Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 4, 2259-2266
2025
Publisher: Learning Gate
DOI: 10.55214/25768484.v9i4.6542

The polymorphisms influence of some apelin receptor and apelin genes SNPs on the eclampsia pregnancy women's

Mustafa Saleam Khalaf[1*], Alaa Saleh Mahdi[2], Rawa M.M. Taqi[3]
[1]Department of Chemistry and Biochemistry, College of Medicine, University of Fallujah, Anbar, Iraq; mustafa.saleam@uofallujah.edu.iq (M.S.K.).
[2]Department of Pharmaceutics, Collage of Pharmacy, Al-Bayan University, Baghdad, Iraq.
[3]Department of Pharmaceutical Chemistry, College of Pharmacy, Al- Nahrain University, Baghdad, Iraq.

Abstract: Eclampsia is a condition that occurs in pregnant women. This condition is associated with genetic and environmental factors that cause changes in the function of the vascular system, placenta, and other components. Genetic polymorphism in the apelin gene may play an important role in the risk of developing eclampsia in pregnant women and also affects the outcome of the birth process. Therefore, the current study aimed to compare the gene polymorphisms of apelin rs56204867 with apelin receptor rs11544374 and investigate their effects on mothers' and infants' weight gain between the control group of women and the eclampsia group for Iraqi women. This study included the selection of 35 pregnant women suffering from eclampsia and 35 healthy pregnant women of a specific age for the study. The biochemical method PCR–RFLP was applied to both groups to determine the genotype of apelin rs56204867 and apelin receptor rs11544374 gene polymorphisms. The study results showed that according to rs11544374 SNP polymorphisms of apelin receptor genes, TC and TT variant genotypes are significantly associated with eclampsia. On the other hand, this study found that the genotype AA and AG for rs54204867 SNP is higher in healthy women compared with eclampsia women. There is also a significant association between obesity and rs54204867 SNP and rs11544374 polymorphisms in the eclampsia women's group. This study concluded that the rs54204867 SNP polymorphisms of apelin and rs11544374 SNP polymorphisms of apelin receptor genes affect the body weight of the eclampsia women's group because they impact metabolic function, but with specific genotypes. Additionally, these SNP polymorphisms affect blood pressure regulation, leading to elevated proteinuria in the eclampsia women's group.

Keywords: *Apelin, Apelin receptor, Eclampsia.*

1. Introduction

Eclampsia is considered one of the important disorders that accompany in pregnancy women's , as there are many risks for eclampsia women's such as high blood pressure, edema , proteinuria and others . Eclampsia is often caused by different conditions like environmental and genetic , the condition eclampsia can result palcental ischemic , decrease in uterine blood pressure and etc. [1] The ischemic placenta can support releasing biological active factor lead like proangiogenic vascular endothelial growth factor (VEGF) and transforming growth factor-β(TGF-β) that cause imbalance or un-regulation among antiangiogenic factors . These situation can reduced the vasodilators (such as nitric oxide (NO)) with elevated the vasoconstrictors(such as endothelin-1 [1] . Also , eclampsia has association with liver complications . Hepatic enrolled at eclampsia can appear as the hemolysis, elevated Liver enzymes, and low Platelets syndrome (HELLP) [2]. The pathophysiology is involve impaired arterial remodeling via cytotrophoblast invasion by decidual spiral arteries, . Genetics factor plays the important role in the eclampsia development , this study explain association between the

History: Received: 10 February 2025; Revised: 11 April 2025; Accepted: 14 April 2025; Published: 24 April 2025
* Correspondence: mustafa.saleam@uofallujah.edu.iq

inherited (genetic polymorphisms) and eclampsia development in pregnancy women's . Apelin receptor and apelin have the potential to cause complications in pregnant women like eclampsia , this has been proven in many studies that have shown the relationship between genetic polymorphism of apelin and eclampsia [3]. Apelin which is encoded by apelin gene (on Xq25-q26 chromosome) has other functions such as antioxidant and anti-inflammatory effects . It was found that apelin level are lower in eclampsia pregnant women's compared to healthy women's [4]. On the other hand , apelin and its receptors may have other important functions and roles such as blood pressure regulation and salt absorption regulation , and other pathological functions such as contributing to acute kidney injury and heart failure . The current study is the firstly to demonstrate the relationship between the genetic polymorphism of apelin and its receptors SNP with the risk of eclampsia in Iraqi women [5].

