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Research Article

Appetite-inducing effect and safety evaluation of Habb-e-Hilteet in patients with *Ḍu'f al-Ishtihā* (anorexia): An open prospective clinical trial

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Abstract

Objectives: Anorexia is one among the most prevalent conditions triggering malnutrition, drastic weight loss and serious health issues in people especially older adults. Habb-e-Hilteet is commonly prescribed Unani pharmacopoeial formulation for anorexia. However, no scientific data is available as to its safety and efficacy. The current study assessed the appetite-inducing effect and safety of Habb-e-Hilteet in *Ḍu'f al-Ishtihā* (anorexia) patients.

Methods: An open prospective clinical trial was carried out in 95 clinically diagnosed anorexia patients of either gender (19-65 yrs old). The study was approved by Institutional ethic committee and conducted in accordance with the GCP guidelines. Habb-e-Hilteet, 1 pill (500mg) was administered orally in patients twice daily for 14 days. The safety of the formulation was assessed by important pathological and biochemical indices and monitoring adverse events. The efficacy was assessed on the basis of improvement in the Simplified Nutritional Appetite Questionnaire (SNAQ) score.

Results: Out of 95 patients recruited, 78 completed the trial and 17 patients lost to follow-up. The mean age of patients was 29.8 yrs, with the majority (59.0%) being female. Overall therapeutic response was found to be 96%. A significant (P<0.05) increase in the mean SNAQ score was observed after 7 and 14 days of treatment when compared to baseline. No significant difference before and after treatment was observed in pathological and biochemical indices. No adverse events were reported during the entire study period.

Conclusion: The study results indicate that Habb-e-Hilteet could be a viable treatment option for anorexia with no safety concerns.

Keywords: *Ḍu'f al-Ishtihā*; *Buṭlān al-Shahwa*; Anorexia; Habb-e-Hilteet; Unani pharmacopoeal formulation.

INTRODUCTION

Appetite is a person's desire of eating food to fulfill the bodily need. It can be divided into three components i.e. hunger, satiation and satiety. Hunger is the sensation that stimulates the consumption of food, satiation is the sense of fullness during eating that leads to meal termination and satiety is the fullness that exists between eating occasions [1]. When a person lacks the urge to eat and his daily food intake is extremely decreased, it is termed as anorexia. Anorexia or loss of appetite is a major digestive system disorder that affects a majority of people particularly in advanced age. It is characterized by the absence of hunger in patients and caused due to varied reasons such as age, acute or chronic disease conditions, and use of medications [1,2]. Anorexia is reported to be a common symptom present in cancer patients and has frequently been observed in patients during chemotherapy [2,3]. Between 15% and 30% of older people are estimated to have anorexia of ageing, with higher rates in women, nursing home residents, hospitalized people and with increasing age [1].

Anorexia or reduced appetite can cause nutritional deficiency leading to drastic weight loss and associated complications that can negatively impact the overall health, well-being, and quality of life of the patient [1,2,4]. Anorexia associated nutritional deficiency results in physical and mental growth retardation in children and also makes elderly immunocompromised and susceptible to infection [2]. Weight loss associated with anorexia complicates several diseases such as cancer, AIDS, cardiac failure, and may result in devastating consequences in people regardless of their age group with seriously negative impact in elderly. The complications of anorexia associated weight loss in advanced age include frailty, falls, hip fractures, compromised immunity, and pressure ulcers. Regaining the lost weight is also challenging in elderly [1,4]. Anorexia may be acute or chronic and long-lasting in nature. Acute decrease or loss of appetite occurs in response of digestive problems or acute illnesses such as viral or bacterial infections. Chronic anorexia is caused due to serious underlying conditions and persists for long. It usually occurs in elderly and patients suffering from chronic kidney disease, cardiac diseases, cancer, dementia, depression and attention deficit hyperactivity disorder [1,5-8].

