THERAPEUTIC EFFECTS OF FERMENTED SOYBEAN (*GLYCINE MAX*) SUPPLEMENTATION ON BLOOD GLUCOSE LEVELS AND HAEMATOLOGICAL INDICES IN HIGH-FAT DIET-INDUCED INSULIN RESISTANT RABBITS

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ABSTRACT

Background: Excess adiposity is a major contributor to insulin resistance and the development of type 2 diabetes mellitus, a metabolic disorder characterised by chronic hyperglycaemia and systemic complications. Dietary modification is crucial in insulin resistance and diabetes management, and therefore functional foods derived from plant sources are increasingly being explored for their therapeutic potential. **Objective:** This study investigated the effects of fermented soybean supplementation on blood glucose levels and haematological parameters in high-fat diet (HFD)–induced insulin-resistant rabbits. **Methods:** Insulin resistance was induced in twenty-five rabbits over eight weeks using a HFD (2% cholesterol, 20% groundnut mill, 10% groundnut oil). Rabbits with fasting blood glucose $\geq$140 mg/dL were distributed into five groups (n=5): Group I (normoglycaemic control), Group II (untreated insulin-resistant control), and Groups III, IV, and V (insulin resistant rabbits supplemented with 12.5%, 25%, and 50% fermented soybean respectively) for six weeks. Fasting blood glucose levels were monitored weekly, while haematological parameters were assessed at the end of the treatment. **Results:** High-fat diet produced sustained hyperglycaemia in the HFD fed rabbits. Fermented soybean supplementation significantly ($p< 0.05$) reduced blood glucose levels in Groups III – V in a time-dependent manner, with Group IV (25% supplementation) showing the most consistent glycaemic improvement. Erythrocytic indices and platelet counts were not significantly altered following supplementation, while modest changes were observed in selected white blood cell indices, suggesting haematological safety and potential attenuation of diet-induced inflammatory responses. **Conclusion:** Fermented soybean supplementation effectively lowered blood glucose without compromising haematological parameters in high-fat diet–induced insulin resistant rabbit model, suggesting its potential as a safe, cost-effective functional dietary intervention for managing insulin-resistance.

Keywords: Fermented soybean; High-fat diet; Insulin resistance; Blood glucose; Haematological parameters.

1. INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders characterised by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. This leads to derangement in

carbohydrate, protein, and fat metabolism, which is associated with long-term damage to various organs including the eyes, kidneys, nerves, heart, and blood vessels (American Diabetes Association [ADA], 2023). Formerly considered a disease of the wealthy, diabetes now presents a critical public health crisis in developing regions, particularly in sub-Saharan Africa (World Health Organization [WHO], 2022).

Globally, the burden of diabetes is on the rise. While earlier reports estimated 415 million cases in 2015 (IDF, 2015), the International Diabetes Federation (IDF), reported an estimated 537 million adults living with diabetes in 2021, a figure projected to rise to 783 million by 2045 (IDF, 2021). A major part of this increase is occurring in low- and middle-income countries, including those in sub-Saharan Africa. This occurs largely due to rapid urbanisation, population growth, ageing, and lifestyle transitions (WHO, 2022).

Nigeria bears the largest diabetes burden in Africa. Recent reports indicate a steadily rising prevalence, particularly in urban populations, driven by dietary westernisation, reduced physical activity, and increasing rates of overweight and obesity (IDF, 2021; Olamoyegun *et al*., 2024). A recent systematic review estimated the prevalence of type 2 diabetes in Nigeria at approximately 7.0%, with marked regional variation (Olamoyegun *et al*., 2024). Diabetes mellitus imposes a substantial socioeconomic burden on individuals, families, and national health systems due to its high cost of long-term care and management of the complications associated with it (IDF, 2021).

Diet-induced insulin resistance plays a key role in the pathogenesis of type 2 diabetes mellitus. Chronic consumption of high dietary saturated and trans fatty acids has a harmful impact on health and has been shown to promote lipid accumulation in insulin-sensitive tissues such as skeletal muscle and liver, leading to impaired insulin signalling through mechanisms involving lipotoxicity, oxidative stress, and low-grade inflammation (Mooradian *et al*., 2000; Ma *et al*., 2025). Experimental high-fat diet (HFD) models reliably reproduce these metabolic disturbances and are widely used to investigate nutritional and therapeutic interventions targeting insulin resistance (Kolawole *et al*., 2012).

