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(REVIEW ARTICLE)

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Multifaceted roles of herbal compounds in dyslipidemia management: Mechanistic and therapeutic perspectives of herbal medicine

Kante Manjusha *, K. Jhansy Sree,Macha Indhu, Kausar Fatima, V. Padmaja and M. Sumakanth.

Department of Pharmaceutical Chemistry, RBVRR Women's College of Pharmacy, Hyderabad, Telangana, India.

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Abstract

Dyslipidemia, marked by abnormal lipid levels in the blood, is a significant risk factor for cardiovascular diseases. Although conventional treatments, including statins, bile acid sequestrants, and fibric acid derivatives, are widely prescribed, they are often associated with side effects, long-term use concerns and limited efficacy in certain individuals. This has spurred growing interest in alternative treatments, particularly herbal medicine to manage dyslipidemia. This project investigates the potential of various phytochemicals in regulating lipid profiles via several mechanisms such as inhibiting cholesterol absorption in enterocytes, Reducing cholesterol synthesis, Enhancing reverse cholesterol transport, Regulating hepatic lipid uptake, and Promoting cholesterol excretion in the liver. Additionally, many phytochemicals in herbal medicine exhibit other pharmacological properties including antioxidant, anti-inflammatory and cardioprotective effects. These complementary actions improve the overall management of dyslipidemia and contribute to reducing the risk of cardiovascular diseases.

Keywords: Dyslipidemia; Herbal Medicine; Phytochemicals; Anti Hyperlipidemics; Pharmacological Actions

1. Introduction

Lipids such as cholesterol and triglycerides are absorbed in the intestines and transported throughout the body by lipoproteins. They play vital roles in providing energy, producing steroid hormones and forming bile acids. Key elements involved in these processes include total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides which are shown in Figure1. An imbalance in any of these lipid components can lead to dyslipidemia—a condition marked by abnormal lipid levels in the blood, which increases the risk of cardiovascular diseases.[1]

* Corresponding author: Kante Manjusha

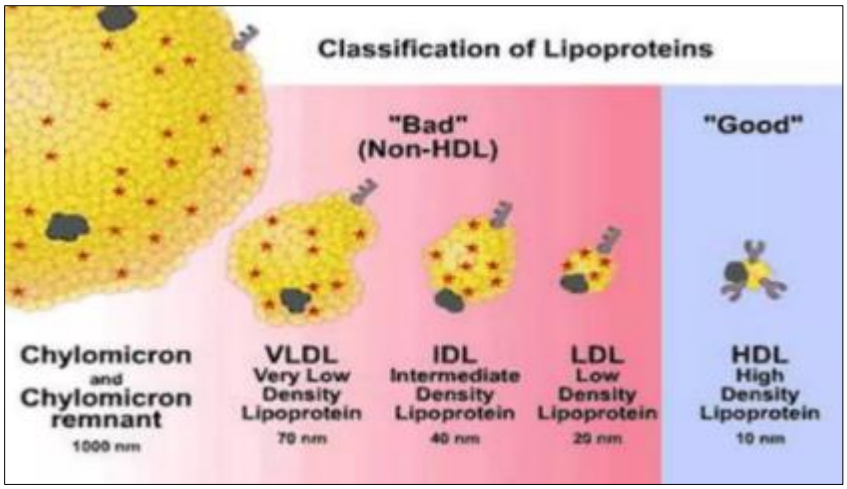

Figure 1 Lipoprotien classification

Dyslipidemia is classified into 2 types

- Primary Dyslipidemia: it is also called familial due to genetic defects; it may be monogenic (single gene defect) or polygenic (multiple gene defects). Primary hyperlipidemia can usually be resolved into one of the abnormal lipoprotein patterns based on their deficiency.
- Secondary Dyslipidemia: it is acquired and caused by lifestyle factors or other medical conditions that alter lipid levels.

1.1. Symptoms

Generally, hyperlipidemia does not have any obvious symptoms but they are usually discovered during routine examination or until it reaches the danger stage of a stroke or heart attack. Patients with high blood cholesterol level or patients with the familial forms of the disorder can develop xanthomas which are deposits of cholesterol may form under the skin, especially under the eyes. At the same time, patients with elevated levels of triglycerides may develop numerous pimple-like lesions at different sites in their body shown in Figure2 and 3 [2]

