Indian Journal of Traditional Knowledge
Vol 19(4), October 2020, pp 889-896

Comparative study on the intervention of 'Spice' Mixture (SM) prepared by Natural Food Additives (NFA) alone or intervention of SM with mind calming exercise in the management on female obesity

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Received 16 May 2019; revised 28 September 2020

Obesity has become huge health problem in the entire world. In Sri Lanka, the prevalence of obesity is estimated to be 20.3% in men and 36.5% in women in four provinces. Further, the highest prevalence rate in Western Province, especially in Colombo was estimated to be 32.2%, among adults. Obesity is associated with osteoarthritis, obstructive sleep apnea, gall stones, and hiatus hernia. In addition to this obesity is related to numerous other problems, such as menstrual and mental disorders and varicose vein etc. According to the concept of Unani four treatment modalities are there; they are known as Dieto therapy (Ilaj Bil Ghiza), Pharmaco therapy (Ilaj Bil Dawa), Regimental therapy (Ilaj Bit Tadbeer) and Surgery (Ilaj Bil Yad). Biomarkers such as Lipid profile (VLDL, LDL, HDL And Serum triglycerides), Haemoglobin percentage, SGPT and SC (Serum Creatinine) were considered. Blood sample analysis was performed at NATH (National Ayurvedic Teaching Hospital), Borella, National Diabetic Centre, Rajagiriya and Asiri Hospitals Ltd. According to Unani or Greco-Arabic medical concept, improper digestion may play a main role to cause obesity. Improper digestion was corrected by using a 'spice' mixture made by Natural Food Additives (NFA), which possesses the actions of carminative, digestive and strengthens the gastro-intestinal tract. The preparation of 'spice' mixture included Natural Food Additives (NFA). They are Cumin (Cuminum cyminum), Garlic (Allium sativum), Curry Leaves (Murraya koenigii), Ceylon Cinnamon (Cinnamomum zeylanicum) and Black Pepper (Piper nigram). Studies revealed that waist circumferences (WC) is closely linked to CV disease risk factors. Also, WHO Expert Committee on Obesity in Asian and Pacific populations suggested that revised cutoff points for WC: 90 cm for men and 80 cm for women to identify patients with abdominal obesity. South Asians are more prone to insulin resistance and dyslipidaemic state of abdominal obesity. Study concluded that the intervention of 'spice' mixture reduces obesity and the effective mind calm exercises would give more beneficial effect in weight reduction.

Keywords: Intervention, Mind calm exercise, Obesity, Overweight, 'Spice' mixture

IPC Code: Int. Cl.[20]: A63B 21/00, A61F 5/01

Obesity has become huge health problem in the entire world. Sri Lankans are also gradually affected by the epidemic and in Sri Lanka the obesity prevalence is estimated to be 20.3% in men and 36.5% in women in four provinces. The highest prevalence was found in Western Province, Colombo and was estimated to be 32.2% among adults[1]. Further, a recent study revealed that including Sri Lanka, many South Asian countries are also significantly affected by the obesity epidemic[2].

Obesity can lead to may non-communicable diseases such as type 2 diabetes, hypertension, hyper lipidemia, cardiovascular disease, stroke and depression[3]. In addition, obesity is associated with some other conditions like osteoarthritis, obstructive sleep apnea, gall stones, and hiatus hernia. Further, to this obesity is related to various other gynecological problems such as menstrual disorder, poly cystic ovarian syndrome, infertility and also, mind related disorders and varicose vein[4].

Studies reveal that the reason of increasing obesity is due to demographic changes, sudden urbanization, and life pattern changes that took place within these few decades. Greatest risk factors are fallen on behavioral changes that are influenced by urbanization and unnatural life styles, such as a transfer from the traditional Sri Lankan diet to fast-food likers with less or no physical activity[5].

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Dietetic changes with proper physical exercise including therapies are the best for both prevention and treatment of obesity; unfortunately, both require much dedication for sustainable improvement. Medications offer a possible part, but their effect is modest and their uses are limited by side effects. The weight loss lasts only as long as the patient is under the medication and if the treatment is stopped the weight regain. Sibutramine, a sympatho-mimetic medication which had been available for long-term treatment, was withdrawn from the market due to the side effects as it causes increased risk of cardiovascular events[6].

