

## **Lipid Profile Normalization Effect of Hunteria Umbellata Aqueous Fruit Extract in Wistar Rats Induced with Aloxan Monohydrate**

**Dr Solomon M. Uvoh<sup>1</sup>, Dr Kiridi Emily Gabriel E<sup>2</sup>, Dr Blessing L Dum-awara<sup>3</sup>**

<sup>1,3</sup> Department of Human Physiology, Faculty of Basic Medical Sciences, College of Health Sciences University of port Harcourt, Rivers State Nigeria.

<sup>2</sup>Department of Human Physiology, Faculty of Basic Medical Sciences, College of Health Sciences Niger Delta University, Wilberforce Island Amossoma Bayelsa state Nigeria.

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### **ABSTRACT**

The present study investigated the potential effect of *Hunteria Umbellata* fruit extract on lipid profile reduction administered at different daily doses ie 200mg/kg, 400mg/kg compared with control (1) and group5 treated at 0.3ml standard drug insulin following aloxan monohydrate induction. The lipid profile- HDL,LDL,vLDL,Triglycerides and Total cholesterol were determine using precipitant (mmol), enzymatic hydrolysis, enzymatic and point methods. Results from this study indicate that the lipid profile reduction potential of H.U fruit extract was most effective in group2 administered 200mg/kg body weight with no aloxan induction. This was closely followed by group3 treated at 400mg/kg and group5 treated with the standard drug insulin after aloxan induction compared with the control. However, goup4 induced with aloxan and treated at 200mg/kg body weight has an elevated lipid profile compared with the control and other groups studied. Findings from this study have shown that moderate dose intake of *Hunteria umbellata* fruit extract by subjects with hyperlipidaemia can be beneficial in the reduction of lipid profile but the rapidity of its reduction rate is dose dependent.

**KEYWORDS:** Lipid, triglyceride, *Hunteria*, total cholesterol, high density lipoprotein, hyperlipidaemia.

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### **INTRODUCTION**

Lipids are fat-like substances in the body that are essential for proper functioning. They are sources of energy and are stored both in blood and tissues. High level of lipid in the body leads to diseases such as coronary artery disease, stroke or heart attack. While Lipid profile is a panel of blood tests used to assess the level of lipids in the body, it entails four basic parameters thus such as Total cholesterol, Low-density lipoprotein (LDL) cholesterol, High-density lipoprotein (HDL) cholesterol, and Triglycerides

#### **Total cholesterol**

Cholesterol is a sterol type of lipid synthesized by animal cells, it is an essential structural component of the cell membranes. it serves as a precursor for the biosynthesis of steroid hormones, bile acids and vitamin D.It is required to build and maintain membranes and modulates fluidity of the membrane above the range of physiological temperatures.

Through the interaction with the phospholipids fatty-acid chains, cholesterol increase membrane packing, which alters membrane fluidity and maintains membrane integrity so that animal cells do not build cell walls? The membrane remains stable and durable without being rigid, allowing animal cells to change shape and animals to move. (Sadava *et al.*, 2011). Cholesterol is involve in cell signaling processes that assist in the formation of lipid rafts in the plasma membrane, which brings receptor proteins in close proximity with high concentrations of second messenger molecules (Incardona and Eaton, 2000).

#### **Low-density lipoprotein (LDL) cholesterol**

**Low-density lipoprotein (LDL)** is one of the five major groups of lipoprotein that transport all fat molecules around the body in extracellular water, its particles are formed when triglycerides are removed from VLDL by the lipoprotein lipase enzyme and they become smaller and denser that

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contains higher proportion of cholesterol esters (Pirahanchi *et al.*, 2022) LDL interferes with the quorum sensing system that upregulates genes required for invasive *Staphylococcus aureus* infection. This mechanism involves the binding of apolipoproteins B to a *S. aureus* auto inducer pheromone which prevent the signaling through its receptor (Peterson *et al.*, 2008) LDL is grouped based on its size as large low density, its particles are described as *pattern A*, and small high density LDL particles as *pattern B*. *Pattern B* has been associated with a higher risk for coronary heart disease (Ivanova *et al.*, 2017).because is believed that smaller particles are more easily able to penetrate the endothelium of arterial walls. There has also been noted a correspondence between higher triglyceride levels and higher levels of smaller, denser LDL particles, also lower triglyceride levels and higher levels of the larger, less dense LDL (Superko *et al.*, 2002).

