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Effects of sunflower seeds powder on insulin related genes in high Fat diets fed and streptozotocin induced prediabetes in Wistar Rats

Augustine Oko Adugba [1], Sunday Adakole Ogli [1,*], Emmanuel Ukonu Eru [1], Oko Fidelis Ojedor [2], Omini Peter [2], Onahinon Christian [1], Nndunno Akwaras [1] and Olasupo Stephen Adeniyi [1]

[1] *Department of Physiology, Faculty of Basic Medical Science, College of Health Sciences Benue State University Makurdi, Nigeria.*
[2] *Department of public health, Life First College of Health Technology, Okuku Yala, Cross River State, Nigeria,*

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Abstract

Obesity and prediabetes are significant global health issues that may progress to diabetes mellitus and associated complications. High-fat diets and streptozotocin treatment are known to contribute to these conditions. Sunflower seeds (Helianthus annuus), even at high doses have demonstrated potential in lowering blood sugar levels. This study investigated the effects of sunflower seed powder on insulin-related gene expression in Wistar rats subjected to a high-fat diet (HFD) and streptozotocin-induced prediabetes. A total of 27 male Wistar rats (350–400 grams) were randomly assigned to 9 groups and fed for 6 weeks. Pancreatic tissue was analyzed for gene expression of insulin (INS), insulin-like growth factor 1 (IGF-1), glucose transporter 2 (GLUT2), and insulin receptor (INSR). The results revealed that HFD and streptozotocin treatment decreased expression of INSR, IGF-1, and GLUT2 while increasing INSR expression. However, sunflower seed powder dietary supplementation significantly enhanced messenger ribonucleic acid (mRNA) expression of INS, IGF-1, GLUT2, and INSR, suggesting a potential preventing of prediabetes and insulin resistance. This study highlights the beneficial effects of sunflower seed powder in modulating key genes involved in insulin signaling and glucose metabolism, providing a potential therapeutic strategy for managing prediabetes and obesity-related metabolic disorders.

Keywords: High fat diet; Prediabetes; Diabetes; Insulin; Glycated hemoglobin

1. Introduction

Overweight and obesity result from the accumulation of fat in the body. Recently, the increasing fat-to-fiber ratio in Western diets has been identified as a major factor contributing to metabolic disorders, such as obesity, prediabetes, and diabetes mellitus (DM) [1]. Consuming large amounts of fats (> 40 grams per kg per day) raises the risk of these conditions [2], but the underlying mechanisms remain poorly understood. Rehman et al. [3] projected that over half of the global population will be overweight or obese by 2035 following consumption of high fat diets. Attempts at management of overweight and obesity have been associated with high economic burden. This has necessitated the increasing reliance on herbal means of management. Sunflower seeds have shown to reduce blood glucose level and decrease BMI in rats [4,5].

Sunflower (Helianthus annuus) is an annual herb with a rough, hairy stem, fine flowers, and economically valuable seeds. Both its roots and seeds are edible and widely available in Nigeria, as well as in other parts of Africa, America, and Asia [6]. In Nigeria, it is known as Orangila in Igbo, Tozalin in Hausa, Yunyum in Yoruba, and Edemedong in Efik. Despite its potential health benefits, sunflower seeds are under-researched. They are known to contain bioactive

* Corresponding author: Sunday Adakole Ogli

compounds such as phenolic acids, cardiac glycosides, flavonoids, tocopherols, tannins, saponins, and terpenes [7,8]. A protein complex, chlorogenic acid, found in sunflower seeds, has been shown to have hypoglycemic and hypolipidemic effects when consumed [9]. Supplementation with sunflower seeds has been shown to significantly lower blood sugar levels in diabetic patients with minimal adverse effects [10].

High-fat diets and intraperitoneal (IP) administration of streptozotocin (30 mg/kg) in rats lead to insulin resistance and elevated HbA1c levels, biomarkers for prediabetes, which may progress to DM. Despite its importance, pre-diabetes has received less attention in Nigeria compared to other progressive medical conditions, such as HIV. This study aims to investigate the effects of sunflower seed powder on the expression of insulin-related genes (INSR, INS, GLUT-2, and IGF-1 mRNAs) in pancreatic tissues of rats subjected to a high-fat diet and streptozotocin-induced pre-diabetes.

2. Materials and Method

2.1. Experimental Protocol

A total of 27 male Wistar rats, 14-16 weeks old, weighing 350-400 g was obtained from the Animal house of College of Health Sciences, Benue state university, Makurdi where the study was also conducted. The Animals were housed in plastic cages with sawdust bedding and allowed to acclimatize for 2 weeks before treatment began. The rats were kept under standard conditions at room temperature (27 ± 2°C) and relative humidity (50 ± 5%) with a 12-hour light/dark cycle.