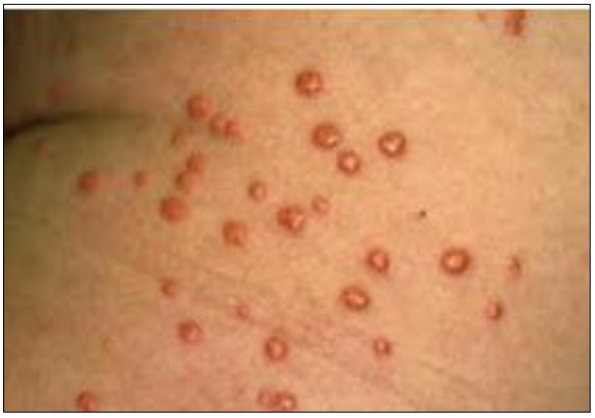

Figure 2 Lesions

Figure 3 Xanthomas

1.2. Mechanism of Dyslipidemia

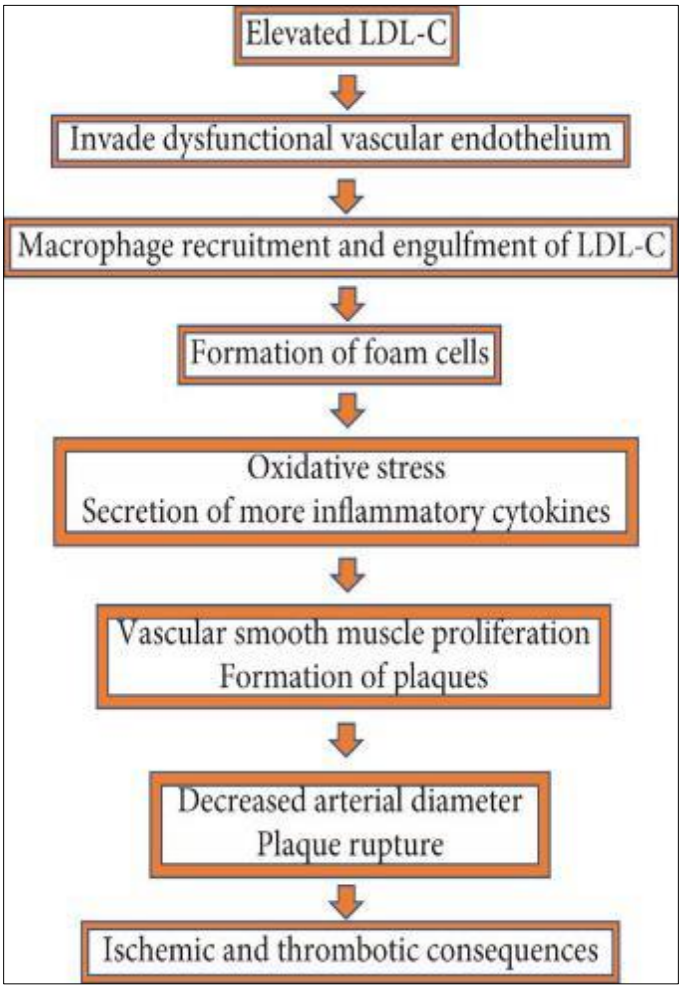

Figure 4 Mechanism of dyslipidemia

1.3. Factors causing Dyslipidemia:

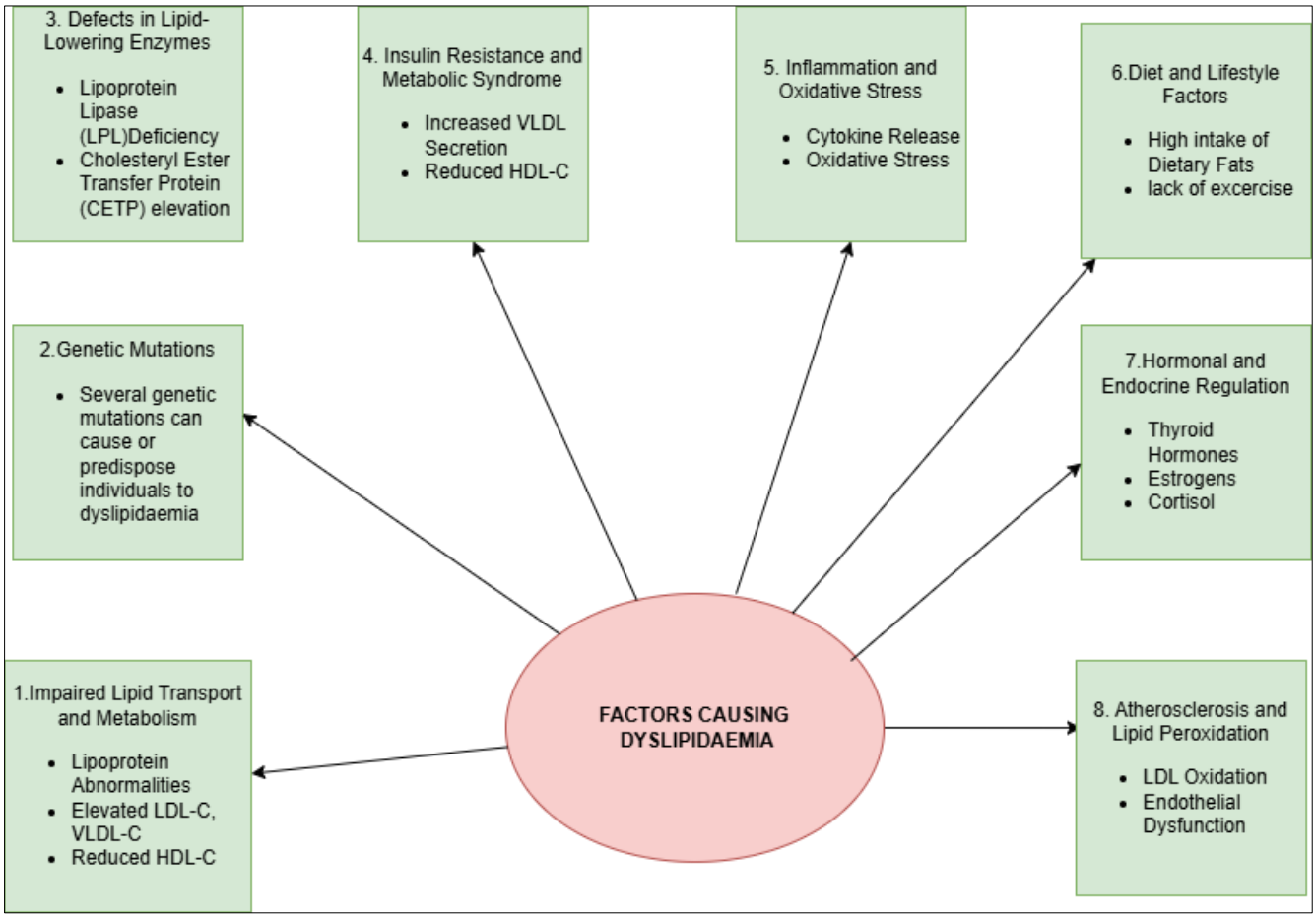

Figure 5 Factors causing dyslipidemia

1.4. Complications of Dyslipidemia

Hyperlipidemia can lead to a variety of complications, including atherosclerosis, fatty liver,cardiovascular and cerebrovascular diseases and impaired vision . Hyperlipidemia can also increase the risk of high blood pressure, pancreatitis, hepatitis, and Alzheimer's disease . It is recognized as a significant risk factor for the development of coronary heart disease and is strongly linked to conditions such as diabetes, insulin resistance, and obesity.

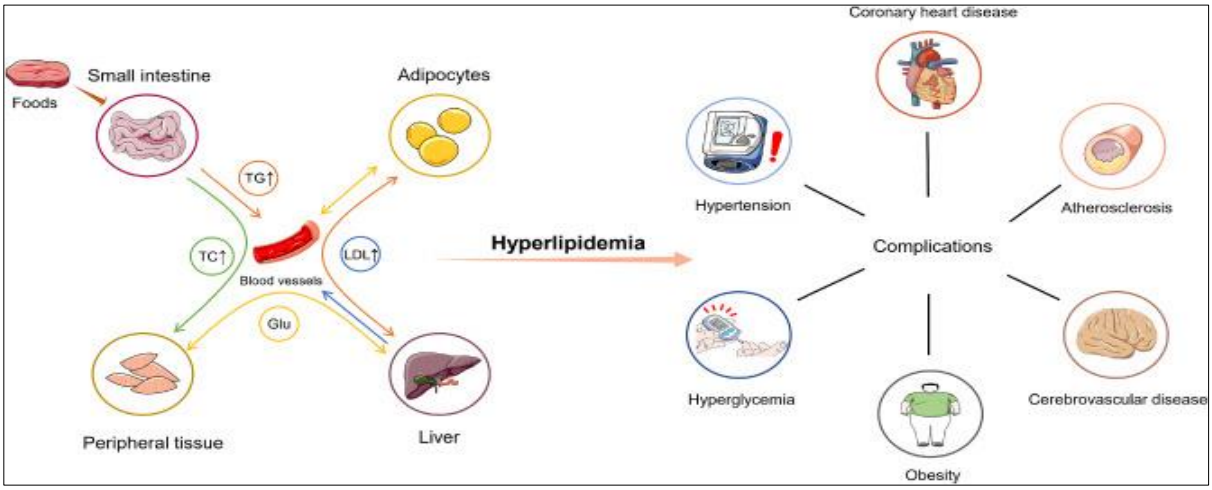

Figure 6 Complications

1.5. Anti Hyperlipidemic Agents[2]

Statins, Bile acid sequestrants, Fibric acid derivatives, Nicotinic acid derivatives, cholesterol absorption inhibitors are the mostly used anti hyperlipidaemic agents. But on long term use these drugs produce various side effects like Myalgia, Arrythmia, Gall stones, Myopathy and various GI disorders.

