

Dietary Supplementation with Powdered *Cucumeropsis mannii* Seeds Mitigates High-Fat Diet–Induced dysmetabolism and Hepatorenal injury in Pubertal RatsDamilola Tunrayo MOGBOJURI¹, Olakunle James ONAOLAPO², Adejoke Yetunde ONAOLAPO^{3*}¹Department of Anatomy, Ladoké Akintola University of Technology, Ogbomoso, Oyo State, Nigeria²Behavioural Neuroscience/Neuropharmacology Unit, Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, Ladoké Akintola University of Technology, Ogbomoso, Oyo State, Nigeria. ojonaolapo@lautéch.edu.ng ORCID: 0000-0003-2142-6046³Behavioural Neuroscience/Neurobiology Unit, Department of Anatomy, Faculty of Basic Medical Sciences, Ladoké Akintola University of Technology, Ogbomoso, Oyo State, Nigeria. ayonaolapo@lautéch.edu.ng ORCID: 0000-0001-7126-7050

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Abstract

High-fat diet (HFD)-induced obesity is associated with metabolic dysfunction, oxidative stress, chronic inflammation, and progressive injury to metabolically active organs including the liver and kidneys. *Cucumeropsis mannii* is an underutilised oilseed rich in bioactive phytochemicals with reported antioxidant and hypolipidaemic properties. This study investigated the protective effects of dietary *C. mannii* supplementation against HFD-induced metabolic, biochemical and histopathological alterations in pubertal male Wistar rats. Sixty-four pubertal male Wistar rats were randomly assigned into eight groups (n = 8/group) receiving standard diet, HFD, *C. mannii* (5%, 10%, or 20%) incorporated into standard diet, or HFD supplemented with corresponding concentrations of *C. mannii* for four weeks. Body weight and feed intake were monitored throughout the study. Serum glucose, insulin, adiponectin, leptin, amylase and lipase were assayed, while hepatic and renal oxidative stress markers (total antioxidant capacity and malondialdehyde) and inflammatory cytokines (TNF- α and IL-10) were determined. Liver and kidney tissues were evaluated histologically using haematoxylin and eosin and periodic acid-Schiff staining. HFD significantly increased body weight, blood glucose, insulin, leptin, amylase, lipase, lipid peroxidation, and TNF- α , while reducing adiponectin, total antioxidant capacity and IL-10 compared with controls (p < 0.05). HFD also produced marked hepatic and renal histopathological lesions characterised by hepatocellular degeneration, sinusoidal disruption, glomerular swelling and tubular injury. Dietary supplementation with *C. mannii* significantly ameliorated these metabolic abnormalities by reducing hyperinsulinaemia, restoring adipokine balance, enhancing antioxidant capacity, suppressing lipid peroxidation and inflammatory responses, and improving hepatic glycogen storage and tissue architecture. Histological examination confirmed concentration-dependent protection of both liver and kidney against HFD-induced injury. Dietary *Cucumeropsis mannii* supplementation protects against HFD-induced metabolic, oxidative and inflammatory damage while preserving hepatic and renal structure. These findings support its potential as a functional food and nutraceutical for the prevention of obesity-associated metabolic

KEYWORDS: *Cucumeropsis manii*, Diet, Inflammation, Lipid dysmetabolism, Metabolism, Nutrients**1. Introduction**

The increasing prevalence of diet-related metabolic disorders has become a major global health challenge [1, 2]. Research from our laboratory has demonstrated severally that diets rich in saturated fats and refined sugars are strongly associated with obesity, dyslipidaemia, insulin resistance, and type 2 diabetes mellitus, all of which contribute to multiple organ dysfunctions [3-9]. The pancreas, liver and kidney play pivotal roles in

maintaining glucose and lipid homeostasis, and their impairment often represents an early event in the pathogenesis of metabolic syndrome [10, 11]. Chronic exposure to a high-fat diet promotes oxidative stress, lipid peroxidation, inflammation, and cellular injury within pancreatic tissue, ultimately leading to biochemical and morphological alterations that compromise both endocrine and exocrine functions [12, 13].

Oxidative stress has been identified as a key biochemical mechanism linking high fat or high sugar dietary patterns to pancreatic injury [14]. Excessive fat and/or sugar intake overwhelms endogenous antioxidant defences, leading to an overproduction of reactive oxygen species (ROS) that damage cellular membranes, proteins, and DNA [15]. These oxidative processes can alter insulin synthesis and secretion, impair β -cell viability, and disrupt enzymatic activities critical for digestion and metabolism [14]. Consequently, strategies aimed at enhancing antioxidant capacity through dietary bioactive compounds have gained increasing research attention [14, 15]. Natural products of plant origin are rich sources of phytochemicals such as flavonoids, phenolic acids, and unsaturated fatty acids, which possess antioxidant and anti-inflammatory properties [16-18]. These bioactive compounds have been shown to modulate redox balance, improve lipid metabolism, and protect tissues from diet-induced toxicity [19, 20]. *Cucumeropsis mannii* (*C. manii*) Naudin (commonly known as white melon or egusi-ito), an underutilised oilseed crop in West Africa [21], is traditionally consumed as food and used in ethnomedicine. The *C. manii* seeds are rich in essential amino acids, unsaturated fatty acids, vitamins, and minerals, and have been reported to exhibit hypolipidaemic, antioxidant, and antidiabetic properties [22]. Despite these beneficial attributes, the potential of *C. mannii* to protect against High fat diet (HFD)-induced hepatic and renal toxicity remains poorly characterised. Understanding the biochemical and morphological effects of *C. mannii* on the liver and kidneys could provide valuable insight into its possible nutraceutical potential as a functional food ingredient. Therefore, this study investigated the protective role of powdered *Cucumeropsis mannii* seed supplementation against HFD-induced hepatic and renal alterations in rats. We hypothesised that *C. mannii* would mitigate oxidative stress, normalise biochemical markers of liver and kidney function, and preserve tissue morphology in the face of diet-induced metabolic toxicity.

2. Materials and Methods

2.1 Chemicals and Drugs

All chemicals and reagents used in this study were of analytical grade and obtained from reputable suppliers. Glucose, Insulin, leptin and amylase assay kits were purchased from Randox Laboratories Ltd (Crumlin, UK). All other reagents were sourced from Sigma-Aldrich (St. Louis, MO, USA).

