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Article

Mangosteen shows a potent insulin sensitizing effect in obese female patients: a prospective randomized controlled pilot study

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Abstract: Insulin resistance is the most important underlying cause of obesity and type 2 Diabetes (T2DM), and insulin sensitizing treatments have proved effective in preventing diabetes and inducing weight loss. Obesity and T2DM are also associated with increased inflammation. Mangosteen is a tropical tree, whose fruits, widely known for their antioxidant properties, have been recently suggested having a possible further role in the treatment of obesity and T2DM. The objective of this pilot study has been to evaluate safety, compliance and efficacy of mangosteen on insulin resistance, weight management, and inflammatory status in obese female patients with insulin resistance. 22 patients were randomized 1:1 to behavioral therapy alone or behavioral therapy and mangosteen and 20 completed the 26-week study. The mangosteen group reported a significant improvement in insulin sensitivity (HOmeostatic Model Assessment-Insulin Resistance, HOMA-IR -53.22% vs -15.23%, p=.0037), and a trend decrease in inflammation markers serum levels, together with trend greater weight loss and trend increased HDL levels. No side effect attributable to treatment was reported. Given the positive preliminary results we report and the excellent safety profile, we suggest a possible role of mangosteen in the treatment of obesity, insulin resistance and inflammation.

Keywords: Garcinia Mangostana, Inflammation, Insulin Resistance, Metabolic Syndrome, Diabetes, Xanthones, Mangostin, Phytotherapy, Dietary supplements

1. Introduction

In recent years industrialized countries have witnessed a rapid and progressive increase in the prevalence of obesity, both for improved economic conditions and the spread of a sedentary lifestyle. According to the World Health Organization, 39% of adults were overweight, and 13% were obese worldwide in 2016 [1]. Obesity is a chronic disease and is one of the major risk factors for the development of type 2 diabetes (T2DM) and its comorbidities. Insulin resistance is the most important underlying cause of obesity and T2DM, and insulin sensitizing treatments have proved effective in preventing diabetes and inducing weight loss [2,3]. First-line clinical intervention for obesity and T2DM is lifestyle change, but this is insufficient in many patients, and so drug therapy is often needed. Obesity and T2DM are also associated with increased inflammation, with elevations of serum C Reactive Protein (CRP), plasma fibrinogen and other acute-phase proteins [4].

Garcinia mangostana Linn., also known as mangosteen, is an evergreen tree native to Southeast Asia, whose fruits have been used in traditional medicine to treat several conditions for centuries. The main phytochemicals present in mangosteen are alpha and gamma mangostins, isoprenylated xanthones, a class of secondary metabolites widely known for their antioxidant properties [5], but recent evidence has suggested a possible further role in the treatment of obesity and T2DM. Preclinical studies show in fact glucose lowering properties possibly through an alpha glucosidase activity and pancreatic beta cells hyperplasia in mangosteen treated animals [6-8]. Moreover, *in vitro* evidence suggests that alpha-mangostin is a potent inhibitor of pancreatic lipase, similarly to commercially available anti-obesity drug orlistat [9], and is able to induce apoptosis and lipolysis in preadipocytes through inhibition of fatty acid synthase, potentially inhibiting fat accumulation *in vivo* [10]. Mangosteen was also reported to reduce inflammation through several pathways [11-13]. Moreover, animal research conducted on Diet Induced Obesity (DIO) mice treated with alpha-mangostins report weight loss, attenuated hepatic steatosis, decreased serum glucose, and improved lipid profile through Sirtuin1-AMP-activated protein kinase and Peroxisome proliferator-activated receptor (PPAR) gamma pathways [14,15]. Pilot studies conducted on human subjects point in the same direction as preclinical ones, with reported significant improvements in inflammatory markers, weight loss and waist circumference reduction, and an excellent safety and tolerability profile [16-19].

To date, no study has been conducted to primarily assess the effect of mangosteen on insulin resistance. The objective of this pilot study has been to evaluate safety, compliance and efficacy of mangosteen on insulin resistance, weight management, and inflammatory status in obese female patients with insulin resistance. We report promising results, with a potent insulin reduction.

