

# A Meta-analysis of *Sphaeranthus indicus* and *Garcinia mangostana* Products on Cardiometabolic Outcomes in Obese Patients

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## Phimarn *et al.*: Meta-analysis of *S. indicus* and *G. mangostana* on cardiometabolic outcomes

This study aimed to assess the efficacy of *Sphaeranthus indicus* and *Garcinia mangostana* in improving anthropological parameters, lipid profile, blood glucose and blood pressure in obese patients. The databases used included PubMed, Scopus, Web of Science from inception to March 2019. For this analysis, a randomized placebo versus *Sphaeranthus indicus* and *Garcinia mangostana* intervention trials were selected and performed a quality assessment of the retrieved data studied using Jadad's scoring and Cochrane's risk of bias assessment. Three studies (215 participants) met inclusion criteria. Meta-analysis revealed a reduction in body weight (weight mean difference; -3.84 kg; 95 % CI: -3.98, -3.70), BMI (weight mean difference -1.56 kg/m<sup>2</sup>; 95 % CI: -1.65, -1.47), waist circumference (weight mean difference -5.90 cm; 95 % CI: -6.36, -5.43). Similar results were observed for low density lipoprotein-cholesterol (weight mean difference -10.74 mg/dl; 95 % CI: -19.04, -2.44), total cholesterol (weight mean difference -22.05 mg/dl; 95 % CI -32.33, -11.76), triglyceride (weight mean difference -27.40 mg/dl; 95 % CI -30.55, -24.24) and increased high density lipoprotein significantly (weight mean difference 2.32 mg/dl; 95 % CI 0.56, 4.07). No serious adverse effects were found in either the *Sphaeranthus indicus* and *Garcinia mangostana* treated groups or comparator groups. It was concluded that *Sphaeranthus indicus* and *Garcinia mangostana* improved anthropological parameters and lipid profile.

**Key words:** *S. indicus* and *G. mangostana*, anthropological parameters, lipid profile, blood glucose, blood pressure

Cardiovascular disease (CVD) is the single leading cause of mortality worldwide<sup>[1]</sup> and also the most common cause of morbidity and mortality in individuals among patients with metabolic profile abnormality<sup>[2]</sup>. Metabolic profile abnormality is related to the elevation of glycemic profile, lipid profile, blood pressure and anthropological parameters. CVD

and metabolic profile abnormality could potentially be prevented or managed by addressing modifiable risk factors, for instance, physical activity and diet<sup>[3]</sup>. Therefore, effective prevention strategies are urgently needed to reduce mortality from CVD<sup>[4]</sup>. Earlier studies reported that a herbal formulation, Meratrim consisting of extracts of the flower heads from *Sphaeranthus*

*indicus* L. (Asteraceae) and the fruit rinds of *Garcinia mangostana* L. (Clusiaceae) demonstrated significantly improved metabolic outcomes in obese populations<sup>[5]</sup>. Furthermore, experimental studies also showed protective effects of *S. indicus* and *G. mangostana* products, including reduction in peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ )<sup>[6]</sup> and down regulation fatty acid synthetase (FAS) resulting to alter *de novo* lipogenesis<sup>[7]</sup>. Preclinical trials have suggested that intake of *S. indicus* and *G. mangostana* products has been decreased anthropological outcomes<sup>[8]</sup>. However, these studies were performed in a small number of participants and there was no previous systematic review or meta-analysis of effects of *S. indicus* and *G. mangostana* products on cardiometabolic outcomes. Therefore, a systematic review and meta-analysis was conducted to compare the effectiveness and safety of *S. indicus* and *G. mangostana* products on cardiometabolic outcomes in obese participants.

This systematic review was conducted according to the Cochrane Collaboration framework guidelines<sup>[9]</sup>, and reporting follows the PRISMA Statement<sup>[10]</sup>. All reports of double blind randomized controlled trials of *S. indicus* and *G. mangostana* in obese participants were identified through a systematic literature search of PubMed, Scopus and Web of Science databases. All databases were searched right from their inception to March 2019. The following MeSH terms were used: *Sphaeranthus indicus*, *Garcinia mangostana*, *Sphaeranthus indicus* and *Garcinia mangostana*, *S. indicus*, *G. mangostana*, obesity, obese, anthropological parameter, body weight, body mass index (BMI), waist circumference. No language restriction was imposed. References of papers derived for full text review were scanned to identify potential studies not indexed in the above databases.

