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Feiolix feijoa fruit powder improves metabolic markers in a high fat diet mouse model

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ABSTRACT

Background: Feiolix®, a freeze-dried feijoa fruit powder contains ellagitannins, abscisic acid, and xyloglucans, each of which may independently and synergistically support metabolic health.

Objective: To examine the dose-response effects of Feiolix® on metabolic parameters in high-fat diet-induced diabetic mice.

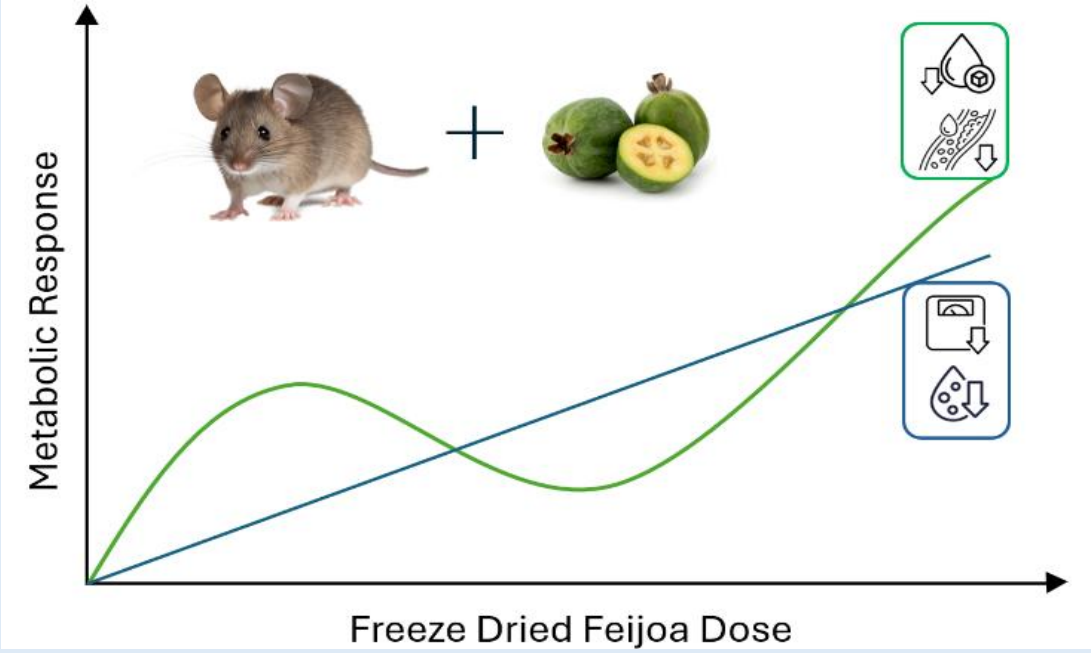
Methods: Swiss albino mice were fed a high-fat diet for 8 weeks to induce diabetes, followed by daily oral gavage of Feiolix at five doses (0.7-11.6 mg/20 g body weight), metformin control, non-diabetic control, or continued high-fat diet for an additional 16 weeks.

Results: A biphasic xenohormetic dose-response pattern was observed. The low dose (1.5 mg) demonstrated significant efficacy, significantly reducing fasting blood glucose (-10.1 mg/dL, $p<0.0001$ vs high-fat diet control) and triglycerides (-14.7 mg/dL, $p<0.0001$) with performance comparable to metformin and normal controls. Surprisingly, the mid-range 3.5 mg dose was less effective than the 1.5 mg dose for glucose and triglyceride management. The highest 11.6 mg dose showed comprehensive benefits across all metabolic parameters, significantly reducing fasting blood glucose (-30.1 mg/dL), triglycerides (-29.5 mg/dL), total cholesterol (-47.3 mg/dL), and LDL cholesterol (-20.7 mg/dL), while also promoting weight loss and improving liver histology.