1.6. Introduction to herbal medicine

- Herbal medicine is a type of medicine that uses plant parts to treat diseases, prevent illness and improve health.
- Herbal medicine can serve as an alternative to conventional medicine owing to its low toxicity and beneficial effects.
- Herbal medicine has the potential to enhance therapeutic effects with fewer side effects.3

1.7. Herbal Medicine in Management of Dyslipidemia

- As many plants derived products have Anti-oxidant activity, they are very much helpful in management of Dyslipidemia.
- Phytochemicals with antioxidant and anti-inflammatory properties have been used to protect the vascular endothelium, prevent lipid oxidation, and lower lipid levels.
- The diversity and complexity of multicomponent Herbal Medicine enable the targeting of alternative pathways and biological processes to treat complex diseases such as dyslipidemia which is a consequence of multiple factors.therefore, its clinical manifestations are also complicated not only in terms of elevated serum lipid levels but also multifarious disorder .4
- A single phytochemical exhibits multiple mechanisms in management of Dyslipidemia
- eg: Curcumin,Berberine{Inhibition of cholesterol absorption,suppression of cholesterol synthesis,hepatic lipid uptake regulation}, Naringin {Inhibition of cholesterol absorption,Promotion of reverse cholesterol synthesis},Puerarin{Inhibition of cholesterol absorption,Acceleration of cholesterol excretion in liver}

1.8. Mechanisms of Herbal Medicine in management of Dyslipidemia

Many varieties of phytochemicals are used in Management of Dyslipidemia.

Five lipid-lowering mechanisms of herbal medicines are:

- Inhibition of cholesterol absorption in enterocytes
- Reduction of cholesterol synthesis
- Elevation of reverse cholesterol transport
- Regulation of Hepatic lipid uptake
- Promotion of cholesterol excretion in the liver.

2. Literature review

2.1. Inhibition of cholesterol absorption in enterocytes

Herbal medicine inhibits cholesterol absorption. Dietary components and bile enter intestinal cells through the transmembrane protein Niemann-Pick C1-like 1 (NPC1L1), which transports them from the intestinal lumen to the brush border membrane of enterocytes. After entering enterocytes, freecholesterol (FC) is esterified to cholesterol esters (CEs) by acyl CoA: cholesterol acyl transferase (ACAT)-2 in the endoplasmic reticulum (ER). Cholesterol esters (CEs) and triglycerides (TGs) are then combined to form chylomicrons with the help of microsomal triglyceride transfer protein (MTTP), which are subsequently secreted into the lymphatic system.phytochemicals from herbal medicines could regulate these processes.

- Inhibition of NPC1L1 substantially decreases intestinal cholesterol absorption, which is modulated by sterol regulatory element binding protein-2 (SREBP)-2 exhibited by curcumin, lycopene.
- Berberine is responsible for the cholesterol-lowering effect by inhibiting intestinal ACAT activity.
- Naringin, hesperetin inhibits the MTTP (microsomal steroid regulatory protien).
- Inhibition of MTTP leads to decreased apolipoprotein B (APOB) secretion and chylomicron assemblage by puerarin.
- Camphene upregulates the expression of SREBP-1 and blocks MTTP activity. The MOA is explained in Figure75

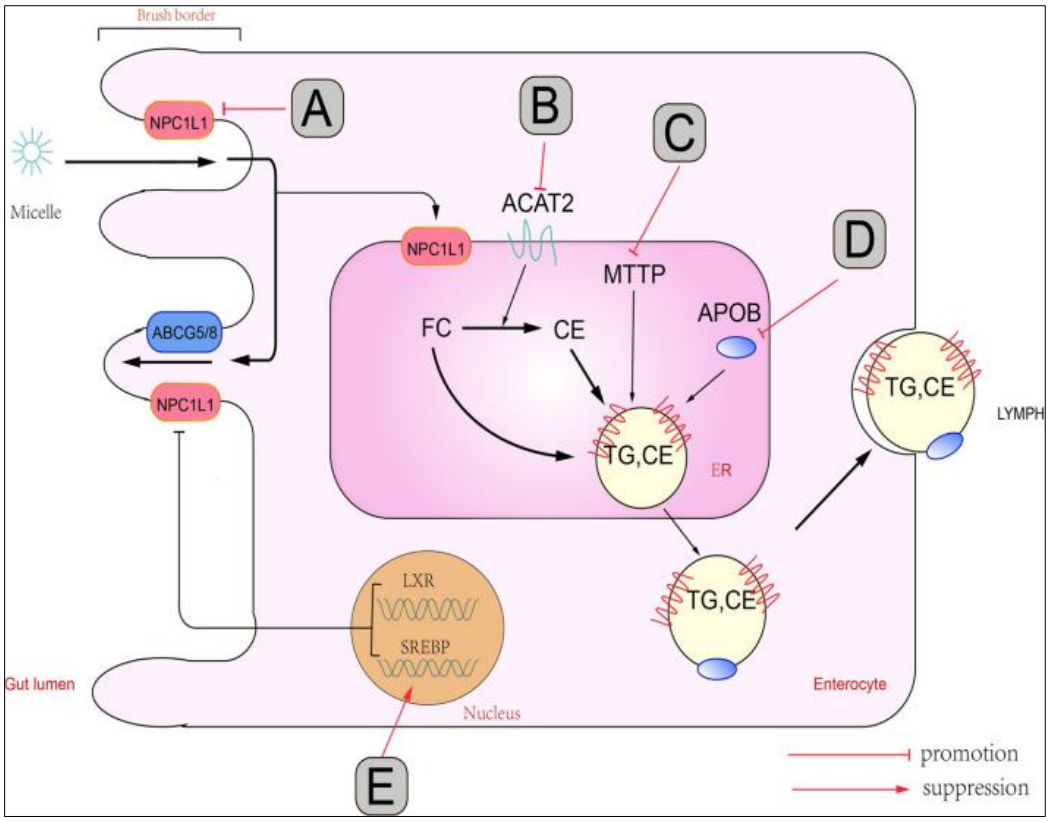

Figure 7 Mechanism of Inhibition of cholsterol absorption

2.1.1. Curcumin

It is a polyphenol obtained from rhizomes of *Curcuma longa* belonging to the family Zingiberaceae.The dosage is 200mg/day for 2weeks.Experimental studies were performed on Cancer coli cell lines and HFD (high fat diet) fed miceand it exhibits various pharmacological actions like Anti-inflammatory, Antioxidant, Antibacterial, Antifungal and anti-diabetic [5]6][7]

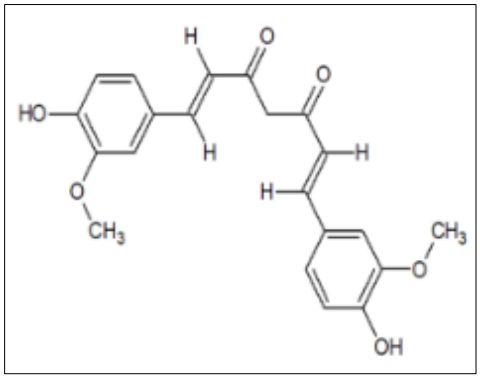

Figure 8 curcumin structure

Figure 9 Turmeric powder

2.1.2. Berberine

It is an alkaloid obtained from roots of *Coptis chinesis* belonging to the family Berberidaceae.

