**International Journal of Environmental Sciences**
ISSN: 2229-7359
Vol. 11 No. 12S, 2025
https://www.theaspd.com/ijes.php

# Effect of Cephalexin on Rosuvastatin Therapeutic Response in Rabbits with Induced Hyperlipidemia

**Mahmood Shaker[1], Ahmed N. Abedsalih[2]**
[1,2]Department of Physiology, Biochemistry and Pharmacology
College of Veterinary Medicine, University of Baghdad, Iraq

**Abstract**
Hyperlipidemia is the rise in plasma triglycerides and cholesterol; It is caused by a disruption in the metabolism of plasma lipoproteins. Either delayed breakdown or rapid synthesis might be the cause of the rise in lipoproteins or plasma lipids. This study was to determination how Cephalexin affected on the normal microbiota that could affect Rosuvastatin pharmacodynamic in rabbits with induced hyperlipidemia. 20 rabbits were divided into four groups were given a diet containing 1.3% cholesterol and 3% saturated fat for 40 days. the experiment was (pharmacodynamic): G1: Positive control with induced hyperlipidaemia; G2: Negative control; G3: Rosuvastatin-treated hyperlipidaemia group and G4: Rosuvastatin + Cephalexin combination treatment hyperlipidaemia group, 28 days. The Rosuvastatin therapy resulted in significant reductions in TC, TAG, LDL, VLDL and Fibrinogen levels and increases in HDL levels were markedly lowered. Furthermore, Short chain fatty acid decrease in the combination group and increases in TC, TAG, LDL, VLDL and Fibrinogen levels and increases in HDL levels comber with rosuvastatin alone. In conclusion combination Rosuvastatin with Cephalexin significantly unimproved the therapeutic efficacy of Rosuvastatin in hyperlipidaemia rabbits. The combination therapy exerts antagonism antioxidant, anti-inflammatory, and lipid-lowering effects.

- **Keywords: Hyperlipidemia, Rosuvastatin, pharmacodynamic and Cephalexin**

## INTRODUCTION

Hyperlipidemia is the greatest risk factor for cardiovascular disease (CVD), which claims the lives of almost 17 million individuals globally each year. Hyperlipidemia affects one-third of Americans, and its prevalence is rising. This is especially troublesome for women since hyperlipidemia raises the risk of cardiovascular disease (CVD) by 47% and is the leading cause of death in the US, accounting for 1 in 4 fatalities each year (Wenger,. 2019). A high blood cholesterol level raises the risk of cardiovascular diseases (CVD) (Rozha *et al*, 2021). In the past several years, diseases linked to elevated blood cholesterol, plasma triglycerides, atherosclerosis, and ischemic heart disease have received a lot of attention. The best course of treatment for hyperlipidemia is diet along with other natural routines (Taher *et al*, 2015 ; Kafi., 2014).

There are numerous lifestyle-related risk factors for hyperlipidemia that can be changed to lower these risks. Evidence-based interventions that have been shown to reduce hyperlipidemia and cardiovascular disease (CVD) include maintaining a healthy weight, avoiding smoking, cutting back on drinking, increasing exercise, and maintaining a body mass index (BMI) below 25.(Lemp *et al*, 2022). Through the action of lipoprotein lipase and by changing the expression of genes linked to lipids and cholesterol (Jadaan and Khudair., 2023).

One of lipid reducing drugs also known in HMG-CoA Reductase inhibitors drugs that inhibit cholesterol formation and increase low density lipoprotein (LDL) elimination, this group of drugs served as the main lipid reducer drugs and the main protector from atherosclerosis and heart

attack that resulted from hyperlipidemia (Mollazadeh *et al.*, 2021). Rosuvastatin considered relatively one of the potent inhibitors drugs that reduce HMG-CoA reductase and has very high level of selectivity effect inside liver cells in comparative with another of non-liver cells, such as skeletal muscle cells (McTaggart, 2003). Mechanism of action Rosuvastatin stop the function of HMG-CoA reductase enzyme by direct competition. This enzyme that responsible for changing the HMG_CoA to mevalonic acid during the first cholesterol synthetic process (Pehlivanovic et al., 2021). Thus, HMG that regulated the synthesis of cholesterol (Bera et al., 2020). Statins increase HDL-C levels to a lesser degree and decrease triglycerides. Inhibiting Since water-soluble and hydroxymethylglutarate, a the amino acid HMG result of a reversible reaction regulated by transfers, may function as an input in other processes of metabolism, the enzyme HMG-CoA reductase does not manufacture potentially harmful sterol intermediates. (Pierzchlińska et al., 2021).

