**Advances in Bioresearch**
Adv. Biores., Vol 14 (2) May 2023: 135-139
©2023 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.14.3.135139

Advances in Bioresearch

## ORIGINAL ARTICLE

# Assessment effects of pyrimidine derivative on pancreatic function and sexual hormones in female rats induced with diabetes

**Ahlam A. AL-Rikaby[1],Maitham Ali. AL-Rikabi[2],*Wasfi A. Al- Masoudi[1]**
[1]Department of Physiology, Pharmacology and Biochemistry, College of Veterinary medicine, University of Basrah, Iraq.
[2]Department of Clinical Pharmacy, College of Pharmacy, University of Basrah, Iraq.
*Corresponding author :Wasfi A. Al- Masoudi; almasoudi59@yahoo.com

**ABSTRACT**
*The purpose of this work is to assess the hyperglycemia effect on body weight, estradiol, Testosterone, FSH and LH and to investigate the effect of pyrimidine derivative(6-chloro-4-methoxy-1,2-dihydropyrimidin-2-amine) administration against hyperglycemia induced by alloxan and histopathological alteration a concomitant in female rats induced with diabetes. Thus, we declared the validity in this hypothesis in the restoration function of pancreas especially within hyperglycemic rats induced by alloxan. This work attempt declare if pyrimidine derivative supplement exhibits antidiabetic effect in hyperglycemia rats or not .32 of adult healthy rats distributed into 4 groups, each group composed of 8 rats as following; Group one (as negative control) comprise of intact rats was given 0.5 ml dimethyl sulphoxide (DMSO) intrapertoineal, group two comprise of intact rats was given (46.86 mg/kg) of pyrimidine derivative dissolved by 0.5ml (DMSO) intrapertoineal, group three (as positive control) comprise of alloxanized rats was given 0.5 ml dimethyl sulphoxide (DMSO) intrapertoineal, group four comprise of diabetic rats was given (46.86 mg/kg) of pyrimidine derivative dissolved by 0.5ml (DMSO) intrapertoineal, the treatment continue for 28 days. Out comes revealed in this study the insulinopenia -induced by alloxan resulting hyperglycemia a concomitant with significantly higher in HbA1c level and lowering in body weight as well as pronounced alteration were seen in sexual hormones, in addition the histological examination revealed prominent changes in pancreatic islets of langerhans in diabetic rats comparison with negative control and intact rats treated with pyrimidine groups, Whereas, the administration of pyrimidine that ameliorating blood glucose and HbA1c levels are evidenced by restoration function of pancreas and significantly improve in body weight and sexual hormones status. The outcomes are confirm the pyrimidine derivative improvement the suppressive effects of diabetogenic on pancreatic islets and sexual hormones in female rats, that index the pyrimidine derivative may be used as antidiabetic drug, however further investigation are required.*
***Key words:*** *Pyrimidine, pancreatic islets, Estradiol, Insulin*

Received 19.02.2023 Revised 26.03.2023 Accepted 21.05.2023

**How to cite this article:**
Ahlam A. AL-Rikaby, Maitham Ali. AL-Rikabi, Wasfi A. Al- Masoudi. Assessment effects of pyrimidine derivative on pancreatic function and sexual hormones in female rats induced with diabetes. Adv. Biores. Vol 14 [3] May 2023. 135-139

## INTRODUCTION

Diabetes mellitus: is a metabolic disorder characterized by insulin insufficiency or insensitivity of target cells to insulin both leading to disturbances of carbohydrate, fat and protein metabolism, as well as dysfunction and failure of various organs [1,2]. Hyperglycemia causes high level of free radicals production thereby creating oxidative stress leads to membrane damage because of membrane lipids peroxidation, protein glycation and the simultaneous decline of antioxidant defense mechanisms [3]. Diabetes is commonly accompanied by cardiovascular risk factors such as dyslipidemia, hypertension, prothrombic factors and microvascular problems involving eyes, kidney and peripheral nerves [4, 5]. The current experiment was aimed to estimate antihyperglycemia and ameliorating effects of pyrimidine derivative on body weight, sexual hormones indices and attenuating adverse effect of alloxan on pancreatic tissue in female rats.

## MATERIAL AND METHODS

### Animals

Thirty two female albino rats weighing between (200 –220g), the animals were maintained in well ventilated cages under standard conditions and provided standard rat pellet and tap water *ad libitum*. They were allowed to acclimatize to the laboratory conditions for two weeks before the experiment.