The dosage is 300-400mg. Experimental studies were performed on male sprague-Dawley rats on atherogenic diet and it exhibits various pharmacological actions like Anti-inflammatory, anti-cancer.[5][8]

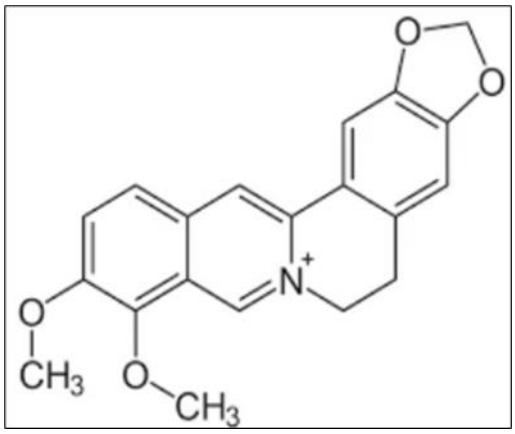

Figure 10 Berberine structure

Figure 11 *coptis chinensis*

2.1.3. Camphene

It is a monoterpene obtained from bark of chiosmastic gum oil which is a resinous secretion of *Pistacia lentiscus* belonging to the family Anacardiaceae . The dosage is 300 mg Experimental studies were performed on HepG2cells. It exhibits various pharmacological actions like Anti-inflammatory [5][9]

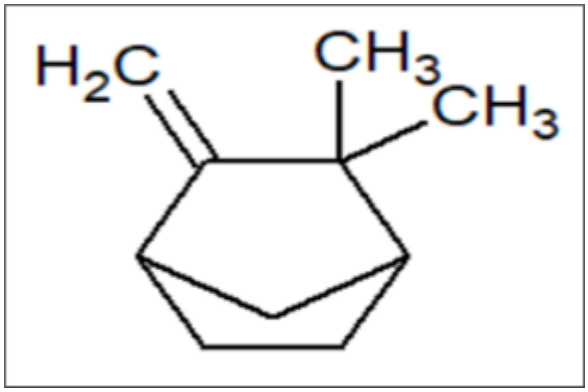

Figure 12 Camphene structure

Figure 13 *pistacia lentiscus*

2.1.4. Hesperetin and Naringin

These are flavonoids obtained from citrus fruit, specifically from the peel of orange, grapefruits, lemons, and mandarins belonging to the family Rutaceae, Vitaceae. The dosage is 300mg per day. Experimental studies were performed on HepG2 cells (human hepatoma cells line) and it exhibits various pharmacological actions like Lowering blood sugar levels, reducing Lipid levels, anti-inflammatory activity.[5][10]

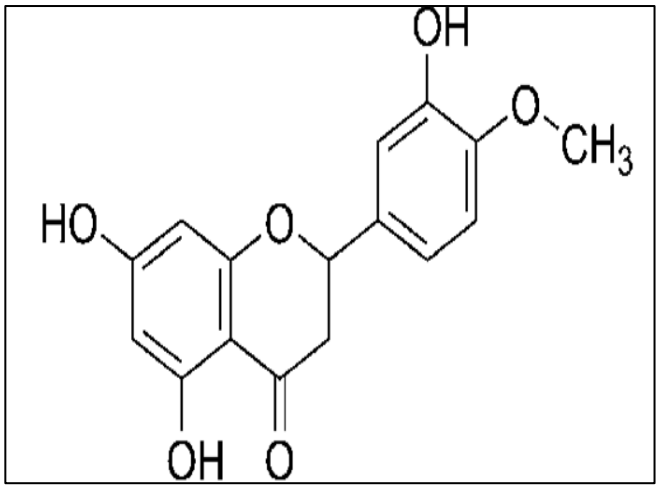

Figure 14 Hesperetin structure

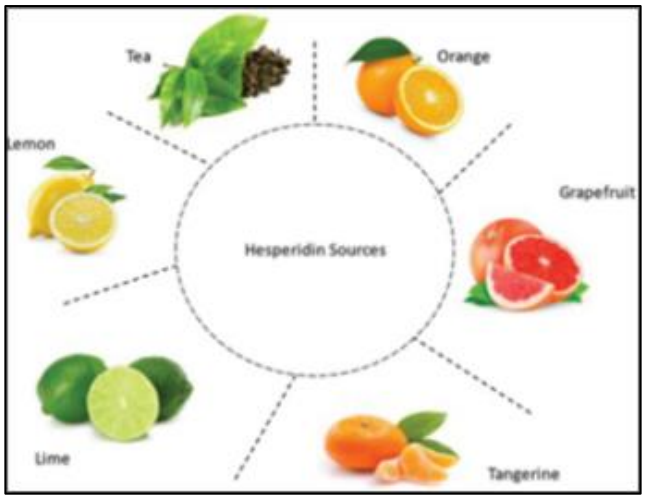

Figure 15 Hesperetin containing fruits

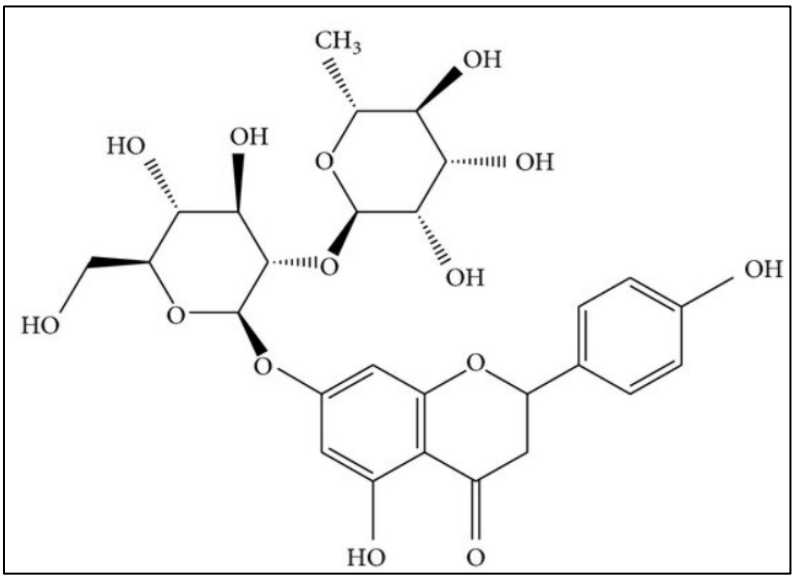

Figure 16 Naringin structure

2.1.5. Lycopene:

Lycopene is a carotenoid obtained from fruits of *Solanum lycopersium* belonging to the family Solanaceae.The dosage is 15-45 mg per day. Experimental studies were performed on caco-2 cells. It exhibits various pharmacological actions like antioxidant activity [5][11]

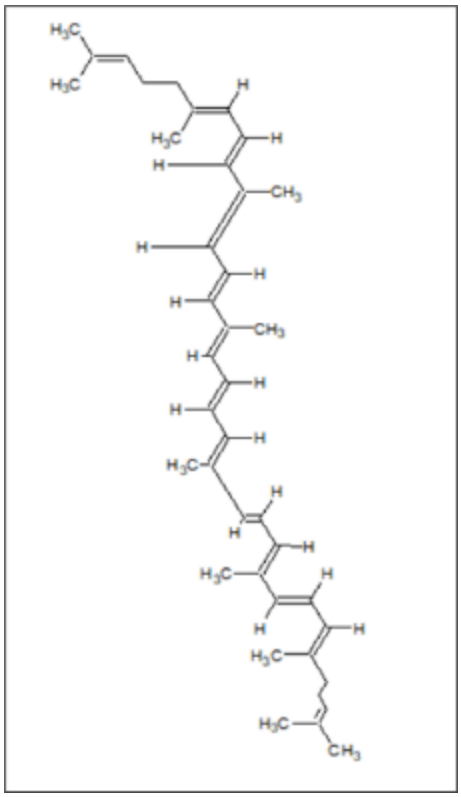

Figure 17 lycopene structure

Figure 18 lycopene containing fruits

2.1.6. Psyllium

Psyllium obtained from soluble fibers *Plantago ovata* belonging to the family Plantaginaceae.

