MONOSODIUM GLUTAMATE INDUCED HYPOINSULINEMIA AND HYPERGLYCEMIA IN ALBINO WISTAR RATS

***Eiya B. O. and Inneh C.A.**
Department of Physiology, School of Basic Medical Sciences, College of Medical Sciences University of Benin.
***Corresponding Author:** Eiya Bibiana Omozee
Email: eiyabibiana@gmail.com and Churchillinneh@yahoo.com; +2348081953639
Received: 5th January, 2022 **Accepted:** 4th November, 2022 **Published:** 8th December, 2022

Background of Study: Monosodium glutamate (MSG) is a sodium salt of glutamic acid used as a flavor enhancer, which are consumed globally. Although it is of high benefit to the food industry, its consumption has been associated to weight gain a predisposing factor to most metabolic syndromes. This has raised some concern as to the safety of this food addictive.
Aim: The aim of the research was to ascertain the effects of varying doses of MSG on plasma insulin, glucose and lipid profile.
Methods: Three (3) doses of MSG 5.3g, 8g and 16g per Kg body weight were administered to the rats in the different test groups while the control group was given water for 60 days. Blood samples were collected at the end of the study for the following assay, serum insulin, fasting blood sugar and lipid profile (Cholesterol, triglyceride, HDL, LDL, and VLDL). Insulin was determined by ELISA Microwells method by Turkington *et al;* (1982), Fasting blood sugar was determined using ALL-CHECK active glucometer as described by Leigh *et al;* (2015). Lipid profile was determined spectrophotometrically. Graph Pad Prism Statistical Software, version5.0 was used to analyze data.
Results: Our results showed a significant decrease ($P<0.05$) in insulin concentrations in the various groups when compared with control (3.00± 0.34 SEM.), low dose (1.78± 0.8 SEM.), moderate dose (1.37± 0.09 SEM.) and high dose (08 ±0.07 SEM.), and the decrease were dose dependent. This ultimately reflected in blood glucose concentrations which increased significantly ($P<0.05$) when compared with control (60.40mg/dl ±2.4 SEM.), low dose, (70.20 mg/dl ± 21 SEM.), moderate dose (86.67 mg/dl ± 1.33 SEM.) and high dose (108.33 mg/dl ±4.9 SEM.), these increase were dose dependent. There was however no significant difference in blood lipid profile values of the various experimental groups when compared with control.
Conclusion: Data obtained from this study shows that intake of MSG can induce hyperglycemia and hypoinsulinemia without changes in lipid profile.
Keywords: Monosodium glutamate, Insulin, Blood glucose, Lipid profile, Rats.

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia resulting from deficiencies in insulin secretions or resistance of cells to insulin even when present in high levels. Globally, the prevalence of diabetes have been on the increase and further increase in the future have been estimated, (Kengne *et al;* 2005). In Nigeria, the prevalence of DM has been on the increase (ranging between 0.8% - 4.4% (Olatunbosun *et al;* 1998, Akinkugbe, 1997) in some rural communities and 4.6 -7 % (Kengne *et al.,* 2005) in urban communities. The rise in most metabolic syndromes e.g. like diabetes mellitus has been attributed to life style changes, the type of food we eat and how these foods are prepared has a very important role in most metabolic syndromes. Monosodium glutamate (MSG), a sodium salt of glutamic acid, is used as a flavor enhancer in food industry (Walker and Lupien, 2000; Boonnate *et al*., 2015).