Although conventional pharmacological therapies such as insulin, metformin, and sulfonylureas are effective for glycaemic control, their use in resource-limited settings is often constrained by cost, accessibility, and adverse effects associated with prolonged therapy (Adeneye & Agbaje, 2024). These challenges have intensified interest in functional foods and dietary strategies that provide metabolic benefits beyond basic nutrition and may serve as complementary approaches in diabetes management (WHO, 2016).

Soybean (*Glycine max*) is a nutritionally dense legume distinguished by its high-quality protein, dietary fibre, polyunsaturated fatty acids, and phytochemicals, in particular isoflavones (Hamada *et al*., 2002; Ren *et al*., 2006). Fermentation enhances the functional properties of soybeans by improving protein digestibility, increasing the bioavailability of isoflavone aglycones, and generating bioactive peptides with antioxidant, anti-inflammatory, and insulin-sensitising effects (Jayachandran & Xu, 2019; Sanlier *et al*., 2019, Seo, 2024). Previous studies in high-fat diet–induced diabetic rabbit models have also demonstrated that fermented soybean supplementation improve lipid profile, oxidative stress, and modulate metabolic hormones such as insulin and leptin levels (Sada *et al*., 2018).Recent evidence further indicates that fermented soy products concentrate bioactive compounds and produce peptides capable of modulating metabolic and inflammatory pathways (Fatima *et al*., 2025; Künili *et al*., 2025).

Insulin resistance is increasingly recognized as a state of chronic low-grade systemic inflammation that affects circulating blood cells as well as glucose metabolism. Alterations in leukocyte counts, platelet activity, and erythrocyte indices have been linked to inflammatory activation, endothelial dysfunction, and cardiovascular risk in insulin-resistant states (Haffner, 2006; Raya-Cano *et al*., 2023). In particular, elevated white blood cell counts and neutrophil-derived indices correlate with worsening insulin sensitivity and metabolic syndrome features (Rodríguez-Rodríguez *et al*., 2022;

He *et al*., 2022, Mahmood *et al*. 2024). Consequently, routine haematological parameters obtained from complete blood counts serve as accessible integrative biomarkers of inflammatory burden and cardiometabolic risk. Evaluating these indices alongside glycaemic measures therefore provides a more comprehensive assessment of both metabolic efficacy and systemic safety of dietary interventions in insulin resistance. Therefore, this study evaluates the effects of graded dietary inclusion levels of fermented soybean supplementation on fasting blood glucose and haematological parameters in high-fat diet–induced insulin-resistant rabbits.

2. MATERIALS AND METHODS

2.1 Experimental Animals and Ethical Considerations

Twenty-five (25) adult rabbits of both sexes, weighing between 1.0 and 2.0 kg, were used for this study. The animals were obtained from the animal house of the Faculty of Veterinary Medicine, Ahmadu Bello University (ABU), Zaria, Nigeria. They were housed in well-ventilated cages in the Department of Human Physiology, ABU, and allowed to acclimatise for two weeks prior to experimentation. Animals were maintained under standard laboratory conditions and fed commercial grower's mash with water provided *ad libitum*. All experimental procedures were conducted in accordance with institutional guidelines for the care and use of laboratory animals and were approved by the appropriate ethical review committee, ABU, Zaria.

2.2 Preparation of Fermented Soybean Supplement

Soybean seeds were purchased from the National Animal Production Research Institute (NAPRI), ABU, Zaria. The seeds were sorted, washed thoroughly, and soaked in clean water for 48 hours to allow natural fermentation, following established protocols for legume fermentation (Uyoh *et al*., 2009). After fermentation, the seeds were drained and air-dried to remove excess moisture before being prepared as a moist mash to ensure homogeneous distribution of the fermented soybean supplement and facilitate accurate consumption of the graded doses. Such formulations are commonly used in nutritional intervention studies involving rabbits when incorporating modified or experimental feed components. The fermented soybean mash was then incorporated into the basal animal feed at graded inclusion levels for dietary supplementation.

