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EFFECTS OF SUNFLOWER SEEDS POWDER ON SOME CYTOKINES, 1, 5 ANHYDROGLUCITOL AND ADIPONECTIN IN HIGH FAT DIET INDUCED PREDIABETES IN WISTAR RATS

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ABSTRACT

Background: This study is to show the involvement of high fat diets in the etiology of prediabetes. Sunflower seeds (*Helianthus Anuus*) powder have shown significant effects on high blood glucose, adiponectin, Pro-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-1beta) ,1, 5 Anhydroglucitol in both human and animal studies.

Method: 27 male Wistar rats were randomly assigned to 9 groups of 3 animals each. Group1 served as ccontrol, Group2 (high fat diet for 6weeks); Group3 (high fat diet + high dose of sunflower seed for 6weeks); Group4 (high fat + medium dose of sunflower seed for 6 weeks); Group5 (high fat diet + low dose of sunflower seed for 6 weeks); Group6 (high fat diet for 5 weeks+ high dose of sunflower seed for 1week); Group7 (high fat diet for 5weeks + medium dose of sunflower seed for 1wk); Group8 (high fat diet for 5 wks+ low dose of sunflower seed for 1wk); Group9 (high fat diet for 5 wks + Metformin for 1 week). Animals were anesthesized with 30% isoflurane and blood collected via cardiac puncture to quantifiedIL-6, IL-1beta, 1, 5 Anhydroglucitol and adiponectin using ELISA kits.

Results:IL-6, IL-1beta and adiponectin results in group2 were significantly lower ($p<0.05$) compared to control and other treated groups, 1, 5 Anhydroglucitol in group2 and group9 were significantly higher ($p<0.05$)compared to group1 and all the treated groups.

Conclusion: *Helianthus anuus* significantly increased IL-6, IL-1beta and adiponectin but significantly reducedAnhydroglucitol.

Keywords: Adeponectin; Pro-inflammatory; Anti-inflammatory cytokine; 1, 5 Anhydroglucitol.

1 INTRODUCTION

Pre-diabetes affects a significant number of people across the whole globe (Cheenam and Leena, 2016), which is due to a gradual resistance to insulin metabolic effects that are mediated by a broad array of tissue-specific actions that involve rapid changes in protein phosphorylation and function, as well as changes in gene expression (Musa et al., 2021).

The health condition in which the level of blood sugar is higher than normal but is not high enough to be categorized as diabetes is medically termed as pre-diabetes, although most people with pre-diabetes have no symptoms, but most people are symptomatic and they often notice polydypsia, polyuria and having blurred vision or extreme fatigue in the pre-diabetes conditions (Rashmi and Shilpy, 2016). 'Impaired glucose tolerance' is another term to describe the same condition (Bansal, 2015). Pre-diabetic condition can be diagnosed by performing two or three different blood tests, the fasting plasma glucose test, the oral glucose tolerance test, or the hemoglobin A1C test and glycosylated heamoglobin, pro-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-1beta), 1, 5 Anhydroglucitol and adiponectin. These biomarkers, can predicts those at high risk for developing prediabetes and subsequent progression to diabetes.

Mechanism of Insulin Resistance (IRs): The initial molecular signal for insulin action involves activation of the insulin receptor tyrosine kinase, which results in phosphorylation of insulin receptor substrates (IRSs) on multiple tyrosine residues. These phosphotyrosine residues act as docking sites for many SH2 domain-containing proteins, including the p85 regulatory subunit of phosphoinositide 3' kinase (PI3K). Binding of the p110 catalytic subunit of PI3K to p85 activates the lipid kinase that promotes glucose transport amd the insulin action in adipocytes also involves changes in gene transcription. Functional defects in insulin resistance may be due to impaired insulin signalling in all three target tissues i.e. in adipose tissue, skeletal muscle and liver, in both muscle and adipocytes, insulin binding to its receptor, receptor phosphorylation and tyrosine kinase activity, and phosphorylation of IRSs are reduced (Shuangshuang et al., 2017). Recent studies have indicated that defective signaling from the insulin receptor is an important component of insulin resistance associated with obesity in humans (Rosenbaum et al., 2017). There are also tissue-specific alterations observed in adipocytes of obese humans, IRS-1 expression is reduced, resulting in decreased IRS-1-associated PI3K activity, and IRS-2 becomes the main docking protein for PI3K. In contrast, in skeletal muscle of obese individuals, IRS-1 and IRS-2 protein levels are normal but PI3K activity associated with both IRSs are impaired (Gray et al., 2019).

