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IMPACT OF INTERVENTION USING 'COPPS' FORMULATION ON THE NUTRITIONAL AND HEALTH STATUS OF SUBJECTS WITH PULMONARY TUBERCULOSIS: A PILOT STUDY

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ABSTRACT

Tuberculosis (TB) is one of the top 10 causes of death worldwide in 2015 with an estimated 10.4 million incident cases globally. The objective of this study was to evaluate the effect of 'COPPS', a formulation made from *Curcuma longa, Ocimum sanctum, Piper nigrum* and *Plectranthus amboinicus* on the nutritional and health status of subjects with active pulmonary tuberculosis on DOTS therapy. Six among the 9 subjects in the study, were severely malnourished, 6 had low albumin levels and 8 had elevated C- reactive protein levels. All of them had adverse GI symptoms. After intervention for 45 days, the mean increase in BMI (1.79 ± 0.784 kg/m^2), weight gain (10.92 ± 5.04 %) and reduction in C-reactive protein (-26.32 ± 25.1 mg/L) and ESR (-27 ± 18 mm/hr) were seen in 5 subjects. The use of COPPS was successful in the reducing the adverse gastrointestinal symptoms, but the complementary effect in reducing infection and inflammation needs further research.

KEYWORDS

Phytochemicals, Cachexia, PGSGA, Anti-mycobacterial herbs and Inflammation.

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INTRODUCTION

Tuberculosis (TB) is a deadly infectious disease caused by mycobacteria, mainly by *mycobacterium tuberculosis that* attacks the lungs and other organ systems. The World Health Organization (WHO) estimated 10.4 million incident cases of TB in the world, which is equivalent to 142 cases per 1,00,000 population globally in the year 2015[1]. Evidence suggests the presence of higher burden of TB disease in India. The estimated incidence of

tuberculosis in India was reported to be 28,00,000 individuals in 2015, representing 25% of the individuals with tuberculosis in the world. In absolute numbers, the estimated prevalence of TB is reported to be 320 per lakh population in the year 2015[2]. In the year 2015, 1.4 million deaths from TB among HIV-negative people have been reported. TB is one of the top 10 causes of death worldwide in 2015. India accounted for 48% of global TB deaths among HIV-negative people and for 43% of the combined total TB deaths in HIV-negative and HIV-positive people. Globally, the number of TB deaths among HIV-negative people per lakh was reported to be 19 in 2015 and 24 per lakh, when TB deaths among HIV-positive people were included. Drug-resistant strains of M. tuberculosis arise from spontaneously occurring chromosomal mutations. Misuse of anti-tuberculosis drugs such as mono drug therapy or the addition of single drug to failing regimen results in the emergence of resistant strains and out of the 500,000 cases of MDR-TB reported annually, 5% to 7% represent Extensively Drug Resistant (XDR-TB)[1,3].

Directly Observed Treatment Short course (DOTS) is one of the measures taken by the Revised National Tuberculosis Control Programme (RNTCP) under the Ministry of Health and Family welfare, Government of India. An extension of the same referred to as DOTS-Plus is aimed towards the control of MDR-TB in India[4]. Among the approved drugs, Rifampicin, isoniazid, ethambutol and pyrazinamide are the main drugs used today as the first line drugs. The adverse effects of first-line drugs include hepatotoxicity, gastrointestinal (Nausea, vomiting, epigastric pain, anorexia etc.) and hepatitis[5].