MSG contains 78% of glutamic acid, 22% of sodium and water. Glutamic acid is one of the most abundant amino acids found in nature and the main component of many proteins and peptides of most tissues (Ibukun *et al*., 2015). It is produced in many countries around the world through a fermentation process of molasses from sugar cane or sugar beets, as well as starch and corn sugar (Enameli and Danielson, 2014). MSG is sold in most open market stalls and stores in Nigeria as "Ajinomoto" marketed by West African Seasoning Company Limited; as "Vedan". It is commonly consumed as food additive in both household and restaurants (Michael and Peter, 2015). Locally and globally, there have been contradictory reports concerning the safety of this food additive (Eweka *et al*., 2011). Both animal model experiments and human clinical reports have suggested its harmful effects when consumed overtime (Ibukun *et al.*, 2015). In Nigeria, despite epidemiological studies report on the negative consumer response to MSG (Inuwa *et al*., 2011), reputable international organizations like the Food and Drug Administration (FDA) and National Agency for Food and Drug Administration and Control (NAFDAC), as well as nutritionist have continued to endorse that MSG safe as a flavor enhancer, without any adverse reactions in humans (Eweka *et al*., 2010). Nonetheless, consistent metabolic effects of MSG have been demonstrated in animal studies including pancreatic pathology in these models (Sasaki *et al*., 2009). In a normal physiologic function of pancreas, the right amount of insulin is produced to transport glucose into the cells. Previously, Nagata *et al.* (2006) had done a study where MSG was used to induce obesity in type 2 (non-insulin dependent) diabetes mellitus in mice, (Chen *et al.,* 2006). In pathological pancreas, little or no insulin is produced, or the body cells do not respond to the insulin that is produced leading to accumulation of glucose in the blood or elevation of its levels (hyperglycaemia) resulting in diabetes mellitus (Emanuele *et al*., 2009). Over dose of MSG can increase both insulin secretion and blood glucose level suggesting presence of insulin resistance (Elshaikh and Abuelgassim, 2018). Due to conflicting reports on consumption of MSG, the aim of this study is therefore to specifically ascertain the effects of MSG intake on insulin, blood glucose and lipid profile levels in wistar albino rats.

MATERIALS AND METHODS

Popular brand of monosodium glutamate (Ajinomoto, 99% monosodium glutamate) was purchased Oba market, Benin City, Edo State.

Experimental Design: This study was conducted on 24 normal adult male wistar rats weighing between 150-200g. The rats were kept in clean plastic cages and healthy laboratory conditions of temperature between 18-24^{o}C and appropriate humidity and lightening was maintained. The animals received appropriate care in line with the appropriate care and guideline of the national institute of health USA for ethical treatment of laboratory animals. The rats were allowed to acclimatize for two (2) weeks before administration of MSG. After acclimatization, the rats were randomly assigned into four(4) groups of A, B, C and D, of six (6) rats per group, Group A (Control), Group B (Low dose), Group C (Moderate dose), Group D (High dose). The control group (A) was given 2.5ml water, Groups B, C and D was treated with monosodium glutamate. The monosodium glutamate was dissolved in distilled water in doses of 5.3g/Kg body weight (low dose), 8g/kg body weight (moderate dose), and 16g/kg body weight (high dose). 2.5ml of MSG was administered orally using oral gastric tube once daily for 8 weeks.

Blood Collection: The rats were anaesthetized using chloroform (CHCl4). Blood samples were collected from the rats through the abdominal aorta and cardiac puncture using 5ml syringes and placed in plain tubes. The blood samples were allowed to clot and centrifuged, and the serum was collected for assay.

Biochemical Assays

Blood Glucose: Fasting blood glucose level was determined using the Accu-Chek active glucometer and method described by Leigh *et al.* (2015).

Lipid profile: Total cholesterol was determined enzymatically by hydrolysis and oxidation according to the method described by Allian *et al.* (1974). Serum triacylglycerol was estimated using the Tiez (1990) method. High Density Lipoprotein fraction was determined by a method described by Grove (1979), while very low density lipoprotein was determined by method described by Sallah *et al.* (2015).

Insulin: Insulin level was determined by Elisa Microwells, a method described by Turkington *et al.* (1982).

Statistical Analysis: Data obtained from the biochemical assay of the enzymes were presented as mean ± standard error of the mean (SEM) and analyzed for statistical significance by one-way analysis of variance (ANOVA) using the Graph Pad Prism Statistical Software, version 7.0. Confidence limit was set at 95% and p value <0.05 was regarded as significant.

