Proteins

Proteins are large biomolecules, or macromolecules, consisting of one or more long chains of amino acid residues. Proteins perform a vast array of functions within organisms, including:

1-catalyzing metabolic reactions

2-DNA replication

3-Responding to stimuli

4-Providing structure to cells and organisms

5-Transporting molecules from one location to another.

Proteins differ from one another primarily in their sequence of amino acids, which is dictated by the nucleotide sequence of their genes, and which usually results in protein folding into a specific 3D structure that determines its activity.

Most proteins consist of linear polymers built from series of up to 20 different L-α- amino acids. All proteinogenic amino acids possess common structural features, including an α-carbon to which an amino group, a carboxyl group, and a variable side chain are bonded. Only **proline** differs from this basic structure as it contains an unusual ring to the N-end amine group, which forces the CO–NH amide moiety into a fixed conformation.

Classification of proteins

I. Classification of protein; on the basis of structure, composition and function

Proteins can be classified according to composition as:

(a) Simple proteins. On hydrolysis they yield only the amino acids and occasional small carbohydrate compounds. Examples are: albumins, globulins, glutelins, albuminoids, histones and protamines.

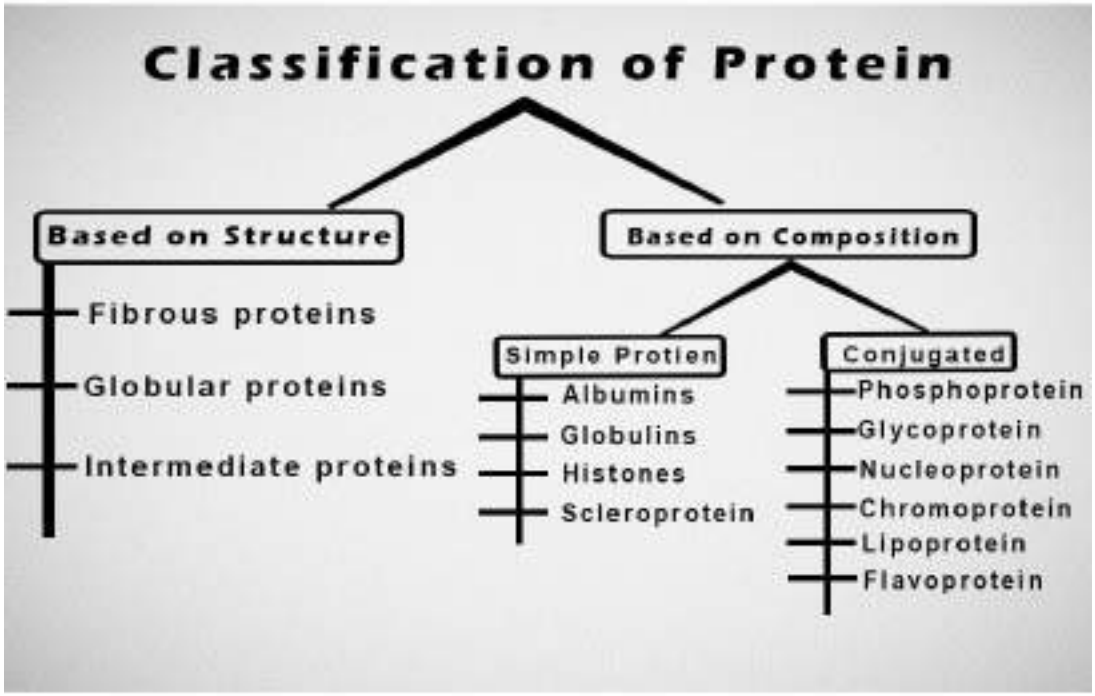
(b) Conjugated proteins. These are simple proteins combined with some non-protein material in the body. Examples are: nucleoproteins, glycoproteins, phosphoproteins, haemoglobins and lecithoproteins.

And can be classified according to structure as

(a) Fibrous protein

(b) Globular protein

(c) Intermediate protein



II. Classification of protein on the basis of biological functions:

1. Catalytic protein

They catalyze biochemical reaction in cells. e.g. **Enzymes** and **Co-Enzymes**

2. Structural protein

They make various structural components of living beings. e.g. **Collagen** makes bone, **Elastin** make ligaments and **keratin** make hair and nails

3. Nutrient protein

They have nutritional value and provide nutrition when consumed. e.g. Casein in milk

4. Regulatory protein

They regulate metabolic and cellular activities in cell and tissue. e.g. **Hormones**

5. Defense protein

They provide defensive mechanism against pathogens. e.g. **Antibodies**

6. Transport protein

They transport nutrients and other molecules from one organ to other. e.g. **Haemoglobin**