1.1 Pro-inflammatory cytokines (IL-1beta and IL6)

Prediabetes and insulin Resistance (IR) are characterized by a marked inflammatory state, biochemical markers of acute-phase reactants and inflammatory cytokines are elevated on the onset of T2DM and may even further increase with disease progression, these markers, such as C-reactive protein (CRP), white blood cell count, and fibrinogen, have been investigated as potential predictors for the development of T2DM such as in the atherosclerosis risk in communities study (Ding et al., 2015).

1, 5 Anhydroglucitol:(1,5 AG):A dietary monosaccharide, has been suggested as a prediabetes marker, as the proximal tubules in the kidney have a greater affinity for glucose than 1,5 AG, high glucose levels prevent 1,5 AG reabsorption resulting in elevated 1,5 AG urinary excretion, therefore, plasma 1,5 AG concentrations are inversely correlated with plasma glucose levels (Shagshuang et al., 2017) demonstrated in a study in which the 1,5 AG level was highest in the control group followed by the prediabetes and diabetes groups, respectively. Some studies, but not all, have found an inverse relationship between 1,5 AG and OGTT 2-hour post-glucose levels (Diaconeasa et al., 2015). Studies have also shown an inverse relationship between 1,5 AG and HbA1c as well as FPG levels (Bansa et al., 2015).

1.1.1 Adiponectin

Derived from adipose tissue, exhibits insulin-sensitizing, anti-inflammatory and anti-atherogenic properties and is an independent predictor of diabetes (Charokopou et al., 2015). Lower levels of adiponectin are associated with increased insulin resistance (IR) and obesity, while higher levels have been related to lifestyle intervention groups in diabetes prevention trials, the association of adiponectin with diabetes risk appears to be evident at a much earlier stage in the progression to diabetes mellitus; more specifically, lower adiponectin levels were observed a decade before diabetes was diagnosed, particularly in men, additionally, in offspring of parents with T2DM, baseline adiponectin levels are inversely related to the risk of incident prediabetes independent of ethnic or sex differences (Musa et al., 2022). Using the hyperinsulinemic euglycemic clamp and intravenous glucose tolerance test, adiponectin levels were directly correlated with insulin sensitivity and indirectly with insulin secretion (Wagas et al., 2017). The normal range of Interleukin 1 and 6 :< 1.0-5.0 Pg/ML &< 5.0 -7.0 Pg/ML, respectively., Glycated albumin: 11.9 - 15.8 % of total serum albumin, 1,5Anhydroglucitol: 6.8 - 32.0 ug/ML, Glycated haemoglobin (HbA1c): < 5.7% or < 39 mmol/Mol, Adiponectin: 4 -37 ug/ML.

1.2 Ethical clearance

Ethical clearance for the use of animals for experiment was obtained from the ethical committee in the College of Health Sciences, Rev. Fr. Moses Adasu University, Makurdi (CHS REC No: CREC/THS/002). The sunflower seeds were submitted to the botany department Benue state university for identification and sample was placed at the herbarium, with voucher number 001-23.

2 METHODOLOGY

2.1 Materials

- Weighing balance (Ohaus Navigator NVA422) was used to monitor the rats' weight weekly.
- Syringes and needles were used to collect blood sample during the experiments.
- Cotton wool and methylated spirit were used to clean the tables during the experiments.

Test tubes were used for sample collection and were all obtained from Vincal pharmacy Wadata Makurdi, Benue State. Accu- check Active glucometer amd LG electric grinding machine were used to check blood sugar & grind the sunflower seeds to powder respectively.

Drug: Mixture of isoflurane 30% (inhalational anesthesia) by API Manufacturer with FDA, UK and marketed by Macfes medical high level Markurdi.

The hand gloves, hand sanitizer, scissors obtained from Macfes medical shop Makurdi, Benue State.