RESULTS

Our results showed a significant decrease in insulin concentrations (Figure 1) in the various groups when compared with control and the decrease were dose dependent. This ultimately reflected in blood glucose concentrations (Figure 2) which increased significantly when compared with control, the increase in blood glucose concentrations were also dose dependent. There was a negative correlation between blood glucose and blood insulin concentrations (Figure3) as decrease in blood insulin level resulted to increase in blood glucose level. There was however no significant difference in blood lipid profile values (Table 1) of the various experimental groups when compared with control. Weights (figure 4) of the high dose group significantly increased when compared with control.

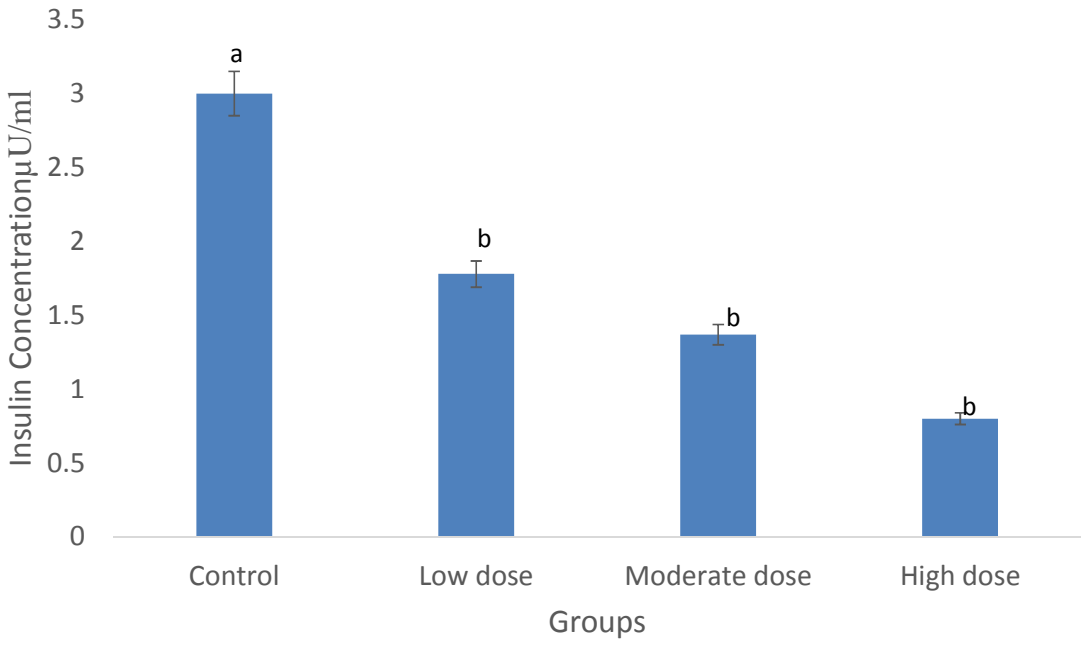


Figure 1: Graph Showing Insulin Concentration (µU/ml) Across All Groups. All Experimental Groups (Low Dose, Moderate Dose & High Dose) Showed Statistical Significant Decrease In Insulin Concentration Levels When Compared To The Control Group (P<0.001).

Bars not sharing same letters are significantly different at P<0.05.