2. Methodology

2.1. Study Design

This study included the selection of 35 pregnancy women's suffering from eclampsia and 35 healthy pregnancy women's with a specific age for the study after take consent from all the study individuals . The University of Fallujah was agree on this protocol of study via special ethical committee . the current study depended on the American College of Obstetricians and Gynecologists (ACOG) characteristics to selected the study individuals [6]. This study was conducted after obtaining ethical approvals for conducting scientific research from the scientific and ethical committee , as well as obtaining oral and written approvals from the study subjects by the researchers.

2.2. Inclusion and Exclusion Criteria

The gynecologists doctors were depend on specials criteria from ACOG to selected this study individuals (eclampsia pregnancy women's and healthy pregnancy women's) . The specials criteria applied included blood pressure after 20th week of pregnancy ,proteinuria after 20th week of pregnancy , body mass index (BMI) and clinical examination to confirm eclampsia condition . On the other hand , the exclusion criteria was all situation have polycystic ovary syndrome , liver disease , diabetes and renal disease [7].

2.3. Extraction of DNA and Analysis of Genotype

To DNA extraction used salting out method to use it applied for polymerase chain reaction (PCR) . The PCR was used special primers (see Table : 1) . Condition of PCR was as following :

Initial denaturation (95°C to2 min.)-

- Continue denaturation (30 cycles) (95°C to 30 sec.)
- Annealing of rs54204867 (64°C to 30 sec.)
- Annealing of rs11544374 (65°C to 30 sec.)
- Extension (72°C to 30 sec.)
- Finish extension (72°C to 3 min.)

The products of PCR for rs11544374 and rs5420487 were digest with DdeI and XhoI respectively , than the all digested products incubation for 24 hours at 37 °C . Agaros gel (2% concentration) used for electrophoresis perform . For restriction fragment length polymorphism (RFLP) determination used 100 bpDNA, and UV light used for determination of polymorphic genotypes types . (see Figure 1 and 2).

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 4: 2259-2266, 2025
DOI: 10.55214/25768484.v9i4.6542

Table 1.
Apelin receptor and apelin gene primers with products of PCR.

SNP	Gene ID	Primer 5` → 3`		Product size (bp)	Restriction enzyme	Digest products (bp)
Rs54204867	8862	F	GACCTAGAACAGTACCTGC	254	XhoI	A:254 G:156&90
		R	GAATGGTCTCCTGCTACCC			
Rs11544374	187	F	CAGACTGGTTGTCTGCCCCA	215	Hpyf31	C:215T:150&50
		R	GAGGCAGCTCCTCCTGAG			

.