The dosage is 19-50 g per day.Experimental studies were performed on HFD fed mice.it exhibits various pharmacological actions like treats constipation [5]

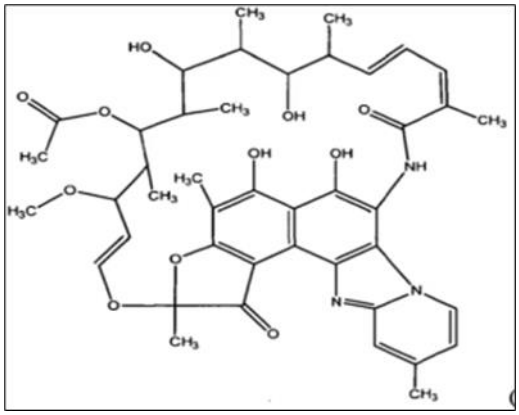

Figure 19 Psyllium structure

Figure 20 Psyllium husk

2.2. Suppression of cholesterol synthesis

Cholesterol synthesis is strictly regulated by a negative feedback mechanism. Low cholesterol can be achieved by inhibiting the biosynthesis of cholesterol.

- Inhibition of HMGCOA activity by geraniol,Leoligin,curcumin,puerarin.
- Promotion of the expression of AMPK by allicin, and curcumin.
- Emodin could reduce the SCAP/SREBP pathway.

- Epicatechin could attenuate the expression of SREBP.
- Berberine alleviates squalene synthase activity to block cholesterol synthesis.

The MOA is explained in Figure 21 below

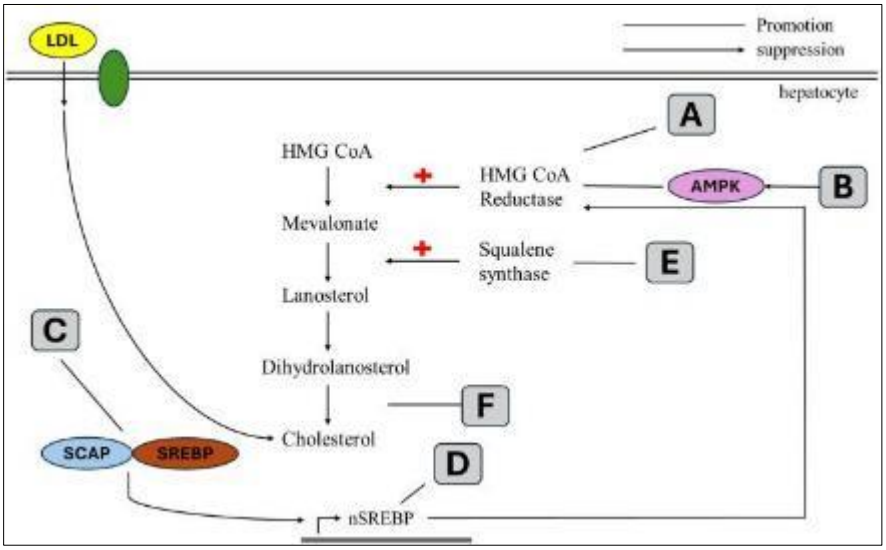

Figure 21 Mechanism of suppression of cholesterol synthesis

2.2.1. Geraniol

Geraniol is a monoterpenoid alcohol obtained from *Pelargonium graveolens* belonging to the family Rosaceae. Experimental studies were performed on Female NIH nu/nu mice. The dosage is 250mg per day and it exhibits various pharmacological actions like anti-inflammatory, anti-cancer,neuroprotective [5]

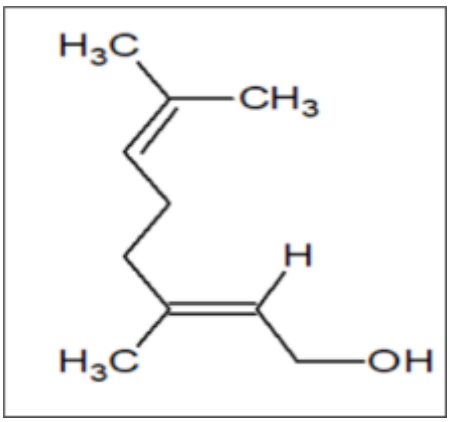

Figure 22 Geranoil structure

Figure 23 *pelagorium graveolens*

2.2.2. Puerarin

It is a flavonoid obtained from roots of *pueraria lobata* belonging to the family Fabaceae.The dosage is 200mg per day. Experimental studies were performed on HepG2 cells; C57BL/6 J mice and it exhibits various pharmacological actions like Cardioprotective, neuroprotective, anti-inflammatory and antioxidants.[5][12]

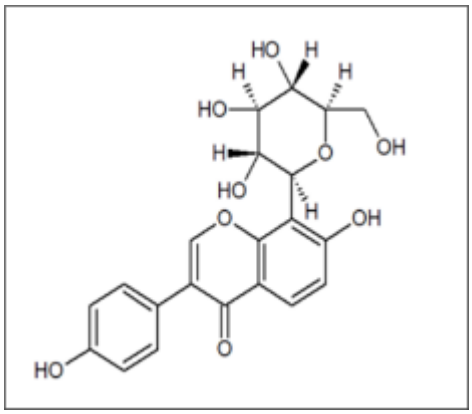

Figure 24 Peurarin structure

Figure 25 Roots of *peuraria lobata*

2.2.3. GinsenosideRb2

It is a saponin obtained from *Panax ginseng belonging* to the family Araliaceae.The dosage is 10 mg/day.Experimental studies were performed on 3T3-L1 adipocyte cells; HFD-fed obese C57BL/6 J mice and it exhibits various pharmacological actions like Antioxidant, anti-inflammatory, cardioprotectiveeffect.[5][15]

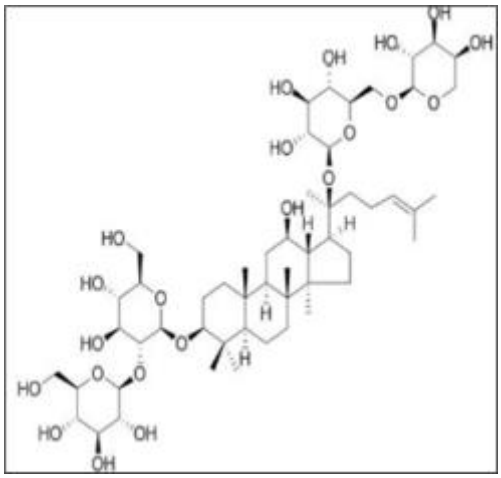

Figure 26 Ginsenoside Rb2 structure

Figure 27 Roots of *Panax ginseng*

2.2.4. Epicatechin

Epicatechin is a polyphenol obtained from the *Camellia sinensis* belonging to the family Theaceae. The dosage is 200 mg at body weight. Experimental studies were performed on Hyperlipidemic rats and it exhibits various pharmacological actions like Anti diabetic, anticancer property.[5][16]