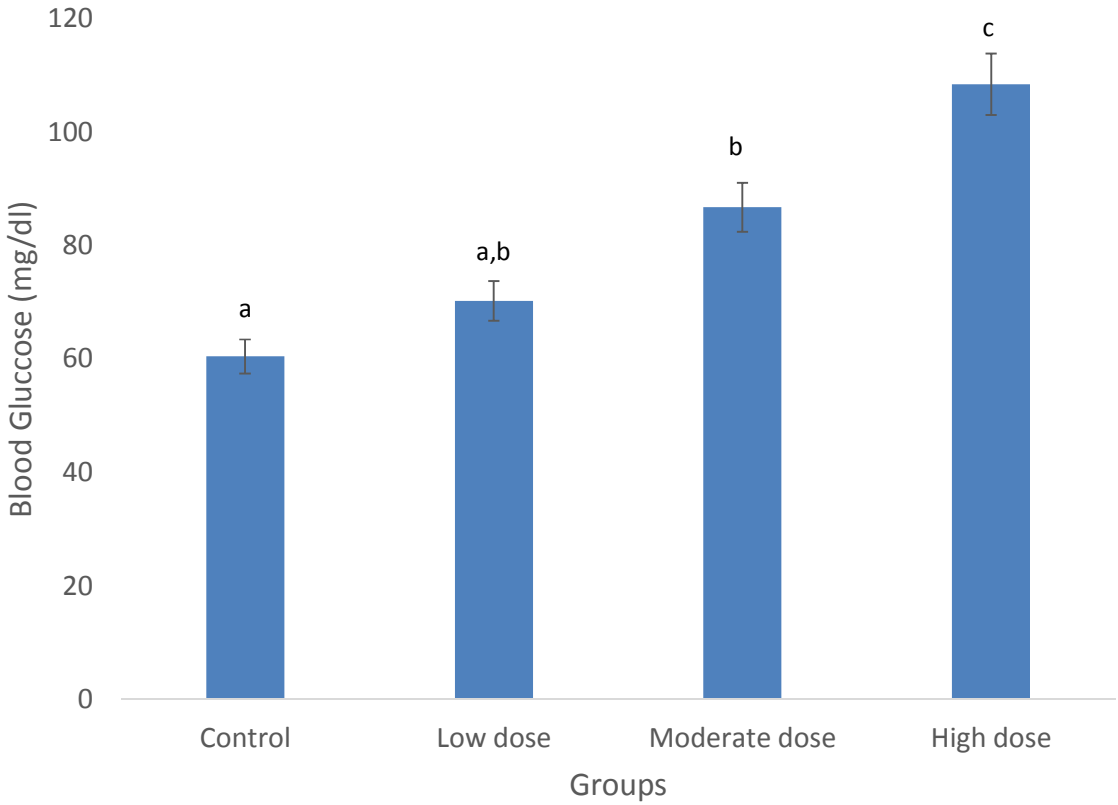
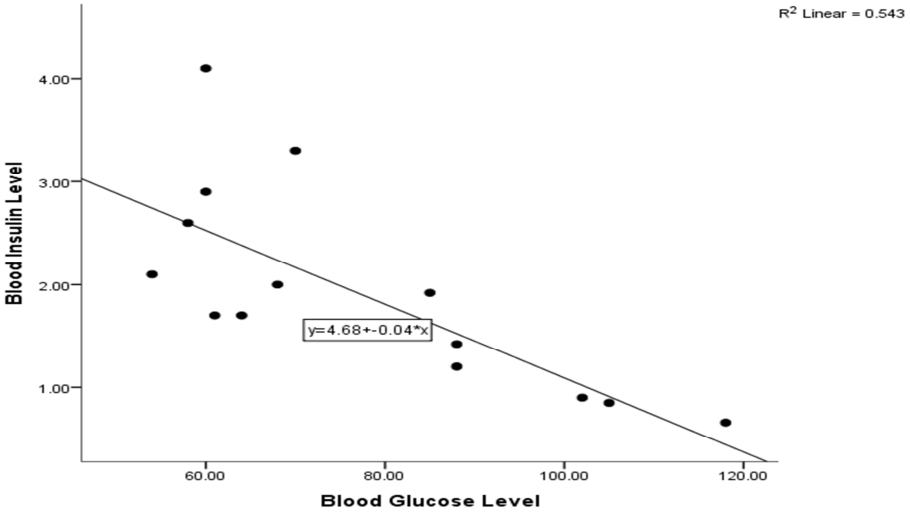


Figure 2: Graph Showing Blood Glucose Levels Across All Groups. Moderate Dose Group & High Dose Group Showed Statistical Significant Increase in Blood Glucose Levels When Compared to The Control Group (P<0.001).
Bars not sharing same letters are significantly different at P<0.05.