Hippocrates, the architect of Unani Medicine and considered as Father of Medicine by the West mentions as "let foods be your drugs". Further he says most of the natural healing products have therapeutic values in addition to the nutritive values. Considering the Hippocrates view and according to Unani concept, there are four treatment methods: Dieto therapy (Ilaj Bil Ghiza), Pharmaco therapy (Ilaj Bil Dawa), Regimental therapy (Ilaj Bit Tadbeer) and Surgery (Ilaj Bil Yad). Hence, obesity is a food related condition; intervention by diet is the first line of modality to be administered under the guidance of a physician supported by lifestyle modification[7]. It is presumed based on the information available in the classical texts and empirical observations, that the present study was aimed to obtain promising outcome to solve overweight, obesity and their co-morbidities by incorporating natural food additives (a 'spice' mixture) in diet. Therefore, the present study was focused to manage, mainly adulthood female obesity by using intervention of traditional diet with natural food additives (a 'spice' mixture), incorporation of selected mental relaxing exercises for the participants in the clinical trials to prevent the above mentioned co morbidities.

Methodology

Study participants

The study was conducted at the Borella, Ayurveda Teaching Hospital, Sri Lanka. This research study was conducted from July 2012 to December 2014 and the participants constituted a convenience sample of 247 representing different socio-economic districts who were attended the outpatient's department (OPD). With the exclusion criteria each 100 participants were placed into two groups. Two hundred and nine participants completed the intervention and were eligible for the analysis.

Criteria for selection of patients

This study from 18 to 60 years old Overweight (BMI between 25 -30 Kg/m^2) and Obese (BMI > 30 Kg/m^2) females were included. However, if participants taking a weight loss medication, GI disorders, psychiatric disease/s under the care of a psychiatrist, Cushing's syndrome, hypothalamic causes of obesity, thyroid diseases, bulimia like eating sickness, surgery completed in the past 3 months or surgery planned to fix, expecting mothers or disabled females and Individuals on a special diet for medical reasons were excluded.

Study design

To this study the research project was approved by the Ethics Review Committee, Institute of Indigenous Medicine, University of Colombo, Sri Lanka. All the voluntary participants were read the Information Sheet (IFS) and signed Informed Consent Form (ICF) for the purpose of the research. IFS informed that each survey respondent had a possibility of voluntary withdrawal at any time. Thereafter, each patient was given a personal number, from 1 to 200. The questionnaire developed for the study was organized in different areas such as symptomatic checklist including general and co-morbidity related symptoms, Anthropometric measures and clinical and biochemical examination.

The questionnaire was prepared for collecting the research data and it was first developed in English, and then it was transferred into Sinhala and Tamil. Finally, they were back interpreted into English by an expert translator to ensure that both surveys had equivalent meanings. No discrepancy was found between Tamil and Sinhala version. Participants were given the option to hold the interview in English or Tamil or Sinhala upon their preference. The information asked in the questionnaire was completed from a direct interview by a bilingual trained person who had more than five years of experience in conducting surveys. The clinical trial was assessed using physical measurements, questionnaire based-assessment and biochemical assessments.

Collection of data

Data collection on anthropometric measurements

The complete set of anthropometric measurements was performed twice, but not consecutively. Body Mass Index (BMI), blood pressure, pulse, waist and hip measurements (WHR) of each participant were measured. For the assessment BMI, weight and height of each subject were obtained by standardized procedures (WHO expert consultation, 2004).

Participants were categorized by weight status according to the cut-off values for BMI proposed by World Health Organization[8]. Standardized procedures were maintained to measure the BP. Patients were asked to sit quietly with arm bared and supported on the same level of the heart. Blood pressure and the pulse were measured using a digital automatic blood pressure monitor made in Taiwan (Medical Rossmax). The cut off values for BP used in the present study are shown in the Table 1.

When the height was measured the patients were asked to remove their shoes and to stand with the height rule. Height ruler tape was used to measure the height of each patient to nearest 0.5 cm. When the weight was measured the patients were asked to remove their shoes and heavy garments and to stand on the centered of the leveled platform scale (Beurer Living-PS07, Germany). Patients' weight reading was recorded to the nearest to 0.1 kg using the above digital scale. Waist circumference (WC) was taken at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, using a stretch-resistant tape[9]. Then Hip circumference was taken around the widest portion of the buttocks, with the tape parallel to the ground. The Waist to Hip Ratio (WHR) was calculated and categorized according to WHO's cut off values[9] (Table 2).

