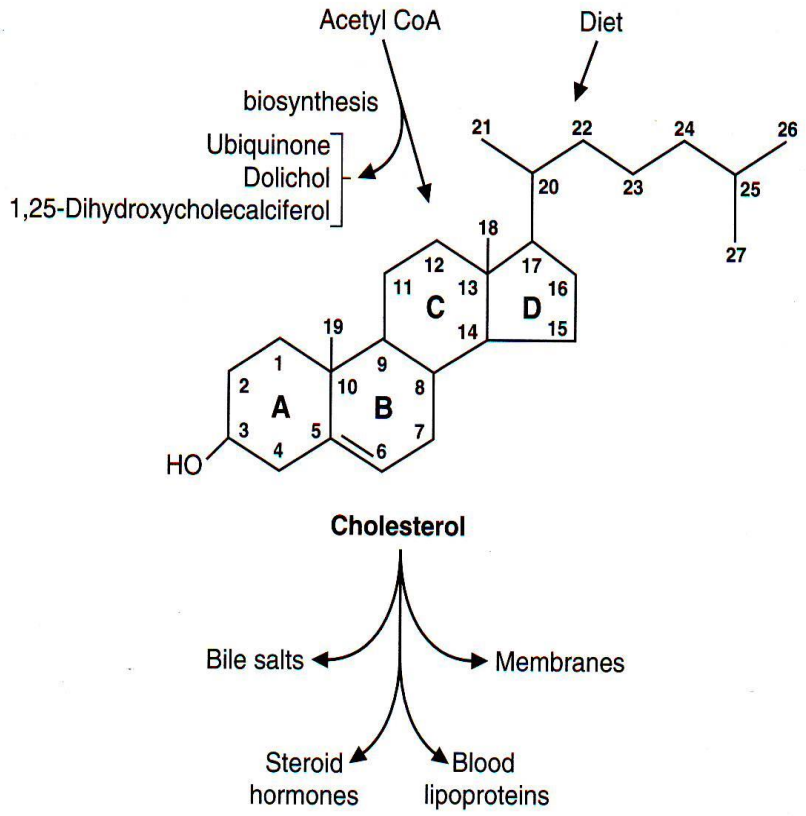
CHOLESTEROL & Bile Salts

- Cholesterol is the most common sterol in the body ; serves as :
  1. a **stabilizing** component of cell membranes and
  2. a precursor of the **bile salts** and **steroid hormones** ;
  3. precursors of cholesterol are converted in the skin to **cholecalciferol** , the active form of vitamin D .



l. Overview of cholesterol metabolism.

- Cholesterol is present in **tissues** and in **plasma** either as free cholesterol(C) or esterified cholesterol (CE) .
  - In tissues , the free cholesterol is mainly in the cell membranes and the esterified cholesterol is the storage form inside the cells .
  - In the plasma , the greater part of cholesterol (75%) is esterified and the rest is free ; both are transported in the plasma in **different lipoproteins** ; **the highest proportion** is found in LDL and transports cholesterol into peripheral tissues .

- **The enzymes that esterify cholesterol are :**

  (a) **Lecithin –Cholesterol Acyl Transferase** (**LCAT**) which is located in the blood and esterifies cholesterol associated with the lipoprotein HDL ;

  (b) **Acyl: Cholesterol Acyl Transferase** (**ACAT**) which is located in cells (particularly cells that need to store cholesterol for the synthesis of steroid hormones)

Sources of cholesterol :

- Cholesterol can be **synthesized** in the body (endogenous , about 700 mg/day) **or** obtained from the **diet** in foods of animal origin mainly meat and egg (exogenous , about 300 mg/day) .

BIOSYNTHESIS :

- Cholesterol is synthesized by a pathway that occur in most cells of the body but to a greater extent in cells of the **liver** , **intestine** , **adrenal cortex** and **gonads** ; **Liver** is responsible for **80%** of endogenous synthesis .
- Enzymes involved in cholesterol synthesis are located in the **cytoplasm** and in **endoplasmic reticulum** .
- **All carbon atoms** of cholesterol are derived from **cytosolic acetyl CoA** produced mainly from dietary glucose or caloric excess of dietary protein .