Conclusions: These findings demonstrate that feijoa exhibits xenohormetic effects with metabolic benefits at low doses (300 mg human equivalent) and enhanced comprehensive benefits at high doses (2300 mg human equivalent), supporting its potential as a natural intervention for metabolic dysfunction management.

Novelty of the Study: This study provides evidence that freeze dried feijoa powder (Feiolix®) can act as functional food ingredient with potential therapeutic application to improve metabolic health.

Keywords: feijoa; metabolism; blood glucose; cholesterol; triglycerides; body weight; liver health; dose-response; xenohormesis



Graphical Abstract: Supplementation with Feiolix® freeze dried Feijoa resulted in a biphasic dose response curve for reductions in fasting blood glucose and triglycerides, and a linear dose response for body weight and LDL cholesterol in a high fat diet mouse model.

INTRODUCTION

Preliminary data and traditional knowledge suggest that feijoa fruit (*Acca sellowiana*) are beneficial for metabolic health in humans [1]. Feijoa fruits contain high levels of polyphenols, abscisic acid, and cell wall xyloglucans, each of which may independently and collectively support metabolic health through multiple mechanisms. This study sought to identify the lowest effective dosage of a proprietary freeze-dried feijoa powder, Feiolix, in a High Fat Diet (HFD) mouse model of diabetes. The results indicate a potential xenohormetic effect wherein a lower dose of Feiolix is more effective than a moderate dose at reducing fasting blood glucose (FBG) and triglycerides. Higher doses demonstrate a predictable dose-response curve.

Feijoas are rich in bioactives from across chemical classifications. Three bioactives, ellagitannins, abscisic acid and polysaccharides, occur in high concentrations,

each of which have independently been found to support metabolic health [2]. Feijoa ellagitannins comprise approximately 60% of the polyphenol fraction of the fruit and have been shown to inhibit JAK2 and AMPK activity involved in energy management. Ellagitannins are converted by members of the gut microbiome into urolithins with well-documented metabolic and longevity benefits [4-5]. Feijoas are high in abscisic acid, containing approximately 35 µg/g in the freeze-dried fruit (unpublished data). Abscisic acid is a universal signaling hormone that is endogenous to both plants and humans, known to be involved in separation of fruit from stem in plants, and secreted from the pancreas in humans [6]. Abscisic acid binds to LANCL1/2 receptors across nearly all tissue types and organs in humans and contributes to insulin-independent glucose uptake [7-9]. Polysaccharides in Feijoa fruit cell walls are rich in xyloglucans that selectively feed *Bacteroides* in the mammalian gut microbiome [10]. *Bacteroides* produce bioavailable propionate, which modulates management of systemic energy [11].

Xenohormesis is a biological phenomenon where organisms derive adaptive benefits from consuming low doses of stress signaling compounds, such as polyphenols, produced by other species, typically in response to environmental challenges [12]. This concept, first described by Howitz and Sinclair, suggests that mild stressors from plant secondary metabolites can activate beneficial cellular stress response pathways in consuming organisms, leading to enhanced resilience and longevity [12-13]. Importantly, xenohormetic effects often exhibit non-linear dose-response relationships, where low concentrations trigger hormetic responses that promote cellular protection and metabolic optimization, while mid and high doses may overwhelm these protective mechanisms or activate different biological pathways entirely [14]. This biphasic response pattern provides a compelling theoretical framework for understanding efficacy profiles from plant-derived supplements that demonstrate increased benefits at lower doses, followed by diminished effects at moderate concentrations, before resuming a more conventional dose-dependent response at higher concentrations.

This experiment describes the use of a high-fat diet-induced type 2 diabetes mouse model to examine dose responses to feijoa fruit on FBG, lipid control, and liver health. Freeze-dried feijoa whole fruit powder (Feiolix®) was used.

MATERIALS AND METHODS

The study was conducted at the Mumbai Veterinary College (Mumbai, India) and approved by an institutional animal ethics committee (46th IAEC- MVC/IAEC/05 JULY/2020) following the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, Ministry of Environment, Forests and Climate Change, India.

