A SYSTEMATIC REVIEW ON EFFICACY AND SAFETY OF UNANI MEDICINES USED IN THE TREATMENT OF OBESITY

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Received on: 26/09/18 Accepted on: 12/11/18

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DOI: 10.7897/2277-4343.096178

ABSTRACT

The prevalence of obesity is alarmingly increasing across the world. It is an emerging perplexing issue that not only itself a health problem but also associated with many other diseases ranging from cardiovascular disorders to some type of cancers. Important concern for health care providers is the limited availability of an effective medical treatment for obesity. Some clinical trials conducted recently, reported the efficacy of Unani medicine in obesity. Therefore, a systematic review was conducted to assess the weight reducing effect of Unani therapeutics in overweight and obese adults. A comprehensive search of electronic databases, viz., PubMed, Google Scholar, Cochrane library, MedIND was carried out using keywords like ‘Unani Medicine’, ‘Obesity’, ‘Clinical trial’, ‘Weight loss’ ‘Siman-i-mufrit’ or combination of these. In addition, journals and dissertations in the library of the National Institute of Unani Medicine, Bangalore, India was manually searched. Among the retrieved studies, only six clinical trials met the criteria and were included in the review. Total 267 participants were enrolled in these studies and treatment duration ranged from 2 to 3 months. Included studies reported significant anti-obesity effects (decline in certain parameters) with the administration of test formulations without any adverse effect. Although, overall evidence suggested the efficacy of Unani therapeutics in the treatment of obesity without any adverse effects; however, the effect size found in some studies was very small in comparison to control. Hence, studies with an effect size of clinical relevance are further required to determine the use of these drugs in routine clinical practice.

Keywords: Efficacy; Safety; Obesity; Unani Medicine

INTRODUCTION

Abnormal or excessive fat accumulation in the body that presents a risk to health is known as overweight and obesity1. The crude population measure for obesity is body mass index (BMI). A person with a BMI of >25 kg/m² is generally considered as overweight and with BMI ≥30 kg/m² is considered as obese. As per W.H.O. estimates, worldwide prevalence of obesity has nearly tripled between 1975 and 20162. About 13% of the world’s adult population (11% of men and 15% of women) was obese in 20162. Despite the increasing magnitude of obesity, a little attention has been paid to this health problem in both developed and developing countries3. Obesity increases the risk of morbidity and mortality; hence, it is considered as the fifth leading risk of death globally4. Moreover, it is also associated with several disorders like diabetes, hypertension, dyslipidemia, cardiovascular disease and even some cancers5. Due to the emergence of obesity as an important public health problem, its prevention and treatment are important concern for health system; whose focus is to reduce the prevalence of obesity and problems associated with it across the globe6.

Various treatment modalities for weight reduction like dietary restrictions, lifestyle modifications, and pharmacotherapy (appetite suppressing drugs, lipase inhibitors etc.) have been considered by the health professionals5,6. Nonetheless, these treatment approaches does not fulfill the need of the population in terms of efficacy and safety7. Moreover, studies show that only 5-10% subjects can maintain their weight loss over the years8. Due to this limited availability of effective conventional medical treatments for obesity, patients are seeking alternative forms of health care for weight loss9.

In India, a considerable proportion of population is using Unani medicine for various health problems and obesity is one among them. Clinical trials conducted recently also reported the efficacy of Unani therapeutics in the treatment of obesity. However, the systematic reviews to provide reliable information on its efficacy were lacking. Hence, this review is conducted to provide up-to-date information on the efficacy and safety of Unani therapeutics in the treatment of obesity.

MATERIALS AND METHODS

Comprehensive search of electronic databases like PubMed, Google Scholar, Cochrane library, MedIND was carried out to retrieve the clinical studies (published in English between 2000 to 2017) investigating the effect of Unani therapeutics in overweight and obese subjects. In addition, journals and dissertations in the library of the National Institute of Unani Medicine were also searched manually. For electronic databases search, medical subject headings (MeSH) and other relevant terms to the topic were used as major constructs to build the search strategy. The MeSH or other relevant terms were related to Unani medicine, obesity and intervention constructs. To combine these, Boolean operators “AND” “OR” and “NOT” as appropriate were used. The search terms were ‘Siman-i-mufrit’, ‘Unani Medicine’, ‘Greco-Arabic medicine’, ‘Obesity’, ‘Traditional medicine’, ‘Clinical trial’, ‘RCT’, and ‘Unani therapy’.

