ENGLISH

Efficacy and tolerability of Mangosteen extract in the management of insulin resistance and severe obesity: a prospective randomized controlled pilot study

Mikiko Watanabe[1], Elena Gangitano[1], Davide Francomano[1], Eleonora Poggiogalle[1], Dario Tuccinardi[2], Stefania Mariani[1], Sabrina Basciani[1], Giovanni Spera[1], Lucio Gnessi[1], Carla Lubrano[1]

[1]Department of Experimental Medicine, Section of Medical Pathophysiology, Food Science and Endocrinology, Sapienza University of Rome, 00161 Rome, Italy

[2]Department of Endocrinology and Diabetes, University Campus Bio-Medico of Rome, 00128 Rome, Ital

Corresponding author:

Mikiko Watanabe MD

Department of Experimental Medicine, Section of Medical Pathophysiology, Food Science and Endocrinology, Sapienza University of Rome, 00161 Rome, Italy mikiko.watanabe@uniroma1.it

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. 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. 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.

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, 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. Moreover, *in vitro* evidence suggests that alpha-mangostin is a potent inhibitor of pancreatic lipase, similarly to commercially available anti-obesity drug orlistat, and is able to induce apoptosis and lipolysis in preadipocytes through inhibition of fatty acid synthase, potentially inhibiting fat accumulation *in vivo* [7]. Mangosteen was also reported to reduce inflammation through several pathways [8-10]. 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. 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.

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 severely obese female patients with insulin resistance. We report promising results, with a potent insulin reduction.

Materials and methods

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; moderate obesity (Body Mass Index BMI>35 kg/m^2 with body weight less than 155 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)

Study protocol

We conducted a 26-week prospective randomized, parallel group, controlled 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.

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.

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 C-reactive Protein (hs-CRP), fibrinogen]. DXA total body scan was performed to evaluate body composition (fat/lean mass).

Product description

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

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 variance analysis. Differences were considered statistically significant when $p < .05$.

Results

Population

After a clinical assessment and evaluation of inclusion and exclusion criteria, 22 female patients, aged between 18 and 65, with severe obesity (BMI> 35 Kg / m2) were enrolled and randomized 1: 1 to mangosteen and lifestyle intervention (n=11) 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 hs-CRP (Table 1).

Glucose metabolism

Insulin levels decreased significantly in the treatment group compared to control at 26 weeks (-53.22% vs -15.23%, p=.0037 (Fig. 1A). HOMA IR % change went in the same direction

with a -51.3% vs -10% (p=.0037 Fig 1B) in favor of the mangosteen group that showed a frank improvement in insulin resistance. Glucose levels did not significantly change in any of the studied arms (Fig. 1C).

Inflammation markers

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

Anthropometric parameters

No statistically significant difference was seen regarding weight loss, BMI change, waist circumference and body composition in any of the groups. However, the mangosteen arm experienced a trend in BMI reduction (-4.2±6.4%, p=.0666) and weight loss (-4.1±6.0 kg, p=.061) that the control failed to show (Fig. 3 A-D)

Lipids profile

No significant change in serum lipids was detected in neither of the groups (Table 2).

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). All patients autonomously recovered within a week. 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. It did not appear to exist a cause-effect connection between mangosteen extracts treatment and GI distress.

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).

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.

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. *In vitro and in vivo* studies prove that mangosteen also shows glucose lowering and insulin sensitizing effects, 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. 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. We calculated our sample size based on the primary outcome of insulin resistance, and we therefore might have failed to prove a weight loss effect due to the small population enrolled. However, we observed a trend in weight reduction that might have proved statistically significant 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. 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.

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 absence of placebo treatment could be a 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.

	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
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
hs-CRP (mg/L)	1,00	±	1,155	,80	±	,632

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 hs-CRP.

	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
Triglycerides mg/dL	124	±	61	111	±	41	92	±	30	88	±	21

Table 2 Lipids profile of the treatment arms at baseline and 26 weeks. No significant change in serum lipids was detected in neither of the groups.