Anorexia and decreased appetite have been discussed in detail in Unani classical literature. *Ḍu'f al-Ishtihā / Nuqṣān al-Shahwa / Qilla al-Shahwa* are the terms used to describe loss or poor appetite, whereas the Arabic terms used to describe complete loss of appetite are *Buṭlān al-Shahwa / Suqūṭ al-Shahwa / Dhahāb al-Shahwa*. The term '*Shahwa* and *Ishtihā*'

means appetite, *Nuqṣān / Qilla* or *Ḍu'f* means decrease or weakness, whereas *Buṭlān / Suqūṭ / Dhahāb* means complete loss. However, the term *Ḍu'f al-Ishtihā* is commonly used to denote anorexia. These are the conditions where a patient lacks the urge to eat and his daily food intake is reduced or completely lost [9,10]. According to the Unani literature *Ḍu'f al-Ishtihā* is caused due to varied reasons which may include *Su'-i-Mizāj Ḥārr* (impaired hot temperament), *Su'-i-Mizāj Bārid* (impaired cold temperament), accumulation of *Ṣafrā'* (yellow bile), *Balgham Māliḥ* (saline phlegm), *Balgham Lazij* (viscid phlegm), *Balgham Muntin* (mephitic phlegm), *Balgham Khām* (raw phlegm) and *Khām Akhlāt* (raw humours) in the stomach. It may also be caused due to *Ḍu'f al-Mi'da* (gastric debility), Qurūḥ-i-Mi'da (gastric ulcers), *Ḍu'f al-Kabid* (hepatic insufficiency), *Waram al-Kabid* (hepatitis), *Sudad al-Kabid* (obstruction in liver) and other *Amraḍ Muzmina* (chronic diseases). Anorexia or decreased appetite can be a symptom of fever which is usually pronounced in epidemic fever. It may also be present in patients with anxiety, depression, sorrow, grief and anger. Loss of sensory response of pylorus may also cause anorexia [9,11-13].

Patients suffering from anorexia or decreased appetite may present different symptoms other than decreased or lost appetite based on the factor involved in the causation of the diseases. Common symptoms may include belching, burning sensation in epigastrium, excessive thirst, excessive salivation, nausea, vomiting, halitosis weight loss and general weakness. Anorexia is usually more pronounced after eating food as the digestive system of the person is unable to properly digest the food. In case, the person tries to eat, frequent or occasional vomiting occurs expelling the undigested food [9,11,12]. A temporary loss in the appetite is an opportunity to have a look at the eating habits and personal health of the patient, whereas, long continuous stretches of loss of appetite may be a matter of serious concern. An early detection of appetite loss before nutritional deficiencies and weight loss occur, may allow an early intervention resulting in prevention and restoration of health [1].

STUDY RATIONALE

The prevalence of mild to severe anorexia in India has been reported to be as high as 93% in patients with severe illness, especially infectious diseases with typhoid being the most common cause. The risk of anorexia was found to be 1.5 times higher in patients with a past history of any disease [14]. It is highly crucial to understand and rule out the underlying conditions of anorexia for choosing appropriate treatment option. The use of appetite stimulating medications appears to be better treatment option for alleviating anorexia that may help patients enhance their appetite and gain weight, thereby improving their quality of life [2]. In Unani medicine, numerous treatment options for anorexia and poor appetite have been advocated by Unani physicians, based on the factors involved in the causation of the disease. There are so many *Mufrad* (single) as well as *Murakkab* (compound) formulations mentioned in Unani classical texts that have been used since ages for the successful management of anorexia. Habb-e-Hilteet is one such important Unani pharmacopoeial formulation prescribed frequently by Unani physicians to relieve anorexia and decreased appetite. However, no scientific data is available as to its safety and efficacy, therefore, proposed for the present clinical trial in patient with *Ḍu'f al-Ishtihā* (anorexia).