2.2 Collection and Preparation of *Cucumeropsis mannii* Seeds

Mature *Cucumeropsis mannii* seeds were obtained from a local market in Osun State, southwestern Nigeria, and authenticated at the Department of Pure and Applied Biology, Ladoke Akintola University of Technology (LAUTECH), Ogbomoso, Nigeria. The seeds were washed, air-dried, manually deshelled,

milled into a fine powder, and stored in airtight containers at 4 °C until use. Acute oral toxicity was evaluated in accordance with the Organization for Economic Co-operation and Development (OECD) guidelines.

2.3 Experimental Animals

Pubertal male Wistar rats (90–120 g) were obtained from the Ladoke Akintola University of Technology (LAUTECH) animal facility. Animals were housed in groups in polypropylene cages under controlled environmental conditions (temperature 22 ± 2 °C; 12 h light/dark cycle; relative humidity 50–60%) and had ad libitum access to standard laboratory chow and water during the acclimatisation period. All experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Ethical Committee of the College of Health Sciences, LAUTECH (approval year: 2019).

2.4 Diet

All animals were fed a commercially available standard rodent chow from weaning. At the onset of the experimental period, rats were allocated to receive either standard chow (29% protein, 11% fat, 58% carbohydrate) or a high-fat diet (18% protein, 42% fat, 36% carbohydrate). The high-fat diet was formulated using palm olein and hydrogenated vegetable shortening, as previously described [6-8]. Powdered *Cucumeropsis mannii* was incorporated into either the standard or high-fat diet at 5%, 10%, or 20% (corresponding to 50, 100, and 200 g/kg feed, respectively), following established protocols [23]. All diets were provided *ad libitum* for four weeks.

2.5 Experimental method

Sixty-four pubertal male Wistar rats (90–120 g) were randomly allocated into eight experimental groups ($n = 8$ per group). Group 1 received standard diet (control), Group 2 received high-fat diet (HFD control), Groups 3–5 received *Cucumeropsis mannii* incorporated into the standard diet at 50 g/kg (5%), 100 g/kg (10%), or 200 g/kg (20%), respectively, and Groups 6–8 received *C. mannii* incorporated into the high-fat diet at the same concentrations. Body weight was recorded weekly and feed intake measured daily using a precision balance (Mettler Toledo BD6000, Greifensee, Switzerland). Animals were maintained on their assigned diets for four consecutive weeks. At the end of the experimental period (day 29), animals were fasted overnight, and fasting blood glucose was measured from tail vein blood using the glucose oxidase method. Animals were subsequently euthanised, and blood was collected via intracardiac puncture for the determination of insulin, leptin, adiponectin, amylase, lipase, malondialdehyde, total antioxidant capacity, tumour necrosis factor- α , interleukin-10, and interleukin-1 β . The liver and kidneys were excised, weighed, and processed for routine histological evaluation.

2.6 Biochemical Analysis

Serum glucose, leptin, adiponectin, amylase, lipase, were estimated using standard enzymatic colorimetric methods according to kit protocols. Oxidative stress indices, including malondialdehyde (MDA) levels (an index of lipid peroxidation), and Total antioxidant capacity (TAC), were assayed following standard spectrophotometric methods according to the instructions of the manufacturer. Inflammatory cytokines including interleukin 10, Tumour necrosis factor- α and Interleukin 1 β were assayed following standard techniques as described by the manufacturer.

2.7 Histopathological Examination

Formol-saline fixed liver and kidney tissues were dehydrated in ascending grades of ethanol, cleared in xylene, and embedded in paraffin wax. Sections (5 μ m thick) were cut using a microtome and stained with haematoxylin and eosin (H&E) for general histological evaluation and periodic acid Schiff stains for estimation of glycogen. Slides were examined under a light microscope, and photomicrographs were taken for histomorphometric assessment

2.8 Statistical Analysis

Data was analysed using Chris Rorden's ezANOVA for windows. Hypothesis was tested using analysis of variance (ANOVA). Tukey (HSD) test was used for post-hoc analysis. Results were expressed as mean $\pm$ S.E.M, and $p < 0.05$ considered significant.

3 Result

3.1 Effect of *Cucumeropsis mannii* on body weight

Figure 1 shows the effect of *Cucumeropsis mannii* (CM) on Mean body weight (upper panel) and change in body weight (lower panel). There was a significant [F (7, 72) = 42.5, $p < 0.001$] increase in mean body weight and relative change in body weight in the groups fed CM alone at 5, 10 and 20 %, HFD and HFD/CM at 5 and 10 % compared to control. Compared to HFD, there was a significant decrease in body weight with HFD/CM at 10 and 20 %. Intra-group comparisons revealed a significant decrease in body weight with HFD/CM at 20 % compared to respective group of rats fed CM alone.

3.2 Effect of *Cucumeropsis mannii* on feed intake

Figure 2 shows the effect of *Cucumeropsis mannii* (CM) on Mean Total feed intake (upper panel) and change in feed intake (lower panel). Feed intake decreased significantly [F (7, 72) = 11.2, $p < 0.04$] with HFD/CM at 5% and increased significantly with HFD/CM at 10 and 20 % compared to standard diet control. Compared to HFD, feed intake increased significantly with HFD/CM at 10 and 20%. Intra-group comparisons revealed a significant decrease in feed intake with HFD/CM at 5% and an increase at 10 and 20 % compared to respective group of rats fed CM alone.

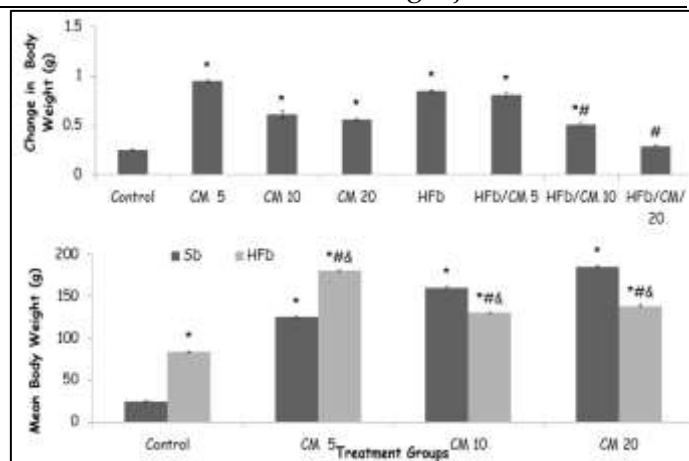


Figure 1: Effect of *Cucumeropsis mannii* on change in body weight (upper panel) and food intake (lower panel). Each bar represents Mean $\pm$ S.E.M, * $p < 0.05$ vs. control, # $p < 0.05$ vs. HFD, & $p < 0.05$ CM alone CM /HFD. Number of rats per treatment group =10. HFD: High fat diet, CM: *Cucumeropsis mannii*.