Treatments were done concurrently for 6 weeks. The Animals were divided into nine groups, with three animals per cage as follows:

- **Group 1 (Control)**: Received normal rat chow and water ad libitum for 6weeks.
- **Group 2 (Pre-diabetic model)**: Received a high-fat diet (HFD) alone (50 g/kg body weight per rat/day), mixed with 5 g sunflower powder per kg rat/day, and allowed to feed ad libitum for 6 weeks.
- **Group 3**: Received HFD (50 g/kg body weight per rat/day) plus sunflower seed powder (5000 mg/kg body weight per rat/day), mixed and fed ad libitum for 6 weeks.
- **Group 4**: Received HFD (50 g/kg body weight per rat/day) plus sunflower seed powder (3000 mg/kg body weight per rat/day), mixed and fed ad libitum for 6 weeks.
- **Group 5**: Received HFD (50 g/kg body weight per rat/day) plus sunflower seed powder (2000 mg/kg body weight per rat/day), mixed and fed ad libitum for 6 weeks.
- **Group 6**: Received HFD (50 g/kg body weight per rat/day) for 5 weeks, followed by sunflower seed powder (5000 mg/kg body weight per rat/day) and normal rat chow (20 g/kg body weight per rat/day) for 1week, fed ad libitum.
- **Group 7**: Received HFD (50 g/kg body weight per rat/day) for 5 weeks, followed by sunflower seed powder (3000 mg/kg body weight per rat/day) and normal rat chow (20 g/kg body weight per rat/day) for 1week, fed ad libitum.
- **Group 8**: Received HFD (50 g/kg body weight per rat/day) for 5 weeks, followed by sunflower seed powder (2000 mg/kg body weight per rat/day) and normal rat chow (20 g/kg body weight per rat/day) for 1week, fed ad libitum.
- **Group 9**: Received HFD (50 g/kg body weight per rat/day) for 5 weeks, followed by intraperitoneal streptozotocin (30 mg/kg body weight per rat/day) and normal rat chow (20 g/kg body weight per rat/day) for one week, fed ad libitum.

2.2. Treatments

Streptozotocin (STZ) is an antibiotic that can cause pancreatic β-cell destruction, so it is widely used experimentally as an agent capable of inducing insulin-dependent diabetes mellitus (IDDM), also known as type 1 diabetes mellitus (T1DM) [11].

Streptozytocin, manufactured by Simson Pharm limited, (Cas no. 18883-66-4), marketed Pfizer, was procured from Macfes medical store, high level Markurdi, Benue State, Nigeria.

Compounded High Fat Diet Meal: High fat diet (HFD) was constituted locally by an animal nutritionist of faculty of Veterinary Medicine, Joseph Tarka Sarwuan University, Makurdi. Benue State, Nigeria. The formula was designed using the method of Abi et al. [12], with slight modification. The diet was made from chow, tallow and soy oil at an inclusion

rate of 60%, 25% and 15% respectively. The caloric value was about 5340 kcal/kg, energy contribution of fat was about 70%, while the fat component comprises of 60% saturated fat and 40% unsaturated fat.

2.3. Phytochemical screening of sunflower seeds (*Hellianthus annus* seeds)

The fresh sunflower seeds were submitted to Dr. Mrs. Dooshima Shirki, a Botanist in the Botany Department, Benue State University, for identification. Sample of the seeds was kept in the herbarium with the voucher number HBI - 001 - BSU23. The seeds were washed, sundried for one day, pulverized, and stored in an airtight container for laboratory analysis. Phytochemical analysis was performed to identify secondary metabolites, including glycosides, flavonoids, terpenoids, alkaloids, steroids, phenols, saponins, and tannins, using standard qualitative and quantitative methods [13]. Detection of Saponins was by frothing when mixed with water and olive oil, tannins by a color change with ferric chloride, glycosides by a brown ring in the Keller-Killiani test, flavonoids by yellow coloration with ammonia and sulfuric acid, alkaloids by a yellow precipitate with Mayer's reagent, steroids by a color change with sulfuric acid, and terpenoids by a reddish-violet color after treatment with chloroform and sulfuric acid.

Tannin content was determined using a modified Folin and Ciocalteu method. Briefly, 0.5 g of the seeds were mixed with 3.75 mL distilled water, 0.25 mL Folin phenol reagent, and 0.5 mL of 35% sodium carbonate solution. Absorbance was measured at 725 nm, using tannic acid dilutions (0–0.5 mg/mL) as standards. Results were expressed as tannic acid equivalents in mg/mL.