Inclusion and Exclusion Criteria

To select the relevant studies for this review, screening of titles and abstracts were done, and it was guided by the following inclusion criteria: Original research articles conducted to assess
the efficacy of Unani therapeutics (single or compound formulations or regimen trials) in overweight and obese subjects were considered for review. Studies of at least 4 weeks duration were included. Studies published in peer-reviewed journals of English language between 2000 and 2017 were included. Any comparison arm or group used against the Unani therapeutic was accepted for this review. The main outcome measures sought at the end of treatments as anti-obesity effects were body weight, body mass index, waist circumference, wrist-hip ratio, skin-fold thickness and mid-upper arm circumference. Animal studies, review articles, single group studies and studies those primarily examined obesity related complications such as infertility were excluded.

Data Extraction and Synthesis

Two reviewers independently examined the title, abstract and full text of each article meeting the inclusion criteria and eliminated duplications and those showing exclusion criteria. Two reviewers extracted data using a standardized data extraction form built according to the Consolidated Standards of Reporting Trials for Herbal interventions (CONSORT). Data extracted included participant, interventions, comparator, and outcome detail (PICO). The third reviewer checked the extracted data and any discrepancy found in the data was resolved through discussion between reviewers.

Quality Assessment of the Articles

The Cochrane risk of bias tool10 was used to assess the quality of the studies included in this systematic review by determining the risk of bias. This validated tool consists of six categories namely: (1) random sequence generation (2) allocation concealment (3) blinding of participants (4) incomplete outcome data (5) selective outcome reporting (6) other bias. Scoring for each category was done as high, uncertain or low risk of bias.

RESULTS

From an initial search of electronic databases, 55 studies were identified and reviewed for inclusion or exclusion. After initial screening, 35 studies (2 duplicated studies, 3 animal trials, 3 systematic reviews and 27 review articles) were excluded. After that 20 RCTs were identified, among which 14 studies (7 on herbal medicines, 6 were primarily on obesity associated complications and 1 single group study) were excluded. Finally 6 RCTs fulfilling the inclusion criteria were included for review. Summary of the included trials is given in Table 1.

One RCT was conducted in Iran and others in India. Five RCTs had a two-arm parallel design (test and control group) and one study had three-arm parallel design. These studies enrolled 267 participants and the treatment duration ranged from 2 to 3 months. All these studies included overweight and obese adults with BMI between 25-50 kg/m². Outcome measures encountered in these studies were body weight, body mass index, waist circumference, hip circumference, wrist-hip ratio, and mid-upper arm circumference and skin-fold thickness. Assessment of the efficacy parameters was done weekly12, fortnightly13, monthly11,16 and even before and after treatment.14,15 Four included trials studied Unani medicine versus a placebo; one studied Unani medicine versus a Unani control and one study compare the effect of single herb and steam bath separately and in combination. No trial was restricted to participants based on sex, while age restriction was found.

Obesity status was determined by anthropometric measurements (weight, BMI, MUAC, HC, WHR and SFT). Comparison of the effect size of Unani therapeutics and comparator on the outcome variables is given in Table-2. None of the included study reported any adverse event (Table 3).

The risk of bias assessment for the included trials is presented in Table-4. Random sequence generation, allocation concealment, blinding of the patient/practitioner or assessor, and reporting of drop-outs were clearly described in one of the included studies11. Four studies13-16 described the random sequence generation, and drop-outs; while the allocation concealment and blinding methods were inadequately described. One12 was lacking in providing the detail of random sequence generation, allocation concealment and blinding method.

DISCUSSION

Single herbs or compound formulations containing plants and minerals or regimen techniques were investigated in included studies for their anti-obesity effect; the ingredients of compound formulations and scientific names17 of single herbs used in this review are given in table 5 and 6.

All included studies11-16 reported anti-obesity effects (such as decline in body weight, body mass index, waist and hip circumferences, waist-hip ratio, skin-fold thickness and mid-upper arm circumference) of the test drugs. Summary of the included studies and the effect size of test drugs on outcome variables in comparison to control are presented in table 1 and 2. Anti-obesity mechanism of test drugs has been given in included studies. Kamali et al., (2012) mentioned that anti-obesity effect of Itrifal Saghir can be attributed to its metabolism stimulant, appetite suppressant, serotonin inhibitor, antioxidant and impeding the digestion of fat properties11.

Minhaj et al., (2014) mentioned that the effect of test formulation may be due to its har-yabis mizaj (hot and dry temperament). Because, obesity results due to the preponderance of shaham (fat) and sameen in the body and the drugs of har-yabis mizaj (hot and dry temperament)17 act against this accumulation of shaham and sameen and dissolve them slowly12.