7. Storage protein

They store various molecules and ions in cells. e.g. **Ferritin** store Iron

8. Contractile or mobile protein

They help in the movement and locomotion of various body parts. e.g. **Actin**, **Myosin**, **Tubulin ….** etc

9. Toxic protein

They are toxic and can damage tissues. e.g. **Snake venom**, **bacterial exotoxins** etc

Protein structures

Increasingly, drug developers are looking to large molecules, particularly proteins, as a therapeutic option. Formulation of a protein drug product can be quite a challenge, and without a good understanding of the nature of protein structure and the conformational characteristics of the specific protein being formulated, the results can be ruinous.

The term, structure, when used in relation to proteins, takes on a much more complex meaning than it does for small molecules. Proteins are macromolecules and have four different levels of structure – primary, secondary, tertiary, and quaternary.

1-Primary Structure

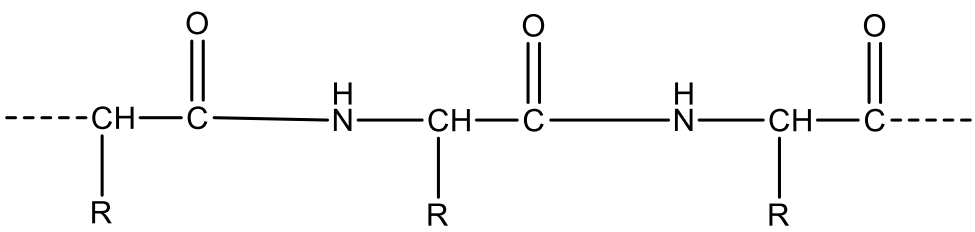
There are 20 different standard L-α-amino acids used by cells for protein construction. Amino acids, as their name indicates, contain both a basic amino group and an acidic carboxyl group. This difunctionality allows the individual amino acids to join in long

chains by forming peptide bonds: amide bonds between the -NH_2 of one amino acid and the -COOH of another. Sequences with fewer than 50 amino acids are generally referred to as peptides, while the terms, protein and polypeptide, are used for longer sequences. A protein can be made up of one or more polypeptide molecules. The end of the peptide or protein sequence with a free carboxyl group is called the carboxy-terminus or C-terminus. The terms, amino-terminus and N-terminus, describe the end of the sequence with a free α-amino group.

The amino acids differ in structure by the substituent on their side chains. These side chains confer different chemical, physical, and structural properties to the final peptide or protein. The structures of the 20 amino acids commonly found in proteins are shown in amino acids chapter. Each amino acid has both a one-letter and three-letter abbreviation. These abbreviations are commonly used to simplify the written sequence of a peptide or protein.

Depending on the side-chain substituent, an amino acid can be classified as acidic, basic, or neutral. Although 20 amino acids are required for the synthesis of various proteins found in humans, we can synthesize only ten. The remaining 10 are called essential amino acids and must be obtained in the diet.

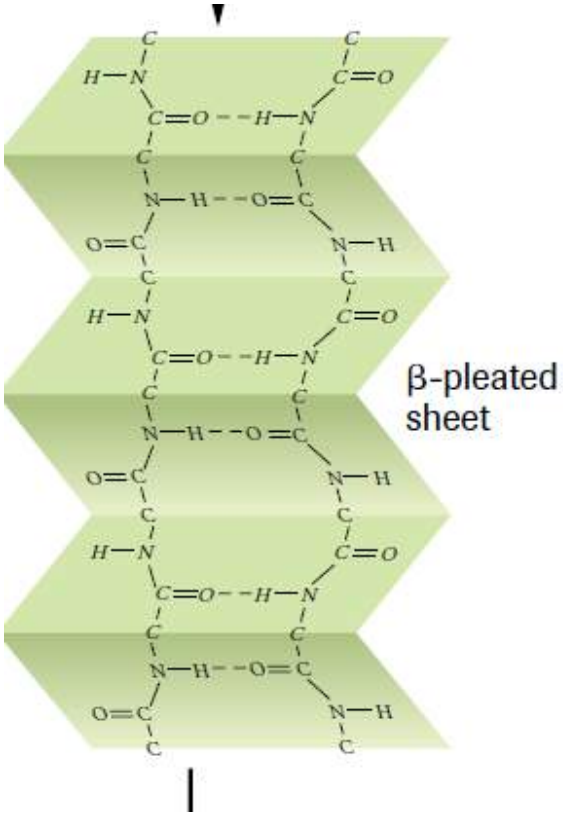
The amino acid sequence of a protein is encoded in DNA. Proteins are synthesized by a series of steps called transcription (the use of a DNA strand to make a complimentary messenger RNA strand - mRNA) and translation (the mRNA sequence is used as a template to guide the synthesis of the chain of amino acids which make up the protein). Often, post-translational modifications, such as glycosylation or phosphorylation, occur which are necessary for the biological function of the protein. While the amino acid sequence makes up the primary structure of the protein, the chemical/biological properties of the protein are very much dependent on the three-dimensional or tertiary structure.

