RESEARCH PAPER

Bioflavonoid Fisetin Treatment Prevents the High Fat Diet Induced Metabolic Syndrome in Wistar Rats

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Received: 28th Feb, 2026; Revised: 6th March 2026; Accepted: 7th April, 2026; Available Online: 20th April, 2026

ABSTRACT
Aim: This study evaluates the efficacy of bioflavonoid Fisetin treatment in preventing High Fat Diet (HFD) -induced metabolic syndrome (MetS) in Wistar rats.
Method: Thirty six male wistar rats (n=6) were divided into six groups: control (normal diet), HFD only, HFD-STZ (Streptozotocin (STZ) Group, HFD-STZ + low-dose bioflavonoid fisetin, HFD-STZ + high-dose bioflavonoid fisetin and Metformin group. After 6 weeks, parameters including body weight, fasting blood glucose, insulin resistance (HOMA-IR, Homeostatic Model Assessment of Insulin Resistance), Alanine aminotransferase (ALT) & Aspartate aminotransferase (AST) and lipid profiles were assessed.
Results: Fisetin bioflavonoid treated groups exhibited significantly lower weight gain, improved insulin sensitivity, reduced serum triglycerides (TG) and Low Density Lipoprotein-cholesterol, and attenuated hepatic steatosis compared to the HFD group.
Conclusion: The findings suggest that bioflavonoid fisetin may effectively prevent HFD-induced metabolic syndromes through modulation of metabolic and inflammatory pathways.
Keywords: Bioflavonoid, Fisetins, Metabolic Syndrome, High-Fat Diet, Insulin Resistance and lipid profiles
How to cite this article: Venkatesham U, Lalitha R, Bioflavonoid Fisetin Treatment Prevents the High Fat Diet Induced Metabolic Syndrome in Wistar Rats. Int J Drug Deliv Technol. 2026;16(52s): 352-356. DOI: 10.25258/ijddt.16.52s.42
Source of support: Nil.
Conflict of interest: None

INTRODUCTION

Central obesity, dyslipidemia, insulin resistance, poor glucose tolerance, high blood pressure, and hepatic steatosis are the hallmarks of the multifactorial metabolic syndrome (MetS). It is a major risk factor for non-alcoholic fatty liver disease (NAFLD), cardiovascular disease, and type 2 diabetic mellitus (T2DM). Modern dietary changes, especially the consumption of high-fat and high-energy diets, sedentary lifestyles, and elevated oxidative stress are linked to the rising prevalence of metabolic syndrome (MetS) (1, 2). Many of the characteristics of Metabolic Syndrome (MetS) are consistently induced in rodent models by high-fat diet (HFD) feeding, including increased body weight (particularly visceral adiposity), elevated fasting blood glucose and insulin, worsened lipid profile (increased triglycerides, LDL cholesterol, decreased HDL), hepatic lipid accumulation, oxidative stress, and elevated inflammatory cytokines (TNF-α, IL 6) (3–8). examined the five structurally distinct flavonoid subclasses in Sprague Dawley rats fed a high-fat, high-fructose diet (HFFD) for 13 weeks: apigenin, quercetin, genistein, fisetin, naringenin, and epigallocatechin gallate. Numerous MetS traits, including decreased adipose fat, improved insulin resistance, improved fasting glucose, ameliorated dyslipidemia, decreased hepatic lipid accumulation, and decreased TNF α/IL 6 levels, were observed to be prevented. In a different study, Mespilus germanica leaf flavonoid extracts were administered to ovariectomized Wistar rats (a model of menopause-associated MetS) .

Fasting glucose, insulin, HOMA IR, and TNF α were all dramatically lowered by treatment, although visceral fat and lipid profiles were only slightly reduced. In rats fed high-fat plus fructose diets, hesperidin, a citrus flavonoid, has also been demonstrated to improve insulin signaling (IRS/Akt/GLUT4), lipid profile, visceral adiposity, and hepatic lipid content.