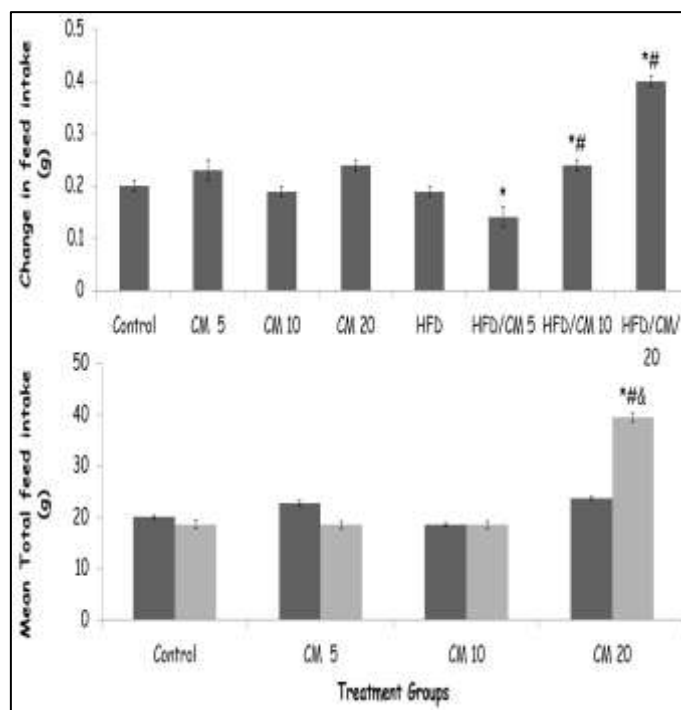


Figure 2: Effect of *Cucumeropsis mannii* on change in body weight (upper panel) and feed intake (lower panel). Each bar represents Mean $\pm$ S.E.M, * $p < 0.05$ vs. control, # $p < 0.05$ vs. HFD, & $p < 0.05$ CM alone CM /HFD. Number of rats per treatment group =10. HFD: High fat diet, CM: *Cucumeropsis mannii*

3.3 Effect of CM on Glucose Homeostasis, Adipokines, and Pancreatic Enzymes Activities

Table 1 shows the effects of dietary supplementation with *Cucumeropsis mannii* (CM) on glucose homeostasis, adipokine concentrations and pancreatic enzyme activities in control and high-fat diet (HFD)-fed rats. Administration of CM alone significantly increased fasting blood glucose levels compared with the control group ($p < 0.05$). Blood glucose increased progressively from 85.33 ± 0.42 mg/dl in the control group to 106.50 ± 1.59 , 107.50 ± 0.67 , and 115.50 ± 1.01 mg/dl in the CM 5%, CM 10%, and CM 20% groups, respectively. In contrast, insulin concentrations showed slight, non-significant reductions

in all CM-treated groups. Adiponectin levels were marginally declined from 10.21 ± 0.13 to 5.65 ± 0.21 mM TE ($p < 0.05$ versus reduced following CM supplementation, whereas leptin control). Concurrently, hepatic MDA increased more than five-fold (35.10 $\pm$ 1.11 μ m versus 6.24 $\pm$ 0.11 μ m in controls), while CM 10% groups relative to control ($p < 0.05$). Serum amylase and renal MDA more than doubled (15.10 $\pm$ 0.10 μ m versus 7.22 $\pm$ lipase activities remained largely unchanged in animals receiving 0.10 μ m), confirming marked oxidative stress following HFD CM alone, indicating that dietary supplementation did not administration. Co-administration of CM significantly attenuated adversely affect pancreatic exocrine function under normal these HFD-induced oxidative changes. Hepatic TAC increased physiological conditions. Feeding rats with HFD produced progressively from 9.18 $\pm$ 0.10 mM TE in the HFD/CM 5% group marked metabolic disturbances. Compared with the control group, to 12.28 $\pm$ 0.11 mM TE in the HFD/CM 20% group, the latter HFD significantly increased fasting blood glucose (127.00 $\pm$ 0.45 approaching the control value. Similarly, renal TAC increased mg/dl), insulin (173.20 $\pm$ 1.08 ng/ml), leptin (8.25 $\pm$ 1.10 ng/ml), significantly in all HFD/CM-treated groups, reaching 13.28 $\pm$ amylase (70.60 $\pm$ 1.10 U/L) and lipase (380.22 $\pm$ 2.50 U/L) ($p < 0.10$ mM TE in the HFD/CM 20% group. In parallel, hepatic 0.05). Conversely, adiponectin levels decreased significantly MDA concentrations were significantly reduced from 35.10 $\pm$ from 26.10 $\pm$ 0.70 to 10.11 $\pm$ 0.10 ng/ml ($p < 0.05$), indicating 1.11 μ m in the HFD group to 22.20 $\pm$ 1.11, 20.50 $\pm$ 1.30, and profound disruption of glucose metabolism, adipokine balance 18.20 $\pm$ 1.21 μ m in the HFD/CM 5%, 10%, and 20% groups, and pancreatic function. Co-administration of CM significantly respectively ($p < 0.05$ versus HFD). Renal MDA levels also ameliorated several HFD-induced metabolic abnormalities. declined significantly following CM supplementation, decreasing Insulin concentrations decreased progressively with increasing to 10.20 $\pm$ 0.10, 10.50 $\pm$ 0.10, and 9.04 $\pm$ 0.11 μ m in the respective CM supplementation, reaching 125.10 $\pm$ 1.12 ng/ml in the treatment groups. Overall, these findings demonstrate that HFD HFD/CM 20% group ($p < 0.05$ versus HFD). Adiponectin induced severe oxidative stress in both hepatic and renal tissues, concentrations increased significantly in all HFD/CM-treated characterised by depletion of endogenous antioxidant capacity groups, while leptin concentrations decreased significantly and increased lipid peroxidation. Dietary supplementation with compared with untreated HFD animals. Blood glucose was *Cucumeropsis mannii* effectively restored antioxidant status and significantly reduced in the HFD/CM 5% and HFD/CM 10% suppressed lipid peroxidation in a concentration-dependent groups relative to HFD alone, although the HFD/CM 20% group manner, with the 20% supplementation producing the greatest showed glucose values comparable to the untreated HFD group. protective effect, particularly in restoring hepatic and renal TAC. Similarly, CM significantly reduced serum amylase and lipase toward normal values.

