Review Article

Anti-Obesity Effect of Trimad, a Polyherbal Formulation: A Review

Megha Salunke, Supriya Bhalerao*
Interactive Research School for Health Affairs, Bharati Vidyapeeth Deemed University, Dhankawadi, Pune-Satara Road, Pune, India.
***Corresponding author's E-mail:** supriya.bhalerao@gmail.com

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ABSTRACT

Trimad is an Ayurvedic polyherbal formulation consisting of tubers of Mustak (*Cyperus rotundus*), fruits of Vidang (*Embelia ribes*) and roots of Chitrak (*Plumbago zeylanica).* It has been recommended in Ayurveda for management of obesity. This review article attempts to correlate Ayurvedic pharmacology and therapeutic claims of this formulation related to obesity with the evidence generated using scientific research methodology. Obesity has been identified as state of chronic low grade inflammation. It is also associated with oxidative stress and is a major player in metabolic syndrome along with diabetes and cardiovascular diseases. Hence, the research works carried out on these plants to demonstrate their anti-oxidant, anti-diabetic and anti-hyperlipidaemic activities have also been included in the present review. It was observed that 'Trimad' as a combination has not been studied so far. However, the individual ingredients have been shown to possess antioxidant, anti-diabetic, anti-obesity and anti-inflammatory, Anti-hyperlipidemic activities. These reports support the anti-obesity effects of the combination described in Ayurvedic texts.

Keywords: Anti-obesity, *Cyperus rotundus*, *Embelia ribes*, *Plumbago zeylanica*, Trimad.

INTRODUCTION

Trimad is an Ayurvedic polyherbal formulation consisting of tubers of Mustak *(Cyperus rotundus),* fruits of Vidang *(Embelia ribes)* and roots of Chitrak *(Plumbago zeylanica).* It acts as an appetizer, expels worms, and useful in obesity as it prevents weight gain. Trimad also removes plaque deposits in the body and promotes circulation of blood as well as it helps to stop the building of fat deposits and it also help to prevent water retention, a common phenomenon in obesity.[1]

The pharmacological attributes of the ingredients of the formulation as mentioned in the Ayurvedic texts are as follows: *Musta* possesses *Tikta* (bitter), *Katu* (pungent), *Kashaya* (astringent), *Rasa* (taste), while *Vidanga* and *Chitrak* both possess *Katu Rasa* alone. All the ingredients possess *Laghu*(light), *ruksha*(dry) properties. In addition, Chitrak and Vidanga possess *Teekshna* (penetrating) property. The *Vipaka* (after metabolites) of all the ingredients is *Katu* (pungent). The *veerya*(potency) of Chitrak and Vidanga is *Ushna*(hot) while that of Musta is *sheeta* (cold).[2-4]

The formulation is prescribed in various disorders such as excessive thirst, fever, anorexia, abdominal pain, flatulence, worm infestation, skin diseases, diabetes, headache, swelling on the body, piles etc. In the present article, we have compiled the scientific information about the formulation or its individual ingredients related to obesity and have attempted to substantiate the therapeutic claims made in Ayurveda.

Methodology

We searched the databases viz. Google, Google Scholar, PubMed for the study. The search was restricted for a period of 16 years ranging from 1998 to 2014.

The search terms included Trimad, *Cyperus rotundus, Embelia ribes, Plumbago zeylanica*, and obesity along with allied activities viz. anti-inflammatory, anti-oxidant, anti-diabetic, anti-hyperlipidaemic and anti-hyperhomocystemic activities. Duplication was avoided by excluding review of multiple copies of the same article in several databases.

RESULTS

The search yielded a total of 26 articles in various databases, which were included for the review. Interestingly, no article was found on Trimad as a combination. The activity for which the individual ingredients have been explored is shown in the Table 1.