When a cell needs extra cholesterol, it synthesizes the necessary LDL receptors and a proprotein convertase (PCSK9), that marks the LDL receptor for degradation (Zhang *et al.*, 2008), the LDL receptors are inserted into the plasma membrane and diffuse freely to associate with clathrin-coated pits. The LDL receptors bind LDL particles in the bloodstream; the clathrin-coated pits are endocytosed into the cell.

The Vesicles that contain LDL receptors bind to LDL and are delivered to the end some in the presence of low pH. The LDL receptors undergo a conformation change that release LDL, and is shipped to the lysosome, where cholesterol esters in the LDL are hydrolyzed. The LDL receptors are returned to the plasma membrane, where they repeat this cycle. If LDL receptors bind to PCSK9, transport of LDL receptors is redirected to the lysosome, where they are degraded (Santulli *et al.*, 2021).

### High-density lipoprotein (HDL) cholesterol

High-density lipoprotein (HDL) is the smallest of the lipoprotein particles and the dense that contains the highest proportion of protein to lipids, Its most abundant apolipoproteins are apo A-I and apo A-II. The liver synthesizes these lipoproteins as complexes of apolipoproteins and phospholipids that resemble cholesterol-free flattened spherical lipoprotein particles (Deng *et al.*, 2022). It's been documented to be more effective in protecting against and regressing arterial diseases. HDL transports cholesterol to the liver or organs such as adrenals, ovary, and testes by both direct and indirect pathways. increase concentrations of HDL particles are associated with decrease accumulation of atherosclerosis within the walls of the arteries (Casula *et al.*, 2021), which then reduce the risk of cardiovascular diseases, stroke and other vascular diseases(Deng *et al.*, 2022). HDL particles are said to be good cholesterol because they transport fat molecules out of the arterial walls,

reduce macrophage accumulation, and help in the prevention of atherosclerosis.

Studies have shown that very high concentrations of HDL particles can be associated with increased mortality (Madsen *et al.*, 2017), and cardiovascular risk, especially in hypertensive patients (Trimarco *et al.*, 2022).

### Triglycerides

These are esters formed from glycerol and three acids. They are tri-esters that consist of a glycerol bound to three fatty acid molecules, and are the main constituents of body fat as well as vegetable fat (Nelson and Cox, 2000), they are present in blood to enable the bidirectional transference of adipose fat and blood glucose from the liver (Lampe *et al.*, 1983).Triglycerides specific classification focuses on saturated and unsaturated types. Saturated fats have *no* C=C groups; unsaturated fats feature one or more C=C groups. Unsaturated fats tend to have a lower melting point than saturated analogues; as a result, they are often liquid at room temperature. Triglycerides store unused calories and provide the body with energy. Triglycerides bind to lipoproteins to enable them travel through the blood. It provides the body with energy and store energy for later use. High levels of triglycerides in the blood may lead to atherosclerosis, the clogging and hardening of the arteries. (Gerhard and Eleesha, 2018) It is usually done in fasting blood specimen.

It has been established that *Hunteria umbellata* in herbal medicine is used for the treatment of diabetes, peptic ulcers, piles, yaws, dysmenorrhoea, fevers, infertility, and helminthes infections. (Ighodaro *et al.*, 2013). *Hunteria umbellata* caused significant increase in the levels of cholesterol, triglycerides, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol with high reduction in high-density lipoprotein cholesterol level (Ajiboye *et al.*, 2017).It is also established that aqueous seed extract of *Hunteria umbellata* possesses hypoglycemic, hypolipidemic and antioxidants abilities as evident from its capability to extenuate insulin resistance, dyslipidemia, inflammation and oxidative stress in high-fructose diet-induced metabolic syndrome rats. (Ajiboye *et al.*, 2017).

Studies have shown that *Hunteria Umbellata* has antihyperlipidaemic effects may partly be mediated through inhibition of intestinal lipid absorption and *de novo* biosynthesis of cholesterol, thus justifies the ethno pharmacological use of the extract in the management of hyperlipidaemia.