Table 1: Effect of *C. mannii* on glucose levels, insulin, adiponectin, leptin, amylase and lipase levels

Groups	Glucose (mg/dl)	Insulin (ng/ml)	Adiponectin (ng/ml)	Leptin (ng/ml)	Amylase (U/L)	Lipase (U/L)
Control	85.33 $\pm$ 0.42	88.60 $\pm$ 1.13	26.10 $\pm$ 0.70	2.80 $\pm$ 0.11	25.22 $\pm$ 1.50	148.60 $\pm$ 1.50
CM 5	106.50 $\pm$ 1.59*	78.22 $\pm$ 1.10	24.20 $\pm$ 0.35	2.11 $\pm$ 0.12*	28.10 $\pm$ 1.40	150.10 $\pm$ 1.40
CM 10	107.50 $\pm$ 0.67*	79.10 $\pm$ 1.10	24.10 $\pm$ 0.10	2.15 $\pm$ 0.11*	23.60 $\pm$ 1.20	149.20 $\pm$ 1.20
CM 20	115.50 $\pm$ 1.01*	80.10 $\pm$ 1.20	22.20 $\pm$ 0.20	2.41 $\pm$ 0.10	22.10 $\pm$ 1.20	150.10 $\pm$ 1.20*
HFD	127.00 $\pm$ 0.45*	173.20 $\pm$ 1.08*	10.11 $\pm$ 0.10*	8.25 $\pm$ 1.10*	70.60 $\pm$ 1.10*	380.22 $\pm$ 2.50*
HFD/CM 5	100.33 $\pm$ 1.40*#	155.10 $\pm$ 1.10*#	18.20 $\pm$ 0.10*#	6.32 $\pm$ 1.12*#	53.30 $\pm$ 1.60*#	283.30 $\pm$ 2.50*#
HFD/CM 10	110.50 $\pm$ 1.46*#	140.15 $\pm$ 1.10*#	19.07 $\pm$ 0.10*#	6.11 $\pm$ 1.10*#	50.10 $\pm$ 1.20*#	260.20 $\pm$ 2.10*#
HFD/CM 20	126.00 $\pm$ 0.89*	125.10 $\pm$ 1.12*#	20.01 $\pm$ 0.10*#	5.20 $\pm$ 1.10*#	45.60 $\pm$ 1.50*#	256.60 $\pm$ 2.20*#

Values are presented as Mean $\pm$ S.E.M, * $p < 0.05$ significantly different from control, # $p < 0.05$ significantly different from HFD, CM: *Cucumeropsis mannii*, HFD: high fat diet, number of animals/group-10.

3.4 Effect of *Cucumeropsis mannii* on Hepatic and Renal Oxidative Stress Markers

Table 2 presents the effects of *Cucumeropsis mannii* (CM) supplementation on hepatic and renal oxidative stress markers in control and high-fat diet (HFD)-fed rats. In normal animals, CM supplementation significantly increased hepatic total antioxidant capacity (TAC) at the 5% (17.20 $\pm$ 0.15 mM TE) and 10% (14.10 $\pm$ 0.15 mM TE) concentrations compared with the control group (12.18 $\pm$ 0.23 mM TE; $p < 0.05$). Renal TAC was similarly elevated in the CM 5% (15.18 $\pm$ 0.15 mM TE) and CM 10% (13.15 $\pm$ 0.21 mM TE) groups relative to control (10.21 $\pm$ 0.13 mM TE; $p < 0.05$). Although the CM 20% group showed numerically higher TAC values in both liver and kidney, the increase was not statistically significant in the liver. Hepatic and renal malondialdehyde (MDA) concentrations remained largely comparable to control values in all CM-treated groups, indicating that CM supplementation alone did not induce significant lipid peroxidation. High-fat diet feeding markedly impaired the antioxidant defense system. Hepatic TAC decreased significantly from 12.18 $\pm$ 0.23 to 7.28 $\pm$ 0.11 mM TE, while renal TAC

3.5 Effect of CM on Hepatic and Renal Inflammatory Cytokines

Table 3 presents the effects of dietary supplementation with *Cucumeropsis mannii* (CM) on hepatic and renal inflammatory

cytokines in control and high-fat diet (HFD)-fed rats. Administration of CM alone had little effect on hepatic and renal tumour necrosis factor- α (TNF- α) concentrations compared with the control group. Liver TNF- α values remained comparable to controls across all CM-treated groups, while kidney TNF- α also showed only slight, non-significant reductions. In contrast, CM supplementation significantly increased the anti-inflammatory cytokine interleukin-10 (IL-10) in both liver and kidney tissues ($p < 0.05$). Hepatic IL-10 increased from 28.35 ± 0.40 pg/ml in the control group to 39.20 ± 0.40 , 40.22 ± 0.25 , and 35.12 ± 0.33 pg/ml in the CM 5%, CM 10%, and CM 20% groups, respectively. Similarly, renal IL-10 concentrations were elevated following CM administration, with the greatest increase observed in the CM 10% group (47.22 ± 0.23 pg/ml). High-fat diet feeding induced a pronounced inflammatory response. Hepatic TNF- α increased significantly from 24.35 ± 1.11 ng/L in controls to 87.20 ± 1.50 ng/L in the HFD group ($p < 0.05$), while renal TNF- α increased from 18.10 ± 0.62 to 41.10 ± 0.50 ng/L. Conversely, IL-10 concentrations were significantly reduced in both tissues following HFD administration. Hepatic IL-10 decreased to 18.14 ± 0.44 pg/ml, while renal IL-10 declined to 9.14 ± 0.24 pg/ml, indicating suppression of endogenous anti-inflammatory activity. Co-treatment with CM significantly ameliorated the HFD-induced inflammatory changes. Hepatic TNF- α decreased progressively from 87.20 ± 1.50 ng/L in the HFD group to 65.20 ± 1.33 , 55.20 ± 1.20 , and 48.10 ± 1.30 ng/L in the HFD/CM 5%, 10%, and 20% groups, respectively ($p < 0.05$ versus HFD). A similar concentration-dependent reduction was observed in renal TNF- α , with values decreasing to 35.23 ± 0.52 , 32.04 ± 0.55 , and 27.20 ± 0.30 ng/L following CM supplementation. CM also restored IL-10 concentrations in HFD-fed rats. Hepatic IL-10 increased from 18.14 ± 0.44 pg/ml in the HFD group to 30.22 ± 0.24 , 35.20 ± 0.22 , and 25.22 ± 0.35 pg/ml in the HFD/CM 5%, 10%, and 20% groups, respectively. Likewise, renal IL-10 increased significantly following CM supplementation, reaching 15.20 ± 0.22 , 18.18 ± 0.25 , and 15.22 ± 0.23 pg/ml in the corresponding treatment groups. Although IL-10 levels improved substantially relative to HFD, complete restoration to the values observed in CM-treated normal animals was not achieved at all supplementation levels. Overall, these findings demonstrate that HFD induced marked hepatic and renal inflammation, characterised by elevated TNF- α and suppressed IL-10 production. Dietary supplementation with *Cucumeropsis mannii* significantly attenuated this inflammatory response by suppressing the pro-inflammatory cytokine TNF- α while enhancing the anti-inflammatory cytokine IL-10. The anti-inflammatory effects were generally concentration-dependent for TNF- α , whereas the greatest restoration of IL-10 occurred at the 10% CM supplementation level, suggesting that this concentration may provide the optimal anti-inflammatory benefit.

