PILOT STUDY

Co-administration of saffron and chamomile: to determine the efficacy as an adjuvant therapy for mild to moderate depression in human subjects. A pilot randomized clinical trial

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Abstract

Objective: To determine the combined effects of chamomile and saffron herbs as an adjuvant therapy in patients with metabolic alterations associated with mild to moderate depression.

Method: The prospective, randomised, blinded, end-point pilot study was conducted at the Aga Khan University, Karachi, from August to October 2020, and comprised patients with mild to moderate depression with or without diabetes, hypertension and dyslipidaemia. The subjects were randomised into intervention group A, which was given herbal tea sachets containing saffron 1mg and chamomile 20mg for twice a day oral use for a month along with medications, and control group B, which was advised to continue their routine medications. Data was collected at baseline and post-intervention using Patient Health Questionnaire-9 for assessing depression severity, and blood samples for cholesterol estimations. Data was analysed using SPSS 20.

Results: Of the 50 subjects, 25(50%) were in each of the two groups. Cholesterol, high-density lipoprotein, low-density lipoprotein and depression values were significantly better in group A than in group B ($p<0.05$).

Conclusion: Potential benefits of combined doses of chamomile and saffron were found in depressive patients by improving metabolic alterations.

Key Words: Chamomile, Saffron, Depression, Hyperlipidaemia

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Introduction

Depression is a widespread psychological disorder that can be exacerbated by a variety of traumatic situations, seasonal changes and postpartum conditions[1]. It often manifests as unpleasant sensations, insomnia, psychomotor agitation, changes in appetite, recurrent thoughts of death and premature mortality. In older people, depression increases risks of cardiac diseases and death, and reduces the ability of older people to rehabilitate. Worldwide, cases of depression are on the rise, with the prevalence of depression in Karachi being as high as 25-30%[2]. The etiopathogenesis of depression is frequently associated with altered concentration and function of biogenic amines, like serotonin, dopamine and norepinephrine, in the brain[3].

The lack of pathophysiological understanding endures a challenging situation in the diagnosis and management of depression, therefore, identification is done on the basis of psychiatric rating scales. Patient Health Questionaire-9 (PHQ-9) is phenomenologically based on the usage of questionnaires that are regularly updated, but have remained conceptually unchanged for several decades. The latest being Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5). As such, the classification systems currently used are mainly created on observational agreements, but not primarily on empirical findings. The assessment of peripheral markers along with rating scale might be more reliable to diagnose the condition. Cellular integrity is highly affected by the level of biomolecules, notably lipids, as they have the critical role of maintaining cellular permeability. Additionally, transport of neurotransmitters is also affected by the presence of lipids in the cell membrane. Despite their abundance in brain, cholesterol levels are tightly controlled for brain functions. The normal physiological functions of neurons are reflected by the synaptic transmission. The regulation of lipids is critical for membrane fluidity and synapse formation[4].

The average life expectancy of depressive patients has reduced due to high rates of comorbid diseases, mostly cardiovascular diseases (CVDs) associated with altered cholesterol metabolism. However, the association between CVD and depression is not clear. It has been seen that depressive patients are more prone to develop CVD.

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It is hypothesised that the altered level of cholesterol in depression may have some link with CVD[5]. CVD is manifested by atherogenic lipids, including low-density lipoprotein (LDL), and deficiency of high-density lipoprotein (HDL) promotes atherosclerosis. Likewise, increased LDL/HDL ratio is reported in depressive patients. Increased level of LDL with its apolipoprotein B (apo B) and significant decrease in HDL level with its apolipoprotein A (apo A) is reported in depression [6]. High levels of serum cholesterol are often seen in generalised anxiety disorder (GAD). Studies have reported increased lipid profile in major depressive disorder (MDD) and GAD cases. The overemphasised serum cholesterol may contribute to elevating of the production of cytokines, including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) following the inflammatory response in neuronal cells, it compromises neuronal plasticity[7]. Moreover, cholesterol and glycosphingolipid-rich lipid microdomains or rafts are important components of neuronal cell membrane that facilitates transport of monoamines and neurotransmitters that play important role in saneness, rationality and neuronal stability. Any abnormal alteration in synthesis, composition or functionality of these lipid-rich rafts may lead to neurological mayhem, especially depression[8]. Therefore, abnormal cholesterol metabolism elicits clinical symptoms, such as mood disorders, impaired cognition, insomnia, fatigue and depressive emotions[9].