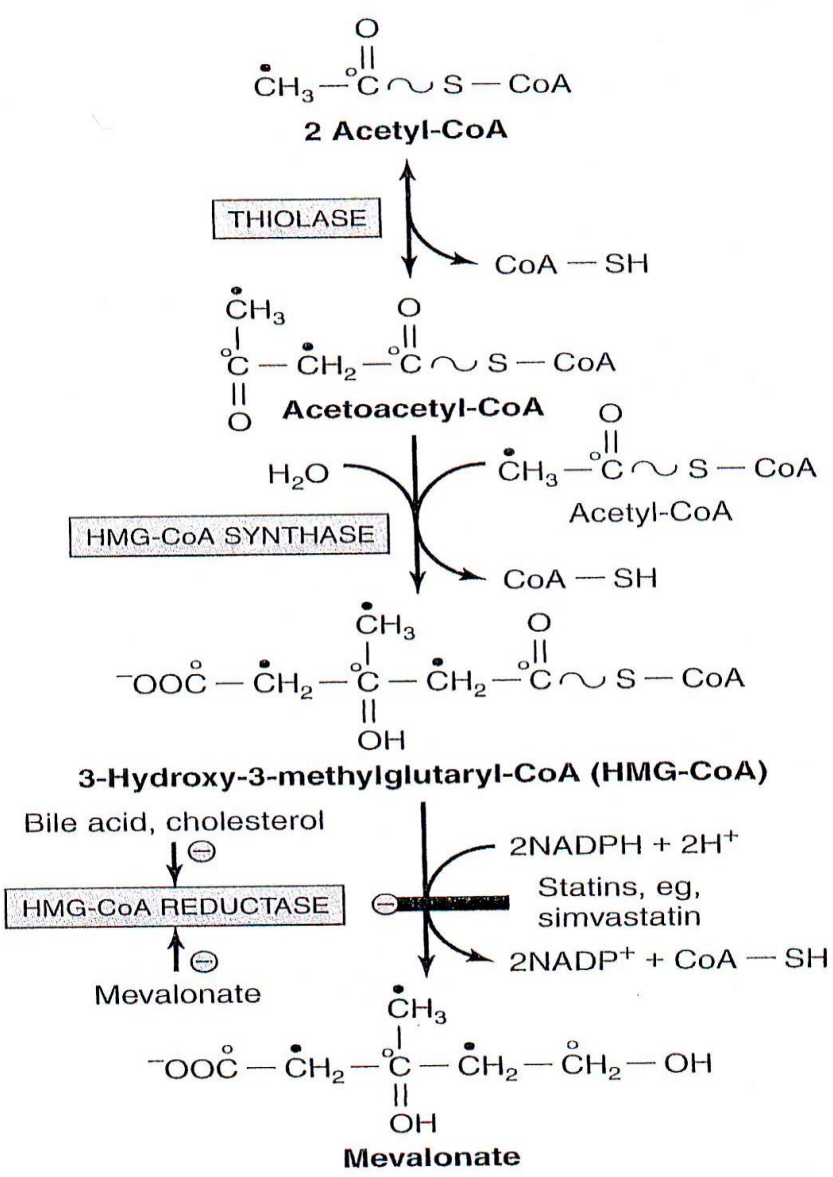
The pathway for the synthesis of cholesterol occurs in three phases :

Phase I : Synthesis of Mevalonate from acetyl CoA : Include **three** reactions :

1. Two molecules of cytosolic acetyl CoA **condense** to form **acetoacetyl CoA** catalyzed by cytoplasmic **thiolase** .

2. Another molecule of acetyl CoA combine with acetoacetyl CoA to form **β-hydroxy-β-methyl glutaryl CoA** (**HMG-CoA**) catalyzed by **cytoplasmic HMG-CoA synthase-II** (mitochondrial fraction of this enzyme is involved in the synthesis of ketone bodies) .