**Diabetes induction:** Diabetes mellitus type I was induced by a single intraperitoneal dose of 125 mg/kg of alloxan dissolved in 1ml normal saline into 12 h-fasted rats according to [6]. After 3 days the fasting blood sugar levels were monitored with a glucometer, the rats having fasting blood glucose levels more than 200 mg/dl were selected for experimentation.

**Experimental design**: The rats were divided into 4 groups of 8 rats each. Group one (as negative control) comprise of intact rats was given 0.5 ml dimethyl sulphoxide (DMSO) intrapertoineal, group two comprise of intact rats was given 1/10 LD50 (46.86 mg/kg) of6-chloro-4-methoxy-1,2-dihydropyrimidin-2-amine [7] dissolved by 0.5ml (DMSO) intrapertoineal, group three (as positive control) comprise of alloxanized rats was given 0.5 ml dimethyl sulphoxide (DMSO) intrapertoineal, while group four comprise of diabetic rats was given 1/10 LD50 (46.86 mg/kg) of pyrimidine derivative (6-chloro-4-methoxy-1,2-dihydropyrimidin-2-amine) dissolved by 0.5ml (DMSO) intrapertoineal daily for 28 days.

Post-treatment period (28days), the animals were fasted overnight and weighing for recorded changes in the final body weight, then the animals anesthetized with chloroform, the blood was collected in test tubes and left to clot, serum was separated for evaluation of biochemical indices: blood glucose level was assessed by the glucose oxidase method [8], the serum insulin was assayed by method [9], estradiol hormone was estimated as described by method [10], the testosterone hormone was evaluated using the method described by [11], while the FSH and LH were measured according to [12]. So in another heparinized tube, the whole blood sample put in it and used for HbA1c assayed according to method [13]. All rats sacrificed, pancreas was removed and its placed in formalin 10% containers and prepared according to [14] for microscopy examination.

**Analysis of histopathological:** pancreas fixed in formalin was embedded in paraffin and 5µm thick section was processed by a microtome. Tissue slide was stained with haematoxylin and eosin (H&E) and examined using a light microscope for histopathological alteration.

**Analysis of data:** Values are represent as mean ± SE, the findings were analyzed by using one-way analysis of variance (ANOVA) was used to evaluated the relationship of the indices, P Value $P<0.05$was considered to be statistically significant.

## RESULTS

Table(1):Shows the initial and finial body weight, fasting blood glucose, HbA1c and insulin levels in health control, health treated with pyrimidine, untreated hyperglycemic and treated hyperglycemic rats with pyrimidine(PYR)

| Group | Initial body weight gm | Final body weight gm | FBG mg/dl | Insulin ng/ml | HbA1c % |
|---|---|---|---|---|---|
| Health control DMSO0.5ml | 216 ±0.13 B | 220.00±0.21A | 102.25±0.01 C | 2.69±0.05 B | 5.33±0.10 C |
| Health group treated (46.86 mg/kg) PYR | 214.31±0.12 B | 240.16±0.23 A | 87.57 ±0.02 D | 2.75±0.09 A | 4.89±0.16 D |
| Untreated hyperglycemic | 218.61±0.17 A | 185.12±0.11 B | 220.43 ±0.05 A | 1.46±0.06 D | 8.65±0.19 A |
| Hyperglycemic treated with (46.86 mg/kg )PYR | 219±0.15 A | 208.33±0.31 B | 125.49.±0.02 B | 2.57±0.02 C | 6.43±0.11 B |

Values are expressed mean ± standard error: Different capital litters represent a significant difference at ($P <0.05$) between control and treated groups

Table(2): Shows the serum estradiol, testosterone, FSH and LH levels in health control, health treated with pyrimidine , untreated hyperglycemic and treated hyperglycemic rats with pyrimidine (PYR)

| Groups | Estradiol Pg/ml | testosterone ng/ml | FSH ng/ml | LH ng/ml |
|---|---|---|---|---|
| Health control DMSO0.5ml | 72.68 ±23 B | 2.33±0.15 C | 3.37±0. 11 B | 5. 48±0.23 B |
| Health group treated (46.86 mg/kg) PYR | 76.45±0.14 A | 2.00 ±0.18 D | 3.46±0. 14 A | 5.56±0.21 A |
| untreated hyperglycemic | 51.24±0.25 D | 3. 34±0.14 A | 2.14±0. 16 D | 3.69±0.32 D |
| Hyperglycemic treated with(46.86 mg/kg) PYR | 60. 44±28 C | 2.44.±0.17 B | 3.00 ±0.19 C | 4.97±0.20 C |

Values are expressed mean ± standard error: Different capital litters represent a significant difference at (P <0.05) between control and treated groups