Since antibiotics are the most effective antibacterial agents for bacterial infections, they are a sort of antimicrobial chemical that is active against bacteria. Antibiotic drugs are frequently used to treat and prevent bacterial illnesses (Boyd *et al.*, 2017). In 1970, the FDA approved One drug categorized as an immigrants cephalosporin is cephalexin. Because of its high security and efficacy description, this medication is a popular choice across hospitalized and clinic medical facilities, The creation of novel products derived from the recognized classes of antibiotics has been the primary focus of pharmaceutical corporations (Ibrahim et al., 2016). A Gram-negative, non-spore-forming rod, obligate anaerobic and fastidious bacterium called D. nodosus (Sulaiman et al., 2024). Cephalexin is commonly utilized for treating a variety of illnesses including upper respiratory and urinary tract and bone infections caused by Proteus mirabilis or Staphylococcus aurous, and infections of skin and soft tissue that are primarily caused by bacteria called Streptococcus. Cephalexin is used as a preventative measure to reduce the incidence of bacterial infections and wound infections. These illnesses can be brought on by both streptococci and staphylococci species (Bailey *et al.*, 1971). Antibiotics in animal feedhave also been demonstrated to influencegut microbiome, emphasizing the demand for effective antimicrobials to minimize damagingmicroorganisms and promote animal healthand wellbeing (Dakheel, et al., 2021). Different groups of antibacterial are used to treat infections with determinant criteria to select the suitable antibiotic for a specific bacterial infection depending on its pharmacokinetics-pharmacodynamics properties, potential adverse effects, toxicity, infection severity, and antibiotic spectrum (Al-Jumaili, et al., 2024).

Changes in the intestinal environment brought on by disruptions in lipid metabolism may result in internal microbiota dysbiosis. We can now better comprehend the makeup of the many inflammation in people's intestine and metabolic functioning thanks to the advancement of highthroughput technologies (Fukuda and Ohno, , 2014). The structure and function of gut flora have been demonstrated to be disturbed in people having hyperlipidemia. Adolescents and children with hyperlipidemia had low quantities of propionate, which butyrate, and acetate in the feces.These concentrations are link ed to microorganisms that produce SCFA, including those from the taxa this region, bacteria, rose mary, and fecal , along with those from the tribes Lachnospiraceae and Ruminococcaceae (Gargari et al ., 2018). Additionally, gut microbiota can alter the integrity of intestinal epithelial cells and the intestine, control hepatic cholesterol metabolism, encourage muscle lipid oxidation, and control adipose tissue lipid storage, all of which affect the metabolic balance of lipids (Bäckhed et al., 2004). Additionally, individuals with greater gut biodiversity are more likely to respond favorably to statins, exhibiting decrease levels of LDL cholesterol and total cholesterol. Reduced Lactobacillus and Bifidobacterium and a substantial rise in Bacteroides, Holdemanella, and

Clostridium indicate a poor response to statin treatment and greater side effects (Wilmanski et al., 2022). The systemic quantities of intact medicines, their metabolites, or both may change as a result of antibiotic therapy's potential to affect xenobiotic metabolisms more widely and powerfully than previously thought and to reduce gut microbiota-mediated transformation of oral drugs (Kim, 2015). This study was to determination how Cephalexin affected on the normal microbiota that could affect Rosuvastatin pharmacodynamic.

## MATERIALS AND METHODS

### Animals

There were 20 mature rabbits (weighing 1.5–2 kg and aged 10–12 months) in all used in this study. Animals at every step of the experiment were housed in plastic cages in a conditioned space (22–25 °C) at the College of Veterinary Medicine-University of Baghdad's animal house. The lighting was controlled by an automatic electrical timer that provided twelve hours of light per day (7–19.00). the animals had unrestricted access to water and a typical, cholesterol-containing pellet meal.

### Ethics

At the College of Veterinary Medicine (Number P.G/340) of the University of Baghdad, the local committee for animal care and uses received ethical permission.

