https://africanjournalofbiomedicalresearch.com/index.php/AJBR
Afr. J. Biomed. Res. Vol. 27 (November 2024); 1563 - 1572

Research Article

The Role of Cytochrome P450 and Organic Anion Transporting Polypeptide on Interaction of Atorvastatin and Macrolides in hyperlpidmic Rabbits

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Abstract

Patients on multiple medications are at risk of adverse drug interactions. Atorvastatin, which is metabolized by cytochrome P450 (CYP3A4) and transported by organic anion-transporting polypeptides OATPs, may interact with macrolide antibiotics and vary in their ability to inhibit these pathways. Such drug-drug interactions can lead to significant clinical effects. In this study, evaluated the interaction of atorvastatin and macrolide medications (azithromycin and clarithromycin) in hyperlipidemic rabbits, focusing on their influence on the CYP P450 (CYP 3A4) isoenzyme and OATP. Twenty-five rabbits were randomly divided into five groups: A (healthy control), B (hyperlipidemic control), C (hyperlipidemic treated with atorvastatin), D (atorvastatin for 4 weeks, plus clarithromycin 43.7 mg/kg in the last 5 days), and E (atorvastatin for 4 weeks, plus azithromycin 43.7 mg/kg in the last 5 days. The results showed that a high reduction in the blood lipid levels in group D which was significantly lower ($P<0.05$) when compared to group C and E. Parameters of cytochrome CYP3A4 in liver and intestine appeared significantly lower ($p<0.05$) in groups D and E (0.154±0.21, 0.572±0.42ng/ml) and (0.319+0.32, 1.18±0.67ng/ml) respectively, than in group C (0.322±0.36ng/ml) and (1.131±0.62ng/ml) respectively. On the other hand, the same effect has been reported in group D (i.e. in percentage activity of OATP compared to groups C and E). In conclusion, combining drugs like clarithromycin or azithromycin with atorvastatin can suppress or enhance drug-drug interaction, potentially affecting the activity of the CYP3A4 enzyme and OATP in metabolism of drug administer.

Keywords: Azithromycin, Clarithromycin, hyperlipidemia, Rabbits and Polypharmacy.

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Received 5/11/2024, Acceptance 12/11/2024

DOI: https://doi.org/10.53555/AJBR.v27i3.3585

INTRODUCTION

Polypharmacy refers to the simultaneous use of numerous pharmaceuticals or the delivery of more medications than are therapeutically recommended (Fick et al., 2003; Vegada et al., 2020). The concurrent use of antibiotics and other medications presents challenges for clinical prescribing procedures because antibiotics frequently have different adverse reactions and side effects that may result in pharmacodynamic synergy (Spanakis et al., 2023).Certain categories of antibiotics possess a higher propensity for interaction (Al-Ameedi and Al-Rekabi 2023). A group of antibiotics that commonly administered is macrolides, like azithromycin and clarithromycin which acts as an inhibitor of CYP3A (Mueck 2013). Also it is known to reduce the hepatic uptake of statin transporters; organic anion transporting polypeptide OATPs, which are expressed in hepatocytes and enterocytes, control the pharmacokinetics of drugs like atorvastatin (Hougaard et al. 2020).Statins are a type of medication that lowers lipids level and are now the most

commonly prescribed treatment for hyperlipidemia (Chen et al.,2020). Statins have an impact on lipid profile because of their ability to competitively inhibit hydroxymethylglutaryl-CoA (HMG-CoA) reductase, which is a critical for regulating cholesterol synthesis in hepatocytes (Spanakis *et al.*, 2023).Atorvastatin (ATV) is widely recognized as one of the safest and most effective options for reducing cholesterol levels of statins (Kareem and Abdulaziz 2010). The oral bioavailability of ATV is approximately 12% due to a significant first-pass impact (Croitoru et al., 2015). When taken by mouth, the drug undergoes pre-systemic clearance in the gut and is metabolized in the liver by the cytochrome P450 (CYP450) 3A4 enzyme (Thomas et al., 2021).The CYP450 enzymes play a role in roughly eighty percent of drug oxidative metabolism and fifty percent of commonly used medications (Wilkinson 2005). The elimination of the drug atorvastatin is primarily determined by the rate at which it is taken up by the liver through three polypeptide transporters that organic anion transport polypeptide OATP1B1, OATP1B3, and OATP2B1(Choi et al., 2011).OATP1B1, OATP1B3 are expressed in the basolateral membranes of hepatocytes and transport substances from the blood into the hepatocytes (Keitel et al., 2005) while OATP 2B1 found in the hepatocytes and enterocyte (Lau et al., 2007). Thus, statins vary in their impact on oxidative metabolism and on transporters involved in, for example, intestinal absorption, hepatic uptake, biliary excretion, or renal clearance (Vrkić Kirhmajer et al., 2018). When macrolides are taken together with drugs that are highly potent inhibitors of CYP3A4, pharmacodynamic drug-drug interactions (DDIs) may occur. This risk particularly affects individuals diagnosed with hyperlipidemia who are currently undergoing lipid-lowering treatment to manage their cholesterol levels (Farhan et al., 2014). This study aimed to evaluate the interaction effects of atorvastatin with azithromycin and clarithromycin in hyperlipidemic rabbits by assessing their impact on CYP450 isoenzymes and OATPs

MATERIALS AND METHOD

ETHICS

The Scientific Committee of the Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Baghdad, as well as the local Committee for Animal Care and Use at the College of Veterinary Medicine, University of Baghdad, reviewed and approved all procedures used in this experiment in accordance with Baghdad, Iraq's animal welfare ethical standards (P.G. 123, 15-1-2024).

