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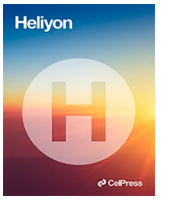

Antioxidant and antilipidemic action of ketogenic diet and tomato powder mix in high sugar and fat fed Harwich fruit flies

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ABSTRACT

Numerous studies have demonstrated the role of oxidative stress in metabolic disorders which presents as a major global problem. The antioxidant properties of the tomato fruit and the ketogenic diet has likewise been established by different authors. This study uses a fruit fly model to examine the synergistic effect of a ketogenic diet and tomato powder mix on biochemical alterations induced by the High-Fat Diet (HFD) and the High-Sugar Diet (HSD). Six groups of male fruit flies consisting of fifty flies per vial were administered Normal Diet (ND), High-Fat Diet (HFD), High Sugar Diet (HSD), Ketogenic Diet (KD), Tomato Powder-mix (TP), and HSD + HFD, for ten days. Further treatment of KD and TP was administered to group six vials to constitute groups seven to nine: HSD + HFD + KD, HSD + HFD + TP, and HSD + HFD + KD + TP for another five days. Biochemical parameters of oxidative stress were analyzed in the fly homogenates using standard procedures. There were significant increases ($P < 0.05$) in the concentration of malondialdehyde, total cholesterol, LDL-Cholesterol, Triglycerides, atherogenic index, nitric oxide, total weight gained, and a significant decrease ($p < 0.05$) in levels of catalase and HDL-Cholesterol in flies treated with HF and HS diets. Further administration of KD and TP to the flies for five days reversed most of the parameters to near control values. The KD diet combination with TP however gave the best ameliorative changes. The dietary model may therefore be effective as adjuvant therapy for the management of metabolic disorders developed and made progressive by oxidative stress and hyperlipidemia.

1. Introduction

Metabolic syndrome has been estimated to affect over a billion people worldwide and is more common in women than men of all ages and races [1,2]. The metabolic syndrome, which increases the risk of some metabolic diseases like cancers, type 2 diabetes mellitus, and cardiovascular diseases that are responsible for mortality, morbidity, and disability all over the world, is a collection of interrelated physiological, biochemical, clinical, and metabolic factors [3]. Hyperglycemia, dyslipidemia, hypertension, and obesity are independent risk factors that have been connected to clinical and public health perspectives [4]. The phenotypic appearance of these factors, which are connected to insulin resistance, is typically brought on by weight gain, particularly fat storage around the waist [5]. According to Arulselvan [6] and Panchal [4], metabolic syndrome complications such as Diabetes mellitus (type 2), obesity, cardiovascular disease, stroke, and myocardial infarction are linked to oxidative stress and inflammation. Oxidative stress and inflammation in the cell are linked to the onset and progression of metabolic diseases [7,8]. The perturbation in the equilibrium

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between oxidant formation (Reactive Nitrogen Species (RNS), Free Radicals (FR), and Reactive Oxygen Species ROS) and available endogenous antioxidants lead to excessive radicals that cause cell damage (oxidative stress) [9]. Oxidative stress has been connected to diseases like rheumatoid arthritis, cardiovascular diseases, ischemia/perfusion injuries, neurodegenerative diseases, and ageing amongst others [10–12].

Decreasing the incidence and mortality rate of metabolic diseases is a global objective [13]. Most times non-pharmacological therapies-lifestyle modifications like dietary adjustment (in terms of caloric restriction, improved quality of food taken, reduction in consumption), increased physical activity, decrease in tobacco smoking, alcohol consumption, and increased intake of vegetables and fruits are often used as the primary intervention which are cheaper, safer with no toxicity but often, not effective enough [12,14]. The use of pharmacological therapies; surgery, medications, chemotherapy, and immunotherapy becomes obligatory but it may also come with higher costs, unwanted side effects, and effectiveness in the long run [8,15]. Consequently, improving the non-pharmacological therapies, especially the dietary aspect may increase the effectiveness and also serve as a preventive measure for those genetically predisposed to the development of these diseases if the global objective is to be achieved.

Research has shown that a diet known as a "ketogenic diet" with increased fat, moderate protein, and reduced carbohydrate has therapeutic effects on epilepsy management for over a century, as well as amelioration of some metabolic diseases [16].