### Induction of hyperlipidemia

twenty rabbits were divided into four groups ware fed a diet containing 1.3% cholesterol and 3% saturated fat for 40 day (Shediwah *et al.*, 2019 ; El Nabetiti *et al.*, 2023 ) ( each group five rabbits ).

### Experimental Design

Study the effect of Cephalexin and Amoxicillin on pharmacodynamics of Rosuvastatin on hyperlipidemia in Rabbits

Group one**:** animals in this group ware induced hyperlipidemia and treated with distilled water as positive control group

Group two: animals in this group are negative control non induced hyperlipidemia and treated with distilled water.

Group three: animals in this group are induced hyperlipidemia and treated with Rosuvastatin for 28 days.

Group four: animals in this group are induced hyperlipidemia and treated with Rosuvastatin (orally) for 28 days and the last 7 days given Cephalexin (orally).

### Blood sampling and timing

Blood was collected with jell test tube and anticoagulant EDTA tube and In 2 ml Eppendrof tubes, the serum and plasma were obtained after centrifuging for 10 minutes at 4000 rpm. Until the analysis could be completed, the Eppendrof tubes were placed in a freezer at -20 degrees Celsius and marked with the date.

**Measurement of the lipid profil**

Total Cholesterol (TC), Triacylglycerol (TAG), High density lipoprotein (HDL) kit was used for measuring serum concentration enzymatically and Friedwald formula (Friedwald ., 1972) was used for measuring Serum LDL and VLDL concentration.

**Estimation of the short chain fatty acids in plasma**

This SCFA ELISA kit should only be used in laboratories for research purposes; it should not be used for therapeutic or diagnostic purposes.A spectrophotometer is used to detect the color's intensity at 450 nm after the Stop Solution turns the blue to yellow. This SCFA ELISA Kit comes with a set of calibration standards to determine the amount of SCFA present in the sample. The operator can create a standard curve of optical density vs SCFA concentration by assaying the calibration standards concurrently with the samples. The O.D. of the samples is then compared to the standard curve to ascertain the amount of SCFA present in the samples.

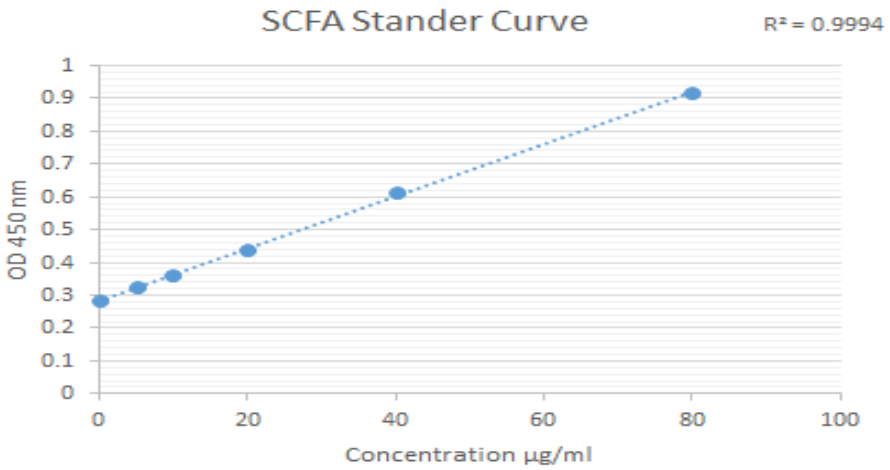


**Figure (1): stander curve of SCFA**

**Hematological analysis (fibrinogen)**

This Fbg ELISA kit should only be used in laboratories for research purposes; it should not be used for therapeutic or diagnostic purposes.A spectrophotometer is used to detect the color's intensity at 450 nm after the Stop Solution turns the blue to yellow. This Fbg ELISA Kit comes with a set of calibration standards to determine the amount of Fbg present in the sample. The operator can create a standard curve of optical density vs Fbg concentration by assaying the calibration standards concurrently with the samples. The O.D. of the samples is then compared to the standard curve to ascertain the concentration of Fbg in the samples The O.D. of the samples is then compared to the standard curve to ascertain the concentration of Fbg in the samples.

