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Review Article

Selecting an Appropriate Animal Model for Dyslipidemia

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ABSTRACT

In recent years, dyslipidemia, a major risk factor for cardiovascular diseases is on the rise globally due to sedentary lifestyles and unhealthy diets. Though abundant data pertaining to the factors influencing dyslipidemia, the mechanism of action of various drugs and the pathogenesis of the disease are available in the literature, the disease is poorly understood. Animal models play a crucial role in investigating the pathophysiology and aid in developing effective formulations. Despite extensive research being carried out in the arena of dyslipidemia, there is no adequate knowledge about the most suitable *in vivo* model. A systematic literature search was carried out to review the animal models such as rats, mice, rabbits and zebrafish models with chemical-induced, diet-induced and drug-induced methods that have been used to study dyslipidemia. This review focuses on the mechanism involved in the dyslipidemia induction techniques explored by researchers along with their applications and limitations. The induction methods reported are expected to provide better insight in selecting an appropriate model to draw precise conclusions.

Keywords: Dyslipidemia, Animal models, Cardiovascular diseases, Animal research, High-fat diet, *in vivo* model.

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INTRODUCTION

Dyslipidemia, a metabolic disorder is a significant cause of Cardiovascular Disease (CVD) accounting for the mortality of 2 million people and disabilities in about 30 million people, annually. This condition is a result of a disturbance in the synthesis and plasma lipid clearance leading to abnormal lipid levels. The diagnosis is mainly based on the fasting lipid profile, including High-Density Lipoproteins (HDL-C), non-HDL-C, Low-Density Lipoproteins (LDL-C), Very Low-Density Lipoproteins (VLDL-C), Chylomicrons (CM), Triglycerides (TG) and Total Cholesterol (TC).[1,2] Current research findings renamed the subtype of dyslipidemia arising from obesity and insulin resistance as metabolism related dyslipidemia. It is characterised by elevated serum levels of TG, LDL-C and VLDL-C coexisted with decreased HDL-C levels.[3] AHA guideline in addition to European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) guidelines recommend heart-healthy lifestyle for blood cholesterol level management as a first-line treatment for CVD.[4] Clinical evaluations include estimating levels of fasting lipid levels, uric acid (a CVD risk factor), Thyroid Stimulating Hormone (TSH) and Haemoglobin A1C (HbA1C).[5]

Animal studies serve as a vital link between cell lines and clinical studies. The animal models have been extensively used in drug development and biological research due its resemblance with human anatomy and physiology. However, factors such as circulation, hormones, tissue, cellular and organ structure and functions must be foreseen. Inappropriate model selection leads to improper findings. Mice, rabbits, rats and zebra fish have been well accepted globally for their genetic similarity to humans.[6] The present review is mainly focused on the dyslipidemia animal models, induction procedure and their mechanism in various species for the evaluation of lipid lowering drugs and their formulations. A literature search for this review was conducted for articles published between 2016 to 2023 using electronic databases Scopus, Google Scholar, PubMed and ScienceDirect. In the time course of the literature search, keywords used were "Dyslipidemia", "Hyperlipidaemia", "Animal models", "induction" and "pre-clinical studies".

Types of Animal Models

With the expansion of research related to dyslipidemia, a significant number of animals are used as models for disease induction and studies. Currently, the animal models explored in dyslipidemia research include mice, rats, rabbits and zebrafish. Mice and rats fed with high cholesterol diet comprising sucrose, saturated fats and cholate are known to induce hypercholesterolaemia. Genetic manipulation by feeding High Cholesterol Diet (HCD) or High Fat Diet (HFD) disrupts normal regulation and metabolism of lipoproteins leading to hypercholesterolemia.[7] Reproducibility

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of the reported induction method is of utmost importance in adopting a method for *in vivo* studies. However, in our study, in spite of following the procedure reported for induction of dyslipidemia with poloxamer 407,[8] the rats failed to maintain sustained lipid levels which led to inconclusive results. This prompted us to probe further the various methods explored for induction of dyslipidemia. Consequently, these findings provide insight for future research using relevant animal models. The models explored for the study of dyslipidemia along with their mechanism of action have been discussed in Table 1.