Table 1: Number of studies reported on various activities of the plants

Activity	*Cyperus rotundus*	*Embelia ribes*	*Plumbago zeylanica*
Anti-obesity	4	1	1
Anti-diabetes	4	3	2
Anti-oxidant/ Oxidative stress	3	5	2
Anti-hyperlipidemic			1

The details of these studies are presented below:

Cyperus Rotundus

Figure 1: *Cyperus rotundus* Linn Tubers

Anti-obesity activity

In a study carried out on a mixture of *Cyperus rotundus (*60 mg/kg), *Iris versicolor*(20 mg/kg) and *Holoptelia integrifolia*(1.66 g/kg), a rapid decrease of weight in *ad libitum* fed obese rats was seen. This mixture increased energy expenditure and metabolic rate in obese rats.[5]

In another study by the same authors, the same mixture was used in three different forms viz. powder in fine suspension, aqueous and alcoholic extracts. These preparations were used in both *in vitro* and *in vivo* studies. The mixture was found to have significant lipolytic action on adipose tissue as revealed by increase in glycerol and free fatty acid release. In the *in vivo* study, the rats were fed with mixture at three different doses viz. 60 mg/kg, 20 mg/kg and 1.66 g/kg. The results showed that the preparation exhibited lipolytic action to mobilize fat from adipose tissues in rats and thereby resulted in the reduction of weight.[6]

In another study, hexane extract of *C. rotundus* tubers was administered to Zucker rats in 2 different doses (45 or 220 mg/kg/day) for 60 days. The treatment significantly reduced weight without any adverse effect. In the same study, the effect of the extract was evaluated on 3T3-F442 adipocytes. The extract stimulated lipolysis at 250 µg/mL concentration. The additional studies indicated that the weight loss by *C. rotundus* treatment may be mediated through the activation of the beta3-Adrenergic Receptor (AR). [7]

Aqueous extract of tubers of *Cyperus rotundus* with doses of 100mg/kg, 200mg/kg and 300mg/kg for 40 days showed a significant reduction in the body and organ weight (liver, kidney, spleen, fat pads) in a model of High Fat Cafeteria Diet in rats. It also demonstrated reduction in biochemical parameters (serum triglycerides, total cholesterol, LDL cholesterol, VLDL cholesterol & glucose) with increase in HDL cholesterol in a dose dependent manner. Further, the elevated levels of liver markers (Aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP)) returned to normal after treatment. Moreover, the extract reduced oxidative stress by enhancing the levels of glutathione (GSH), glutathione peroxidase (GPx), super oxide dismutase (SOD) and catalase in the hepatic tissue of rats with HFCD induced obesity.[8]

Anti-diabetic activity

The ethanolic extract of *Cyperus rotundus* rhizomes (CRRE) has been studied with relation to age associated changes. The oral administration of CRRE (500mg/kg body weight) to aged rats for 30 days prevented the age associated changes in glucose and lipid parameters. The improvements indicate decreased risk of diabetes mellitus and cardio vascular diseases associated with advancing age.[9]

In another study, treatment with the different doses of alcoholic extract of *Cyperus rotundus* have demonstrated the potential to exert significant reduction in serum total cholesterol, LDL, TG, HDL levels at the end of 15 days of intervention comparable to the standards used in the study[Simvastatin (5 mg/kg/day) and Fenofibrate (20 mg/kg/day)].[10]

Oral administration of hydroethonolic extract of *Cyperus rotundus* daily at a dose of 500mg/kg for seven days has been reported to significantly lower the blood glucose levels in alloxan induced diabetic rats.[11]

Anti-oxidant activity

Cyperus rotundus rhizomes ethanolic extract (CRRE) was evaluated in a series of *in vitro* assay involving free radicals and reactive oxygen species. CRRE exhibited its scavenging effect in concentration dependent manner on superoxide anion radicals, hydroxyl radicals, nitric oxide radical, hydrogen peroxide, property of metal chelating and reducing power. The extract was also studied for inhibition of lipid peroxidation by Thiobarbituric acid–reactive substances (TBARS) assay, using young and aged rat brain mitochondria, where it was found effective in preventing mitochondrial lipid peroxidation induced by FeSO4/ ascorbate in concentration dependent manner.[12]

The anti-oxidant potential of a hydro-alcoholic extract of *Cyperus rotundus* rhizomes (CRE) has been evaluated in different antioxidant assays and compared to standard antioxidants such as butylatedhydroxytoluene, tocopherol, L-ascorbic acid, and catechin. The extract exhibited high reduction capability and powerful free radical scavenging, especially against DPPH and superoxide anions. It also has a moderate effect on NO.[13]

In yet another study, aqueous and ethanolic extracts of *Cyperus rotundus* rhizome showed significant free radical scavenging activity though ethanolic extract which was reported to be better than its aqueous extract. [14]