METHODOLOGY

An open prospective clinical trial was carried out to assess the safety and efficacy of Unani Pharmacopoeial formulation 'Habb-e-Hilteet' in patients with anorexia at Regional Research Institute of Unani Medicine (RRIUM), Chennai in OPD setting. Ethical approval was obtained from the Institutional Ethics Committee, RRIUM, Chennai, and study protocol was registered in Clinical Trial Registry-India with the registration number CTRI/2018/12/016577, prior to initiation of the study. The study was conducted in accordance with the GCP guidelines. Patients of either gender in the age group of 19-65 yrs with the chief complaint of *Ḍu'f al-Ishtihā* (anorexia) without any specific cause, willing to participate in the study were recruited after getting duly signed voluntary informed consent. Patients having anorexia nervosa, any systemic disease including cardiac, hepatic and renal ailments; patients with chronic debilitating diseases, tuberculosis, diabetes mellitus; pregnant and lactating women; patients with the history of alcohol or drug addiction and patients with the history of hypersensitivity to the study drug or any of its ingredients were excluded. The temperament of the study participants was assessed based on the standard format developed by CCRUM, Ministry of Ayush, Govt. of India, at baseline and after 14 days of treatment.

Study drug details and mode of intervention

The study drug, Habb-e-Hilteet comprising 4 ingredients *viz.* Zanjabeel (*Zingiber officianale* Roscoe), Hilteet (*Ferula foetida* Regel), Tankar (borax) and Namak-e-Sang (rock salt) [15] was prepared in a single batch at the Council's GMP certified drug manufacturing Unit at National Research Institute of Unani Medicine for Skin Disorders (NRIUMSD), Hyderabad and made available to the study site. All study drugs were kept in a secure place under adequate storage conditions - protected from moisture and stored at room temperature. The study participants were dispensed drug for one week at a time with instructions to return the unconsumed drug (if any) at the next visit. This procedure was repeated for the whole duration of the study. Each l weeks' supply of drug comprising 1 pack of Habb-e-Hilteet (14 Pills of 500 mg each) was dispensed in sealed plastic containers. A total number of 28 pills were dispensed to each patient as the study duration was 14 days. Patients were advised to take one pill twice daily with water one hour after meal. No concomitant therapy was allowed during the study. The patients were assessed clinically after 7 days and 14 days of treatment. The subjective and objective clinical observations were recorded in the Case Record Form.

Assessment of efficacy and safety

The efficacy of the drug was assessed on the basis of improvement observed in the appetite for which the Simplified Nutritional Appetite Questionnaire (SNAQ) was employed. All the patients were asked to complete the SNAQ, which is a 4-item single-domain questionnaire. Responses are scored by using a 5-point (A to E), verbally labeled, Likert-type scale. The total SNAQ score is the sum of scores on the items, with lower scores indicating deterioration in appetite. The SNAQ score may range from 4 (worst) to 20 (best). A SNAQ score ≤ 14 may identify persons with anorexia at significant risk of at least 5% weight loss within six months [4]. The results of the study were recorded in terms of percentage efficacy as calculated from the increment in SNAQ score. The safety of the drug was assessed by recording adverse events (if any) and relevant pathological and biochemical indices such as haemoglobin, erythrocyte sedimentation rate (ESR), serum bilirubin, serum glutamic-oxaloacetic transaminase (SGOT/AST), serum glutamic-pyruvic transaminase (SGPT/ALT), alkaline phosphatase (ALP), serum creatinine and blood urea nitrogen (BUN). These laboratory investigations were carried out at baseline and after 14 days of treatment and the results obtained were compared.

Statistical analysis

After completion of the study, data obtained was analyzed statistically to evaluate the significance of results. The discrete

variables were expressed as frequency (percentage) and continuous variables were expressed as mean with standard deviation (Mean SD). To assess the mean SNAQ score changes and the mean difference in pathological and biochemical indices between the baseline and last follow up of treatment, paired t-test was used. All tests are two tailed and the P-value <0.05 was considered as significant. Repeated measures ANOVA was used to find out the mean change in weight and BMI with respect to SNAQ score groups (<=14 and >14) between baseline and last follow-up.