Data collection on biomarkers

Biomarkers such as lipid profile, Haemoglobin percentage, SGPT and SC (Serum Creatinine) were considered. Lipid profile includes of the total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL) and very low-density lipoprotein (VLDL). To find the changes in levels of biomarkers, 5 mL of blood sample from each patient fasted overnight (12 – 14 hours) was drawn twice (at the first arrival and at the completion of the study) by a trained laboratory technician. Analysis of blood sample was performed at Borella, National Ayurvedic Teaching Hospital, National Diabetic Centre, Rajagiriya and Asiri Hospitals Ltd.

Questionnaire based assessment was carried out to identify the risk factors that may contribute to weight gain. Therefore each participant was requested to provide the medical history as medication for certain diseases can cause weight gain[10]. Factors that might influence treatment strategies were identified and excluded from our study as there co-morbidities should be managed by a specialist.

Grouping the patients

The patients were randomized and grouped into two, each comprising 100 patients. Subsequently one group was advised to follow the proposed diet intervention with 'spice' mixture and the other group was advised to follow the proposed diet intervention with 'spice' mixture and mind calm exercises. The intervention was continued for 4 months.

The intervention of 'Spice' mixture

According to Unani or Greco-Arabic medical concept, improper digestion may play a main role to cause obesity. Further this condition is very common among phlegmatic temperament individuals[11]. In our study improper digestion was corrected by using a 'spice' mixture made by Natural Food Additives (NFA), which possesses the actions of carminative, digestive and strengthens the gastro-intestinal tract[12].

The 'spice' mixture was prepared by using common natural spices available in Sri Lanka. The preparation of 'spice' mixture included Natural Food Additives (NFA). They are Cumin *(Cuminum cyminum)*, Garlic *(Allium sativum)*, Curry Leaves (*Murraya koenigii*), Ceylon Cinnamon *Cinnamomun zeylanicum* and Black Pepper (*Piper nigram*). The dose mentioned in Unani

Table 1 — Cut off values of Blood Pressure

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 Hypertension (mild)	140–159	90–99
Grade 2 Hypertension (moderate)	160–179	100–109
Grade 3 Hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90

BP: Blood Pressure
Source: WHO Regional Office for the Eastern Mediterranean, 2005

Table 2 — Cut-off points of WC, HC and WHR and risk of metabolic complications

Indicator	Cut-off points	Risk of metabolic complications
Waist circumference	> 94 cm (M) ; > 80 cm (W)	Increased
Hip circumference	>102 cm (M) ; > 88 cm (W)	Substantially increased
Waist–hip ratio	≥ 0.90 (M); ≥ 0.85 (W)	Substantially increased

M, men; W, women
Source: Adapted from Report of a WHO Expert Consultation, 2008.

Medicine was followed to decide the amount. They were dried, powdered and mixed.

The dose of the 'spice' mixture was decided according to the patient's temperament, the extent of overweight and obesity (level of BMI) and the level of biomarkers. If the level of BMI between 25.0 – 29.9 Kg / m^2, the dose was 1 g three times daily: level of BMI between 30.0 – 34.9 Kg / m^2, the dose was 2 g three times daily : level of BMI between 35.0 – 39.9 Kg / m^2, the dose was 3 g three times daily and level of BMI above 40 Kg / m^2, the dose was 3 ½ g three times daily.

The intervention of mind calm exercises

Further, Unani medical concept mentioned that any stress condition may be a cause for improper digestion which leads to obesity[11]. It is reported that a proper mind relaxant can reduce the stress and calm the mind[13]. Therefore, one group of patients was advised to take 'spice' mixture and do the meditation practice morning and/or evening for 15–30 minutes daily as a mind calming exercise[13] and the other group was advised to take the same 'spice' mixture, only.

Monitoring

Weight, obesity-related co-morbidities, biomarkers and interventions of each patient were monitored as described in Table 3. Participants were advised to visit the clinic more than 4 occasions all through the study period.

Statistical analysis

Statistical Package for the Social Sciences for IBM SPSS version 19 was used to perform statistical analysis. Univariate and bivariate analysis was run for diet related variables. Weight reduction was categorized and analyzed using Chi square test and Kendall-tau correlation. Association between the two variables such as BMI categories and weight reduction categories, were found using Chi square test. Kendall-tau correlation was done to discover the correlation level of BMI categories and weight reduction categorical variables. Apart from the above correlation method Pearson correlation method was also used to analyse the BMI differences as interval scale variables.