For alkaloid content, 40 mL of 10% acetic acid in ethanol was added to 1 g of powdered seeds, which was allowed to stand for 4 hours. The filtrate was concentrated, ammonium hydroxide was added until precipitation occurred, and the precipitate was washed, filtered, dried, and weighed.

Total flavonoid content was determined using the aluminum chloride method. Seed extracts were mixed with NaNO2 solution, followed by AlCl3 solution, NaOH, and distilled water. The optical density at 510 nm was recorded, and total flavonoid content was expressed as rutin equivalents in mg/g.

For saponin content, 0.5 g of seeds was dissolved in 80% methanol, followed by the addition of Vanillin in ethanol and sulfuric acid. The mixture was heated and absorbance measured at 544 nm. Diosgenin was used as a standard for comparison.

Terpenoid content was determined by macerating 1 g of seeds in 50 mL ethanol, filtering, and adding phosphomolybdic acid and concentrated H_2SO4. Absorbance was measured at 700 nm.

Steroid content was determined by mixing 2 mL of the plant extract with NaOH, chloroform, acetic anhydride, and concentrated H_2SO4. The absorbance at 420 nm was measured.

For extraction, 10 g of sunflower seeds was mixed with 25 mL methanol, shaken, centrifuged, and the supernatant collected. After evaporation, the sample was reconstituted in dimethyl sulfoxide (DMSO) for analysis.

2.4. Sample Collection and Tissue Harvesting

Blood glucose levels were measured weekly through tail blood sampling using a needle prick and recorded over the six-week duration of the experiment. After six weeks, anesthesia was induced using a mixture of 30% isoflurane (inhalational anesthesia) from API Manufacturer, FDA-approved in the UK and marketed by Macfes Medical Store, High Level, Makurdi, Benue State, Nigeria. A 3.5% concentration of isoflurane (from the 30% mixture) was administered with 100% oxygen by placing the isoflurane-soaked cotton wool in a clean, covered plastic container. This method was used to anesthetize the rats for the purpose of harvesting pancreatic tissues, which were then analyzed for gene expression.

2.5. Statistical analysis

The results are presented as mean ± SD. Differences between two groups were determined using an independent t-test, while differences among more than two groups were analyzed using one-way ANOVA with Tukey's post hoc test. A p-value of less than 0.05 was considered significant. Data were analyzed using SPSS version 23.0 software. Gene expression was calculated using the formula: $2-\Delta\Delta Ct$, also known as the delta-delta Ct method (Levak method) [14]. This method calculates the relative fold change in gene expression by performing real-time polymerase chain reaction (qPCR). ΔCt is defined as Ct (target gene) − Ct (reference gene), and $\Delta\Delta Ct$ is the difference between the ΔCt values of the target sample and the reference sample: $\Delta\Delta Ct = (CtD - CtB) - (CtC - CtA)$.

3. Results and Discussion

3.1. Phytochemical Content

Table 1 Phytochemical Content of sunflower seeds powder (*Hellianthus annus* Seeds powder)

Sample	Alkaloid	Saponin	Sterols	Tanins	Phenol	Terpenoid	Glycoside	Flavonoid
Quanl.	+	++	++	+++	+++	++	++	++++
Quant.	0.s2327	1.068	28.0951	3.5314	7.3526	15.7209	12.4345	96.0313

Key: Alkaloid and Saponins are in percentage (%), others in (mg QE/g); Qaul: Qaulitative; Quant: Quantitative

3.2. Gene Expression Study

The study investigated the effects of sunflower seed powder (Helianthus annuus) consumption on gene expression in high-fat diet-fed and streptozotocin-induced Wistar rats using RNA extraction and real-time polymerase chain reaction (qPCR). The results revealed that treatment with sunflower seed powder significantly ($P < 0.05$) increased the expression of insulin receptor (INSR), insulin coding gene (INS), insulin-like growth factor gene (IGF), and glucose transporter gene (GLUT2) mRNA. Fold change values were notably higher in all treatment groups compared to the high-fat diet (HFD) alone and streptozotocin groups.