ITALIANO

Negli ultimi anni i paesi industrializzati hanno assistito ad un rapido e progressivo aumento della prevalenza dell'obesità, sia per il miglioramento delle condizioni economiche che per la diffusione di uno stile di vita sedentario. Secondo l'Organizzazione mondiale della sanità, il 39% degli adulti era sovrappeso e il 13% era obeso in tutto il mondo nel 2016. L'obesità è una malattia cronica ed è uno dei principali fattori di rischio per lo sviluppo del diabete di tipo 2 (T2DM) e delle sue comorbilità. L'insulino-resistenza è la principale causa di obesità e DM2 e i trattamenti sensibilizzanti dell'insulina si sono dimostrati efficaci nella prevenzione del diabete e nell'induzione della perdita di peso. L'intervento clinico di prima linea per l'obesità e il DMT2 è il cambiamento dello stile di vita, ma questo è insufficiente in molti pazienti, pertanto è spesso necessaria una terapia farmacologica. L'obesità e il T2DM sono anche associati ad un'aumentata infiammazione, con aumenti della proteina reattiva C (CRP), fibrinogeno plasmatico e altre proteine in fase acuta.
Garcinia mangostana Linn., Noto anche come mangostano, è un albero sempreverde originario del sud-est asiatico, i cui frutti sono stati utilizzati nella medicina tradizionale per trattare diverse condizioni per secoli. I principali fitochimici presenti nel mangostano sono le alfa e gamma mangostine, gli xantoni isoprenilati, una classe di metaboliti secondari ampiamente noti per le loro proprietà antiossidanti, ma recenti evidenze hanno suggerito un possibile ulteriore ruolo nel trattamento dell'obesità e del DMT2. Studi preclinici mostrano infatti proprietà ipoglicemizzanti possibilmente attraverso un'attività alfa-glucosidasi e iperplasia delle cellule beta pancreatiche negli animali trattati con mangostina. Inoltre, l'evidenza in vitro suggerisce che l'alfa-mangostina è un potente inibitore della lipasi pancreatica, analogamente al farmaco anti-obesità reperibile in commercio, ed è in grado di indurre apoptosi e lipolisi nei preadipociti attraverso l'inibizione della sintasi dell'acido grasso, potenzialmente inibendo l'accumulo di grasso in vivo [7]. È stato anche riportato che il mangostano riduce l'infiammazione attraverso diversi percorsi [8-10]. Inoltre, la ricerca sugli animali condotta su topi con obesità indotta dalla dieta (DIO) trattati con alfa-mangostina riportano perdita di peso, steatosi epatica attenuata, diminuzione del glucosio nel siero e profilo lipidico migliorato attraverso la proteina chinasi attivata da Sirtuin1-AMP e il recettore attivato dal proliferatore del perossisoma (PPAR)) percorsi gamma. Gli studi pilota condotti su soggetti umani puntano nella stessa direzione di quelli preclinici, con significativi miglioramenti riportati nei marcatori infiammatori, perdita di peso e riduzione della circonferenza della vita e un eccellente profilo di sicurezza e tollerabilità.
Ad oggi, non è stato condotto alcuno studio per valutare principalmente l'effetto del mangostano sulla resistenza all'insulina. L'obiettivo di questo studio pilota è stato quello di valutare la sicurezza, la compliance e l'efficacia del mangostano sulla resistenza all'insulina, sul controllo del peso e sullo stato infiammatorio in pazienti donne gravemente obese con insulino-resistenza. Segnaliamo risultati promettenti, con una potente riduzione di insulina.