It's been establish that oral treatments of normal rats with *H. umbellata* result in significant decreases in serum lipid profile parameters except for high density lipoprotein which increase significantly (triglycerides, total cholesterol and low density lipoprotein.(Adejuwon and Peter, 2015).

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## MATERIALS AND METHODS

### Fruits and Extraction

The fresh fruits of *Hunteria Umbellata* were purchased from Ahoada market River State Nigeria. They were weighed and measured in the University of port Harcourt pharmaceutical laboratory (4861g) while still fresh, washed in running tap water, sliced into pieces and immediately macerated in absolute ethanol JHD brand (1.02 kg in 1500 mL absolute ethanol) to quench possible enzymatic action (Harbourne 1973) and left for 72 hours with intermittent shaking. After the period of 72 hours, the ethanol was filtered off and the residue further pulverized using an electric blender and subsequently macerated in 1500 mL absolute ethanol for another 72 hours with intermittent shaking. After filtration, the residual marc was similarly macerated for yet another 72 hours to make room for exhaustive extraction of the metabolites. All the filtrates were combined and concentrated using a rotary evaporator to remove the ethanol and the concentrated extract further dried on a water bath at 50°C and thereafter kept in a desiccator to remove residual moisture to afford the crude ethanol extract used for this study. The yield of the dried crude ethanol extract was then calculated using the formula: % yield =  $\frac{[\text{Weight of dried crude ethanol extract}]}{[\text{Weight of the fresh fruits of } \textit{Hunteria Umbellata} \text{ used}]} \times 100$

[Weight of the fresh fruits of *Hunteria Umbellata* used]

The extraction and photochemical analysis was done in the Central Laboratory for Phytomedicines, Department of

Pharmacognosy and Phytotherapy, Faculty of Pharmaceutical Sciences, University of Port Harcourt by a Principal investigator (Natural products, Analytical and Functional Food Chemistry Research) Nuclei for Phytomedicines and chemical Ecology Research Group

### PHYTOCHEMICAL ANALYSIS

The photochemical constituents detected from the fruit extract include alkaloids, phenolic, triterpenoids, carbohydrates and Saponins.

### RESEARCH ANIMALS

The Research animals were forty (40) male wistar rats in number weighing between 147 -312g. The animals were purchased from the animal house of the University of Port Harcourt Faculty of medical Sciences and housed in wire mesh cage under environmental condition of 25-29°C. The animals were exposed to 12hours daylight and dark circle according to standard protocols. The research animals were acclimatized for two weeks (14 days) and during the period they were fed with water ad libitum. The and standard diet for animal feeds before the induction with aloxan monohydrate. The study was carried out in accordance with Helsinki recommendation in 1983 on guiding principles in care and use of animals.

## EXPERIMENTAL DESIGN

### Study Design

Table 1. Groupings of the Animals and Dosage Administered

Groups	Route of Administration	Daily Dosage Administered (ml)
1 (control)	Orally-Water and feeds	ad libitum.
2	Oral	200mg/kg (0.5ml) body weight extract daily and water ad libitum without induction
3	Orally	400mg/kg (1ml) body weight extract daily after induction
4	Intraperitoneal and orally	200mg/kg (0.5ml) extract daily and water after single dose intraperitoneal induction with aloxan.
5	Intraperitoneal	0.3ml insulin

### Weight Measurement

The animals weight were measured weekly using an electric scale weight Balance-Golden Meter USA calibrated in grammes during the twenty-eight (28) days period of the study.

### Blood Sample Collection

The blood samples were collected directly from the left ventricle of the anaesthetized animals through cardiac

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puncture using a 23G needle mounted on a 5ml syringe plunger. The samples were then introduced into EDTA and plain bottles (15 x 15) purchased from Agari pharmaceuticals LTD China.

### STATISTICAL ANALYSIS

The statistical analysis was done using statistical packaging for social sciences version 23.0. The results are presented as mean± standard deviation and p-value of <0.05 considered significant.