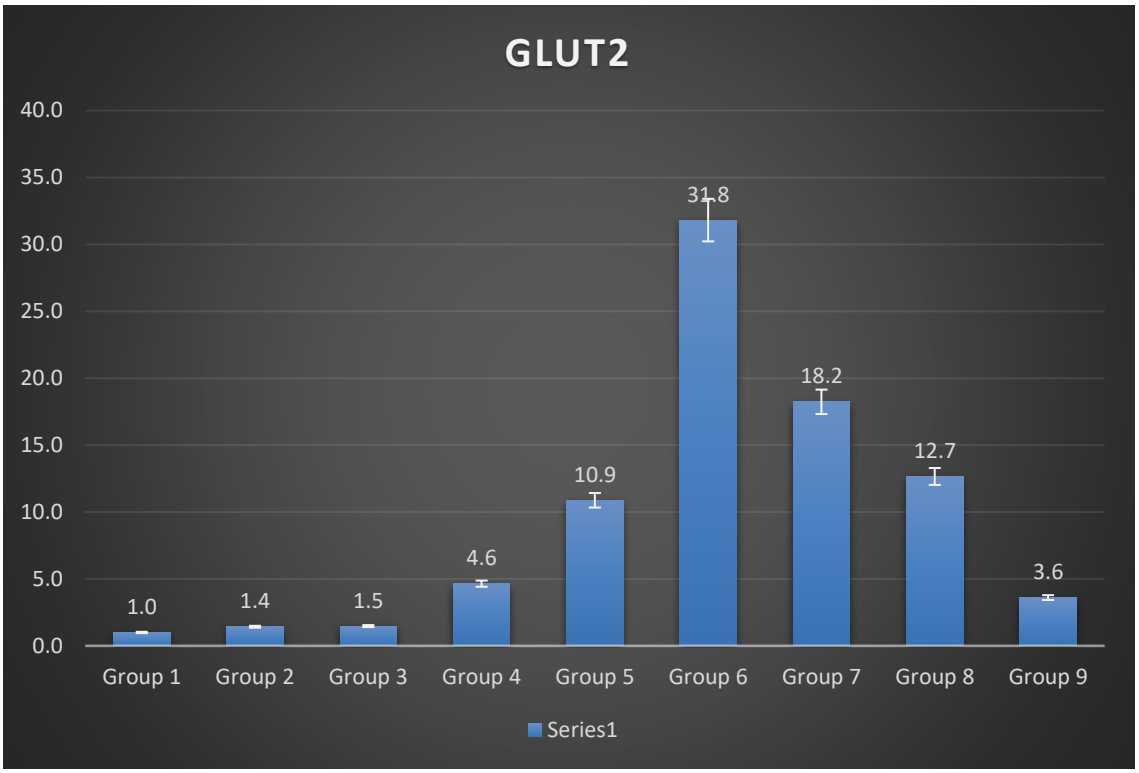

Figure 1 RealTime PCR Expression of the effects of *Helianthus annuus* Seed powder Consumption on GLUT2 mRNAin High Fat Diet Fed and streptozotocin induced Wistar Rats. Showed increase expression of INSR mRNA in treated groups with sunflower seed powder and the Control group compared to the HFD alone and Streptozotocin group.

The expression of GLUT2 mRNA exhibited significant interactions between dietary interventions and glucose transport regulation. Wistar rats consuming Helianthus annuus seed powder (HASP) showed an overall increase in GLUT2 mRNA levels compared to those fed only a high-fat diet or treated with streptozotocin. The control group maintained a baseline GLUT2 expression, while the HFD group experienced reduced GLUT2 levels, consistent with prior findings linking HFD to impaired glucose transporter regulation due to metabolic stress and insulin resistance [15]. In the six-week HASP treatment groups, GLUT2 expression demonstrated moderate recovery. The 5000 mg dose (Group 3) yielded slight improvements, while 3000 mg (Group 4) and 2000 mg (Group 5) doses produced similar moderate responses, suggesting limited benefits of prolonged HASP administration under HFD conditions. These findings align with research

indicating that chronic dietary interventions may only partially improve GLUT2 expression in the context of ongoing metabolic challenges [16].

In contrast, short-term HASP treatment following five weeks of HFD exposure resulted in more pronounced effects. Rats treated with 5000 mg (Group 6) for one week exhibited significant improvement in GLUT2 expression, while the 3000 mg dose (Group 7) produced the most substantial increase. The 2000 mg dose (Group 8) showed an intermediate response, indicating a dose-dependent effect of HASP on GLUT2 mRNA. These results suggest that acute dietary interventions can effectively upregulate glucose transporter expression, supporting rapid metabolic adaptations.

Interestingly, the streptozotocin-treated group (Group 9) exhibited baseline GLUT2 mRNA expression similar to the control group. This indicates that while streptozotocin-induced beta-cell dysfunction impairs insulin production, it has minimal direct effect on GLUT2 expression without concurrent dietary or therapeutic interventions. This observation aligns with studies highlighting GLUT2's role in glucose-dependent insulin secretion and its stability despite reduced insulin production [17].