Tomatoes are a globally popular vegetable consumed in a variety of ways due to their high nutritional content, which has been shown to be associated with a lower risk of developing metabolic disorders like cardiovascular diseases (along with disorders like coronary heart diseases, dyslipidemia, and myocardial infarction) [17,18], obesity (along with diseases like hypertension, type 2 diabetes mellitus, atherosclerosis) [19] and cancer (including pancreatic, uterine, prostate, breast, and lungs cancers) [20,21]. The health benefits of tomato have been linked to lycopene, which is its most abundant bioactive compound [22,23]. The research aimed to develop an effective nutritional remedy option for the management of metabolic syndrome by exploring a ketogenic diet and tomato powder mix, which is relatively safe and affordable.

2. Material and methods

2.1. Experimental animals

The *Drosophila melanogaster* Harwich strain stock was purchased from the Drosophila laboratory of the Department of Biochemistry, University of Ibadan, Nigeria. The flies were allowed to habituate for 7 days in the Biochemistry post-graduate laboratory at Mountain Top University in Ogun State with a 12-h light/dark cycles, and a temperature range of 20–22 °C. They were reared on the standard cornmeal medium containing 1% w/v brewer's yeast, 1% w/v agar, and 0.08% w/v nipagin.

2.2. Diets preparation

2.2.1. Ketogenic diet preparation

This was prepared according to the method of Kayode [24] with slight modifications. Fish powder (5.2 g), Food binder (5.2 g), Coconut oil (4 mL), Yeast (5.2 g), and Cabbage flour (104 g), were measured and added to boiling 1000 mL of water and allowed to cook for 5 min, 1 g of Nipagin dissolved in ethanol was added and mixed thoroughly, it was thereafter poured into clean glass vials and allowed to cool before administration to the flies.

2.2.2. High-fat diet preparation

The High-Fat Diet was prepared according to Kayode [24] with slight modifications from the Corn meal medium (basal diet/control diet) containing Agar (1% w/v), Brewer's yeast (1% w/v), and Nipagin (0.08% v/w). Coconut oil (33% v/w) was added to 1.8 g of basal diet mixed thoroughly into clean glass vials and allowed to cool before administration to the flies.

2.2.3. High-Sugar Diet preparation

The High Sugar Diet was prepared according to Kayode [24] from Corn meal medium (basal diet/control diet) containing Agar (1% w/v), Brewer's yeast (1% w/v), and Nipagin (0.08% v/w). Sucrose (0.25 M, 50% v/w) was added to 1.8 g of basal diet mixed thoroughly into clean glass vials and allowed to cool before administrations to the flies.

2.2.4. Tomato powder mix diet preparation

The Tomato Powder Diet was prepared according to Kayode [24] with slight modification from the corn meal medium (basal diet/control diet).containing Agar (1% w/v), Brewer's yeast (1% w/v), and Nipagin (0.08% v/w). Tomato powder mix (20% w/v) was added to 1.8 g of basal diet mixed thoroughly into clean glass vials and allowed to cool before administration to the flies.

2.3. Experimental design

Six groups of male fruit flies consisting of fifty flies per vial (except group six which consisted of two hundred fruit flies) were administered Normal Diet (ND), High-Fat Diet (HFD), High Sugar Diet (HSD), Ketogenic Diet (KD), Tomato Powder-mix (TP), and HSD + HFD, for fifteen days. On day ten, group six was further divided into four groups where one of the groups still maintained the HSD + HFD group and the remaining three new groups were administered the KD and TP treatments to constitute groups seven to nine: HSD + HFD + KD, HSD + HFD + TP and HSD + HFD + KD + TP for the remaining five days.

2.4. Homogenisation

The administrations lasted for 15 days after which the flies were anaesthezisedd in ice, weighed, and homogenized in 0.1 M phosphate buffer saline PBS (pH 7.4) with a dilution factor of 1 mg–10 μL (μl). The homogenate was spun at 5000 g for 10 min at 4 °C using thermoscientific Heraeus megafuge 8R (TX-150) centrifuge. The supernatant was collected and stored at 4 °C prior to further biochemical analysis [24].

