Title of Study:	Mango Modulates Body Fat and Plasma Glucose and Lipids in Mice Fed High Fat Diet

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Introduction

Mango fruit contains substantial amounts of vitamin A (beta carotene) as well as other carotenoids, vitamin C (ascorbic acid), vitamin E (alpha tocopherol), and phenolic compounds. Studies have demonstrated that mango varieties can vary widely in its nutrient content, with 'Tommy Atkins' having the least amount of vitamins A, C, and total phenolics. Regardless, a serving of 'Tommy Atkins' variety provides at least 10% of the recommended daily intake of these vitamins and was the selected mango variety for our study. Success with this variety should indicate that other varieties, expressing higher amounts of vitamins and phenolics, may even be more effective in reducing body fat or altering blood lipids and sugar (glucose).

The objective of this research was to determine the effectiveness of mango pulp in modulating blood glucose and lipid values in mice fed a high fat diet to induce obesity. In humans, obesity is associated to the development of many chronic diseases such as type 2 diabetes and heart disease. To combat these diseases, healthcare providers often prescribe drugs capable of lowering blood glucose (rosiglitazone) and lipids (fenofibrate). However, the use of these drugs can be associated with deleterious side effects, such as liver enlargement, fluid retention, heart failure, and increase risk for bone fracture. Our findings demonstrate that mango pulp is a promising adjuvant that can be useful in preventing obesity and reducing blood glucose. The findings of our research are summarized below.

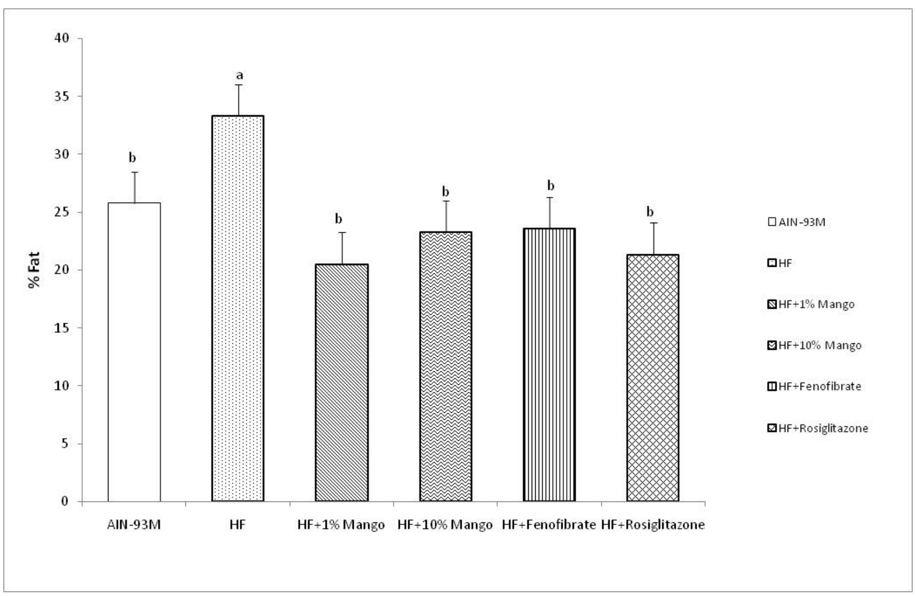
Fresh Tommy Atkins mangos where peeled, cut, freeze-dried, and ground to a fine powder. Samples were analyzed for vitamin and mineral content and added to a standard mouse diet. Dietary treatment consisted of control (regular mouse diet, AIN-93M), high fat (HF), high fat plus 1% mango powder (HF+1% mango), high fat plus 10% mango powder (HF+10% mango), high fat plus fenofibrate (HF+fenofibrate), and high fat plus rosiglitazone (HF+rosiglitazone). All high fat diets were adjusted to have similar carbohydrate, fiber, protein, fat, calcium, and phosphorous content. Mice were assigned to one of six diets (8 mice per group) for 2 months and were allowed to drink and eat without restriction.

Mango, similar to rosiglitazone, attenuated the rise in body fat, blood glucose, cholesterol, and non-esterified fatty acids after two months of consuming a high-fat diet. The effects of mango on these parameters are discussed below.