2.2 Treatment and Animal Grouping

Preventive and Curative studies in animals were done concurrently for 6weeks, twenty seven (27) Wistar rats, weighing between 350 - 400 grams (g) were randomly assigned to 9 groups consisting of 3 rats each. Animals had access to feed and water *ad libitum.*

- **Group 1:** (Control): Received normal rat chow plus water for six weeks.
- **Group 2:** (Pre-diabetic model): Received HFD alone for six weeks
- **Group 3**: Received HFD plus *Hillianthus annus* seeds powder (5000mg/kg) mixed completely together for six weeks.
- **Group 4:** Received HFD plus *Hillianthus annus* (3000mg/kg) mixed completely together for six weeks.
- **Group 5:** Received HFD plus *Hillianthus annus* (2000 mg/kg) mixed completely together for six weeks
- **Group 6:** Received HFD alone for 5 weeks. Then, after 5 weeks, rats received normal rats chow plus *Hillianthusannus*(5000 mg/kg)mixed completely together for one week.
- **Group 7:** Received HFD alone for 5 weeks. Then, after 5 weeks, rats received normal rats chow plus *Hillianthus annus* (3000 mg/kg) mixed completely together for one week.
- **Group 8:**Received HFD alone for 5 weeks. Then, after 5 weeks, rats received normal rats chow plus *Hillianthus annus* (2000 mg/kg) mixed completely together for one week.
- **Group 9:** Received HFD alone for 5 weeks. Then, after 5 weeks, rats received normal rats chow plus metformin (70 mg/kg) mixed completely in water for one week (Kurma, 2011

2.3 Addition of *Helianthus anuus* Seeds Powder To Feeds

Addition of sunflower seed powder to feed; from pilot study it was estimated that one rat consumed about 50g/kg feed perday (20 g/ 400 g rat per day); therefore with this the mixture of *Helianthus anuus* seed powder with HFD was calculated as follow:

For rats fed on high dose (5000mg/kg) *Helianthus anuus* seed powder in HFD (50 g / 1 kg rat).

- If 5000mg, is to be given to 1000g rat, then 400g rat will take 2000mg *Helianthus anuus* seed powder
- If rat consumed HFD, 50g/kg feed per day (HFD 20 g/ 400 g rat per day); then 2000mg (2g) *Helianthus anuus* seed powder was added to 20g feed for each 400 g rat, to make a total of 22 g feed per 400 g rat per day.
- By extension, 100g *Helianthus anuus* seed powder was mixed with 1 kg HFD

For rats fed on medium dose (3000mg/kg) *Helianthus anuus* seed powder in HFD (50 g / 1 kg rat).

- If 3000 mg is to be given to 1000g rat, then 400g rat will take 1200mg *Helianthus anuus* seed powder

- If rat consumed HFD, 50g / kg feed per day (HFD 20 g/ 400 g rat per day); then 1200mg (1.2 g) of*Helianthusanuus* seed powder was added to 20g HFD feed to make a total of 21.2 g feed per 400 g rat per day.
- By extension, 60g *Helianthus anuus* seed powder was mixed with 1 kg HFD

For rats fed on low dose (2000 mg/kg) *Helianthus anuus* seed powder in HFD (50 g / 1 kg rat).

- If 2000mgis to be given to 1000g rat, then 400g rat will take 800mg*Helianthus anuus* seed powder
- Ifrat consumed HFD, 50g/kg feed per day (HFD 20 g / 400 g rat per day); then 800mg (0.8 g)of*Helianthus anuus* seed powder was added to 20 g HFD feed to make a total of 2.8 g feed per 400 g rat per day.
- By extension, 40g of *Helianthus anuus* seed powder was mixed with 1 kg HFD