Tuberculosis can lead to malnutrition and a state of under nutrition is known to increase the risk of development of tuberculosis. Patients who are malnourished at the time of diagnosis are at increased risk of death and relapse of a dormant state of TB. In patients with tuberculosis, reduction in appetite, nutrient malabsorption and altered metabolism leads to wasting[6]. Nutrition status is a principal determinant of morbidity and mortality from tuberculosis. Inability to meet the increased nutrient needs of the body in response to the infection can lead to malnutrition. The state of infection can affect the food intake by causing alterations in appetite leading to reduced food intake. The adverse side effects of anti TB drugs further includes nausea, vomiting and diarrhea that can worsen the nutrient intake to critically low levels that leads to deficiency of both macro and micronutrients. Malnutrition exerts detrimental effects on several aspects of host immune responses mainly by leading to thymic atrophy and impaired generation and maturation of T-lymphocytes, which can result in compromised immune function[7]. Malnutrition is known to increase the risk of developing tuberculosis and is the highest population attributable risk for TB in India. Tuberculosis can lead to the development of malnutrition or worsen the pre-existing malnutrition by inducing changes in appetite regulation, nutrient malabsorption and catabolism leading to wasting[8]. Several studies indicate higher magnitude of malnutrition among patients with tuberculosis. A cross sectional study on 247 adult tribal males between the age group of 20-40 years from Manipur, Northeast India found chronic energy deficiency (CED) in 64.5% of the patients before initiation of DOTS therapy. 43.5% of the patients had MUAC <22.0 cms indicating protein loss[9]. In a retrospective cohort study by Bhargava A *et al*[10], under-nutrition was the most prevalent co-morbidity among 1440 out of 1695 patients. More than two thirds were moderately to severely underweight according to BMI based classification.

A number of medicinal plants have been reported for anti-mycobacterial activity across the globe. Some plants of Indian origin among these are *Piper nigrum*, *Ocimum sanctum*, *Emblica officinalis*, *Withania somnifera*, *Piper longum*, *Curcuma longa*, *Plectranthus amboinicus*, *Adhatodavasica Nees* and *Aloe vera*[11]. These plants are also known to exert additional physiological benefits such as antioxidant, anti-inflammatory and hepatoprotective action owing to the nature of phytochemicals present in them. Use of herbal or food based

adjuvant with antitubercular action can hasten the recovery and reduce the amount/duration of drug therapy and thus can also avoid the secondary complications arising from the drugs itself. The objective of the current study was to assess the health and nutritional status of subjects with active pulmonary tuberculosis on DOTS therapy and to evaluate the effect of intervention using a formulation developed from commonly consumed herbs and spices with reported antimycobacterial activity.

METHODOLOGY

Phase I: The initial phase of the study involved 9 subjects of both genders aged between 20-60 years who were diagnosed with active pulmonary tuberculosis at PKTB and CD hospital, Mysuru. Subjects who were critically ill, on nutrition support, with co-morbidities mainly HIV, diabetes mellitus, cardio vascular disease, renal and liver conditions were excluded. Approval was obtained from the university Human Ethics Committee for conducting the study (IHEC-UOM No.55/M.Sc/2016-17). Informed consent was obtained from all the subjects. A structured questionnaire was used to elicit data on food behavior, recall of foods consumed, personal information, socio-economic status, duration of disease and medications used. Anthropometry included analysis of height using a stadiometer, weight using a digital weighing machine, mid upper arm circumference (MUAC) using a fiber glass tape and triceps skin fold thickness (TSF) using a lange skinfold caliper. They were also assessed for nutritional status using patient generated subjective assessment tool (PGSGA). The resting metabolic rate (RMR) was calculated using Harris Benedict equation and multiplied with suitable stress and activity factors to derive the calorie needs and subsequently protein and fat needs were determined. Intake of micro nutrients were compared with recommended dietary allowances for Indians[12] to evaluate adequacy. Biochemical analyses included hemoglobin, leukocyte count, red blood cell count, platelet count, C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR) and liver function test. 5 ml of blood sample was collected by the staff nurse at the hospital or at the diagnostic laboratory. All the tests were outsourced to SRL Diagnostics, Mysuru for the biochemical analyses as the blood sample carried a 'biohazard' risk.

Phase II: 'COPPS', a formulation was developed that was composed of usingdried and powdered leaves of powdered root of *Curcuma longa,* dried and powdered leaves of *Ocimum sanctum, Plectranthus amboinicus* and powdered *Piper nigrum* seed (COPPS). The amount of the ingredients used in the formulation is provided in Table No.1. Standard AOAC methods were used for determining proximate composition of the formulation[13,14]. The formulation was qualitatively screened for the presence of selected phytochemicals by the method of Faraz Mojab *et al*[15]. The total phenolic content was analyzed by the method of Jimeneze-Escring et al[16], total flavonoid content by the pharmacopeia method[17] (1986), glutathione (GSH) content by the method of Beutler and Kelly[18] and tannin content by the Folin-Denis method[19]. The subjects were instructed to consume 400mg of the formulation by mixing it with 4.5g of honey twice a day for a period of 45 days. The formulation mix was provided in sachets and a teaspoon with capacity of 4.5g honey was provided to the subjects. No changes were suggested with respect to their food intake pattern. On completion of 45 days, the subjects were re-assessed for nutritional, clinical and biochemical status as performed in the phase I. 3 subjects opted out of the study and 6 subjects completed the intervention.