Rat Models of Dyslipidemia

Rat is extensively used in research to study pharmacology, metabolism and physiology due to ease of feeding, short life span, regulation of environmental factors and resemblance to human anatomy and physiology. The organs can be isolated and blood can be collected for experimental purposes.[9]

Chemical Induced Rat Model

Poloxamer 407 (P407) induced rat model

P407 is a non-ionic surfactant that can affect lipid metabolism by inhibiting lipoprotein lipase and decreasing TG hydrolysis.[10] Chaudhary and Brocks (2013) reported induction of dyslipidemia in rats within 3 hr of P407 intraperitoneal (i.p.) injection (0.5 and 1 g/kg) (Figure 1). The decrease in HDL-C levels sustained for 5.5 and 6.5 days with a dose of 0.5 and 1 g/kg respectively. Whereas, increase in TC and TG sustained for 7.5 and 10 days respectively with 0.5 g/kg dose of P407 and the dose of 1 g/kg increased TG level by 1.5-fold.[11]

The P407 model has been used in evaluating the anti-dyslipidemic activity of berberine,[12] pharmaceutical formulations such as atorvastatin loaded in transferosome gel[13] and nanostructured lipid carrier,[14] transdermal patch of pravastatin,[15] *Clerodendrum glandulosum* and *Allium sativum* herbal formulation,[16] and solid lipid nanoparticles loaded with Simvastatin.[8] Various plant extracts including *Colocasia esculenta* aqueous extract,[17] *Jasminum subtriplinerve* blume Oleaceae extract,[18] methanolic extract of Bambusa bambos,[19] guarana powder,[20] fenugreek,[21] glibenclamide,[22] *Erythrina senegalensis* alcoholic extract,[23] *Buchholzia coricea* leaf extract,[24] *Tephrosia vogelii* stem and leaf extract,[25] hesperidin,[26] *Averrhoa carambola* leaf extract,[10] and an extract derived from brown algae, Fucoidan or *Fucus evanescens*[27] have been investigated for their anti-dyslipidemic activity in P407 induced dyslipidemic rats.

It should be noted that the serum lipid profile is reversible once P-407 dose is discontinued.[28] Interspecies differences should also be carefully considered.[29] Few other limitations of P407 model include insignificant weight gain in animals due to lessened lipid accumulation in adipose tissues and longer time of induction by i.p dose ranging from 3 days to 4 months.[28,30] The sex of the rodents should be considered to avoid distinction in treatment and diagnostic strategies.

Triton X100 Induced Rat Model

Triton X100, a surfactant at a dose of 100 400 mg/kg is known to induce dyslipidemia in rats. Farheen *et al.* reported increase in plasma levels of TC, TG, lipoproteins and reduces HDL-C level upon intravenous (i.v) administration of 400 mg/kg of 10% Triton X-100 solution.[31] Maximum hyperlipidaemia was achieved 48 hr after oral dosing with Triton X-100 (400 mg/kg).[32] In rats receiving single i.p dose of Triton X-100 (100 mg/kg), the serum levels of TG, total lipids, TC, LDL-C and VLDL-C levels increased whereas, HDL-C level decreased after 21 days (Figure 2). Further, histopathological studies reported micro steatosis and acute cell swelling in disease induced rats.[33] Triton X-100 model has

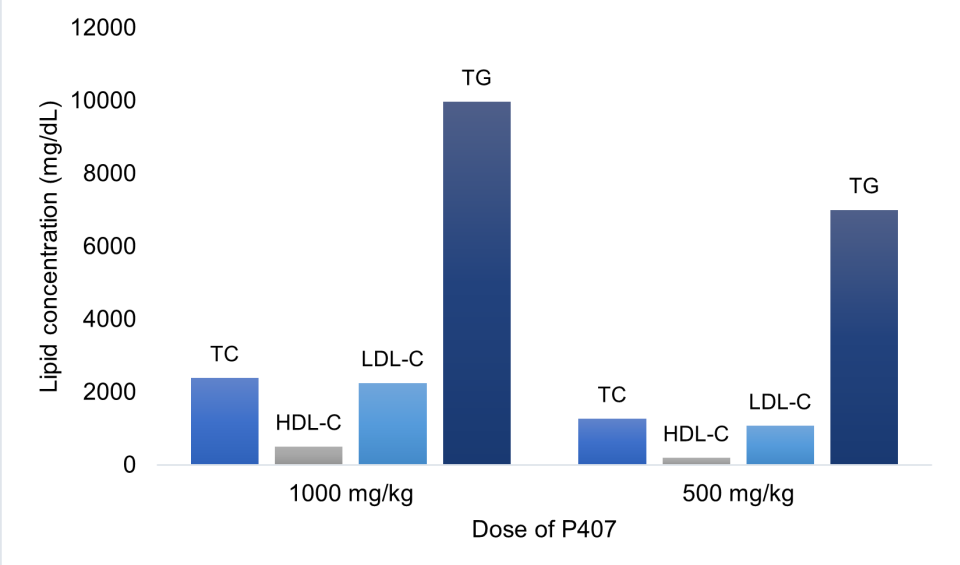

Figure 1: Effect of P407 on the lipid levels in rats.