RESULTS

In the current study, a total number of 95 patients were enrolled, of which 17 participants were lost to follow-up due to varied reasons and 78 patients completed the trial.

Table 1 illustrates the demographic profile of patients with anorexia in the present study. The mean age of the study population was found to be 29.8 ±10.47 y, with a higher rate (59.0%) of occurrence in women. The median and IQR (inter quartile range) for duration of disease was 8 (1-24) months and 51% patients were found to be with less than three months duration of diseases. The data of marital and socio-economic status of the participants revealed that 62.8% patients were married and the remaining 37.2% were unmarried with a slightly higher rate (53.8%) in patients with low socio-economic status. The percentage of temperament wise patients observed in *Damawī* (Sanguineous), *Balghamī* (Phlegmatic), *Ṣafrāwī* (Bilious) and Sawdāwī (Melancholic) were 30.8%, 39.7%, 17.9% and 11.5% respectively.

Table 1: Demographic profile of *Ḍu'f al-Ishtihā* (Anorexia) patients (*n*=78).

Characteristics	Frequency (%)
Age (Year)	
<=30 (%)	46 (59%)
>30 (%)	32 (41%)
Age (years) Mean ± SD	29.8 ±10.47
Gender (%)	
Male	32 (41%)
Female	46 (59%)
Duration of disease (Month)	
<=3 (%)	40 (51.3%)
>3 (%)	38 (48.7%)
Median (IQR)	8 (1-24)
Marital status (%)	
Married	49 (62.8%)
Unmarried	29 (37.2%)
Socio Economic Status (%)	
Lower	42 (53.8%)
Middle	36 (46.2%)
Mizaj (%)	
Damawī (Sanguineous)	24 (30.8%)
Balghamī (Phlegmatic)	31(39.7%)
Ṣafrāwī (Bilious)	14(17.9%)
Sawdāwī (Melancholic)	9(11.5%)

Figure 1 represents the overall treatment response of study participants treated with Habb-e-Hilteet. The results revealed that in study participants, who completed the trial, 79.5% were relieved, 16.7% were partially relieved and 3.8% participants showed no relief. A significant (P<0.05) increase in the mean SNAQ score was observed after 7 days and 14 days of treatment when compared to baseline score. The mean SNAQ score at baseline, first follow up and last follow up was found to be 8.8 ± 2.03, 13.3 ± 2.17 and 16.0 ± 1.68 respectively **(Figure 2)**.

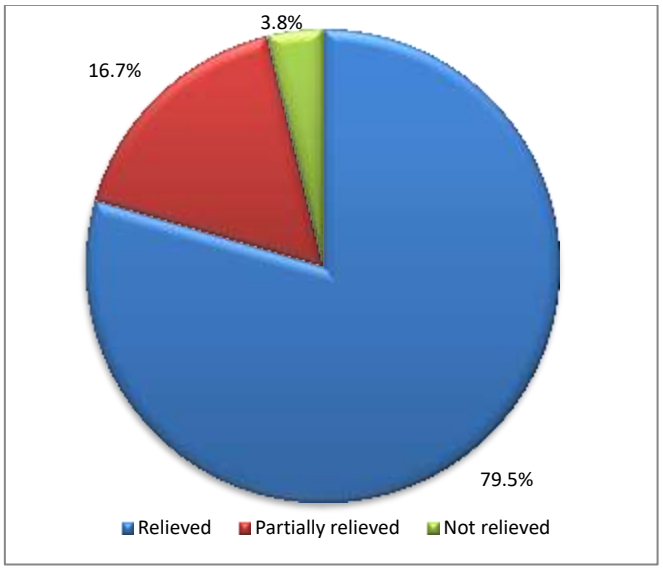
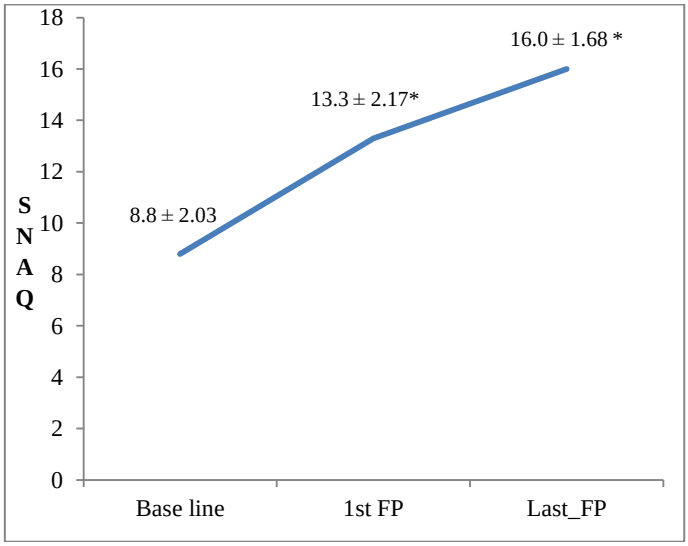