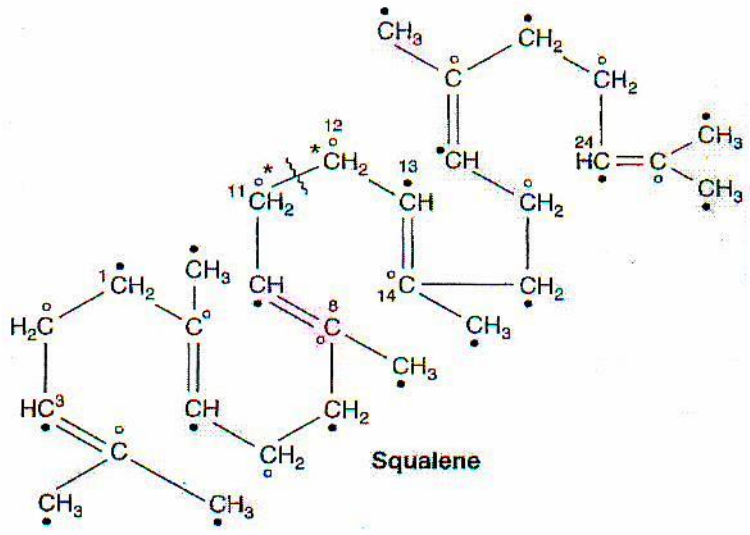
3. HMG-CoA is reduced to **mevalonate** using NADPH as reducing agent .This is catalyzed by **HMG-CoA reductase** located in the endoplasmic reticulum .



Phase II : Synthesis of squalene :

- **Mevalonate** is phosphorylated by ATP and subsequently decarboxylated &reduced to produce 5-carbon **isopentenyl pyrophosphate** (**isoprene unit**) .

- The isoprene units may condense to form 30-carbon compound **squalene** as follows :

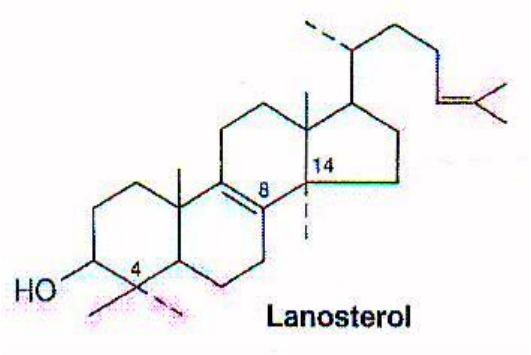


Phase III : Synthesis of cholesterol :

- **Squalene** cyclizes forming **Lanosterol** which contains the rings of the steroid nucleus .

- **Lanosterol** is modified in a series of steps to form **cholesterol** .

Lanosterol ——→ Zymosterol ——→ Desmosterol ——→ Cholesterol



Regulation of Cholesterol Synthesis :

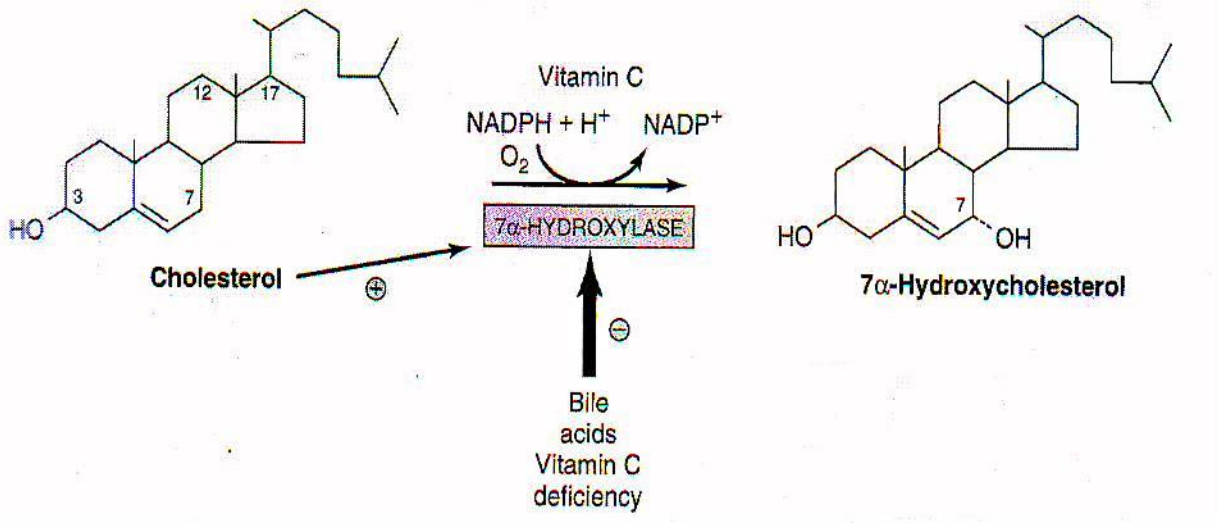
- HMG-CoA reductase step is the rate-limiting and control point in the pathway of cholesterol synthesis . This step is subject to regulation :
  1. **liver** HMG-CoA reductase is activated when **insulin** is high and inactivated when **glucagon** is high .
  2. HMG-CoA reductase is inhibited by high levels of mevalonate (feed-back regulation by immediate product) .
  3. Synthesis of HMG-CoA reductase is repressed by :
     a – cholesterol (final end product of synthesis) .
     b – influx of cholesterol into cells from LDL .
     c – bile salts produced from cholesterol in liver .
  4. Thyroid hormone (T_3) increase the activity of HMG-CoA reductase
  5. Glucocorticoids (cortisol) decrease the activity of HMG-CoA reductase (end product inhibition since glucocorticoids are synthesized from cholesterol .