Analysis of data

The data obtained was analyzed using appropriate statistical methods. All parameters are expressed in triplicates (except for biochemical parameters) and expressed as average ± standard deviation. Student's t-test was used to evaluate the statistical difference between the sub-groups and a *p value*. SPSS version 16 software was used for the statistical analyses.

RESULTS AND DISCUSSION

Phase I- Demographic data

The demographic characteristics of the subjects are presented in table no 2. 9 subjects were assessed for nutritional and health status initially. Majority of the subjects were newly detected with tuberculosis. 7 subjects were evaluated within a week of diagnosis and 2 between 8-15 days since diagnosis. All the subjects were following a non-vegetarian diet pattern and had sedentary level of activity.

Nutritional status

The data of anthropometric assessment is presented in Table No.3. The average body mass index (BMI) indicates gross malnutrition in the study group with male subjects having higher level of malnutrition compared to the female subjects. Higher variation was observed in body fat levels as observed by TSF, with depletion seen more among male subjects. The depletion of protein status is more pronounced in male subjects with lower mean mid upper arm muscle circumference (MUAMC) than female subjects.

Male subjects also had lower percentage of ideal body weight (IBW), whereas female subjects appeared better. On evaluation using PGSGA, 6 (66.7%) subjects were found to have a severe state of malnutrition (stage C) and 3 (33.3%) had a moderate degree of malnutrition (stage B). The higher mean PGSGA scores (overall - 17 ± 3, male -17 ± 3 and females - 16 ± 2) indicate the need for nutritional intervention in all the subjects. The weight loss trend (0-6 months) was found to vary among the subjects with an average weight loss of22.3 ± 11.4 % overall, 23.5 ± 11.5 % among males and 21.9 ± 13.7% in female subjects.

Dietary intake

The data on dietary intake of nutrients is presented in Table No.4. 8 (88.8%) subjects had early satiety and fatigue during eating. Nausea and vomiting were the next predominant symptoms observed in 5 (55.6%) subjects. Diarrhea was reported by 3 (33.3%) subjects. The calorie intake of the subjects was below the RDA which was calculated on an individual basis. Deficiency was seen in the intake of all the macronutrients with a higher degree in the female subjects than male subjects. In terms of macronutrient intake, 5 (55%) subjects had intakes lower than 60% of the needs, whereas fat intake was lower in 8 (88.8%) subjects. Only 1 subject was able to meet the calorie and protein needs adequately and 2 subjects met fat needs adequately. Sub optimal intake of vitamin C and zinc was seen; male subjects had a higher level of intake (vs RDA) compared to female subjects. The intake of calcium was above the RDA in all the subjects.

Cachexia was evident among 6 (66.7%) subjects. Cachexia results in mobilization of body fat and protein. It is known to derange the appetite regulation system leading to decreased food intake and worsening of the ongoing malnutrition. Insufficient energy intake leads to the utilization of dietary protein for energy rather than protein synthesis, creating an anabolic block leading to depletion of whole body protein resulting in low lean body mass. Lower level of serum proteins is a common observation in patients with tuberculosis[20]. This is supplemented further by the cytokine mediated activation of ubiquitin mediated proteolytic pathway, which is the major component of disease induced hyper-catabolism[21]. Anorexia seen in tuberculosis, other hypermetabolic and inflammatory conditions is known to be effect of altered cytokine milieu. Increased activity of Peptide YY and resistin are known to inhibit appetite through increased expression of anorexigenic peptides in the hypothalamus. The increase in levels of tumor necrosis factor alpha, interleukin 1, interleukin 6 and interleukin 1B are known to decrease the expression of orexigenic peptides, increase the secretion of serotonin and cholecystokinin leading to suppression of appetite[22,23].

Biochemical evaluation

The mean values of evaluated biochemical parameters of the subjects are presented in Table No.5.