2. Materials and Methods

2.1 Patients

Patients were recruited among subjects referring to the High Specialization Center for the Care of Obesity (CASCO) at the Department of Experimental Medicine, Sapienza University of Rome. Inclusion criteria were: female gender, age between 18 and 65 years; obesity (Body Mass Index BMI>30 kg/m^2 with body weight less than 135 kg); Insulin resistance (HOMA-IR>2.5); no acute medical conditions in the preceding 6 months. The weight limit was due to the Dual-energy X-ray Absorptiometry (DXA) scan weight limit. Exclusion criteria were: any medical condition that could preclude patient safety according to the opinion of the physician, diabetes, history of cardiovascular disease, use of medications potentially affecting study outcomes, unstable body weight within the previous 3 months, pregnancy, and absence of informed consent. All participants were asked to sign a written informed consent before the beginning of the trial. The study protocol was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Sapienza University of Rome (ClinicalTrials.gov Identifier: NCT02823561)

2.2 Study protocol

We conducted a 26-week prospective randomized, controlled, parallel group study. Subjects were randomly assigned to two different arms of treatment: standard hypocaloric diet and physical activity or standard hypocaloric diet, physical activity and treatment with mangosteen 500 mg once daily (OD). All assessments were performed at baseline and at the end of the treatment.

2.3 Lifestyle Intervention

A hypocaloric diet was prescribed to all subjects at baseline. 300 kcal/day were subtracted from individual estimated total energy expenditure. The daily dietary intake included approximately 45-50% of calories from carbohydrate, up to 30% of calories from fat (< 10% saturated fat) and 20-25% of

calories from protein. Subjects were instructed to have moderate-intensity physical activity (e.g., 30 min walking every day) during the study. Patients met individually with a dietician once a month to assess compliance to prescribed diet and physical activity.

2.4 Outcome measures

The enrolled patients were admitted to our center to evaluate anthropometric parameters (body weight, height, waist circumference and BMI), vital parameters (systolic and diastolic blood pressure, heart rate) and routine biochemical assessment which included lipid profile [total cholesterol, High Density Lipoproteins (HDL) and Low Density Lipoproteins (LDL) cholesterol, triglycerides], glycemic assessment [fasting glucose and insulin, glycosylated hemoglobin A1c (HbA1C)], inflammatory markers [high sensitivity CRP (hsCRP), fibrinogen]. DXA total body scan (4500 RDR, Hologic Inc., Waltham, MA) was performed to evaluate body composition (fat/lean mass).

2.5 Product description

The active ingredient, in a tablet formulation, was Garcinia Mangostana 500 mg, titrated to 40% in alpha and gamma mangostins (Osebo, Sanamedica Group srl, Rome, Italy). Patients were instructed to take one tablet at lunch every day. Treatment compliance was assessed monthly.

2.6 Statistical analysis

Expecting a baseline mean HOMA-IR of 4±1.5 in obese insulin resistant patients, a sample size of 9 patients per group was calculated to detect a 40% HOMA-IR decrease in the treatment group compared to control with an α of 0.05 and a (1-β) of 80%. With a foreseen 20-30% dropout rate, 22 patients were enrolled and randomized 1:1 in the two treatment groups. Statistical tests were performed using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego California USA. All results are expressed as mean ± standard deviation (SD). Differences obtained in the two groups after 26 weeks of treatment were evaluated by ANOVA and ANCOVA variance analysis. Differences were considered statistically significant when $p < .05$.

3. Results

3.1 Population

After a clinical assessment and evaluation of inclusion and exclusion criteria, 22 obese female patients (BMI> 30 Kg / m^2), aged between 18 and 65, were enrolled and randomized 1:1 to mangosteen and lifestyle intervention (n=11), the treatment group, or lifestyle intervention only, the control group (n=11), between November and December 2015 at the Centre of High Specialization for the Cure of Obesity (CASCO), Sapienza University of Rome, Italy. Two subjects did not complete the study due to personal reasons and were therefore excluded from the analysis. The groups were not significantly different at baseline in regard to age, BMI, body composition, fasting glucose and insulin levels and hsCRP (Table 1).

Table 1. General characteristics of the treatment arms. The groups were not significantly different at baseline in regard to age, BMI, body composition, fasting glucose and insulin levels and hsCRP.