Fat Accumulation

No differences in body weight were seen among mice after consuming the different diets for two months. However, the amount of body fat differed among the six groups. The effect of the six dietary treatments on percent body fat is shown in **Figure 1**. Fat mass and percent body fat was highest in the high-fat group. Both the 1% and 10% of mango diet had comparable effects to that of rosiglitazone and fenofibrate in modulating body fat. Mango and the two drugs reduced percent body fat to the level of the mice consuming the normal diet. Mice in the fenofibrate treatment had enlarged livers, a known side effect of this drug. To our knowledge, this is the first study demonstrating the effectiveness of mango in reducing body fat in response to a high fat diet.

Figure 1: Effects of mango, rosiglitazone, and fenofibrate on percent body fat of mice fed high fat (HF) diet for two months



Bars are mean ± SE, n=8/group; bars that do not share the same letters are significantly ($P<0.05$) different from each other.

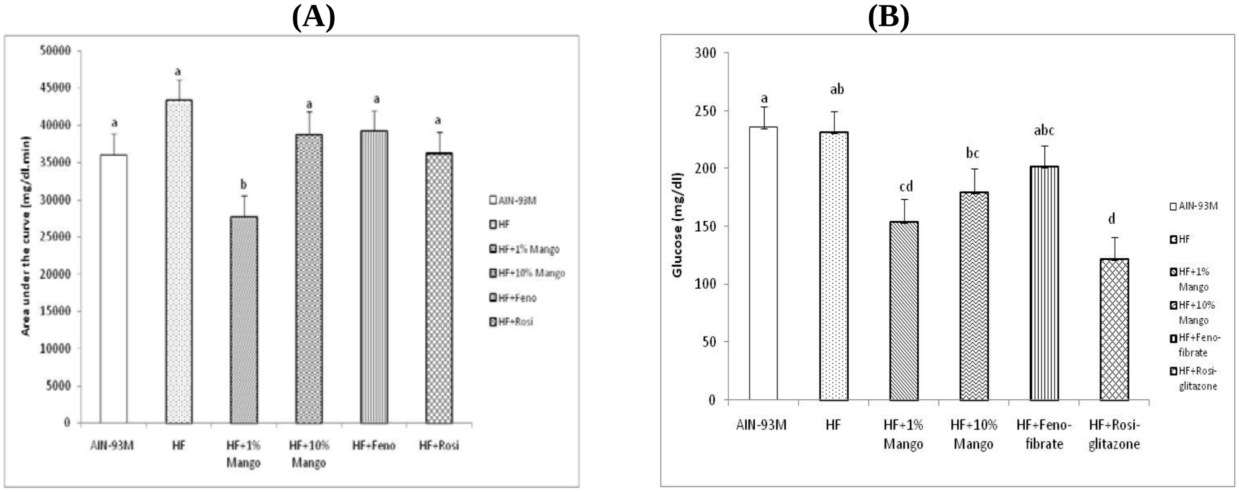
Blood Glucose Modulation

Glucose tolerance tests demonstrated that freeze-dried mango at l% dose exhibited glucose-lowering properties in our animal model. The effect of adding 1% mango to a high-fat diet is more pronounced than the one obtained from adding rosiglitazone, a known glucose-lowering agent. As a comparison, the 10% dose mango is similar to the rosiglitazone group, but not as effective as the 1% dose in lowering blood glucose. Result of the glucose tolerance test is shown in **Figure 2A**.

In addition to the glucose tolerance test, plasma glucose obtained at the end of the study confirmed the glucose-lowering properties of mango (**Figure 2B**). Similar to the findings of the glucose tolerance test, 1% mango was the most effective in reducing plasma glucose. To our knowledge, very few studies have been conducted that investigated the glucose lowering properties of mango and these studies have been limited to the extract of stem bark or leaves.[1-3] Our findings are the first to demonstrate the effectiveness of mango pulp in modulating hyperglycemia induced by a consumption of a high-fat diet.

Figure 2: Effects of mango, rosiglitazone, and fenofibrate on **(A)** glucose area under the curve after a glucose tolerance test and **(B)** plasma glucose of mice fed high fat (HF) diet for two months[1]

(A) **(B)**



[1]Bars are mean ± SE, n=6/group; bars that do not share the same letters are significantly (P<0.05) different from each other.