Table 2: Effect of *C. mannii* on oxidative stress parameters

Groups	LIVER TAC (mM TE)	LIVER MDA (μ m)	KIDNEY TAC (mM TE)	KIDNEY MDA (μ m)
Control	12.18 $\pm$ 0.23	6.24 $\pm$ 0.11	10.21 $\pm$ 0.13	7.22 $\pm$ 0.10
CM 5	17.20 $\pm$ 0.15*	6.80 $\pm$ 0.32	15.18 $\pm$ 0.15*	6.32 $\pm$ 0.10
CM 10	14.10 $\pm$ 0.15*	6.88 $\pm$ 0.41	13.15 $\pm$ 0.21*	5.12 $\pm$ 0.11
CM 20	13.14 $\pm$ 0.13	7.10 $\pm$ 0.22	18.20 $\pm$ 0.21	6.05 $\pm$ 0.10
HFD	7.28 $\pm$ 0.11*	35.10 $\pm$ 1.11*	5.65 $\pm$ 0.21*	15.10 $\pm$ 0.10*
HFD/CM 5	9.18 $\pm$ 0.10**	22.20 $\pm$ 1.11**	10.22 $\pm$ 0.10**	10.20 $\pm$ 0.10**
HFD/CM 10	10.12 $\pm$ 0.25**	20.50 $\pm$ 1.30**	11.32 $\pm$ 0.15**	10.50 $\pm$ 0.10**
HFD/CM 20	12.28 $\pm$ 0.11**	18.20 $\pm$ 1.21**	13.28 $\pm$ 0.10**	9.04 $\pm$ 0.11**

Values are presented as Mean $\pm$ S.E.M, * $p < 0.05$ significantly different from control, ** $p < 0.05$ significantly different from HFD, CM: *Cucumeropsis mannii*, HFD: high fat diet, number of animals per group.

Table 3: Effect of *C. mannii* on inflammatory cytokines

Groups	LIVER TNF- α ng/L	LIVER IL-10 pg/ml	KIDNEY TNF- α ng/L	KIDNEY IL-10 pg/ml
Control	24.35 $\pm$ 1.11	28.35 $\pm$ 0.40	18.10 $\pm$ 0.62	18.22 $\pm$ 0.16
CM 5	23.20 $\pm$ 1.10	39.20 $\pm$ 0.40*	16.10 $\pm$ 0.70	22.20 $\pm$ 0.18*
CM 10	20.22 $\pm$ 0.50	40.22 $\pm$ 0.25*	17.12 $\pm$ 0.90	47.22 $\pm$ 0.23*
CM 20	28.11 $\pm$ 0.10	35.12 $\pm$ 0.33*	19.10 $\pm$ 0.60	33.12 $\pm$ 0.22*
HFD	87.20 $\pm$ 1.50*	18.14 $\pm$ 0.44*	41.10 $\pm$ 0.50*	9.14 $\pm$ 0.24*
HFD/CM 5	65.20 $\pm$ 1.33**	30.22 $\pm$ 0.24	35.23 $\pm$ 0.52**	15.20 $\pm$ 0.22**
HFD/CM 10	55.20 $\pm$ 1.20**	35.20 $\pm$ 0.22*	32.04 $\pm$ 0.55**	18.18 $\pm$ 0.25**
HFD/CM 20	48.10 $\pm$ 1.30**	25.22 $\pm$ 0.35*	27.20 $\pm$ 0.30**	15.22 $\pm$ 0.23**

Values are presented as Mean $\pm$ S.E.M, * $p < 0.05$ significantly different from control, ** $p < 0.05$ significantly different from HFD, CM: *Cucumeropsis mannii*, HFD: high fat diet, number of animals per group.

3.6 Effect of *Cucumeropsis mannii* on Liver histomorphology

Figures 3 and 4 shows representative photomicrographs of haematoxylin & eosin, and periodic acid Schiff (PAS)-stained sections of the liver of rats fed *cucumeropsis mannii* incorporated into control and high fat diet respectively. In the group fed standard diet (Figure 3 and 4 control) sheets of radially arranged hepatocytes with deeply staining nuclei and intervening sinusoids are observed. Scattered within the liver parenchyma are few Kupffer cells with deeply staining nuclei, features are in keeping with normal histology. Slides from sections of the liver of rats in the groups fed *cucumeropsis mannii* incorporated into control diet (Figure 3 and 4 CM 5, 10 and 20%) showed disruption of liver parenchyma, with loss of intervening sinusoidal spaces and degenerating hepatocytes and hepatocyte nuclei. Scattered within the liver parenchyma were micro-vesicles, pale staining and shrunken hepatocyte nuclei and Kupffer cells. Slides from sections of the liver of the group fed HFD (Figure 3 and 4 HFD control) showed marked disruption of liver parenchyma, with loss of intervening sinusoidal spaces and

shrunk hepatocytes; numerous pale-staining shrunken hepatocyte nuclei, Kupffer cells and vesicles; features are in keeping with hepatic injury. Examination of liver slides from the groups fed HFD and *Cucumeropsis mannii* (Figure 3 and 4 HFD+ CM 5, 10 and 20%) revealed a concentration dependent amelioration of changes induced by HFD alone.

PAS and PAS diastase control slides for rats in group fed control diet (figure 5 control), revealed normal liver architecture with hepatocytes that appear mostly mononuclear with cytoplasm stained with coarse granular PAS-positive deposits. In the groups fed *Cucumeropsis* incorporated into control diet at 5, 10 and 20% (Figure 5 CM 5, 10 and 20%), revealed disorganisation of liver architecture with hepatocytes that appear mostly mononuclear with cytoplasm densely stained with coarse granular PAS-positive deposits. Similar deposits were not observed in the diastase-controlled slides these features are in keeping with a concentration dependent increase in glycogen deposits. In the group fed HFD (Figure 5 HFD control), there is also loss of liver architecture with moderate PAS staining, this is in keeping with presence of some glycogen deposits corroborated by loss of staining in the diastase control slide. PAS slide for groups fed *Cucumeropsis mannii* incorporated into HFD (Figure 5 HFD +CM 5, 10 and 20%) concentration dependent reversal of the poor glycogen storage observed with HFD alone.