EXPERIMENTAL ANIMALS

Twenty Five (25) New Zealand White male rabbits, aged 3–4 months old with body weights of 1.7 to 2.0 kg were used. The animals were kept in the animal house at the College of Veterinary Medicine/University of Baghdad for at least two weeks to allow for adaptation.

INDUCTION HYPERLIPIDEMIA

All groups fed with 0.4% cholesterol and 4% hard fat ad libitum. The feeding was done for 8 consecutive weeks (Niimi et al., 2020)

EXPERIMENTAL DESIGN

After induce hyperlipidemia in twenty-five (20) rabbitswere treated starting with schedule as following.

Group A: Healthy rabbits left without induce hyperlipidemia as negative control.

Group B: Hyperlipidemic rabbits without treatment as positive control.

Group C: Hyperlipidemic rabbits were treated orally with atorvastatin (0.86mg/ Kg) for 4 weeks.

Group D: Hyperlipidemic rabbits were treated orally with atorvastatin (0.86mg/Kg) for 4 weeks and in the last 5 days administrated clarithromycin (43.7mg/Kg) once daily.

Group E: Hyperlipidemic rabbits were treated orally with atorvastatin (0.86mg/Kg) for4 weeks and in the last 5 days administrated azithromycin (43.7 mg/Kg) once daily.

PHARMACODYNAMICS PARAMETERS:

Blood collection for Total cholesterol (TC) and Triglyceride (TAG): Before induction, after induction, after 2 and 4 weeks of treatment.

TISSUE CYTOCHROME P450 (CYP3A4):

The analysis of tissue Cytochrome P450 (CYP3A4) in liver and intestine tissues was conducted using to Rabbit Cytochrome P450 (CYP3A4) ELISA kit for Sunlong in China, catalogue number: SL0292Rb. (De Bock et al., 2012).

ORGANIC ANION TRANSPORTING POLYPEPTIDE (OATP)

The analysis of serum, liver and intestine tissue OATP according to the ELISA kit for Feiyue Biotechnology China, catalogue number: FY-ERB4726 (Pan et al., 2023).

BLOOD SAMPLING

Using a disposable syringe, 3 milliliters of blood were collected via cardiac puncture. The blood was then transferred to gelatin tubes and centrifuged for further extraction. The tubes sealed tightly and stored at -20°Cfor subsequent biochemical analysis.

TISSUE HOMOGENATES:

The liver and intestine were weighed and subsequently finely minced. The tissue fragments were thoroughly mixed in phosphate buffer saline using a glass homogeniser while maintaining a low temperature using ice. The ratio between the weight of the tissue (in grammes) and the volume of PBS solution (in millilitres) was 1:9. An ultrasonic cell disrupter was used to sonicate the resultant suspension until the solution turns clear. The homogenates are then centrifuged for a period of 20 minutes at 3000 rotate per minute. The supernatants should be promptly collected for ELISA assay testing or stored at a temperature of -80℃ for later use **(Watzlawik *et al.*, 2021).**

RESULTS

SERUM TOTAL CHOLESTEROL CONCENTRATION (mg/dl)

As shown in **Figure 1,** the concentration of total cholesterol was calculated in mg/dl. There were no significant differences **P≤0.05** among all groups before inducting of hyperlipidemia and significantly increase after 8 weeks of induction compared

to group A. After 2 weeks of treatment with atorvastatin all treated groups **(C, D, and E)** showed decrease the concentration of total cholesterol **(184.64±10.15, 179.48±13.09,** and **171.00±16.21),** respectively, however, there is still a significant difference **P≤0.05** when compared to control group A **(72.88±0.94).** After the end of treatment (after 4 weeks), **group D** register significantly highly decrease in TC **(63.76±2.18)** compared to **group (C and E),** on the other hand, non-significantly between **groups C** and **E** compared with control group A.