Materiali e metodi
pazienti
I pazienti sono stati reclutati tra soggetti che fanno riferimento al Centro di alta specializzazione per la cura dell'obesità (CASCO) presso il Dipartimento di Medicina Sperimentale, Sapienza Università di Roma. I criteri di inclusione erano: genere femminile, età tra 18 e 65 anni; obesità moderata (indice di massa corporea BMI> 35 kg / m2 con peso corporeo inferiore a 155 kg); Insulino-resistenza (HOMA-IR> 2.5); nessuna condizione medica acuta nei 6 mesi precedenti. Il limite di peso era dovuto al limite di peso di scansione Assorbtiometria a raggi X a doppia energia (DXA). I criteri di esclusione erano: qualsiasi condizione medica che potesse precludere la sicurezza del paziente secondo l'opinione del medico, il diabete, la storia delle malattie cardiovascolari, l'uso di

farmaci che possono influenzare i risultati dello studio, il peso corporeo instabile nei 3 mesi precedenti, la gravidanza e l'assenza di informato consenso.
Tutti i partecipanti sono stati invitati a firmare un consenso informato scritto prima dell'inizio del processo. Il protocollo di studio è stato condotto secondo i principi della Dichiarazione di Helsinki ed è stato approvato dal Comitato Etico della Sapienza Università di Roma (Identificatore ClinicalTrials.gov: NCT02823561)

Protocollo di studio
Abbiamo condotto uno studio prospettico randomizzato, parallelo, a 26 settimane, controllato. I soggetti sono stati assegnati in modo casuale a due diversi bracci di trattamento: dieta ipocalorica standard e attività fisica o dieta ipocalorica standard, attività fisica e trattamento con 500 mg di mangostano una volta al giorno (OD). Tutte le valutazioni sono state eseguite al basale e alla fine del trattamento.

Intervento sullo stile di vita
Una dieta ipocalorica è stata prescritta a tutti i soggetti al basale. 300 kcal / giorno sono stati sottratti dalla spesa energetica totale stimata individuale. L'assunzione giornaliera di cibo comprendeva circa il 45-50% delle calorie da carboidrati, fino al 30% delle calorie da grassi (<10% di grassi saturi) e il 20-25% delle calorie da proteine. I soggetti sono stati istruiti per avere un'attività fisica di intensità moderata (per esempio, 30 minuti a piedi

Figura 1. Metabolismo del glucosio. A. I livelli di insulina sono diminuiti significativamente nel gruppo di trattamento rispetto al controllo a 26 settimane. Il cambiamento di HOMA IR% è andato nella stessa direzione a favore del gruppo del mangostano che ha mostrato un franco miglioramento nell'insulino-resistenza. C. I livelli di glucosio non sono cambiati significativamente in nessuna delle braccia studiate.
Figura 2. Marcatori di infiammazione A. Hs-CRP ridotto significativamente nel gruppo del mangostano, con una diminuzione media di .41 ± .34 (p = .0039). Il confronto con il gruppo di controllo non ha mostrato alcuna significativa differenza di gruppo. B. I livelli di fibrinogeno hanno avuto una diminuzione tendenziale nel gruppo del mangostano (-57 ± 93, -9,9% ± 19,0, p = 0,10) ma non sono risultati significativamente diversi rispetto al controllo.
Figura 3 Parametri antropometrici A. Il braccio del mangostano ha registrato una tendenza alla riduzione del BMI (-4,2 ± 6,4%, p = 0,0666) che il controllo non è riuscito a fare. B. Nessuna differenza statisticamente significativa è stata osservata per quanto riguarda la circonferenza della vita in nessuno dei gruppi. C. Il braccio del mangostano ha registrato una tendenza alla perdita di peso (-4,1 ± 6,0 kg, p = 0,661) che il controllo non è riuscito a fare. D. Nessuna differenza statisticamente significativa è stata osservata per quanto riguarda la percentuale di grasso corporeo in nessuno dei gruppi.
Contributi degli autori
CL ha ideato e progettato lo studio. DF ha acquisito i dati. MW e CL analizzati e interpretati i dati. MW e EG hanno scritto il manoscritto e DT EP StM SB GS LG e CL lo hanno revisionato. Tutti gli autori hanno approvato l'articolo finale.
Conflitto d'interesse
Gli autori non hanno nulla da rivelare.
Ringraziamenti
Vorremmo ringraziare tutti i pazienti per la loro partecipazione allo studio e Sanamedica Group srl per la fornitura di compresse di mangostano (Osebo).
Approvazione etica
Tutte le procedure eseguite sono state conformi agli standard etici del comitato di ricerca istituzionale e / o nazionale e alla dichiarazione di Helsinki del 1964 e alle sue successive modifiche

o standard etici comparabili. Lo studio è stato approvato dal Comitato Etico della Sapienza Università di Roma.