2.4 Preparation of *Helianthus annuus* Seeds Powder

Helianthus annuus (Seeds and leaves) also known assunflower is non-toxic even in a dose > 5000mg / kg in mice. LD_{50}> 5000mg /kg (Kurma, 2011). Dry seed of *Helianthus annuus* were procured from modern Market Makurdi and the fresh leaves with its flowers were collected from farm in Makurdi, andboth were presented to the plant Science and Biotechnology Laboratory, Biological Department Benue State University for identification, it was identified by the Botanist (Dr. MrsDooshima Shirki), with voucher number, HBI - 001- BSU23 and was placed at the herbarium. The *Helianthus annuus*seeds was manually selected, cleaned and made free of sand and other impurities using clean water. The dried seed of *Helianthus annuus* seeds were kept for ten days and were grinded with LG electric grinding machine into powder finely grinded seed of *Helianthus annuus* weighing 10kg was kept in plastic container, from where about 5kg of the *Helianthus annuus* seedspowder was mixed with high fat diet appropriately for the animals in different groups, the remaining *Helianthus annuus* seeds powder was stored in the freezer (4 or -20°C) for effective preservation for use when appropriate.

2.5 Induction of Prediabetes

High fat diet with total caloric value of the diet was about 5340kcal/kg of which energy contribution of fat was about 70%, the fat component comprises of 60% saturated fat and 40% unsaturated fat was used to feed rats for six weeks in preventive study groups and one week curative study groups respectively (Ming et al., 2018).

2.6 Experiments

2.6.1 Pro-inflammatory cytokines (IL-1beta and IL6)

10% of the supernatant was centrifuged at 4000xg for 15 min. Using ELISA kits in accordance with the manufacturer's instructions, pro-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-1beta) were quantified. We made sure that the highest standards were followed, in pg/ml, the cytokines' concentration was expressed. Interleukin- 1 and 6: Was measured using serum sample of rats on ELISA Kit (E-EL-R0015) 96 strip well marketed by abcam.com was used.

1, 5 Anhydroglucitol: Serum sample of rats was used to measure 1, 5 Anhydroglucitol on ELISA kit (MBS267430) 96 strip well marketed by Mybiosource.com was used.

2.6.2 Adiponectin

Additionally, the quantitative sandwich enzyme-linked immune sorbent assay method was used to evaluate the levels of leptin and adiponectin (Elabscience,Wuhan,China). First, the rat monoclonal antibody for leptin and adiponectin was used to precoat a microplate. The sample was then put into the microplate. An enzyme-linked detection antibody for leptin and adiponectin was added following incubation and washing. Then an enzyme substrate linked to the detecting antibody was added. At450nm,thecolour of the reaction mixture was measured.

2.7 Statistical analysis

Results were presented as mean ± SD. Differences between two groups was determined using independent t test, while differences between more than two groups was determined using One-Way ANOVA with Tukey post hoc test. Differences were considered significant when $P < 0.05$ Data were analyzed using SPSS version 23.0 software.

3 RESULTS

3.1 Effect of *Helianthus annuus* Seed Powder Consumption on Pro-Inflammatory Cytokines (IL-1 and IL-6) in High Fat Diet Fed Wistar Rats

Rats that consumed HFD alone showed a significant ($P < 0.05$) decrease in Pro-inflammatory cytokines(IL-1beta and IL-6) level compared to control. However rats that consumed sunflower seed along with HFD significantly ($P < 0.05$) have increased IL-1 beta and IL-6 levels compared with rats fed with HFD alone. Likewise the IL-1 beta and IL-6 levels were significantly ($P < 0.05$) higher in rats that were given *Helianthus annuus* seed powder after 5 weeks of HFD when compared with rats fed with HFD alone. Results are as seen in figure 1 and 2.