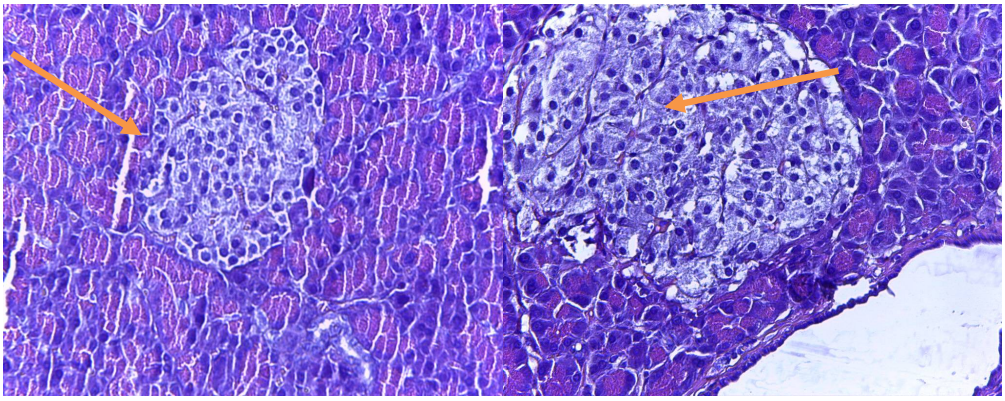
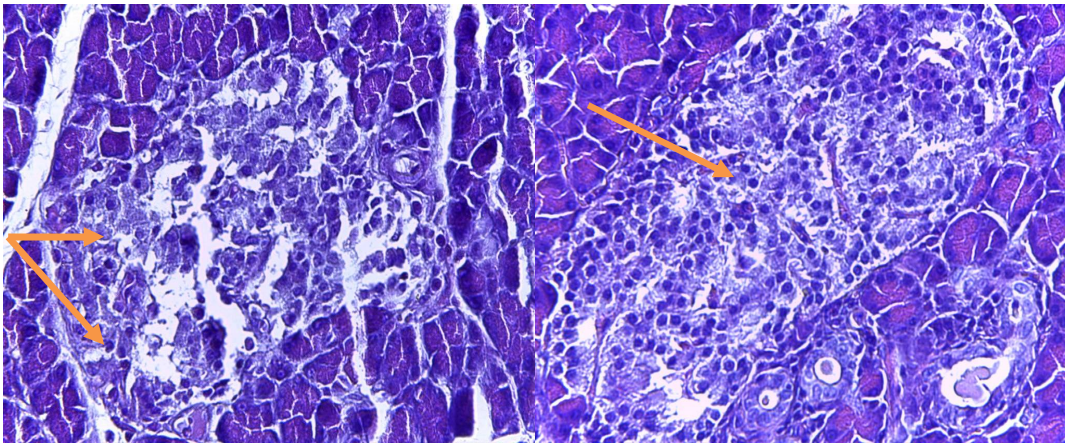


Figure (1):Pancreas section revealed normal structure of islets of the langerhans from negative control rats H & EX400

Figure (2):Pancreas section revealed islets of the langerhans within normal limits and an increase in number of islets from intact rats treated with pyrimidine H&EX400



Figure(3): Pancreas section revealed vaccuolar degeneration of islets of the langerhans from alloxanized rats H&EX400

Figure (4): Pancreas section revealed restoration of islets of the langerhans and an increase in number of islets with within normal limits from hyperglycemic rats treated with pyrimidine H & EX400

In current work project we showed that alloxan administration induced adverse effects on the pancreatic islets, its selectively toxic to beta cell that cause to damage of the cell by producing of ROS resulting insulin in deficiency and pronounced hyperglycemia which indicator to diabetic animals [15, 16]. In table (1) seen the outcomes exhibit a significantly lowered body weight in diabetic rats as comparison with control and intact rats treated with pyrimidine groups. The explanation for this decreased in body weigh may be attributed to both loss appetite and diminished daily diet consumption, also as a result increased lipid lysis and protein synthesis disorder [17]. Results in this experiment are in agreement with other researchers on male and female rats [18, 19]. The outcome on the body weight is also similar with the previous report by [20]. At same table, markedly elevation in average of blood glucose while a significant declined in average of insulin were recorded in diabetic animals comparable to the normal values in control and intact rats treated with pyrimidine groups. So the elevation in value of blood glucose as a result insulinopenia induced by alloxan resulting in declined of influx of glucose to tissues causes to elevated its concentration in blood stream [21]. In addition, the diabetogen connects with SH-groups in the sugar binding side of glucokinase causing to production of the disulfide bound and inhibited of enzyme it also prevent the reabsorption of glucose by renal tubules [22], the data are similar with findings that observed by [5].Since hyperglycemia is characterized by elevation of glycosylation of proteins as hemoglobin, therefore high level of HbA1c is usually a concomitant with rises level of blood glucose, this elevation is considered as index for loss control of hyperglycemia[1], the outcome in this study is in accordance with reports by [23, 24] have shown that high level of HbA1c as a result decreased affinity of Hb to oxygen a process that aid free radical release which lead to hyperglycemia and then Hb glycosylation.