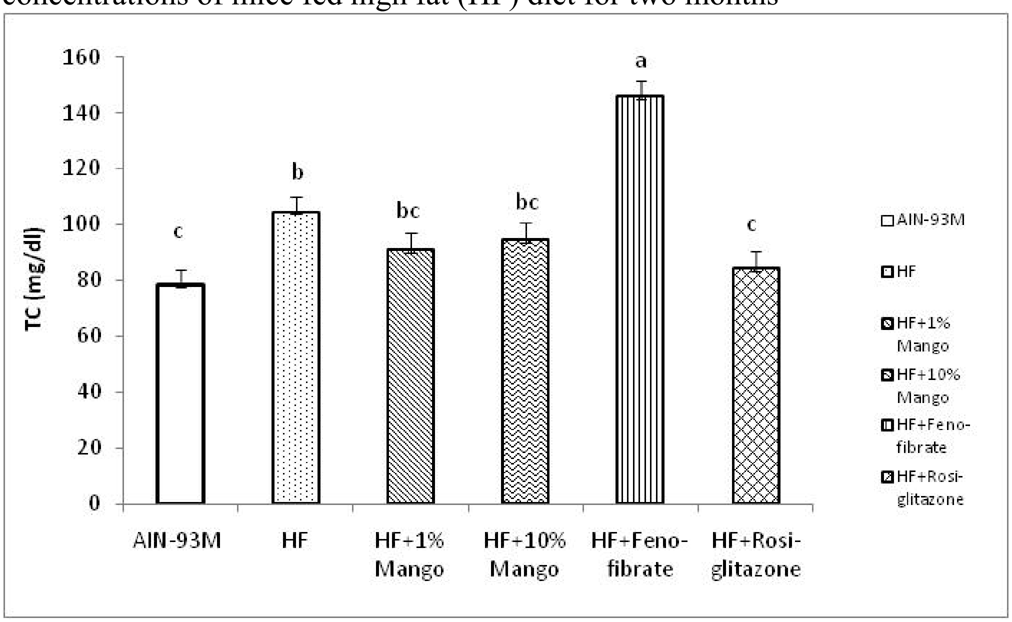
It is not clear what component(s) of mango pulp is responsible for its glucose-lowering properties. In addition to the phenolic content of mango, a component that may have contributed to its glucose-lowering property is its fiber content. The mango used in this study contains approximately 4% dietary fiber and fiber has been shown to lower blood glucose level in laboratory animals and in humans.[4-5]

The mechanism of how mango alters blood glucose remains unclear. Our analyses of gene expression suggest that mango does not normalize blood glucose by increasing the capacity of glucose uptake by fats and muscle. Instead, this unique glucose-lowering property of mango may be attributed to its effect on the pancreas to increase the release of the hormone insulin that regulates blood glucose.[2] Alternatively, mango may directly or indirectly suppress the absorption of glucose from the small intestine.[3] And lastly, mango may normalize blood glucose by promoting its storage in the liver and preventing its release in the blood. However, these are all speculative and warrant closer examination in future studies.

Effects on Blood Cholesterol

In addition to lowering glucose, mango consumption exhibited moderate effects on plasma total cholesterol. Mice receiving the normal diet and the high-fat diet containing rosiglitazone showed the lowest plasma total cholesterol concentrations (**Figure 3**). Interestingly, mice receiving a high-fat diet containing fenofibrate had the highest total cholesterol while those receiving the high-fat diet alone had an intermediate total cholesterol values (**Figure 3**). Plasma total cholesterol concentrations of mice fed the high-fat diet containing either the 1% or 10% mango were similar to the rosiglitazone and the normal diet group (**Figure 3**).

Figure 3: Effects of mango, rosiglitazone, and fenofibrate on plasma total cholesterol (TC) concentrations of mice fed high fat (HF) diet for two months[1]