	Control			Mangosteen		
Age (years)	46,00	±	12,009	43,70	±	12,248
BMI (kg/m2)	37,60	±	7,043	37,10	±	4,725
Body Weight (kg)	101,90	±	23,662	101,10	±	16,690
Waist Circumference (cm)	120,40	±	15,601	115,44	±	8,748

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Body Fat (%)	40,20	±	2,781	39,60	±	3,777
Serum glucose (mg/dL)	93,20	±	14,250	86,20	±	8,979
Serum Insulin (mg/dL)	19,11	±	6,431	22,40	±	15,072
HOMA-IR	4,44	±	1,509	4,90	±	3,872
Fibrinogen (mg/L)	360,25	±	65,876	454,78	±	83,215
hsCRP (mg/L)	1,00	±	1,155	,80	±	,632

3.2 Glucose metabolism

Insulin levels at 26 weeks decreased significantly in the treatment group compared to control (-53.2% vs -15.2%, p=.0037 (Fig. 1A). HOMA IR % change went in the same direction with a reduction of -51.3% vs -10% (p=.0037 Fig 1B) in favor of the mangosteen group that showed a frank improvement in insulin resistance. These results remained significant after correction for BMI change over time. Glucose levels did not significantly change in any of the studied arms (Fig. 1C).

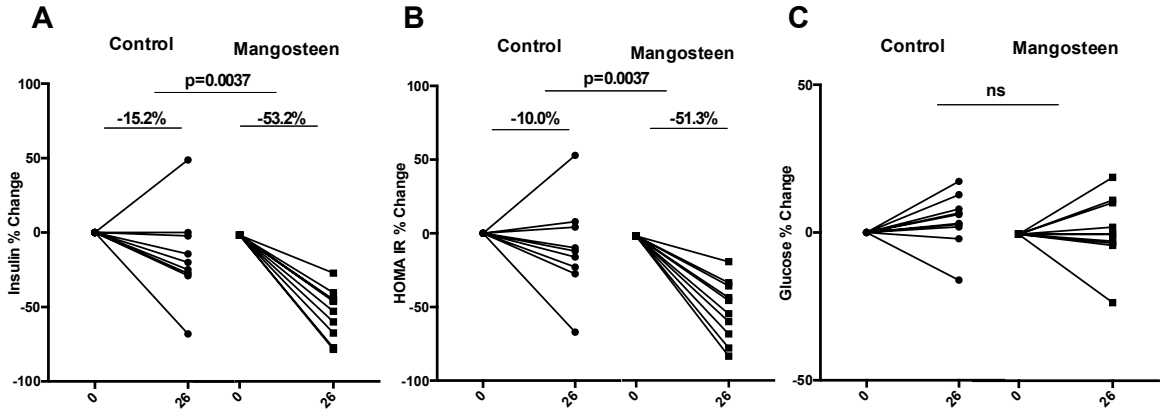

Figure 1. Glucose metabolism. **(a)** Insulin levels decreased significantly in the treatment group compared to control at 26 weeks; **(b)** HOMA IR % change went in the same direction in favor of the mangosteen group that showed a frank improvement in insulin resistance; **(c)** Glucose levels did not significantly change in any of the studied arms.

3.3 Anthropometric parameters

The mangosteen arm experienced a weight loss (-4.5±6.2%, p=.048) that the control failed to show (Fig. 2 A), but groupwise comparison was not significant. No statistically significant difference was seen regarding waist circumference and body composition in any of the groups (Fig. 2 B-C).

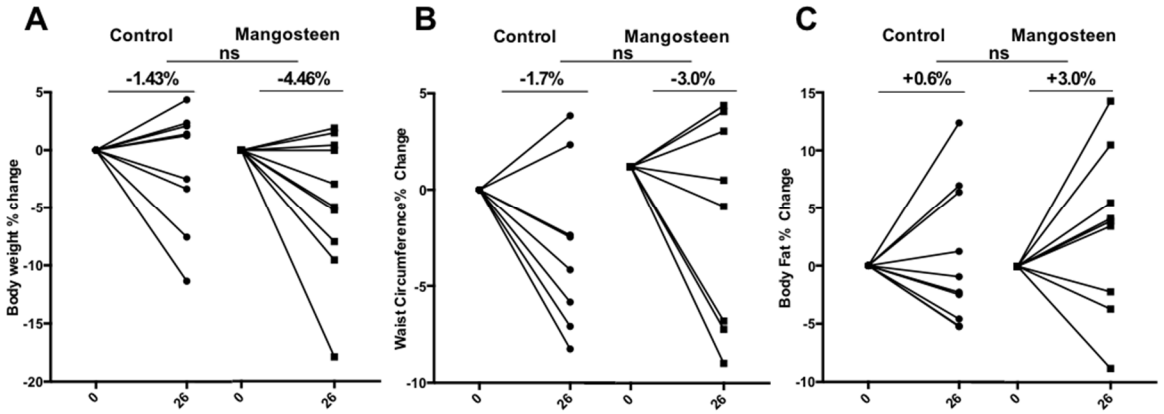

Figure 2 Anthropometric parameters: (a) The mangosteen arm experienced weight loss (-4.5±6.2%, p=.048) that the control failed to do, however groupwise comparison was not significant; **(b)** No statistically significant

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difference was seen regarding waist circumference in any of the groups; **(c)** No statistically significant difference was seen regarding body fat percentage in any of the groups.