Figure 1: Response of treatment in patient with *Ḍu'f al-Ishtihā* treated with Habb-e-Hilteet (*n*=78).



**significant at 5% level*

Figure 2: The mean SNAQ score in *Ḍu'f al-Ishtihā* patients treated with Habb-e-Hilteet at 1st follow up and last follow up when compared to baseline (P<0.05). All values are expressed as Mean ± SD (*n*=78).

The mean weight (kg) and BMI (kg/m^2) in patient with SNAQ score equal to or less than 14 at baseline was found to be 46.9 ± 8.4 and 18.9 ± 3.5 respectively, whereas in patients with SNAQ score more than 14, the mean weight and BMI was found to be 52.5 ± 11.4 and 20.4 ± 4.5 respectively. After 14 days of treatment, the mean weight and BMI in patient with SNAQ score equal to or less than 14 was recorded as 47.8 ± 8.3 and 19.3 ± 3.6 respectively, whereas in patients with SNAQ score more than 14, the mean weight and BMI was 53.8 ± 11.2 and 20.8 ± 4.1 respectively **(Table 2)**.

Table 3 represents the findings of pathological and biochemical indices, carried out at baseline and after treatment to assess the safety of Habb-e-Hilteet. No significant (P>0.05) difference was found in the mean value between the baseline and after the treatment of all pathological and biochemical parameters except alkaline phosphate which was found significant (P<0.05).

Table 2: The mean weight and BMI in *Ḍu'f al-Ishtihā* patient by SNAQ score at baseline and after treatment with Habb-e-Hilteet.

Variable	SNAQ score	Mean ± SD (Baseline)	Mean ± SD (After treatment)	P-value
Weight (kg)	<= 14	46.9 ± 8.4	47.8 ± 8.3	0.097
	>14	52.5 ± 11.4	53.8 ± 11.2	
BMI (kg/m^2)	<= 14	18.9 ± 3.5	19.3 ± 3.6	0.262
	>14	20.4 ± 4.5	20.8 ± 4.1	

All values are expressed as Mean ± SD, (*n* = 78). BMI represents body mass index; SNAQ, Simplified Nutritional Appetite Questionnaire.

Table 3: Pathological and biochemical indices at baseline and after treatment in *Ḍu'f al-Ishtihā* patients treated with Habb-e-Hilteet (*n*=78).

Parameter	Base line Mean ±S.D	After Treatment Mean ± S.D	P-value
Hb (mg/dL)	12.8 ± 1.81	12.8 ± 1.75	0.851
ESR (mm)1st hour	17.6 ± 16.13	16.0 ± 14.51	0.263
S. bilirubin (mg/dL)	0.6 ± 0.16	0.5 ± 0.11	0.055
SGOT Units/L	17.6 ± 4.18	17.4 ± 3.61	0.527
SGPT Units/L	18.3 ± 4.73	18.7 ± 4.75	0.368
ALP (U/L)	74.4 ± 21.61	70.12 ± 17.87	<0.05*
S. creatinine (mg/dL)	0.68 ± 0.18	0.68 ± 0.16	0.655
BUN (mg/dL)	18.6 ± 5.21	18.8 ± 3.74	0.534

**significant at 5% level*

All values are expressed as Mean ± SD, *n* = 78, (p-value <0.05 significant). SGOT represents serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; ALP, alkaline phosphatase; BUN, blood urea nitrogen.