Before and after intervention, the mean comparison of weight reduction was compared. To analyze the effectiveness of the intervention in the clinical trial 'paired sample *t* test' was done at the 0.05 significant levels. The variables like BMI and the selected biomarkers both before and after therapeutic intervention were compared, separately. Effectiveness of therapeutic intervention among groups was analyzed. The two groups (Group 1 was given a 'spice' mixure while Group 2 was given the same 'spice' mixure plus mind calm exercises and both groups were advised about their diet in accordance with Unani food guidelines) were selected and 'paired sample *t* test' was carried out, separately to the variables of BMI and selected biomarkers before and after intervention to find the effectiveness of therapeutic intervention.

Results and Discussion

BMI with age group

BMI with age group variables underwent cross tabulation and the results are shown in the Table 4. The age group was defined according to Unani concept i.e. between 18 – 30 years grouped as Young Adult, between 31 – 40 years grouped as Middle age and between 41- 60 years grouped as Pre Old age. In this study population, more participants were obese than overweight and age wise the "pre old age" group was affected more by obesity than the other age groups. Out of this whole population, 44.9% was affected by "Obese-I" and this obesity level is common in all age groups.

The result of the "excess weight" variable is described below. The excess weight of the participants in kilograms is given in this result. Out of

Table 3 — Monitoring process used in the clinical trial

Strategies	Initial Visit	2nd Week	1st Month	2nd Month	4th Month
BMI	√	√	√	√	√
WHR ratio	√	√	√	√	√
Measurement of pulse and BP	√	-	-	-	√
Physical Examination	√	-	-	-	√
Findings of lipid Profile	√	-	-	-	√

Table 4 — BMI categories and Age groups

BMI categories	Age in Groups			Total
Overweight	Young Adult	Middle age	Pre Old Age	
Obese I	7	17	14	38
Obese II	14	20	24	58
Obese III	3	7	13	23
Total	0	6	4	10
	24	50	55	129

BMI: Body Mass Index

the participants, 20.2% were above their ideal body weight by "less than 10 kg". Most of the participants (63.5%) had "Between 10 -29.9 Kg" excess weight. Only 16.3% of participants had more than 30 Kg excess weight.

WC and HC

In our study, the minimum Waist Circumference (WC) was 86 cm and the maximum was 137 cm with the mean of 104.8 ± 10.7 cm (Table 3.6). In Hip circumference (HC), minimum was 92.5 cm and the maximum was 135 cm with the mean 109.0 ± 9.8 cm. The mean waist to hip ratio was 0.96 ± 0.05.

Studies revealed that waist circumferences (WC) is closely related to cardiovascular disease risk factors[14] and the WHO Expert Committee on Obesity in Asian and Pacific populations proposed revised cutoff points for waist circumference: 90 cm for men and 80 cm for women to identify patients with central obesity[15]. This is because the Asians are more likely to develop obesity-related diseases even at a lower BMI. This means that even though some Asian populations had a lower prevalence of overweight and obesity than those in the West, they had a disproportionately high percentage of people with diabetes [16]. It is said that currently, 60% of the world's diabetic population are from Asians[17]. It has been discovered that Asians of a healthy BMI have more fat around their organs and in their belly areas than Europeans with the same BMI[16]. In the present study, much higher mean values were found for WC, HC and WHR for all age groups than that at the reported results and they are 104.8 ± 10.7, 109.0 ± 9.8 and 0.95 ± 0.06 respectively. Studies revealed that central obesity, (fat deposition around the abdominal region) most obviously contributes to cardiovascular outcomes[18] and it was also said that South Asians are likely to be resistant to insulin and dyslipidaemic state of abdominal obesity[19]. Through this study it can be concluded that central obesity is a much prevailing state among the obese or overweight women.

The effectiveness of the intervention

The efficacy of the intervention was analyzed using Pearson correlation. The results indicates that there is a moderate positive correlation between 'BMI before intervention' and 'change in weight reduction' ($r = 0.411$, $N= 129$, $p < 0.05$).

Table 5 shows the results of 'paired sample *t* test' before and after the intervention, in the Body Mass Index and the selected biomarkers in the total population. The efficacy of the intervention on the whole population was exposed by this. At the enrollment of the study, the mean BMI was 32.92 Kg/m^2. The analysis the data after the intervention shows that the reduction has occurred by 2.7 Kg/m^2 (Mean BMI after the intervention was 30.23 Kg/m^2). The association between the BMIs of the participants at the enrollment of the study and after the intervention was highly significant ($t=29.20$, $df =128$, $p < 0.01$).