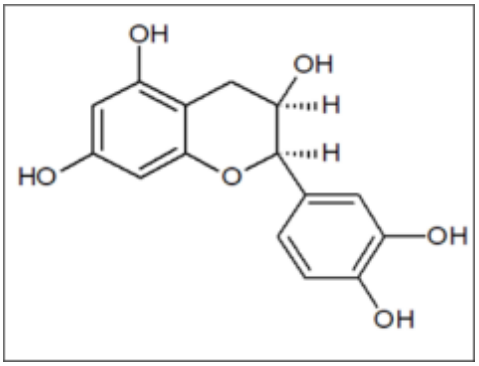

Figure 28 Epicatechin structure

Figure 29 Dried leaves of *camellia sinensis*

2.3. Induction of reverse cholesterol transport

Reverse cholesterol transport (RCT) is a multi-organ process that enables the transfer of excess cholesterol from the arterial walls to the liver for elimination. The process of RCT includes the following: cholesterol efflux, where these lipoproteins remove excess cholesterol from cells;lipoprotein remodeling, where HDL undergoes structural modifications with possible impact on their function; hepatic lipid uptake, where HDL releases cholesterol to the liver for final excretion into bile and faeces.The process of RCT is shown in figure 30

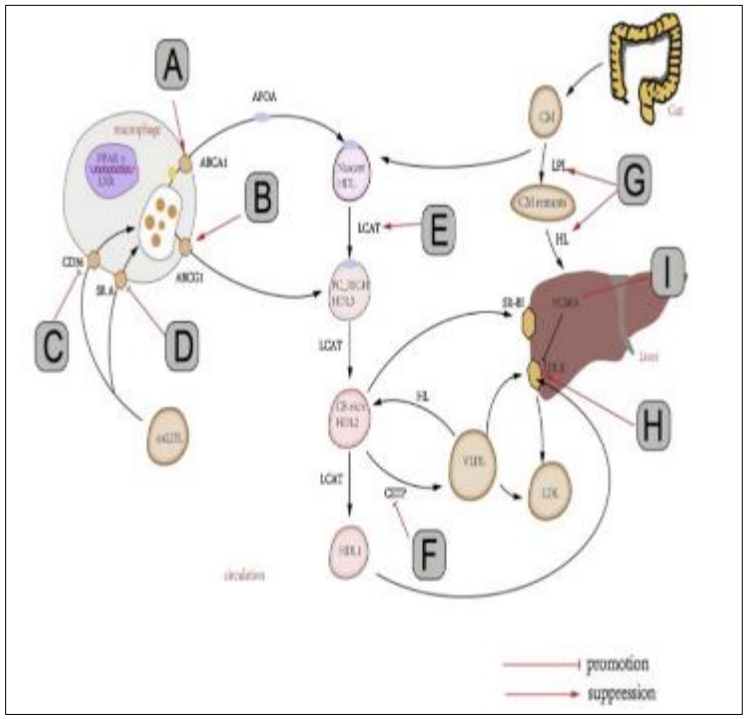

Figure 30 Mechanism of induction of RCT

- Leoligin, leoneurine, Allicin, peurarin Promotes cholesterol Efflux:Transporters ABCA1(ATP binding casatte transporter A1) and ABCG1 contributes to cholesterol efflux by binding to APOA(apo lipoprotien A) to form Nascent HDLc.
- CD36 PROTIEN and SR-A converts cholesterol into foam cells which affects RCT Negatively hence, herbal medicine like Icarin,paenol,peurarin inhibits these protiens to induce RCT.
- Nascent HDL is converted into mature HDL by LCAT(Lecithin cholesterol acyl transferase) hence phytochemicals like curcumin,berberine act by promoting the function of LCAT.
- CETP (cholesteryl ester transfer protien) transfers cholesteryl esters (CEs) from HDL to APOB lipoprotien which leads to decrease in conc. of APOA1 and HDL and increase in conc. Of VLDL and LDLc hence inhibition of CETP is done by Anthocyanins.
- LDL binds to LDL receptors binds and transports it to liver and eliminates it hence enhancing LDLr activity is done by Berberine
- HL (hepatic lipase) and LPL (lipoprotien lipase) contributes to RCT by breaking down chylomicrons and their remenents in gut hence enhancing their function helps in Induction of RCT which is done by Tanshinone IIa

2.3.1. Leoligin

It is a lignan is obtained from Roots of *Leontopodium nivale ssp* belonging to the family Asteraceae. The dosage is 0.14mg/day for 2days. Experimental studies were performed on THP-1 macrophages and it exhibits various pharmacological actions like Anti-inflammatory, antimicrobial, antioxidant and cardiovascular [5][17]

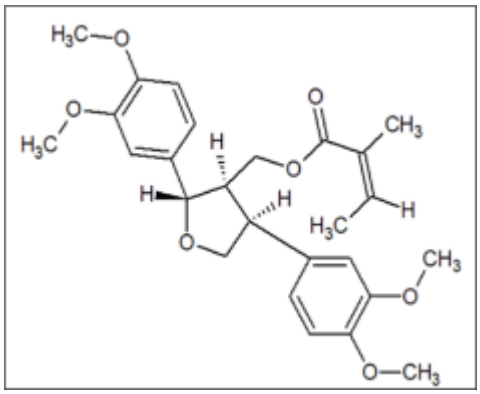

Figure 31 leoligin structure

Figure 32 *Leontopodium nivale* plant

2.3.2. Leonurine

It is an alkaloid is obtained from Herbs of *Leonurus cardaica* l belonging to the family Lamiaceae.The dosage is 7.5-15mg/day. Experimental studies were performed on THP-1 macrophages; apoE-/- mice. it exhibits various pharmacological actions like Anti-inflammatory, antioxidant,and anti-tumor effects.[5][18]

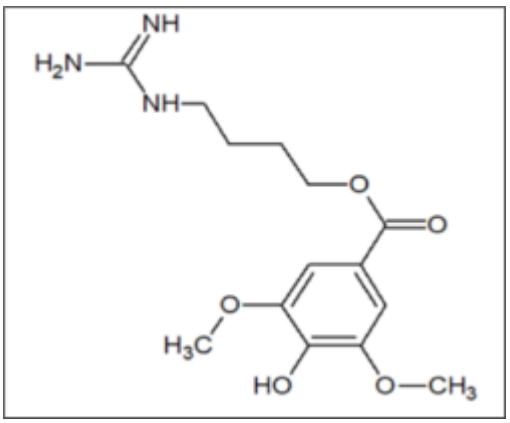

Figure 33 leonurine structure

Figure 34 *Leonurus cardaica* plant

2.3.3. Andrographolide

It is a diterpenoid is obtained from Leaves of *Andrographis paniculata* belonging to the family Acanthaceae. The dosage is 90-600mg/kg. Experimental studies were performed on Mouse macrophage cells and it exhibits various pharmacological actions like Anti-inflammatory, antioxidant,and anti-cancer properties [5][19]