2.3 Formulation of High-Fat Diet and Induction of Insulin Resistance

Commercial grower's mash was used as the animal feed. To induce insulin resistance, a high-fat diet (HFD) was formulated by supplementing the animal feed with 2% cholesterol, 20% groundnut mill, and 10% groundnut oil, based on the protocol for diet-induced insulin resistance in rabbits (Kolawole *et al*., 2012). Rabbits were fed the HFD for eight weeks. At the end of this period, fasting blood glucose (FBG) levels were measured, and animals with FBG values of $\geq$140 mg/dL were considered insulin resistant and included in the treatment phase, consistent with previous experimental definitions of diet-induced hyperglycaemia (Kolawole *et al*., 2012).

2.4 Experimental Design and Treatment Protocol

Insulin-resistant rabbits were randomly assigned into five groups (n = 5 per group) and treated for six weeks as follows:

S/N	Group	Treatment
1	Group I	Normal control (normoglycaemic rabbits administered distilled water)
2	Group II	Untreated insulin-resistant control (high-fat diet–induced insulin-resistant rabbits administered distilled water)
3	Group III	Insulin-resistant rabbits fed 12.5% fermented soybean–supplemented diet
4	Group IV	Insulin-resistant rabbits fed 25% fermented soybean–supplemented diet
5	Group V	Insulin-resistant rabbits fed 50% fermented soybean–supplemented diet

2.5 Determination of Fasting Blood Glucose

Baseline fasting blood glucose was measured after the induction phase and prior to initiation of supplementation (Week 0). Fasting blood glucose levels were measured weekly using the glucose oxidase method with a digital glucometer (Accu-Chek Advantage), a technique widely employed for experimental glucose monitoring in animal studies (Trinder, 1969).

2.6 Determination of Haematological Parameters

At the end of the treatment period, animals were euthanised by cervical dislocation. Blood samples were collected via cardiac puncture into ethylenediaminetetraacetic acid (EDTA) bottles for haematological analysis. Parameters assessed included red blood cell count, white blood cell count, haemoglobin concentration, packed cell volume, platelet count, and differential white blood cell counts, using standard haematological methods and automated analysers (Bain *et al*., 2017).

2.7 Statistical Analysis

Data were expressed as mean ± standard error of mean (SEM). Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Duncan's post hoc test where appropriate, in line with standard statistical procedures for biomedical research (Pallant, 2020). A p-value of less than 0.05 was considered statistically significant.

3. RESULTS

3.1 Effects on Blood Glucose Levels

The impact of fermented soybean supplementation on fasting blood glucose (FBG) in rabbits with high-fat diet-induced insulin resistance. The induction phase successfully established sustained hyperglycaemia in group II, which peaked at 179.80 ±8.54 mg/dL. All groups supplemented with fermented soybean (groups III, IV and V) demonstrated a significant ($p \leq 0.05$) and time-dependent reduction in blood glucose levels compared to group II. Notably, group IV, supplemented with the 25% inclusion level provided the most consistent glycaemic stability throughout the six weeks treatment period, achieving a 37.6% reduction by the final week.

Table 1: Effect of fermented soybean supplement on fasting blood glucose (FBG) levels (mg/dl) of high fat diet– induced insulin-resistant rabbits.

Group	FBGWeek 0 (mg/dL)	FBGWeek 1 (mg/dL)	FBGWeek 2 (mg/dL)	FBGWeek 3 (mg/dL)	FBGWeek 4 (mg/dL)	FBGWeek 5 (mg/dL)
Group I	59.80 ± 3.14[a]	73.20 ± 9.71[a]	51.80 ± 5.88[a]	66.00 ± 12.36[a]	52.20 ± 2.63[a]	52.60 ± 2.27[a]
Group II	139.00 ± 2.59	167.00 ± 4.68	170.20 ± 4.96	179.80 ± 8.54	156.80 ± 4.80	164.00 ± 2.35
Group III	138.40 ± 3.23	108.80 ± 13.38[a] (34.9%)	114.20 ± 14.20[a] (32.9%)	128.20 ± 3.73[a] (28.7%)	103.80 ± 7.90[a] (33.8%)	114.40 ± 6.76[a] (17.3%)
Group IV	141.80 ± 8.39	122.00 ± 6.86[a] (26.9%)	113.00 ± 2.93[a] (33.6%)	117.00 ± 5.01[a] (34.9%)	100.40 ± 4.86[a] (36.0%)	102.40 ± 1.60[a] (37.6%)
Group V	137.60 ± 1.81	123.20 ± 12.87[a] (26.2%)	121.40 ± 4.74[a] (28.7%)	125.00 ± 5.32[a] (30.4%)	99.00 ± 6.02[a] (36.9%)	104.20 ± 2.82[a] (36.5%)