R = -0.737; R^2 = 0.543
Figure 3: Graph showing correlation between Blood insulin level and Blood glucose level. There was a negative correlation between blood glucose and blood insulin as decrease in blood insulin level resulted to increase in blood glucose level.

Table 1: Serum lipid profile concentrations in the various doses

	GROUP			
	Control	Low (5g/kgbwgt)	Moderate (8g/kgbwgt)	High (16g/kgbwgt)
LDL	29.40 ± 4.86a	13.20 ± 1.93a	31.00 ± 7.09a	33.00 ± 15.62a
HDL	12.60 ± 1.99a	14.60 ± 1.60a	12.00 ± 1.53a	13.00 ± 1.00a
TC	54.40 ± 6.38a	41.80 ± 2.22a	52.67± 7.06a	56.00 ± 16.29a
TAG	62.60 ± 6.28a	69.40 ± 11.87a	48.00 ± 8.96a	50.33 ± 12.20a

Values are Mean ± SEM

Note: Values in the same row and sub table not sharing the same subscript are significantly different at $p < 0.05$ in the two-sided test of equality for column means.

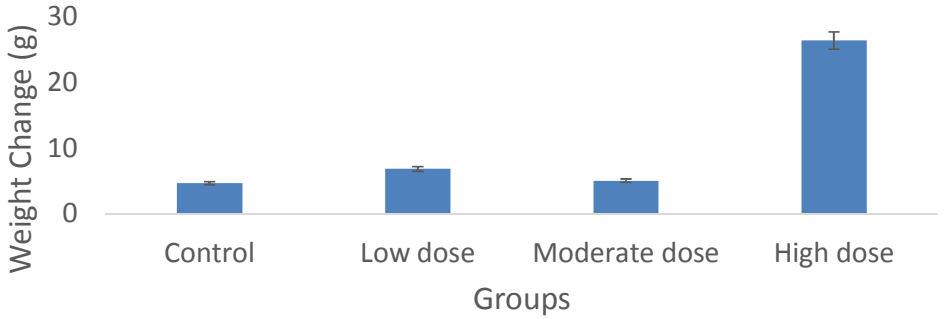


Figure 4: Chart showing absolute weight change values of experimental animals.

DISCUSSION

There have been conflicting reports regarding the effect of monosodium glutamate which is used as a flavor enhancer in food industries. It is a major constituent (99%) of a popular food seasoning known as "Ajinomoto" which has been approved by the National Agency for Food and Drug Administration and Control (NAFDAC). However, there have been reports of its harmful effects when consumed overtime and also contradictory reports on its effect on blood glucose and blood insulin levels. We specifically set out to investigate its effect on blood glucose concentration, blood insulin levels as well as blood lipid profile. Findings from this study showed there was a significant decrease in insulin levels in all groups treated with MSG when compared with control this decrease was dose dependent. We also observed a significant increase in blood glucose concentrations of rats administered MSG when compared with control. Our results did not agree with results of Hiratal *et al;* (1997), Nagata *et al;* (2006), who reported increased in both insulin concentration and blood glucose level in MSG groups when compared with control, the differences in these results could be attributed to the route of administrations, while we administered the different doses of MSG using oral gastric tube, Hiratal and colleagues administered theirs intravenously, the route or course an active substance takes from application location to location where it has its target effect is usually a matter of pharmacokinetics (Lee *et al;* 2004). Also our finding did not agree with findings of Yeda *et al*; (2005) and that of Okunlola and Omolara (2020) who also reported increase in insulin and fasting glucose concentrations, they supplemented the rats feeds with different doses of MSG, the addition of MSG directly to the rat feeds may have made it very palatable resulting in over feeding which could have induced metabolic syndrome.

However, the reduction in the insulin concentration observed in this study can be explained by findings of Piyanard *et al;* (2015), who reported reduction in pancreatic beta cells of rats after administration of MSG over a period of up to 9 months.