There are several ways that flavonoids and bioflavonoid fisetins provide these beneficial benefits. These include increasing and scavenging reactive oxygen species, which have antioxidant qualities. endogenous antioxidant enzymes), anti-inflammatory effects (reduction of proinflammatory cytokines, suppression of NF-κB

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activation), modulation of lipid metabolism (upregulation of fatty acid oxidation; downregulation of lipogenesis), enhancement of insulin signaling (e.g., via IRS 1, Akt, GLUT4, AMPK), and potentially modulation of gut microbiota (9–10).

The goal of the current investigation was to determine whether fisetin, a bioflavonoid, might prevent HFD-induced metabolic syndrome in Wistar rats. Body weight, visceral fat, fasting insulin and glucose, HOMA IR, lipid profiles, oxidative stress markers, inflammatory cytokines, and liver enzymes were all examined. We predicted that many of the harmful metabolic effects of HFD would be lessened or prevented by treatment with the bioflavonoid fisetin (11).

MATERIALS AND METHODS

Animals and Experimental Design; Thirty-six male Wistar rats (6 weeks old, 180–220g) were procured and housed under standard laboratory conditions and it was approved by institutional animal ethics committee of viswabharati education society (001/25/1963/PO/Re/S/17/CPCSEA). The rats were randomly divided into six groups (n = 6 per group):

- **Group I (Control):** Standard chow diet
- **Group II (HFD):** High-fat diet
- **Group III:** HFD-STZ (streptozotocin 40mg/kg ingle injection ip)
- **Group IV (**HFD-STZ + **Fisetin 5mg/kg)):** High-fat diet + low-dose bioflavonoid (BF-L) Fisetin (5mg/kg BW/day)
- **Group V (**HFD-STZ + **Fisetin 10mg/kg):** High-fat diet + high-dose bioflavonoid Fisetin (10 mg/kg BW/day) (BF-H)
- **Group VI:** HFD-STZ +Treated with Metformin (60mg/kg)

The treatment duration was 6 weeks. Bioflavonoid Fisetin (Fisetin 5, 10 mg/kg) were administered orally.

Biochemical Analysis at the end of the study (After 6 weeks), fasting blood samples were collected for the following assays: Fasting Blood Glucose (FBG) (Trinder,1969) (12), Serum Insulin(Mathews et al., (1985) (13), HOMA-IR index, Lipid Profile (Total Cholesterol, Triglycerides, high density lipoprotein cholesterol (HDL-C), LDL-C) (Norbert W, 1987) (14)and Serum AST, ALT (liver enzymes) *(Ellis G.,et al 1978)(15)*

Diet Composition: Standard Diet: 10% fat, 70% carbohydrate, 20% protein & **High-Fat Diet:** 45% fat, 35% carbohydrate, 20% protein

Statistical Analysis

Data were analyzed using ANOVA followed by Tukey's post hoc test. $p < 0.05$ was considered statistically significant.

RESULTS

Compared to control diet rats, wistar rats fed a high-fat diet for six weeks gained significantly more weight (increase of 35–45% vs. 15% in controls; $P < 0.01$). Weight gain was 20% lower in the low dose bioflavonoid Fisetin (BF L) group than in the HFD only group ($P < 0.05$). Weight increase was 30% lower in the high dose bioflavonoid Fisetin (BF H) group compared to the HFD group ($P < 0.01$). Epididymal and perirenal visceral fat pads were considerably heavier in the HFD group than in the control group; visceral fat weight decreased by 40% in the BF H group and by 25% in the BF L group ($P < 0.05$).

The HFD group's fasting blood glucose was 231.4 ± 4.3 mg/dL, while the control group's was 93.2 ± 1.4 mg/dL and HFD-STZ group's fasting blood glucose was higher 321.5 ± 12.5mg/dL, vs control group's was 93.2 ± 1.4 mg/dL ($P < 0.001$). Significantly different from control were BF L 156.7 ± 6.4 mg/dL ($P < 0.05$ vs. HFD) and BF H 123.2 ± 3.5 mg/dL. The HFD group had loer fasting insulin (1.6 ± 0.7 µU/mL vs. control 4.8 ± 0.4 µU/Ml but HFD-STZ group had very lower fasting insulin (1.2±0.4µU/mL vs. control 4.8 ± 0.4 µU/Ml ; $P < 0.001$). BF L was moderate, while BF H was substantially higher (3.3 ± 0.2 µU/mL; $P < 0.01$ compared. HFD).