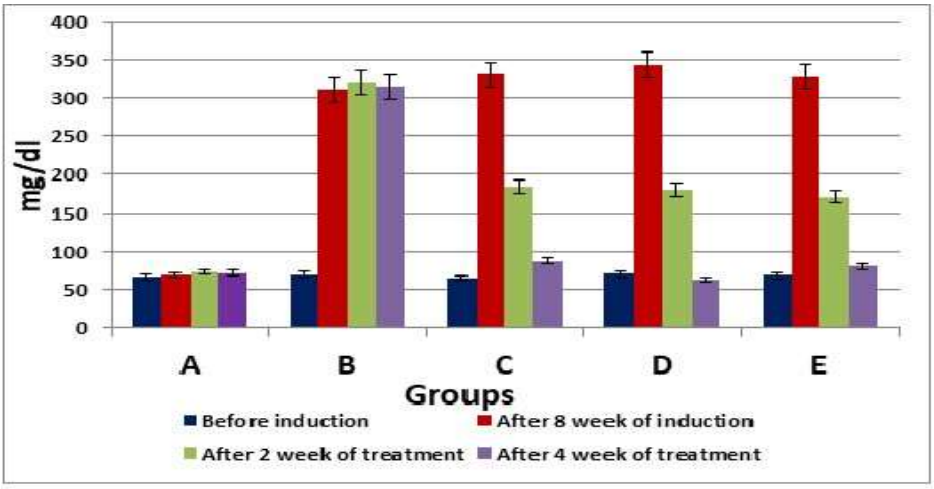

Figure1: Mean total Cholesterol value (mg/dl) of health and rabbits before and during treatment with atorvastatin alone and combination with clarithromycin or azithromycin.A: negative control, B: positive control, C: Atorvastatin, D: Atorvastatin+ clarithromycin, E: Atorvastatin +Azithromycin

SERUM TRIGLYCERIDE CONCENTRATION (mg/dl)

The acquired result from the **Figure 2** revealed that there was no significant difference in the level of TAG in all groups before induction. Significant increase in TAG after 8 weeks of inducing hyperlipidemia was noticed in all groups compared to group A. After 2 weeks of treatment with atorvastatin, all treated groups (C, D, and E) showed decrease the concentration of total triglyceride **(105.90 ±1.64, 98.74 ±1.14, and 100.12±2.58)mg/dl,** respectively, however, there is still a significant difference **P≤0.05** when compared to negative control group **A (84.22 ±1.57 mg/dl).** After 4 weeks of treatment, **group D** register significantly highly decrease in **TAG (45.78±0.96 mg/dl)** compared to group **(C and E),** on the other hand, there was no statistical difference between **group C and E** compared to negative control group.

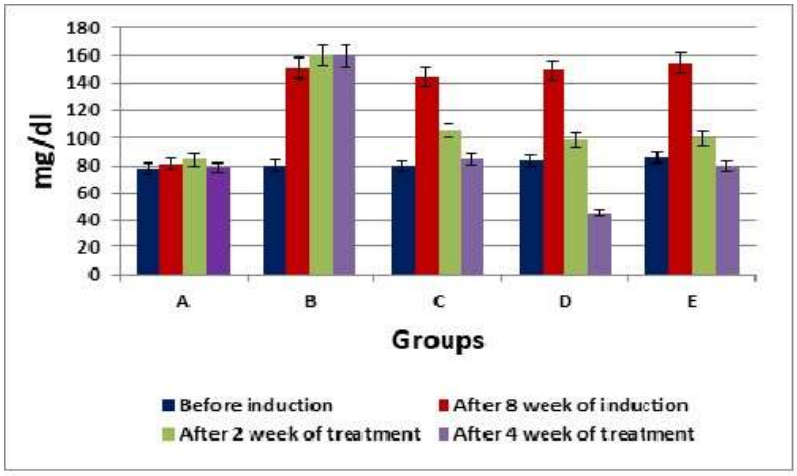

Figure 2 : Mean total triglyceride (mg/dl) of health and hyperlipidemic rabbits before and during treatment with atorvastatin alone and combination with clarithromycin or azithromycin .A: negative control, B: positive control, C: Atorvastatin, D: Atorvastatin+ clarithromycin, E: Atorvastatin +Azithromycin

MEASUREMENT OF TISSUE CYP 450 CYP3A4 ISOZYME

Figure (3) and Figure (4) illustrated the mean concentration cytochrome CYP 450 3A4 reduction value in hyperlipidmic rabbits. The liver and intestine tissue samples were collected at the end of treatment were analyzed, atorvastatin at group C and negative group A recorded active concentrations of cytochrome CYP 450 3A4 with non-significantly between them (0.322±0.36

and 0.329±0.27)ng/ml in liver, (1.313 ±0.62and 1.340±0.17) ng/ml in intestine. Therapeutic multiple dose of clarithromycin with atorvastatin did alter the normal cytochrome CYP 450 3A4 concentration and exhibited significant $p \leq 0.05$ decrease in concentration compared to other groups (0.154±0.21 and 0.572±0.42) ng/ml in liver and intestine respectively, while in group E the values were (0.319+0.32 and 1.18±0.67ng/ml) in liver and intestine respectively. The decline of cytochrome CYP 450 3A4 concentration at azithromycin with atorvastatin group reach minor reduction, however, the results were found significant $p \leq 0.05$ when comparison to groups A, C, and D. On the other hand, the concentration of cytochrome CYP 450 3A4 in the hyperlipidemic untreated positive group showed a greater decline in the liver than in the intestine. Additionally, there was no significant difference ($p \leq 0.05$) between the azithromycin and atorvastatin groups in the intestine. Finely, the CYP3A4 fold inhibition was (2.13 and 1.03 fold) in liver and (2.34 and 1.13 fold) in intestine when administration of atorvastatin plus clarithromycin and atorvastatin plus azithromycin, respectively.