The present study included only reports that were, double blind randomized controlled trial of *S. indicus* and *G. mangostana* against placebo in obese patients, the duration of the study was at least 8 w and reporting at least one outcome measures in terms of body weight, BMI, waist circumference, lipid profiles, blood glucose, and blood pressure.

All titles and abstracts were scanned based on inclusion criteria. Full-text articles of the potential studies were subsequently assessed independently by two

researchers. Disagreements between these reviewers were resolved by discussions with a senior researcher. All data were independently extracted by these two researchers using a standardized extraction form. The following information was sought from each article, author, year of publication, type of study design, patient and intervention characteristics, sample size, duration of therapy, and outcome measurements.

Studies included in this review were assessed for methodological quality using the Cochrane risk of bias 2.0 tool<sup>[11]</sup>, which contained 5 domains; bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result. The overall risk of bias for each study was classified as low risk of bias (low risk of bias for all domains), some concern (some concerns in at least one domain and no high risk of bias in any domain), and high risk of bias (high risk of bias in at least one domain or some concerns for multiple domains in a way that substantially lowers confidence in the results). Disagreements between the reviewers were settled through discussion and consensus with a third party.

Primary outcomes were anthropological parameters, lipid profile, blood glucose and blood pressure. Secondary outcomes were laboratory measurements such as liver function test and renal function test and adverse events. Pooled effects were calculated and stratified according to outcomes data. Summary statistics of continuous outcomes were expressed as weighted mean difference (WMD) with 95% confidence intervals (CI), whereas summary statistics dichotomous outcomes were expressed as a risk ratio (RR) with 95% CI. Statistical heterogeneity between studies was assessed using the chi-squared test and  $I^2$ . Significant difference for heterogeneity test was considered at  $p < 0.05$ , and substantial heterogeneity was represented by  $I^2$  of 50% or more<sup>[11]</sup>. If there was evidence of high heterogeneity, attempts were made to explore the reason and subgroup analyses were performed if possible. The

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random effects model was used if the included studies were heterogeneous; alternatively, the fixed effects model was used if homogeneity was found. Publication bias was evaluated using a funnel plot for a particular outcome<sup>[12]</sup>.

The PRISMA flow diagram of studies is shown in fig. 1. The 103 related articles were identified through database searching. After duplication removal, 8 articles were eligible for further screening based on title and abstract screened. A total of 5 articles were excluded after full

text review. Therefore, 3 articles were included in this study<sup>[5,13,14]</sup>.

The characteristics and methodological quality of included studies are summarized in Table 1. All included studies were conducted in India. Periods of study ranged from year 2010 to 2015. All studies were not multicenter with double blind randomized controlled trial and enrolled sample size less than 100 patients. A total of 215 participants were involved including overweight and obese participants. The age of included patients ranged from 21 to 50 y. All studies used herbal blend comprises of extracts from *S. indicus* and *G. mangostana* in a 3:1 ratio. A final product containing at least 3 % 7-hydroxyfrullanolide and 2 %  $\alpha$ -mangostin. All included studies administered *S. indicus* and *G. mangostana* products at 800 mg/d and the treatment courses ranged from 8 to 16 w. For methodological quality of included studies, all were high quality trials (Jadad score >3 points) with rated low risk of bias (Tables 1 and 2).

Three trials<sup>[5,13,14]</sup> involving a total of 215 patients reported clinical therapeutic efficacy of *S. indicus* and *G. mangostana* products on the treatment of