The expression of INS, INSR, IGF, and GLUT2 mRNA significantly ($P < 0.05$) increased across all sunflower seed powder-treated groups, particularly those receiving short-term treatment after five weeks of HFD. However, in rats consuming sunflower seed powder concurrently with HFD for six weeks, fold change expression of INS, IGF, and GLUT2 mRNA significantly decreased ($P < 0.05$), despite a consistent upregulation of INSR expression. These findings underscore the nuanced impacts of dietary interventions on gene expression under varying conditions.

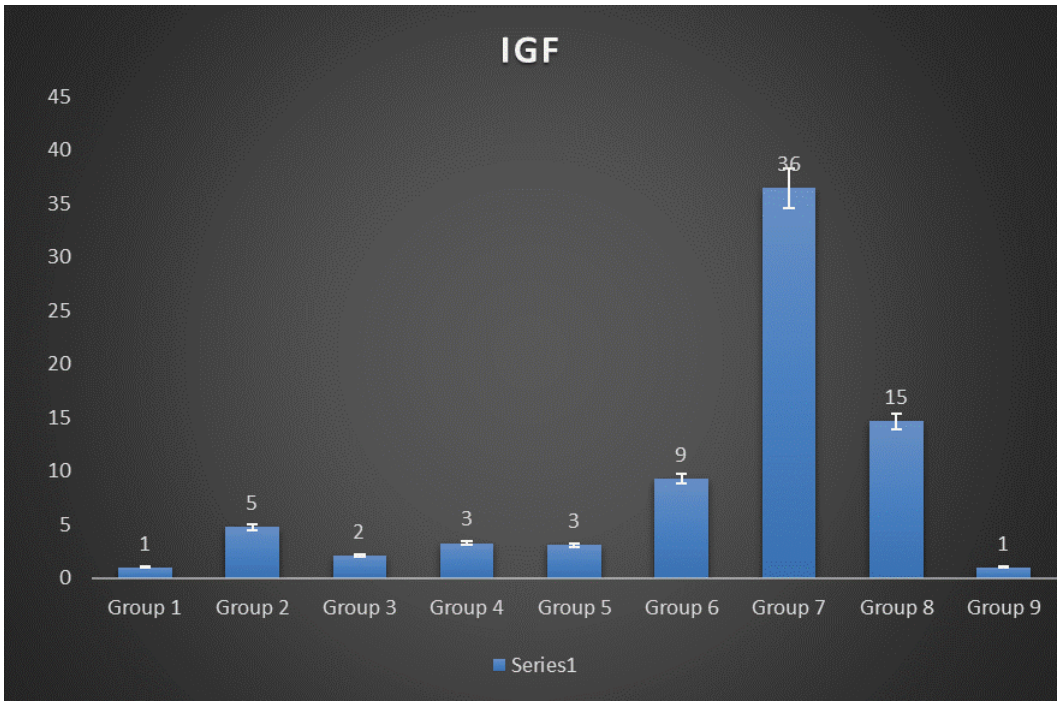

Figure 2 Real Time PCR Expression results of the effects of sunflower Seed powder consumption on IGF mRNAin High Fat Diet Fed and streptozotocin induced Wistar Rats. Showed increase expression of INSR mRNA in treated groups with sunflower seed powder and the control group compared to the HFD alone and Streptozotocin group.

The bar chart illustrates (Fig 3) IGF mRNA expression levels in Wistar rats, stating the effects of sunflower seed powder (HASP) under high-fat diet (HFD)-induced and streptozotocin-treated conditions. The findings reveal a dose- and duration-dependent relationship between HASP consumption and IGF regulation, showcasing its potential therapeutic role in managing metabolic stress. The control group maintained a baseline IGF mRNA expression of 1, while HFD alone (Group 2) elevated expression to 5, reflecting an adaptive metabolic response to dietary stress. This aligns with IGF's established role in growth and metabolic regulation under stress conditions [18].

