ORIGINAL ARTICLE

Effects of Retinoic Acid on Liver Triglyceride Level and Diacylglycerol Acyltransferase-2 *(DGAT2)* Gene Expression in Rats with High-Cholesterol Diet-Induced Steatosis

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ABSTRACT

INTRODUCTION: Non-alcoholic fatty liver disease (NAFLD) incidence is rising globally without effective treatment available. Serum retinoic acid level was found to be low in NAFLD patients. Thus, this study investigated the effects of retinoic acid administration on liver triglyceride levels and Diacylglycerol acyltransferase 2 (*DGAT2*) gene expression in high-cholesterol diet-induced steatosis rats. **MATERIALS AND METHODS:** Forty male Sprague-Dawley rats were divided into five groups (n=8/group). Groups A and B received a normal diet, while groups C, D, and E were fed a high cholesterol diet (HCD) for four weeks to induce steatosis (Phase 1) and continued with the same diet for the next four weeks (Phase 2). In Phase 2, Group D received vehicle (Olive oil), while Groups B and E received retinoic acid (7.5mg/kg subcutaneously) twice weekly with their respective diet. Liver triglyceride levels were measured using the Bligh and Dyer's method, and hepatic *DGAT2* gene expression was quantified using Real-Time qPCR. Data was analysed using the One-Way Analysis of Variance (ANOVA) test. **RESULTS:** Retinoic acid-treated groups showed a reduced pattern in liver triglyceride levels, in which Group E level is 3.6±0.88 mg/g compared with Group C 4.12±1.5 mg/g, but statistically insignificant ($p>0.05$). The *DGAT2* expression was significantly reduced in Group E by 0.63-fold (63%) when compared to Group C. **CONCLUSION:** These findings suggest that retinoic acid administration might reduce the liver triglyceride level by down-regulating *DGAT2* gene expression. However, further studies are required to confirm retinoic acid as a potential candidate for improving NAFLD.

Keywords
Nonalcoholic fatty liver disease, High cholesterol diet, Retinoic acid, liver Triglyceride, *DGAT2* expression

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Received: 13th August 2025; Accepted: 26th October 2025

Doi: https://doi.org/10.31436/imjm.v25i01/3055

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome, characterised by the presence of more than 5% of macrovesicular steatosis in the liver cells, with the absence of secondary triggering factors.[1] The incidence and prevalence of the disease are rapidly growing.[2] It affects more than a quarter of the world's population,[3,4] with the highest 42% in Southeast Asian countries and specifically 37.4% in Malaysia.[5,6] NAFLD manifestations range from simple steatosis to non-alcoholic steatohepatitis (NASH). Then it progresses to cirrhosis and hepatocellular carcinoma (HCC), which is the leading cause of liver-related death.[7–10]

The liver processes a large number of fatty acids, but only a tiny quantity is stored as triglycerides in cytoplasmic lipid droplets, which account for less than 5% of liver weight.[11] Insulin resistance, metabolic syndrome, and type II diabetes disrupt fat metabolism, creating a build-up of free fatty acids in hepatocytes, resulting in lipotoxicity, inflammation, and fibrosis.[12] Many factors, like accelerated

modernisation, increased Western diet, aged population, physical inactivity, and genetics, are ascribed to be the contributing factors involved in the dramatic escalation of NAFLD worldwide.[13–15] However, to date, no Food and Drug Administration (FDA) approved prescription is available for NAFLD therapy.[13,16] Studies showed that liver storage ability was reduced in NAFLD, affecting vitamin A metabolism[17,18,] and serum retinol level was negatively associated with the severity of NAFLD.[19]