Results obtained from the study group revealed that the mean 'total cholesterol' of the population at the enrollment and after the intervention was 210.76 ± 44.61 and 193.62 ± 39.9, respectively. The difference between the 'total cholesterol' at the enrollment and after the intervention was highly significant ($t=5.53$, $df =127$, $p < 0.01$).

At the enrollment the intervention mean "triglyceride" level was 118.94 ± 52.57. After the intervention it was noticed that the reduction of "triglyceride" was by 8.41 ± 47.15 for the whole set up. Hence, the correlation between triglycerides at the enrollment and after the intervention was positive and significant ($t=2.02$, $df=127$, $p< 0.05$). The mean values of "LDL" at the enrollment and after the intervention were 138.35 ± 41.44 and 122.59 ± 34.74, respectively. The average "LDL" reduction or mean change was by 15.75 ± 35.25 after the intervention. The association between the "LDL"s at the enrollment and after the intervention was highly significant ($t=5.04$, $df=126$, $p< 0.01$). The analysis showed that the "VLDL" values at the enrollment and after the intervention were 24.23 ± 10.60 and 22.29 ± 8.15, respectively. The mean reduction of "VLDL" after the intervention was by 1.93 ± 9.87 and the association was significant at the enrollment and after the intervention ($t=2.22$, $df = 127$, $p < 0.05$). The "HDL" levels of the population at the enrollment and after the intervention was 49.77 ± 13.24 and 47.07 ± 9.46, respectively. The mean "haemoglobin" at the enrollment and after the intervention was 12.11 ± 1.3 and 12.7 ± 1.22, respectively.

View of the biomarkers' effectiveness in the two groups (Group 1 & 2)

The changes in the biomarkers of the two groups (Group 1 & 2) before and after the intervention were shown in Table 6.

Paired sample *t* test was used to separately find the changes in the biomarkers of the two groups (Group-1 and Group-2). Table 6 displays that the changes in the

Table 5 — Changes in BMI and Biomarkers of total population before and after the intervention

Variables	Mean		N	Mean change	Correlation	*t*	df	Sig
	Before	After						
	32.92 (SD=4.5)	30.23 (SD=4.1)			0.976			
BMI	210.76 (SD=44.61)	193.62 (SD=39.91)	129	2.69(SD=1.0)	0.661	29.20	128	0.000**
Total Cholesterol	118.94 (SD=52.57)	110.53 (SD38.38)	128	17.15 (SD=35.08)	0.499	5.53	127	0.000**
Triglycerides			128	8.41 (SD=47.15)		2.02	127	0.046*
	49.77 (SD=13.24)	47.07 (SD=9.46)			0.184			
HDL	138.35 (SD= 41.44)	122.59 (SD=34.74)	127	2.69 (SD=14.79)	0.584	2.06	126	0.042*
LDL	24.23 (SD=10.60)	22.29 (SD=8.15)	127	15.75 (SD=35.25)	0.471	5.04	126	0.000**
VLDL	12.11 (SD=1.30)	12.70 (SD=1.22)	128	1.93 (SD=9.87)	0.635	2.22	127	0.028*
Haemoglobin			127	-0.59 (SD=1.07)		-6.18	126	0.000**

** $p < 0.01$ level ,* $p < 0.05$ level

Table 6 — Paired *t* test among groups before and after the intervention

Variables	Mean (Group 1)		Mean change	Signi	Mean (Group 2)		Mean change	Sig (CI=0.95)
	Before	After	2.64	0.000*	Before	After	2.82	0.000*
			(1.08)				(0.96)	
BMI	32.40	29.76	16.82	0.000*	34.17	31.35	17.93	0.006*
	(4.27)	(3.87)	(34.22)		(4.90)	(4.40)	(37.57)	
Total Cholesterol	211.14	194.31	9.10	0.083	209.83	191.90	6.70	0.332
	(44.25)	(44.50)	(49.45)		(46.09)	(25.77)	(41.52)	
Triglycerides	119.60	110.50	2.35	0.143	117.30	110.58	3.58	0.134
	(54.54)	(35.47)	(15.16)		(48.07)	(49.30)	(13.98)	
HDL	48.74	46.39	16.87	0.000*	52.37	48.80	12.93	0.047*
	(13.80)	(9.59)	(34.40)		(11.48)	(9.01)	(37.69)	
LDL	139.66	122.79	2.07	0.065	135.03	122.10	1.62	0.230
	(41.22)	(37.65)	(10.55)		(42.38)	(26.46)	(8.08)	
VLDL	24.52	22.45	-0.69	0.000*	23.51	21.89	-0.35	0.041*
	(11.16)	(7.85)	(1.09)		(9.20)	(8.93)	(1.02)	
Haemoglobin%	11.98	12.67			12.41	12.76		
	(1.35)	(1.21)			(1.14)	(1.25)		

* $p < 0.05$ level

biomarkers are significant in both the groups (Group-1 & Group-2) on the variables of "BMI", "total cholesterol", "LDL" and "haemoglobin %" at the level $p < 0.05$.