BILE SALTS

Synthesis :

- Bile salts are synthesized in the **liver** from cholesterol by reactions that hydroxylate steroid nucleus and cleave the side chain .

1ST **Step :** an oxygen atom is added to carbon-7 of cholesterol forming an **7α-hydroxy cholesterol** ; this is catalyzed by the enzyme **7α–hydroxylase** which is the **rate-limiting** step ; the enzyme **activity is decreased** by high levels of bile salts (feedback inhibition) & **activated** by vitamin C .

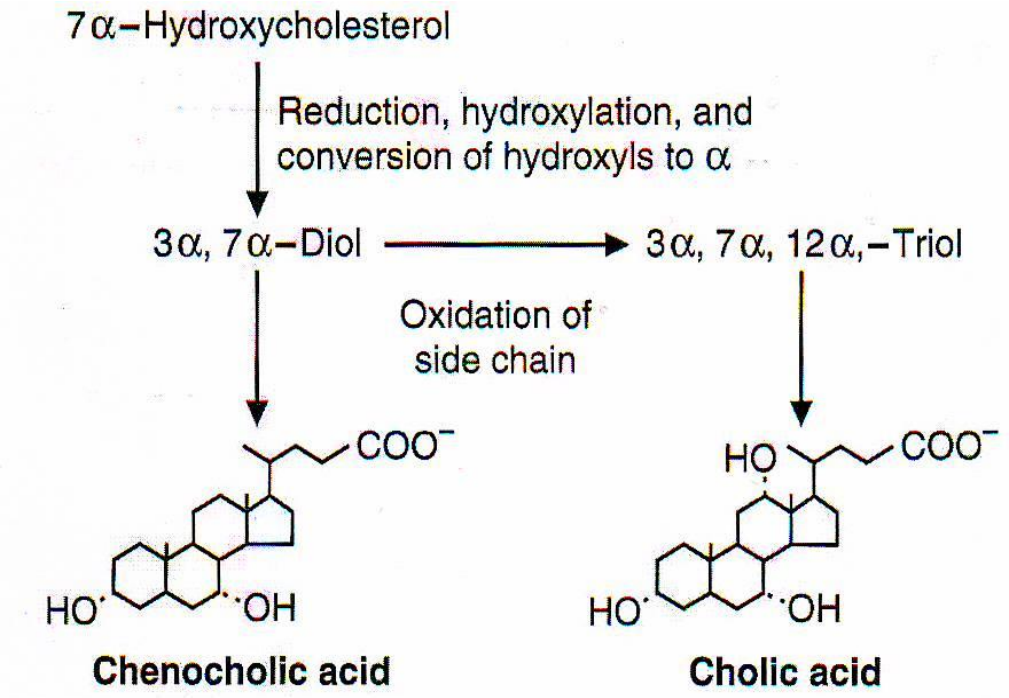


2nd **Step :** the double bond (between carbons 5& 6) is reduced and **two** different sets of bile salts are produced :