Healthy young (6-7 weeks) Swiss albino mice (Krantisinh Nana Patil College of Veterinary Science, India) were acclimatized for 5 days in solid floor polypropylene cages at 21-23°C, 60-70% relative humidity with 12 h light/dark cycles, with standard feed (VRK Nutritional Solutions, Sangli, India) and water *ad libitum*.

After acclimatization, seven out of the eight groups were fed a high fat diet (HFD) for eight weeks, and the animals with blood sugar exceeding 150 mg/dL were included in the study (Table 1). Feiolix (Anagenix Ltd, Auckland, New Zealand) at five dosages and a positive metformin control were administered through daily oral gavage to HFD-fed groups. Also included were a HFD control and standard nondiabetic (ND) diet control. Feiolix dosages were 11.6, 5.8, 3.5, 1.5 and 0.7 mg/20 g mouse, with 11.6 mg/20 g equivalent to the human dosage of feijoa fruit extract used in the previous clinical study (150 mg of Feijoa extract standardized to polyphenol content) [1]. Mice were observed after dosing for morbidity and mortality and weighed

regularly. After 16 weeks of dosing (24 weeks overall) animals were sacrificed and blood metabolic markers measured.

The study assessed random blood glucose (Accucheck Active); and lipid profiles: triglycerides, total cholesterol, High Density Lipoprotein (HDL)-cholesterol and LDL-cholesterol (Quantification Kits, Sigma Aldrich); body weight, and liver histology according to standard methods.

Statistical analyses were performed using R version 4.4.3. Statistical analysis was conducted to assess the magnitude of change (delta values) from 24 weeks (end of intervention) to 8 weeks (disease development). A one-way ANOVA was performed, followed by pairwise comparisons using Tukey's adjustment. Each dosage was compared against the three control groups, with a significance threshold of $p < 0.05$. Data presented are mean ± SD of all available observations. Statistical comparisons were performed using paired t-test on matched pairs.

The lowest effective dose was defined as that which was not significantly different compared to either the Metformin control or the standard diet control but was significantly improved compared to the HFD control.

RESULTS

Body weight: Results are shown in Table 1 and Figure 1(a). The highest Feiolix dose (11.6 mg) showed significant weight loss compared to the metformin group ($p< 0.02$), the ND control group ($p< 0.003$), and the HFD group ($p< 0.0006$). The lowest Feiloix dose, 0.7 mg, showed trending non-significant weight gain compared to the HFD group (8.1 g, $p=0.08$). The low and mid Feiolix doses, 1.5 mg, 3.5 mg, 5.8 mg, did not lead to significant reductions in weight gain relative to the HFD control group (5.0 g, 4.3 g, 3.6 g, p values of 0.99,0.99, and 0.93). The metformin group and non-diabetic control group also did not show significantly different change in body weight compared to the HFD group.

Fasting blood glucose: Results are shown in Table 1 and Figure 1(b). The largest increase in FBG was in the HFD control group with an increase of 41.4 mg/dL. The low dose of 0.7 mg and the mid-range dose of 3.5 mg showed significantly lower increase in FBG compared to the HFD control group (5.9 and 12.0 respectively), however, the overall trend showed increased FBG at both of these doses and they were significantly greater than the ND Control and the Metformin Control. The low 1.5 mg dose reduced 10.1 mg/dL during the intervention period, which was significant compared to the HFD control ($p<0.0001$) and not significant compared to the ND Control group ($p=0.9981$) nor the metformin control group ($p= 0.3809$). The second highest dose group, 5.8 mg, decreased by the same amount as the low 1.5 mg dose, with very similar significance values. The high 11.6 mg dose group showed the largest decrease, 30.1 mg/dL, which was significantly decreased compared to all control groups ($p<0.0001$ compared to HFD control and ND control, $p=0.0002$ compared to metformin control).