Insulin is produced by the pancreatic beta cells and reduction in these cells could result in low secretion of insulin by the cells. We also observed a significant increase in fasting blood sugar in all groups administered the MSG when compared with control, this agrees with findings of the studies done by (Hiratal *et al;* 1997, Nagata *et al*; 2006) as well as studies done by (Yeda *et al;* 2005, Okunlola and Omolara 2020), however while they attributed the increase in fasting glucose level to insulin resistance since there was simultaneous increase in insulin level along with glucose level, the increase in fasting blood glucose observed in this current study could be as a result of the reduction in insulin concentration thus unavailable to transport glucose from blood into the cells for energy. This could be due to reduction in pancreatic beta cells upon administration of MSG (Piyanard *et al;* 2015), or as a result of the pharmacokinetics of MSG due to route of administration. There was no significant difference in total Cholesterol, triglyceride, HDL and LDL in all the groups fed MSG when compared with control, this did not agree with findings of other researchers who reported increase in total lipid profile (cholesterol, triglyceride, LDL,CLDL) and reduction in HDL after administration of MSG. (Saeed*,2016*, Egbuome &Osakwe 2011, El Malik & Sabahelkhier,2019), the high Lipid profile levels reported by other authorities can be attributed to the route of administration of the MSG, addition of MSG directly to the standard feeds makes the feeds more palatably thus resulting in overfeeding by the rats. Alteration of blood lipid profile may be elicited by several factors such as defective gene, consequences of diet and drug administrations or disorders that encompass diabetes and hepatic dysfunction.

The administered dose of MSG and duration of exposure of the rats to MSG were critical factors that might have influenced the level of insignificant effect of LDL, VLDL, Triglyceride and Cholesterol respectively in the other experimental groups compared to the control group. Also, the method of administration and concentration of MSG administered might have resulted in dissimilarities in the results of previous studies. This study reveals an increase in body weights of group D (high dose) though not much difference in group B and C compared to the control group, these results disagrees with findings by Maluly *et al*., (2013) who reported that ingestion of MSG had no effects on body weight gain however it deviates at the point of food consumption in albino rats as an increasingly voracious appetite was reported by the present study. Tordoff *et al*., (2012) also reported that MSG did not influence body weight or energy levels in adult rats and mice. The findings of the present study however are in tandem with the findings of Abd *et al*; (2014) who reported that MSG was found to cause a significant increase in the body weight and food consumption of animals fed with 4 g/L of MSG and similarly Hermanussen *et al*; (2009). El-Helbaway *et al*; (2017), demonstrates a significant increase in body weight of neo-natal albino rats exposed to 10 g/L Monosodium Glutamate. Nosseir *et al*; (2012) reported that through the stimulation of orosensory receptors, MSG influenced the appetite positively, thus induced weight gain. Nosseir *et al*; (2012) also reported that there was a significant reduction in the body weight after a recovery period of 6 weeks cessation of MSG indicating that the effects of MSG on body weight is temporary.

CONCLUSION

This study has shown that intake of MSG can induce hypoinsulinemia and hyperglycemia thus diabetes mellitus, also high intake of MSG can result in weight gain resulting in obesity, however there was no significant impact in lipid profile after intake of MSG. We therefore recommend for further studies to ascertain the mechanisms involved in the hyperglycemia observed in this study.

REFERENCES

Abd, E., Magdy, O., Gamal, S., El-Fark., Sherif, M. and Hassan ,M. H.(2014). Effects of Prolonged Oral Intake of Monosodium Glutamate (MSG) on Body Weight and Its Correlation to Stomach Histopathological Changes in Male Rats.*Thai Journal of Vetinary Medicine.***44**(2): 201-208.

Allian, C.C., Poon, L.S., Chan, G.S.C., Richmond, W. and Fu, P.C. (1974).Enzymatic determination of total serum cholesterol.*Journal of Clinical Chemistry*.**20**:470-475.

Akinkugbe OO (1997). The non-communicable diseases in Nigeria-Report of a national survey. Ibadan, Nigeria: intec printers limited.

Chen, X., Zheng, Y., Shen, Y. and Voglibose, B.A. (2006).One of the most important α-glucosidase inhibitors.*Current Medical Chemistry.***13**:109-116.