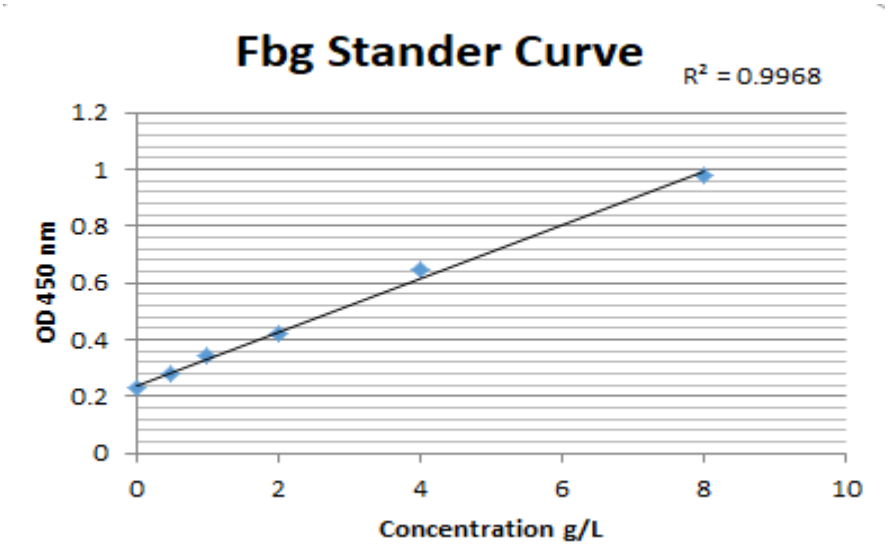


**Figure (2): stander curve of Fibrinogen**

**Statistical analysis Data**

SAS was used for statistical analysis of the data (Statistical Analysis System, version 9.1). The experiment was designed using one-way analysis of variance (ANOVA). To evaluate significant differences between means, the Least Significant Differences (LSD) post hoc test was employed. $P < 0.05$ is regarded as statistically significant.

## RESULTS

**Induction of hyperlipidemia**

The current study's findings showed that when the negative control group was given a diet with 3% saturated fat and 1.3% cholesterol for 40 days, there were substantial improvements in the positive hyperlipidemia group. at the end of forty dyes as the positive control group showed a significant elevation of serum cholesterol in hyperlipidemia rabbits induced in mean value 254.83±2.21 mg/dl as compared with negative control rabbits 92.52±1.97 mg/dl, as shown in the (Figures3).

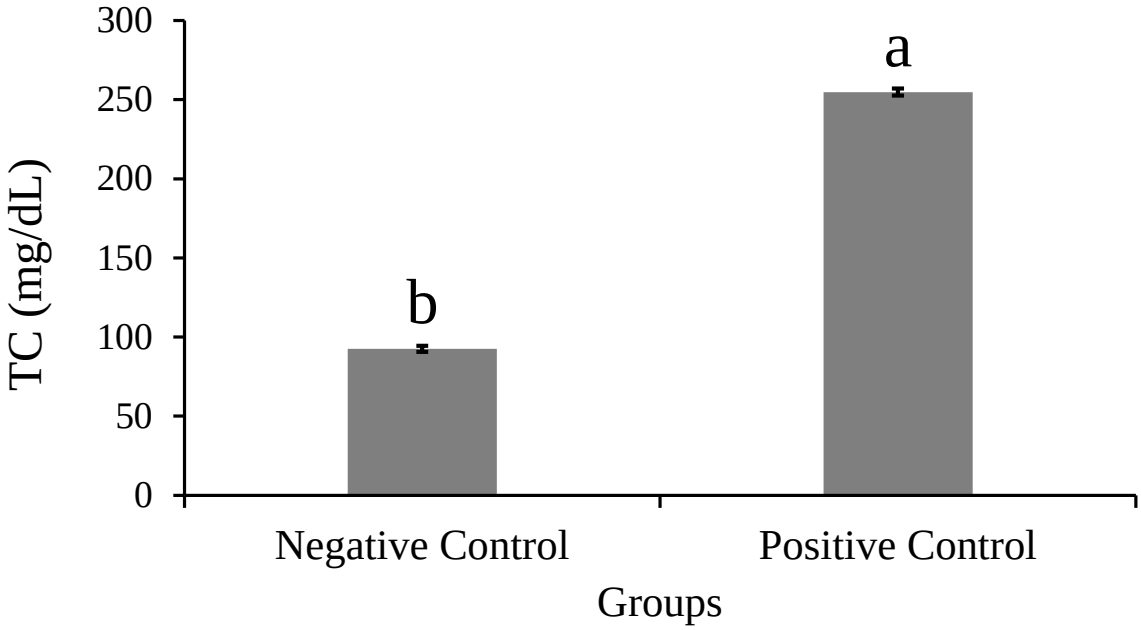


Figure (3): Comparison of the cholesterol level between the positive control group and negative control group.