Overall, 6 subjects were found to be anemic, which included all the 3 female subjects in the study and 3 male subjects out of 6. Total leucocyte count was found to be higher in 2 subjects (1 male and female

subject each). 3 subjects had lower red blood cell (RBC) count and all of them male subjects. 5 out of 9 subjects had a higher platelet count which included 3 male and 2 female subjects. CRP was found to be high in all the subjects. ESR was found to be elevated in 8 out of 9 subjects. The liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated in 1 male subject only, whereas alkaline phosphatase (ALP) was found to be high in 4 subjects, which included 3 male and 1 female subjects. Although, the total protein was found to be normal in all the subjects, serum albumin was low in 6 subjects among whom were 3 male and female subjects each. 5 subjects among them had high levels of globulin and 4 among them had a low albumin to globulin ratio. The level of transaminases and serum bilirubin levels in the subjects indicate absence of drug induced liver injury (DILI) on evaluation with the criteria reported by Saha *et al*[24].

The increase in the levels of pro inflammatory cytokines and induction of acute phase response secondary to infection is a well understood mechanism[25]. Evaluation of the circulating levels of factors involved in immune-inflammatory-endocrine-metabolic responses in 53 patients with tuberculosis by Santucci *et al*[26] revealed reduced levels of leptin and dehydroepiandrosterone, and increased concentrations of C-reactive protein (CRP), Interleukin-6 (IL6), cortisol, Interleukin-1β (IL-1β) in patients compared to healthy controls. A positive correlation was found between the BMI and leptin levels of TB patients, with a decreasing trend with increasing disease severity. Higher concentrations of IL-6, CRP, IL-1b, cortisol, and ghrelin were seen in cases with moderate to severe tuberculosis compared to healthy controls[26].These cytokines are known to negatively affect appetite thus leading to decreased food intake which further leads to weight loss. The increase in platelets in the blood in inflammatory conditions is established. This increase is related to increases in ESR and acute phase reactants including cytokines such as interleukin 6, TNF alpha etc. and proteins such as C-reactive protein, fibrinogen. The increase in platelets is known to curb the spread of tuberculosis by the formation of micro thromboses around tuberculosis cavities in the lungs. The extent of increase in platelets is related to the severity of tuberculosis also[27,28].

Phase II –Characteristics of 'COPPS' formulation

Several plants of Indian origin have been reported for their *in vitro/in vivo* anti-mycobacterial activity namely *piper nigrum, ocimum sanctum, emblica officinalis, withania somnifera, curcuma longa, adhatoda vasica nees, aloe vera, allium sativum*, *plectranthus amboinicus* etc[8]. Few among them which are commonly used as a herb or as a part of cuisine were selected to prepare the formulation. The proximate and phytochemical composition of the formulation (powder without added honey) is presented in Table No.6.

The formulation was found to be rich in dietary fiber and protein. Quantitative analyses of phytochemicals indicated the presence of alkaloids, steroids, terpenoids, flavonoids, tannins, glycosides and phenolic compounds. Terpenoids and glycosides were present in all the extracts except for aqueous extracts. The formulation was found to be rich in total phenolic antioxidants (6149$\pm$ 205.1 mg/100gm). The total flavonoids expressed as rutin equivalent, glutathione and tannin content were found to be 608.9$\pm$46 mg/100gm, 63.79mg/100gm and 1466.6±38.5 mg/100gm on dry basis respectively. The herbs used in the formulation are also known to have a hepato-protective activity against damage induced by anti-tubercular drugs[29]. On comparison with LIV52 (a commercially available ayurvedic preparation as a hepato-protectant or liver function enhancer) containing 130 gm of ascorbic acid,1296 mg of total phenols, 692 mg of total flavonoids and 6730 mg of glutathione per 100g[30], our formulation had a higher phenolic content and a similar flavonoid content, but lower levels of ascorbic acid and glutathione.

Phase 3- Intervention

Out of the 9 subjects screened initially, 5 successfully completed the intervention. Three subjects discontinued their participation during the

study and one subject met death due to the development of acute complications before initiation of intervention. The anthropometric indicators, nutrient intake and biochemical parameters of the subjects before and after intervention are presented in Table No.7, 8 and 9 respectively. Improvements were seen in all the anthropometric measurements at the end of intervention in all the subjects.