#### Determination of Cholesterol (Enzymatic End-Point Method)

- Principle: The cholesterol is determined after enzymatic hydrolysis and oxidation. The indicator quinoneimine is formed from hydrogen peroxide and 4-aminopyridine in the presence of phenol and peroxidase.
- Procedure: Label the tubes as test, std and blank.
- Pipette 1.0ml of the reagent into all the tubes
- Add 10ul of the standard, samples and d/w into appropriate tubes.
- Mix and incubate for 10mins at 25°C.
- Read and record the absorbance at 540nm. Unit mmol/l

#### Determination of Triglycerides (Unit Mmol/L)

- Principle: The triglycerides are determined after enzymatic hydrolysis with lipases. The indicator is a quinoneimine is formed from hydrogen-peroxide, 4-aminophenazone and 4-chlorophenol under the

catalytic influence of peroxidase.

- Procedure: Label the tubes as test, std and blank
  - Pipette 1.0ml of the rgt into all the tubes
  - Add 10ul of std, sample & d/w into appropriate tubes: Mix and
- Incubate for 10mins at 25°C
- Read and record the absorbance at 540nm.

#### Determination of HDL – Cholesterol (Precipitant Method) Unit mmol/L

- Principle: Low density lipoprotein, VLDL and Chylomicron fractions are precipitated by the addition of phosphotungstic acid in the presence of magnesium ions. After centrifugation the cholesterol concentration in the HDL fraction which remains in the supernatant is determined.
- Procedure: Labeled the tubes as standard, blank and test.
- Pipette 0.7ml of the reagent into all the tubes.
- Add 40ul of the std, sample and d/w into respective tubes
- Mix and centrifuge 10mins at 4000rpm
- Label the tubes as, test std and blank
- Pipette 1.0ml of Cholesterol (reagent) into all the tubes.
- Add 0.1ml of the supernatant into appropriate tubes
- Mix and incubate for 10mins at 25°C.
- Read and record the absorbance at 540nm

## RESULTS

Table 2. Lipid Profile Of Treated Groups With The Extract And Control

Parameters	Group1	Group2	Group3	Group4	Group5	Sig (<0.05)
TC(mmol/L)	4.45±0.07	3.50±0.56	4.00±0.98	4.65±0.21	4.30±0.14	0.04
TG(mmol/L)	1.66±0.17	1.59±0.04	1.68±0.05	1.75±0.03	1.40±0.21	0.42
HDL(mmol/L)	1.49±0.22	1.29±0.05	1.42±0.49	1.62±0.08	1.40±0.03	0.04
LDL(mmol/L)	3.77±0.07	2.94±0.54	3.36±0.95	3.82±0.28	3.54±0.78	0.21
VLDL(mmol/L)	0.76±0.78	0.73±0.02	0.76±0.02	0.79±0.01	0.64±0.09	0.42

NB: 0.01-0.05 =significant, TC=Total cholesterol, TG=Triglyceride, HDL=High density lipoprotein, LDL=Low density lipoprotein, VLDL=Very low density lipoprotein. Group1 is the control, group2 was treated at 200mg/kg, group3 at 400mg/kg, group4 at 200mg/kg extract daily and group5 was treated with standard drug insulin at 0.3ml daily

Table 3. Correlation Between Total Cholesterol And Other Lipids

Measured variables	r-values	p-values	Significant
TC versus TG	0.19	0.65	Non-significant
TC versus HDL	0.58	0.04	Significant
TC versus LDL	0.98	0.00	Significant
TC versus VLDL	0.19	0.59	Non-significant

NB: Significant is at 0.00 to 0.05 (2-tailed).

Table 4. Correlation Between Triglycerides Versus Othr Parameters

Measured variables	r-values	p-values	Significant
TG VERSUS TC	0.19	0.58	Non-significant

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TG VERSUS HDL	0.63	0.05	Significant
TG VERSUS LDL	0.19	0.59	Non-significant
TG VERSUS VLDL	0.99	0.00	significant

**Table 5. Correlation Between High Density Lipoprotein Versus Othr Parameters**

Measured variables	r-values	p-values	Significant
HDL VS TC	0.65	0.04	Significant
HDL VS LDL	0.55	0.10	Non-significant
HDL VS VLDL	0.61	0.06	Non-significant

### DISCUSSION

This study was carried out to investigate the effect of aqueous fruit extract of *Hunteria umbellata* on lipid profile using wistar rats induced with aloxan monohydrate. The animals were subjected to two weeks (14 days) acclimatization before induction. Results from the study indicate that all the lipid profiles in group2 that was not induced with the aloxan monohydrate but were treated at 200mg/kg body weight had lower TC, TG, HDL, LDL, and VLDL compared with control group. However group3 treated at 400mg/kg extract following induction had a lower TC, HDL and LDL compared with the control. The lipid profile in group4 treated at 200mg/kg body weight extract were all higher than the control group while all the lipid profile of group5 administered the standard drug insulin were significantly lower in comparison with the control.