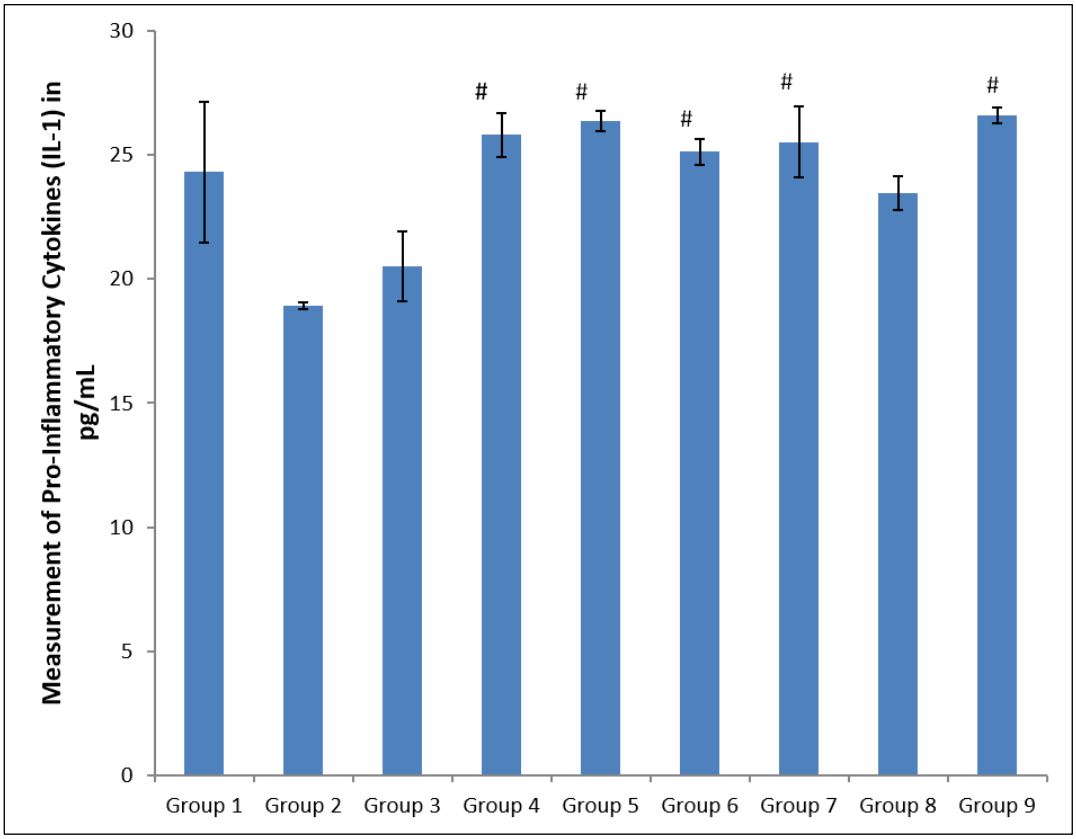

Figure 1: Results of the effect of *Helianthus annuus* seed powder consumption on Serum Pro-Inflammatory Cytokines (IL-1beta)in HFD fed Wistar rats. n = 3, Values presented as Mean ± SEM., # = significantly relative to group 2 at P < 0.05.

Keys: Group1: (Control group),Group2: (HFD Alone group),Group3: (HFD + HASP 5000 mg x 6 wks), Group4: (HFD + HASP 3000 mg x 6 wks), Group5: (HFD + HASP 2000 mg x 6 wks), Group6: (HFD 5wks + HASP 5000 mg x1 wk), Group7: (HFD 5wks + HASP 3000 mg x 1 wk), Group8 ; (HFD 5wks + HASP 2000 mg x 1 wk), Group9: (Exp. Drug Metformin group).