Carotenoids and retinyl esters are the dietary sources of vitamin A. Retinoids are vital transcriptional factors that regulate the expression of over 500 genes.[20] The hepatic stellate cells (HSCs) store retinoic acid (RA) in the form of retinyl ester-filled lipid droplets.[21] Lacking RA in both clinical and animal studies showed the development of NAFLD and NASH.[9] In mammals, structurally two unrelated diacylglycerol acyltransferases (DGAT) enzymes, DGAT1 and DGAT2, catalyse the terminal step of triglyceride (TG) biosynthesis.[22] DGAT1 is abundant and expressed in the intestine, while DGAT2 is found in the liver and adipose tissues. Many studies suggest that inhibition of DGAT2 led to the suppression of *de novo* lipogenesis.[23,24] However, the role of DGAT2 in causing lipid aggregation and the benefit of its inhibition in NAFLD is still unclear. While these studies highlight the roles of RA and DGAT2 in hepatic lipid metabolism, further research is necessary to directly establish RA's impact on *DGAT2* gene expression and its subsequent effects on lipolysis and lipogenesis. Therefore, this research aimed to evaluate the effects of RA on liver triglyceride levels and *DGAT2* gene expression in high cholesterol-induced steatosis rats.

MATERIALS AND METHODS

Animal model

Ethical approval for this study was obtained from Institutional Animal Care and Use Committee IACUC of the International Islamic University Malaysia (IIUM/IACUC/2019(14)). All the rats were treated following the institutional Guidelines for the Care and Use of Laboratory Animals.

This experimental study was conducted on adult male healthy Sprague-Dawley rats with an average body weight of 200 to 300 grams. They were individually housed with appropriate facilities in standard plastic cages and fed on a standard dry pellet diet and water *ad libitum*. They were kept under closely controlled environmental conditions with a 12:12-hour light-dark cycle. They were kept in a room at 21-22 °C temperature and 50-55% humidity. The animals were acclimatised for 2 weeks. The rats were randomly divided into 5 groups, with n=8 rats per group. The total sample size of 40 rats was determined using G*Power version 3.1 with a power of 95%. The calculation was performed using the mean and standard deviation of serum triglyceride levels in the control and treated animal groups, as reported by Geng et al. (2017).

For the first four weeks (Phase 1), rats in Groups A (control) and B received a normal diet (ND). While rats in Groups C to E received 12% cholesterol daily as a high cholesterol diet (HCD) to induce steatosis, based on the established method.[25] For the second 4 weeks (Phase 2), the rats in the control group continued receiving a normal diet. The rats in group B (ND+RA) were injected with RA (7.5mg/kg subcutaneous) twice weekly. The rats in group C received HCD throughout the experiment as a positive control. The rats in group D received HCD with vehicle (olive oil), and rats in group E received HCD and RA (7.5mg/kg subcutaneous) twice weekly to evaluate the effects of RA on the steatotic liver. The dose and duration of drug administration were determined based on the previous reports.[26,27]

At the end of the experimental study, all animals were fasted overnight and euthanised with an overdose mixture of anaesthesia. The abdomen was opened with a midline incision, and the liver tissues were removed *in toto*. Part of the central lobe of the liver was cut gently, directly to avoid *in vivo* lipolysis. The liver tissue was collected, washed with cold saline, and stored at -80°C for further analysis of liver triglyceride (TG) estimation and *DGAT2* gene expression.

Liver Triglyceride Measurement

Bligh and Dyer's method was used to measure liver triglyceride levels, with some minor changes.[28] Firstly, 75% ice-cold methanol (32µl/mg methanol and 10.6 µl/mg HPLC-graded water) was added to the samples and homogenised using SilentCrusher M homogenizer (Germany) for 5x60s at 7500 rpm. Each homogenate was transferred into 10 ml glass vials, and 16 µl/mg of chloroform was added. Samples were mixed using a vortex mixer for 3 minutes at 2000 rpm and then centrifuged at 18°C for 10 minutes at 2420xg using a refrigerated centrifuge (Eppendorf, Germany) to pellet the protein and tissue particles. The whole supernatant layer (5ml) was transferred to another clean 10ml glass vial. A total of 16 µl/mg of chloroform and 18.2 µl/mg of HPLC-graded water were added to induce phase separation. Samples were then mixed again on the vortex mixer for 1 minute at 2000 rpm and incubated at 18°C for 10 minutes to allow the partitioning of the solvent system, and then centrifuged at 18°C for 10 minutes at 2420xg. The non-polar parts of each tube were aliquoted into a clean 5ml glass tube and then dried down using a nitrogen blow-down evaporator (Mini-Vap 6-port evaporator). The dried lipid was resuspended in 250 µl of 2-propanol and measured by using an AU680 Beckman Coulter Chemistry analyzer. All samples were run in triplicate.