2.5. Evaluation of biochemical parameters

The nitric oxide concentration was determined following the procedure described by Ding [25], and catalase activity was analyzed according to the method of Beer and Sizer [26] Lipid peroxidation (Malondialdehyde concentration) was determined according to the method described by Varshney and Kale ([27]. Lipid profiles (total cholesterol, triglycerides and High-density lipoproteins (HDL) were analyzed using Randox kits (Randox limited, County Antrim, United Kingdom). Low-density lipoprotein and atherogenic index were calculated from the other lipid profile results[28].

$$\text{LDL} = \text{total cholesterol} - \frac{\text{triglyceride}}{5} - \text{HDL (Randox kit)}$$

$$\text{Atherogenic index (AI)} = \frac{\text{Log triglycerides}}{\text{HDL}}$$

2.6. Statistical analyses

Data are expressed as the mean ± SEM (standard error mean) (n = 5) Significant differences between the control and the diet groups were determined using one-way analysis of variance (ANOVA), followed by the Duncan post hoc test using SPSS, version 2020. Values of $P < 0.05$ was considered statistically significant for all calculations.

3. Results

KD & TP treatments and combination significantly ($p < 0.05$) reduced the weight of the HSD + HFD fed flies; significantly ($p < 0.05$) decreased weight in KD &TP flies and no significant difference in TP treatment when compared to the control (Fig. 1).

KD and TP treatments and combination significantly ($p < 0.05$) increased the catalase activity in HSD + HFD flies and no significant difference in TP treatment, KD and TP administration when compared with the control (Fig. 2).

A significant elevated ($p < 0.05$) malondialdehyde level was observed in HSD, HFD, and HSD + HFD group (Fig. 3), and combined-fed flies (Fig. 3), when compared to KD, TP administration, treatment and combination-fed flies with respect to their controls.

The KD, TP treatments and combinations significantly ($p < 0.05$) reduced the concentration of the total cholesterol in the HSD + HFD fed flies (Fig. 4), with no significant difference between HSD and TP treatment, combined treatment, KD and TP when compared to the control.

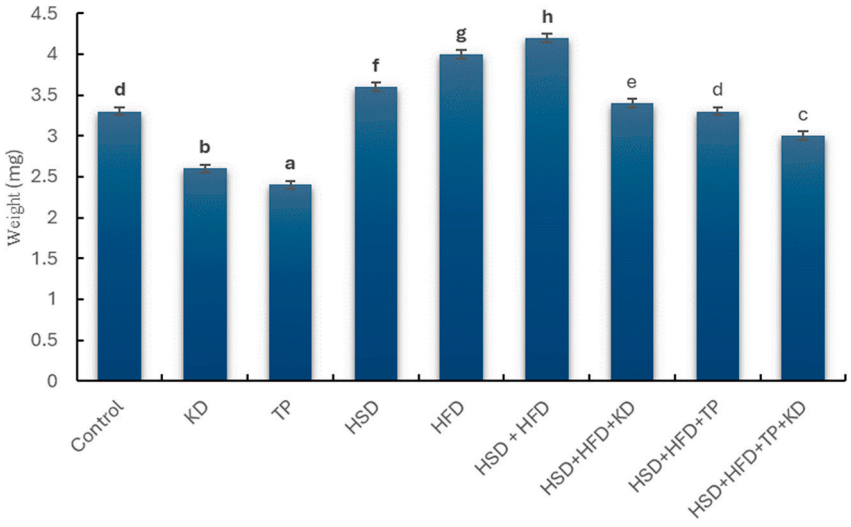

Fig. 1. Effect of KD and TP on the weight of high sugar and fat-fed fruit flies.
Values are expressed as mean ± SEM. KD: ketogenic diet; TP: tomato powder mix; HSD: high sucrose diet; HFD: high-fat diet. Subscript a-g, values from lowest to highest show the class of variance between the groups' significance at $p < 0.05$ versus control.