Ali M et al., (2014) stated that weight reducing effect observed with the test formulation can also be attributed to its muhallil (resolvent), muazzil, mulattif (demulcent), mudir (diuretic), qatae balgham (concoctive of phlegm) and qatae akhlate ghaleez (concoctive of morbid humours) properties14. Because accumulation of morbid humours, particularly ghalmee balgham (dominance of phlegm) is the main cause of obesity and the drugs possessing the above-mentioned properties can evacuate the fasid maddae balghamia (morbid matter of phlegm) from the body and thereby effective in the management of obesity. Similarly Siddiqui et al., (2014) attributed the anti-obesity effect of test formulation to the diverse pharmacological action of its ingredients, like mulattif (demulcent) action of marzanjosh (Origanum majorana), hazim (digestive) wa mulattif (resolvent) effect of ajwain (Trachyspermum ammi), zeera (Carum carvi) and badyan (Foeniculum vulgare), musakhin (colorific) effect of ajwain (Trachyspermum ammi), zeera (Carum carvi), karafs (Apuum graveolens) and marzanjosh (Origanum majorana) and gate akhlate ghaleez (concoctive of morbid humour) properties of bora armani (Armenian bole) that might complement or synergize each other and facilitate the anti-obesity effect14.
Table 1: Summary of included clinical trials investigating the effect of Unani interventions in overweight/obese persons

| Author (Year) Place of study | Study design | Sample size & Target population | Intervention/test drug (dose and duration) | Control | Effect on main outcome variable(s) |
|-----------------------------|--------------|--------------------------------|-------------------------------------------|---------|-----------------------------------|
| Kamali HS et al. (2012); Iran | Randomized controlled trial [Double blind] | N=62 [31 in test and 31 in control group] | Irrifal Saghir [5 gms twice a day before breakfast and after dinner for 3 months] | Placebo [Same dose and duration as test drug] | Comparing mean differences between group, significant decline in body weight, BMI, waist and hip circumferences (p<0.001) were found in test group, while no remarkable changes in these variables were noticed in placebo group. |
| Minhaj S et al. (2014); India | Randomized controlled trial [single blind] | N= 60 [30 in test and 30 in control group] | Sudab, Zarawand mudahraj, Juntiyana and Tukhme Karafs [5 gm thrice a day for 2 months] | Placebo [Same dose and duration as test drug] | Comparing mean differences between group, significant reduction in body weight, BMI, skin fold thickness (p<0.001) and MUAC (p<0.0071) was observed in test group in comparison to control group. No significant reduction was observed in waist-hip ratio (P= 0.1075). |
| Ali M et al. (2014); India | Randomized controlled trial [single blind] | N=30 [20 in test and 10 in placebo group] | Ajwain desi, Tukhme Sudab, Zeera siyah, Marranjosh, Bora Armani [5 gm once a day with cane vinegar 7.5ml just after breakfast for 2 months] | Placebo [Same dose and duration as test drug] | In test group, significant effect was noted after completion of treatment as compared to baseline values on body weight, BMI, MUAC, waist-hip ratio and skin fold thickness (p<0.001). On inter-group comparison, effect on MUAC, waist-hip Ratio were found significant (p<0.05) in test group; while effect on body weight, BMI and skin fold thickness were found insignificant (p>0.05). |
| Siddiqi M et al. (2014); India | Randomized controlled trial [single blind] | N=40 [25 in test and 15 in placebo group] | Saffoofe Muhazzil Khaas [5 gm (tablet form) once a day in the morning for a duration of 2 months] | Placebo [Same dose and duration as test drug] | In test group, significant effect was noted after completion of treatment as compared to baseline values on Body weight, BMI and waist circumference (p<0.001). On inter-group comparison, effect was found to be insignificant in comparison to control on above mentioned variables (p>0.05). |
| Danishmand et al. (2015); India | Randomized controlled trial [single blind] | N= 30 [20 in test and 10 in control group] | Qurs-e-Luk [5 gm (powder form) twice a day for a duration of 2 months] | Lipotab [2 tablets twice a day for 2 months] | Significant effect on body weight was observed in both test and placebo groups, but the test drug (p<0.001) was comparatively found to be more effective than placebo (p=0.0171). |
| Fatima S et al. (2017); India | Randomized three arm, comparative clinical study | N= 45 [15 in each group] | **Gp A:** Kundur gum resin [3 gm in a powdered form orally once daily in the morning]. | Comparison between 3 groups • Kundur • Steam Bath • Kundur+Steam Bath | Significant reduction (p<0.001) in body weight, BMI, waist circumference, waist-hip ratio and skin-fold thickness was found in all the groups. On inter-group analysis, group C followed by group A in comparison to group B had exhibited substantial decrease in weight and waist circumference. |