Triglycerides: Results are shown in Table 1 and Figure 1(c). The largest increase in triglycerides was in the HFD control group (25 mg/dL). Triglycerides in the ND control group also increased by 5.9 mg/dL. Of the intervention groups, only the lowest dose of 0.7 mg increased by 1.2 mg/dLwhich was not significant compared to ND control ($p=0.6699$) or HFD control ($p=0.7510$), but was significantly increased compared to Metformin control ($p= p=0.02$). The low dose of 1.5 mg decreased by 14.7, which was more than subsequent higher doses of 3.5 mg (7.7 mg decrease) and 5.8 mg (6.8 mg decrease) and significantly decreased compared to the HFD control group ($p<0.0001$) and the ND control group ($p=0.0130$)

but not compared to the Metformin control group (p=2.037). The high 11.6 mg dose showed the largest decrease in Triglycerides at 29.5 mg/dL reduction, which was comparable to the Metformin control group which decreased 29 mg/dL (p=0.9999).

Total cholesterol: Results are shown in Table 1 and Figure 1(d). The HFD control group (3.2 mg/dL increase) and ND control group (4.6 mg/dL increase) were the only groups to show an increase in cholesterol. The lowest dose of 0.7 mg decreased by 20 mg/dL, but this was not significant compared to either the HFD control group (p= 0.7510) or the ND control group (p = 0.6699). The low dose of 1.5 mg decreased by 31 mg/dL which was not significant compared to HFD control (p=0.0747) and ND control (p=0.0548). The mid-range dose of 3.5 mg only decreased by 28 mg/dL which was not significant compared to any of the control groups. The high dose of 5.8 mg decreased by 45.5 mg/dL which was significant compared to both the HFD control (p=0.0007) and ND control (p=0.0004) but not significant compared to the metformin control (p= 0.9571) which showed decreased cholesterol by 43.9 mg/dL. Similarly, the highest dosage group of 11.6 mg showed a decrease of 47.3 mg/dL which was significant compared to both the HFD control (p=0.0004) and ND control (p=0.0003) but not significant compared to the metformin control (p= 0.9821).

LDL cholesterol: Results are shown in Table 1 and Figure 1(e). The HFD control group (18.2 mg/dL increase) and ND control group (2.5 mg/dL increase) were the only groups to show an increase in LDL cholesterol. The lowest dose of 0.7 mg decreased by 2.8 mg/dL which was significant compared to HFD control (p= 0.0152). The low dose of 1.5 mg decreased by 2.0 mg/dL which was also significant compared to HFD control (0.0221) but not significant compared to either the ND control or metformin control. The subsequent doses of 3.5 mg, 5.8 mg, and 11.6 mg each decreased by 6.3 mg/dL, 9.1 mg/dL, and 20.7 mg/dL, which were all significant compared to HFD control (p = 0.0024, p = 0005, p = 0.5E-06 respectively). Only the highest 11.6 mg dose was significant compared to ND control (p=0.0049) but not compared to metformin control (p = 0.9998).

HDL cholesterol: Results are shown in Table 1 and Figure 1(f). HDL cholesterol increased in all groups except the HFD control group, where it decreased by 3.5 mg/dL. The low dose of 0.7 mg increased by 6.2 mg/dL, the low dose of 1.5 mg increased by 4.3 mg/dL, the mid-range dose of 3.5 mg increased by 5.4 mg/dL, and the high dose of 5.8 mg increased by 6.0 mg/dL. None of these doses showed a significantly different HDL response compared to the HFD control nor the ND control. The Metformin control and 11.6 high dose groups had the highest HDL levels at 16.7 and 17.0 respectively. The 11.6 mg high dose was significantly elevated compared to ND control (p = 0.0196) and HFD control (p = 0.0003).

Liver histology: Liver histology was scored on a scale of – to +++, where – indicates no change and each + indicates increased damage. The HFD group showed cumulative scores of +++ by the end of the 24-week study. The 0.7 mg dose, 1.5 mg dose, 3.5 mg dose, and 5.8 mg dose showed scores of ++ by the end of the 24-week study, indicating slight improvement from the HFD group. The 11.6 mg high dose and metformin control group both showed scores of +, representing further improvement compared to the mid-range and low doses of Feiolix intervention. Only the ND control group did not show any liver damage.