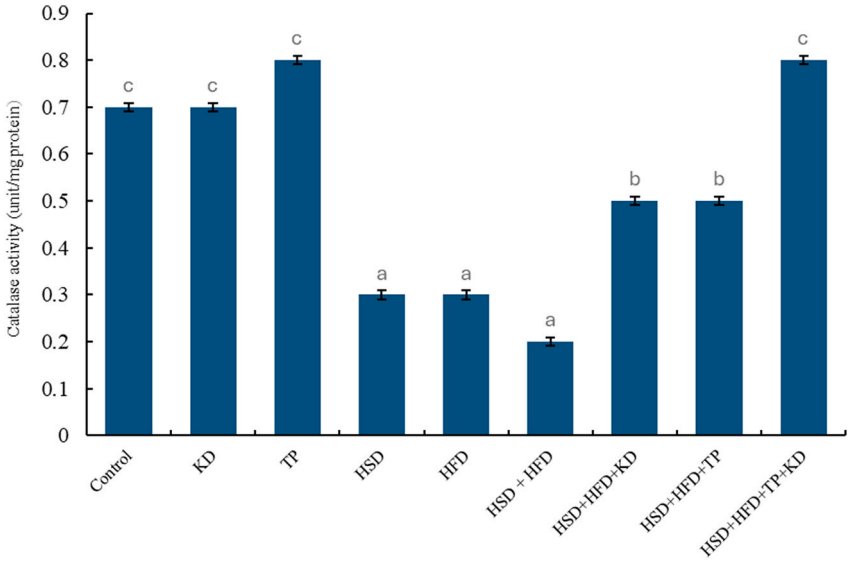

Fig. 2. Effect of KD and TP on catalase activities of high sugar and fat-fed fruit flies.
Values are expressed as mean ± SEM. KD: ketogenic diet; TP: tomato powder mix; HSD: high sucrose diet; HFD: high-fat diet. Subscript a-c, values from lowest to highest show the class of variance between the groups' significance at $p < 0.05$ versus control.

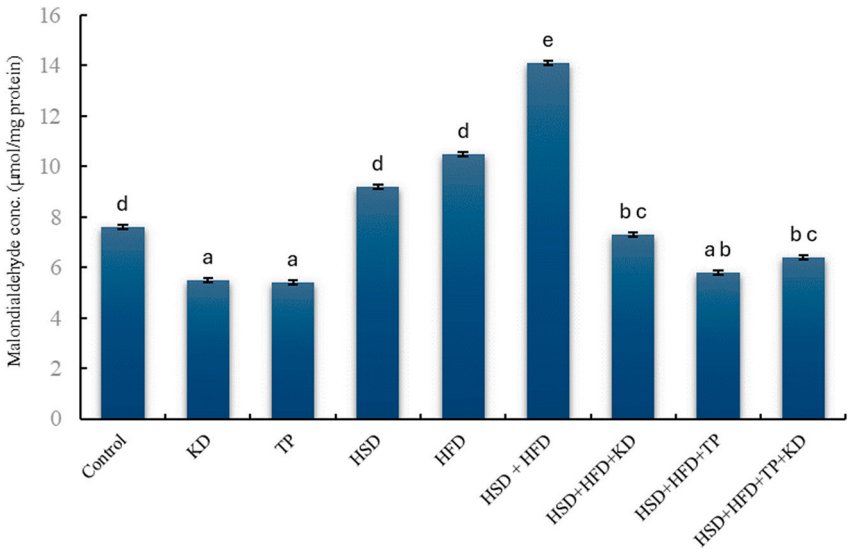

Fig. 3. Effect of KD and TP on Malondialdehyde concentration of high sugar and fat-fed fruit flies.
Values are expressed as mean ± SEM. KD: ketogenic diet; TP: tomato powder mix; HSD: high sucrose diet; HFD: high-fat diet. Subscript a-d, values from lowest to highest show the class of variance between the groups' significance at $p < 0.05$ versus control.

In Fig. 5, KD, TP treatment and their combination significantly ($p < 0.05$) reduced the concentration of triglycerides in HSD + HFD fed flies to an insignificant difference; KD, TP administration also showed no significant difference when compared to the control. The KD, TP administration and treatment groups significantly ($p < 0.05$) increased the concentration of HDL in HSD + HFD fed flies (Fig. 6), with insignificant differences in the TP group and decreased levels in HSD, HFD fed flies compared to their respective controls. KD, TP combined treatment significantly ($p < 0.05$) reduced the LDL concentration in the HSD + HFD fed flies and no significant difference in the KD & TP administration groups when compared with their controls (Fig. 7).