**Determination Lipid profile**

The table (1) shows that the lipid profile parameter significantly increased in the positive control (hyperlipidemia) group as (206.57±1.75, 224.82±3.40, 165.09±3.28a and 41.31±0.35) in the TG, TC, LDL and VLDL concentrations and significant decrease (18.42±1.65) in the HDL respectively when compared with negative control group, while the rosuvastatin group has significant decrease in (100.79±2.29, 112.79±2.03, 64.15±2.44 and 20.15±0.45) in the TG, TC, LDL and VLDL concentrations and significant increase in (28.52±0.57) in the HDL, respectively, when compared with control positive (Hyperlipidemia) Also, the (rosuvastatin and cephalexin) group showed significant decrease in (172.19±2.17, 182.52±2.79, 125.52±2.52 and 34.44±0.44) in the TG, TC, LDL and VLDL concentrations and significant decrease in (22.55±0.93) in the HDL than rosuvastatin group.

**Table 1: Mean total Serum lipid levels (mg/dl) of health and hyperlipidemia rabbit's treatment with rosuvastatin.**

| Group | TAG | TC | HDL | LDL | VLDL |
|---|---|---|---|---|---|
| G1 | 206.57±1.75a | 224.82±3.40a | 18.42±1.65d | 165.09±3.28a | 41.31±0.35a |
| G2 | 81.44±0.64e | 85.44±0.61e | 34.66±0.51a | 34.50±1.00e | 16.28±0.12e |
| G3 | 100.79±2.29d | 112.79±2.03d | 28.52±0.57b | 64.15±2.44d | 20.15±0.45d |
| G4 | 172.19±2.17b | 182.52±2.79b | 22.55±0.93c | 125.52±2.52b | 34.44±0.44b |

| | | | | | |
|---|---|---|---|---|---|
| LSD | 5.44 | 7.02 | 2.99 | 7.30 | 1.09 |

*The value represents mean± SE*N=5 for each group*Means with a different small letter in the same column are significantly different (P<0.05)

**Estimation of the short chain fatty acids in plasma**

The plasma short chain fatty acids concentration (µg/ml) in rabbits is shown in table 4.8. The results showed a significantly increase in the plasma short chain fatty acids concentration (µg/ml) in the positive control group with mean value (54.64±0.99) when compared with negative control group, there was a significantly slightly decrease in the plasma short chain fatty acids concentration in both at means values (31.67±1.34) in the rosuvastatin and cephalexin groups, respectively while the rosuvastatin group registered a significantly increase in plasma short chain fatty acids concentration with mean value (46.01±1.33) compared with both group.

**Table (4-8) Comparison of the short chain fatty acids in plasma in all groups.**

| Groups | SCFA(µg/ml) |
|---|---|
| G1 | 43.09±0.60b |
| G2 | 54.64±0.99a |
| G3 | 46.01±1.33b |
| G4 | 31.67±1.34d |
| LSD | 3.02 |

Means with a different letter in the same column are significantly different (P<0.05)

**Hematological analysis (fibrinogen)**

The serum Fibrinogen concentration g/L in rabbits is shown in table 4.9. The results showed a significantly increase in the serum Fibrinogen concentration g/L in the positive control group with mean value (8.90±0.53) when compared with negative control group, there was a significantly increase in the serum Fibrinogen concentration in both at means values (6.51±0.41) in the rosuvastatin and cephalexin groups, respectively while the rosuvastatin group registered a significantly decrease in Fibrinogen concentration with mean value (3.40±0.36) compared with another group.