Long-term HASP treatment (6 weeks) resulted in modest effects: Group 3 (5000 mg) had an expression level of 2, while Groups 4 (3000 mg) and 5 (2000 mg) both recorded levels of 3. These results suggest limited impact from prolonged HASP administration at these doses, consistent with studies showing that sustained dietary interventions may not always produce significant changes in IGF expression. Short-term HASP treatment after 5 weeks of HFD produced more

substantial effects. Group 6 (5000 mg for 1 week) showed moderate expression at 9, while Group 7 (3000 mg for 1 week) exhibited a striking increase to 36, indicating robust upregulation of IGF mRNA. Group 8 (2000 mg for 1 week) showed an intermediate response at 15. These results emphasize the efficacy of short-term interventions, particularly at moderate doses, in enhancing IGF signaling. The streptozotocin-treated group (Group 9) maintained baseline IGF expression (1), suggesting that beta-cell dysfunction alone does not significantly alter IGF mRNA expression without additional dietary or therapeutic interventions. HASP demonstrates significant potential to modulate IGF mRNA expression in a dose- and duration-dependent manner, with short-term, moderate-dose interventions showing the most pronounced effects.

Likewise, there was no significant ($P > 0.05$) difference in folds change expression of insulin (INS, IGF and GLUT2) mRNA in Wistar rats that consumed sunflowerseed powder alongside with HFD for 6 weeks when compared to HFD as shown in figures 1 to 4. Similar results was seen in serum insulin levels, where we observed that Concurrent treatment of rats with HFD and *Helianthus annuus* powder increased the level of insulin relative to rats fed with HFD alone, although the differences were not significant ($P > 0.05$). Feeding the rats with highdose sunflower seeds powder after 5 weeks of HFD also increase the insulin level, which was significant ($P < 0.05$) at a dose of 3000 mg/100g in rats.

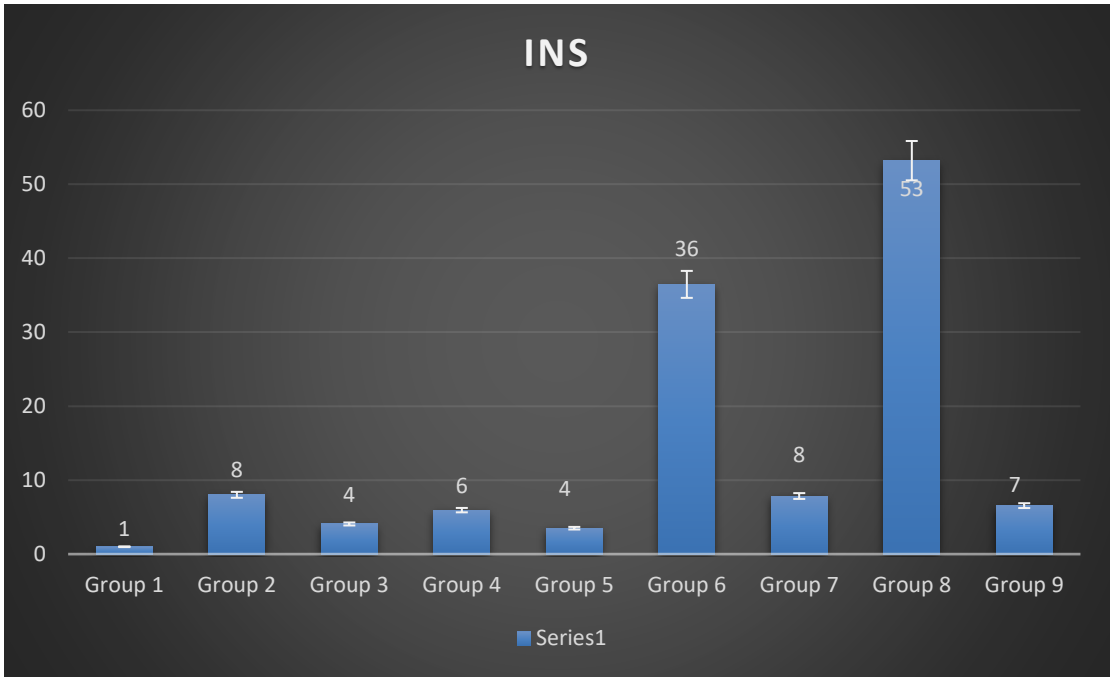

Figure 3 Real Time PCR Expression of the Effects of sunflower Seed Consumption in INS mRNAin High Fat Diet Fed and streptozytocin induced Wistar Rats. Showed increase expression of INSR mRNA in treated groups with sunflower seed powder and the control group compared to the HFD alone and Streptozotocin group.