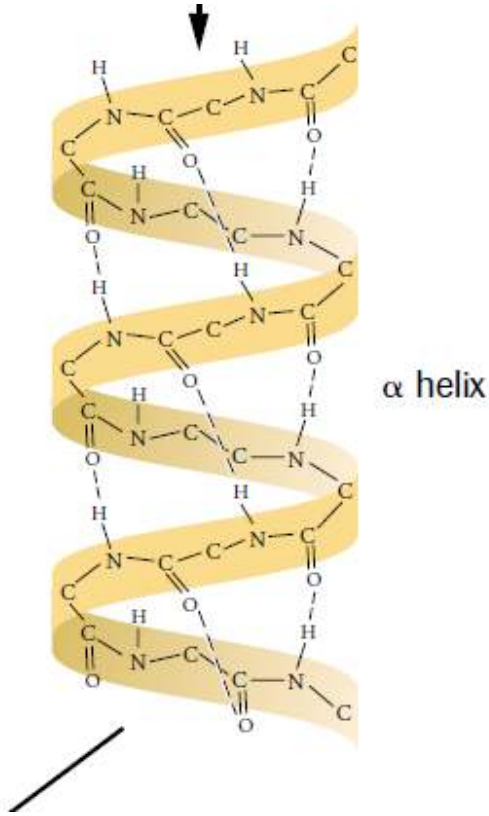


2-Secondary Structure

Stretches or strands of proteins or peptides have distinct, characteristic local structural conformations, or secondary structure, dependent on hydrogen bonding. The two main types of secondary structure are the α-helix and the ß-sheet. The α-helix is a right-handed coiled strand. The side-chain substituents of the amino acid groups in an α-helix extend to the outside. Hydrogen bonds form between the oxygen of each C=O bond in the strand and the hydrogen of each N-H group four amino acids below it in the helix. The hydrogen bonds make this structure especially stable. The side-chain substituents of the amino acids fit in beside the N-H groups.

The hydrogen bonding in a ß-sheet is between strands (inter-strand) rather than within strands (intra-strand). The sheet conformation consists of pairs of strands lying side-by-side. The carbonyl oxygen's in one strand bonds with the amino hydrogen's of the adjacent strand. The two strands can be either parallel or anti-parallel depending on whether the strand directions (N-terminus to C-terminus) are the same or opposite. The anti-parallel ß-sheet is more stable due to the more well-aligned hydrogen bonds.



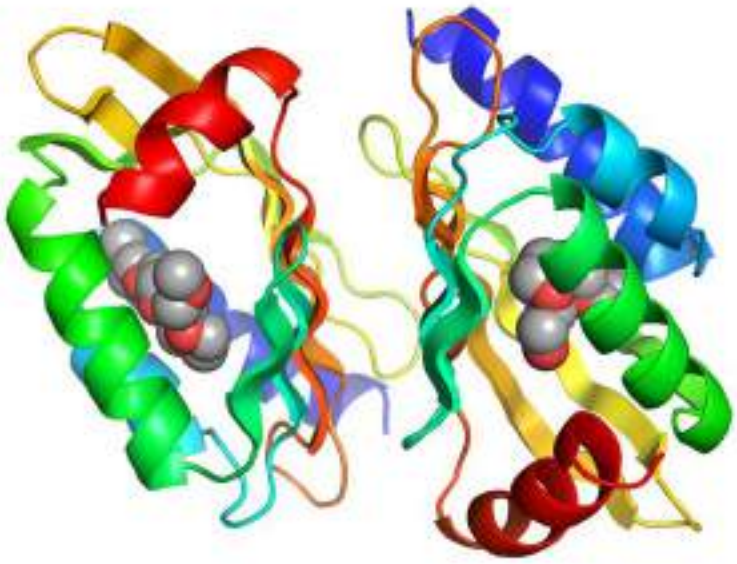


3-Tertiary Structure

The overall three-dimensional shape of a protein molecule is the tertiary structure. The protein molecule will bend and twist in such a way as to achieve maximum stability or lowest energy state. Although the three-dimensional shape of a protein may seem irregular and random, it is fashioned by many stabilizing forces due to bonding interactions between the side-chain groups of the amino acids.