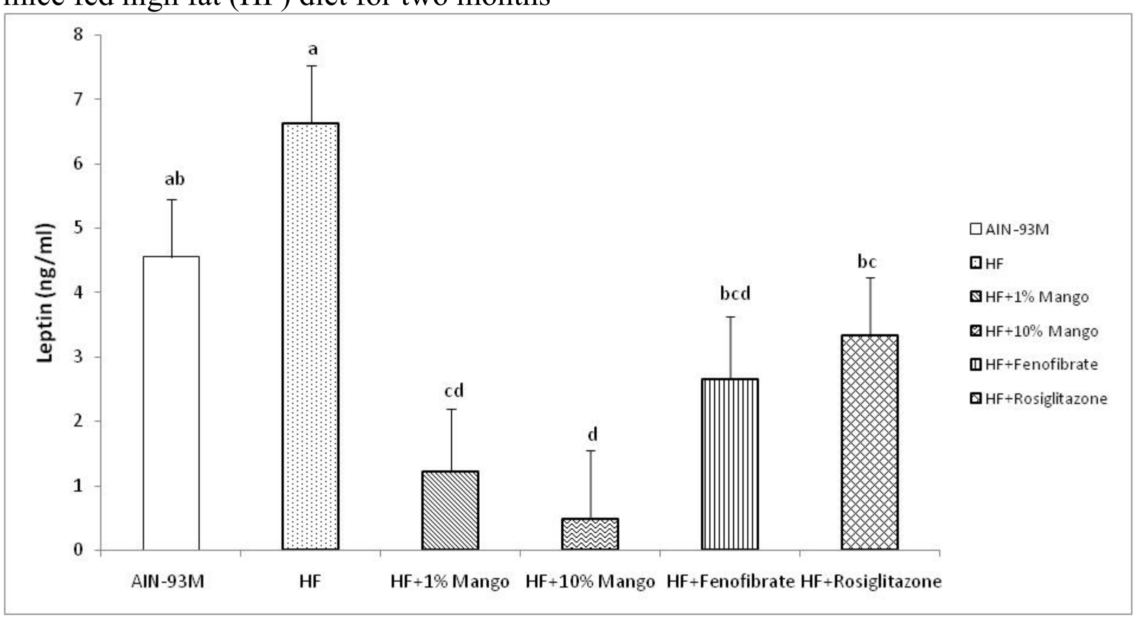
Bars are mean ± SE, n=8/group; Bars that do not share the same letters are significantly (P<0.05) different from each other.

Markers of Fat Metabolism

The fat reducing effects of mango may be similar to that of rosiglitazone. Mango may modulate factors in the development and accumulation of fat in the body. However, exactly how mango is involved in coordinating or regulating these processes should be further investigated.

One factor involved in fat metabolism that was shown to be affected by mango is the hormone leptin. Leptin is a hormone derived from fat cells and is considered a biomarker of body fat content as well as an indicator of overall energy balance. In general, as body fat stores increases, leptin expression and circulating levels of leptin increases, thereby reflecting significant energy stores in the form of body fat. Mice receiving either the normal or a high fat-diet exhibited similar plasma leptin concentrations, and leptin concentrations in these groups were significantly higher than the mice receiving high-fat diets containing mango. Rosiglitazone and fenofibrate had an intermediate effect on plasma leptin concentrations (**Figure 4**).

Figure 4: Effects of mango, rosiglitazone, and fenofibrate on plasma leptin concentrations of mice fed high fat (HF) diet for two months[1]