The treatment of depression mainly comprises pharmacological management through antidepressants drugs, approved by the food and drug administration (FDA), that usually act via mediation of neurotransmitter levels in brain[10]. Studies have shown that these antidepressants can precipitate contrary effects, such as addiction, insomnia, suicidal tendencies, worsening depressive episodes and tolerance for chronic antidepressant medications[11]. Therefore, due to the trepidation of adverse effects, there is a worldwide trend towards the utilisation of alternative remedies for depression management[12].

There are several medicinal plants that possess protective effects against metabolic disorders, like diabetes, hypercholesterolaemia, menstrual disorders and infertility, and pathologies, like pyrexia gastric ulcers, insomnia, anxiety and depression. Crocus sativus L., commonly known as saffron, and Matricaria chamomile L., commonly known as chamomile, are the top botanical plants that possess cardioprotective and neuroprotective effects; safe and tolerated well in high-dose ranges[13]. Saffron has shown to be effective for the treatment of coronary ailments, hypertension, dysmenorrhoea, stomach disorders, dysmenorrhoea, depression and dementia[14]. Evidence through animal studies and clinical trials suggest that administration of saffron as whole or its main constituents (crocetin and safranal) alone can increase brain glutamate, serotonin and dopamine content, leading to antidepressant and anxiolytic effects[15]. Chamomile possess neuroprotective and anxiolytic effects in human and animal studies[16-17]. Based on the medicinal use of these herbs in lipid metabolomics and depression[18], the current study was planned to determine the combined effects of chamomile and saffron herbs as an adjuvant therapy in patients with metabolic alterations associated with mild to moderate depression.

Patients and Methods

The prospective, randomised, blinded, end-point pilot study was conducted at the Aga Khan University (AKU), Karachi, from August to October 2020. The trial was registered with ClinicalTrials.gov (Identifier: NCT04935671). After approval from the institutional ethics review committee, the sample size was calculated while expecting a 20% dropout rate.

Sixty samples were randomly selected for the pilot study considering the prevalence of 30% of depression[2] using OpenEpi Calculator[19].

All potential subjects were examined by a consultant psychiatrist in the outpatient setting at the Aga Khan University Hospital (AKUH), Karachi. Depression scores were obtained through PHQ-9, and data was collected by a researcher who was blinded to treatment allocation. Those included were patients with mild to moderate depression with or without diabetes, hypertension, and/or dyslipidaemia. Those with terminal diseases, cancer and morbid depression requiring hospitalisation were excluded. After obtaining informed written consent, the patients were randomised into intervention group A and control group B.

Dried packed floral parts of chamomile, known as Baboona herb in the native Urdu language, and stamens of saffron, known in Urdu as Zaafaran, were purchased from a local supermarket, and a sample of these plant materials were assigned the herbarium-voucher number MC-FL-08-18-05 for chamomile and CS-ST-08-18-05 for saffron, to be preserved at the Natural Products Research Division of the Department of Biological and Biomedical Sciences, AKU. Tea bags were prepared with 20mg of chamomile and 1mg of saffron. Group A subjects were given the herbal tea sachets for oral intake twice a day oral intake as decoction for one month. The doses were selected based on studies indicating that the herbs

increase positive mood and relieve depression at different doses; chamomile at 30-100mg is beneficial for the management of depression in humans, and saffron at 30mg produces effects similar to that of fluoxetine in patients with major depressive disorder[16, 20]. As saffron bears strong aroma, peculiar taste and is extravagantly expensive, the current study kept its usage at 1mg and the corresponding chamomile dose of 20mg. No specific changes in diet or lifestyle were imposed on the patients. Blood samples were collected for estimating serum levels of fasting lipid profile. The collection of blood samples was done at the AKU clinical laboratory. The entire sample was subjected to blood samples and PHQ-9 at baseline and post-intervention.