The expression of insulin (INS) mRNA in Wistar rats under various dietary and treatment conditions provides important information on the metabolic effects of sunflower seed powder (HASP) in models of insulin resistance. The data indicates a complex interplay between dietary interventions and metabolic challenges, particularly in high-fat diet (HFD)-induced and streptozotocin-treated models. In this study, Group 2, which was exposed to HFD alone, exhibited an INS mRNA expression level of 8, reflecting a compensatory upregulation typical in insulin-resistant states. This finding align with other research [4,19] that shows elevated insulin expression in response to HFDs, highlighting the body's attempt to counteract insulin resistance. Similarly, Group 9, treated with streptozotocin, showed an INS mRNA expression level of 7, indicating beta-cell dysfunction and impaired insulin production. Similar observations have been reported in studies where streptozotocin induction led to reduced pancreatic insulin synthesis and increased insulin resistance in Wistar rats [20]. Groups treated with HASP demonstrated varying effects on INS mRNA expression depending on dosage and duration. Groups 3, 4, and 5 showed expression levels of 4, 6, and 4 for doses of 5000 mg, 3000 mg, and 2000 mg respectively. These results suggest a modest normalization effect from HASP treatment, which aligns with findings that dietary interventions can positively influence metabolic parameters in insulin-resistant models [21].Notably, short-term treatment with HASP revealed significant increases in INS mRNA expression. For instance, Group 6 (5000 mg for one week) exhibited an expression level of 36, while Group 8 (2000 mg for one week) reached an

impressive level of 53. This sharp increase may indicate a potent stimulatory effect of HASP on insulin expression under acute treatment conditions. Previous studies have similarly noted that short-term dietary interventions can lead to rapid metabolic adaptations and enhanced insulin signaling [3].The pronounced effects observed with lower doses of HASP may suggest potential synergistic interactions or rapid metabolic adaptations that warrant further investigation. Other studies have highlighted the importance of nutrient composition and timing in modulating insulin signaling pathways. The findings from this study showed the potential of sunflower seed powder to modulate INS mRNA expression in a dose- and duration-dependent manner. The significant upregulation observed under short-term treatments suggests that dietary interventions can be strategically employed to enhance metabolic regulation in insulin-resistant models.