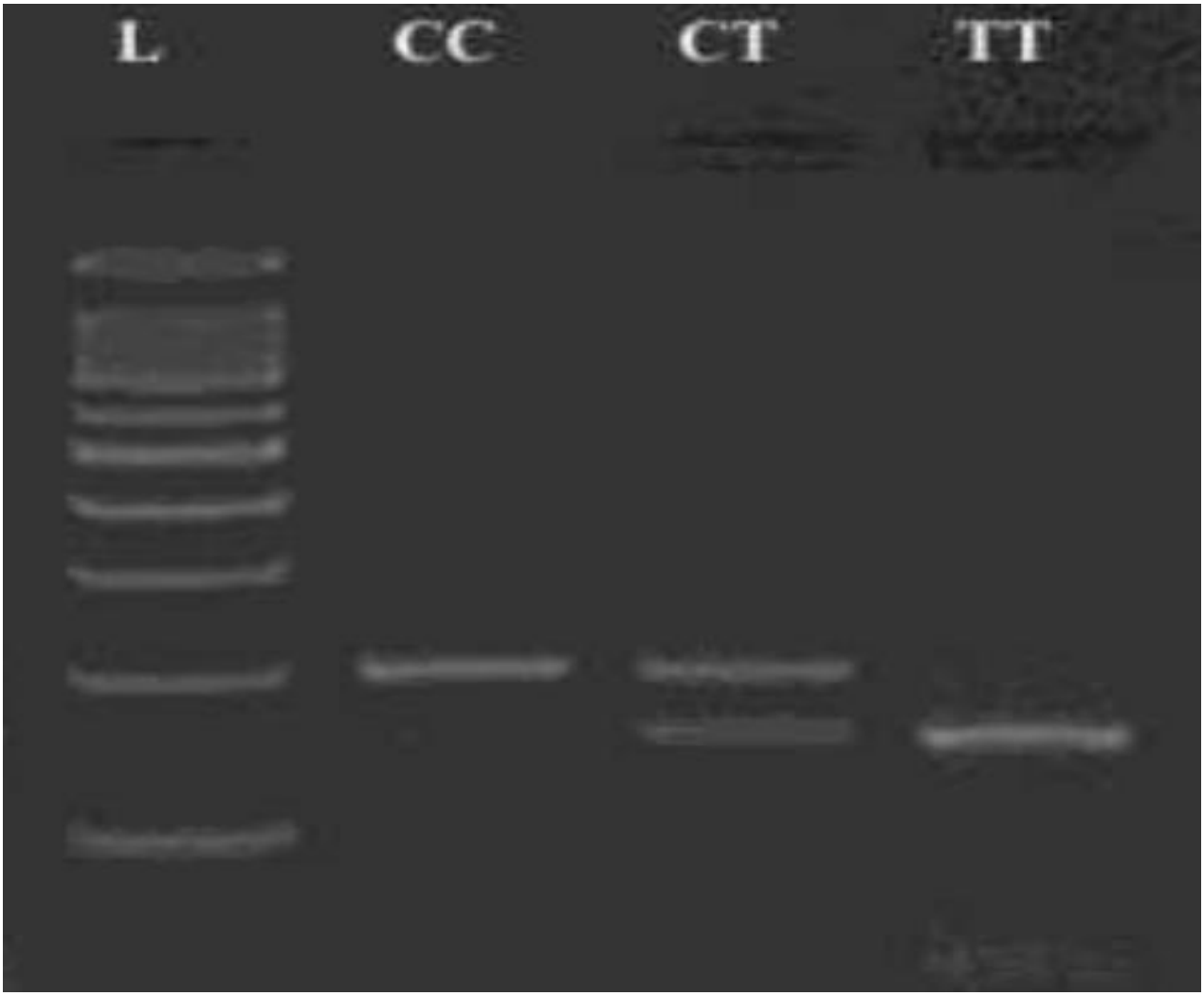

Figure 1.
Apelin receptor polymorphic gene (rs11544374) after digestion as appear on electrophoresis.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 4: 2259-2266, 2025
DOI: 10.55214/25768484.v9i4.6542

