Chapter 4

Drug and Lipid Profile
4.1 DRUG PROFILE (ZIDOVUDINE):

Chemical structure:

![Chemical Structure of Zidovudine]

**IUPAC name**: 1-[(2R,4S,5S)-4-azido-5-(hydroxymethyl) oxolan-2-yl]-5-methyl-pyrimidine-2,4-dione

**Formula**: C_{10}H_{13}N_{6}O_{4}

**Mol. Mass**: 267.242 g/mol

**Bioavailability**: Near complete absorption, following first-pass metabolism systemic availability 65% (range 52 to 75%)

**Protein binding**: 30-38%

**Metabolism**: Hepatic

**Half life**: 0.5-3 hours

**Excretion**: Renal

**Color**: White to off-white

**Odor**: Odor less

**Appearance**: Crystalline solid

Zidovudine is an antiretroviral drug, the first approved for treatment of HIV. Zidovudinewas the first drug approved for the treatment of AIDS and HIV infection^{114}. It was originally intended to treat cancer, but failed to show efficacy and had an unacceptably high side effect profile. After showing that this drug was an effective agent against HIV in vitro, the team conducted the initial clinical trial that...
provided evidence that it could increase CD4 counts in AIDS patients. In AZT subsequently conducted clinical trials could prolong the life of patients with AIDS.

The Food and Drug Administration (FDA) approved the drug for use against HIV, AIDS, on March 20, 1987, and then as a preventive treatment in 1990. It was initially administered in much higher dosages than today, typically 400 mg every four hours (even at night). However, the unavailability at that time of alternatives to treat AIDS affected the risk/benefit ratio, with the certain toxicity of HIV infection outweighing the risk of drug toxicity. One of AZT’s side effects includes anemia, a common complaint in early clinical trials\textsuperscript{115,116}.

**Pharmacology:**

Zidovudine is an inhibitor of the invitro replication of some retroviresus including HIV. Retroviresuscontains reverse transcriptase, an essential enzyme for the life cycle of the retrovirus\textsuperscript{117}.

**Mechanism of action:**

Zidovudine is converted to monophosphate, diphosphate, triphosphate derivativesby host cell thymidine kinase. Zidovudinetriphosphate is the active which competes with thymidine 5- triphosphate to binding to HIV RT. The HIV by mistake incorporates zidovudine triphosphate in viral replication consequently zidovudine acts as a chain terminater in the DNA synthesis resulting in inhibition of HIV replication\textsuperscript{118,119}.

**Antimicrobial activity:**

Zidovudine has effect on different types of bacteria -

(a) Gram negative bacteria- Salmonelle typhimurium, Esherichia ccoli, Klebsela pneumoniae.

(b) Gram positive bacteria- Staphylococcus aureus, Staphylococcus pyogenes, Pseudomonas aaeurinosa, Mycobacterium tuberculosis\textsuperscript{120}.
4.2 LIPID PROFILE:

4.2.1 Cholesterol:

Structure:

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CH3
CHCH2CH2CH2CH

CH3
CH3

CH3

H3C

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Formula: $C_{27}H_{46}O$

IUPAC name: (10S,13R)-10,13-dimethyl-17-(6-methyl heptane-2-yl)-2,3,4,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopent[a], phenanthren-3-ol.

Molecular weight: 386.7

Appearance: White crystalline color

Melting point: 147°C-150°C

Solubility: Insoluble in water, Soluble in organic solvents

Storage: In well closed container, protect from light

General Description:

This molecule is composed of three regions: a hydrocarbon tail, a ring structure region with 4 hydrocarbon rings, and a hydroxyl group. The hydroxyl (OH) group is polar, which makes it soluble in water. This small 2-atom structure makes cholesterol an alcohol. The alcohol that we drink, ethanol, is a much smaller alcohol that also has a hydroxyl group ($C_2H_5OH$).

The 4-ring region of cholesterol is the signature of all steroid hormones (such as testosterone and estrogen). All steroids are made from cholesterol. The rings are called hydrocarbon ring because each corner of the ring is composed of a carbon atom, with two hydrogen atoms extending off the ring. The combination of the steroid
ring structure and the hydroxyl (alcohol) group classifies cholesterol as a "sterol." Cholesterol is the animal sterol. Plants only make trace amounts of cholesterol, but make other sterols in larger amounts. The last region is the hydrocarbon tail like the steroid ring region; this region is composed of carbon and hydrogen atoms. Both the ring region and tail region are non-polar, which means they dissolve in fatty and oily substances but will not mix with water. Because cholesterol contains both a water-soluble region and a fat-soluble region, it is called Amphipathic.

**Sources of Cholesterol:**

Cholesterol is found in animal fats: all food containing animal fats contains cholesterol; food not containing animal fats contains no cholesterol or negligible amounts. Major dietary sources of cholesterol include eggs, beef and poultry. Plants have trace amounts of cholesterol, so even a vegetarian diet, which includes no animal foods, has traces of cholesterol. However, the amounts are very small. For example, the amount of cholesterol in one egg is approximately equal to the amount in 9.6 liters (19.57 pounds) of pure peanut oil. Plant products (e.g. peanut), also contain cholesterol-like compounds, phytosterol, which are suggested to help lower serum cholesterol.