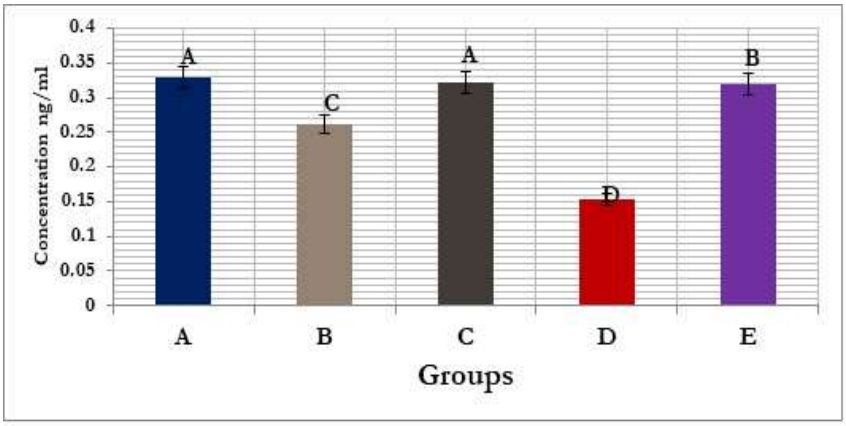

Figure (3): Liver cytochrome P450 3A4 concentration (ng/gm) hyperlipidemic rabbits treated with atorvastatin and atorvastatin with clarithromycin or azithromycin once daily for 28 days Capital letters mean significant (P< 0.05) between periods A: negative control, B: positive control, C: Atorvastatin, D: Atorvastatin+ clarithromycin, E: Atorvastatin +Azithromycin

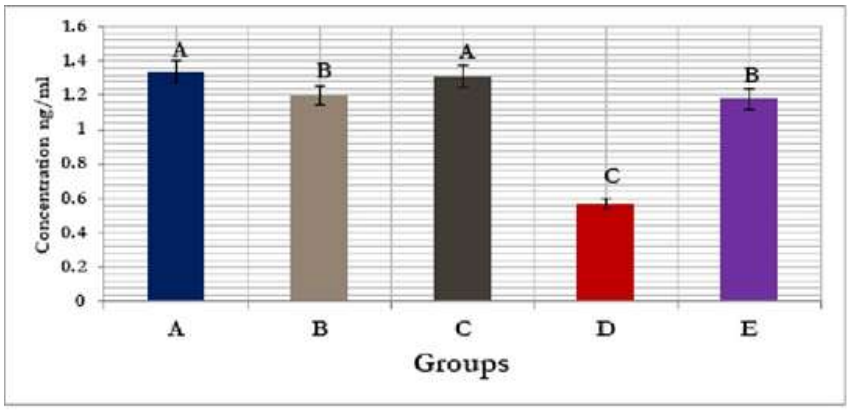

Figure (4): Intestine cytochrome P450 3A4 concentration (pg/gm) of hyperlipidemic rabbits and treated with atorvastatin and atorvastatin with clarithromycin or azithromycin once daily for 28 days. Different capital letters mean significant (P< 0.05) between periods A: negative control, B: positive control, C: Atorvastatin, D: Atorvastatin+ clarithromycin, E: Atorvastatin +Azithromycin.

MEASUREMENT OF ORGANIC ANIONIC TRANSPORT POLYPEPTIDE

At the end of treatment, the concentration and percentage activity of OATP were significantly reduced in the hyperlipidmic rabbits. Concerning serum, liver and intestine tissue samples that were taken at the end of treatment found that atorvastatin plus clarithromycin were significantly decreased the amount of OATP in the intestine, serum, and liver, with a difference that was statistically significant $p \leq 0.05$ compared to the other groups. Figures 5, 6, and 7, as well as Table 1, show a significantly lower percentage activity of OATP in the intestine compared to the serum and liver (18.75%, 22.56% and 34.35 %), respectively. On the other hand, the group E that was treated with the atorvastatin plus azithromycin showed low inhibition of percentage of OATP activity in intestine, serum, and liver (79.07%, 61.46% and 56.88%) respectively. Highly percentage activity of OATP was recorded in group C that was treated with atorvastatin only in intestine, serum, and liver (85.57%, 97.40% and 88.90%) respectively. Through the results, we noticed inhibition the percentage of OATP activity in intestine, serum and liver (98.59%, 69.87% and 59.17%).

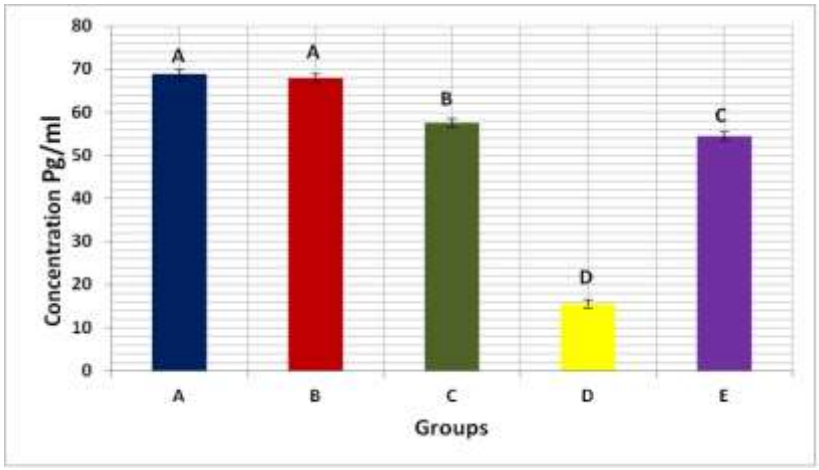

Figure 5 : Serum OATP concentration (ng/ml) of hyperlipidemic rabbit and treated with atorvastatin for 28 days and atorvastatin with clarithromycin or azithromycin once daily for last 5 days. A: negative control, B: positive control, C: atorvastatin, D: atorvastatin+ clarithromycin, E: atorvastatin +Azithromycin