Values are expressed as mean ± SEM; n = 5. Value considered statistically significant when compared with control group: $P \leq 0.05$ = a.

Parenthesis index ( ) means percentage (%) glycaemic change.

% Glycaemic change = $\frac{\text{Glucose concentration – fasting blood glucose}}{\text{Fasting blood glucose}}$ x 100

3.2 Effect on Haematological Parameters

Table 2 presents the effect of the dietary intervention on primary blood indices. Supplementation with fermented soybean did not lead to statistically significant changes in red blood cell (RBC) count, haemoglobin (Hb) concentration, packed cell volume (PCV), or platelet count (PLC) across the treatment groups. This suggests that the supplement is haematologically safe and does not interfere with erythropoiesis or thrombopoiesis. However, a highly significant ($p \leq 0.05$) reduction in total white blood cell (WBC) count was observed in the 12.5% fermented soybean group (4.10 ± 0.12 × 10^9/L) compared to the untreated insulin-resistant group (5.10 ± 0.14 × 10^9/L), indicating a potential attenuation of the systemic inflammatory response associated with insulin resistance.

Table 2: Effect of fermented soybean supplement on haematological parameters of high fat diet–induced insulin-resistant rabbits.

Group	RBCs ($x10^{12}$/L)	WBCs (10^9/L)	Hb (g/dL)	PCV (%)	PLC ($x10^5$/L)
Group I	5.20 ± 0.42[a]	4.68 ± 0.09	9.82 ± 1.68	29.00 ± 5.02	7.46 ± 0.16
Group II	6.32 ± 0.19	5.10 ± 0.14	9.84 ± 1.86	30.60 ± 5.54	7.82 ± 0.11
Group III	6.58 ± 0.22	4.10 ± 0.12[a]	10.54 ± 0.82	31.80 ± 2.37	7.68 ± 0.22
Group IV	6.16 ± 0.12	5.14 ± 0.17	10.34 ± 0.80	31.20 ± 2.33	7.32 ± 0.12
Group V	6.68 ± 0.10	4.42 ± 0.22	9.60 ± 1.39	28.40 ± 3.79	7.24 ± 0.10

Values are expressed as mean ± SEM; n = 5. Value considered statistically significant when compared with control group: $P \leq 0.05$ = a.

3.3 Effect on Differential White Blood Cell Counts

The effect of fermented soybean supplementation on the differential white blood cell counts is summarized in Table 3. While the levels of basophils, eosinophils, and monocytes remained stable and showed no significant differences among the groups, there was a notable shift in the leucocyte profile of the high-dose group. Specifically, the 50% fermented soybean group exhibited a significant ($p \leq 0.05$) reduction in neutrophil percentage (17.40 ± 1.60%) compared to the untreated insulin-resistant control (22.80 ± 0.86%). This reduction was accompanied by a non-significant increase in the lymphocyte percentage, further supporting the immunomodulatory potential of fermented soybean in managing metabolic inflammation.

Table 3: Effect of fermented soybeans supplement on differential white blood cell parameters (%) of high fat diet– induced insulin-resistant rabbits.