Results from previous studies have shown the antihyperlipidaemic and cardiovascular protective effect of *Hunteria umbellata* alkaloids administered at 25 and 50mg/kg daily in hyperlipidaemia induced wistar rats (Adejuwon *et al.*, 2015). Human research studies conducted by Solomon *et al.*, 2017 and 2021 observed significant increase in total cholesterol among adult subjects and pregnant women during the first through third trimesters with resultant increased in blood pressures. Further observation from this study is the positive correlation between total cholesterol, high density lipoprotein and low density lipoprotein with a significant p-value of 0.04 and 0.00 respectively. Other observations from this study indicate that as the triglycerides level increases, the high density lipoprotein and very low density lipoprotein also significantly increases to produce a positive correlation among the lipoproteins. Significant weight reduction in experimental animals induced with aloxan monohydrate and phenylhydrazine treated with *Hunteria umbellata* fruits extract are now established facts by medical and clinical researchers (Emily *et al.*, 2022; Charles *et al.*, 2022). Clinical studies have shown that decreased serum lipids reverses heart dysfunction while elevated lipid profile increase the risk of non-ischemic heart failure by promoting the development of plaques formation within the intima of blood vessels (Yu Si *et al.*, 2020; Uvoh *et al.* 2017). Dietary disorders, obesity and abnormal fat metabolism are attributed causes of hyperlipidaemia in patients with cardiovascular diseases. Elevated serum cholesterol reduces coronary blood flow

reserved, capillary density which could lead to left ventricular dysfunction.

### CONCLUSION

The decrease lipoproteins observed in group3 treated at 400mg/kg extract and group5 treated with standard drug insulin after with aloxan monohydrate compared with the control (1) group were dose dependent.

### CONFLICT OF INTEREST

The authors hereby declare that there is no conflict of interest.

### REFERENCES

- I. Adejuwon Adewale Adeneye, Olufunmilayo Olaide Adeyemi and Esther Oluwatoyin Agbaje (2010). Anti-obesity and antihyperlipidaemic effect of *Hunteria umbellata* seed extract in experimental hyperlipidaemia. *Journal of Ethnopharmacology* 130(2):307-314
- II. Adejuwon AA and Peter AC (2015). Weight losing, antihyperlipidemic and cardioprotective effects of the alkaloid fraction of *Hunteria umbellata* seed extract on normal and triton-induced hyperlipidemic rats. *Asian Pacific Journal of Tropical Biomedicine*. Volume 5(5):387-394
- III. Ajiboye TO, Hussaini AA, Nafiu BY, Ibitoye OB. (2017). Aqueous seed extract of *Hunteria umbellata* (K. Schum.) Hallier f. (Apocynaceae) palliates hyperglycemia, insulin resistance, dyslipidemia, inflammation and oxidative stress in high-fructose diet-induced metabolic syndrome in rats. *J Ethnopharmacol*. 198:184-193.
- IV. Casula M, Colpani O, Xie S, Catapano AL, Baragetti A (2021). "HDL in Atherosclerotic Cardiovascular Disease: In Search of a Role". 10 (8): 1869.
- V. Charles NN, Solomon MU, Kiridi Emily GE (2023). Renal profile of aloxan-induced diabetic wistar rats treated with *Hunteria umbellata* fruit extract. *Scientific Research Journal of Medical Sciences*. 1(1):10-16.
- VI. Deng S, Xu Y, Zheng L (2022). "HDL Structure". *Adv Exp Med Biol. Advances in Experimental Medicine and Biology*. 1377: 1–11
- VII. Gerhard Whitworth and Eleesha Lockett (2018).