been used to evaluate the potential of lipid lowering drugs such as Atorvastatin and Picolinate,[34] tetracosanol and policosanol,[35] and alendronate[36] in the treatment of dyslipidemia. Plant extracts such as Meniran derived from *Phyllantus niruri*,[37] *Sesbania grandiflora* methanolic extract,[38] *Trachyspermum ammi*,[39] and an alcoholic extract of Psyllium husk.[33] Triton X-100 is generally used to induce acute hyperlipidemia.[36,40] However, it is necessary to combine Triton-X with HFD to induce hyperlipidaemia in rats that is caused by inhibiting lipase enzyme.[37]

Levofloxacin Induced Rat Model

Levofloxacin is a broad-spectrum antibiotic belonging to the class of fluoroquinolones with a profound potential to induce lipid peroxidation.[41] Owoade *et al.* reported an increase in TG, phospholipid and TC was observed 7 days of treatment with

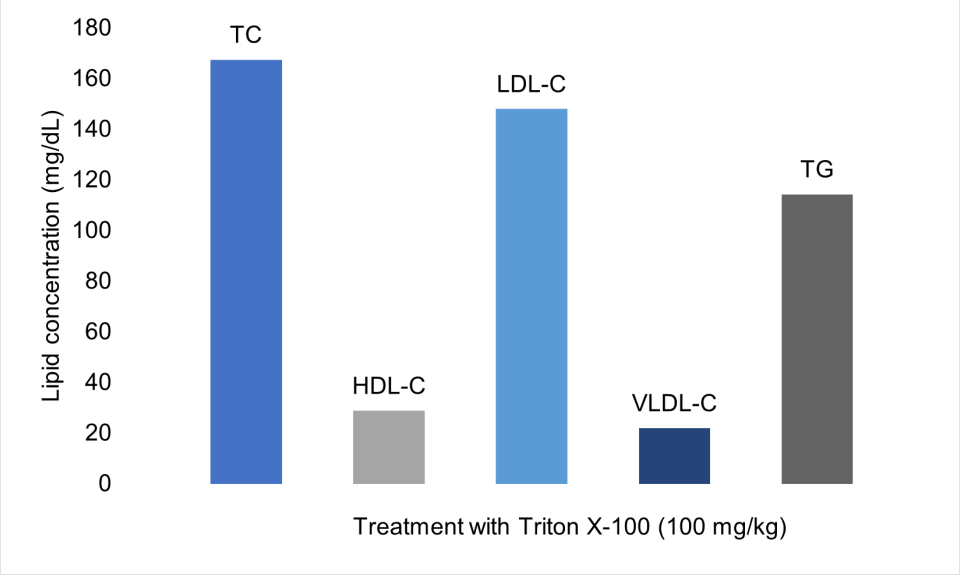

Figure 2: Effect of Triton X-100 on the lipid levels in rats.

Table 1:Mechanism of action of various animal models used in the induction of dyslipidemia.

Method of induction	Model animal	Mechanism	Consequence	References
Chemical induced	P407 induced rats	Indirect stimulation of HMGCoA reductase, inhibition of lipoprotein lipase, catalase enzyme and cholesterol-7α-hydroxylase.	Increase in TC, TG and decrease in HDL-C.	11,19,20
	Triton X100 induced rats	Increased hepatic synthesis of cholesterol and absorption of lipids from the intestine via emulsification.	Increase in TC, TG, LDL-C, VLDL-C and decrease in HDL-C.	33
	Triton WR-1339 induced mice	Inhibition of lipoprotein lipase and increases 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity.	Increase in TC and TG levels.	70
	Levofloxacin induced rats	Activation of HMG-CoA reductase, cholesterol 7α-hydroxylase inhibition and limiting synthesis of bile acids.	Increase in TC, TG, LDL-C, PL and decrease in HDL-C.	42
Diet induced	High-fat diet-induced rats	Upregulates expression of HMGCoA reductase.	Increase in body weight, energy intake, TC, TG, LDL-C and decrease in HDL-C.	47,105
	Sucrose induced rats	Increased degradation of lipids in the tissues of liver.	High blood glucose, triacylglycerol, cholesterol, LDL-C and VLDL-C and low HDL-C.	55

levofloxacin (7.14 mg/kg; i.p), while HDL-C-TG levels elevated by 8-folds after 10 days. The increase in TG, PL and TC levels were sustained for a week even after discontinued dose. The HDL-TG level was increased without significant increase in HDL-C.[42] Another study by Khatab and coworkers reported increase in serum levels of TC, TG and LDL-C, whereas there was significant reduction in HDL-C level when the rats were orally administered with 10 mg/kg levofloxacin for five consecutive days.[43] The levofloxacin induced model has been used to evaluate lipid lowering effect of Vitamin E, *Panax ginseng*,[43] curcumin and ginger.[44] Considerable research is necessary to draw the effectiveness of model and its reliability in dyslipidemia research.