Hypolipidaemic activity

Aqueous extract of *Cyperus rotundus* when administered in a dose of 500 mg/kg body weight for 15 days has shown hypolipidaemic activity in CCl_4 Induced Dyslipidemia in rats.[15]

Embelia Ribes

Figure 2: *Embelia ribes Linn Fruits*

Anti-obesity activity

The ethanolic extract of *Embelia ribes* (ERE) ata dose of 100mg/kg administrated orally to High Fat Diet (HFD) fed rats for 21 days showed significant improvement in body weight, body mass index (BMI), blood pressure and serum parameters. ERE showed reduction in serum levels of leptin, insulin, glucose, cholesterol and triglycerides. HDL levels were increased along with decreased lipid peroxidation and increased antioxidant levels. [16]

Anti-diabetic activity

Oral administration of the ethanolic extract of *Embelia ribes* (200 mg/kg) for 20 days to diabetic rats significantly decreased blood glucose, serum total cholesterol & triglycerides and increased HDL- cholesterol levels. It also lowered the hepatic and pancreatic MDA. The results were comparable to gliclazide (25 mg/kg, orally), a standard anti- hyperglycemic agent. [17]

In another study HFD-fed and low dose STZ (35 mg/kg) induced diabetic rats were treated with ethanolic extract of *Embelia ribes* [EER] (100 and 200 mg/kg/day) for 21 days while continuing on HFD. There was significant reduction in weight gain, fasting blood glucose, blood pressure, serum lactate dehydrogenase (LDH), creatinine, ALP, total cholesterol and TGL levels observed in these rats. EER also showed insulin sensitizing effect during oral glucose tolerance testing. Further, it significantly decreased the kidney MDA levels, while increasing the SOD, CAT and GSH levels in diabetic rats. The findings from histological studies of kidney also supported these claims.[18]

50% Ethanolic extract of *Embelia ribes* berries has been shown to reduce blood sugar levels in normal as well as diabetic rats. While the reduction in blood sugar levels in normal rats was 13.1% and 20.3% after 3 and 5 hours of the treatment respectively, in alloxan induced diabetic rats, this reduction was up to 28.1% and 34.5% after similar time period. [19]

Antioxidant activity

A study carried out in diabetic rats revealed that 40 days of oral feeding of the ethanolic extract of *Embelia ribes* (100 mg/kg and 200 mg/kg) resulted in significant decrease in blood glucose, blood glycosylated hemoglobin, serum lactate dehydrogenase, creatine kinase and increase in blood glutathione levels. The extract also significantly decreased the pancreatic MDA levels and significantly increased the SOD, CAT, and GSH levels in pancreatic tissue. The difference in all these activities was statistically significant between treated and diabetic rats.[20]

In vitro antioxidant activity of *Embelia ribes* fruit is further proven by its capacity to scavenge DPPH free radical, superoxide, nitric oxide, hydrogen peroxide, hydroxyl radical and lipid peroxides. The *Embelia ribes* fruit extract is able to inhibit lipid peroxidation and scavenge hydroxyl radicals very effectively compared to the natural antioxidant, ascorbic acid and rutin (flavonoid).[21]

Administration of ethanolic extract of *Embelia ribes* extract (100mg/kg body weight)orally for 30 days to methionine induced hyper homocysteinemic rats produced a significant decrease in homocyteine, total cholesterol, triglycerides, LDH, Low density lipoprotein-C, Very low density lipoprotein-C and Lipopolysaccharide levels in brain with significant increase in High density lipoprotein-C levels and GSH content.[22]

In yet another study, obese male Wistar rats fed on HFD for 28 days were treated with *embelin* (50 mg/kg) or orlistat (10 mg/kg) for 21 days. Parameters tested were body weight , body mass index (BMI), blood pressure, visceral fat pad weights, serum levels of glucose, insulin, leptin, apolipoprotein B (ApoB), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), hepatic thiobarbituric acid-reactive substances (TBARS), superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH). Twenty-one days of embelin (50 mg/kg) treatment produced effects similar to orlistat in reducing body weight, blood pressure, visceral fat pad weight, serum lipid levels as well as coronary artery disease risk and atherogenic indices of HFD-fed rats. [23]

Free radical scavenging reactions and antioxidant activity of *Embelia ribes* has also been studied. Embelin was found to inhibit lipid peroxidation and restore impaired Mn-superoxide dismutase in rat liver mitochondria. Further, kinetics and mechanism of the reactions of embelin with hydroxyl, one-electron oxidizing, organo-haloperoxyl and thiyl radicals have been studied using nanosecond pulse radiolysis technique. Its redox potential has also been evaluated with cyclic voltammetry. These studies suggest that embelin can act as a competitive antioxidant in physiological conditions. [24]

Plumbago Zeylanica

Figure 3: *Plumbago zeylanica* Linn roots.