Data was analysed using SPSS 20. Repeated measures two-way analysis of variance (ANOVA) was used in which time course (baseline vs treatment phase) was the within-subjects factors, while groups (interventions vs controls) represented the between-subjects factor. The primary dependent measures were PHQ-9 score and lipid profile. Pair-wise comparisons by Bonferroni test were applied, and p≤0.05 was considered statistically significant.

Results

Of the 50 subjects, 25(50%) were in each of the two groups (Figure 1). Cholesterol levels showed a significant effect of time course (F1,48=53.043, p<0.01), treatment (F1,48=0.510, p<0.479) and significant interaction between time course and treatment (F1,48=0.510, p<0.01). There were no significant differences in cholesterol levels between the groups at baseline (p>0.05), but the level of cholesterol was significantly reduced within group A (p<0.01) and in comparison with group B (p<0.01).

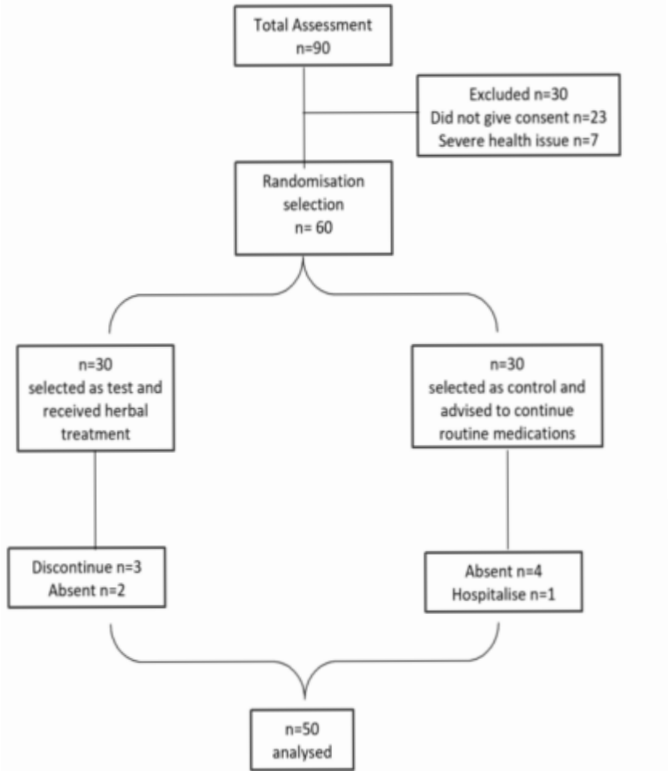

Figure-1: Flow chart of the study protocol and selection process.

Table: The effects of saffron and chamomile herbal tea on cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL).

	Control (Before: Beginning of trial- no herbs)	Control (After: End of trial- no herbs)	Test (Beginning of trial - no herbs)	Test (End of trial herbs used 4 weeks)
Cholesterol	217±2.6	206±1.9	216±2.3	173±2.2 $^{a'b'c'}$
HDL	37±0.9	36±0.5	35±0.9	46±0.7 ^{abc}
LDL	155±1.8	148±1.2	127±1.6a′	97±1.4 $^{a'b'c'}$

Values are presented as mean ± SD., HDL=High Density Lipoprotein LDL=Low Density Lipoprotein

HDL levels showed a significant effect of time course (F1,48=9.227, p<0.01) and treatment (F1,48=9.321, p<0.01), while the interaction between time course and treatment (F1,48=5.831, p<0.479) was not significant. HDL levels significantly increased (p<0.05) in group A post-treatment compared to baseline and in relation with group B (p<0.05).