Evaluation of BMI levels of participants before and after the Intervention

Percentage difference of BMI before and after the intervention is exposed in the Figure 1. Variable was defined according to WHOs' international categorization. 18.5 – 24.9 (Normal BMI), 25 – 29.9 (Over weight), 30 – 34.9 (Obese – 1), 35 – 39.9 (Obese – 2) and > = 40 (Morbid obese)[8].

Figure 1 clearly depicts that there no participants had normal BMI before the intervention. The above chart also reveals the fact that 7% of the participants have reached normal BMIs after the intervention. It can also be observed that the range of 25-29.9 (overweight) has increased by decrease the ranges

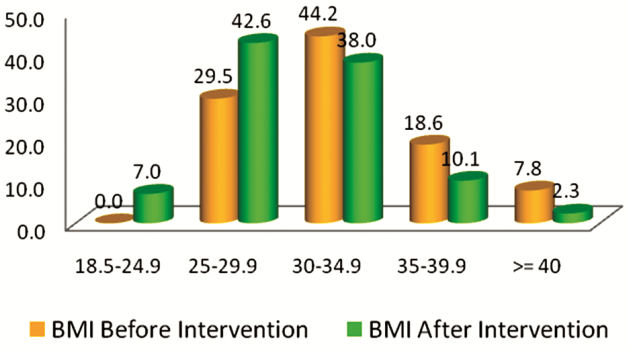

Fig. 1 — Evaluation of BMI levels of the study participants before and after the intervention

30 – 34.9 (Obesity 1), 35 - 39.9 (Obesity 2) and >= 40 (Morbid obesity). Considering the whole population, a significant change of BMI was analyzed ($p < 0.05$) and the same was evaluated in both the groups ($p < 0.05$) separately.

Conclusion

The overall weight reduction of the entire population was significant (CI = 0.95) in this study. Also, there was a significant change in the whole lipid profile before and after the weight reduction intervention. The total cholesterol, VLDL, LDL, and triglycerides were reduced significantly after the weight reduction intervention. The level of HDL was significant and inside the normal limit. The changes in the levels of haemoglobin were significant and it was also revealed that the haemoglobin level has increased after the weight reduction intervention. SGPT and Serum Creatinine showed a significant change in the direction of a normal limit and that indicates that there is no adverse result to the liver or kidney by the 'spice' mixture, which was used by the participants during the weight reduction intervention.

With regard to the two groups (Group 1 and Group 2) as it is mentioned in the Table 6 weight reduction was observed more in Group 2 (participants who consumed 'spice' mixture with engaged in mind calm exercises) than that in Group 1 (though Group 1 was also significant). Similarly, the lipid profile, total cholesterol, haemoglobin level and LDL were significant between the both groups before and after weight reduction intervention.

Benefit of mind calm exercise as anti-obese intervention

It was analyzed in this study that the pre-intervention BMI was significantly correlated with the mood swing. The mood swing was significantly correlated with "nervousness", "anxiety" and "excess work load". In brief, it is clear that the factors that cause any kind of stress may contributes towards a high BMI. Effectiveness of mind calm exercises was found and it describes that mind calm exercises would give beneficial effect to reduce excess weight.

Acknowledgement

Financial support was given by the National Centre for Advanced Studies (NCAS) and authors acknowledged for the grant given. Grant No: NCAS/D/G/11/2011

Conflict of Interest

Authors declare they have no conflict of Interest.

Author Contribution Statement

MIM formed the project, the main conceptual ideas and performed the computation. PPA, NBM, & INZ worked out most of the methodological outline and gave the shape of the project. MIM carried out the clinical trial and PPA verify the analytical methods and encouraged, helped MIM in numerous ways and supervised the project. NBM and INZ also helped supervise the project in other different aspects. MIM took the lead in writing the manuscript. All the other authors are provided critical feedback and helped shape the research, analysis and the manuscript.

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