In our experiment the outcomes revealed significantly lower levels of estradiol FSH and LH hormones in a accompanied with the significantly high level of testosterone in the alloxanized animals comparison with negative control and intact rats treated with pyrimidine groups in table (2).The explanation for this decreased in level of estradiol may be attributed to probably suppression in aromatase enzyme due to ROS generation by diabetogen lead to reduction transform of testosterone into estradiol,then this cause to cut the sequence of the processes which leading to this is the negative feedback control on pituitary LH and FSH by estradiol [25]. Also alloxan probably blocked LH and FSH synthesis and their release by the pituitary gland or exerted a negative feedback suppressive on the hypothalamus -pituitary-gonadal (HPG) axis that subsequently reduced serum LH and FSH levels [26]. Outcomes in this experiment are similar with results obtained by [27]. These findings are also noted in another study who found serum estradiol, FSH and LH concentrations were significantly lower in all phases of estrus cycle [28].

The histopathological alterations in pancreatic tissue were accordance with biochemical indices, the exanimation of pancreas section exhibited the islets within normal limits and an increase in number of islets were notable in intact rats treated with pyrimidine derivative in fig (2), while, markedly vaccuolation in pancreatic islets of langerhans in diabetic rats in fig (3) comparison with negative control in fig (1), whereas showed restoration the adverse effect of alloxan on islets and an increase in number of islets in diabetic group treated with pyrimidine derivative fig(4)as comparison to the diabetic rat in fig (3) in current outcomes revealed the pyrimidine derivative administration improvement adverse effect of alloxan on pancreatic islets which by controlling the level of blood glucose and function of pancreas are evidenced by an increase insulin secretions well as ameliorating sexual hormones status. This is consistent with reported by [29] concluded that the pyrimidine compound and its derivatives have major importance in treatment biology as anti-inflammatory ,antiviral, anticancer, heart stimulatory, anithyroid and Diarrhea. In another study by [30] demonstrated the pyrimidine derivative exerts on thyroid hormones which are play important role in metabolic rate and sex hormones regulation.

## CONCLUSION

The outcomes are confirm the pyrimidine derivative improvement the suppressive effects of diabetigen on pancreatic islets and sexual hormones in female rats, that index the pyrimidine derivative may be used as antidiabetic drug, however further investigation are required.

## REFERENCES

1. Marwa AH, Jabbar HY and Essam NS. (2018). Study the effect of type 2 diabetes mellitus on level of reproductive hormones in a sample of iraqi women. Int..J.Sci. and Nature. 9 (1): 90-93.
2. Mohammad RK, Fatemeh M, Elham G, Maryam F and Mozafar KF. (2018). Overview of effective herbal and antioxidant compounds on diabetes. J Contemp Med Sci. 4(3): 126–133.