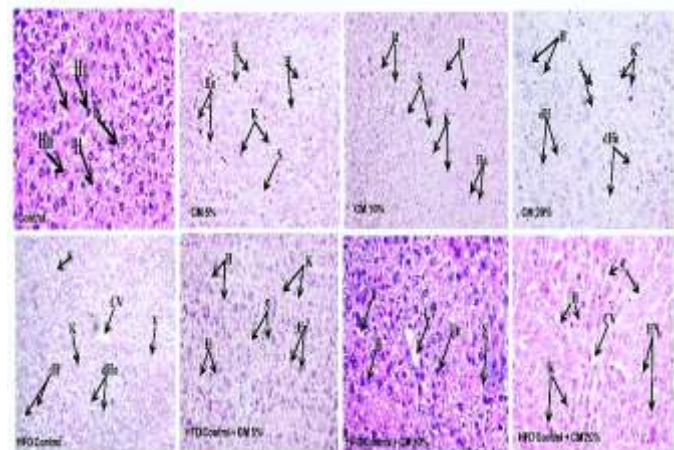


Figure 3: Effect of *Cucumeropsis mannii* on the liver. Representative photomicrographs of hematoxylin and eosin (H&E) stained sections of the mouse liver showing central vein (CV), Hepatocyte (H), nucleus of the hepatocytes (Hn), Sinusoids (S), degenerating hepatocyte (dH) and hepatocyte nuclei (dHn). Magnification: x160,

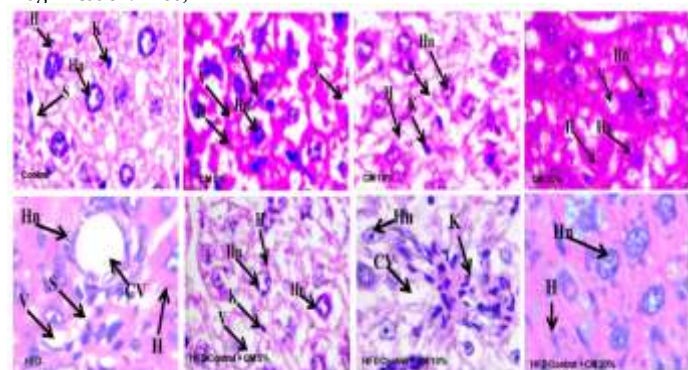


Figure 4: Effect of *Cucumeropsis mannii* on the liver. Representative photomicrographs of hematoxylin and eosin (H&E) stained sections of the mouse liver showing central vein (CV), Hepatocyte (H), nucleus of the

hepatocytes (Hn), Sinusoids (S), degenerating hepatocyte (dH) and hepatocyte nuclei (dHn), Magnification: x560

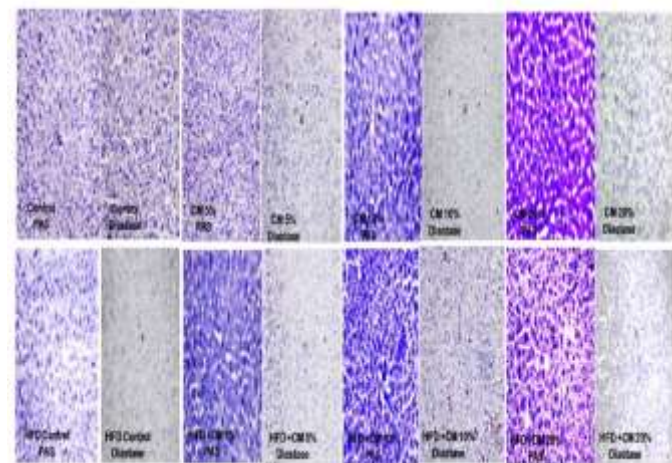


Figure 5: Effect of *Cucumeropsis mannii* on the liver. Representative photomicrographs of periodic acid Schiff (PAS) and diastase control-stained sections of the mouse liver, x100.

3.7 Effect of *Cucumeropsis mannii* on Renal histomorphology

Figures 6 and 7 show representative photomicrographs of haematoxylin and eosin (H&E)-stained sections of the kidneys of rats fed standard diet, *Cucumeropsis mannii* (CM), high-fat diet (HFD), or HFD supplemented with CM. Kidney sections from the control group exhibited normal renal histoarchitecture characterised by a clear distinction between the renal cortex and medulla, with well-preserved renal corpuscles containing intact glomeruli enclosed within Bowman's capsules. Bowman's spaces were clearly defined, while the proximal and distal convoluted tubules possessed intact epithelial linings with deeply stained nuclei, indicating normal cellular morphology. Similarly, sections from rats receiving CM alone (5%, 10%, and 20%) maintained normal renal architecture comparable to the control group. The renal corpuscles remained intact with well-defined Bowman's capsules and Bowman's spaces. The glomeruli exhibited normal cellularity, while the proximal and distal tubules retained normal epithelial organisation with no obvious evidence of tubular degeneration, inflammatory cell infiltration, or structural distortion, indicating that dietary CM did not adversely affect renal morphology. In contrast, kidneys from the HFD group showed marked histopathological alterations. This included distortion of the normal renal architecture characterised by enlarged and congested glomeruli, narrowing or partial obliteration of Bowman's space, and disruption of Bowman's capsule. The tubular epithelium appeared disorganised with areas of tubular contraction and degeneration. Both glomerular and tubular epithelial nuclei appeared pale staining, suggesting cellular injury. These features are consistent with HFD-induced renal damage. Dietary supplementation with CM attenuated the renal lesions induced by HFD in a concentration-dependent manner. In the HFD + CM 5% group, partial restoration of renal architecture was observed, with improved definition of Bowman's spaces, reduced glomerular enlargement, and preservation of tubular epithelial cells compared with the HFD group. The HFD + CM 10% group demonstrated further improvement, characterised by

well-preserved renal corpuscles, restoration of Bowman's spaces, and improved tubular organisation with increased numbers of deeply stained glomerular and tubular epithelial nuclei. The HFD + CM 20% group exhibited the greatest degree of recovery, with renal histology closely resembling that of the control animals. Glomeruli appeared well organised within intact Bowman's capsules, Bowman's spaces were largely restored, and the proximal and distal tubules displayed preserved epithelial architecture with minimal evidence of degeneration. Overall, histological examination demonstrated that chronic HFD feeding induced significant renal structural damage characterised by glomerular and tubular injury, whereas dietary supplementation with *Cucumeropsis mannii* provided marked, concentration-dependent nephroprotection. The highest dietary concentration (20%) produced the greatest preservation of renal architecture, corroborating the improvements observed in oxidative stress and inflammatory biomarkers.