DGAT2 gene expression by reverse transcription quantitative polymerase chain reaction (RT-qPCR)

Reverse transcription quantitative polymerase chain reaction (RT-qPCR) was conducted to measure the relative *DGAT*2 gene expression. Total RNA was extracted from the rat's liver tissue using the SV Total RNA Isolation System kit (Promega, U.S.). Complementary DNA (cDNA) was synthesized from 100ng of RNA using the PROMEGA GoScript™ Reverse Transcription system according to the manufacturer's protocols. The cDNA samples were stored at -30°C before qPCR amplification. The synthesized cDNA was then subjected to qPCR using gene-specific primers and a TaqMan probe (as shown in Table I) and GoTaq® qPCR Master Mix, 2X (Promega, USA). Each PCR reaction was performed at a total volume of 13 µL per reaction. The mixture consisted of 6.5 µL of GoTaq® qPCR Master Mix, 2X (Promega, USA), 0.4 µL of the forward primer, 0.4 µL of the reverse primer, and 0.25 µL of the TaqMan probe. The reaction was completed with 2.45 µL of RNase-free water and 3 µL of the cDNA template, which was diluted 1:16 prior to use. All samples were run in triplicate and analysed on a 96-well plate. RNase-free water was used as a non-template control (NTC). The qPCR reaction was accomplished on a Bio-Rad CFX96 Maestro Real-time system. The thermal profile consisted of an initial single cycle for Taq DNA activation at 95◦C for 2 minutes. This was followed by 38 cycles of three steps: denaturation at 94◦C for 30 seconds, annealing at 53◦C, and extension at 72◦C, both for 30 seconds. The entire cycling program concluded with a single cycle of final extension at 72◦C for 1 minute.

Data was analysed using the relative quantitative expression method. The data were normalised to glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) and presented relative to the control. The C_T value for the target gene (*DGAT2*) was normalized to the endogenous control (*GAPDH*) to obtain the ΔC_T value using this formula:

$$\Delta C_T = C_T\,(DGAT2) - C_T\,(GAPDH)$$

The relative fold change in gene expression was then calculated using the comparative cycle threshold (C_T) method, also known as the $2^{-\Delta\Delta CT}$ method.

Table I: Sequences of primers and probes for Quantitative RT-PCR

Gene	Forward	Reverse	Probe
DGAT2	GCTGATGCTGCTCTC TACTTCACC	TGTGATCTCCTGC CACCTTTCT	TGGCATTTGACTGGA ACACGCCCA
GAPDH	GAACATCATCCCTGC ATCCA	CCAGTGAGCTTCC CGTTCA	CTTGCCCACAGCC TTGGCAGC

Statistical analysis

Data was analysed using IBM SPSS Statistics version 23. Comparison of liver triglycerides and *DGAT2* gene expression among the control and the high cholesterol diet-induced steatosis rats was analysed by conducting the One-Way Analysis of Variance (ANOVA) test. Post Hoc multiple testing was amended by using LSD correction to find out the significant differences among different treatment groups. The data were expressed as means ± standard deviation (SD) with a 95% confidence interval (95% CI). The P-value of <0.05 was considered statistically significant.

RESULTS

Liver triglyceride level

Results for the liver triglyceride levels are shown in Figure 1. The positive control group, Group C (HCD only), had the highest liver triglyceride (TG) level with a mean of 4.12±1.50 mg/g, demonstrating an increased pattern compared to Group A (ND), which had 2.42±1.78 mg/g, but not statistically significant. In the retinoic acid (RA)-treated groups, a reduced pattern in liver TG levels was observed. Group B (ND+RA) had the lowest TG level overall at 0.98±0.16 mg/g. Meanwhile, Group E (HCD+RA) had a mean TG level of 3.60±0.88 mg/g, which showed a reduced pattern in comparison to Group C (4.12±1.50 mg/g) and Group D (4.05±0.76 mg/g), but statistically insignificant (p>0.05).