Atherogenic Index significantly ($p < 0.05$) decreased in KD & TP treatments and combination in HSD + HFD fed flies, with no significant difference in TP administration and significantly increased when compared with the control (Fig. 8). KD &TP treatments and combination significantly ($p < 0.05$) reduced the nitric oxide (NO) concentration in HSD + HFD fed flies, reduced in HFD, KD & TP administered flies and insignificant difference in the combined treatment when compared to the control (Fig. 9).

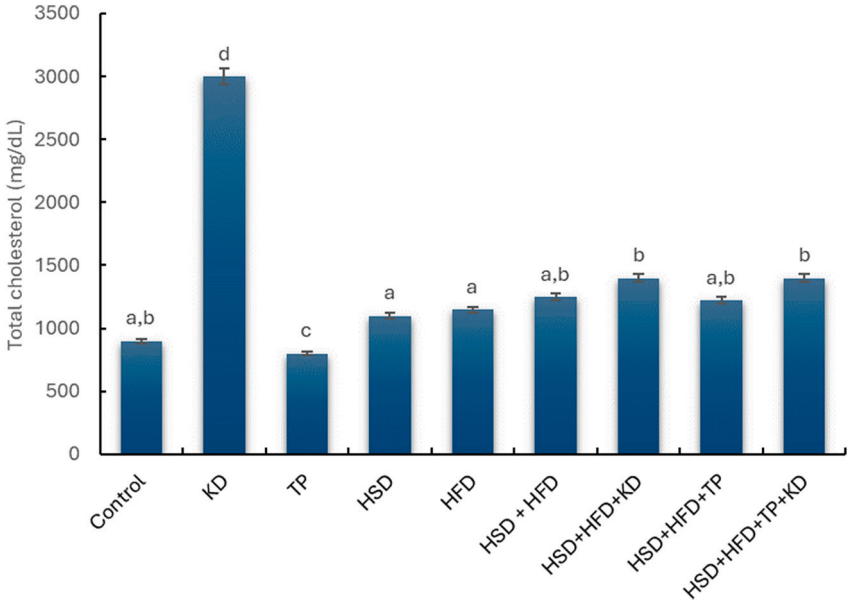

Fig. 4. Effect of KD and TP on the total cholesterol concentration of high sugar and fat-fed fruit flies.
Values are expressed as mean ± SEM. KD: ketogenic diet; TP: tomato powder mix; HSD: high sucrose diet; HFD: high-fat diet. Subscript a-d, values from lowest to highest show the class of variance between the groups' significance at $p < 0.05$ versus control.

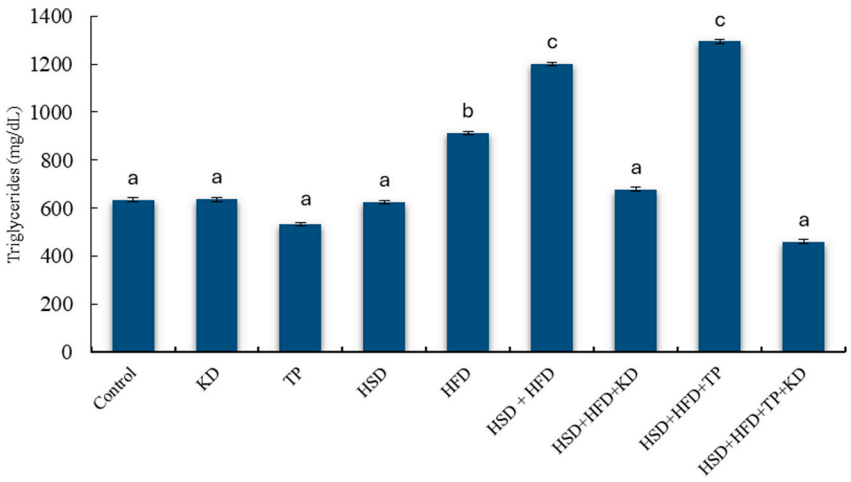

Fig. 5. Effect of KD and TP on triglyceride of high sugar and fat-fed fruit flies.
Values are expressed as mean ± SEM. KD: ketogenic diet; TP: tomato powder mix; HSD: high sucrose diet; HFD: high-fat diet. Subscript a-c, values from lowest to highest show the class of variance between the groups' significance at $p < 0.05$ versus control.