Table 1. Means, standard deviations, and inter-group comparisons of p-values of body weight, blood glucose, triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol.

Treatment Group	Mean	SD	Mean	SD[1]	Δ	p-value Δ Treatment Group vs Δ HFD control	p-value Δ Treatment Group vs Metformin control	p-value Δ Treatment Group vs ND control
	Body weight (g) wk 8		Body weight (g) wk 24					
11.6 mg	29.3	1.2	29.4	1.8	0.1	**0.0006****	**0.01549***	**0.0026****
5.8 mg	33.2	3.2	36.8	2.8	3.6	0.9305	0.9999	0.9962
3.5 mg	40.2	2.9	44.5	3.5	4.3	0.9992	0.99991	0.9999
1.5 mg	39.3	4.1	44.3	4	5.0	0.9999	0.9672103	0.9999
0.7 mg	37.2	4.5	45.3	5.1	8.1	0.0827	**0.0040****	**0.02475***
Met Control	29.8	1.9	33.7	3.5	3.9	0.9672	-	-
HFD Control	46.7	2.4	51.7	3.2	5.0	-	-	0.9999
ND Control	30.3	1.9	34.8	2.6	4.5	-	0.9992	-
	Blood glucose (mg/dL) wk 8		Blood glucose (mg/dL) wk 24					
11.6 mg	189.3	3.1	159.3	3.8	-30.0	**<0.0001****	**0.0002*****	**1.0E-06****
5.8 mg	175.3	3.5	165.2	3.4	-10.1	**<0.0001****	0.3919001	0.9984
3.5 mg	197.1	3.9	209.1	3.3	12.0	**<0.0001****	**<0.0001****	**<0.0001****
1.5 mg	204.1	3.6	194	3.9	-10.1	**<0.0001****	0.3809	0.9981
0.7 mg	186.4	3.9	192.3	4.3	5.9	**<0.0001****	**<0.0001****	**1.2E-06****
Met Control	182.3	5.1	166.1	3.3	-16.2	**<0.0001****	-	-
HFD Control	171.7	2.3	213.1	4.2	41.4	-	-	**<0.0001****
ND Control	108.2	2.2	96.3	2.4	-11.9	-	0.8283	-
	Triglycerides (mg/dL) wk 8		Triglycerides (mg/dL) wk 24					
11.6 mg	103.5	10.1	74	9.7	-29.5	**<0.0001****	0.9999	0.0000021
5.8 mg	106	22.1	99.2	20.8	-6.8	**1.82E-5****	**0.0054****	0.3506
3.5 mg	99	12.3	91.3	18.3	-7.7	**1.1E-05****	**0.0085****	0.2708
1.5 mg	120.7	10.2	106	11.3	-14.7	**1.0E-07****	0.2037	**0.0131***