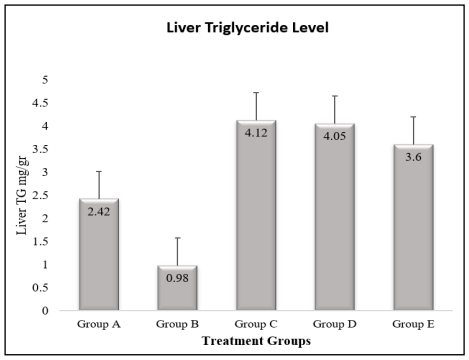

Figure 1: Liver Triglyceride levels in Normal Diet & HCD groups: Group A- Normal diet; Group B -Normal diet & Retinoic acid, Group C -High cholesterol diet, Group D -High cholesterol diet & Vehicle, Group E -High cholesterol diet & Retinoic acid. Data is expressed as mean ± standard deviation (n=8).

Gene Expression Analysis of Hepatic *DGAT2* by TaqMan qPCR

GAPDH was used as the reference gene for the analysis of *DGAT2* gene expression. The relative expression values were calculated using the $2^{-\Delta\Delta CT}$ method and are represented in Figure 2. In Group C, hepatic *DGAT2* gene expression was upregulated compared to Group A, but not statistically significant. *DGAT2* gene expression was downregulated in the RA-treated groups (B and E) compared to their respective control groups (A and C). In Group B (ND+RA), *DGAT2* expression was reduced by 0.15-fold (15% decrease) compared to Group A (ND), but not statistically significant. In Group E (HCD+RA), *DGAT2* gene expression was significantly ($p<0.05$) reduced when compared to the positive control group. Specifically, *DGAT2* expression was significantly reduced by 0.63-fold (63% decrease) when compared to Group C (HCD). The reduction was also 0.54-fold (54% decrease) when compared to Group D (HCD+vehicle), but statistically insignificant.

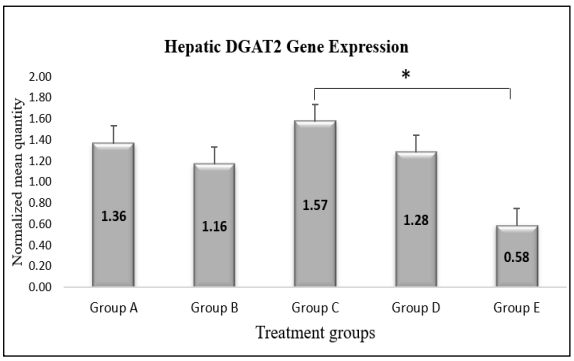

Figure 2: Hepatic *DGAT2* gene expression in normal diet and HCD groups. Group A-Normal diet; Group B- Normal diet & Retinoic acid; Group C- High cholesterol diet; Group D- High cholesterol diet & Vehicle; Group E- High cholesterol diet & Retinoic acid. Data is expressed as mean ± standard deviation (n=8). *P <0.05.

DISCUSSION

This study explored the effects of retinoic acid (RA) on liver triglyceride levels and the expression of the Diacylglycerol Acyltransferase 2 *(DGAT2)* gene in a high-cholesterol diet (HCD) induced steatosis rat model.

Liver triglyceride levels

This study revealed a trend toward reduced liver TG levels in RA-treated groups, both under normal dietary conditions and following HCD induction. However, these reductions did not reach statistical significance. The downward trend in TG levels suggests that RA may play a protective role in hepatic lipid homeostasis, particularly under lipotoxic dietary challenges. This observation is in agreement with recent reports indicating that RA can attenuate hepatic steatosis by modulating lipid metabolism pathways.[29–31] A study by Zarei L, et al. showed that rabbits lacking retinoic acid receptors (RARs) developed microvesicular hepatic steatosis and had poorer fatty acid oxidation capability. The study discovered that RA considerably reduces liver steatosis, comparable to atorvastatin. It also reported a decrease in liver oxidative stress marker-protein carbonyl, serum total antioxidant capacity, and serum lipid in high-fat diet-induced steatosis rabbits. It is stated that RA's antioxidant and anti-inflammatory characteristics might be the primary effective mechanisms for it.[31] Moreover, RA is known to influence hepatic lipid partitioning, not

only by suppressing lipogenesis but also by enhancing mitochondrial β-oxidation.[32,33]