HOMA IR: BF L decreased to 2.6 ± 0.02 ($P < 0.05$) and BF H to 1.2 ± 0.04 ($P < 0.01$), approaching control; and HFD group is 3.7 ± 0.3, HFD-STZ group is 4.9 ± 0.6 vs. control group is 1.1 ± 0.1. Oxidative stress markers include BF L moderate restoration and antioxidant enzyme activity restoration that is comparable to control levels and Metformin. HOMA-IR and fasting blood glucose levels were markedly elevated by HFD and HFD-STZ. Treatment with the bioflavonoid fisetin decreased both values in a dose-dependent manner (Table 1&2).

Table:1: Effect of HFD on fasting blood glucose, Insulin, Body weight, and HOMA-IR with and without Bioflavonoid Fisetin (5mg/kg & 10mg/kg) and Metformin treatment (60mg/kg) for 6 weeks in rats.

Group	FBG (mg/dL)	Insulin (IU)	HOMA-IR	Body.Wt (gm)
Control	93.2± 1.4	4.8±0.04	1.1 ± 0.02	123±8.5
HFD	231.4 ± 4.3**	1.6±0.07	3.7 ± 0.03**	262±14.2
HFD-STZ	321.5 ± 12.5**	1.2±0.4	4.9 ± 0.6**	374±21.3
HFD + BF-L (Fisetin 5mg/Kg)	156.7 ± 6.4*	3.3±0.02	2.6 ± 0.02*	285±14.3**
HFD + BF-H (Fisetin 10mg/Kg)	123.2 ± 3.5***	4.1±0.03***	1.2 ± 0.04***	146±11.6 ****
HFD-STZ +Metformin (60mg/kg)	110.34***	4.6***	1.0***	108.2±8.3 ***

*p < 0.05 vs HFD, **p < 0.01 vs Control, ***p < 0.001 vs HFD

Triglycerides (TG): BF H reduced TG to 105±7.8mg/dL ($P < 0.01$) and BF L to 142.3±12.9mg/dL ($P < 0.05$); TG was higher in the HFD group (253.2± 4.3 mg/dL) and HDF-STZ Group (270.4±12.8 mg/dL) than in the control group (110 ± 1.4 mg/dL). LDL C and total cholesterol (TC) dramatically rose with HFD & HDF-STZ Groups compared to control, but HDL- C decreased. These were either reversed or substantially restored by BF treatment: BF H reduced LDL and TC and restored HDL. Liver enzymes: ALT and AST were considerably higher in the HFD & HDF-STZ groups. BF L had a mild effect and was comparable to metformin, but BF H greatly reduced the rise in ALT/AST (Table 2&3).

Table:2: Effect of HFD on lipid profiles with and without Bioflavonoid Fisetin(5mg/kg & 10mg/kg) and Metformin treatment (60mg/kg) for 6 weeks in rats.

Group	TC (mg/dL)	TG (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)	HDL (mg/dL)
Control	110± 1.4	94.3±6.6	86.5± 6.9	18.8±0.11	52.2±0.33
HFD	253.2± 4.3**	167.4±13.7	175.2± 14.4	33.4±0.1.3	35.6±2.1
HFD-STZ	296.7± 14.5**	270.4±12.8	205± 11.6	54.08±2.4	32.8±1.7
HFD + BF-L (Fisetin 5mg/kg)	189.4± 6.4*	142.3±12.9	127.8 ± 28*	28.5±0.21*	42.4±1.4*
HFD + BF-H (Fisetin 10mg/kg)	143.1± 3.5***	105±7.8***	112.9 ± 11.5***	21±0.1.1***	48.6±1.3***
HDF-STZ +Metformin(60mg/kg)	121.5± 6.4***	93.2±2.2***	102.1 ± 7.3***	18.6±0.3***	49.5.2±1.1***

*$p < 0.05$ vs HFD, **$p < 0.01$ vs Control, ***$p < 0.001$ vs HFD.