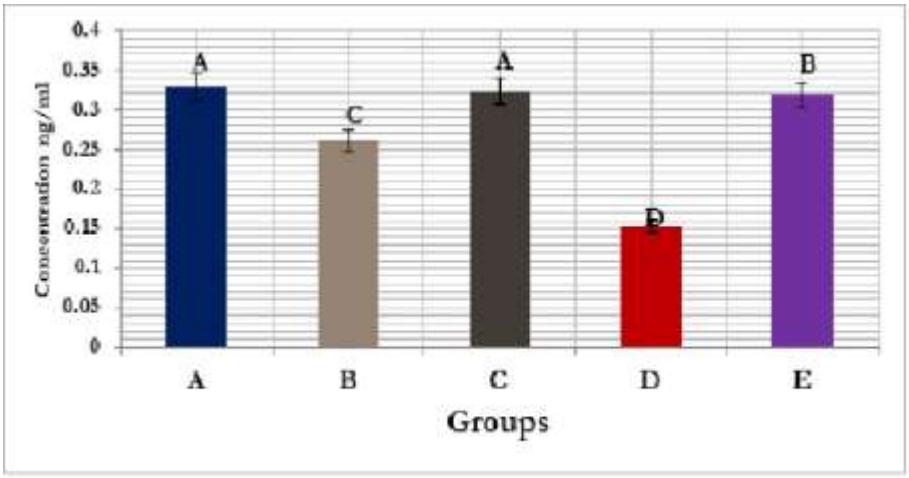

Figure 6: Liver OATP concentration (ng/gm) of hyperlipidemic rabbit and treated with atorvastatin for 28 days and atorvastatin with clarithromycin or azithromycin at last 5 day A: negative control, B: positive control, C: atorvastatin, D: atorvastatin+ clarithromycin, E: atorvastatin +Azithromycin

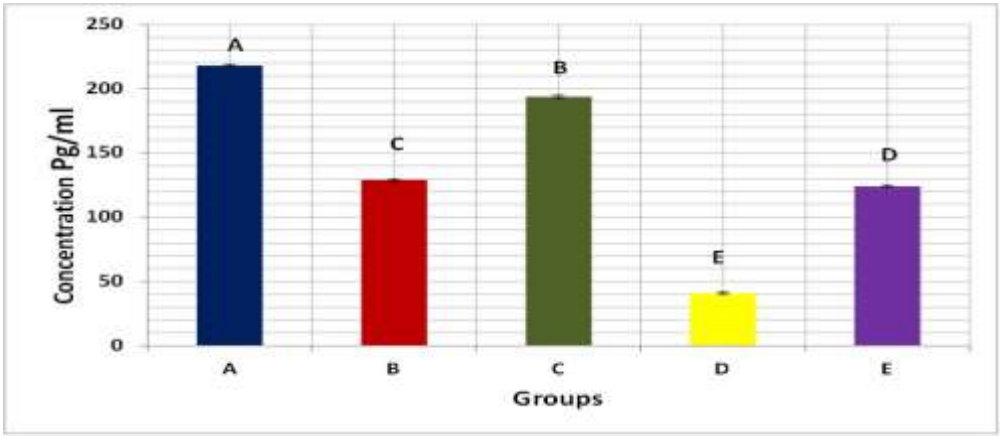

Figure 7 : Intestine OATP concentration (ng/gm) of hyperlipidemic rabbit and treated with atorvastatin for 28 days and atorvastatin with clarithromycin or Azithromycin at last 5 day A: negative control, B: positive control, C: atorvastatin, D: atorvastatin+ clarithromycin, E: atorvastatin +Azithromycin

HISTOPATHOLOGICAL EXAMINATION:

The liver sections in negative control group appeared with normal architecture from radiating hepatocytes and portal areas (Figure9). Positive control group revealed multi-massive focal necrotic areas in liver parenchyma (Figure10), each necrotic area represented by massive necrosis of hepatocytes and heavy infiltration of mononuclear cells mainly from lymphocytes and macrophages also infiltrates the interstitial of portal areas with marked hyperplasia of epithelial cells represented as newly formed of bile ductless. While, the liver tissue sections from experimental groups revealed in (Atorvastatin group) disorganization of hepatic lobules resulted from swelling and enlargement of hepatocytes which appeared foamy in their microscopic appearance, and the portal areas infiltrated with mononuclear cells and dilation of portal veins (figures 11). In (azithromycin group) the histopathological sections in liver shows disorganization of hepatic lobules caused narrowing of the central veins and sinusoidal capillaries, figure (11) revealed the lobulation and small hepatic lobules and swelling of hepatocytes. The sections from (Clarithromycin group) appeared with marked congestion of central veins dilated and contain blood, the hepatic cords atrophied with moderate swelling of sinusoids as in (Figure 12). The peripheral and mid-zonal regions in hepatic lobules showed cellular swelling of hepatocytes; which appeared enlarged have foamy cytoplasm.