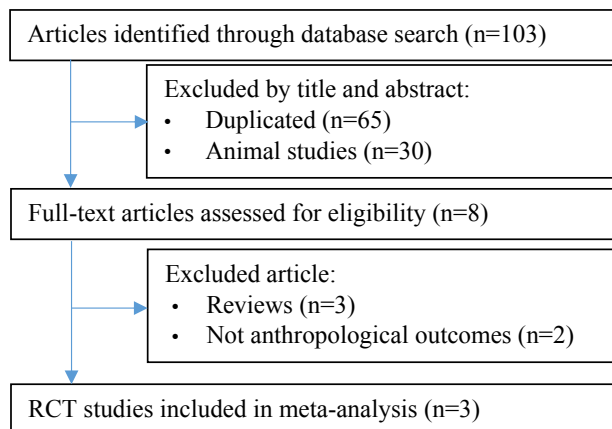


Fig. 1: Flow diagram for selection of trials

TABLE 1: CHARACTERISTIC OF THE INCLUDED STUDIES

Study (year)	Study design	Duration	Participants	Treatment characteristic		Outcomes	Jadad score
				Treatment (n)	control (n)		
Stern <i>et al.</i> , 2013A <sup>[13]</sup>	DRCT	8 weeks	Obese (BMI 30-40 kg/m <sup>2</sup> )	<i>S. indicus</i> <i>G. mangostana</i> (3:1 ratio) 400 mg twice daily (n=30)	Placebo twice daily (n=30)	BW, BMI, WC, SBP, DBP, FBS, LDL, HDL, TC, TG, LFT, AEs	5
Stern <i>et al.</i> , 2013B <sup>[14]</sup>	DRCT	8 weeks	Obese (BMI 30-40 kg/m <sup>2</sup> )	<i>S. indicus</i> <i>G. mangostana</i> (3:1 ratio) 400 mg twice daily (n=49)	Placebo twice daily (n=46)	BW, BMI, WC, SBP, DBP, FBS, LDL, HDL, TC, TG, LFT, RFTs, Hematology, AEs	5
Kudiganti <i>et al.</i> , 2016 <sup>[5]</sup>	DRCT	16 weeks	Obese and overweight (BMI 27-32 kg/m <sup>2</sup> )	<i>S. indicus</i> <i>G. mangostana</i> 400 mg twice daily (n=30)	Placebo twice daily (n=30)	BW, BMI, WC, FBS, LDL, HDL, TC, TG, LFT, RFTs, AEs	5

DRCT, double blind randomized controlled trial; BMI, body mass index; BW, body weigh; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglyceride; LFT, liver function test; RFTs, renal function test; AEs, adverse events

TABLE 2: RISK OF BIAS

Studies	Sequence generation	Allocation concealment	Investigator blinding	Patients blinding	Incomplete outcomes data	Selective outcome reporting	Other source of bias	Overall risk of bias
Stern <i>et al.</i> 2013A <sup>[13]</sup>	Low	Low	Low	Low	Low	Low	Low	Unclear
Stern <i>et al.</i> 2013B <sup>[14]</sup>	Low	Unclear	Low	Low	Low	Low	Low	Unclear
Kudiganti <i>et al.</i> 2016 <sup>[5]</sup>	Low	Low	Low	Low	Low	Low	Low	Unclear

anthropological parameter. The pooled effect from meta-analysis demonstrated that clinical efficacy on body weight was significantly better than those of controlled treatment (WMD=-3.84, 95 % CI was -3.98 to -3.70) with no evidence of heterogeneity among studies ( $I^2 = 32\%$ ,  $p = 0.23$ ). Moreover, *S. indicus* and *G. mangostana* product decreased BMI (WMD= -1.56, 95 % CI was -1.65 to -1.47) and waist circumference (WMD= -5.90, 95 % CI was -6.36 to -5.43). However, heterogeneity was observed in these outcomes.

*S. indicus* and *G. mangostana* product reduced LDL, total cholesterol and triglyceride level significantly (WMD= -10.74, 95 % CI was -19.04 to -2.44; -22.05 -32.33 to -11.76; -27.40 -30.55 to -24.24, respectively). Moreover, there was significant increase in HDL level (WMD 2.32 mg/dl; 95 % CI 0.56, 4.07) and there was evidence of heterogeneity (Table 3).

Two trials<sup>[12,13]</sup> contributed to data on the effect of *S. indicus* and *G. mangostana* product on blood pressure. *S. indicus* and *G. mangostana* product was not superior to comparators in systolic blood pressure (WMD: -1.81; 95 % CI -4.01 to 0.38), diastolic blood pressure (WMD: -2.03; 95 % CI -5.34 to 1.28) and pulse rate (WMD: 0.61; 95 % CI -1.58 to 2.79). A statistically significant heterogeneity was detected with these 3 outcomes (Table 3).

The effect of *S. indicus* and *G. mangostana* on fasting blood glucose (FBS) indicated a non-significant reduction in FBS level was observed in participants who were administrated herbal product (WMD: -1.53; 95 % CI -5.15 to 2.08). A significant heterogeneity was detected in this outcome (Table 3).

There were 208 participants in 3 trials that compared liver function tests. The results were found to be significantly heterogeneous. Therefore, the random effects model was used in combining the results among trials. The results showed that *S. indicus* and *G. mangostana* products reduced both SGOT and SGPT levels. The pooled estimate of WMD effects were -1.54 U/l (95 % CI -2.52 to -0.57) and -1.56 U/l (95 % CI -1.65 to -1.47), respectively. However, there were no significant difference between 152 participants in two trials in blood urea nitrogen (BUN) level (WMD 1.57; 95 % CI -1.50 to 4.64) and serum creatinine (WMD 0.50; 95 % CI -0.05 to 0.15). Heterogeneity was observed in these outcomes (Table 4).