LDL levels showed significant effects of time course (F1,48=78.588, p<0.001) and treatment (F1,48=47.723, p<0.01), but no significant interaction was found between time course and treatment (F1,48=76.728, p<0.479). Post-intervention LDL levels within group A and in comparison with group B were significantly better (p<0.01) (Table 1).

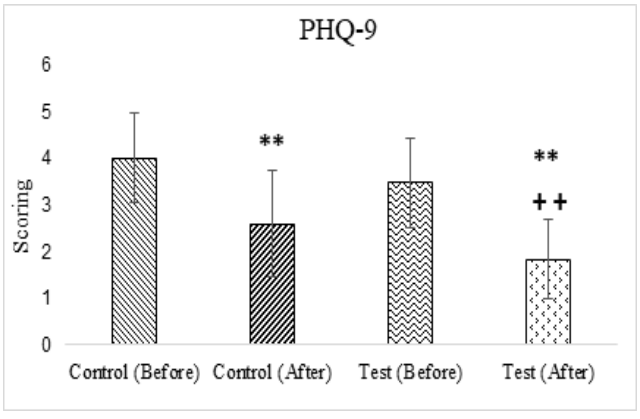

Figure-2: The effects of saffron and chamomile herbal tea on Patient Health Questionnaire-9 (PHQ-9) scoring.
**p<0.01 compared to baseline, ++p<0.01 compared to baseline.

PHQ-9 score showed a significant effect of time course ($F_{1,48}$= 81.832, $p<0.001$) and treatment ($F_{1,48}$=8.23, $p<0.01$), but there was no significant interaction between time course and treatment ($F_{1,48}$=0.510, $p<0.479$). The severity of depressive behaviour reduced significantly ($p<0.01$) in both groups after one month compared to the baseline ($p<0.05$), but group A showed highly significant improvement ($p<0.01$) compared to group B (Figure 2).

Discussion

Depression is a frequently diagnosed psychological disorder associated with mood disturbances commonly triggered by biogenic amine deficiency in the brain. The normal physiological metabolism of biogenic amines depends upon the bioavailability of their precursor amino acids[5], and their depletion may cause multiple neuronal alterations, especially depression. The first-line treatment for depression are antidepressants that modulate neurotransmitter concentration by blocking their reuptake [21]. Recent studies are involved in unveiling new mechanistic targets effective for depression and associated metabolic disorders. As a result, novel agents extracted from natural products and synthetic compounds produced are meticulously tested in the hope of finding a curable and cost-effective treatment of depression associated with altered lipid metabolism. The present randomised clinical trial (RCT) was designed to evaluate the antidepressant effects of combined chamomile and saffron herbal tea in depressed patients. It was observed that the herbal tea twice a day for a month along with routine antidepressants showed significant improvement in the PHQ-9 scale and lipid profile of the depressed subjects.