**Table (4-9) Comparison of the fibrinogen in serum in all groups.**

| Group | Fibrinogen g/L |
|---|---|
| G1 | 8.90±0.53a |

| | |
|---|---|
| G2 | 2.82±0.18c |
| G3 | 3.40±0.36c |
| G4 | 6.51±0.41b |
| LSD | 1.15 |

Means with a different letter in the same column are significantly different (P<0.05)

## DISCUSSION

The positive control group showed an increase in the serum concentration of increased concentrations of TC, TAG, LDL and fibrinogen in hyperlipidemia. However, hypercholesterolemia is widely recognized as an important risk factor for hyperlipidemia development. The result of the study agrees with the result of (Devries *et al.,* 2010; Yang *et al.*, 2000**)**, also demonstrated that feeding a high-cholesterol diet to rabbits resulted in marked hypercholesterolemia and the development of hyperlipidemia. this agrees with (Boustany Kari *et al.,*2007**)** . Rosuvastatin, a potent HMG-CoA reductase inhibitor, significantly reduced TG, TC, LDL, VLDL and fibrinogen levels, while significantly increasing HDL compared to the hyperlipidemic group. These results are consistent with previous studies showing that rosuvastatin effectively lowers atherogenic lipids and improves HDL levels by upregulating LDL receptors and enhancing reverse cholesterol transport (Luvai *et al.*, 2012; Cortese *et al.*, 2016). Additionally, the observed increase in HDL may stem from enhanced reverse cholesterol transport and improved expression of ApoA-I, a major HDL. Such mechanisms contribute not only to lipid regulation but also to rosuvastatin's pleiotropic effects, including anti-inflammatory and endothelial-stabilizing actions (Liao & Laufs, 2005; Wazir *et al.*, 2023).
The combination of rosuvastatin with cephalexin exhibited higher levels of TG, TC, LDL, and VLDL, and lower HDL and fibrinogen than the rosuvastatin group and decrease in SCFA. Though cephalexin itself is not traditionally associated with lipid changes, its antibacterial activity against gut flora likely influences systemic lipid metabolism. Cephalexin, a first-generation cephalosporin antibiotic, has not been traditionally associated with lipid metabolism. However, it is possible that alterations in gut microbiota caused by cephalexin may indirectly impact lipid absorption or metabolism (Kootte et al., 2012). Antibiotic-induced changes in intestinal flora have been shown to affect bile acid metabolism and lipid regulation (Vourakis *et al.*, 2021). Gut Microbiota Interference Cephalexin may reduce bacterial populations responsible for Bile salt deconjugation**,** affecting cholesterol emulsification and absorption. Short-chain fatty acid (SCFA) production, which is linked to lipid homeostasis, insulin sensitivity, and energy balance (den Besten et al., 2013).Conversion of primary to secondary bile acids, which impacts nuclear receptors like FXR and TGR5 that regulate cholesterol metabolism (Ridlon et al., 2006). Disruption of these microbial pathways might impair cholesterol clearance**,** thereby diminishing rosuvastatin's maximal efficacy. This trend suggests that disruption of the gut microbiota impairs the systemic immune balance and may potentiate low-grade inflammation. Antibiotics can disrupt intestinal homeostasis, reduce

short-chain fatty acid (SCFA) production, and increase gut permeability, leading to microbial translocation and activation of pro-inflammatory signaling pathways**,** such as TLR4-NF-κB, ultimately increasing fibrinogen expression (Tang et al., 2017).

**Conclusion**

Rosuvastatin alone significantly improved lipid profiles (TG, TC, LDL, and VLDL), its combination with antibiotics showed less pronounced improvements, suggesting a loss of therapeutic efficiency. The use of antibiotics may reduce indirectly affect bile acid metabolism and cholesterol regulation. This interplay highlights the importance of host-microbiome-drug interactions in determining the outcome of pharmacotherapy.