Consenso informato

Il consenso informato è stato ottenuto al momento dell'iscrizione da tutti i partecipanti inclusi nello studio.

finanziamento

Lo studio è stato avviato dal ricercatore, interamente pianificato e condotto sotto la supervisione scientifica di CL. La fornitura di mangostano è stata fornita da Sanamedica Group srl. Sanamedica Group srl non ha avuto alcun ruolo nel disegno dello studio, l'analisi o l'interpretazione dei dati o la stesura del manoscritto. I finanziatori non hanno avuto alcun ruolo nella decisione di presentare questo manoscritto per la pubblicazione.

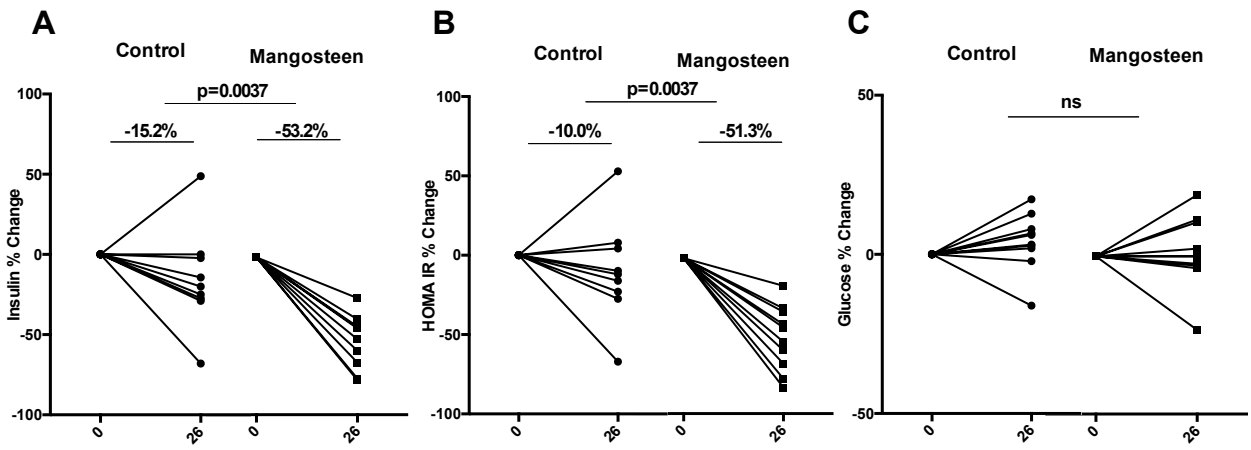

Figure 1. Glucose metabolism. A. Insulin levels decreased significantly in the treatment group compared to control at 26 weeks **B.** HOMA IR % change went in the same direction in favor of the mangosteen group that showed a frank improvement in insulin resistance. **C.** Glucose levels did not significantly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