Anti-Obesity activity

In a clinical study, *Plumbago zeylanica* and *Curcuma longa* powders were administered to obese patients at the dose of 500mg and 1gm respectively, 4 times a day in a capsule form for 45 days with restricted diet schedule. The results showed that the intervention of *Plumbago zeylanica* resulted in highly significant weight loss than intervention with *Curcuma longa*.[25]

Anti-diabetic activity

Plumbagin (15 and 30 mg/kg), a phyto constituent from *Plumbago zeylanica* was orally administered to STZ-induced diabetic rats for 28 days. An oral glucose tolerance test was performed on 21stday. Plumbagin significantly reduced the blood glucose and significantly altered all other biochemical parameters to near normal. Further, plumbagin increased the activity of hexokinase and decreased the activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase significantly in treated diabetic rats. Enhanced GLUT4 mRNA and protein expression were observed in diabetic rats after treatment with plumbagin.[26]

Yet another study has reported effect of ethanolic extract of *Plumbago zeylanica* (100, 200 mg/kg) on hepatic enzymes in streptozotocin induced diabetic rats. Oral administration of the extract increased hepatic hexokinase activity and decreased hepatic glucose-6-phosphatase, serum acid phosphatase (ACP), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH).[27]

Antioxidant activity

A study involving pretreatment with the alcoholic root extract of *Plumbago zeylanica* (250 and 500 mg/kg body weight orally for 5 days) has shown significant reduction in the frequency of micronucleated polychromatic erythrocytes (MnPCEs), increase the PCE (polychromatic erythrocytes)/NCE (normochromatic erythrocyte) ratio in the bone marrow, and decrease in the levels of lipid peroxidation products with concomitant changes in the status of antioxidants against cyclophosphamide-induced genotoxicity in Swiss albino mice.[28]

The methanolic extracts of different plants viz. *Plumbago zeylanica* (Root), *Acorus calamus* (Rhizome), *Hemidesmus indicus* (Stem) and *Holarrhena antidysenterica* (Bark) were evaluated for their antioxidant activity by ferric thiocyanate (FTC) assay and compared with thiobarbituric acid (TBA) method. The antioxidant potential according to FTC assay was found to be highest for *Plumbago zeylanica* among all plants.[29]

Anti-hyperlipidemic activity

The oral administration of the aqueous extract of *Plumbago zeylanica* in diet-induced hyperlipidemic rats at the dose of 20, 40 and 80 mg/kg was found to ameliorate the hyperlipidemic condition as evidenced by a reduction of cholesterol and triglyceride levels. Further, the aqueous extract, at all doses, and demonstrated a significant increase in fecal cholesterol excretion indicating a reduction in intestinal cholesterol absorption. Additionally, the activity of lipogenic enzymes like HMG CoA reductase in the liver remained significantly low on treatment of aqueous extract (80 mg/kg) decreasing the cholesterogenesis. The aqueous extract (20, 40 and 80 mg/kg) also significantly reduced the total lipid content in the liver significantly. Moreover, the aqueous extract demonstrated potential antioxidant capacity in DPPH and TBARS *invitro* antioxidant assays.[30]

SUMMARY

It was seen that 'Trimad' as a combination has not been studied so far. However, the individual ingredients have been shown to possess antioxidant, anti-diabetic, anti-obesity, anti-inflammatory and anti-hyperlipidemic activities. These reports support the anti-obesity effects of the combination described in Ayurvedic texts.

Although all three ingredients have been explored for almost all the activities mentioned in the key words, the available literature indicate that the individual plant agent may have one prominent activity e.g. *Cyperus rotundus* may be a more potent anti-diabetic agent as compared to other ingredients. The combination, therefore, may exhibit a wide range of activities synergistically.

There is a need to examine the effect of the combination in experimental models. Further pharmacological evidence at molecular level is required to establish the mechanism of action of the combination. The next step may be to generate therapeutic evidence by evaluating the effect of combination in well planned clinical studies.

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