The lowest TG levels were observed in Group B, which was fed a normal diet with RA, indicating that RA might have a triglyceride-lowering effect even under baseline conditions. This aligns with a previous report showing treatment of male mice with all-trans retinoic acid (AtRA) significantly reduced body weight, body fat content, and hepatic TG levels.[34]

Hepatic *DGAT2* gene expression

In this study, hepatic *DGAT2* gene expression was found to be upregulated in rats fed a high-cholesterol diet (HCD; Group C) compared to those on a normal diet (Group A). *DGAT2* encodes a key enzyme responsible for the final step in triglyceride (TG) synthesis, and its elevated expression has been implicated in the pathogenesis of nonalcoholic fatty liver disease (NAFLD) through promotion of hepatic lipid accumulation.[24,35]

Notably, administration of retinoic acid (RA) in HCD -fed rats (Group E) led to a statistically significant downregulation of *DGAT2* expression compared to Group C. This suggests that RA may suppress hepatic triglyceride synthesis by modulating *DGAT2* transcription. These findings support the hypothesis that RA influences hepatic lipid metabolism by targeting key enzymatic regulators of lipogenesis. Supporting this, a study demonstrated that knockout of *DGAT2* in C57BL/6J and ob/ob mice for six weeks resulted in significant reductions in liver triglyceride content and overall body weight, underscoring the central role of DGAT2 in lipid homeostasis.[36]

Interestingly, RA treatment also reduced *DGAT2* expression in rats on a normal diet (Group B), showing a 0.15-fold (15%) decrease relative to Group A. Furthermore, in Group E, *DGAT2* expression was significantly reduced by 0.63-fold (63%) and 0.54-fold (54%) when compared to Group C (HCD) and Group D (HCD+vehicle), respectively. These transcriptional findings are consistent with immunohistochemical data, which showed a pronounced decrease in hepatic DGAT2 protein expression following subcutaneous RA administration in HCD-fed rats.[37]

Overall, the significant suppression of *DGAT2* expression in RA-treated HCD rats (Group E) suggests a protective role for RA in ameliorating diet-induced hepatic lipid accumulation. While the precise molecular mechanisms remain to be fully elucidated, these results highlight that RA has a potential role as a modulator of liver triglyceride metabolism and a candidate for therapeutic intervention in NAFLD.

CONCLUSION

The administration of RA in this study led to a reduced pattern of liver TG levels and a significant downregulation of *DGAT2* gene expression in HCD-induced steatosis rats. This suggests that RA could be a potential therapeutic approach for treating fatty liver disease and preventing conditions like NAFLD and NASH. However, there are several limitations, primarily related to its scope and duration of the study. Specifically, while a beneficial trend toward reduced liver triglyceride levels was observed in the RA-treated groups, this reduction did not reach statistical significance, suggesting a lack of sufficient statistical power or treatment duration. Therefore, further investigation into a larger sample size and longer study durations, i.e., more than 4 weeks of RA treatment, would achieve a statistically significant reduction in liver TG levels. Furthermore, more rigorous molecular and mechanistic studies beyond *DGAT2* gene expression are necessary to fully elucidate the pathway through which RA modulates hepatic lipid metabolism. Such studies should target downstream factors like fatty acid oxidation (e.g., CPT-1), inflammatory markers, and the specific retinoic acid receptor (RAR) mediating the effect to confirm the exact beneficial mechanism of RA in NAFLD.