Egbuonu A.C and Osakwe O.N (2011). Effects of high monosodium glutamate on serum markers of lipid profile status in male wistar rats, *Journal of Medicine and Medical Sciences* Vol.2(1) pp. 653-656

Elshaikh, A.F. and Abuelgassim, A.I. (2018).Effect of monosodium glutamate on plasma insulin, glucose levels, and Toxicity in rats.*Agricultural and Veterinary Research.***102**:1-15

Emanuele, N., Klein, R. and Moritz, M. (2009). Comparison of dilated fundus examinations with seven- field stereo fundus photographs in the Veterans Affairs Diabetes Trial. *Journal of Diabetes Complications*.**23**(5):323-329.

Enemali, M.O. and Danielson, E.U. (2014). The acute effect of monosodium glutamate orally administered to male Wistar rats on the serum activities of AST, ALT and ALP. *Transnational Journal of Science and Technology*.**4**(1):1-9.

Erasmus RT, Fakeye T, Olukoga O, Okesina AB, Ebomoyi E, Adeleye M, Arije A. Prevalence of diabetes mellitus in a Nigerian population. *Trans R Soc Trop Med Hyg.* 1989;**83**:417–418.

Eweka, A.O., Eweka, A. and Om'iniabohs, F.A. (2010). Histological Studies of the Effects of Monosodium Glutamate on the Fallopian Tubes of Adult Female Wistar Rats. *North American Journal of Medical Sciences*.**2**(**3**):146-149.

Eweka, A.O., Igbigbi, P.S. and Ucheya, R.E. (2011).Histochemical Studies of the Effects of Monosodium Glutamate on the Liver of Adult Wistar Rats. *Annal of Medical and Health Sciences Research.***1**(**1**):21-29.

Hermanussen, M., Garcia, A.P., Sunder, M., Voigt, M., Salazar, V., Tresguerres, J.A.F. (2009). Obesity, Voracity, and Short Stature: The Impact of Glutamate on the Regulation of Appetite. *European Journal of Clinical Nutrition.***60**: 25-31.

Hirata, A. E., Andrade, I. S., Vaskevicius, P. and Dolnikoff, M. S. (1997). Monosodium glutamate (MSG) - obese rats develop glucose intolerance and insulin resistance to peripheral glucose uptake. *Journal of Medical and Biological Research*.**30**:671-674

Ibukun, O.O., Monday, T., Abiola, S.O. and Ololade, S.O. (2015).Haematological effect of ethanolic extract of Uvariachamae on monosodium glutamate-induced toxicity in sprague-dawley rats.*Annals of Biological Research.***6**(7):17-22.

Inuwa, H.M., Aina, V.O., Baba, G., Aim-Ola, I. and Leehman, J. (2011).Determination of nephrotoxicity and hepatoxicity of monosodium glutamate consumption. *British Journal of Pharmacology and Toxicology*.**2**(3):148-153. Jayeola O.C, Okunlola O, Oyagbemi A.A. Jayeola T.G (2020),Hypoglycemic Potential of Cocoa Powder in Monosodium Glutamate-Diet Induced Diabetic Mice Sumerianz *Journal of Agriculture and Veterinary,* Vol. 3, No. 7, pp. 90-96

Kengne AP, Amoah AG, Mbanya JC. Cardiovascular complications of diabetes mellitus in sub-Saharan Africa. Circulation. 2005;**112**:3592–3601.

Lee P, Cunningham FM, Elliot J. (2004). Principles of Pharmacodynamics and their applications in veterinary pharmacology. *Journal veterinary Pharmacol. Ther.* 27(60):397-414.

Leigh, S., Idris, I., Collins, B., Granby, P., Noble, M. and Parker, M. (2015). Promoting health and reducing costs: a role for reform of self-monitoring of blood glucose provision within the National Health Service. *Diabetic Medicine.* **33** (5): 681–90.