Group	Neutrophil (%)	Basophil (%)	Eosinophil (%)	Monocyte (%)	Lymphocyte (%)
Group I	21.80 ± 1.20	0.00 ± 0.00	2.00 ± 0.00	3.00 ± 0.45	73.20 ± 1.56
Group II	22.80 ± 0.86	0.00 ± 0.00	1.60 ± 0.24	2.80 ± 0.37	72.80 ± 1.39
Group III	19.60 ± 0.93	0.00 ± 0.00	1.40 ± 0.24	2.20 ± 0.37	77.00 ± 1.26
Group IV	22.00 ± 1.14	0.00 ± 0.00	2.40 ± 0.24	3.20 ± 0.58	72.40 ± 1.17
Group V	17.40 ± 1.60[a]	0.00 ± 0.00	1.60 ± 0.24	2.40 ± 0.50	78.60 ± 1.75

Values are expressed as mean ± SEM; n = 5. Value considered statistically significant when compared with control group: $P = 0.05$ = a.

4. DISCUSSION

The present study investigated the therapeutic effects of fermented soybean (*Glycine max*) supplementation in ameliorating hyperglycaemia and associated haematological disturbances in a high-fat diet (HFD)-induced insulin resistance, a well established precursor of type 2 diabetes mellitus. The findings demonstrate that dietary inclusion of fermented soybean significantly improved fasting blood glucose levels while maintaining a stable haematological profile and exhibiting potential immunomodulatory effects.

4.1 Blood Glucose Regulation

The administration of the HFD successfully induced sustained hyperglycaemia in group II (untreated insulin-resistant group), with fasting blood glucose (FBG) levels reaching a peak of 179.80 ± 8.54 mg/dL by the third week. This elevation aligns with established lipotoxic mechanisms, where the chronic intake of high-fat meals leads to the accumulation of lipid metabolites, such as ceramides, diacylglycerol, and acyl-CoA within the liver and skeletal muscle. These metabolites activate serine/threonine kinase cascades that disrupt insulin signalling and glucose transport pathways, thereby promoting insulin resistance (Delarue & Magnan, 2007; Kraegen & Cooney, 2008; Petersen & Shulman, 2018).

Dietary supplementation with fermented soybean significantly ($p \leq 0.05$) reversed this hyperglycaemic trend from the first week through to the fifth week across all treated groups. The 25% inclusion level (group IV) provided the most stable reduction in blood glucose. These outcomes align with previous reports demonstrating the glucose-lowering efficacy and enhancement of insulin sensitivity of fermented legumes in metabolic models (Kwon *et al*., 2010; Choi *et al*., 2016). The glucose-lowering efficacy is likely due to the conversion of isoflavone glycosides into bioactive aglycones like genistein (Kikuchi-Hayakawa *et al*., 1998; Okabe *et al*., 2011; Seo, 2024; Fatima *et al*. 2025, Künili *et al*. 2025). Genistein acts as an alpha-glucosidase inhibitor, binding to intestinal enzymes to prevent the hydrolysis of starches into absorbable sugars, delaying carbohydrates absorption (Kojima *et al*., 2010; Nakanishi *et al*., 2011). Furthermore, soy peptides may activate AMP-activated protein kinase (AMPK) pathways, stimulating peripheral glucose uptake and improving insulin signalling pathways (Cederroth *et al*., 2008; Jayachandran & Xu, 2019). These bioactive peptides and isoflavones have been shown to enhance beta-cell function and stimulate insulin secretion through the activation of cyclic adenosine monophosphate (cAMP) and protein kinase-A (PKA) pathways (Sorenson, 1994; Liu *et al*., 2006; Wang *et al*., 2021; Mamoudou, 2025).

The observed "ceiling effect" at the 50% inclusion level, where no significant additional glycaemic benefit was observed compared to the 25% group is a common phenomenon in nutritional interventions. This is likely due to the saturation of metabolic pathways or alterations in feed palatability (Kwon *et al*., 2010). This may be partly attributed to residual anti-nutritional factors such as saponins and oxalates, which, despite reduction during fermentation, may persist at higher inclusion levels and interfere with nutrient absorption and metabolic efficiency (Künili *et al*., 2025).

4.2 Haematological Parameters

The haematological results provide important evidence that fermented soybean supplementation is systemically safe across the graded dietary inclusion levels of soybean tested. Erythrocyte indices, including Red Blood Cell (RBC) counts, Haemoglobin (Hb) concentration, and Packed Cell Volume (PCV), were preserved. This suggests that the supplement does not impair erythropoiesis or induce anaemia, likely because fermentation reduces anti-nutrients like phytates and tannins that typically hinder mineral bioavailability (Adeyemo & Onilude, 2013).