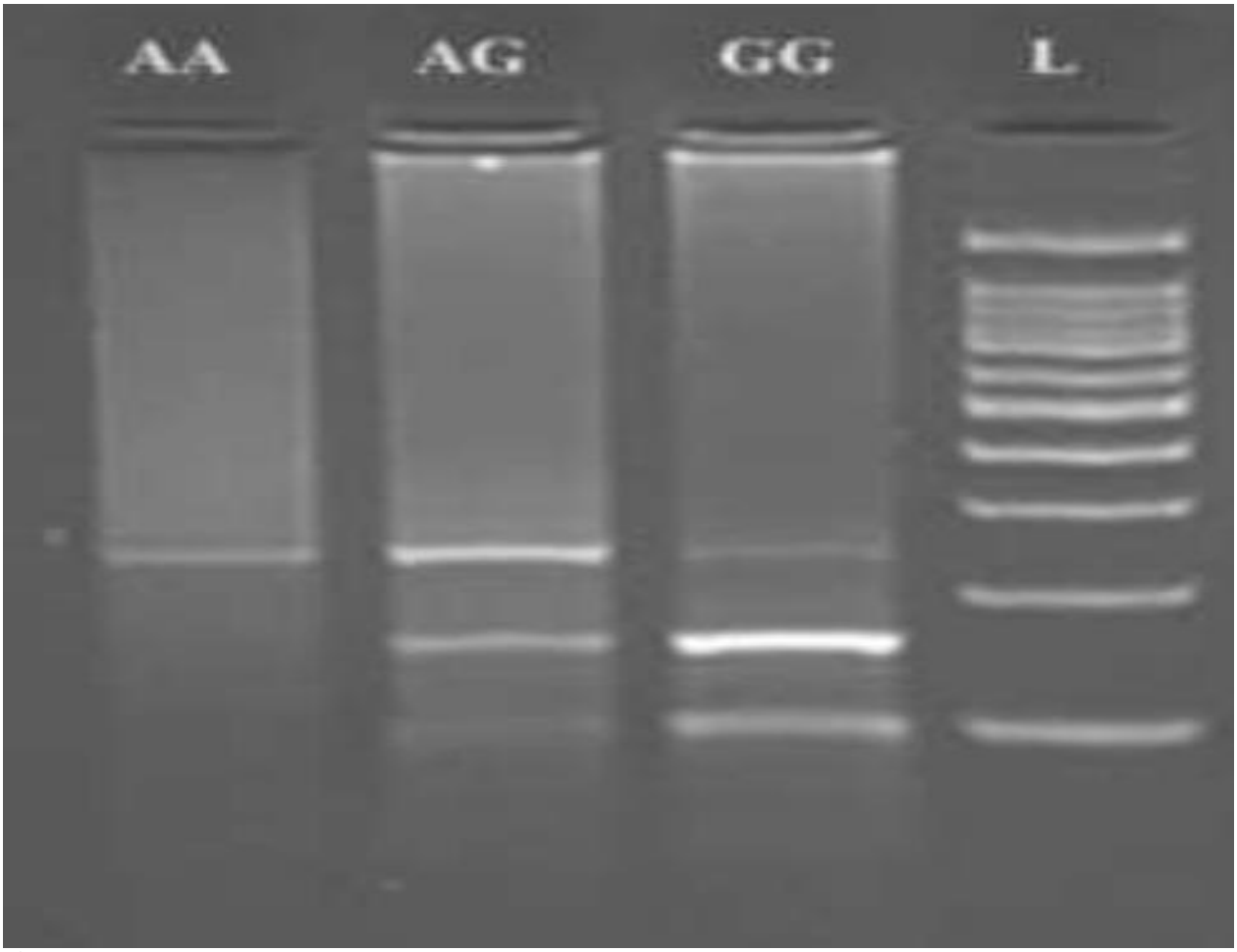

Figure 2.
Apelin polymorphic gene (rs54204867) after digestion as appear on electrophoresis .

2.4. Statistic Analysis

At the current study used SPSS computer program (26 version) to analysis of the results , the statistics of descriptive variables for 2 groups included the following : mean , standard deviation (SD) , frequency and percentage [8, 9].

The statistical significant differences between 2 groups by used independent t-test , also the eclampsia risk evaluated depended on gene polymorphism by binary logistic regression model and odds ratio (OR) . ANOVA statistical method used to determined significant values depended on clinical markers between 2 groups (P-p-value < 0.05 consider significant) [10, 11].

3. Results

At this study , observed after comparison between 2 groups (pregnancy women's suffering from eclampsia group and healthy pregnancy women's group) according various parameters some of them significant and non-significant different , as following :

- Non-significant different according to age
- Significant different according to blood pressure and proteinuria (more in pregnancy women's suffering from eclampsia group)

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 4: 2259-2266, 2025
DOI: 10.55214/25768484.v9i4.6542

- Significant different according to the age of gestational (less in pregnancy women's suffering from eclampsia group)
- Significant different according to BMI (more in pregnancy women's suffering from eclampsia group) See table: 2 .

Table 2.
Differences between pregnancy women's suffering from eclampsia and Healthy pregnancy women's groups according to various biochemical and physiological markers.

p-value	Healthy pregnancy women's (No.35)	Pregnancy women's suffering from eclampsia (No.35)	Markers
0.201	27.9 ± 2.2	29.2 ± 3.1	Women's age (years)
<0.05*	37.0 ± 1.6	34.5 ± 1.8	Age of gestational (weeks)
<0.05*	109 ± 13.9	154 ± 15.4	Blood pressure (mmHg)
<0.05*	501.8 ± 14.3	306.8 ± 21.9	Proteinuria (mg/L)
<0.05*	23.1 ±2.4	26.6 ± 5.2	BMI (Kg/m2)