DISCUSSION

Anorexia or poor appetite is a common problem triggering malnutrition, weight loss and serious health issues in people of all age groups with a higher rate in elderly. Anorexia associated weight decrease in elderly has been considered as an independent predictor of morbidity and mortality [16]. Eating disorders such as anorexia nervosa, bulimia nervosa, binge eating among various others are different entities from loss or poor appetite. These are life threatening conditions grossly affecting physical and mental health of an individual. Eating disorders seek more attention in diagnosing and treating it thoroughly, whereas loss or poor appetite usually requires no serious medical intervention [17]. However persistent decrease in food intake can influence serious consequences. Though certain medications such as megestrole acetate and cyproheptadine hydrochloride have effectively been used to treat anorexia, the adverse effects produced by their use cannot be ignored [16]. Appetite stimulation through traditional pharmacological interventions and dietary approaches may prove vital in enhancing nutrient intake, reducing the risk of malnutrition and weight loss and improving the health status of the patient.

The present study investigated the safety and efficacy profile of Habb-e-Hilteet in patients with *Ḍu'f al-Ishtihā* (anorexia). The demographic profile of patients enrolled in the study demonstrated a significantly higher rate of anorexia presence in young adults below the age of 30 yrs (59%), being more common in students, when compared to the patient above 30 yrs of age (41%). The presence of anorexia in students may be due the excessive stress and pressure in their daily life, as stress, depression and anxiety are known to suppress appetite and reduce food intake [18]. The data of the present study is inconsistent with the previous studies which reported anorexia as more commonly present in elderly [1,19]. The inconsistency may be due to small sample size and limitation of the present study as the patients above 65 yrs of age were excluded from the study. Similar to the literature [19], the present study revealed that anorexia was present more often in female and low income group participants than their other counterparts. The mean duration of disease was 8 months suggesting that most of the participants have already taken other medications before they recruited in the present study. The temperament of majority of patients enrolled in the study was found to be *Balghamī* (Phlegmatic 39.7%) followed by *Damawī* (Sanguineous 30.8%), affirming the phenomenon that excessive *Harārat* or *Burūdat* alone or along with morbid matters is the leading cause of anorexia or poor appetite [10,12,13].

The screening of anorexia using reliable appetite assessment tools is very critical in planning the treatment modalities to limit the chance of malnutrition and weight loss. Assessment tools with high inter-rater reliability, less time consuming and convenient to use are considered to be the best suited tools for assessing anorexia [20]. Various nutritional risk assessment tools have been employed for the assessment of appetite, including Mini Nutritional Assessment tool (MNA), short-form of the MNA (MNA-SF), Seniors in the Community Risk Evaluation for Eating and Nutrition tool (SCREEN), and Functional Assessment of Anorexia Cachexia Therapy (FAACT)

questionnaire. However, these are more time consuming and mostly evaluate multiple interdependent nutritional domains [4]. The Appetite, Hunger and Sensory Perception (AHSP) questionnaire is also a valid and reliable tool, but with scarce adaptability [21]. It is inconvenient to use as it consists of 29 questionnaires and evaluates multiple interdependent domains [20]. The Simplified Nutritional Appetite Questionnaire (SNAQ), a short version of the Council of Nutrition Appetite Questionnaire (CNAQ), is a simple, valid, reliable and more efficient clinical tool used for the assessment of appetite. Both CNAQ and SNAQ were specifically validated for use among elderly individuals, however they were found equally effective and valid among younger adults [4].