The present study showed that the concomitant administration of saffron and chamomile maintained blood glucose and cholesterol levels within a healthy range. This may be manifested through modulation of carbohydrate metabolism through augmentation of either peripheral glucose uptake, increased glycogen storage, or insulin secretion[21,22]. The hypoglycaemic effects of chamomile are shown to be independent of insulin secretion and it has protective effects on pancreatic beta cells. The combined treatment supported the synergic effects of chamomile and saffron. The extract of saffron, due to the presence of its biochemical constituents such as crocin, is previously reported to regulate the serum lipids concentration, including cholesterol, triglycerides (TG) and LDL with positive impact on the concentration of HDL, and the mechanism behind the effect is mainly the suppression of pancreatic lipase activity[23]. Chamomile, likewise, also exerts the lipid-lowering effects by the activation of peroxisome proliferator-activated receptors (PPARs) in the liver. The bioactive compound of chamomile, coumarin, has drawn attention due to pharmacological effects in hyperglycaemia. Umbelliferone, another active compound of chamomile, reduced TGs and free fatty acid in alcoholic fatty liver[17]. The flavonoids of chamomile, like luteolin, quercetin and rutin, exert the antioxidative effects and suppress the level of inflammatory cytokines, including IL-6 and TNF-α. The regulation of adenosine 3′,5′-monophosphate (AMP)-activated protein kinase (AMPK) pathway, which is the regulatory pathway for glucose and lipid, is often seen by luteolin supplementation. These cardioprotective effects are often seen by the active chemicals of saffron. The presence of crocetin is reported to reduce the cholesterol and promote cardioprotective effects in rabbits. It is suggested that the proportion of flavonoid, including apigenin, exert the antidepressant effects by modulatng monoamine neurotransmitters, especially serotonin and dopamine[23]. Traditionally, chamomile has been used in aromatherapy as tranquiliser for the treatment of insomnia. It may be due to the binding effects of apigenin, a flavonoid of chamomile that has been reported to exert benzodiazepine-induced hypnotic effects. The inhalation of chamomile in aromatherapy reduced the plasma adrenocorticotropic hormone (ACTH) levels[24]. A study, done in animal models of diabetes and its associated complications to evaluate the pharmacological effects of combined half doses of chamomile and saffron, confirmed that diabetes-associated complications are initiated by metabolic disturbances due to hyperglycaemia which led to increase in oxidative stress and lipid peroxidation. Two-week treatment of saffron and chamomile produces strong antidiabetic as well as anti-hyperlipidaemic effects by preserving the structural stability of the pancreas due to the presence of crocin and safranal entities of saffron. The administration of herbal extract reduced the total lipid contents by augmentation of HDL concentration. The antioxidative effects were seen in hippocampus and cortex which improved the cognitive performance and neurotransmitter levels in depressed murine model[25].

Flavonoid content of chamomile can produce anxiolytic activity by affecting and modulation of γ-amino butyric acid (GABA), noradrenaline (NA), dopamine (DA), and serotonin neurotransmission as well as hypothalamic-pituitary-adnercontical (HPA) axis modulation[16]. Saffron has been implicated in producing neuroprotective effects possibly through preservation of the brain neurochemistry and conservation of neuronal structure and functions. The administration of chamomile is associated with monoamine release in amygdala and

hypothalamus which is responsible for reduced immobility in forced swim test (FST) of rats, hence producing antidepressant effects[26]. A preclinical trial reported that multiple parts of saffron inhibited serotonin high affinity reuptake inhibitors to ensure long-term availability of serotonin in combatting depression. These therapeutic effects of saffron may be attributed to a number of its compounds, such as crocins, crocetin and safranal, containing strong antioxidant properties against proinflammatory cytokines and reactive oxygen species[18]. Previous research has shown that the distribution of dyslipidaemia and depression are known to be normally distributed in the population[27]. In addition to these attributes, normalisation of cholesterol genesis and metabolism lead to higher functionality of the lipid microdomains and rafts that act as regulators of monoaminergic signalling in brain bringing forth emotional and mood regulation.

The current study has imitations. The depression scale used can only be executed through a questionnaire in a small number of subjects suffering from mild to moderate depression. To validate the current findings, an phase 2 trial RCT comprising a large sample size, including patients suffering from severe depression, is needed.

Despite the limitations, however, the current study serves the purpose of finding a novel alternative treatment option for depression through co-administration of saffron and chamomile. The dosage of the drug used was much lower than the dosage required for a single herb, and that makes the treatment easily affordable and highly acceptable to local depression patients

Conclusion

The effectiveness of the combination of Saffron and chamomile herbs in treating mild to moderate depression was established within the sample.

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Conflict of Interest: None.

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