4. Discussion

Metabolic syndrome (MetS) is a cluster of metabolic disorders like insulin resistance, glucose intolerance, obesity, dyslipidemia, and hypertension that are more likely to cause cardiovascular diseases as a whole than any of their individual components [29]. This present study was designed to validate if the combination of the two therapies can yield a synergetic effect better than their individual effect since, they are readily available and cheap. A lipid profile measures total cholesterol, LDL-C, HDL-C, and triglycerides, all of which can be used to forecast pathological conditions [30,31].

High-calorie intake (HSD/HFD) can lead to an imbalance in energy homeostasis which often results in increased fat synthesis and storage (high adiposity). These studies have been shown to initiate the cascade of events that provoke different aspects of metabolic syndrome like dyslipidemia, insulin resistance, and obesity [32].

Obesity has been associated with dysfunctional fat metabolism or its repletion leading to reduced free fatty acids oxidation which is accompanied by its increased accumulation in the adipose tissues and increases in body mass [4,33]. The rise in the concentration of

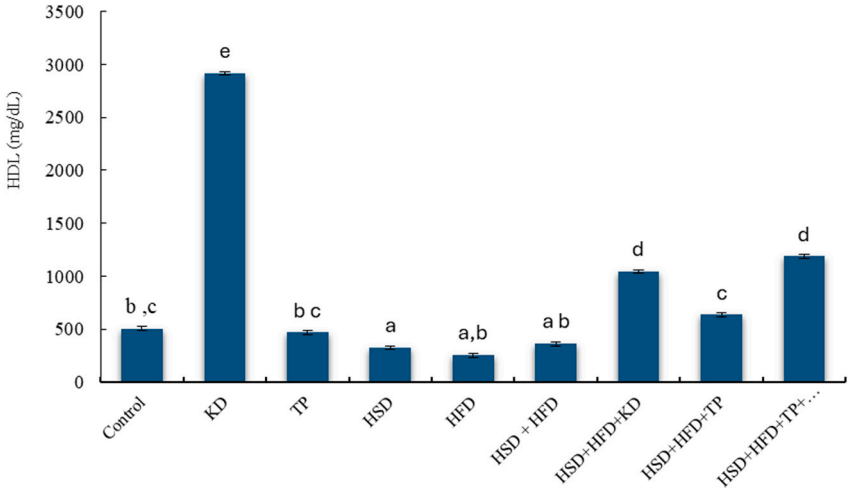

Fig. 6. Effect of KD and TP on HDL level of high sugar and fat-fed fruit flies.
Values are expressed as mean ± SEM. KD: ketogenic diet; TP: tomato powder mix; HSD: high sucrose diet; HFD: high-fat diet. Subscript a-e, values from lowest to highest show the class of variance between the groups' significance at $p < 0.05$ versus control.