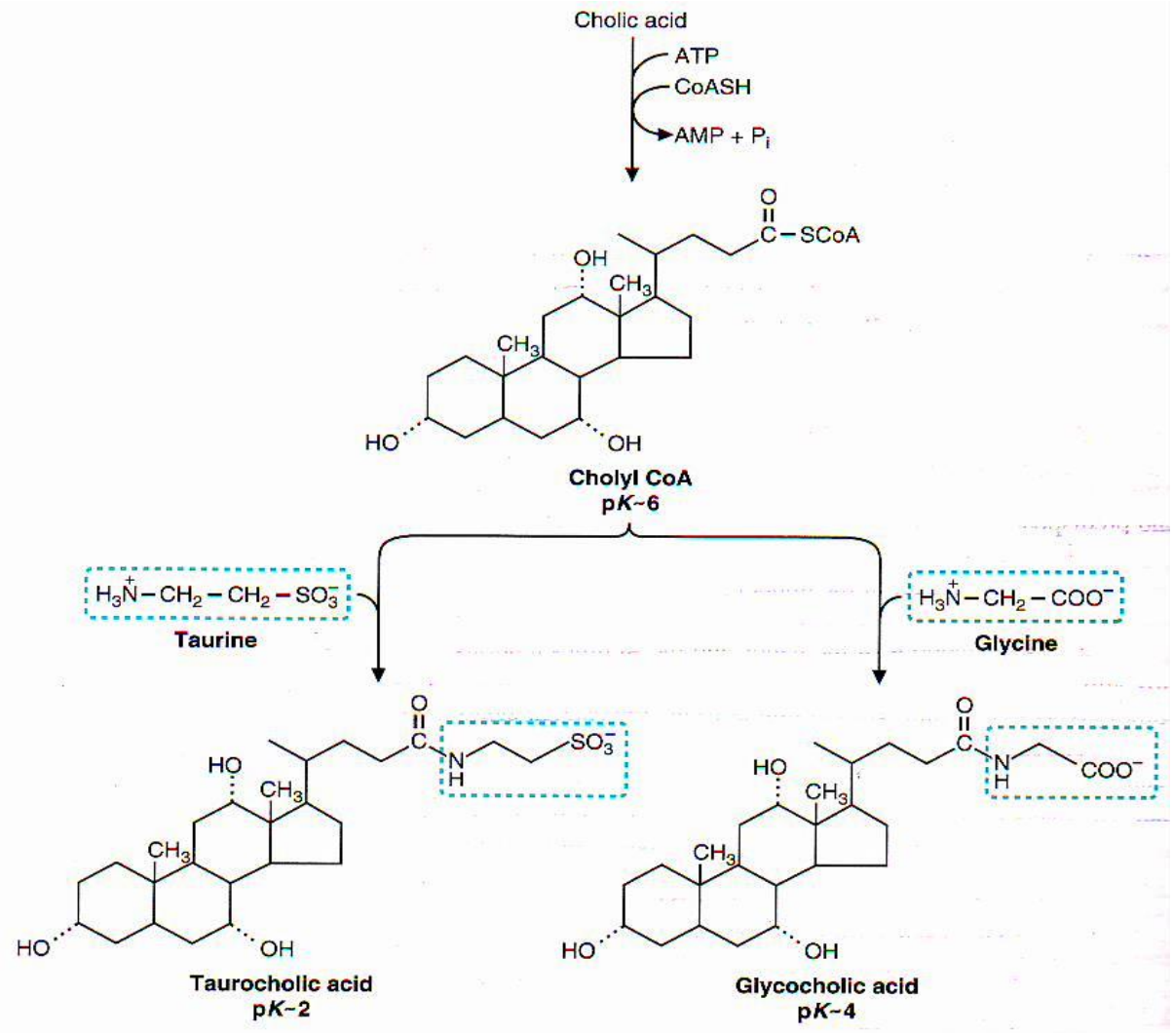
Dihydroxy set (Diols) produces the **chenocholic acid** series .

Trihydroxy set (Triols) forming the **cholic acid** series of bile salts . **Cholic acid** is the major bile acid .

3rd **Step** : three carbons are removed (as propionate derivative) from the side chain by an oxidation reaction so the side chain becomes carboxylated .



4th **Step :** the **carboxyl group** is activated by reacting with **coenzyme A** (ATP required) producing the **CoA-derivative** of bile acids which can then react with either **glycine** or **taurine** forming conjugated bile acids , *for example* : cholic acid conjugated with glycine to form **glycocholic acid** .