At this study find ,the genotype of apelin receptor rs11544374 gene were CC (5.3%) , TC (41.6%) and TT (53.1%) in pregnancy women's suffering from eclampsia group , while , the genotype of apelin receptor rs11544374 gene were CC (6.8%) , TC (48.7%) and TT (44.5%) in healthy pregnancy women's group .The alleles frequency T (71.7%) more than C (28.3%) in pregnancy women's suffering from eclampsia group , while ,the alleles frequency T (74.1%) more than C (25.9%) in healthy pregnancy women's group . According to CC genotype , these mean consider as the non-significant value when comparison between the groups because the p-value more than 0.05 , and this gene polymorphism has not any correlation with eclampsia . While , according to TC and TT genotypes consider significant differences .

At this study find ,the genotype of apelin rs54204867 gene were GG(6.2%) , AG(12.2%) and AA(81.6%) in pregnancy women's suffering from eclampsia group , while , the genotype of apelin rs54204867 gene were GG(1.5%) , AG(7.2%) and AA(91.3%) in healthy pregnancy women's group .The genotype of AG is high percent (significant different) in pregnancy women's suffering from eclampsia group compared with healthy pregnancy women's group , this can consider protective factor form eclampsia .The alleles frequency G (7.6%) less than A(92.4%) in pregnancy women's suffering from eclampsia group , while ,the alleles frequency A (91.3%) more than G (8.7%) in healthy pregnancy women's group .According to GG, these mean consider as the non-significant value when comparison between the groups because the p-value more than 0.05 , and this gene polymorphism has not any correlation with eclampsia . While , according to AG and AA genotypes consider significant differences.
See Table 3.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 4: 2259-2266, 2025
DOI: 10.55214/25768484.v9i4.6542

Table 3.
Differences between pregnancy women's suffering from eclampsia and Healthy pregnancy women's groups according to genotypes of rs11544374 SNP apelin receptor gene polymorphisms and genotypes of apelin rs54204867 gene polymorphisms.

OR	p-value	Healthy pregnancy women's (No.35)	Pregnancy women's suffering from eclampsia (No.35)	genotype
apelin receptor rs11544374				
1.4	0.361	6.8	5.3	CC%
0.86	<0.05*	48.7	41.6	TC%
1	<0.05*	44.5	53.1	TT%
alleles				
1	<0.05*	47.1	71.7	T%
0.99	0.062	25.9	28.3	C%
apelin rs54204867				
1.61	0.051	1.5	6.2	GG%
0.48	<0.05*	7.2	12.2	AG%
1	<0.05*	91.3	81.6	AA%
alleles				
0.77	0.059	8.7	7.6	G%
1	0.065	91.3	92.4	A%

4. Discussion

Eclampsia is a neuro-psychiatric disorder that affects pregnant women, causing health complications for the mother and fetus. Such a disorder is caused by genetic and environmental factors [12]. This is what the current study addressed, as it showed some genetic polymorphisms of a specific gene, which is apelin and the gene concerned with the apelin receptor. The current study showed significant differences between the pregnancy women's suffering from eclampsia group and healthy pregnancy women's group according to the genetic SNP polymorphism of the apelin gene (rs54204867 SNP) [4]. The genotype AG was higher while genotype AA was lower in pregnancy women's suffering from eclampsia group . On the other hand, there were significant differences between both groups according to the SNP polymorphisms of the apelin receptor gene (rs11544374 SNP). The genetic type TT was higher while TC was lower in the pregnancy women's suffering from eclampsia group [5].

Such results indicate that the polymorphism (rs54204867 SNP) of the apelin gene can contribute to affecting the amount of apelin encoded by this gene, and the polymorphism (rs11544374 SNP) of the apelin receptor gene can contribute to affecting the nature of the protein forming the apelin receptor, and thus both of these things lead to affecting the effectiveness of apelin in the body of pregnant women, which may cause eclampsia disorder.

According to this study, apelin has two important effects, the first is that the amount and effectiveness of apelin encoded in pregnant women can affect the metabolic activities in the body, which leads to an increase in the body mass index, and this is what was proven in this study [12]. The presence of an increase in the body mass index in pregnant women with eclampsia is accompanied by the appearance of the polymorphism (rs54204867 SNP) apelin gene represented by AG and AA , and (rs11544374 SNP) apelin receptor gene represented by TC and TT proves that these polymorphisms contribute to affecting the coding of apelin protein and its activity, which in turn affects the body mass index in pregnant women with eclampsia disorder [13].