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- Should You Be Worried If Your Triglycerides Are Low? <https://www.healthline.com/health/low-triglycerides>
- VIII. Ighodaro Igbe, Gerald Ikechi Eze and Oghenekevwe Ojameruaye (2013). Sub- acute Toxicity of Aqueous Fruit Pulp Extract of Hunteriaumbellata in Albino Wistar Rats. *Niger. J. Physiol. Sci.* 28; 077 –082
- IX. Incardona JP, Eaton S (2000). "Cholesterol in signal transduction". *Current Opinion in Cell Biology.* **12** (2): 193–203.
- X. Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN (2017). "Small Dense Low-Density Lipoprotein as Biomarker for Atherosclerotic Diseases". *Oxidative Medicine and Cellular Longevity.* **2017** (10): 1273042.
- XI. Kiridi Emily GE, Solomon MU, Charles NN (2022). Hematological restoration effect of Hunteria umbellata fruit extract on phenylhydrazine induced anemia in wistar rats. *Gph-International Journal of Applied Science.* 05 (12):01-13
- XII. Lampe, MA, Burlingame AL, Whitney J, Williams ML, Brown BE, Roitman E, Elias M (1983). "Human stratum corneum lipids: characterization and regional variations". *J. Lipid Res.* **24** (2): 120–130.
- XIII. Madsen CM, Varbo A, Nordestgaard BG (2017). "Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies". *Eur Heart J.* 38 (32): 2478–2486.
- XIV. Nelson, D L.; Cox, MM. (2000). *Lehninger, Principles of Biochemistry* (3rd ed.). New York: Worth Publishing. ISBN 1-57259-153-6.
- XV. Peterson MM, Mack JL, Hall PR, *et al.* (2008). "Apolipoprotein B Is an innate barrier against invasive *Staphylococcus aureus* infection". *Cell Host & Microbe.* **4** (6): 555–66
- XVI. Pirahanchi, Yasaman; Sinawe, Hadeer; Dimri, Manjari (2022). "Biochemistry, LDL Cholesterol", *StatPearls*, Treasure Island (FL): StatPearls Publishing, PMID 30137845, retrieved 2022-12-26
- XVII. Sadava D, Hillis DM, Heller HC, Berenbaum MR (2011). *Life: The Science of Biology 9th Edition*. San Francisco: Freeman. pp. 105–114.
- XVIII. Santulli G, Jankauskas SS, Gambardella J (2021). "Inclisiran: a new milestone on the PCSK9 road to tackle cardiovascular risk". *Eur Heart J Cardiovasc Pharmacother.* **7** (3): e11–e12
- XIX. Solomon MU, Azibalua AA, Kiridi Emily GE, Alagha Bibi-Welson E (2021). Total Serum cholesterol and selected electrolytes during pregnancy among women residents in Yenagoa metropolis, Bayelsa state Nigeria. *The Journal of Medical Research* 7 (6):191-194
- XX. Solomon MU, Bonnie KG, Tabowei OC, Ngaikedi FCN (2017). The serum cholesterol and blood pressure of selected adults in Bayelsa state Nigeria. *European Journal of pharmaceutical and medical research.* 7 (6):191-194.
- XXI. Superko HR, Nejedly M, Garrett B (2002). "Small LDL and its clinical importance as a new CAD risk factor: a female case study". *Progress in Cardiovascular Nursing.* **17** (4): 167–73.
- XXII. Trimarco V, Izzo R, Morisco C, Mone P, Maria Virginia M, Falco A, Pacella D, Gallo P, Lembo M, Santulli G, Trimarco B (2022). "High HDL (High-Density Lipoprotein) Cholesterol Increases Cardiovascular Risk in Hypertensive Patients". *Hypertension.* **79** (10): 2355–2363.
- XXIII. Yu Si y, Tu DL, Zhi HZ, (2020). Mechanisms underlying direct actions of hyperlipidaemia on myocardium: an updated review PMID: PMC7007679/PMID:32035485.s
- XXIV. Zhang, Da-Wei; Garuti, Rita; Tang, Wan-Jin; Cohen, Jonathan C.; Hobbs, Helen H. (2008-09-02). "Structural requirements for PCSK9-mediated degradation of the low-density lipoprotein receptor". *Proceedings of the National Academy of Sciences of the United States of America.* **105** (35): 13045–13050.