3. Dattatreya A, Sarangi TK. A (2015). Review on Diabetes Mellitus: Complications, Management and Treatment Modalities. J. of Medical and Health Science. 4 (3): 1-16.
4. ZengX, YuX, XiaoS, YaoH, ZhuJ. (2017). Effect of 1,25-dihydroxyvitaminD3 on pathological changes in rats with diabetic cardiomyopathy. J.Lipid in Health and Disease. 16:109-115
5. Al-AzawiS. N. and Al-MahdawiZ. M. (2018). Effect of olive oil and sesame oil on some biochemical parameters in local male rabbits induced with diabetes.Tikrit Journal of Pure Science. 23 (7): 36-41.
6. Al-Fartosi KG, Hussein SH. (2016). Effect of Panax ginseng on glucose level and lipid profile of normal and diabetic male rats (*Rattus norvegicus*). World J Pharm Sci.; 4(3): 543-548.
7. Al-Masoudi WA, Abeer LM ,WamedhHA and Al-Masoudi NA. (2015). Synthesis, Antimicrobial Activity and Molecular Modeling Study of Some New Pyrimidine Derivatives. Eur. J. Chem. 6 (2): 127-130.
8. Trinder P. (1969). Modified assay procedure for the estimation of serum glucose using microwell reader. Indian J ClinBiochem. 6: 24-27.
9. Hales CD and Randle PJ. (1963). Immunoassay of insulin with insulin-antibody precipitate. J. Biochem. 88:137-146
10. AbrahamGE, Manlimos FS. and Govza R. (1977)."Radioimmunoassay of steroids. In: Handbook of Radioimmunoassay." Abraham G.E. ed., M. Dekker Inc., New York. 591.
11. Jaffe B M. and Behrman A R.(1974). "Methods of hormone radioimniunoassay." Academic press, London.
12. Abdul Rahaman SY, Abdul Majeed AF, AIkatan MM. (2009). Effect of sesame seeds on blood physiological and biochemical parameters in broiler breeder hens. Iraq J Vet Sci. 23(1): 25-28.
13. Parker KM, England JD, Da Costa J, Hess RL and Goldstein DE. (1981). Improved colorimetric assay for glycosylated hemoglobin. Clin Chem. 27: 669–672.
14. Luna L G. (1993). Manual of histological staining methods of the Armed Forces Institute of Pathology. 3rd Ed. New York, Mcgraw-Hill.
15. Rohilla A and Ali S. (2012). Alloxan induced diabetes: Mechanisms and effects. Inter J Res Pharmaceut Biomed Sci. 3(2):819-823.
16. Iranloye GO, Makinde O. (2014). Anti-diabetic and antioxidant effects of virgin coconut oil in alloxan-induced diabetic male rats. Journal of Diabetes Mellitus. 3(4) 221-226.
17. Arikawe A P,Daramola A O, Odofin A O and Obika L F O. (2006). Alloxan-induced and insulin-resistant diabetes mellitus affect semen parameters and impair spermatogenesis in male rats. African Journal of Reproductive Health. 10(3):106-113
18. Iranloye BO, Arikawe AP, Medubi OO, Ogboneyenetan KS, Adejana AI, and U.M. Mbama UM. Alloxan-induced diabetes and insulin resistant effects on ovulation and phases of estrous cycle in virgin female Sprague-Dawley rats. J. Afr. Ass. Physiol. Sci. 2017; 5 (1): 15-21.
19. Mohammed IHand Kakey ES. (2020). Effect of Prosopisfarcta extracts on some complications (hematology and lipid profiles) associated with alloxan induced diabetic rats. Iraqi Journal of Veterinary Sciences. 34 (1): 45-50.
20. CatenaC, GiacchettiG, NovelloM, *et al*. (2003). Cellular mechanisms of insulin resistance in rats with fructose-induced hypertension. Am. J. Hypertens. 16 (11 Pt 1): 973-978.
21. Shenoy AG, Ramesh KG. (2002). Improvement of insulin sensitivity by perindopril in spontaneously hypertensive and streptozotocin induced diabetic rats. Indian J Pharmacol. 34:156-164.
22. Weam AS and Luma WK. (2015). The protective role of alcoholic extract of (Anethum graveolens) seeds on renal function in alloxan induced diabetic rabbits. The Iraqi Journal of Veterinary Medicine. 39(2): 1-6
23. d'Emden M. (2014). Glycated hemoglobin for the diagnosis of diabetes. Australian Prescriber J. 37: 98- 100.
24. Khazrai YM, Defeudis G, Pozzilli P. (2014). Effect of diet on type 2 diabetes mellitus: a review, Diabetes & Metabolism Research and Reviews, 1: 24-33.
25. Arikawe AP, Daramola AO, Morakinyo AO, Obika LF. (2008). Effects of diabetes and insulin resistance on estrous cycle, corpus luteum function and pregnancy in female rats. Pakistan Journal of Pathology, 19 (2): 38- 43.
26. Kovacs P, Morales JC, KarkaniasGB. Central insulin administration maintains reproductive behaviour in diabetic female rats. Neuroendocrionology. 2003; 78(2): 90- 95.
27. Ballester J, Munoz MC, Dominguez J. (2007). Tungstate administration improves the sexual and reproductive function in female rats with streptozotocin-induced diabetes. Hum. Reprod. 22 (8): 2128-2135
28. ChabrolleC, JeanpierreE, Tosca L. (2008). Effects of high levels of glucose on the steroidogenesis and the expression of adiponectin receptors in the rat ovarin cells. Reprod. Biol. Endocrinol. 2008; 19 (6): 6-11.
29. Bano T, Nitin K N, Dudhe R. (2012). Free radical scavenging properties of pyrimidine derivatives. Org,Med.Chem.Lett. 2(1):34-39.
30. 30-Fatima I, Munawar MA, Taseem A. (2010). Synthesis and antithyroid activity of some 3-Substituted purine derivatives. J. Mex. Chem. Soc. 54(4): 227-232.