0.7 mg	102.5	12.5	103.7	13.1	1.2	0.751	**0.0283***	0.6699
Met Control	101.3	10.5	72.3	7.7	-29.0	**<0.0001****	-	-
HFD Control	87.2	15.1	112.2	14.8	25.0	-	-	**0.0257***
ND Control	52.3	13	58.2	7.3	5.9	-	**2.8E-06****	-
	Total cholesterol (mg/dL) wk 8		Total cholesterol (mg/dL) wk 24					
11.6 mg	158.5	16.7	111.2	18.3	-47.3	**0.0004*****	0.9821	**0.0003***
5.8 mg	167.3	10.3	121.8	10.8	-45.5	**0.0007****	0.9571	**0.0004***
3.5 mg	166	15.3	137.4	14.1	-28.6	0.4994	0.0681	0.4168
1.5 mg	161	20.19	137.2	18.5	-23.8	0.0747	0.4180	0.0548
0.7 mg	140.8	10.5	120.8	11.5	-20.0	0.7510	**0.0283***	0.6699
Met Control	150.4	26.7	106.5	17.7	-43.9	0.0000	-	-
HFD Control	146.8	21.8	150	9.2	3.2	-	-	0.9999
ND Control	48.1	5.5	52.7	12.6	4.6	-	**6.3E-05****	-
	LDL cholesterol (mg/dL) wk 8		LDL cholesterol (mg/dL) wk 24					
11.6 mg	72.2	23.9	51.5	7.7	-20.7	**0.5E-6****	0.9998	**0.0049****
5.8 mg	71.3	11.2	62.2	7.8	-9.1	**0.0005*****	0.8335	0.5231
3.5 mg	86	7	79.7	17	-6.3	**0.0024****	0.5308	0.8277
1.5 mg	72.4	13.2	70.4	19.1	-2.0	**0.0221***	0.1462	0.9968
0.7 mg	85.5	9.4	82.7	10.3	-2.8	**0.0152***	0.1932	0.9905
Met Control	60.4	8	42.5	5.8	-17.9	**0.3E-05****	-	-
HFD Control	81.7	20.9	99.9	17.5	18.2	-	-	0.1481
ND Control	34.7	8.3	37.2	10.6	2.5	-	**0.0217***	-
	HDL cholesterol (mg/dL) wk 8		HDL cholesterol (mg/dL) wk 24					
11.6 mg	29.3	2.7	46.3	4.1	17.0	**0.0003*****	0.9999	**0.0196***
5.8 mg	37.6	10.5	43.6	8.9	6.0	0.3504	0.2035	0.9900
3.5 mg	31.2	8.6	36.6	5	5.4	0.4528	0.1438	0.9975
1.5 mg	36.3	8.6	40.6	6.8	4.3	0.6122	0.0834	0.9999
0.7 mg	30.3	5.8	36.5	4.4	6.2	0.3257	0.2218	0.9864
Met Control	33.6	7.7	50.3	6.9	16.7	**0.0003*****	-	-
HFD Control	36.6	6.6	33.1	5.7	-3.5	-	-	0.8942
ND Control	46	13.4	48.2	8.5	2.2	-	**0.0228***	-