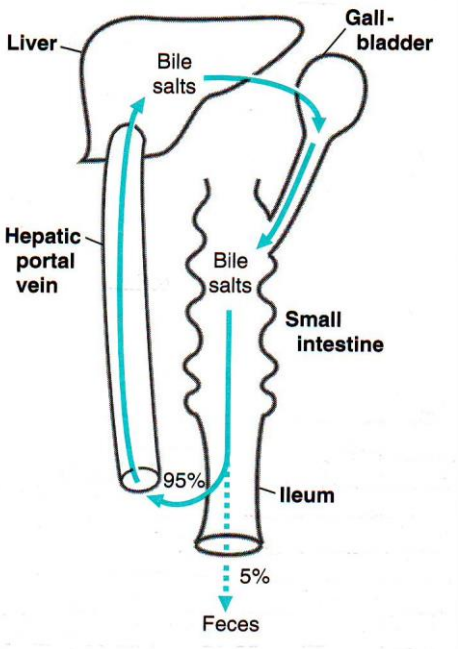


- The bile acids and their conjugates produced in the liver are secreted into the bile ; stored in the gallbladder and released into the intestine during a meal .

- Conjugation of bile acids with Glycine or Taurine decreases the pK value of the bile acids .
- In the alkaline bile and in the intestinal lumen which normally have a pH = 6 , most of the bile acids & their conjugates are **ionized** so that can bind cations and are termed "**primary bile salts** " having better detergent action .

- Greater than 95% of the bile salts are reabsorbed in the ileum and return to the liver via the **enterohepatic circulation** and re-secreted into the bile . Less than 5% of the bile salts entering the gut are excreted in the feces every digestive cycle .

- Intestinal bacteria **deconjugate** and **dehydroxylate** the bile salts removing the glycine and taurine residues and the hydroxyl group at position 7 . These bile salts are termed "**secondary bile salts** " ; are less soluble and less reabsorbed from the intestinal lumen than the primary bile salts so their major fate is excretion .



- **Bile salts regulate cholesterol level** in the body . Bile salts serve as a major route for removal of the steroid nucleus and thus of cholesterol from the body . Bile salts form molecular complex with cholesterol and keep cholesterol soluble in solution thus facilitate cholesterol excretion .
- In the intestine , part of the excreted cholesterol is reabsorbed and returns to liver .

Clinical Aspects :

Serum cholesterol levels :

In normal persons , cholesterol level varies from 150 to 200 mg/dl . It should be below 200 mg/dl (**desired level**) . Concentrations between 200 – 220 are considered **borderline** ; between 220 – 240 mg/dl considered as elevated (**low risk**) ; and above 240 mg/dl has definite risk for heart attack (**high risk**) .

Regulation of body cholesterol level :

- The concentration of cholesterol in tissues and body fluids is decided by a balance between the rate of synthesis and the rate of metabolism (**metabolism** include steroid & bile salt synthesis plus excretion) .
- The rate of cholesterol synthesis is determined by the amount of cholesterol in diet :
  - Synthesis is increased if cholesterol in diet is low .
  - **Hepatic** synthesis is inhibited by high levels of cholesterol in diet .
- **Overall** , the amount of cholesterol that is added daily to the body pool which is about 1000 mg/day (synthesis plus diet) is balanced by an equal amount of cholesterol excreted in the bile either as unchanged free cholesterol or as bile salts since the amount utilized for steroid synthesis is small .

Raised blood cholesterol level :

1. Diabetes mellitus : there is increased lipolysis and subsequent increased formation of very low density lipoprotein (VLDL) rich in cholesterol .
2. Nicotine , caffeine and emotional stress : all cause enhanced lipolysis .
3. Bile duct obstruction .
4. liver diseases : impaired synthesis of bile .
5. Hereditary .
6. Hypothyroidism (T_3 increases HDL receptors on liver cells) .

Cholelithiasis :

- A defect in the rate of synthesis of bile salts (as in liver diseases) or if the molecular complex between the bile salts and cholesterol is broken down within the gallbladder (as in **infectious** process) then the cholesterol tend to precipitate forming cholesterol stones (**cholelithiasis) .**

Hypolipidimic drugs :

- HMG-CoA reductase step is the target for the **statins** drugs (e.g**. Pravastin) .** These drugs inhibit the enzyme HMG-CoA reductase and lower blood cholesterol .

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