ACKNOWLEDGEMENT

The authors acknowledge the International Islamic University Malaysia (IIUM) Research Management Centre for financial support under the Research Management Centre Grant 2020 (RMCG), Project ID RMCG20-069-

0069, for the project titled "Effect of Vitamin A (Retinoic Acid) on Serum, Liver Biochemical Parameters and Diacylglycerol Acyltransferase 2 *(DGAT2)* Expression in High Cholesterol Diet-Induced Rat's Steatosis."

REFERENCES

1. Lin S, Huang J, Wang M, et al. Comparison of MAFLD and NAFLD diagnostic criteria in real world. Liver International. 2020;40(9).
2. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nature Reviews Gastroenterology and Hepatology. 2021; Vol. 18.
3. Mundi MS, Velapati S, Patel J, et al. Evolution of NAFLD and Its Management. Nutrition in Clinical Practice. 2020; Vol. 35.
4. Eguchi Y, Wong G, Lee E, et al. Epidemiology of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in Japan: A focused literature review. JGH Open. 2020; Vol. 4
5. Yip TCF, Lee HW, Chan WK, et al. Asian perspective on NAFLD-associated HCC. Journal of Hepatology. 2022; Vol. 76.
6. Khammas ASA, Hassan HA, Salih SQM, et al. Prevalence and risk factors of sonographically detected non alcoholic fatty liver disease in a screening centre in Klang Valley, Malaysia: an observational cross-sectional study. Porto Biomed J. 2019;4(2).
7. Pierantonelli I, Svegliati-Baroni G. Nonalcoholic Fatty Liver Disease: Basic Pathogenetic Mechanisms in the Progression from NAFLD to NASH. Transplantation. 2019;103(1).
8. Jarvis H, Craig D, Barker R, et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. PLoS Medicine. 2020; Vol. 17.
9. Allam AS, Salama MM, Nasser HM, et al. Comparison between NAFLD fibrosis score and retinoic acid serum level in NAFLD. Egyptian Liver Journal. 2020;10(1).
10. Rada P, González-Rodríguez Á, García-Monzón C, et al. Understanding lipotoxicity in NAFLD pathogenesis: is CD36 a key driver? Cell Death and Disease. 2020; Vol. 11.
11. Alves-Bezerra M, Cohen DE. Triglyceride metabolism in the liver. Compr Physiol. 2018;8(1).
12. Marušić M, Paić M, Knobloch M, et al. NAFLD, Insulin Resistance, and Diabetes Mellitus Type 2. Canadian Journal of Gastroenterology and Hepatology. 2021; Vol. 2021.
13. El-Agroudy NN, Kurzbach A, Rodionov RN, et al. Are Lifestyle Therapies Effective for NAFLD Treatment? Trends in Endocrinology and Metabolism. 2019; Vol. 30.
14. Eslam M, George J. Genetic contributions to NAFLD: leveraging shared genetics to uncover systems biology. Nature Reviews Gastroenterology and Hepatology. 2020; Vol. 17.
15. Tong J, Guo JJ. Key molecular pathways in the progression of non-alcoholic steatohepatitis. Eur Rev Med Pharmacol Sci. 2019;23(19).
16. Mantovani A, Dalbeni A. Treatments for NAFLD: State of art. International Journal of Molecular Sciences. 2021; Vol. 22.
17. Saeed A, Dullaart RPF, Schreuder TCMA, et al. Disturbed vitamin A metabolism in non-alcoholic fatty liver disease (NAFLD). Nutrients. 2018; Vol. 10.
18. Czuba LC, Wu X, Huang W, et al. Altered vitamin A metabolism in human liver slices corresponds to fibrogenesis. Clin Transl Sci. 2021;14(3).
19. Jeon D, Son M, Shim J. Dynamics of serum retinol and alpha-tocopherol levels according to non-alcoholic fatty liver disease status. Nutrients. 2021;13 (5).
20. Yadav AS, Isoherranen N, Rubinow KB. Vitamin A homeostasis and cardiometabolic disease in humans: lost in translation? Journal of Molecular Endocrinology. 2022; Vol. 69.
21. Haaker MW, Vaandrager AB, Helms JB. Retinoids in health and disease: A role for hepatic stellate cells in affecting retinoid levels. Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids. 2020; Vol. 1865.