Diet Induced Rat Model

Three primary rat models of diet-induced metabolic syndrome include high carbohydrate diet, HFD and high carbohydrate high fat diet. Rodríguez-Correa and coworkers recommend 30 to 50% fat composition in HFD as a higher proportion may lead to metabolic abnormalities distinct to metabolic syndrome. The type of fat added to the HFD has an impact on the energy metabolism. The most common type of added fat for HFD is made up of equal amounts of saturated and monounsaturated fats, which are typically found in lard.[45] Muniz and co-workers revealed that feeding high-lard diet alone to Wistar rats could only increase body weight but not dyslipidemia. Whereas, high lard diet supplemented with cholesterol increased body weight as well as induced dyslipidemia.[46]

Udomkasemsab and Prangthip reported that the rats with defective cholesterol metabolism can have dyslipidemia. Rats that are fed a HFD consisting of different types of fats, such as coconut, lard, palm oil, or soybean, etc., constitute a common method for dyslipidemia induction. This could be due to the direct correlation between prolonged consumption of saturated fats and dyslipidemia. Typically, rats are fed with HFD for four to six weeks in order to develop dyslipidemia. The successful induction is characterised by increase in the TG, LDL-C and TC and decrease in HDL-C level.[47,48] Sprague Dawley (SD) and Wistar rats are vulnerable to diet induced dyslipidemia and obesity. Acharya and Talahalli (2019) reported that HFD with 35% fat content induces dyslipidemia and also disrupts inflammatory and oxidative defence mechanism.[49] Herbal compounds such as Xiexin Tang,[50] quinoa polysaccharides,[51] mulberry leaf,[52] Fucoidan and galactooligosaccharides[53] have been evaluated for anti-hyperlipidaemic activity using HFD induced model. Hyperlipidaemia in rats was observed after 4 weeks of HFD consumption. However, the elevated lipid levels tend to decrease from 10th to 17th week regardless of body weight.[54]

The sucrose enriched diet is lipogenic. In the rats fed with Sucrose Rich Diet (SRD), triacylglycerol levels were high in hepatic tissues. The SRD fed rats exhibited weight gain, increase in BMI and abdominal circumference compared to control.[55] Typically, 100-800 mg/kg sucrose is required to induce dyslipidemia in rats. It increases TC, TG and decreases HDL-C levels following 4-12 weeks of diet.[56,57] In rats, oral solution of sucrose (40% sucrose) for a period of 8 weeks is reported to induce the disease.[58] Lipid lowering activity of Cepharanthine,[59] *Solanium melongena*,[60] *Salvia hispania*,[61] garlic and avocado seed extract[62] have been evaluated using high sucrose diet induced dyslipidemia models. Other than rat and mice models, guinea pig fed with high fat high sucrose diet (35% sucrose) for 12 weeks resulted in dyslipidemia.[63] Combining high sucrose diet with HFD are necessary for successful induction of dyslipidemia. Although preclinical study results are someway consistent with clinical data, species differences impede any direct translation to human beings. Further research is necessary to rule out the possibility of other variables such as oxidative stress, insulin resistance, or hyperlipidemia.[64] High fructose is one of the causes of metabolic syndrome. It is necessary to maintain high proportion of fructose in the diet contributing to 40 to 70% energy intake by rats and dyslipidemia. Feeding rats such a high amount of fructose is an unrealistic sugar intake instead, glucose is a suitable choice to induce weigh gain and fat deposition in a way that is comparable to a human diet.[65]

Mice Models of Dyslipidemia

Mouse models are proven to be beneficial in the study of diseases such as obesity, type-2 diabetes and its associated complications such as insulin resistance and inflammation.[66] A few advantages of using mice in research include facile gene modification, the ability to stimulate a sequence of biological characteristics, suitability in feeding, moderately short reproductive cycle besides being economical.[67,68]

Chemical Induced Mouse Model

Triton WR 1339 Induced Mouse Model

Triton WR 1339 or Tyloxapol is a non-ionic surfactant been used widely used to induce dyslipidemia.[69] In a study carried out by Ibrahim *et al.* (2016) evaluating dyslipidemia potential of Marrbium vulgare extract, Triton WR 1339 (200 mg/kg; i.p) was able to increase the TC, TG, LDL levels and decrease HDL levels in mice compared to healthy control following 7 hr of treatment with Triton which persisted up to 24 hr (Figure 3).[70] Abdou *et al.* (2018) reported significant increase in the plasma levels of TC, LDL, TG and VLDL. Whereas, the levels of HDL decreased significantly compared to that in normal mice.[71] Triton WR 1339 induced model have been explored to determine the hypolipidemic potential of a few phytochemicals such as rutin,[72] chrysin,[73] and resveratrol.[74] Triton WR 1339 at a single i.v dose induces hyperlipidaemia within 20 hr following which the lipid levels decline.[75] Therefore, continuous dosing with Triton WR 1339 is required to maintain dyslipidemia throughout the treatment period.