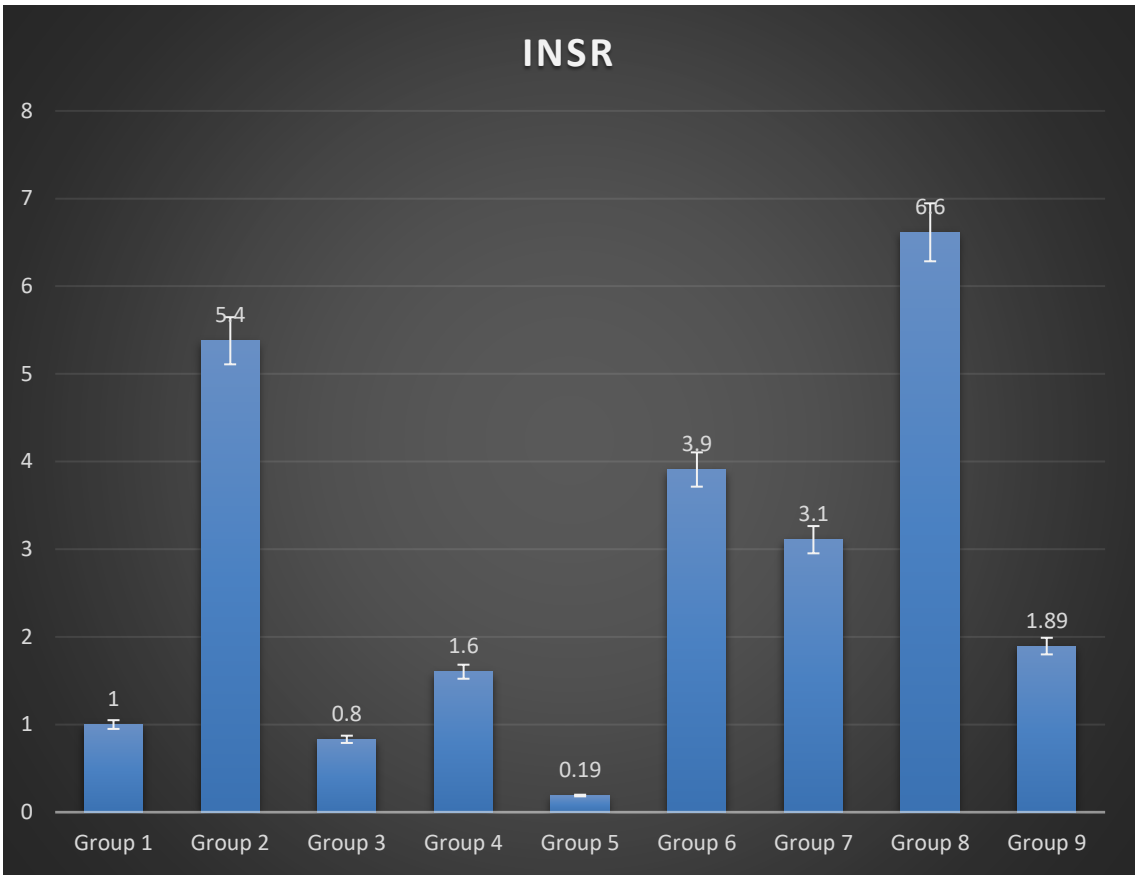

Figure 4 Real Time PCR Expression of the Effects of *Helianthus annuus* seed powder Consumption on INSR mRNAin High Fat Diet Fed and streptozytocin induced Wistar Rats. Showed increase expression of INSR mRNA in treated groups with sunflower seed powder and the control group compared to the HFD alone and Streptozotocin group.

The expression of insulin receptor (INSR) mRNA in Wistar rats under various dietary conditions reveals significant insights into the mechanisms of insulin resistance and potential therapeutic interventions. The bar chart data indicates that a high-fat diet (HFD) alone leads to a marked increase in INSR mRNA expression, suggesting a compensatory response to insulin resistance. This aligns with findings from other studies [3,4] that demonstrate similar upregulation of INSR in models of insulin resistance, presenting the body's attempt to counteract reduced insulin sensitivity. In the current study, Group 2, consisting of rats on an HFD alone, showed an INSR expression of 5.4, a significant increase compared to the control group at 1.0. This is consistent with research indicating that HFDs can lead to elevated INSR levels as a compensatory mechanism in insulin-resistant states [15].

Groups treated with Helianthus annuus seed powder (HASP) displayed varied effects on INSR expression depending on dosage and duration. For instance, Group 3, treated with 5000 mg of HASP for six weeks, exhibited a reduced expression level of 0.8, suggesting a normalization effect after HFD exposure. Group 4, receiving 3000 mg for six weeks, showed a moderate increase in expression to 1.6, while Group 5, treated with 2000 mg for the same duration, displayed minimal expression at 0.19, indicating limited therapeutic efficacy at lower doses. Interestingly, the short-term treatment groups showed more pronounced effects. Group 6, treated with 5000 mg of HASP for one week following five weeks of HFD exposure, exhibited an INSR expression of 3.9, and Group 7, receiving 3000 mg under the same conditions, showed a

slightly lower expression of 3.1. Notably, Group 8, treated with 2000 mg of HASP for one week after prolonged HFD exposure, had the highest INSR expression at 6.6. This unexpected result suggests that metabolic adaptations or synergistic interactions might enhance the therapeutic impact of a short-term, lower-dose intervention [22].

The observed dose-dependent responses of HASP treatment are consistent with previous findings showing that phytochemicals can positively modulate insulin sensitivity and INSR expression, although specific mechanisms vary based on the compound and dosage. These findings highlight the importance of optimizing dosage and treatment duration to achieve desired metabolic effects. The mild increase in INSR expression observed in Group 9, consisting of rats exposed to 30 mg of streptozotocin, reflects a compensatory response to beta-cell dysfunction caused by the toxin. Taken together, the data suggest that HASP offers potential as a therapeutic intervention for insulin resistance, but careful consideration of dosage and timing is critical to maximize its efficacy and minimize variability in outcomes [23].

4. Conclusion

The study revealed that rats fed a high-fat diet (HFD) alone and those administered streptozotocin exhibited decreased expression of INS, IGF, and GLUT2 mRNA in the pancreas. In contrast, rats treated with sunflower seed powder (*Helianthus annuus*) showed a significant upregulation of INS, INSR, IGF, and GLUT2 mRNA expression in the pancreas. These findings highlight the potential of sunflower seed powder to modulate insulin signaling pathways, offering promising therapeutic implications for the prevention and management of pre-diabetes and diabetes. Further research is warranted to explore these effects in greater depth.

Compliance with ethical standards

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Statement of ethical approval

Ethical clearance for the use of animals in this experiment was obtained from the ethical committee at the College of Health Sciences, Benue State University, Makurdi (THS REC No: CREC/THS/002).

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Declarations

On behalf of all the authors, the corresponding author states that there is no conflict of interest

Author contributions

Author Augustine Oko Adugba contributed to the study conception and design. Material preparation, data collection and analysis were performed by Augustine Oko Adugba., Sunday Adakole Ogli, Emmanuel UkonuEru, Oko Fidelis Ojedor and Omini Peter. The frst draft was written by Onahinon Christian, NndunnoAkwaras, Olasupo Stephen Adeniyi, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

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