22. Chitraju C, Walther TC, Farese R V. The triglyceride synthesis enzymes DGAT1 and DGAT2 have distinct and overlapping functions in adipocytes. J Lipid Res. 2019;60(6).
23. Amin NB, Saxena AR, Somayaji V, et al. Inhibition of Diacylglycerol Acyltransferase 2 Versus Diacylglycerol Acyltransferase 1: Potential Therapeutic Implications of Pharmacology. Clinical Therapeutics. 2023; Vol. 45.
24. Rong S, Xia M, Vale G, et al. DGAT2 inhibition blocks SREBP-1 cleavage and improves hepatic steatosis by increasing phosphatidylethanolamine in the ER. Cell Metab. 2024;36(3).
25. Abdul Rahim R, Ghani ASA, Muhammad N, et al. Non-Alcoholic Steatohepatitis Animal Model Induction. World J Pharm Pharm Sci. 2019;8(4):1523–38.
26. Yucel C, Erdogan Yucel E, Arslan FD, et al. All-trans retinoic acid prevents cisplatin-induced nephrotoxicity in rats. Naunyn Schmiedebergs Arch Pharmacol. 2019;392(2).
27. Ewees MG, Abdelghany TM, Abdel-Aziz AAH, et al. All-trans retinoic acid mitigates methotrexate-induced liver injury in rats; relevance of retinoic acid signaling pathway. Naunyn Schmiedebergs Arch Pharmacol. 2015;388(9).
28. Sostare J, Di Guida R, Kirwan J, et al. Comparison of modified Matyash method to conventional solvent systems for polar metabolite and lipid extractions. Anal Chim Acta. 2018;1037.
29. Liu Y, Chen H, Wang J, et al. Association of serum retinoic acid with hepatic steatosis and liver injury in nonalcoholic fatty liver disease. American Journal of Clinical Nutrition. 2015 Jul 1;102(1):130–7.
30. Cassim Bawa FN, Xu Y, Gopoju R, et al. Hepatic retinoic acid receptor alpha mediates all-trans retinoic acid's effect on diet-induced hepatosteatosis. Hepatol Commun. 2022 Oct 1;6(10):2665–75.
31. Zarei L, Farhad N, Abbasi A. All-Trans Retinoic Acid (atRA) effectively improves liver steatosis in a rabbit model of high fat induced liver steatosis. Arch Physiol Biochem. 2022 Jul 4;128(4):1010–5.
32. Tripathy S, Chapman JD, Han CY, et al. RETRACTION: All-Trans-Retinoic Acid Enhances Mitochondrial Function in Models of Human Liver. Mol Pharmacol. 2016 May;89(5):560–74.
33. Kim SC, Kim CK, Axe D, et al. All-trans-Retinoic Acid Ameliorates Hepatic Steatosis in Mice by a Novel Transcriptional Cascade. Hepatology. 2014 May;59(5):1750–60.
34. Tung YT, Lyu KN, Chun Chen Y, et al. Supplementation comprising dietary fish oil with all-trans retinoic acid decreased blood lipids and fat accumulation in C57BL/6J mice. J Funct Foods. 2019 Jan;52:310–5.
35. Gluchowski NL, Gabriel KR, Chitraju C, et al. Hepatocyte Deletion of Triglyceride-Synthesis Enzyme Acyl CoA: Diacylglycerol Acyltransferase 2 Reduces Steatosis Without Increasing Inflammation or Fibrosis in Mice. Hepatology. 2019 Dec 26;70(6):1972–85.
36. Song XS, Zhang J, Chen X, et al. Identification of DGAT2 Inhibitors Using Mass Spectrometry. SLAS Discovery. 2016 Feb;21(2):117–26.
37. Ahmed Mohamed Ben-Amer N, Buyong Z, Abdullah NZ, et al. Retinoic acid targeting DGAT2 in non-alcoholic fatty liver disease model. Med Health. 2023 Dec 19;s18(7):1–164.