BMI: Body mass index; MUAC: Mid- upper arm circumference
Table 2: Comparison of the effect size of Unani medicines and control drug on outcome variables in overweight/obese persons

| Study | Intervention and duration | Body weight (kg) | BMI (kg/m²) | WC (cm) | HC (cm) | WHR | MUAC (cm) | Skin-fold thickness (mm) |
|-------|---------------------------|------------------|-------------|---------|---------|------|-----------|------------------------|
| Kamali HS et al. (2012); Iran | Iriful Saghir (3 months) | 4.82 | 1.47 | 4.01 | 3.21 | - | - | - |
| | Placebo | -0.45 | +0.18 | -0.5 | +0.43 | - | - | - |
| Minhaj S et al. (2014); India | Sudab, Zarawand mudahraj, Juntiyana and Takhme Karafs (2 months) | 2.99 | 0.9 | - | - | 0.03 | 1.55 | 6.0 |
| | Placebo | 1.42 | 0.57 | - | - | +0.08 | 0.03 | +1.4 |
| Ali M et al. (2014); India | Ajwain desi, Tukhme Sudab, Zeera siyah, Marzanjosh and Bora Armani (2 months) | 4.13 | 1.59 | - | - | 0.09 | 2.45 | 14.25 |
| Siddiqi M et al. (2014); India | Safoofe Muhazzil Khaas (2 months) | 1.36 | 0.56 | - | - | 0.03 | 0.68 | 5.3 |
| | Placebo | 2.1 | 0.9 | 0.8 | - | - | - | - |
| Danishmand et al. (2015); India | Qurs-e-Luk (2 months) | 1.38 | 0.53 | - | - | - | - | - |
| | Lipotab | 0.51 | 0.35 | - | - | - | - | - |
| Fatima S et al. (2017); India | Kundur (8 weeks) | 4.06 | 1.75 | 7.17 | - | 0.02 | - | 9.53 |
| | Steam Bath | 2.99 | 1.22 | 3.39 | - | 0.02 | - | 9.13 |
| | Kundur + Steam Bath | 5.19 | 2.19 | 8.18 | - | 0.02 | - | 14.06 |

BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist:hip ratio; MUAC: Mid: upper arm circumference, + Sign indicate increase in the value of variable in comparison to baseline values

Table 3: Reported adverse events from included studies

| Adverse events [n/N] | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Study 6 |
|---------------------|---------|---------|---------|---------|---------|---------|
| Serious adverse events [n/N] | I= 0/31 | C= 0/31 | T= 0/62 | I= 0/30 | C= 0/30 | T= 0/60 |
| Drop-out due to adverse events[n/N] | I= 0/31 | C= 0/31 | T= 0/62 | I= 0/30 | C= 0/30 | T= 0/60 |
| Hospitalization due to adverse events [n/N] | I= 0/31 | C= 0/31 | T= 0/62 | I= 0/30 | C= 0/30 | T= 0/60 |
| Liver toxicity [n/N] | I= 0/31 | C= 0/31 | T= 0/62 | I= 0/30 | C= 0/30 | T= 0/60 |
| Renal toxicity [n/N] | I= 0/31 | C= 0/31 | T= 0/62 | I= 0/30 | C= 0/30 | T= 0/60 |
| Other side effects [n/N] | I= 0/31 | C= 0/31 | T= 0/62 | I= 0/30 | C= 0/30 | T= 0/60 |

I: Intervention group; I: Intervention group 1; I: Intervention group 2; I: Intervention group 3; C: Control group; T: Total number of participants
Studies 1 and 2 reported the efficacy of Itrifa, an extract of Trachyspermum ammi, in reducing BMI and WHR, respectively. However, Studies 3 and 4 did not find significant results.

Fatima S et al. (2017) reported that weight reduction with weight loss agents (e.g., Amla, Garam masala, and Juntiyana) was found to have acceptable anti-obesity effects. None of the included studies have reported adverse effects, but, we believe that safety of these drugs remains to be elucidated on larger population by further long-term studies.

CONCLUSION

Although, overall evidence suggesting the efficacy and safety of Unani therapeutics in the treatment of obesity. However, effect size found in some studies was very small in comparison to control. Hence, further studies with a sufficient magnitude of effect size to determine relevant clinical effects are needed to validate the use of these therapeutics in routine clinical practice.

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Cite this article as:
Saima Saleem et al. A systematic review on efficacy and safety of Unani medicines used in the treatment of obesity. Int. J. Res. Ayurveda Pharm. 2018;9(6):91-96 http://dx.doi.org/10.7897/2277-4343.096178

Source of support: Nil, Conflict of interest: None Declared

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