et al., 2020). In this study, in the baseline conditions, most students experienced mild depression (53% in the saffron group and 55% in the control group), and more than 40% of students experienced moderate depression. Symptoms of depression experienced by many respondents in this study were feelings of sadness and feelings of inferiority. This result is similar to a WHO study, which shows that 17.3% of college students experience depression (Auerbach et al., 2018)). WHO reported the prevalence of depression experienced by students varies according to its severity, with details are follows: 21.1% for mild depression, 17.7% for moderate depression, and 3.4% for severe depression. The same study also reported the prevalence of moderate depression is 41.2%, followed by mild depression, which is 26.6% and severe depression at 11.4% (Naushad et al., 2014). Several factors have contributed to the high incidence of depression in college students. In previous studies, students perceived stressors such as high academic pressure, course workload, and academic competition (Bekova, Dementeva, & Smirnov, 2021). According to this current study, some of the stressors perceived by students have similarities with previous studies. These stressors include academic stressors such as writing scientific papers, final exams (thesis), and course load. In addition, problems with friends and experiencing failure are other stressors most students perceive in this study (Pedrelli, Nyer, Yeung, Zulauf, & Wilens, 2015).

Our study revealed that daily consumption of saffron for two weeks significantly reduced the severity of depression and alleviated students' moods and emotions. In this study, saffron is prepared as a brewed-drinks, which is made by boiling five dried saffron strands in 200 ml of warm water. These saffron-brewed drinks were consumed twice daily (morning and evening) for a therapeutic effect. Following this treatment, students reported the therapeutic effect of saffron and a mood stabilizer. Most students said that while consuming saffron, their mood was more stable, and their emotion was more positive.

Furthermore, students revealed alleviation of depressive symptoms (being sad or feeling of inferiority). This result agrees with other studies which conducted saffron supplementation in depressed-mood adults with a similar result that saffron has a beneficial effect on subjective mood and emotional well-being. The saffron extract improves subclinical depressive symptoms and may increase resilience against developing lower mood-related psychiatric disorders (Marx et al., 2019). Depression is a psychiatric illness, with the primary symptom being mood disturbances.

The significant symptoms were prolonged sadness, anxiety, loss of interest and joy, lack of energy, and decreased activity. Therefore, relieving mood was the leading indicator of improvement in depressive symptoms. Our study finding reflects a growing body of evidence supporting using saffron as an antidepressant with no adverse effects. This is consistent with the previous study where giving saffron for eight weeks to postpartum mothers who experienced depression was clinically established to reduce depression. Other studies have also supported that saffron can reduce depression scores in depressed patients (Ghaderi et al., 2020).

Theoretically underlying, saffron contains compounds that have the same effect as antidepressant drugs such as fluoxetine, imipramine, and citalopram. The mechanism of action of saffron as an antidepressant is explored through in-vivo studies on mice (Hosseini, Razavi, & Hosseinzadeh, 2018). Scientifically evident, traditional uses of saffron as an antidepressant proposed that saffron exerts its antidepressant effect by increasing certain protein secretion levels that lead to structural and functional modification of the hippocampus or neurogenesis in the hippocampus (Hassani et al., 2014). The hippocampus is a region in the brain that plays a central role in processing emotions and controlling behaviour in response to fear, anxiety, and depression. The primary cause of depression is a neurochemical imbalance in the brain responsible for regulating mood, anxiety, cognition, and feelings afraid in the hippocampus (Kemp, Lickel, & Deacon, 2014). Antidepressants can stimulate the proliferation of neural progenitor cells in the hippocampus and restore lost volume hippocampus in depressed patients (Kemp, Lickel, & Deacon, 2014).

Moreover, the administration of saffron was indicated to cause antidepressant effects in the mice by modulating the level of certain neurotransmitters in the brain, including serotonin (a mood-elevating neurotransmitter). Saffron is strongly suspected of inhibiting the reuptake of monoamine neurotransmitters, including norepinephrine, dopamine, and serotonin; therefore, it can improve mood. Apart from inhibiting the secretion of certain neurotransmitters, saffron is also indicated to inhibit the formation of pro-inflammatory profiles and free radicals (Hosseini, Razavi, & Hosseinzadeh, 2018). The release of cytokine pro-inflammatory and lack of anti-inflammatory production causes depression in individuals. Experiments on animals show that pro-inflammatory cytokines stimulate the hypothalamus to release Corticotropin-Releasing Hormone (CRH) via the hormone adrenocorticotropic (ACTH), which then induces glucocorticoid (GC) secretion. The excess secretions of GC cause interference with GC receptors in the hippocampus, which affect the GC feedback system. Similar neuroendocrine changes also occur in patients with cytokine-induced depression and reduced serotonin. Thus, the administration of saffron, which inhibits the formation of pro-inflammatory cytokines, eventually increases serotonin levels in the brain and reduces depression. The current study shows that administering saffron for two weeks lowers depression rates and relieves depressive symptoms among college students.

Conclusion

The prevalence of depression among college students at mild and moderate levels is high. It concluded that depression is a significant health problem that requires ongoing management. According to the study, saffron consumption for two weeks effectively treats depression in university students. Available evidence suggests that saffron may be a safe alternative treatment that can reduce symptoms of depression. Future studies were required to validate our findings with different populations of interest.

Author's declaration

The authors made substantial contributions to the conception and design of the study and took responsibility for data analysis, interpretation, and discussion of results. For manuscript preparation, all the authors read and approved the final version of the paper.

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