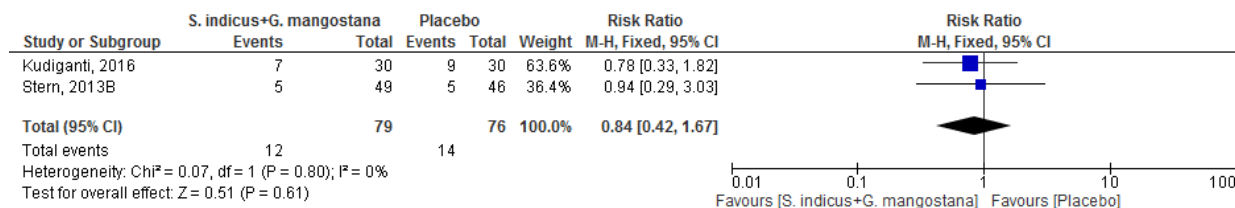
Adverse events were reported in 2 randomized clinical trials (RCTs)<sup>[5,14]</sup>. Among these, there were no differences in the adverse effects of *S. indicus* and *G. mangostana* product compared to placebo (RR 0.84; 95 % CI 0.42, 1.67;  $p=0.80$ ). Heterogeneity was not observed in this

**TABLE 3: META-ANALYSIS OF EFFECTS OF *S. INDICUS* AND *G. MANGOSTANA* ON ALL OUTCOMES**

Outcomes (ref)	No. of studies	Outcome difference		Heterogeneity	
		Mean (95%CI)	p-value	$I^2$	p-value
Anthropological parameter <sup>[5,13,14]</sup>					
Body weight	3	-3.84 kg (-3.98 to -3.70)	<0.00001	32 %	0.23
Body mass index	3	-1.56 kg/m <sup>2</sup> (-1.65 to -1.47)	<0.00001	63 %	0.07
Waist circumference	3	-5.90 cm (-6.36 to -5.43)	<0.00001	68 %	0.05
Lipid profile <sup>[5,13,14]</sup>					
LDL	3	-10.74 mg/dl (-19.04 to -2.44)	0.01	99 %	<0.00001
HDL	3	2.32 mg/dl (0.56 to 4.07)	0.01	98 %	<0.00001
Total cholesterol	3	-22.05 mg/dl (-32.33 to -11.76)	<0.0001	98 %	<0.00001
Triglyceride	3	-27.40 mg/dl (-30.55 to -24.24)	<0.0001	74 %	0.02
Blood pressure <sup>[13,14]</sup>					
Systolic blood pressure	2	-1.81 mmHg (-4.01 to 0.38)	0.23	98 %	<0.0001
Diastolic blood pressure	2	-2.03 mmHg (-5.34 to 1.28)	0.23	98 %	<0.0001
Pulse rate	2	0.61 (-1.58 to 2.79)	0.59	97 %	<0.0001
Blood glucose <sup>[5,13,14]</sup>					
Fasting blood sugar	3	-1.53 mg/dl (-5.15 to 2.08)	0.41	98 %	<0.0001

**TABLE 4: META-ANALYSIS OF EFFECTS OF *S. INDICUS* AND *G. MANGOSTANA* ON LABORATORY TEST**

Outcomes	No. of studies	Outcome difference		Heterogeneity	
		Mean (95 %CI)	p-value	$I^2$	p-value
SGOT <sup>[5,13,14]</sup>	3	-1.54 U/l (-2.52 to -0.57)	0.002	91 %	<0.00001
SGPT <sup>[5,13,14]</sup>	3	-1.56 U/l (-1.65 to -1.47)	<0.00001	63 %	0.07
BUN <sup>[5,14]</sup>	2	1.57 mmol/l (-1.50 to 4.64)	0.32	100 %	<0.00001
SCr <sup>[5,14]</sup>	2	0.05 mg/dl (-0.05 to 0.15)	0.31	99 %	<0.00001



**Fig. 2: Meta-analysis of effects of *S. indicus* and *G. mangostana* on adverse effects**

outcome. In summary, serious or intolerant adverse events were low compared to placebo (fig. 2).