The mean increase in weight and BMI was found to be 4.84 ± 1.96 kg and 1.8 ± 0.74 kg/m^2 respectively. Increase in MUAC, TSF and MUAMC which are indirect indicators of muscle and fat status were also observed. The mean increase in the MAC, TSF and MUAMC were 1.9 ± 1.02 cm, 1.9 ± 0.97 mm and 1.36 ± 1.31 cm respectively. All the subjects reported decrease or absence of nutrition intake symptoms (nausea, early satiety, vomiting etc.) indicating better tolerance of oral diet consumed. The mean decrease in PGSGA score was found to be 14 ± 3 and was statistically significant with a *p* value of 0.00019, indicating the reversal of malnutrition. Subjects 1, 5 and 7 had improvements in their nutritional status from severely malnourished state to moderately malnourished state. Subjects 4 and 7 returned to a normally nourished state post intervention from a moderately malnourished state at the beginning of the intervention. Increased intake of energy, protein carbohydrate and calcium was seen in all the subjects at the end of intervention and the increase was 437 ± 280 kcals, 16 ± 12 g, 74 ± 42 g and 108 ± 62 mg respectively. Reductions in intake of fat, iron and zinc was seen in subject 4 only, whereas among the other 4 subjects the mean increase in intake of fat, iron and zinc was 12.1 ± 12.6 g, 3.75 ± 1.3 mg and 1.4 ± 1.12 mg respectively.

Four among the five subjects who participated in the intervention had increase in their hemoglobin levels (mean increase of 0.7 ± 0.32 g/dl. Decrease in lymphocyte count was seen in 3 subjects and 2 subjects had increased lymphocyte counts compared to the baseline values. Increase and decrease in RBC count was observed in one subject each respectively. The platelet count was found to be decreased in all the subjects with a mean decrease of 30.85 ± 9.8% of initial value. ESR and CRP were also found to be decreased in all the subjects. The overall degree of reduction observed in the ESR was 46 ± 11 % and CRP level was 56 ± 29 %. The mean decrease in ESR was 27 ± 1 mm/hr and the mean decrease in CRP levels was 26 ± 25 mg/L. Serum albumin levels were increased in three subjects who had hypoalbuminemia before intervention (mean - 0.31 ± 0.17 g/dl). The AST and ALT enzyme levels of four subjects were within the normal limits at the beginning and at the end of intervention. The elevated AST and ALT enzyme levels of subject no 9 at the beginning of intervention had returned to normal limits post intervention. Similar reduction was seen in the ALP enzyme levels among two subjects at the end of intervention period, whereas the other 3 subjects ALP within the normal limits before and after intervention.

The use of multi drug therapy is the standard treatment of drug susceptible mycobacteria worldwide and its effectiveness is well established. Nausea, vomiting and anorexia in patients on anti-tubercular drugs are among the other known adverse effects of the drugs, which can negatively impact food intake[31]. Singh et al reported presence of GI symptoms in 27-30% of the subjects evaluated for side effects of DOTS therapy among 100 subjects; GI symptoms were also found to be the most common adverse drug reaction (ADR) seen in 24.55% of 125 subjects with MDR-TB in a retrospective study by Dela *et al*[32]. Naser *et al*[33] reported gastrointestinal ADR s in 72 (24.3%) subjects among 296 subjects who were evaluated for ADR following DOTS therapy. In our study, 5 out of 9 subjects reported nausea and vomiting before initiation of the intervention and all of them reported absence of the same at the end of intervention period.

Improvement in nutrient intake of majority of the subjects in our study could be due to the reduction in nutrition impact symptoms as observed by the absence of early satiety, nausea and vomiting. As discussed earlier, the negative role of inflammatory

responses on appetite and food intake is clear. The reductions seen in the serum levels of CRP indicate suppression of inflammatory response and thus could have led to restoration of appetite. The intervention along with the prescribed anti-tubercular therapy seems to have provided multiple benefits in terms of disease status and nutritional status. Since the stress response generated in tuberculosis is due to the infection itself, the effect of combined therapy could have reduced the microbial load physiologically and thus led to improvements.