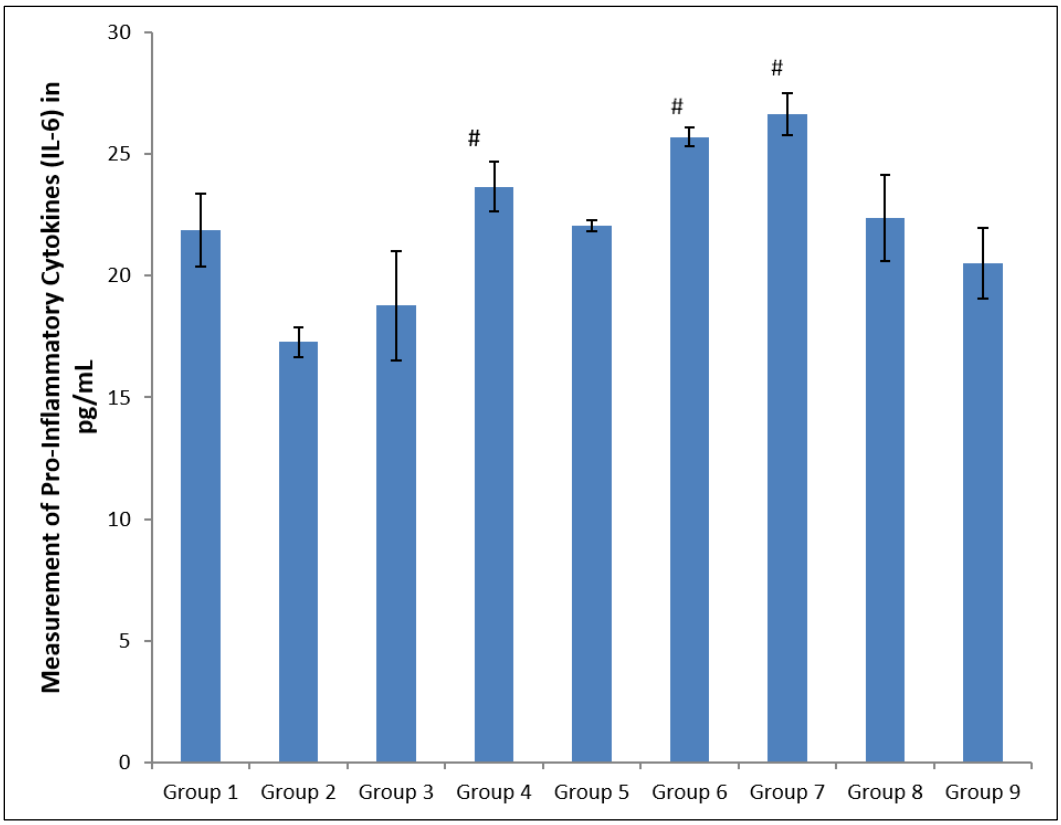

Figure 2: Results of the effect of *Helianthus annuus* seed powder consumption on Serum Pro-Inflammatory Cytokines (IL- 6)in HFD fed Wistar rats. n = 3, Values presented as Mean ± SEM., # = significantly relative to Group 2 at P < 0.05.

Keys: Group1: (Control group),Group2: (HFD Alone group),Group3: (HFD + HASP 5000 mg x 6 wks), Group4: (HFD + HASP 3000 mg x 6 wks), Group5: (HFD + HASP 2000 mg x 6 wks), Group6: (HFD 5wks + HASP 5000 mg x1 wk), Group7: (HFD 5wks + HASP 3000 mg x 1 wk), Group8 ; (HFD 5wks + HASP 2000 mg x 1 wk), Group9: (Exp. Drug Metformin group).

3.2 Effect of *Helianthus annuus* Seed Powder Consumption on Serum 1,5-Anhydroglucitol (AG) in High Fat Diet Fed Wistar Rats.

The Rats that consumed HFD alone showed significantly ($P < 0.05$) higher level of 1,5-Anhydroglucitol compared to control. Furthermore, *Helianthus annuus* seeds fed Wistar rats, had significant ($P < 0.05$) lower level of 1,5-Anhydroglucitol relative to HFD alone fed rats, although the decrease was not significant ($P > 0.05$), when compared to the control group.Results are as seen in Figure 3