DISCUSSION

Dyslipidemia is considering a risk factor for cardiovascular (CVD) and cerebrovascular occlusive events. Statin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor, is a class of drug that is used widely in dyslipidaemia. There are various types of statins prescribed worldwide (Morofuji *et al.,* 2022). In this pharmacodynamics study, the mean lipid profile reduction of antihyperlipidemia method of hyperlipidmic treated rabbits are shown in the above results. Atorvastatin had good effect on blood lipid levels (Farhan *et al.*, 2014), but it enhanced the hypolipidemic effect when administered in combination with clarithromycin. There was significant change in multiple doses treatment with clarithromycin on blood lipid levels and response in hyperlipidmic rabbits. In contrast to atorvastatin plus azithromycin, azithromycin had minor effect on serum atorvastatin levels and did not significantly alter blood lipid levels in hyperlipidmic rabbits that were treated with multiple doses of atorvastatin alone. These findings are consistent with (Prasanna et al., 2014) and (Hougaard Christensen et al., 2020). Macrolides induced serious drug interactions by hindering metabolizing enzymes and transporter-mediated drug uptake into cells; the OATP family, which determines drug disposition and is necessary for subsequent metabolism, n addition to inhibit CYP450 (3A4) enzyme (Seithel *et al.,*2007; Ibrahim and Shakir 2017).

This study investigated the potential impact of cytochrome CYP450 (3A4) and uptake transporters on drug interactions that were induced by macrolides. The impact of the macrolides clarithromycin and azithromycin on the OATP-mediated uptake was investigated, along with their metabolism by cytochromes, using the HMG-CoA reductase inhibitor atorvastatin as the substrate. This transporter mediated atorvastatin uptake was inhibited by co-administration of clarithromycin, and azithromycin. In our study, a strong inhibition of atorvastatin uptake was observed by clarithromycin at the therapeutic dose more than azithromycin due to fourteen-membered ring in clarithromycin, while in azithromycin fifteen-membered ring, fourteen-membered ring inhibited the action of CYP450 more than fifteen-membered ring this agree with (Zhang *et al.,* 2020 and Ashraf *et al.,* 2023), but in a study by Strandell et al. (2009), A significant interaction between atorvastatin and azithromycin has been shown. When azithromycin and clarithromycin were given concurrently, the transporter-aided atorvastatin uptake was affected. Uptake transporters are increasingly being recognized as important factors in the directed elimination of drugs out of the body because of their ability to metabolize a variety of compounds and their localization between portal venous blood and important drug-metabolizing enzymes (e.g., CYP3A4) expressed in hepatocytes. Their presence can be a necessity for substances to enter hepatocytes and get metabolized before their elimination over the canalicular membrane into bile (Ballard et al., 2012). Drug-drug interactions can occur when absorption rates are altered due to drug competition, resulting in lower hepatic metabolism and/or biliary clearance, which raises blood concentrations and decreases the absorption of one medication

(Li et al., 2019; Aboktifa. and Abbas 2020). One well-established mechanism of drug interactions is the inhibition of cytochrome P450 isoenzymes. Several studies have demonstrated that macrolides are potent CYP3A4 inhibitors, which can raise the plasma concentrations of co-administered medications that are substrates of CYP3A4. Clarithromycin elevates the levels of atorvastatin in the bloodstream when taken together, as confirmed by (Jacobson 2004) so increased the effect of atorvastatin in lowering blood lipids level. The study emphasizes also the significance drug-drug interactions, the role of solute carriers in the pharmacodynamics. Organic anion transporting polypeptides (OATPs) are essential for the transport of medications such as atorvastatin. Hepatocytes mainly use OATP1B1 and OATP1B3 to absorb endogenous metabolites and xenobiotics. Although it is not as well-characterized as the other two liver OATPs, OATP2B1 is expressed in a variety of tissues, including the liver, skeletal muscles and the intestine. In contrast to OATP1B1, OATP1B3, and OAT1, which are other transporters involved in statin uptake, OATP2B1 might be involved in controlling local statin concentrations. Moreover, its sensitivity to pH raises the possibility of drug-drug interactions and its role in oral drug absorption (Knauer et al., 2010; Chen et al., 2020). The concentration and percentage of OATP activity reduction at hyperlipidmic rabbits (group B) were significant decrease in liver and intestine compared to group A because hypercholesterolaemia may changes hepatic drug-metabolizing enzymes and transporters, possibly impacting drug metabolism and pharmacodynamics as shown by (Xu et al.,2022). Thus, an increased level of lactone is a common feature of patients with atorvastatin-induced myotoxicity in the absence of interacting drugs and patients receiving concomitant treatment with CYP3A4 inhibitors. Therefore, it is expected to have a higher

tissue penetration than the parent drug. Patients, who have higher levels of atorvastatin lactone, either inherently or due to the inhibition of CYP3A4, may be subjected to a greater exposure of the drug in their tissues (Kareem and Abdulaziz 2010). This could potentially explain the higher likelihood of experiencing muscular side effects. The myotoxicity may be associated with atorvastatin lactone or hydroxylated metabolites, or possibly both. However, when atorvastatin is taken together with CYP3A4 inhibitors, there is a higher chance of experiencing muscular side effects (Alfonsi et al., 2016). This is because the level of atorvastatin lactone increases while the levels of hydroxylated metabolites decrease (Hoffart et al., 2012).