## REFERENCES

1. Al-Jumaili, M. A., Al-Abbass, N. N., & Ibrahim, O. M. (2024). Distribution and Elimination of the Third Generation Cephalosporins in Dogs: A Comparative Study. *Diyala Journal for Veterinary Sciences*, *2*(3), 123-131.
2. Bäckhed, F., Ding, H., Wang, T., Hooper, L. V., Koh, G. Y., Nagy, A., ... & Gordon, J. I. (2004). The gut microbiota as an environmental factor that regulates fat storage. *Proceedings of the national academy of sciences*, *101*(44), 15718-15723.
3. Bailey, A., Walker, A., Hadley, A., & James, D. G. (1971). Cephalexin. A new oral antibiotic. *El Torax*, *20*(1), 15-19.
4. Bera, A., Chadha, N. K., Dasgupta, S., Chakravarty, S., & Sawant, P. B. (2020). Hypoxia-mediated inhibition of cholesterol synthesis leads to disruption of nocturnal sex steroidogenesis in the gonad of koi carp, Cyprinus carpio. Fish Physiology and Biochemistry, 46(6), 2421-2435.
5. Boyd, S. E., Moore, L. S. P., Gilchrist, M., Costelloe, C., Castro-Sánchez, E., Franklin, B. D., & Holmes, A. H. (2017). Obtaining antibiotics online from within the UK: a cross-sectional study. *Journal of Antimicrobial Chemotherapy*, *72*(5), 1521-1528.
6. Cortese, F., Gesualdo, M., Cortese, A., Carbonara, S., Devito, F., Zito, A., ... & Ciccone, M. M. (2016). Rosuvastatin: Beyond the cholesterol-lowering effect. *Pharmacological research*, *107*, 1-18.
7. Dakheel, M. M., Al-Mnaser, S. A., Quijada, S., Woodward, M. J., & Rymer, S. (2021). Use of tannin-containing plants as antimicrobials influencing the animal health.
8. den Besten, G., Lange, K., Havinga, R., van Dijk, T. H., Gerding, A., van Eunen, K., ... & Reijngoud, D. J. (2013). Gut-derived short-chain fatty acids are vividly assimilated into host carbohydrates and lipids. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *305*(12), G900-G910.
9. El Nabetiti, S., Eleiwa, N. Z., Kamel, M. A., & Fahmy, A. A. (2023). Hyperlipidemia: Methods of Induction and Possible Treatments. *Zagazig Veterinary Journal*, *51*(2), 169-184.
10. Friedewald, W. T., Levy, R. I., & Fredrickson, D. S. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical chemistry*, *18*(6), 499-502.
11. Fukuda, S., & Ohno, H. (2014, January). Gut microbiome and metabolic diseases. In *Seminars in immunopathology* (Vol. 36, pp. 103-114). Springer Berlin Heidelberg.
12. Gargari, G., Deon, V., Taverniti, V., Gardana, C., Denina, M., Riso, P., ... & Guglielmetti, S. (2018). Evidence of dysbiosis in the intestinal microbial ecosystem of children and adolescents with primary hyperlipidemia and the potential role of regular hazelnut intake. *FEMS microbiology ecology*, *94*(5), fiy045.