Furthermore, the stability of the platelet count (PLC) across all inclusion levels is a significant finding regarding vascular health. High-fat diet consumption is frequently associated with a pro-thrombotic state, but the maintenance of quiescent platelet levels in the soy-treated groups suggests a protective effect against metabolic-induced hyper-reactivity (Schoene & Guidry, 1999). The inhibition of specific platelet signalling pathways by soy isoflavones likely prevents excessive platelet production and activation (Liu *et al*., 2021). These findings align with previous observations in rabbit models where dietary soy was shown to modulate the coagulation profile effectively (Nsa *et al*., 2016). The preservation of the RBC and platelet indices provides indirect toxicological evidence supporting the safety of fermented soybean at the graded inclusion levels, effectively serving as a haematological toxicological clearance for the intervention (Hung *et al*., 2024).

The result of this study also showed a decrease in total leucocyte and neutrophil counts in the soybean-supplemented groups, suggesting an anti-inflammatory effect which represents a key finding of this study. Insulin resistance is a state of chronic, low-grade inflammation, often reflected by elevated circulating leucocytes and neutrophil predominance (Hotamisligil, 2006; Furman *et al*., 2019). Group III (12.5% soybean group) showed a highly significant ($p \leq 0.01$) reduction in total WBC counts (4.10 ± 0.12) compared to group II (5.10 ± 0.14). The modulation of the neutrophil-to-lymphocyte ratio (NLR) in the high-dose soybean group further suggests that soybean-derived peptides may dampen pro-inflammatory cytokines like TNF-α and IL-6 (García-Escobar *et al*., 2023). NLR is recognised as a biomarker of systemic inflammation and a predictor of cardiovascular risk in metabolic disorders, including insulin resistance and type 2 diabetes mellitus (Adane *et al*., 2023; Qiu *et al*., 2024). The reduction in neutrophil dominance relative to lymphocytes suggests improved inflammatory balance and may reflect decreased production of the pro-inflammatory cytokines such as TNF-α and IL-6. Soy-derived bioactive peptides and isoflavones have been shown to down regulate these inflammatory mediators and modulate immune cell activity (García-Escobar *et al*., 2023).

These findings highlight the immunomodulatory potential of fermented soybean and suggest that its benefits extend beyond glycaemic control to include attenuation of inflammation and may therefore be used as a functional dietary supplement in managing metabolic stress.

CONCLUSION

This study demonstrates that fermented soybean supplementation significantly improved fasting blood glucose levels in high-fat diet–induced insulin-resistant rabbits without producing adverse haematological effects. The findings suggest that fermented soybean exerts beneficial metabolic and immunomodulatory effects, with the most consistent glycaemic response observed at 25% inclusion level. These results support the potential role of fermented soybean as a safe functional dietary intervention in the management of insulin resistance.

RECOMMENDATION

1. Further studies are recommended to elucidate the molecular pathways underlying the hypoglycaemic and immunomodulatory effects of fermented soybean, particularly its influence on insulin signalling, inflammatory cytokines, and oxidative stress markers.
2. Long-term feeding studies should be conducted to assess the sustainability, safety, and dose optimisation of fermented soybean supplementation in chronic insulin-resistant states.
3. Clinical and community-based intervention studies are encouraged to evaluate the translational potential of fermented soybean as a functional dietary adjunct for glycaemic control in human populations, especially in low- and middle-income settings.
4. Comparative investigations involving different fermentation techniques and soybean varieties may further enhance the therapeutic efficacy of fermented soybean-based functional foods.

AUTHORS' CONTRIBUTIONS

Sada, Maryam Naiya conceived and designed the study, conducted the experiments, and prepared the manuscript. Sada, Asma'u Naiya, Ciroma, Fatima Lami, and Ja'afar, Fatima Yahya contributed to data collection, analysis and manuscript review. Tanko, Yusuf supervised the study and provided critical revisions. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that no conflict of interest is associated with the information presented in this paper.

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