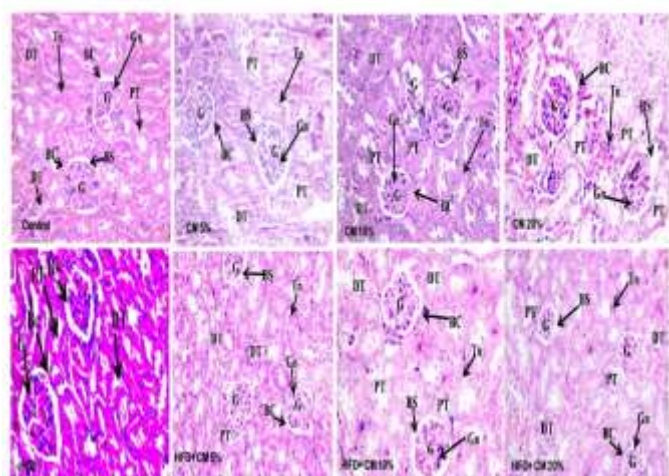


Figure 6: Effect of *Cucumeropsis mannii* on the kidney. Representative photomicrographs of haematoxylin and eosin (H&E) stained sections of the mouse kidney showing; Bowman's capsule (BC), Bowman's space (BS) glomerulus (G), Distal tubule (DT), Proximal tubules (PT), nucleus of the glomerulus (Gn), tubular cell nucleus (Tn) Magnification: X160.

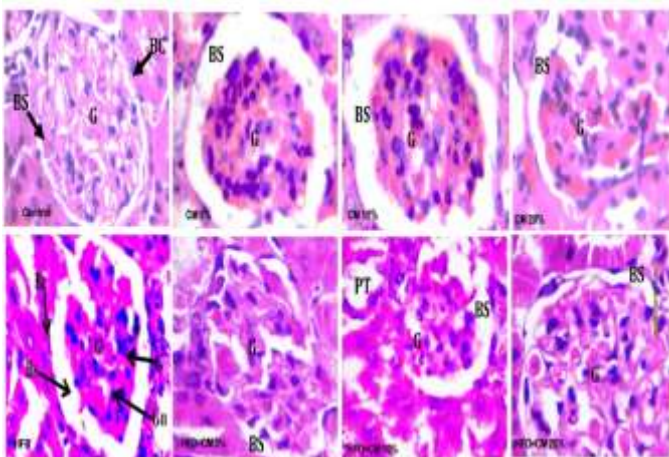


Figure 7: Effect of *Cucumeropsis mannii* on the kidney. Representative photomicrographs of haematoxylin and eosin (H&E) stained sections of the mouse kidney showing; Bowman's capsule (BC), Bowman's space (BS) glomerulus (G), Distal tubule (DT), Proximal tubules (PT), nucleus of the glomerulus (Gn), tubular cell nucleus (Tn) Magnification: X560.

Discussion

The present study demonstrates that dietary supplementation with *Cucumeropsis mannii* (CM) substantially attenuates high-fat diet (HFD)-induced metabolic, oxidative, inflammatory, and histopathological alterations in pubertal male Wistar rats. Chronic consumption of HFD produced the expected metabolic phenotype characterised by increased body weight, hyperglycaemia, hyperinsulinaemia, adipokine dysregulation, elevated pancreatic enzymes, increased oxidative stress, heightened inflammatory responses, and marked hepatic and renal structural damage. Supplementation with powdered *C. mannii* ameliorated many of these abnormalities, suggesting that the seed possesses significant antioxidant, anti-inflammatory and tissue-protective properties capable of mitigating diet-induced metabolic injury.

One of the earliest manifestations of HFD feeding observed in this study was excessive body weight gain. This finding is consistent with previous reports demonstrating that diets rich in saturated fats promote positive energy balance, adipose tissue expansion and obesity through increased caloric intake and altered lipid metabolism [24–26]. Interestingly, although CM supplementation alone slightly increased body weight in animals receiving standard diet, supplementation of the HFD significantly reduced weight gain at the higher inclusion levels. The reduction in body weight despite continued HFD feeding suggests that *C. mannii* may improve energy utilisation, reduce lipid accumulation or enhance metabolic efficiency. The high content of unsaturated fatty acids, dietary fibre and plant phytochemicals present in *C. mannii* seeds may improve lipid oxidation and reduce adipogenesis, thereby limiting excessive weight gain [22, 23].

Alterations in glucose homeostasis observed in HFD-fed animals further confirm successful induction of metabolic dysfunction. Hyperglycaemia accompanied by marked hyperinsulinaemia is characteristic of insulin resistance, where peripheral tissues become less responsive to insulin, forcing pancreatic β -cells to increase insulin secretion in an attempt to maintain glucose homeostasis [27–29]. The significant reduction in circulating insulin concentrations following CM supplementation indicates improved insulin sensitivity, even though complete normalisation of blood glucose was not consistently observed at the highest dietary concentration. Interestingly, the antihyperglycaemic response appeared most pronounced at the lower supplementation level, suggesting that the metabolic actions of CM may exhibit a biphasic or non-linear dose-response relationship. Such responses have previously been reported for several nutraceuticals where higher concentrations may activate additional metabolic pathways that partially counterbalance glucose-lowering effects [30–32]. Nevertheless, the reduction in hyperinsulinaemia suggests improved peripheral insulin responsiveness, which may represent one of the principal mechanisms underlying the protective effects of *C. mannii*.

The observed changes in adipokines further support an improvement in metabolic homeostasis. High-fat feeding markedly reduced adiponectin while increasing leptin concentrations, findings that are widely recognised as hallmarks of obesity-associated chronic inflammation and leptin resistance

[33, 34]. Adiponectin enhances insulin sensitivity, stimulates fatty acid oxidation and suppresses inflammatory signalling, whereas persistent hyperleptinaemia reflects impaired leptin signalling despite increased adipose tissue mass [35]. Restoration of adiponectin together with progressive reduction in leptin following CM supplementation suggests improved adipose tissue function and reduced systemic metabolic inflammation. These findings are particularly important because adipokine imbalance contributes substantially to the progression of metabolic syndrome and multiple organ injury.