The action of the drugs could have been supplemented by use of COPPS formulation due to its phytochemical nature. Polyphenols are known to induce anti-mycobacterial action by adsorbing to the bacterial membranes causing membrane disruption and leakage of cellular contents followed by the generation of hydro peroxide radicals from polyphenols itself[34].

Tulsi leaves and pepper seeds are known to induce immuno-modulatory action by boosting antibody production and release of mediators of hypersensitivity reactions[35,36,37]. Curcumin is known to exert immuno-modulatory activity by stimulation of macrophages to eliminate intracellular bacteria and induction of apoptosis and autophagy[38]. The phenolics, flavonoids, flavones, terpenes, steroids and volatile oils found are identified as the active ingredients in providing the above mentioned bactericidal actions.

FUTURE APPROACHES

The inclusion of a larger number of subjects with active pulmonary tuberculosis and inclusion of controls would strengthen the data on the effectiveness of formulation in rendering the benefits on the nutritional and health status and its use as an adjuvant to DOTS therapy.

Table No.1: Composition of COPPS formulation

S.No	Ingredients per serving of COPPS formulation	Amount
1	Dried and powdered *plectranthus amboinicus* leaves (Doddapatre)	100 mg
2	Dried and powdered *ocimum sanctum* leaves (Tulsi)	100 mg
3	*Curcuma longa* root powder	100 mg
4	*Piper nigrum* seed powder	100 mg
5	Honey 1 teaspoon	4.5 g

Table No.2: Demographic data of the subjects

Age (in years)	36 ± 8
Gender	6 – male / 3 – female
Place of residence	Urban - 100%
Nature of Disease	
I (Newly detected)	6 (66.6%)
II (Relapse)	3 (33.3%)
Days since diagnosis	
1-7 days	7 (77.7%)
8-15 days	2 (22.3%)
Socioeconomic status	
Upper lower class n (%)	5 (55.5%)
Lower middle class n (%)	4 (45.5%)

Table No.3: Anthropometric data of the subjects

S.No	Parameters	Overall	Male	Female	p-value (Male vs female)
	No of subjects	**9**	**6**	**3**	
1	Height (mtr)	1.65± 0.11	1.69± 0.12	1.57± 0.06	**0.094**
2	Weight (kg)	45.61± 13.06	45.18± 12.67	46.47± 16.7	0.914
3	% of IBW	73.99± 16.16	69.28± 11.45	83.40± 22.74	0.398
4	BMI (kg/m^2)	16.61± 3.69	15.63± 2.63	18.58± 5.33	0.445
5	MUAC (cm)	20.61± 4.17	19.75± 3.82	22.33± 5.13	0.494
6	% std	71.06± 14.74	67.41± 13.03	78.36± 18.01	0.415
7	TSF (mm)	10.91± 5.65	9.00± 4.47	14.73± 6.71	0.275
8	% std	77.76± 35.89	72.00± 35.78	89.29± 40.66	0.569
9	MUAMC (cm)	17.18± 2.84	16.93± 2.54	17.67± 3.94	0.787
10	% std	70.01± 12.5	66.93± 10.02	76.18± 16.99	0.454
IBW – Ideal body weight; BMI – Body mass index; MUAC- Mid upper arm circumference; TSF – Triceps skinfold; MUAMC – Mid upper arm muscle circumference					

Table No.4: Dietary adequacy of nutrient intake of the subjects

S.No	Nutrient	Overall n-9	Male n-6	Female n-3
1	Energy (kcals)	1510.45 ± 426.67	1639 ± 472.6	1253.34 ± 145.21
2	% of RDI met	60.25 ± 15.72	61.87 ± 17.28	57 ± 14.76
3	Protein (g)	48.62 ± 16.43	52.09 ± 18.92	41.69 ± 8.76
4	% of RDI met	60.29 ± 22.59	63.66 ± 25.12	53.55 ± 18.94
5	Fat (g)	36.36 ± 17.36	37.61 ± 19.36	33.87 ± 15.97
6	% of RDI met	66.29 ± 31.43	64.7 ± 32.8	69.46 ± 35.21
7	Carbohydrate (g)	246.07 ± 64.51	270.62 ± 66.82	196.96 ± 7.78
8	% of RDI met	58.48 ± 12.54	60.28 ± 13.19	54.90 ± 12.85
9	Calcium (mg)	790.22 ± 320.29	842.8 ± 389.39	685.05 ± 80.01
10	% of RDA met	131.7 ± 53.38	140.47 ± 64.9	114.17 ± 13.34
11	Iron (mg)	14.42 ± 15.87	16.4 ± 5.83	10.44 ± 1.86
12	% of RDA met	80.91 ± 36.08	96.49 ± 34.31	49.73 ± 8.85
13	Vitamin C (mg)	29.52 ± 8.19	29.71 ± 6.41	29.12 ± 12.86
14	% of RDA met	36.89 ± 10.24	37.14 ± 8.01	36.4 ± 16.07
15	Zinc (mg)	5.77 ± 1.93	6.52 ± 1.95	4.26 ± 0.49
16	% of RDA met	50.45 ± 14.36	54.36 ± 16.29	42.64 ± 4.88