Met control= metformin control, HFD control = High Fat Diet control, ND control = Nondiabetic control, SD = Standard deviation.

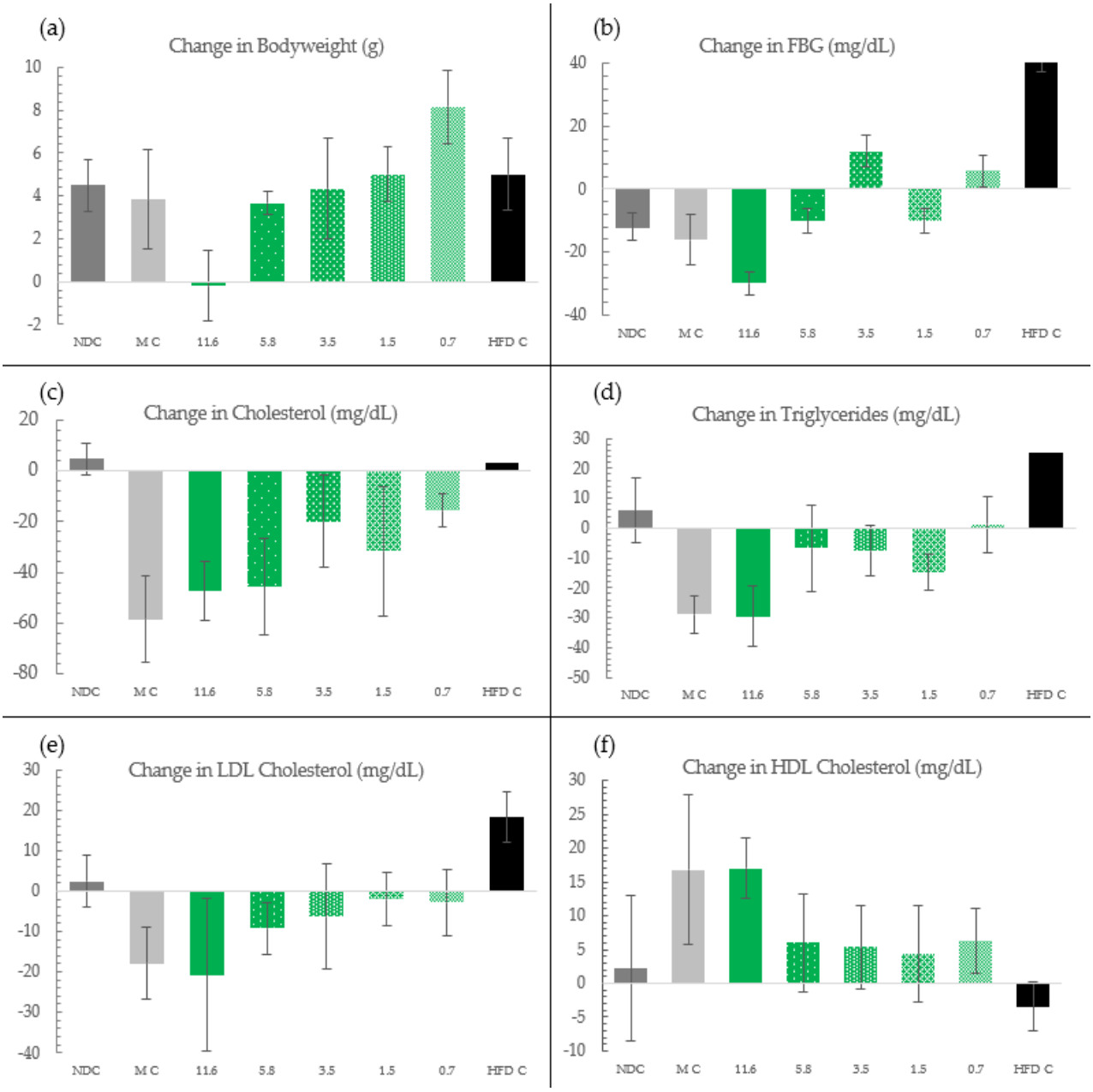


Figure 1. (a) Change in mean Bodyweight (g) between 8-24 weeks of Feiolix intervention. (**b**) Change in mean FBG (mg/dL) between 8-24 weeks. (**c**) Change in mean Cholesterol (mg/dL) between 8-24 weeks. (**d**) Change in mean Triglycerides (mg/dL) between 8-24 weeks. (**e**) Change in mean LDL Cholesterol (mg/dL) between 8-24 weeks. (f) Change in mean LDL Cholesterol (mg/dL) between 8-24 weeks. NDC = Non Diabetic Control, M C= Metformin Control, HFD C= High Fat Diet Control.

DISCUSSION

The results of this study suggest that Feiolix, a freeze-dried feijoa fruit powder, exerts beneficial metabolic effects in a biphasic xenohormetic manner at the low dose of 1.5 mg/20 g (HED 300 mg) and in a dose-dependent manner at higher doses for most metrics of metabolic health measured in this study. The mid-range dose of 3.5 mg was surprisingly less effective than the low 1.5 mg dose for FBG, triglycerides, and cholesterol. The high 11.6 mg dose was the most effective for all metabolic metrics, in particular FBG and body weight, for which it significantly outperformed both the ND control and metformin control.

The observed glucose-lowering effect of Feiolix at low doses may be attributed to the presence of ellagitannins and abscisic acid. Feijoa ellagitannins

modulate AMPK and JAK2 pathways, potentially via urolithins resulting from microbial biotransformation in the gut [3-5,15-18]. Activation of AMPK enhances glucose uptake in peripheral tissues and improves insulin sensitivity, while JAK2 inhibition has been linked to reduced inflammatory signaling, which is often elevated in metabolic disorders [3].