13. Ibrahim, O. M. S., Sarhan, S. R., & Salih, S. I. (2016). Activity of isolated staphylococcal bacteriophage in treatment of experimentally induced chronic osteomyelitis in rabbits. *Adv. Anim. Vet. Sci*, *4*(11), 593-603.
14. Jadaan, G. H., & Khudair, K. K. (2023). Curcumin phytosome as an anti-inflammatory and hypolipidemic in nano-silicon treated female rats. *Adv. Anim. Vet. Sci*, *11*(12), 2023-2029.
15. Kafi, L. A. (2014). A comparative study between olive oil and Nigella Sativa oil in treatment of hyperlipidemia induced in male albino mice. *The Iraqi Journal of Veterinary Medicine*, *38*(2), 123-127.
16. Kim, D. H. (2015). Gut microbiota-mediated drug-antibiotic interactions. *Drug Metabolism and Disposition*, *43*(10), 1581-1589.
17. Kootte, R. S., Vrieze, A., Holleman, F., Dallinga-Thie, G. M., Zoetendal, E. G., de Vos, W. M., ... & Nieuwdorp, M. (2012). The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism*, *14*(2), 112-120.
18. Lemp, J. M., Nuthanapati, M. P., Bärnighausen, T. W., Vollmer, S., Geldsetzer, P., & Jani, A. (2022). Use of lifestyle interventions in primary care for individuals with newly diagnosed hypertension, hyperlipidaemia or obesity: a retrospective cohort study. *Journal of the Royal Society of Medicine*, *115*(8), 289-299.
19. Liao, J. K., & Laufs, U. (2005). Pleiotropic effects of statins. *Annu. Rev. Pharmacol. Toxicol.*, *45*(1), 89-118.
20. Luvai, A., Mbagaya, W., Hall, A. S., & Barth, J. H. (2012). Rosuvastatin: a review of the pharmacology and clinical effectiveness in cardiovascular disease. *Clinical Medicine Insights: Cardiology*, *6*, CMC-S4324.
21. McTaggart, F. (2003). Comparative pharmacology of rosuvastatin. Atherosclerosis Supplements, 4(1), 9-14.
22. Mollazadeh, H., Tavana, E., Fanni, G., Bo, S., Banach, M., Pirro, M., ... & Sahebkar, A. (2021). Effects of statins on mitochondrial pathways. Journal of Cachexia, Sarcopenia and Muscle, 12(2), 237-251.
23. Pehlivanović, B., Čaklovica, K., Lagumdžija, D., Žiga Smajić, N., & Bečić, F. (2021). In-vitro evaluation of pleiotropic properties of rosuvastatin. *Int. J. Pharm. Sci. Res*, *12*(2), 1000-6.
24. Pierzchlińska, A., Droździk, M., & Białecka, M. (2021). A possible role for HMG-CoA reductase inhibitors and its association with HMGCR genetic variation in Parkinson's disease. *International Journal of Molecular Sciences*, *22*(22), 12198.
25. Ridlon, J. M., Kang, D. J., & Hylemon, P. B. (2006). Bile salt biotransformations by human intestinal bacteria. *Journal of lipid research*, *47*(2), 241-259.
26. Rozha, S. O., Hawraz, F. M., Harseen, M. R., Hassan, A. H., Rebin, K. M., Dyary, H. O., ... & Soz, M. M. (2021). Green walnut husk ameliorating the adverse effects induced by high fat diet in rats. *The Iraqi Journal of Veterinary Medicine*, *45*(2), 60-68.
27. Shediwah, F. M. H., Naji, K. M., Gumaih, H. S., Alhadi, F. A., Al-Hammami, A. L., & D'Souza, M. R. (2019). Antioxidant and antihyperlipidemic activity of Costus speciosus against atherogenic diet-induced hyperlipidemia in rabbits. *Journal of integrative medicine*, *17*(3), 181-191.
28. Sulaiman, R. R., Marif, H. F., Ali, B. A., Ali, K. N., & Shekh, M. O. B. (2024). Genetic Variability and Antibacterial Sensitivity of Dichelobacter nodosus and Fusobacterium necrophorum Infection in Sheep Sulaimani Province, Kurdistan Region, Iraq. *The Iraqi Journal of Veterinary Medicine*, *48*(1), 93-100.

29. Taher, M. A., Abdul-Hussain, D. A., Hasan, H. F., Fahmi, Z. M., Luaibi, O. K., & Ali, M. G. (2015). Hypolipidemic effect of caffeic acid isolated from Arctium lappa cultivated in Iraq, in hyperlipidemic rat model. *Iraqi Journal of Pharmaceutical Sciences*, *24*(1), 18-24.
30. Tang, W. W., Kitai, T., & Hazen, S. L. (2017). Gut microbiota in cardiovascular health and disease. *Circulation research*, *120*(7), 1183-1196.
31. Vourakis, M., Mayer, G., & Rousseau, G. (2021). The role of gut microbiota on cholesterol metabolism in atherosclerosis. *International Journal of Molecular Sciences*, *22*(15), 8074.
32. Wang, L., Li, C., Huang, Q., & Fu, X. (2019). Polysaccharide from Rosa roxburghii Tratt fruit attenuates hyperglycemia and hyperlipidemia and regulates colon microbiota in diabetic db/db mice. *Journal of Agricultural and Food Chemistry*, *68*(1), 147-159.
33. Wazir, M., Olanrewaju, O. A., Yahya, M., Kumari, J., Kumar, N., Singh, J., ... & SINGH, J. (2023). Lipid disorders and cardiovascular risk: a comprehensive analysis of current perspectives. *Cureus*, *15*(12).
34. Wilmanski, T., Kornilov, S. A., Diener, C., Conomos, M. P., Lovejoy, J. C., Sebastiani, P., ... & Gibbons, S. M. (2022). Heterogeneity in statin responses explained by variation in the human gut microbiome. *Med*, *3*(6), 388-405.