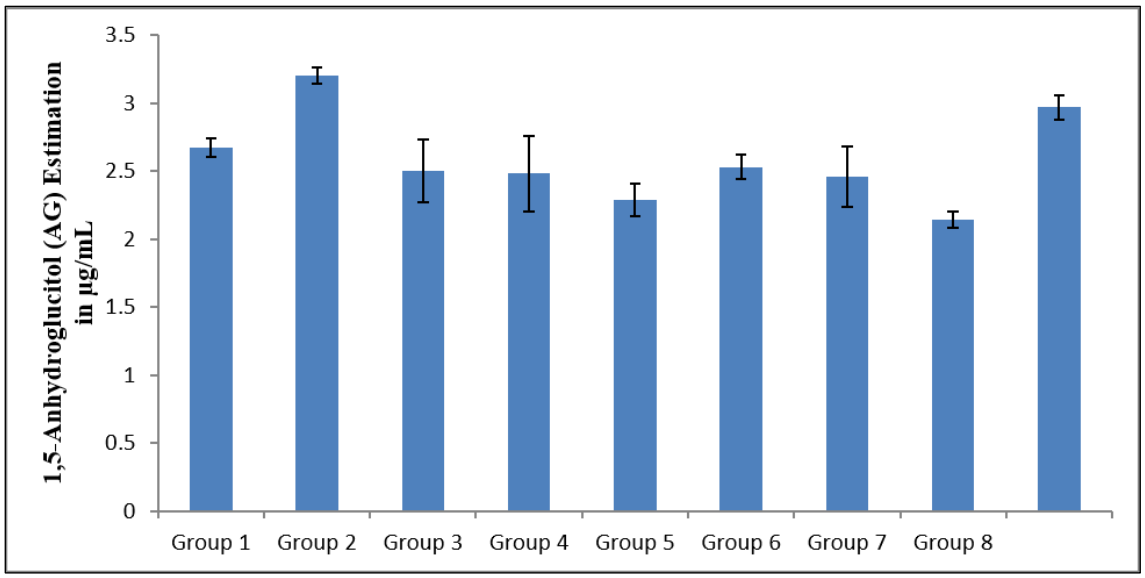

Figure 3. Results of the effect of *Helianthus annuus*seed powder consumption on Serum 1,5-Anhydroglucitol (AG) in HFD fed Wistar rats.n= 3, Values Presented as Mean ± SEM.

Keys: Group1: (Control group),Group2: (HFD Alone group),Group3: (HFD + HASP 5000 mg x 6 wks), Group4: (HFD + HASP 3000 mg x 6 wks), Group5: (HFD + HASP 2000 mg x 6 wks), Group6: (HFD 5wks + HASP 5000 mg x1 wk), Group7: (HFD 5wks + HASP 3000 mg x 1 wk), Group8 ; (HFD 5wks + HASP 2000 mg x 1 wk), Group9: (Exp. Drug Metformin group).

3.3 Effect of *Helianthus annuus*Seed Powder Consumption on Adiponectin Levels in High Fat Diet Fed Wistar Rats.

Rats that consumed HFD alone showed significantly ($P < 0.05$) low level of adiponectin compared to control. Furthermore, *Helianthus annuus* seeds powder fed rats, had significant ($P < 0.05$) increased level of adiponectin relative to HFD alone fed rats, although the increase was not significant ($P > 0.05$), when compared to the control group. Results are as seen in Figure 4.

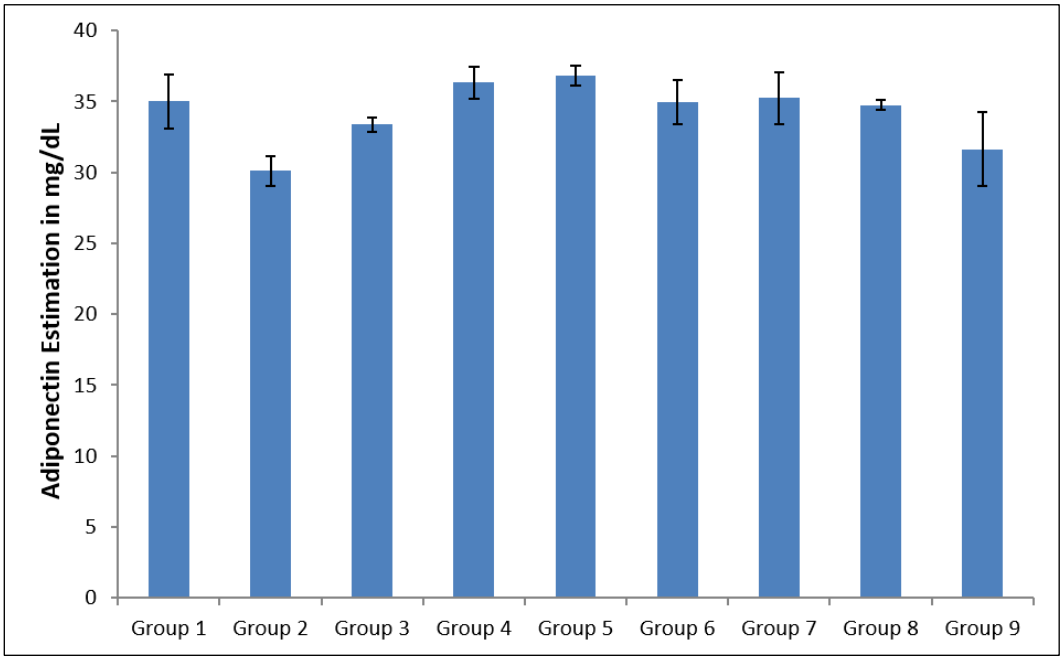

Figure 4: Results of the effect of *Helianthus annuus* seed powder consumption on Adiponectinin HFD fed Wistar rats. n = 3, Values as presented Mean ± SEM