Sensitivity analyses were performed by one-removal study analysis. After removal of studies, the effects of *S. indicus* and *G. mangostana* product on all outcomes were not changed from the pooled data outcomes. Funnel plots were used to investigate the publication bias in all outcomes. The results indicated no publication bias.

This study is the first systematic review and meta-analysis to determine the efficacy and safety of *S. indicus* and *G. mangostana* in obese participants for improving anthropological parameters, lipid profiles, blood glucose and blood pressure. This meta-analysis results suggested significant reduction of anthropological effects including body weight, BMI and waist circumference. Moreover, *S. indicus* and *G. mangostana* product also decreased LDL, TC, TG and increased HDL significantly. Present study found that *S. indicus* and *G. mangostana* products exhibited fewer adverse effects with no statistical difference compared to placebo. The results of subgroup analysis did not show any significant difference to the pooled estimation.

The possible effects of *S. indicus* and *G. mangostana* in the reduction of anthropological outcomes comprise multiple mechanisms. For instance, *S. indicus* and *G. mangostana* effects on the 3T3-L1 adipocytes resulted in a marked reduction in PPAR $\gamma$ , cluster of differentiation 36 (CD36), and adipocyte-differentiation related protein (ADRP) level. In another mechanism, *S. indicus* and *G. mangostana* also reduced expression of perilipin protein on the surface of lipid droplets<sup>[8]</sup>. From the proposed mechanisms, *S. indicus* and *G. mangostana* may attenuate fat accumulation by partially blocking adipogenesis and fat uptake, and by rendering lipid droplets more susceptible to lipases<sup>[6,15]</sup>. Additionally, *S. indicus* and *G. mangostana* extract also increase fat metabolism resulting in significant weight loss<sup>[16]</sup>.

In terms of lipid effect, Claycombe *et al.*<sup>[17]</sup> demonstrated that *S. indicus* and *G. mangostana* extract inhibited adipogenic differentiation and boosted lipid breakdown in mature fat cells and affected hormones, which control

lipogenesis in adipocytes through directly regulating the key enzymes of the lipogenic pathway. Moreover, previous reports of the product activated AMPK associated with the stimulation of fatty acid oxidation, glucose uptake by muscle cells, and inhibition of cholesterol and triglyceride synthesis<sup>[18,19]</sup>.

Most of included trials indicated that *S. indicus* and *G. mangostana* product were safe during the period of study, 8-16 w. Similar to previous animal studies, the product showed no relevant toxicological effects. In a chronic toxicity study in rats, ethanol extract of mangosteen pericarp, given orally at doses of 10 to 1000 mg/kg for 6 mo, showed no overt toxicity or abnormal hematological effects, liver and kidney function test<sup>[8]</sup>. However, this systematic review and meta-analysis revealed that SGOT, SGPT decreased significantly after administering *S. indicus* and *G. mangostana* products. Elevation of liver function enzymes, especially SGPT, caused by liver damage contributes to fatty liver. Long term clinical outcomes of high SGPT were not observed. With maximum duration of trial, 13 w was relatively short to detect any clinical benefit.

The strength of this study is a comprehensive summary of the effects of *S. indicus* and *G. mangostana* products, undertaken in accordance with a high standard of systematic review and meta-analysis and reported in alignment with PRISMA<sup>[10]</sup>. The meta-analysis of RCT is at the top in the hierarchy of the clinical evidence. All of the included studies were high quality. Indeed, this is the first systematic review and meta-analysis of RCT investigating efficacy and safety of *S. indicus* and *G. mangostana* product at 800 mg/d on anthropological, lipid profile, blood glucose and blood pressure. Although studies with the same types of comparisons, and time to follow-up (8-16 w) without language restriction were included in this meta-analysis, efficacy and safety of *S. indicus* and *G. mangostana* product is quite consistent across all studies. This implied that our result can be generalized to wider clinical practices.

Even though the evidence on clinical effects of *S. indicus* and *G. mangostana* product on all outcomes is quite consistent across studies, a number of limitations



should be mentioned. Only 3 RCT met the inclusion criteria and there were small numbers of participants in individual studies.

Based on current evidence, combinations *S. indicus* and *G. mangostana* are found to be effective and safe in obese participants, however, well-designed, large, multicenter, randomized placebo- or active-controlled trials investigating long term effects of *S. indicus* and *G. mangostana* product on cardiometabolic outcomes are needed to further support current evidence.

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### Conflict of interest:

The authors declare that they have no conflict of interest.

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