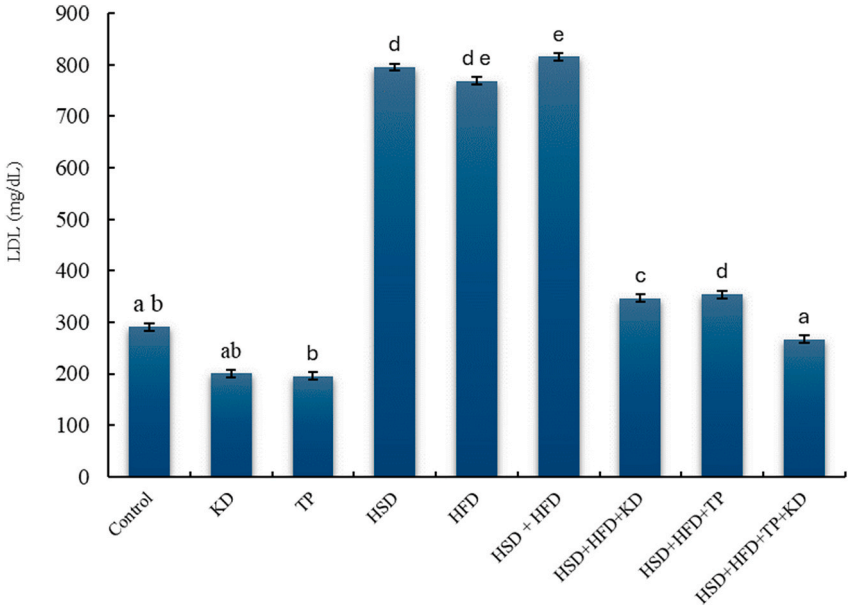

Fig. 7. Effect of KD and TP on LDL level of high sugar and fat-fed fruit flies.
Values are expressed as mean ± SEM. KD: ketogenic diet; TP: tomato powder mix; HSD: high sucrose diet; HFD: high-fat diet. Subscript a-e, values from lowest to highest show the class of variance between the groups' significance at $p < 0.05$ versus control.

triglycerides is associated with a higher risk of developing coronary heart disease (CHD) and is strongly inversely related to low High-density lipoproteins (HDL). Low HDL cholesterol also reflects a low-value low-density lipoprotein (LDL). An effective indicator of the chances of developing cardiovascular disease is the atherogenic index where the risk of developing the disease increases with an elevated value as shown in the results of induced diets which was reduced in the treatment and most especially the KD & TP combination treatment.

The enzyme 3-hydroxy-3- methyl glutaryl coenzyme A reductase (HMG CoA) reductase, catalyses a concomitant step in cholesterol synthesis that is inhibited by a ketogenic diet and tomatoes [34,35]. They also reduce appetite by increasing the concentration of satiety hormones like leptin, and cholecystokinin (CCK) [36]. The presence of phytosterol in tomatoes (stigmasterol, campesterol) can also displace cholesterol from mixed mycelles which eventually limits the absorption of cholesterol [37]. Together, these may account for the synergetic effects of the ketogenic diet and tomatoes on reversing the imbalances in lipid profiles. The exact mechanism used to achieve the synergetic effect of reducing the weight and reducing the lipid parameters is unknown. The administered KD, TP and KD +

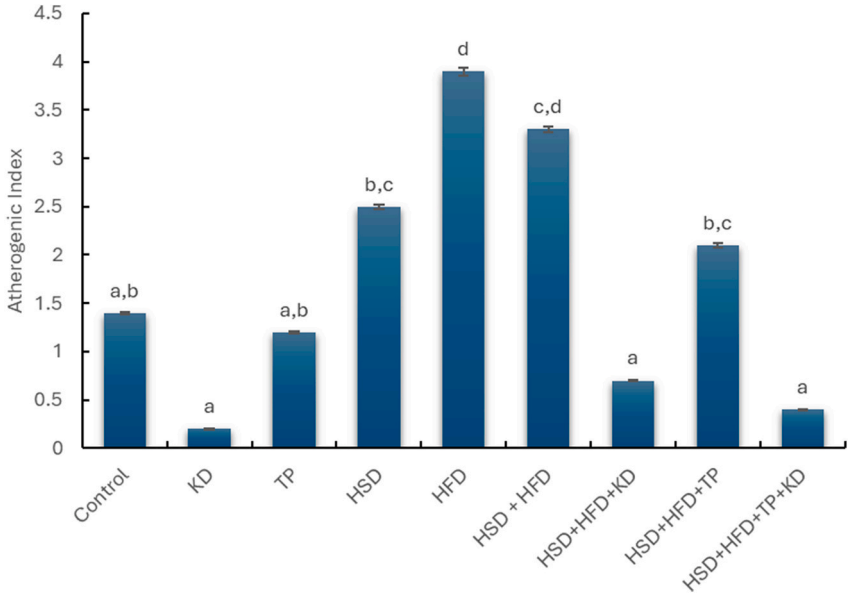

Fig. 8. Effect of KD and TP on AI of high sugar and fat-fed fruit flies.
Values are expressed as mean ± SEM. KD: ketogenic diet; TP: tomato powder mix; HSD: high sucrose diet; HFD: high-fat diet. Subscript a-d, values from lowest to highest show the class of variance between the groups' significance at $p < 0.05$ versus control.