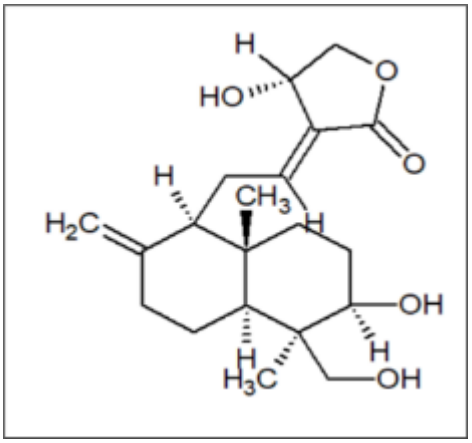

Figure 35 Andrographolide structure

Figure 36 *Andrographis paniculata* plant

2.3.4. Allicin

It is a organosulfur compound obtained from *Allium sativum L* belonging to the family Amaryllidaceae. The dosage is 600mg/daily. Experimental studies were performed on THP1 macrophages and it exhibits various pharmacological actions like antioxidant activity.[5][20]

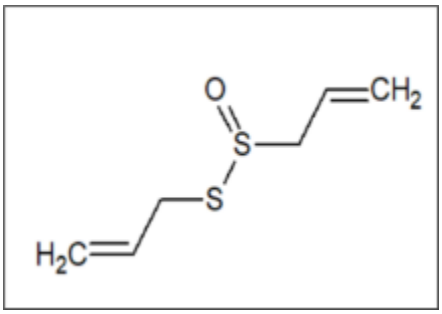

Figure 37 Allicin structure

Figure 38 *allium sativum* roots

2.3.5. Quercetin

It is a flavonoid compound is obtained from leaves of *Ginkgo biloba* belonging to the family Gingkoaceae. The dosage is 250-1000mg/kg daily 12 weeks. Experimental studies were performed on THP-1 cells and HepG2 cells; C57BL/6 mice and macrophages. It exhibits various pharmacological actions like Antioxidant, anti-inflammatory, and anti-viral properties [5][22]

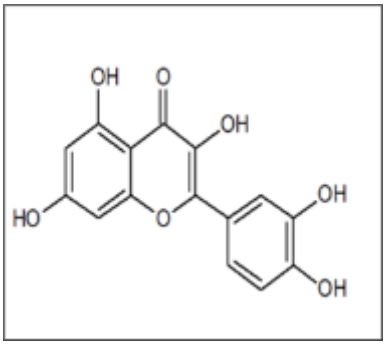

Figure 39 Quercetin structure

Figure 40 *Ginkgo biloba* plant

2.3.6. Icariin

It is a flavoniod glycoside compound is obtained from leaves of *Epimedium brevicornum* belonging to the family Berberidaeceae.

The dosage is 1500mg/kg/5days.Experimental studies were performed on HepG2 cells. It exhibits various pharmacological actions likeAntioxidant, anti-inflammatory, and lipidmodulatory. [5][23]

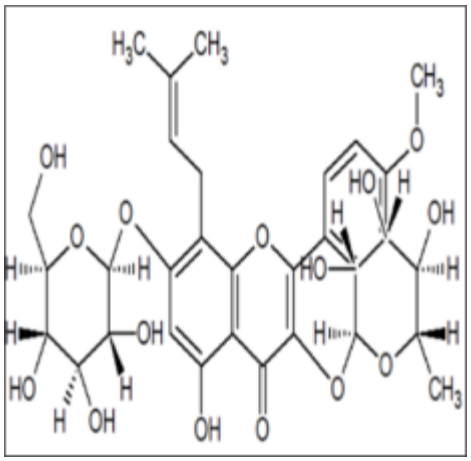

Figure 41 Icariin structure

Figure 42 *Epimedium brevicornum* plant

2.3.7. Paeonol

It is a phenol compound is obtained from Roots and bark of *Paenea suffristicosa andrews* belonging to the family Paeoniaceae The dosage is 24.23mg/kg/day. Experimental studies were performed on RAW264.7 macrophages; ApoE/ mice and It exhibits various pharmacological actions likeAnti-tumor,anti-inflammatory, and anto-diabetic,anti-cardiovascular. [5][24]

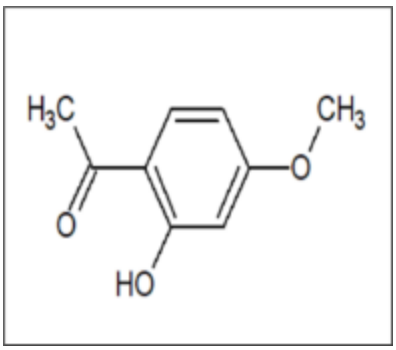

Figure 43 Paeonol structure

Figure 44 Roots of *Suffristicosa andrews*

2.3.8. Salvianolic acid B

It is a polyphenol compound is obtained from Root of *Salvia miltiorrhiza* belonging to the family Lamiaceae. The dosage is 250-300mg/kg/6weeks. Experimental studies were performed on THP-1 cells; HFD-fed ApoE-/-mice and it exhibits various pharmacological actions like Anti-oxidant and in treatment of CVS diseases.[5][25]

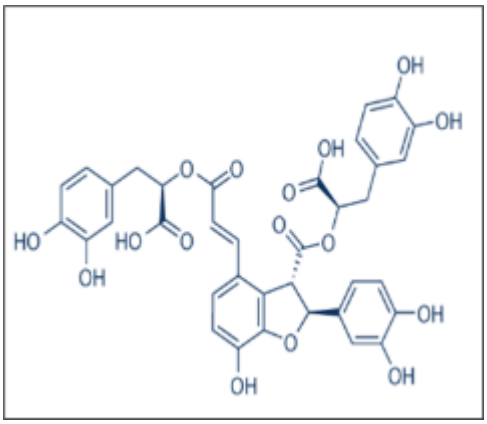

Figure 45 Salvianolic acid B structure

Figure 46 Plant of *salvia miltiorrhiza*

2.4. Regulation Of Hepatic Lipid Uptake

Hepatic lipid levels are governed by the balance between lipid acquisition and disposal constituting the four major pathways of hepatic lipid homeostasis which are, circulating lipid intake, de novo lipogenesis (DNL), fatty acid oxidation (FAO), and export of lipids as very-low-density lipoproteins (VLDLs) explained in fig 47

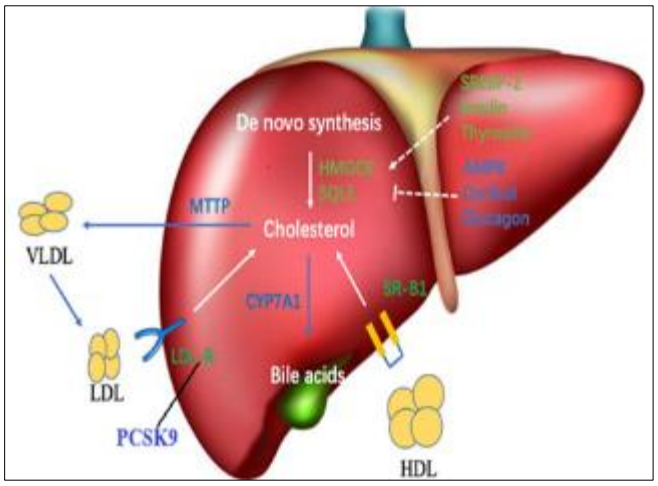

Figure 47 Mechanism of Hepatic lipid uptake Regulation

The liver is the major site for cholesterol metabolism, where it takes up HDL-CE and LDL particles by scavenger receptor class B type I (SRBI) and the low-density lipoprotein receptor (LDLR), respectively. LDLR, a transmembrane glycoprotein, binds to LDL on the cell surface. Proprotein convertase subtilisin/kexin type 9 (PCSK9) post-transcriptionally downregulates the LDLR by binding to the receptor's epidermal growth factor repeat A on the cell surface and shuttling the LDLR to the lysosomes for degradation.