The second effect is that the appearance of such genetic polymorphisms in both genes affects the amount and effectiveness of apelin in pregnant women with eclampsia through the effect of apelin on the contraction and expansion processes in blood vessels by the apelin / APJ pathway , which leads to an increase in blood pressure [14]. The effect on the regulation of blood pressure by apelin may cause the appearance of a quantity of protein in the urine (proteinuria) of pregnant women with eclampsia, which was proven according to the results of the current study. The current study proved that women with eclampsia have higher blood pressure and have more proteinuria compared to the other group [15].

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 4: 2259-2266, 2025
DOI: 10.55214/25768484.v9i4.6542

The analysis of the study results is largely consistent with the results of Rezaei, et al. [7] as both studies showed an significant association between the genotype rs54204867 SNP polymorphism apelin gene and hypertension in pregnancy women's suffering from eclampsia [16]. Such results provide evidence that the women have carriers of this genotype are predisposed to developing eclampsia with hypertension. while , Wang, et al. [17] shown not significant association between the genotype rs54204867 SNP polymorphism apelin gene and hypertension in pregnancy women's suffering from eclampsia [17].

This study results is agreement with the results of Wu, et al. [18] as both studies showed an significant association between the genotype rs11544374 SNP polymorphism apelin receptor gene and metabolic syndrome (hypertension with elevated BMI) in pregnancy women's suffering from eclampsia [18]. While Zhang, et al. [19] shown not significant association between the genotype rs11544374 SNP polymorphism apelin receptor gene and metabolic syndrome in pregnancy women's suffering from eclampsia [19].

5. Conclusion

This study concluded to the rs54204867 SNP polymorphisms of apelin and rs11544374 SNP polymorphisms of apelin receptor genes effect on body weight of eclampsia women's group because it effect on metabolic function , but with specials genotypes . Also , these SNP polymorphisms have effect on blood pressure regulation that lead to elevated proteinuria with eclampsia women's group

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

Acknowledgments:

We would like to thank all those who contributed and helped in completing this scientific research.

References

[1] A. Baylis, W. Zhou, E. Menkhorst, and E. Dimitriadis, "Prediction and prevention of late-onset pre-eclampsia: A systematic review," *Frontiers in Medicine*, vol. 11, p. 1459289, 2024. https://doi.org/10.3389/fmed.2024.1459289

[2] M. Hu, J. Li, P. N. Baker, and C. Tong, "Revisiting preeclampsia: A metabolic disorder of the placenta," *The FEBS Journal*, vol. 289, no. 2, pp. 336-354, 2022. https://doi.org/10.1111/febs.15745

[3] M. W. Socha *et al.*, "The role of NF-κB in uterine spiral arteries remodeling, insight into the cornerstone of preeclampsia," *International Journal of Molecular Sciences*, vol. 22, no. 2, p. 704, 2021. https://doi.org/10.3390/ijms22020704

[4] A. Jafarzadeh *et al.*, "Reciprocal interactions between apelin and noncoding RNAs in cancer progression," *Cell Biochemistry and Function*, vol. 42, no. 7, p. e4116, 2024. https://doi.org/10.1002/cbf.4116

[5] A. A. De Oliveira, A. Vergara, X. Wang, J. C. Vederas, and G. Y. Oudit, "Apelin pathway in cardiovascular, kidney, and metabolic diseases: Therapeutic role of apelin analogs and apelin receptor agonists," *Peptides*, vol. 147, p. 170697, 2022. https://doi.org/10.1016/j.peptides.2021.170697

[6] P. Mota and K. Bø, "ACOG Committee Opinion No. 804: Physical activity and exercise during pregnancy and the postpartum period," *Obstetrics & Gynecology*, vol. 137, no. 2, p. 376, 2021. https://doi.org/10.1097/AOG.0000000000004267