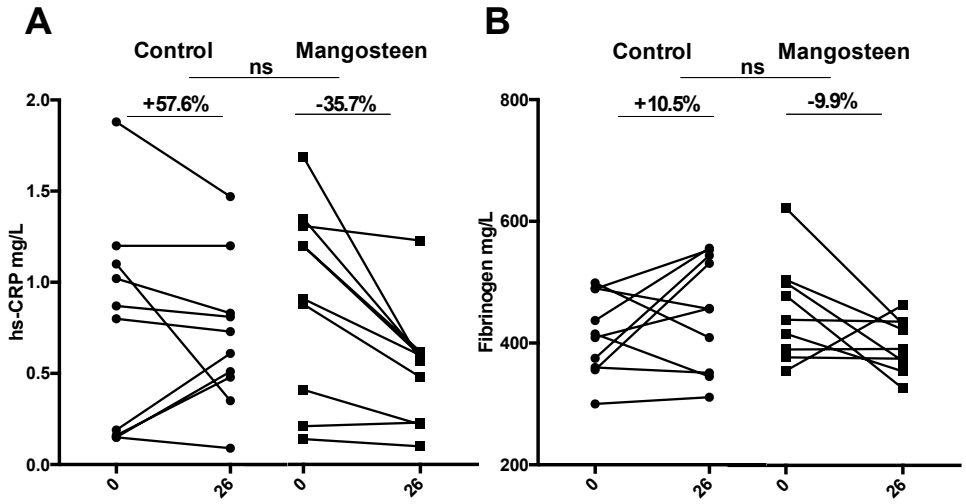

Figure 2. Inflammation markers A. Hs-CRP reduced significantly in the mangosteen group, with a mean decrease of .41±.34 (p=.0039). Comparison with the control group failed to show any significant groupwise difference. **B.** Fibrinogen levels had a trend decrease in the mangosteen group (-57±93, -9.9%±19.0, p=.10) but failed to be significantly different when compared to control.