Keys: Group1: (Control group),Group2: (HFD Alone group),Group3: (HFD + HASP 5000 mg x 6 wks), Group4: (HFD + HASP 3000 mg x 6 wks), Group5: (HFD + HASP 2000 mg x 6 wks), Group6: (HFD 5wks + HASP 5000 mg x1 wk), Group7:

(HFD 5wks + HASP 3000 mg x 1 wk), Group8 ; (HFD 5wks + HASP 2000 mg x 1 wk), Group9: (Exp. Drug Metformin group)

4 DISCUSSION

This study sought to investigate the effect of sunflower seed powder on pre-diabtes in HFD fed rats. Studies have shown that prolonged intake of HFD can cause reduce pro-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-1beta) and also reduce adiponectin levels but significantly increase 1, 5 Anhydroglucitol in Wistar rats.(Ding et al., 2015., Shuangshaug et al., 2017., Diaconeasa et al., 2015., Bansa et al., 2015., Charokopou et al., 2015., Musa et al., 2022). This study also showed similar findings.

Sunflower seeds improved the pro-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-1beta) levels lowered by HFD. Feeding the rats with high sunflower seed powder at a dose of 200 mg to 500 mg/100g plus HFD in all treated groups significantly ($P < 0.05$) increased the plasma pro-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-1beta) levels similar to metformin (Figure 1). This agrees with the work done by Shuangshaug et al, (2017) and Ding et al, (2015), who demonstrated that sunflower seeds prevent pro-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-1beta) levels reduction seen in pre-diabetes and in type 2 diabetes by increasing plasma levels of pro-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-1beta).

Similarly, sunflower seeds ameliorated adiponectin levels lowered by HFD. Feeding the rats with high sunflower seed powder at a dose of 200 mg to 500 mg/100g plus HFD in all treatedgroups significantly ($P < 0.05$) increased the plasma adiponectin levels similar to metformin (Figure 4). This agrees with the work done by Charokopou et al., 2015., Musa et al., 2022). Who demonstrated that sunflower seeds prevent adiponectin levels reduction seen in pre-diabetes and in type 2 diabetes by increasing plasma levels of adiponectin.

Sunflower seeds decreased 1, 5 Anhydroglucitol in Wistar rats, which was increased by HFD. Feeding the rats with high sunflower seed powder at a dose of 200 mg to 500 mg/100g plus HFD in all treatedgroups significantly ($P < 0.05$) increased the plasma 1, 5 Anhydroglucitollevels (Figure 3). This agrees with the work done by Diaconeasa et al., 2015. Who demonstrated that sunflower seeds suppressed 1, 5 Anhydroglucitol levels seen in pre-diabetes and in type 2 diabetes by increasing plasma levels of 1, 5 Anhydroglucitol.

5 CONCLUSION

Sunflower seed significantly ($P < 0.05$) increased pro-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-1beta) and also increased adiponectin levels but significantly reduced 1, 5 Anhydroglucitol in Wistar rats. This amelioration was attributed to its ability in reducing insulin resistance and prevents pre-diabetes in rats fed with high fat diets.

This paper is a valuable addition to the scientific literature

The study proved that checking fasting blood glucose to determine prediabetes is a late assessment. However, increased pro-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-1beta) and also decrease adiponectin levels can both significantly prove prediadetes also increassed 1, 5 Anhydroglucitol can significantly prove prediadetes because it is an analogue of glucose and can easily be displaced and get elevated in the plasma due to increase glucose level in prediabetes.

Recommendation

There will be need for possible clinical studies in future research.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethical approval was obtained from the ethical committee in the College of Health Sciences, Rev. Fr. Moses Adasu University, Makurdi (CHS REC No: CREC/THS/002). The sunflower seeds were submitted to the botany department Benue state university for identification and sample was placed at the herbarium, with voucher number 001-23.

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