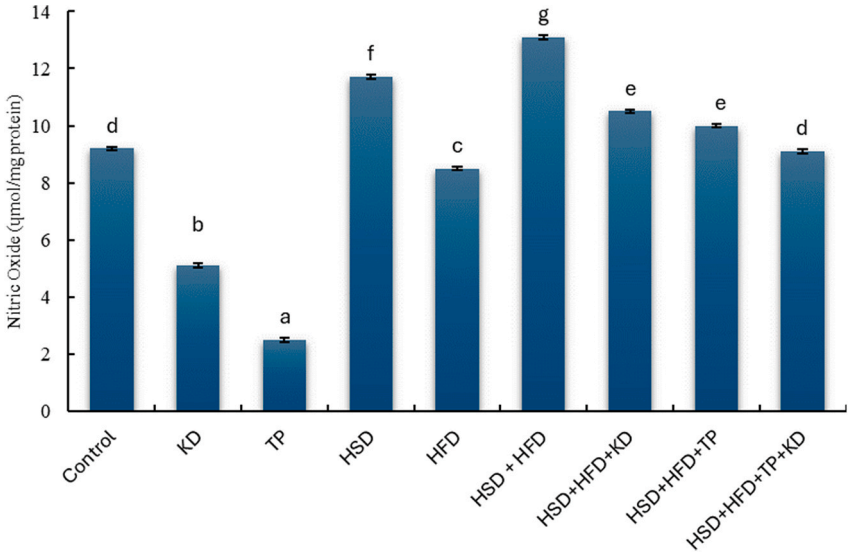

Fig. 9. Effect of KD and TP on Nitric oxide of high sugar and fat-fed fruit flies.
Values are expressed as mean ± SEM. KD: ketogenic diet; TP: tomato powder mix; HSD: high sucrose diet; HFD: high-fat diet. Subscript a-g, values from lowest to highest show the class of variance between the groups' significance at $p < 0.05$ versus control.

TP treatments showed a reversal of the lipid concentrations, indicating a reduction of induced pathological conditions.

Malondialdehyde is one of the products of lipid peroxidation and a marker for oxidative stress [24]. Elevated levels of Malondialdehyde denote the compromise of the immune system and a drop in antioxidant defence. The decrease observed in TP, KD, and combination treatments is an indication of oxidative stress and lipid peroxidation's decline.

In order to reduce reactive oxygen species, catalase, an enzyme-based antioxidant, dismutases hydrogen peroxide, which has been reduced by superoxide dismutase SOD, into free oxygen and water. Reduced catalase in HSD, HFD, and HSD + HFD-fed flies indicated reactive species were present and oxidative stress. The increase in catalase measured by the treatment points to the ketogenic diet's and tomato powder's combination's antioxidant properties in ameliorating oxidative stress.

An increase in nitric oxide (NO) concentration is a marker of the generation of free radicals. Nitric oxide levels were found to be

elevated in HF, HS, and (HF + HS) fly populations, pointing to a probable uprise in free radicals and a higher risk of developing oxidative stress-induced diseases. The same trend was observed in malondialdehyde and triglycerides concentrations in this research work which has been shown by literature to be linked to some metabolic diseases. The decline in nitric oxide levels in TP, KD, and KD + TP also suggests a probable decrease in free radicals generation. This suggests that the HSD, HFD, and HSD + HFD diets caused oxidative stress while the tomato powder mix, ketogenic diet and the combination have a therapeutic benefit in the management of these conditions [38].

5. Conclusion

Metabolic syndrome has been linked to alterations in lipid profile, weight, and insulin resistance among other biochemical parameters leading to diseases like cardiovascular diseases, obesity, hypertension and diabetes mellitus.

The HSD, HFD, and HSD + HFD-fed flies recorded alterations in biochemical parameters as indicators of pathological conditions which were ameliorated by KD, TP, and KD + TP treatments indicating the potential of these treatments in ameliorating the induced biochemical alterations. The combined treatment of KD + TP showed better ameliorative effects when compared with individual treatments indicating a synergetic nutritional remedy which is relatively safe and affordable. Further research would be required to understand the synergic mechanism of action and a possible clinical trial to check the feasibility in humans.

Author contribution statement

Omowumi T. Kayode: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Olatayo A. Afolabi: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Gabriel O. Ajayi: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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