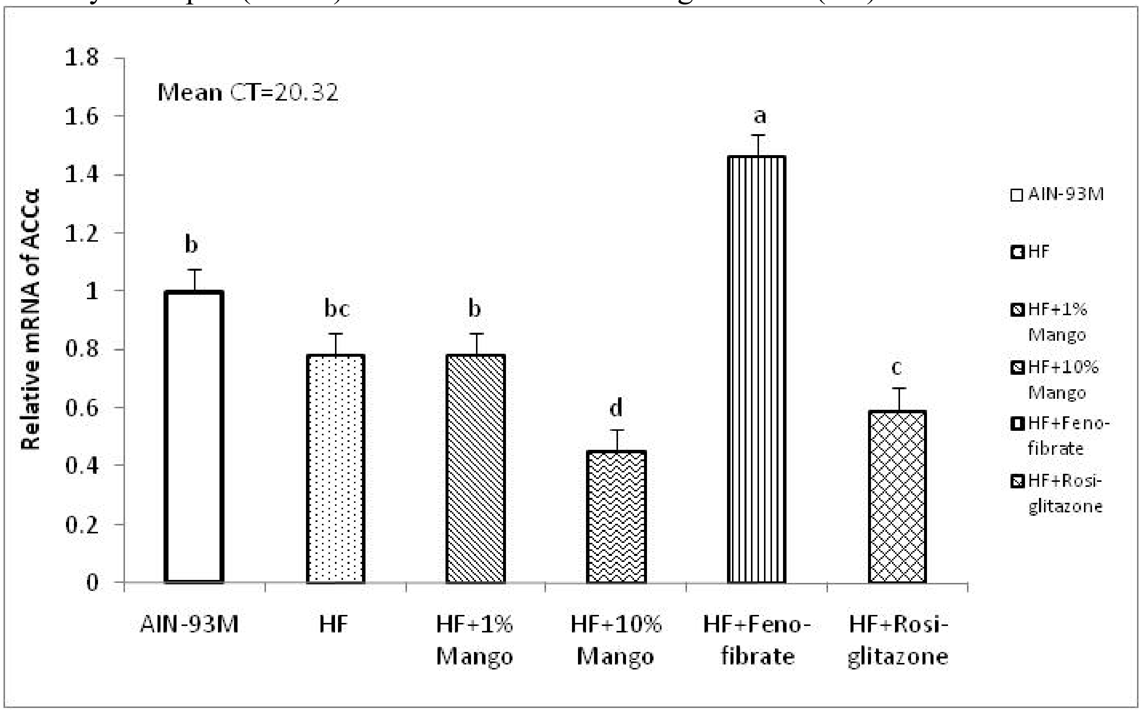


[1]Bars are mean ± SE, n=8/group; Bars that do not share the same letters are significantly ($P<0.05$) different from each other.

In addition to leptin, we have investigated other factors that could possibly explain the effect of mango on fat accumulation. We examined the effects of the diets on enzymes involved in fat synthesis (ACCα) or breakdown (ACOX1 and MCAD). A high-fat diet containing 10%

mango contributed to the lowest expression of ACCα mRNA, a key regulator of fat synthesis (**Figure 5**). Interestingly, a similar pattern was observed in the gene encoding proteins involved in the process of breaking down fat.

Figure 5: Effects of mango, rosiglitazone, and fenofibrate on relative mRNA of acetyl-CoA carboxylase alpha (ACCα) in the liver of mice fed high fat diet (HF) for two months[1]



[1]Bars are mean ± SE, n=6/group; Bars that do not share the same letters are significantly ($P<0.05$) different from each other.

Summary

Mango added to a high-fat diet, prevented the increase in fat mass due to high-fat diet and was similar in efficacy to two well-known drugs used in the treatment of metabolic disorders, rosiglitazone and fenofibrate. This finding suggests that incorporation of mango in the diet may be a possible alternative in helping reduce our increasing problem with obesity. Both glucose tolerance test and plasma glucose were improved by the addition of mango to a high-fat diet. Overall, supplementing a high-fat diet with 1% mango for 8 weeks was more effective than supplementing with 10% mango, rosiglitazone, or fenofibrate in terms of modulating blood glucose. Given the positive effects of mango supplementation, our findings suggest that incorporation of mango in the diet may also lower risk factors for the development and progression of heart disease. Indeed human studies should be conducted to confirm our novel findings using an animal model of diet-induced obesity. Further studies are needed to focus on how and what component(s) in mango are responsible for its positive effect on attenuating increased in body fat and blood glucose and lipids.

References:

1. Ojewole JA, Antiinflammatory, analgesic and hypoglycemic effects of *Mangifera indica* Linn. (Anacardiaceae) stem-bark aqueous extract. Methods Find Exp Clin Pharmacol. 2005; 27 (8): 547-54.
2. Aderibigbe AO, Emudianughe TS, Lawal BS. Evaluation of the antidiabetic action of *Mangifera indica* in mice. Phytother Res 2001, 15:456-8.
3. Muruganandan S, Srinivasan K, Gupta S, Gupta PK, Lal J, Effect of mangiferin on hyperglycemia and atherogenicity in streptozotocin diabetic rats, J Ethnopharmacol. 2005; 97(3): 497-501
4. Fairchild RM, Ellis PR, Byrne AJ, Luzio SD, Mir MA, A new breakfast cereal containing guar gum reduces postprandial plasma glucose and insulin concentrations in normal-weight human subjects, Br J Nutr 1996; 76(1): 63-73.
5. Hannan JM, Rokeya B, Faruque O, Nahar N, Mosihuzzaman M, Azad Khan AK, Ali L, Effect of soluble dietary fibre fraction of Trigonella foenum graecum on glycemic, insulinemic, lipidemic and platelet aggregation status of Type 2 diabetic model rats, J Ethnopharmacol. 2003; 88(1): 73-7.