Diet Induced Mouse Model

The HFD mice are useful in the identification of HFD affected molecular pathways and in evaluating the effectiveness of treatment.[66] In a study by Osae *et al.*, C57/BL mice fed with HFD for ten weeks resulted in 30% increase in body weight of mice, elevated fasting level of lipids were observed compared to control at the end of ten weeks.[76] Hou *et al.*, (2019) evaluated lipid lowering effect of garlic in C57BL/6N mice fed with HFD for 12 weeks. HFD increased TC, TG, HDL, insulin serum levels and body weight at the end of eighteen weeks compared to control (Figure 4). The elevated lipid levels were further decreased upon garlic supplementation. HFD increased n-butyric acid levels thereby impairing lipid metabolism.[77] In mice, high sucrose diet (30% sucrose solution) for 8 weeks resulted in dyslipidemia due to immoderate metabolism of lipids and weakened insulin ability.[78]

Rabbits Model of Dyslipidemia

The lipoprotein metabolism in rabbits resembles that of humans and they develop atherosclerosis and hypercholesterolemia rapidly. Watanabe Heritable Hyperlipidaemic (WHHL) strain of rabbits is the only strain for spontaneous endogenous hypercholesterolemia known to exist at this time as a consequence of genetic defect in its LDL-C receptor (LDLr). Lu *et al.* (2018) generated LDLr Knockout (LDLr-KO) rabbits through the CRISPR/Cas9 technology for spontaneous atherosclerosis and hypercholesterolemia induction by feeding New Zealand rabbits with normal chow diet. Despite of its efficacy, drawbacks such as low lipase activity in the liver and high cost limits its use.[79] Zhang and coworkers in 2020 developed first-ever Cystathionine-β-Synthase (CBS) Knockout (CBS-KO) rabbits with Glycine 307 (G307S) gene mutation in CBS protein by means of CRISPR/

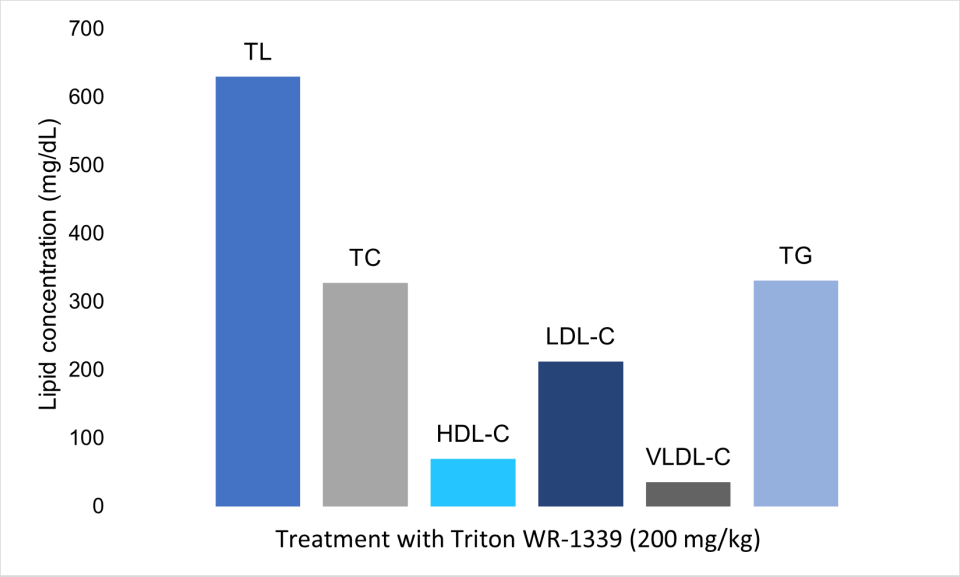

Figure 3: Effect of Triton WR-1339 on the lipid levels in mice.