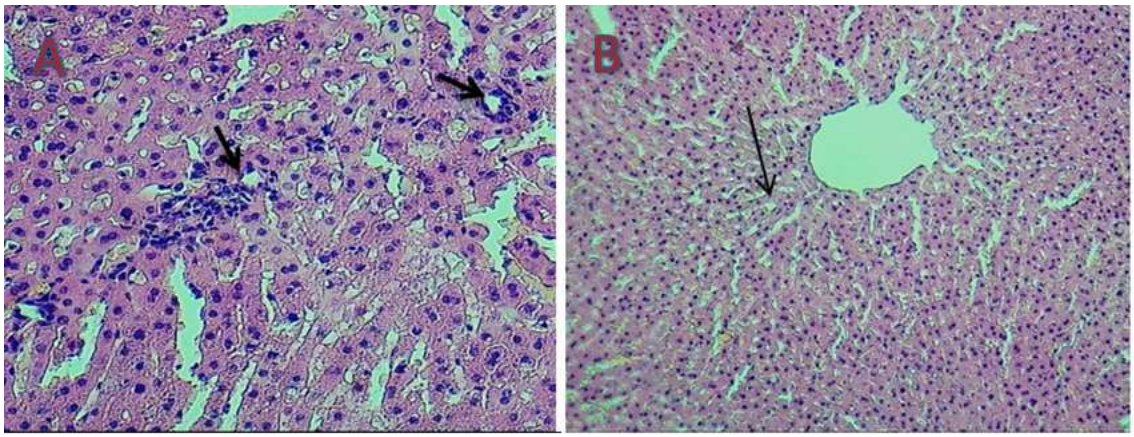

Figure 8: Histopathological section in liver from negative group: (A) shows normal portal areas and normal bile ducts (arrow). (H&E stain, 200X). B; shows normal hepatocytes in radiating manner (arrow) with normal hepatic vasculature from central vein and sinusoidal capillaries. (H&E stain, 400X).

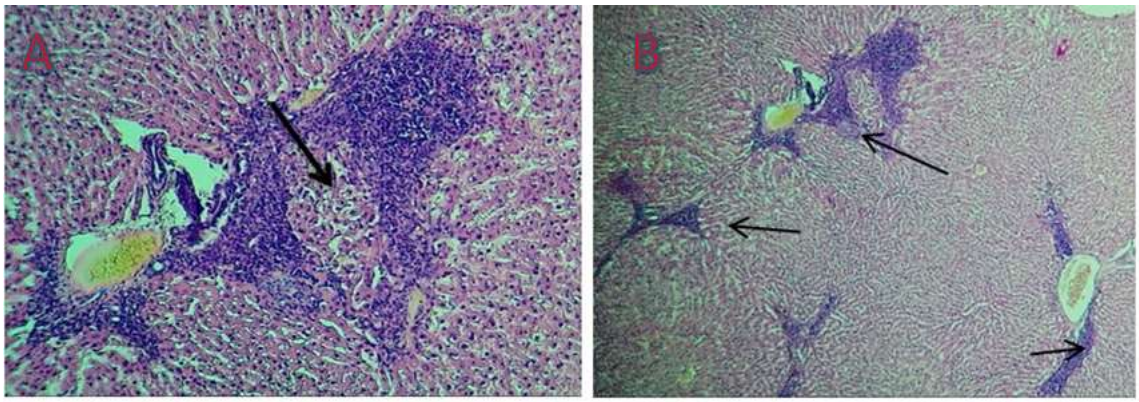

Figure 9: Histopathological section in liver from positive group (A); shows multi-massive focal necrotic areas in liver parenchyma and heavy inflammatory cells in portal areas (arrow). (H&E stain, 40X). (B): shows multi-massive focal necrotic areas in liver parenchyma and heavy inflammatory cells in portal areas (arrow). (H&E stain, 40X).