**Function:**

Cholesterol is required to build and maintain cell membranes it regulates membrane fluidity over a wider range of temperatures. The hydroxyl group on cholesterol interacts with the phosphate head of the membrane, while the bulky steroid and the hydrocarbon chain is embedded in the membrane. Some research indicates that cholesterol may act as an antioxidant. Cholesterol also aids in the manufacture of bile (which stored in the gallbladder and helps digest fats), and is also important for the metabolism of fat soluble vitamins, including vitamins A, D, E and K. It is the major precursor for the synthesis of vitamin D and of the various steroid hormones (which include cortisol and aldosterone in the adrenal glands, and the sex hormones progesterone the various estrogens testosterone and derivatives).
4.2.2 Phosphatidylcholine:

**Chemical structure**

![Chemical structure of Phosphatidylcholine](image)

\[ R \text{ and } R^1 = \text{fatty acids residues} \]

**Synonyms**: L-a-Lecithin, 3-Sn-phosphatidylcholine

**Molecular Weight**: 776.12

**Solubility**: Soluble at room temperature in chloroform, ethanol and Hexane containing 3% ethanol.

**Storage temperature**: 0-4°C

**General description**:

Phosphatidylcholine is a phospholipid that is a major constituent of cell membranes. Phosphatidylcholine is also known as 1, 2-diacyl-sn-glycero-3-phosphocholine.

The term lecithin itself has different meanings when used in chemistry and biochemistry than when used commercially. Chemically, lecithin is phosphatidylcholine. Commercially, it refers to a natural mixture of neutral and polar lipids. Phosphatidylcholine, which is a polar lipid, is present in commercial lecithin in concentrations of 20 to 90%. Most of the commercial lecithin products contain about 20% phosphatidylcholine. Lecithins containing phosphatidylcholine are produced from vegetable, animal and microbial sources, but mainly from vegetable sources. Soybean, sunflower and rapeseed are the major plant sources of commercial lecithin. Soybean is the most common source. Plant lecithins are considered to be GRAS (generally regarded as safe). Egg yolk lecithin is not a major source of lecithin in
nutritional supplements. Eggs themselves naturally contain from 68 to 72% phoshpatidylcholine, while soya contains from 20 to 22% phosphatidylcholine.

The fatty acid makeup's of phosphatidylcholine from plant and animal sources differ. Saturated fatty acids, such as palmitic and stearic, make up 19 to 24% of Soya lecithin; the monounsaturated oleic acid contributes 9 to 11%; linoleic acid provides 56 to 60%; and alpha-linolenic acid makes up 6 to 9%. In egg yolk lecithin, the saturated fatty acids, palmitic and stearic, make up 41 to 46% of egg lecithin. Unsaturated fatty acids are mainly bound to the second or middle carbon of glycerol. Choline comprises about 15% of the weight of phosphatidylcholine.

Pharmacology:

Phosphatidylcholine may have hepatoprotective activity. Phosphatidylcholine is important for normal cellular membrane composition and repair. Phosphatidylcholine is also the major delivery form of the essential nutrient choline. Choline itself is a precursor in the synthesis of the neurotransmitter acetylcholine, the methyl donor betaine and phospholipids, including phosphatidylcholine and sphingomyelin among others. Phosphatidylcholine is involved in the hepatic export of very-low-density lipoproteins.

Mechanism of action:

Phosphatidylcholine's role in the maintenance of cell-membrane integrity is vital to all of the basic biological processes. These are: information flow that occurs within cells from DNA to RNA to proteins; the formation of cellular energy and intracellular communication or signal transduction. Phosphatidylcholine, particularly phosphatidylcholine rich in polyunsaturated fatty acids, has a marked fluidizing effect on cellular membranes. Decreased cell-membrane fluidization and breakdown of cell-membrane integrity, as well as impairment of cell-membrane repair mechanisms, are associated with a number of disorders, including liver disease, neurological diseases, various cancers and cell death.

Pharmacokinetics:

Phosphatidylcholine is absorbed into the mucosal cells of the small intestine, mainly in the duodenum and upper jejunum, following some digestion by the
pancreatic enzyme phospholipase, producing lysophosphatidylcholine (lysolecithin). Reacylation of lysolecithin takes place in the intestinal mucosal cells, reforming phosphatidylcholine, which is then transported by the lymphatics in the form of chylomicrons to the blood. Phosphatidylcholine is transported in the blood in various lipoprotein particles, including very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL); it is then distributed to the various tissues of the body. Some phosphatidylcholine is incorporated into cell membranes. Phosphatidylcholine is also metabolized to choline, fatty acids and glycerol. The fatty acids and glycerol either get oxidized to produce energy or become involved in lipogenesis. Choline is a precursor of acetylcholine. Serum choline levels peak between 2 to 6 hours after oral intake.

**Indication and usage:**

Phosphatidylcholine may be indicated to help restore liver function in a number of disorders, including alcoholic fibrosis, and possibly viral hepatitis. It may also be indicated for the treatment of some manic conditions. There is some evidence that Phosphatidylcholine may be useful in the management of Alzheimer's disease and some other cognitive disorders. A possible future role in cancer therapy is also suggested by recent research.