3.4 Inflammation markers

HsCRP reduced significantly in the mangosteen group, with a mean decrease of .41±.34 mg/L (p=.0039, -35.7±22.51%). However, comparison with the control group failed to show any significant group-wise difference (Fig. 3A, Table 2). Similarly, fibrinogen levels had a trend decrease in the mangosteen group (-57±93 mg/L, -9.9±19.0%, p=.10) but failed to be significantly different when compared to control (Fig. 3B, Table 2).

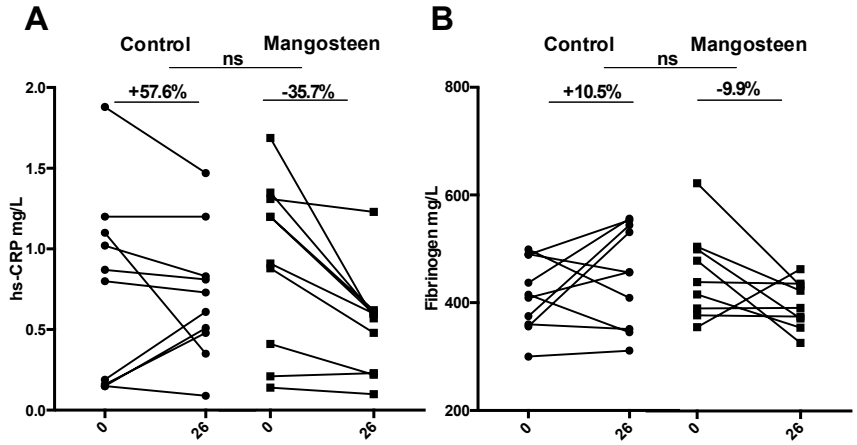

Figure 3. Inflammation markers: (a) HsCRP was significantly reduced the mangosteen group, with a mean decrease of .41±.34 mg/L (p=.0039). Comparison with the control group failed to show any significant groupwise difference; **(b)** Fibrinogen levels had a trend decrease in the mangosteen group (-57±93 mg/L, -9.9±19.0%, p=.10) but failed to be significantly different when compared to control.

Table 2 Lipids profile and inflammation markers of the treatment arms at baseline and 26 weeks. HDL levels increased and hsCRP levels decreased from baseline in the mangosteen group (p=0.0243; p=0.0062), but comparison with control failed to show a statistically significant difference. No changes were observed regarding other serum lipids. A trend decrease in fibrinogen levels in the magosteen group was observed at 26 weeks compared to baseline (p=.1) [c] statistically significant compared to baseline mangosteen.

	Control		Mangosteen	
	0	26	0	26
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Total Cholesterol (mg/dL)	203 ± 39	199 ± 46	193 ± 28	199 ± 34
LDL-C (mg/dL)	130 ± 40	128 ± 44	121 ± 21	123 ± 31
HDL-C (mg/dL)	49 ± 14	49 ± 10	50 ± 12	58 ± 13[c]
Triglycerides (mg/dL)	124 ± 61	111 ± 41	92 ± 30	88 ± 21
hsCRP (mg/L)	.75 ± .58	.71 ± .40	.93 ± .52	.52 ± .31[c]
Fibrinogen (mg/L)	413 ± 67	451 ± 94	455 ± 83	398 ± 44

3.5 Lipids profile

HDL cholesterol levels increased significantly in the mangosteen group suggesting an antiatherogenic effect (p=0.0243). However, comparison with control was not statistically significant. No change was observed regarding other serum lipids (Table 2).

3.6 Safety and Tolerability

3 patients over the course of the 26 weeks follow up reported GastroIntestinal (GI) symptoms, one at 1 month (bloating) and 2 at 4 months (diarrhea and gastric reflux respectively). In the control group, 4 patients experienced GI symptoms, two at 1 month, one at 3 and one at 6 months. The patients reported GI reflux, bloating, constipation and diarrhea, respectively. None of the patients withdrew the study due to side effects. All patients recovered without treatment within a week. It did not appear to exist a cause-effect connection between mangosteen treatment and GI distress.