Table No.5: Biochemical parameters of the subjects

S.No	Parameters	Reference values	Overall (n-9)	Male subjects (n-6)	Female subjects (n-3)
1	Hemoglobin	11.5 – 16.5	10.57 ± 2.86	11.7 ± 2.88	8.3 ± 0.66
2	Leukocyte count	4000 – 11000	9622 ± 2542	9583 ± 2794	9700 ± 2512
3	RBC count	3.8 – 5.8	3.98 ± 0.45	3.98 ± 1.07	4 ± 0
4	Platelet count	150000 - 450000	480444 ± 133149	433500 ± 75556	574333 ± 191855
5	CRP (mg/L)	<6 mg/L	62.66 ± 64	43.87 ± 33.84	100.22 ± 100.38
6	ESR (mm/hr)	0 – 20	64 ± 29.46	53.33 ± 29.16	85.33 ± 17.93
7	*Liver function test*				
8	AST (U/L)	10 – 46	26 ± 12	27 ± 15	23 ± 7
9	ALT (U/L)	10 – 46	20 ± 18	22 ± 22	16 ± 10
10	ALP (U/L)	30 – 120	114 ± 38	114 ± 37	113 ± 48
11	Total protein (g/dl)	6.4 – 8.3	7.3 ± 0.5	7.32 ± 0.4	7.33 ± 0.7
12	Serum albumin (g/dl)	3.5-5	3.4 ± 0.4	3.45 ± 0.5	3.28 ± 0.2
13	Serum globulin (g/dl)	2.3 – 3.6	3.9 ± 0.5	3.9 ± 0.6	4.1 ± 0.6
14	Albumin to Globulin ratio	0.8 – 2	0.89 ± 0.21	0.93 ± 0.24	0.82 ± 0.12
15	Serum bilirubin (mg/dl)	Up to 1.3 mg/dl	0.35 ± 0.08	0.37 ± 0.07	0.32 ± 0.07

Table No.6: Proximate and phytochemical composition of the formulation (per 100g)

S.No	Component	Values (mean ± SD)
1	Moisture (%)	7.5 ± 0.3
2	Total Ash (g)	1.06 ± 0
	Water soluble Ash (g)	0.80 ± 0
	Water insoluble Ash (g)	0.26 ± 0
3	Total sugar (g)	82.5 ± 0.3
4	Protein (g)	12.25 ± 0
5	Fat (g)	0.63 ± 0.05
	Total dietary fiber	22 ± 0
	Insoluble dietary fiber	9 ± 0
	Soluble dietary fiber	12.3 ± 0
6	Iron (mg)	5.04 ± 0.5
7	Phosphorus (mg)	24.65 ± 1.1
8	Vitamin C (mg)	28.4 ± 0

Table No.7: Changes in anthropometry and nutritional status of subjects in the intervention group

Anthropometry	Subject 1 (F)		Subject 4 (M)		Subject 5 (M)		Subject 7 (F)		Subject 9 (M)	
	Before	After	Before	After	Before	After	Before	After	Before	After
Height (m)	1.504		1.6		1.64		1.58		1.88	
Weight (kg)	35.7	38.3	46.8	51.6	39.6	43	38	45.5	67.6	73.5
BMI (kg/m^2)	15.78	16.93	18.28	20.16	14.72	15.99	15.22	18.23	19.13	20.80
MAC (cm)	18	21	23	24	15.5	17	21	24	25	26
SFT (mm)	7	7.5	11	13	6	8	19	20	16	19
MUAMC (cm)	15.82	18.64	19.5	19.9	13.6	14.4	15	17.7	19.9	20
PGSGA rating	C	B	B	A	C	B	C	B	B	A
PGSGA score	16	5	20	3	20	5	18	3	12	1