Another important observation was the significant elevation of serum amylase and lipase following HFD exposure. Although these enzymes are commonly used as indicators of pancreatic injury, increasing evidence suggests that chronic metabolic overload may induce exocrine pancreatic dysfunction through oxidative stress, inflammatory infiltration and lipotoxicity [36, 37]. The ability of CM to significantly reduce circulating amylase and lipase activities suggests preservation of pancreatic integrity and attenuation of pancreatic stress. This protective effect may be secondary to reduced oxidative damage and improved insulin sensitivity, both of which reduce metabolic burden on pancreatic tissue.

Oxidative stress represents one of the central mechanisms responsible for HFD-induced organ dysfunction, and the present findings strongly support this concept [22, 23]. HFD markedly reduced total antioxidant capacity while simultaneously increasing hepatic and renal malondialdehyde concentrations, indicating depletion of endogenous antioxidant defenses and enhanced lipid peroxidation [24]. Excessive production of reactive oxygen species during obesity overwhelms antioxidant systems, leading to oxidation of membrane lipids, mitochondrial dysfunction and cellular injury [36, 37]. CM supplementation significantly restored antioxidant capacity while reducing lipid peroxidation in both liver and kidney tissues, with the greatest protection observed at the highest dietary concentration. These findings indicate potent antioxidant activity that is likely attributable to the abundance of phenolic compounds, tocopherols, unsaturated fatty acids and other bioactive constituents naturally present in *C. mannii* seeds [22, 24]. Restoration of redox homeostasis probably represents one of the major mechanisms through which CM protects metabolically active organs against HFD-induced injury.

Inflammation closely interacts with oxidative stress in the pathogenesis of obesity-related tissue injury. In agreement with previous studies, HFD markedly increased TNF- α while suppressing IL-10 expression in both hepatic and renal tissues [19, 24]. TNF- α is a major pro-inflammatory cytokine that promotes insulin resistance through serine phosphorylation of insulin receptor substrate proteins while simultaneously stimulating oxidative stress and apoptosis [38]. Conversely, IL-10 is an anti-inflammatory cytokine that suppresses macrophage activation and limits excessive inflammatory responses [39]. *Cucumeropsis Manii* significantly reduced TNF- α concentrations while restoring IL-10 expression, indicating effective modulation of inflammatory signalling. Although IL-10 responses did not increase linearly with dose, all treatment groups demonstrated substantial improvement compared with untreated HFD animals. These findings suggest that *C. mannii*

may suppress activation of inflammatory pathways such as nuclear factor-kappa B (NF- κ B), thereby reducing cytokine production and limiting tissue injury [40, 41].

The histopathological findings strongly corroborate the biochemical observations. Liver sections from HFD-fed animals demonstrated marked disruption of hepatic architecture characterised by hepatocyte degeneration, sinusoidal collapse, vesicular changes and nuclear pyknosis, features consistent with diet-induced hepatic steatosis and early non-alcoholic fatty liver disease [42, 43]. Similarly, kidney sections exhibited glomerular swelling, narrowing of Bowman's space, tubular contraction and epithelial degeneration, indicating obesity-associated nephropathy. These structural alterations are well recognised consequences of prolonged oxidative stress, chronic inflammation and lipid accumulation [44, 45]. Dietary supplementation with CM produced concentration-dependent restoration of normal hepatic and renal architecture, with preservation of hepatocytes, glomeruli and tubular epithelial cells. These morphological improvements parallel the reductions observed in oxidative stress and inflammatory biomarkers, further supporting the cytoprotective effects of the seed.

The periodic acid-Schiff staining findings provide additional evidence for improved hepatic metabolic function. HFD feeding disrupted glycogen distribution within hepatocytes, whereas CM supplementation restored hepatic glycogen deposition in a concentration-dependent manner. Improved glycogen storage suggests enhanced hepatic insulin responsiveness and more efficient glucose utilisation. This observation agrees with the improved adipokine profile and reduced hyperinsulinaemia observed following CM supplementation and further supports improved metabolic regulation.

An interesting observation from the present study was that CM administered alone produced modest elevations in blood glucose despite improving antioxidant and inflammatory status. This finding may reflect the relatively high caloric density of the seed or adaptive metabolic responses associated with increased dietary lipid availability rather than direct toxicity. Importantly, these changes were not accompanied by oxidative stress, inflammatory activation or significant histopathological abnormalities, suggesting that under physiological conditions CM remains relatively safe while exerting favourable antioxidant effects. Nevertheless, this observation warrants further investigation to determine the optimal dietary concentration capable of maximising metabolic benefits without influencing glycaemic control.

Collectively, the findings of this study suggest that the beneficial effects of *C. mannii* involve multiple complementary mechanisms, including enhancement of endogenous antioxidant defense systems, suppression of lipid peroxidation, modulation of inflammatory cytokines, restoration of adipokine balance, improvement of insulin sensitivity and preservation of hepatic and renal structural integrity. Such multitarget actions are characteristic of functional foods rich in naturally occurring phytochemicals and support the growing interest in nutraceutical interventions for obesity-related metabolic disorders.

One limitation of the present study is that the molecular pathways responsible for these protective effects were not

directly investigated. Assessment of signalling molecules involved in oxidative stress and inflammation, including nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor-kappa B (NF- κ B), AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma (PPAR- γ), together with detailed phytochemical characterisation of the seed, would provide greater mechanistic insight. In addition, longer treatment durations and evaluation of hepatic and renal functional biomarkers such as alanine aminotransferase, aspartate aminotransferase, creatinine and urea would further strengthen the translational relevance of these findings.

Conclusion

In conclusion, dietary supplementation with *Cucumeropsis mannii* effectively mitigated HFD-induced metabolic disturbances, oxidative stress, inflammatory activation and histopathological injury in the liver and kidney of pubertal rats. The findings support the potential use of *C. mannii* as a functional food or nutraceutical capable of protecting against obesity-associated metabolic organ damage through integrated antioxidant, anti-inflammatory and metabolic regulatory mechanisms. Further mechanistic and clinical investigations are warranted to establish its therapeutic potential in the prevention and management of metabolic syndrome and its complications.

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Availability of data and materials

Data generated during and analysed during the course of this study are available from the corresponding author on request.

Competing interests

All authors of this paper declare that there is no conflict of interest related to the content of this manuscript.

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