Berberine, Tanshinone IIa and curcumin act by

- Decreasing the serum levels of TG, TC, LDL-C levels and increasing serum HDL-C levels by Increasing the expression of PCSK9 via SREBP-2 activation
- Lipid lowering effect by regulation of hepatic LDLR and PCSK9 expression to reduce lipid levels via the ERK signaling pathway

2.4.1. Tanshinone IIA

It is a diterpene quinone compound is obtained from Dried roots of *Salvia miltiorrhiza Bunge* obtained from family Lamiaceae. The Dosage is 20mg/day.Experimental studies were performed on HepG2 cells and it exhibits various pharmacological actions like Anti-inflammatory, anti-oxidant, anti tumor, cardiovascular effects. [5][27]

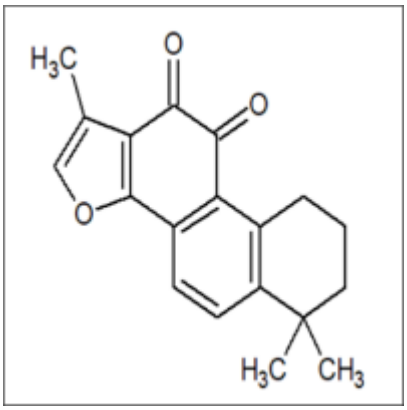

Figure 48 Tanshinone IIa structure

Figure 49 Roots and plant of *salvia miltiorrhiza*

2.5. Acceleration of cholesterol excretion in the liver:

- Cholesterol transported into the liver and endogenously synthesised is lost from the body via biliary secretion after conversion to bile acids.
- Microsomal cytochrome P450 cholesterol 7 alpha hydroxylase (CYP7A1) is the first rate-limiting enzyme in the neutral pathway of bile acid synthesis, which plays a vital role in the maintenance of cholesterol homeostasis explained in figure 50

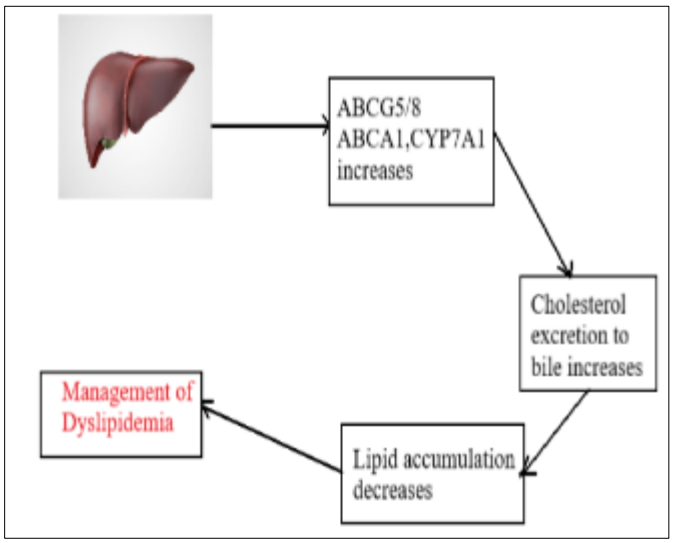

Figure 50 Mechanism of accelaration of cholesterol excretion

- Lipid-lowering effect by Stimulation of CYP7A1 at mRNA level by Epicatechin and palmatine
- Up-regulation of LDLR and CYP7A1 mRNA and protein expression by puerarin and palmatine
- Activation of the PPARγ-ABCA1/CYP7A1 signaling pathway by Punicalagin and pomegranate ellagic acid.

2.5.1. Palmatine

It is a alkaloid obtained from Roots of *Coptis chinensis* belonging to the family Berberdaceae . The Dosage is 100mg/kg every 2 weeks.Experimental studies were performed on HFD-fed hamsters and it exhibits various pharmacological actions like Anti-inflammatory,anti-bacterial, anti-oxidation and antiviral. [5][30]

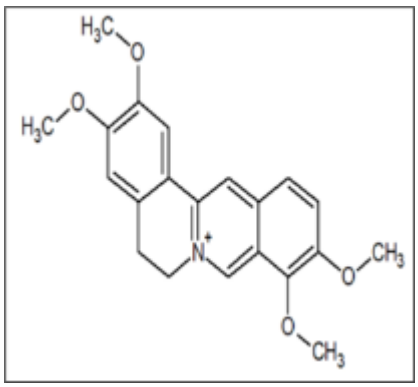

Figure 51 Palmatine structure

Figure 52 *Coptis chinensis* roots

2.5.2. Punicalagin

It is a polyphenol compound is obtained from Fruits of *Punica granatum* belonging to the family Punicaceae. The Dosage is 60mg for 23 days .Experimental studies were performed on Steatotic L-02 hepatocytes and it exhibits various pharmacological actions like Anti-cancer, anti-inflammatory and anti-oxidant.[5][31]

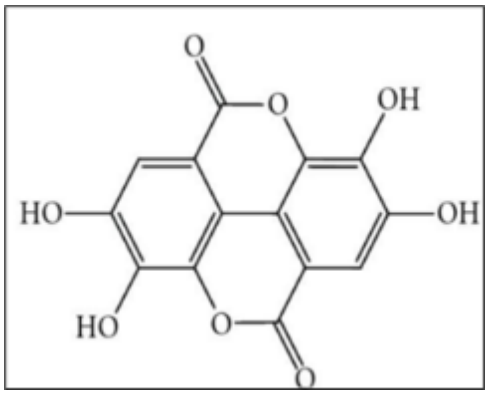

Figure 53 Punicalagin structure

Figure 54 Pomogranate

2.6. Marketed herbal formulations used in management of Dyslipidemia

Figure 55 Himalaya abana tablets

Figure 56 Aimil Trimalip tablets

Figure 57 Krishna's cholesterol care juice

Figure 58 Allen cholesterol drops

3. Conclusion

A single phytochemical exhibits multiple mechanisms in management of Dyslipidemia i.e Curcumin, Berberine by Inhibition of cholesterol absorption, suppression of cholesterol synthesis and hepatic lipid uptake regulation, Naringin by Inhibition of cholesterol absorption and Promotion of reverse cholesterol synthesis, Puerarin by Inhibition of cholesterol absorption and acceleration of cholesterol excretion in liver.

Most phytochemicals exhibit different pharmacological actions other than Anti hyperlipidemic activity like Anti ointment-inflammatory, cardio protective actions which helps in enhanced treatment of Dyslipidemia and also reduces the risk of cardiovascular diseases.

Herbal formulations are able to regulate the transcription factors like LXR, SREBP, PPARα, and PPARγ which are involved in expression of Key molecules like NPC1L1, HMGCR, PCSK9 and CYP7A1 which plays a important role in lipid metabolism.

The active components are diverse and include alkaloids (berberine), saponins (ginsenoside), polyphenols (pomegranate) and flavonoids (quercetin). Herbal medicines provide a promising and multifaceted approach to

dyslipidaemia management, with the potential for complementary benefits beyond lipid regulation, contributing to overall cardiovascular health.

Compliance with ethical standards

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Disclosure of conflicts of interest

The authors have no conflicts of interest to declare.

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