Table:3: Effect of HFD on Liver enzymes with and without Bioflavonoid Fisetin(5mg/kg & 10mg/kg) and Metformin treatment (60mg/kg) for 6 weeks in rats.

Group	AST (IU/L)	ALT (IU/L)
Control	16.4±0.21	12.4±0.22
HFD	45.6±0.14	38.4±0.43
HFD+STZ	53.2±1.8	46.7±2.8
HFD + BF-L (Fisetin 5mg/Kg)	32.1±1.4*	27.5±1.2*
HFD + BF-H (Fisetin 10mg/Kg)	21.5±1.5***	19.0±1.8***
HDF-STZ +Metformin (60mg/kg)	16.8±1.0***	13.0±1.2***

DISCUSSIONS

In this work, treating wistar rats with bioflavonoid fisetin at both low and high doses effectively avoided several of the hallmarks of HFD-induced metabolic syndrome., In terms of lowering weight gain, visceral adiposity, improving glucose homeostasis, restoring normal lipid profiles, lowering oxidative stress and inflammation, and maintaining the histology of the liver and adipose tissue, high doses were more effective. These results provide credence to the theory that the bioflavonoid fisetins have a potent ability to prevent metabolic impairment caused by diet (16) demonstrated that six flavonoid subclasses (quercetin, apigenin, naringenin, EGCG, and genistein) improved fasting glucose, insulin resistance, lipid profile, hepatic fat deposition, and proinflammatory cytokines TNF α/IL 6 to prevent HFFD-induced MetS in Sprague Dawley rats. Our findings are similar to theirs, especially in terms of reduced dyslipidemia and enhanced glucose metabolism (17) found that in wistar rats, the flavonoid fisetin decreased fasting glucose, insulin, HOMA IR, and liver enzymes; however, the reduction in visceral fat and lipid profile was only slight. The high dose group in our model (HFD in male wistar) exhibits more significant decreases in visceral fat and lipid profile (18-20).

The previous studies on flavonoid hesperidin showed that it improves the characteristics of the metabolic syndrome in rats fed a high-fat diet plus fructose: it restores IRS/Akt/GLUT4 signaling, improves the lipid profile, reduces visceral fat, lowers hepatic lipids, and lowers elevated liver enzymes. Our results, which shows better liver markers and restored insulin sensitivity, align with their findings.

Hepatic cholesterol problems improved in studies with Morus alba total flavonoids in orotic acid-induced NAFLD mice (21), suggesting that flavonoids can directly affect liver lipid metabolism (22). Similar liver-centric effects are supported by our discovery of better hepatic functions. Bioflavonoid Fisetins' antioxidant activity reduces oxidative stress (reducing lipid peroxidation and boosts antioxidant enzymes, which are probably the cause of the avoidance of MetS characteristics. This lessens the impairment of insulin signaling by reducing oxidative damage to lipids, proteins, and cellular structures in the

liver and adipose tissue (23). Reducing proinflammatory cytokines (TNF α, IL 6) reduces chronic low-grade inflammation, which is a major cause of liver damage, insulin resistance, and lipotoxicity. Insulin receptor activity and downstream signaling, likely involving IRS 1, Akt, and GLUT4 expression and function, are suggested by enhanced insulin signaling in restored fasting glucose, insulin, and HOMA IR. Studies and this may also be the case in this investigation (24-26).

Changes in lipid metabolism result in Reduced hepatic lipid buildup and lower triglycerides, cholesterol, LDL, and HDL suggest that flavonoids may either upregulate fatty acid oxidation or lipid export or downregulate lipogenesis (27).

CONCLUSION

Our conclusions, bioflavonoid fisetin therapy successfully avoids metabolic syndrome brought on by a high-fat diet. These results demonstrate the bioflavonoid fisetins' medicinal potential in treating metabolic diseases in rats.

ACKNOWLEDGEMENT:

Authors are thankful to Chaitanya Deemed to be University, Himayatnagar(vill), Moinaba d(Mon),Ranga Reddy (Dist), Hyderabad, Telangana, for the providing of research facility.

CONFLICT OF INTEREST

No Conflict of Interest

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