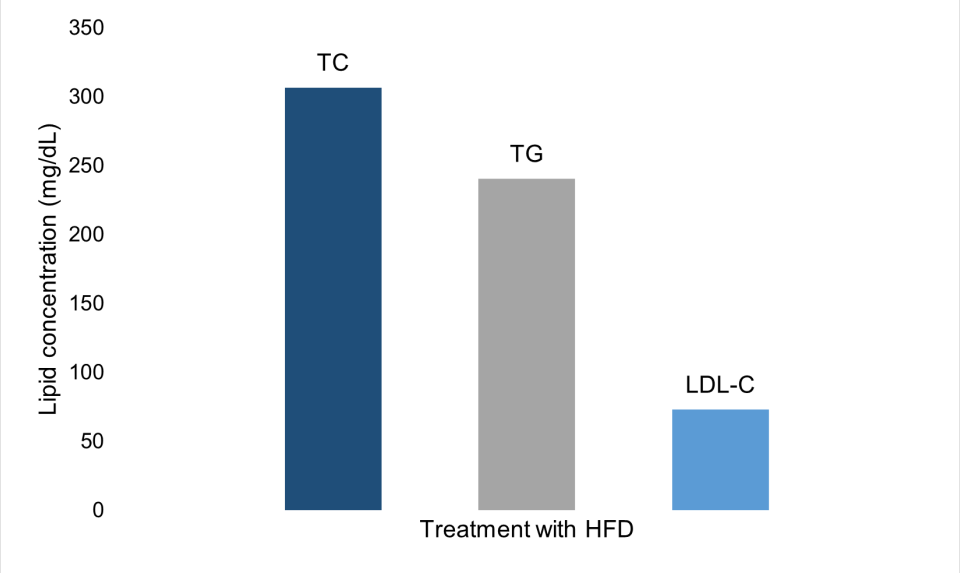

Figure 4: Effect of HFD on the lipid levels in mice.

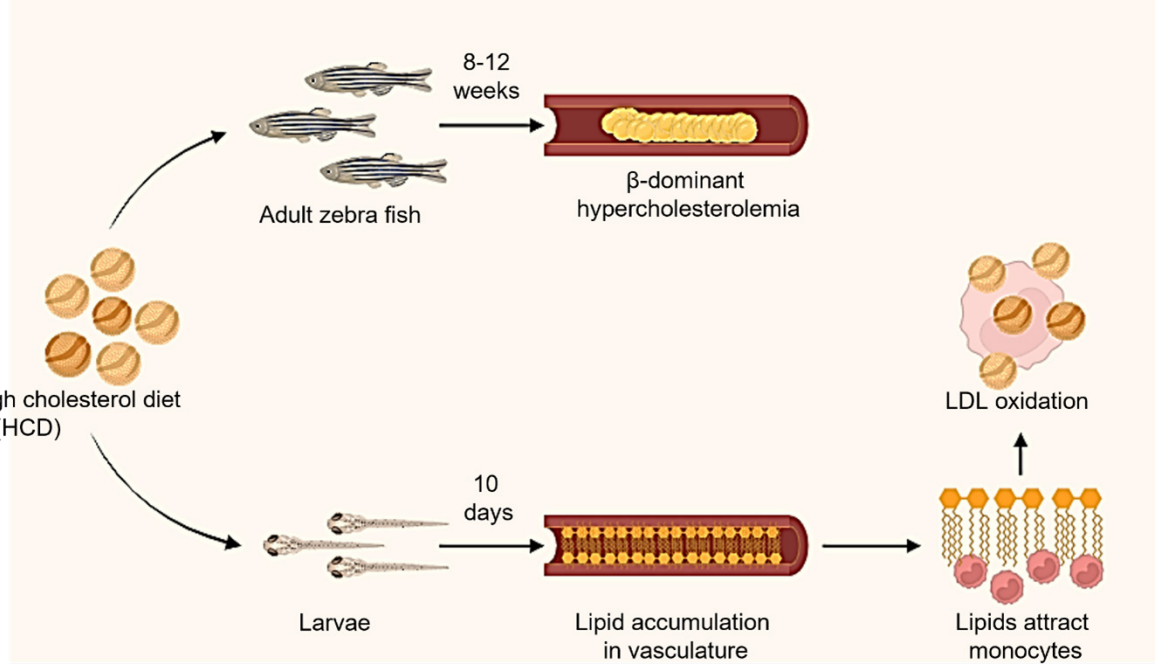

Figure 5: Induction of dyslipidemia in zebra fish by the ingestion of High Cholesterol Diet (HCD) containing 4% cholesterol.