Abscisic acid improves glucose uptake through LANCL1/2 receptor activation [7,9]. Abscisic acid promotes glucose transport into muscle and adipose tissues independently of insulin, making it particularly relevant in insulin-resistant states [7-9]. This aligns with previous research suggesting that dietary sources of abscisic acid can improve metabolic health and reduce hyperglycemia in diabetes models [8]. However, the small increase in anabolic insulin activity from abscisic acid in the lowest 0.7 mg dose may contribute to the increase in body weight observed in this intervention group. Additional metabolic benefits at higher doses of abscisic acid along with additional bioactive compounds may compensate for the anabolic effect contributing to the weight management observed at the highest 11.6 mg dose.

The presence of xyloglucans in feijoa fruit, which selectively promote *Bacteroides* growth and increase propionate production is another potential mechanism for the lipid-lowering effects observed in this study [10]. This is consistent with extensive research into the benefits provided by dietary fibers in nutraceuticals [18-19]. Short chain fatty acids such as propionate are known to influence hepatic lipid metabolism, reduce LDL cholesterol, and modulate energy balance [11]. The observed increase in HDL cholesterol and reduction in triglycerides and LDL cholesterol in the high dose Feiolix-treated group suggest it may also enhance cholesterol transport, a key protective mechanism against cardiovascular disease. Additional beneficial microbiota modulation may also occur in response to the high levels of polyphenols in Feiolix, many of which will reach the gut due to their tight bonds with fibers (fiber-bound polyphenols) [20-22]

Overall, these findings provide a strong rationale for the usage of Feiolix as a functional food ingredient with potential therapeutic applications in metabolic disorders [23]. This study corresponds with Step 3 of the functional food development framework, in which bioactive compound dosage is determined [24]. Additionally, this study provides foundational data for the comprehensive evaluation of Feiolix as a horticulturally derived replacement or addition to metformin treatment [25-26]. However, limitations in translating animal models to human efficacy should be considered, and the results provided here have been interpreted within a limited body of research, considering the lack of existing research on feijoa fruit for metabolic health. Future studies should explore the long-term effects of Feiolix supplementation, its potential synergistic interactions with other dietary components, and its impact on gut microbiome composition and function in human subjects. These findings align with previous studies on polyphenol-rich plant extracts, which have been shown to improve glucose homeostasis and lipid metabolism.

CONCLUSIONS

Feiolix feijoa freeze-dried whole fruit powder may serve as a natural supplement for managing metabolic dysfunction. A low 300 mg HED may support healthy levels of fasting blood glucose, triglycerides, and cholesterol. Mid-range HED doses of 700 mg and 1500 mg may be less effective than the low 300 mg HED dose at managing fasting blood glucose and triglycerides. A high 2300 mg HED dose may support healthy body weight, fasting blood glucose, triglycerides, cholesterol, LDL cholesterol, HDL cholesterol, and liver health.

Abbreviations: The following abbreviations are used in this manuscript: ND – Non-Diabetic; HFD – High-Fat Diet; FBG – Fasting Blood Glucose; HED – Human Equivalent

Dose; LDL – Low-Density Lipoprotein; HDL – High-Density Lipoprotein

Conflicts of Interest: D.R., A.S., and S.M. were employees of Anagenix Ltd, which manufactures and sells Feiolix powder, at the time of the study. C.G. has been employed by Viridis Biosciences, which stands to receive royalties from any sale of Feiolix, during the study and manuscript preparation.

Author Contributions: Conceptualization, D.R. and S.M.; Methodology, C.G. and A.V.; Formal Analyses, A.S.; Investigation, C.G. and A.V.; Resources, C.G. and A.V.; Writing – original draft preparation, D.R. and S.M.; Writing – Review & Editing, S.M.

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Institutional Review Board Statement: The animal study protocol was approved by the Institutional Animal Ethics Committee (46th IAEC- MVC/IAEC/05 JULY/2020).

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