[7] M. Rezaei, M. Ghasemi, M. Saravani, F. Ghahghayi, H. Shahraki-Ghadim, and S. Salimi, "The possible effects of the MTOR polymorphisms on preeclampsia susceptibility, severity, and onset: A case–control study and in silico analysis," *Molecular Biology Reports*, vol. 51, no. 1, p. 335, 2024. https://doi.org/10.1007/s11033-023-09190-x

[8] M. Fiandini, A. B. D. Nandiyanto, D. F. Al Husaeni, D. N. Al Husaeni, and M. Mushiban, "How to calculate statistics for significant difference test using SPSS: Understanding students comprehension on the concept of steam engines as power plant," *Indonesian Journal of Science and Technology*, vol. 9, no. 1, pp. 45-108, 2024.

[9] M. S. Khalaf, B. J. Hussein, and S. A. Abdullah, "The Role of insulin in the Regulation of thyroid function for type 1 diabetic patients," *Journal of Bioscience and Applied Research*, vol. 10, no. 6, pp. 106-113, 2024.

[10] W.-H. Chen *et al.*, "A comprehensive review of thermoelectric generation optimization by statistical approach: Taguchi method, analysis of variance (ANOVA), and response surface methodology (RSM)," *Renewable and Sustainable Energy Reviews*, vol. 169, p. 112917, 2022. https://doi.org/10.1016/j.rser.2022.112917

[11] M. S. Khalaf, "The role of neuregulin 4 status in female's primary infertility patients," *Primary Infertility Patients Journal: Journal of Medicinal and Chemical Sciences*, vol. 6, no. 7, pp. 1577-1581, 2023.

[12] S. M. Shoeib *et al.*, "The ratio of cysteine-Rich angiogenic inducer 61 to MicroRNA-155 expression as a preeclampsia diagnostic marker and predictor of its severity," *Reports of Biochemistry & Molecular Biology*, vol. 12, no. 2, pp. 332-339, 2023.

[13] M. Juyar, M. Ghaemi, and S. Paandeh, "A comparison of apelin Rs56214867 and apelin receptor Rs11644374 genetic polymorphisms with - their relation with risk of eclampsia women," *Reprts of Biochemistry with Moleular Biology*, vol. 23, no. 1, pp. 2.63-2, 2023.

[14] S. Lv, Y. Feng, Q. Jiang, X. Lv, and Y. Yang, "Relationship between apelin/APJ signaling, oxidative stress, and diseases," *Oxidative Medicine and Cellular Longevity*, vol. 2021, no. 1, p. 8866725, 2021. https://doi.org/10.1155/2021/8866725

[15] J. Song, J. Tang, Z. Zhang, Y. Liu, and J. Zhong, "Targeting the elabela/apelin-apelin receptor axis as a novel therapeutic approach for hypertension," *Chinese Medical Journal*, vol. 135, no. 09, pp. 1019-1026, 2022. https://doi.org/10.1097/CM9.0000000000001766

[16] M. Juybar, M. Shahraki, M. Ghasemi, A. Payandeh, S. Saljooghi, and M. Saravani, "A comparison of apelin Rs56204867 and apelin receptor Rs11544374 gene polymorphisms and their association with risk of preeclampsia in southeast Iran," *Reports of Biochemistry & Molecular Biology*, vol. 13, no. 2, p. 273, 2024. https://doi.org/10.61186/rbmb.13.2.273

[17] T. Wang, C. Liu, L. Jia, and J. Ding, "The association between apelin polymorphisms and hypertension in China: A meta-analysis," *Journal of the Renin-Angiotensin-Aldosterone System*, vol. 20, no. 1, p. 1470320319827204, 2019. https://doi.org/10.1177/1470320319827204

[18] X.-d. Wu *et al.*, "Gender-specific association between Apelin/APJ gene polymorphisms and hypertension risk in Southeast China," *Gene*, vol. 669, pp. 63-68, 2018. https://doi.org/10.1016/j.gene.2018.05.079

[19] M. Zhang *et al.*, "Association study of apelin-APJ system genetic polymorphisms with incident metabolic syndrome in a Chinese population: A case-control study," *Oncotarget*, vol. 10, no. 38, p. 3807, 2019. https://doi.org/10.18632/oncotarget.24111

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 4: 2259-2266, 2025
DOI: 10.55214/25768484.v9i4.6542