Cas9 technology. The rabbits were fed with normal chow and displayed dyslipidemia. The lack of G307S in CBS protein resulted in dyslipidemic activity.[80]

High Fructose high Fat Diet (HFFD) fed WHHL rabbits showed increase in the levels of fasting insulin, HOMA-IR, TC, TG and LDL-C after 12 weeks with no difference in HDL-C level in comparison to control group. Increased fructose level stimulates deposition of visceral fat and lipid accumulation in insulin sensitive tissues, which further reduces glucose uptake. The reduced lipid clearance raises cholesterol levels in blood thereby inducing hypercholesterolemia in rabbits. However, study had few limitations of sex-dependant effect of HFFD on the lipid profile and there was no significant difference in glucose levels between control and HFFD groups.[81] 0.5% w/w cholesterol fed for 3 months in albino rabbits significantly increased serum levels of TG. TC and LDL-C whereas HDL-C level was reduced.[82] The rabbits fed with HFD for 28 days increased TC, TG, LDL-C levels and decreased HDL-C level.[83]

The rabbits injected with sodium fluoride (15 mg/kg/day i.p) for 30 successive days displayed significant increase in the serum levels of TC, TG, VLDL-C and LDL-C in comparison to control group. Conversely, HDL-C serum level was reduced. High fluoride in rabbits could result in metabolic disorders leading to hypercholesterolemia. The hypertriglyceridemic effect of fluoride may be associated with lower TG hydrolysis and reduced activity of lipoprotein lipase. Additionally, fluorides inhibit TG lipase, nonspecific esterase and pyrophosphatase resulting in debilitated lipid metabolism, in that instance, dyslipidemia. Fluoride salts generate free oxygen radicals which cause lipid peroxidation resulting in cell membrane damage and toxicity.[84] The rabbit models have been used to study the effect of lipid lowering agents such as imatinib,[85] fenugreek seeds,[84] neem leaves,[83] 10-Dehydrogingerdione,[82] and betaine.[80]

Few advantages of rabbit model of dyslipidemia include a unique metabolism of lipids similar to humans, abundant tissues to perform multiple analyses in a single rabbit and in the development of novel lipid-lowering drugs in translational research. Nevertheless, the use of rabbits is limited due to high price than mice and rats, high price of breeding and requirement for large space.[86] Commercially available rabbits show varied response to lipids and cholesterol rich diet which could restrict the evaluation of therapeutic effects of various drugs and chemicals. Thus, pre-screening is necessary to minimise the variations. The activity of hepatic lipase plasma of rabbits is certainly low compared to rodents and humans.[87]

The dose of various drugs and chemicals used in inducing dyslipidemia has been listed in Table 2 along with their route of administration and time of induction.

Zebra Fish Model of Dyslipidemia

Zebrafish is a small, rapidly evolving animal model in the research areas of genetics, molecular biology, immunity and pathology. It is a highly accepted model for the screening of drugs owing to its small size, rapid growth, embryo transparency and similar anatomy and physiology to humans.[88] They have metabolic characteristics and disease related genes similar to humans.[89] Marnie Halpern and Dr. Steven Farber, forerunners in dyslipidemia research reported several methods to induce dyslipidemia in zebra fish including HFD, HCD, iron and artemia rich diet that eventually results in elevation of plasma

Table 2: Doses of dyslipidemia inducing agents as per the reported literature.

Inducing agents	Route of administration	Dose (mg/kg)	Induction period	References
P-407	Intraperitoneal	500	3 hr	10,11,19,20
Triton X-100	Intravenous	400	24 hr	31
	Oral	400	48 hr	32
	Intraperitoneal	100	24 hr	33,35,36
	Intraperitoneal	300	24 hr	34
	Subcutaneous	150	24 hr	106
Triton X-100+HFD	Injection+oral	20	7 days	37
Levofloxacin	Intraperitoneal	7.14	7-10 days	42
	Oral	10	5 days	43
Sucrose	Oral	100-800	4-12 weeks	56,57
Triton WR 1339	Intraperitoneal	200	7 hr	70
	Intravenous	200	20 hr	75
Sodium fluoride	Intraperitoneal	15	30 days	84

lipid levels.[90] Zebra fish possess MTTP, APOC2, ACS and slc27a which are the primary regulators of lipid metabolism, whereas, leptin and CETP receptors are not expressed in adipose tissues thus resembling lipid pattern that of human.[91]

Generally, HFD or high cholesterol diet is the majorly reported method of inducing dyslipidemia in zebra fish. The mechanism behind the advances in using zebra fish in dyslipidemia research is shown in Figure 5.[92] The efficacy of lipid lowering drugs, HMG CoA inhibitors such as Atorvastatin, Gemfibrozil,[93] Lovastatin, Simvastatin and fibrates including clofibrate, clofibric acid have been studied in zebra fish model.[94] The effect of Nobiletin on lipid metabolism disorders, lipid and glucose metabolic pathways and fat deposition mechanism have been studied using adult zebrafish fed with HFD.[95]

Expression of apoproteins in zebrafish is homologous to the ones in humans. HFD decreased the levels of HDL and increased VLDL and LDL levels.[96] Although HCD is an excellent model for dyslipidemia due to sharp increase in oxidised lipoproteins, small amount of blood collection from zebrafish older than 45 days limits it use.[97]