In the present study, SNAQ tool was employed for the assessment of appetite of study participants before treatment (at baseline) and after treatment (at 7th and 14th day of treatment). The overall therapeutic response of the tested formulation was found to be 96%, whereas 4% patients showed <30 % improvement in their appetite which was considered as no relief. A gradual increase in SNAQ score was observed in time dependent manner, which was highly significant at post treatment follow up when compared to the baseline score. The result of the present study revealed a modest relationship between the body weight, BMI and SNAQ score. It was observed that the patients with SNAQ score less than or equal to 14 had lower values of body weight and BMI when compared to the patients with SNAQ score more than 14. Though the difference was insignificant, it indicates good performance of SNAQ assessment tool in this study, hence could further be utilized for similar studies. The result also revealed a slight increase in the body weight and BMI after 14 days of treatment in both the groups of patients with SNAQ score less than and more than 14. These results confirm the appetite inducing effect of the tested formulation, which may result in increased energy consumption and weight gain in patients with anorexia. Appetizing agents are considered to be beneficial for improving weight by enhancing energy intake. A study demonstrated 1.6% increase in body weight of elderly individuals on an increase of 137 kcal daily energy consumption for 2 months duration [16]. The long term use of tested formulation may also contribute to weight gain in patient with anorexia and improved quality of life.

The ingredients of the formulation *viz* Zanjabeel (*Zingiber officianale*), Hilteet (*Ferula foetida*), Tankar (borax) and Namak-e-Sang (rock salt) are well known spices and food additives which are highly acclaimed in Unani medicine for their medicinal values including digestive and appetizing properties. These drugs act by virtue of their temperament being hot and their inherent capability to cope with the underlying causes of anorexia or poor appetite [22-25]. Hilteet (asafoetida) and Zanjabeel (ginger) alone or in combination with other drugs are highly recommended by Ibn Sīnā for anorexia [12]. Spices are known not only for enhancing the sensory quality of food but also for exhibiting a wide range of medicinal properties [26]. Beside numerous pharmacological activities, asafoetida and ginger have been reported to exert positive influence on the digestive enzyme activity. Asafoetida and ginger among various spices prominently enhanced pancreatic lipase activity and also stimulated pancreatic amylase in vitro and in vivo. This positive influence could be the contributing factor to the established digestive stimulant action of spices [27,28]. It could be inferred from the observation that the combination of these spices may have yielded a synergistic effect in the formulation, leading to the early digestion, decreased feeling of fullness, thus improving the appetite.

In the present study, the safety profile of Habb-e-Hilteet was assessed by relevant pathological and biochemical indices such as haemoglobin, ESR, serum bilirubin, SGOT, SGPT, ALP, serum creatinine and BUN. All the pathological and biochemical indices were found to be within normal range and no significant difference was observed in the mean value between the baseline and after 14 days of treatment. The activity of ALP after 14 days of treatment showed significant ($P<0.05$) decrease when compared to baseline, which was clinically in the normal range and considered to be the beneficial effect of the treatment. No adverse events (AEs) or serious adverse events (SAEs) and drug intolerance were reported during the entire study period. The result indicates that the drug 'Habb-e-Hilteet' is safe and may effectively be used for the treatment of anorexia.

CONCLUSION

The present study provided beneficial information about appetite stimulating effect of Unani pharmacopoeal formulation 'Habb-e-Hilteet' in patients with *Ḍu'f al-Ishtihā* (anorexia). The study data demonstrated statistically significant improvement in the mean SNAQ score on completion of 7 days and 14 days of treatment. The tested formulation was well tolerated and the course of the study was uneventful with no any undesirable side effects. However, long-term human intervention studies with larger sample size are needed to ascertain the study finding and also to exemplify the sustainability of observed short term effect of the drug in anorexia and associated weight loss.

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Author contributions:

All the authors have accepted the responsibility for the entire content of the submitted manuscript and approved submission.

Competing interests:

Authors state that there is no any conflict of interest in conducting this study.

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