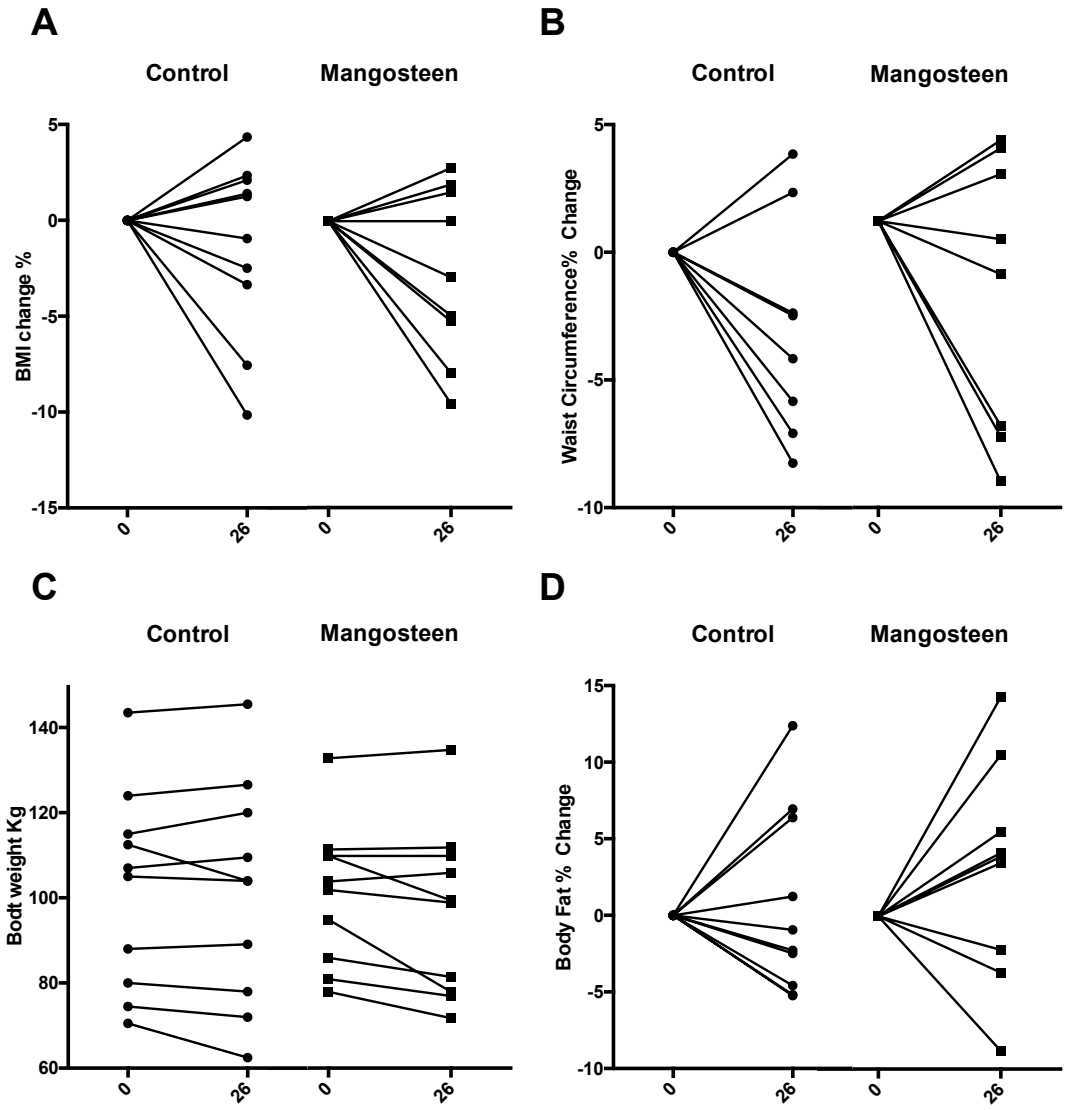

Figure 3 Anthropometric parameters A. The mangosteen arm experienced a trend in BMI reduction (-4.2±6.4%, p=.0666) that the control failed to do. **B.** No statistically significant difference was seen regarding waist circumference in any of the groups. **C.** The mangosteen arm experienced a trend in weight loss (-4.1±6.0 kg, p=.061) that the control failed to do. **D.** No statistically significant difference was seen regarding body fat percentage in any of the groups.

Authors 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 StM SB GS LG and CL revised it. All authors have approved the final article.

Conflict of Interest

The authors have nothing to disclose.

Acknowledgments

We would like to thank all the patients for their participation to the study and Sanamedica Group srl for providing Mangosteen tablets (Osebo).

Ethical Approval

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Sapienza University of Rome Ethics Committee.

Informed Consent

Informed consent was obtained upon enrolment from all participants included in the study.

Funding

The study was investigator-initiated, entirely planned and conducted under the scientific supervision of CL. Supply of Mangosteen was provided by Sanamedica Group srl. Sanamedica Group srl had no role in the study design, the analysis or interpretation of the data, or drafting of the manuscript. The funders had no role in the decision to submit this manuscript for publication.