Alternative Approaches

In vitro Models of Dyslipidemia

Caco-2/TC7 cells are widely used to study intestinal permeability, synthesis of lipoproteins and absorption of lipids. Staels and co-workers developed an *in vitro* model in which apical membrane consisted of bile salt or phospholipid micelles and the basolateral compartment consisted cholesterol labelled plasma. The cholesterol labelled plasma was absorbed by Caco-2/TC7 cells across basolateral membrane and excreted by way of apical membrane, regulated by PCSK9. The mass spectrometry data of samples obtained from apical side reported approximately 12 µg of cholesterol. Further, this model was used to evaluate the lipid lowering activity of Colchicine and nocodazole.[98] In spite of advantages such as lesser time of analysis and requirement of bare minimum of samples for *in vitro* model, it should be noted that interpreting the data is a tedious task and the results should be confirmed with *in vivo* models. Additionally, there is limited cell-cell interaction and the in models are often expensive.[99]

Biomarkers in Dyslipdemia

Vitamin D, Proprotein Convertase Subtilisin Kexin Type-9 (PCSK9), sphingosine-1-phosphate and miRNAs (miR33a, miR33b) have potential to be biomarkers of obesity associated dyslipidemia due to their association with cholesterol synthesis and lipid levels.[100] It should be noted that, the effect of Vitamin D on nature and functionality of lipoproteins should be well established. Sphingomyelin, sphingosine-1-phosphate and ferritin are the beneficial biomarkers for atherosclerosis.[101] Hua Chen and co-workers in their metabolomic review reported amino acids such as tryptophan, proline, tyrosine and phenylalanine, serum lipids such as TC, TG, LDL-C, HDL-C and VLDL-C, oleamide, octadecanamide in urine and citric acid to be biomarkers applicable in the diagnosis of dyslipidemia.[102] miR27b regulates lipid levels and genes associated with dyslipidemia such as GPAM, ANGPTL3 and PPARG. Comprehensive research is necessary to elucidate the consequence of miR-27b in the effective diagnosis and treatment of dyslipidemia.[103] miR3659 is also stated to be a possible biomarker of obesity related dyslipidemia.[104] However, studies reporting interaction between lipids, hormones and miRNA is limited. The biomarkers have not been used routinely in preclinical as well as clinical setup due to inadequate knowledge about the association of biomarkers with disease pathogenesis and various parameters, technical issues, cost and lack of readily available commercial assay.

CONCLUSION

Dyslipidemia imposes a major risk for cardiovascular diseases and metabolic syndrome. In the current scenario, finding a best fit preclinical model is a compelling need to evaluate the efficacy of drugs and formulation in the treatment of dyslipidemia. Treatment using biomarkers and *in vitro* cell lines are complex. Reproducibility and standardization of animal model is a crucial stage in the treatment of any disease. Any discrepancy in the selection of relevant animal model would incumber the research. While P407-induced model is extensively used in dyslipidemia research, reproducibility and sustainability of disease characteristics should be well elucidated. HFD-induced models are promising as it can prolong lipid imbalance. The drug-induced and Triton-induced models are limitedly used due to early reversal of lipid levels. Thus, in-depth research aiming for refinement, reproducibility and validation of animal models is of utmost significance to treat dyslipidemia.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

The authors have made substantial contributions to conception, literature survey and drafting the review.

ABBREVIATIONS

BMI: Body Mass Index; **CM:** Chylomicrons; **HCD:** High Cholesterol Diet; **HDL:** High Density Lipoproteins; **HFD:** High Fat Diet; **HMG CoA:** β-Hydroxy β-methylglutaryl Coenzyme A; **i.p:** Intraperitoneal; **i.v:** Intravenous; **LDL:** Low Density Lipoproteins; **LDLr:** LDL receptor; **P407:** Poloxamer 407; **SRD:** Sucrose Rich Diet; **TC:** Total Cholesterol; **TG:** Triglycerides; **VLDL:** Very Low-Density Lipoproteins.

SUMMARY

This report comprises various animal models explored for studying dyslipidemia. Evidence for the use of animals such as rats, mice, zebra fish and a rabbit in inducing dyslipidemia for the pharmaceutical applications has been described above. Many of the characteristics observed in animal models resemble features of dyslipidemia displayed in humans. The method of inducing dyslipidemia using Poloxamer 407 and levofloxacin follows the mechanism of inhibition of HMG CoA reductase. Whereas, Triton X100 and Triton WR-1339 inhibits the lipoprotein lipase activity. These methods are usually combined with high fat diet to induce the disease. The animal models of dyslipidemia will help researchers in better understanding of the disease and its complications, mechanism thereby leading to improved therapeutic interventions. Along with the applications, our report also addresses limitations of the model, which is crucial in selection of an appropriate animal model for pre-clinical studies.

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