Maluly, H.D.B., Areas, M.A., Borelli, P. and Reyes, F.G.R. (2013). Evaluation of Biochemical, Hematological and Histological Parameters in Non-diabetic and Diabetic Wistar Rats Fed Monosodium Glutamate. *Food and Nutrition Sciences*.**4**: 66-76.

Malik, E.A. and Sabahelkhier, (2019).Changes in lipid profile and heart tissues of wistar rats induced by using monosodium glutamate as food additive. *International Journal of Biochemistry and Physiology*.**4**(**1**):147.

Nagata M, Suzuki W, Iizuka S, Tabuchi M, Maruyama H, Takeda S,(2006). Type 2 diabetes mellitus in obese mouse model induced by monosodium glutamate. *Exp Anim.*; 55(2):109–15.

Nehal F.E, Doaa A.R, Maysa F.S, Manal E.E (2017). Effect of Mono Sodium Glutamate on body weight and the histological structure of ZonaFacciculata of the adrenal cortex in young male albino rats.*Tanta Medical Journal* (45) 104 -113.

Nosseir, N.S., Ali, M.H.M. and Ebaid, H.M. (2012).A Histological and Morphometric Study of Monosodium Glutamate Toxic Effect on Testicular Structure and Potentiality of Recovery in Adult Albino Rats.*Journal of Biology*.**2**:66–78.

Olatunbosun ST, Ojo PO, Fineberg NS, Bella AF.(1998). Prevalence of diabetes mellitus and impaired glucose tolerance in a group of urban adults in Nigeria. *J Natl Med Assoc.* ;**90**:293– 301.

Ohwovoriole AE, Kuti JA, Kabiawu SI (1998)..Casual blood glucose levels and prevalence of undiscovered diabetes mellitus in Lagos Metropolis Nigerians. *Diabetes Res Clin Pract.* ;**4**:153– 158.

Piyanard B,,Sakda W,, Wiphawi H,, Supattra P, Amod S,, Carlo S, Vitoon P,, Ubon C. (2015). Monosodium Glutamate Dietary Consumption Decreases Pancreatic β-Cell Mass in Adult Wistar Rats, *PLOS ONE*, (29)1359-1371

Sasaki, Y., Suzuki, W., Shimada, T., Iizuka, S., Nakamura, S. and Nagata, M. (2009). Dose dependent development of diabetes mellitus and non-alcoholic steatohepatitis in monosodium glutamate-induced obese mice.*Life Science*.**85**(14):490-498.

Saeed, A.A. (2016). Adverse Effects of Monosodium Glutamate on Serum Lipid Profile, Cholesterol Status and Blood Glucose in Adult Rats. *Research Jouenals of Pharmaceutical, Biological and Chemical Sciences*. **7**(1):732-739.

Salah, E., Sabahelkhier, M.K. and Shama, I.Y.A. (2015). Effects of Aluminum Sulphate Treated in Deionizable and Tap Water on Lipid Profile of Wister Rats. *Journal of Science and Technology*. **5**(5):268-270.

Turkington, R. W., Estkowkski, A. and Link, M. (1982). Secretion of Insulin or connecting peptide, a predictor of insulin dependence of obeseddiabetics. *Archives of Internal Medicine*.**142**:1102- 1105.

Tordoff, M.G., Aleman, T.R. and Murphy, M.C. (2012). No Effects of Monosodium Glutamate Consumption on the Body Weight or Composition of Adult Rats and Mice. *Physiological Behaviour*.**107**: 338-345. Walker, R. and Lupien, J.R. (2000).The safety evaluation of monosodium glutamate. *The Journal of Nutrition*.**130**(4):1049-1052.

Yeda M.D. Luciane A. Faine M.D. Cristiano M. Galhardi M.D. Hosana G. Rodrigues M.D. Geovana X. Ebaid M.D. Regina C. Burneiko M.D. Antonio C. Cicogna Ethel L.B. Novelli.. (2005). Monosodium glutamate in standard and high-fiber diets: metabolic syndrome and oxidative stress in rats, *Nutrition***21** (6), 49-755.