References

1. Obesity and overweight factsheet. http://www.who.int/mediacentre/factsheets/fs311/en/ (08/04/2017),
2. Suttirak, W.; Manurakchinakorn, S. In vitro antioxidant properties of mangosteen peel extract. *J Food Sci Technol* **2014**, *51*, 3546-3558.
3. Jariyapongskul, A.; Areebambud, C.; Suksamrarn, S.; Mekseepralard, C. Alpha-mangostin attenuation of hyperglycemia-induced ocular hypoperfusion and blood retinal barrier leakage in the early stage of type 2 diabetes rats. *Biomed Res Int* **2015**, *2015*, 785826.
4. Ryu, H.W.; Cho, J.K.; Curtis-Long, M.J.; Yuk, H.J.; Kim, Y.S.; Jung, S.; Kim, Y.S.; Lee, B.W.; Park, K.H. Alpha-glucosidase inhibition and antihyperglycemic activity of prenylated xanthones from garcinia mangostana. *Phytochemistry* **2011**, *72*, 2148-2154.
5. Taher, M.; Tg Zakaria, T.M.; Susanti, D.; Zakaria, Z.A. Hypoglycaemic activity of ethanolic extract of garcinia mangostana linn. In normoglycaemic and streptozotocin-induced diabetic rats. *BMC Complement Altern Med* **2016**, *16*, 135.
6. Chae, H.S.K.E.Y.H., L.; Kim, N.R.; Chin, Y.W. Xanthones with pancreatic lipase inhibitory activity from the pericarps of garcinia mangostana l. (guttiferae) *Eur. J. Lipid Sci. Technol.* **2016**, *118*, 1416-1421.
7. Quan, X.; Wang, Y.; Ma, X.; Liang, Y.; Tian, W.; Ma, Q.; Jiang, H.; Zhao, Y. Alpha-mangostin induces apoptosis and suppresses differentiation of 3t3-l1 cells via inhibiting fatty acid synthase. *PLoS One* **2012**, *7*, e33376.
8. Chen, L.G.; Yang, L.L.; Wang, C.C. Anti-inflammatory activity of mangostins from garcinia mangostana. *Food Chem Toxicol* **2008**, *46*, 688-693.
9. Cho, B.O.; Ryu, H.W.; So, Y.; Lee, C.W.; Jin, C.H.; Yook, H.S.; Jeong, Y.W.; Park, J.C.; Jeong, I.Y. Anti-inflammatory effect of mangostenone f in lipopolysaccharide-stimulated raw264.7 macrophages by suppressing nf-kappab and mapk activation. *Biomol Ther (Seoul)* **2014**, *22*, 288-294.
10. Tewtrakul, S.; Wattanapiromsakul, C.; Mahabusarakam, W. Effects of compounds from garcinia mangostana on inflammatory mediators in raw264.7 macrophage cells. *J Ethnopharmacol* **2009**, *121*, 379-382.
11. Choi, Y.H.; Bae, J.K.; Chae, H.S.; Kim, Y.M.; Sreymom, Y.; Han, L.; Jang, H.Y.; Chin, Y.W. Alpha-mangostin regulates hepatic steatosis and obesity through sirt1-ampk and ppargamma pathways in high-fat diet-induced obese mice. *J Agric Food Chem* **2015**, *63*, 8399-8406.
12. Chae, H.S.; Kim, Y.M.; Bae, J.K.; Sorchhann, S.; Yim, S.; Han, L.; Paik, J.H.; Choi, Y.H.; Chin, Y.W. Mangosteen extract attenuates the metabolic disorders of high-fat-fed mice by activating ampk. *J Med Food* **2016**, *19*, 148-154.
13. Xie, Z.; Sintara, M.; Chang, T.; Ou, B. Daily consumption of a mangosteen-based drink improves in vivo antioxidant and anti-inflammatory biomarkers in healthy adults: A randomized, double-blind, placebo-controlled clinical trial. *Food Sci Nutr* **2015**, *3*, 342-348.
14. Udani, J.K.; Singh, B.B.; Barrett, M.L.; Singh, V.J. Evaluation of mangosteen juice blend on biomarkers of inflammation in obese subjects: A pilot, dose finding study. *Nutr J* **2009**, *8*, 48.
15. Stern, J.S.; Peerson, J.; Mishra, A.T.; Sadasiva Rao, M.V.; Rajeswari, K.P. Efficacy and tolerability of a novel herbal formulation for weight management. *Obesity (Silver Spring)* **2013**, *21*, 921-927.
16. Kudiganti, V.; Kodur, R.R.; Kodur, S.R.; Halemane, M.; Deep, D.K. Efficacy and tolerability of meratrim for weight management: A randomized, double-blind, placebo-

controlled study in healthy overweight human subjects. *Lipids Health Dis* **2016**, *15*, 136.
17. Mekseepralard, C.; Areebambud, C.; Suksamrarn, S.; Jariyapongskul, A. Effects of long-term alpha-mangostin supplementation on hyperglycemia and insulin resistance in type 2 diabetic rats induced by high fat diet and low dose streptozotocin. *J Med Assoc Thai* **2015**, *98 Suppl 10*, S23-30.
18. Nakatani, K.; Nakahata, N.; Arakawa, T.; Yasuda, H.; Ohizumi, Y. Inhibition of cyclooxygenase and prostaglandin e2 synthesis by gamma-mangostin, a xanthone derivative in mangosteen, in c6 rat glioma cells. *Biochem Pharmacol* **2002**, *63*, 73-79.
19. Yamakuni, T.; Aoki, K.; Nakatani, K.; Kondo, N.; Oku, H.; Ishiguro, K.; Ohizumi, Y. Garcinone b reduces prostaglandin e2 release and nf-kappab-mediated transcription in c6 rat glioma cells. *Neurosci Lett* **2006**, *394*, 206-210.