BMI – Body mass index , MAC – Mid upper arm circumference, SFT – Triceps skinfold thickness, MUAMC – Mid upper arm muscle circumference, PGSGA – Patient generated subjective global assessment

Table No.8: Nutrient intake of subjects in the intervention group

S.No	Nutrients (intake per day)	Before (mean ± SD)	After (mean ± SD)	*p*– value
1	Energy (kcals)	1467 ± 439	1904 ± 208 ↑	ns
2	Protein (g)	48 ± 18	64 ± 12 ↑	ns
3	Fat (g)	37 ± 22	44 ± 6 ↑	ns
4	Carbohydrate (g)	233 ± 56	307 ± 38 ↑	**0.045**
5	Calcium (mg)	721 ± 110	829 ± 112 ↑	ns
6	Iron (mg)	14 ± 5	14 ± 3	ns
7	Zinc (mg)	5 ± 2	6 ± 1 ↑	ns
ns- not significant, ↑ and ↓ indicates increase and decrease in the baseline values respectively				

Table No.9: Changes in biochemical parameters of subjects in the intervention group

Subject and gender →	**Subject 1 (F)**		**Subject 4 (M)**		**Subject 5 (M)**		**Subject 7 (F)**		**Subject 9 (M)**	
Biochemical parameters ↓	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Hemolobin (g/dl)	7.7	8.0	13.6	14.2	10.3	11.3	9.0	9.9	13.7	11.6
Lymphocyte count (/µL)	8300	7000	8400	8200	14900	11900	8200	8300	6900	9300
RBC count (mill/cu.mm)	4	4	5	5	3	4	4	4	4.85	4
Platelets cells/cu.mm)	791000	477000	464000	279000	543000	364000	426000	354000	471000	354000
ESR (mm/hr)	106	53	32	16	72	53	69	31	16	08
C-reactive protein (mg/L)	19.03	4.37	27.03	17.09	72.17	15.55	67.36	17.74	5.26	4.52
Liver function test										
AST (U/L)	30	23	21	25	27	34	17	16	56	45
ALT(U/L)	28	19	15	16	11	17	11	10	66	45
Alkaline Phosphatase (U/L)	161	93	77	93	155	137	66	84	81	77
STP (g/dl)	8.15	7.66	7.33	7.38	7.32	7.93	6.85	7.11	7.17	7.09
SA (g/dl)	3.46	3.76	3.82	3.94	2.88	3.37	3.35	3.5	4.05	3.79
SG (g/dl)	4.69	3.90	3.51	3.44	4.44	4.56	3.50	3.61	3.12	3.30
A/G RATIO	0.74	0.96	1.09	1.15	0.65	0.74	0.96	0.97	1.30	1.15
RBC-Red blood count, ESR- Erythrocyte sedimentation rate, AST- Aspartate aminotransferase, ALT-Alanine aminotransferase, STP-Serum total protein, SA- Serum albumin, SG-Serum globulin, A/G- Albumin /Globulin										

CONCLUSION

Identification of impairment in nutritional status and suitable nutrition therapy is crucial in the treatment of TB. Patients with tuberculosis have elevated nutritional needs due to the active infection. The drug therapy invariably is known to reduce the symptoms of the disease on initiation of treatment, but the adverse effects of drug itself on gastrointestinal symptoms further reduce the dietary intake of nutrients. Reduction in these symptoms lead to increased nutrient intake and improvement in nutritional status of the subjects in the current study. This effect could be due to the synergistic action of COPPS formulation which is rich in phytochemicals reported to have anti-mycobacterial action and anti-inflammatory action. The adverse side effects associated with the long duration drug therapy paves way for exploration and use of adjuvants of nutritional or herbal origin that are safe and effective. Such an approach can reduce the drug induced side effects.

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CONFLICT OF INTEREST

The authors hereby declare that there is no conflict of interest.

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