3.7 Compliance

Treatment compliance was overall very good in the mangosteen arm. Adherence to prescribed physical activity and diet as assessed monthly by a trained dietician did not show any significant difference between groups and did not significantly change over time (data not shown).

4. Discussion

Mangosteen has been widely used in East Asian traditional medicine for centuries, and its favorable effects coupled with an excellent safety profile has attracted the attention of the international scientific community in recent years. *In vitro* and *in vivo* evidence has extensively proved that alpha- and gamma-mangostins are the major bioactive compounds responsible for the empirically known effects [20].

A novel possible role in the treatment of metabolic diseases has been recently suggested. Clinical trials investigating the effect of mangosteen on body weight and inflammation suggest a positive effect on both outcomes. However, the studies are small in sample size and are of short duration (<16 weeks) and need therefore further confirmation of their reported results [16-19]. *In vitro and in vivo* studies prove that mangosteen also shows glucose lowering and insulin sensitizing effects [21], but no clinical trial has been conducted so far to primarily assess glycometabolic parameters. We therefore investigated the effect of mangosteen on obese insulin resistant female subjects for 26 weeks and found very promising results regarding glucose homeostasis improvement. Specifically, we observed a striking effect on insulin resistance, with a marked decrease of HOMA-IR and insulin levels, independent of BMI variations. Conversely, glucose levels at 26 weeks were not significantly changed. Of note, baseline glucose levels were normal in our population and this may have hindered the possibility of detecting a glucose lowering effect.

In vitro evidence suggests that alpha-mangostin is a potent inhibitor of pancreatic lipase and fatty acid synthase, potentially inhibiting lipids gut assimilation and fat accumulation, respectively. Previous clinical trials investigating the effect on weight loss show that mangosteen significantly reduces body weight compared to placebo [18,19]. We observed a weight reduction in the mangosteen arm that might have proved statistically significant compared to control with a wider population or longer study duration.

Mangosteen was also reported to reduce inflammation through several pathways, such as inhibition of conversion of arachidonic acid to prostaglandin (PG)E2 by Cyclooxygenase (COX) and inhibition of COX2 gene transcription [22,23]. We herein showed that hsCRP, a widely used marker of inflammation, significantly decreased over time in patients taking mangosteen, unlike control. However, group-wise comparison failed to show a significant difference between mangosteen and control, possibly due to the high variability of hsCRP we observed in the control group at week 26. hsCRP can be greatly affected by several inflammatory conditions, and particularly in absence of an

anti-inflammatory tratment, such as mangosteen, the observed effect could be more influenced by other concurring conditions, as it may have happened in our cohort.

Currently available medications aimed at treating dyslipidemia decrease total and LDL cholesterol and triglycerides levels. Little or no effect is observed in HDL cholesterol levels [24]. The promising results we show, although failing to show a significant difference compared to control, suggest a possible role of mangosteen in selectively increasing HDL cholesterol, with its known antiatherogenic effect.

We report that mangosteen was well tolerated at the tested dosage, as there were no adverse events (clinical, laboratory, or vital sign) reasonably attributable to the product during the course of the study. This adds to the body of evidence suggesting an excellent safety profile of mangosteen.

In conclusion, our results suggest that mangosteen could potentially represent an appealing treatment for insulin resistance given its favorable cost/benefit ratio. However, our study has several limitations. For its pilot nature, a small number of obese insulin resistant patients who were otherwise healthy were recruited, potentially hindering the possibility of detecting significant changes, especially in regard to body weight and composition and inflammation markers. The duration of the study, although significantly longer than all other clinical trials investigating the effects of mangosteen in human subjects, is still relatively short. Also, only female subjects were enrolled, and we therefore cannot infer that the same results may be applicable to male subjects. Finally, the open label nature of the study could have led to potential bias, although it is unlikely that a placebo effect could have had any consequence on the investigated outcomes given the comparable adherence to prescribed diet and physical activity in both interventional groups.

In our opinion, the promising results we report should be further confirmed by wider interventional studies, possibly involving prediabetic patients, to assess whether mangosteen is not only able to improve insulin resistance in these patients but has also the ability to positively affect serum glucose levels.

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Author Contributions: CL conceived and designed the study. DF acquired the data. MW and CL analyzed and interpreted data. MW and EG wrote the manuscript and DT EP SM SB GS LG and CL revised it. All authors have approved the final article.

Conflicts of Interest: The authors declare no conflict of interest. The funding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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