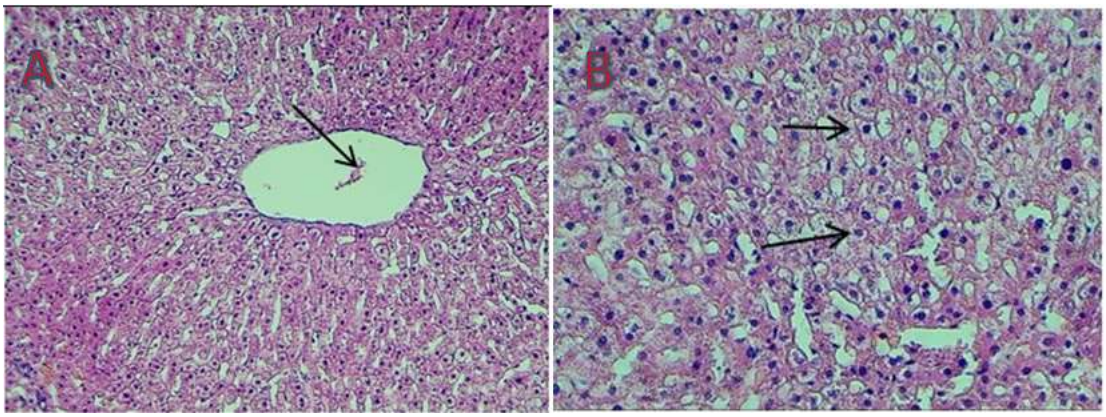

Figure 10: Histopathological section in liver from group atorvastatin (A); shows disorganized hepatocytes around dilated central vein (arrow). (H&E stain, 100X). (B); shows swelling of hepatocytes with foamy cytoplasm (arrow). (H&E stain, 400X).

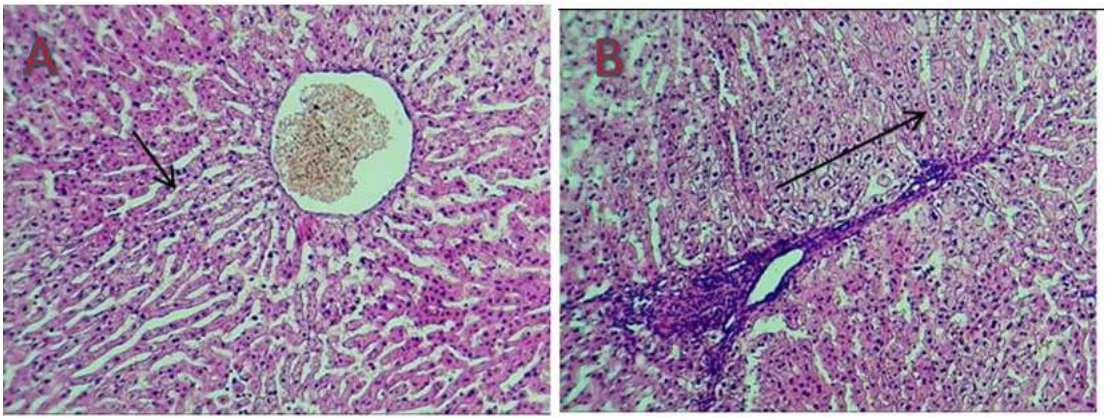

Figure 11: Histopathological section in liver from group (Clarithromycin); (A) high magnification shows atrophy of hepatic cords and moderate swelling of sinusoids (arrow). (H&E stain, 200X). (B) shows peripheral and mid-zonal cellular swelling of hepatocytes (arrow). (H&E stain, 200X).

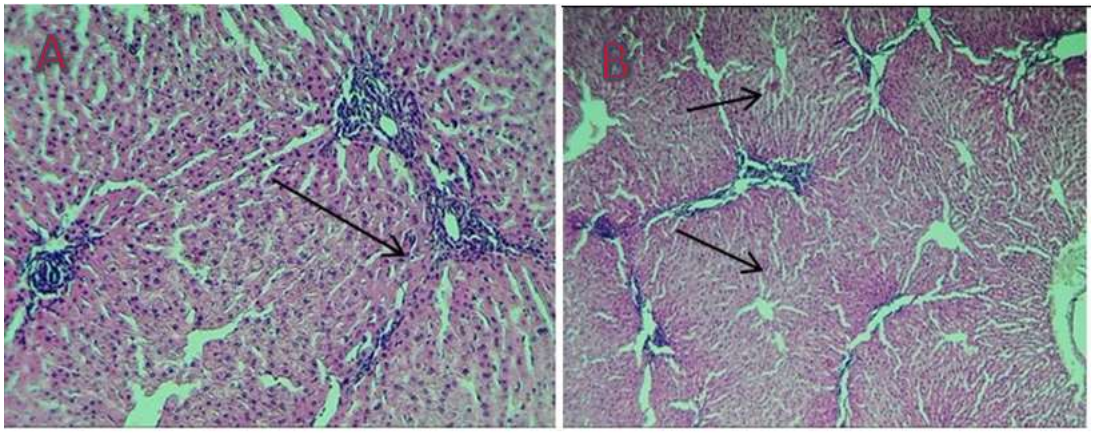

Figure 12: Histopathological section in liver from group (azithromycin); (A) Shows lobulation of radiating hepatocytes (arrow), infiltration of inflammatory cells in portal areas. (H&E stain, 100X). (B) shows disorganized hepatic lobules (arrow) and narrowing central veins and sinusoidal capillaries. (H&E stain, 40X).

CONCLUSIONS AND RECOMMENDATIONS

Clarithromycin can cause drug-drug interactions (DDIs) with statins, leading to decreased metabolism and increased risk of side effects. It interacts with CYP450 3A4 and OATP, increasing atorvastatin levels in the bloodstream. Combining atorvastatin and clarithromycin can result in lipid-lowering effects. It's advised to avoid combining statins and azithromycin. Further research is needed to develop safer medication combinations.

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