Under physiologic conditions, the hydrophobic side-chains of neutral, non-polar amino acids such as phenylalanine or isoleucine tend to be buried on the interior of the protein molecule, thereby shielding them from the aqueous medium. The alkyl groups of alanine, Valine, Leucine and isoleucine often form hydrophobic interactions between one another, while aromatic groups such as those of phenylalanine and tyrosine often stack together. Acidic or basic amino acid side-chains will generally be exposed on the surface of the protein as they are hydrophilic.

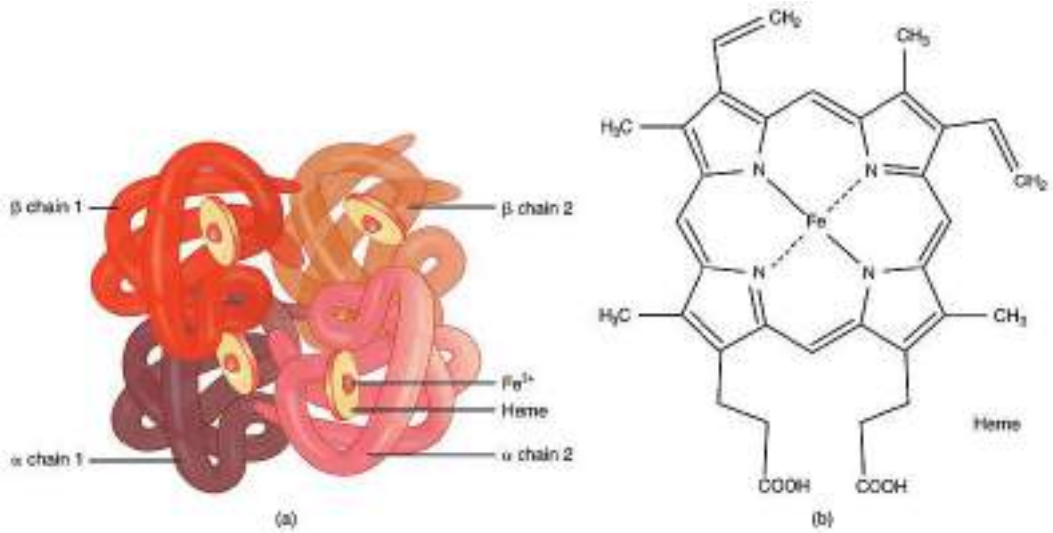
The formation of disulfide bridges by oxidation of the sulfhydryl groups on cysteine is an important aspect of the stabilization of protein tertiary structure, allowing different parts of the protein chain to be held together covalently. Additionally, hydrogen bonds may form between different side-chain groups. As with disulfide bridges, these hydrogen bonds can bring together two parts of a chain that is some distance away in terms of sequence. Salt bridges, ionic interactions between positively and negatively charged sites on amino acid side chains, also help to stabilize the tertiary structure of a protein.

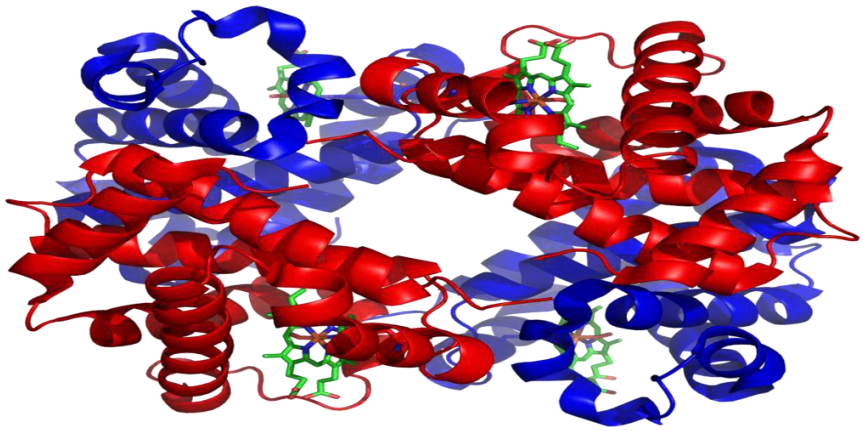


4-Quaternary Structure

Many proteins are made up of multiple polypeptide chains, often referred to as protein subunits. These subunits may be the same, as in a homodimer, or different, as in a heterodimer. The quaternary structure refers to how these protein subunits interact with each other and arrange themselves to form a larger aggregate protein complex. The final shape of the protein complex is once again stabilized by various interactions, including **hydrogen-bonding**, **disulfide-bridges** and **salt bridges**.

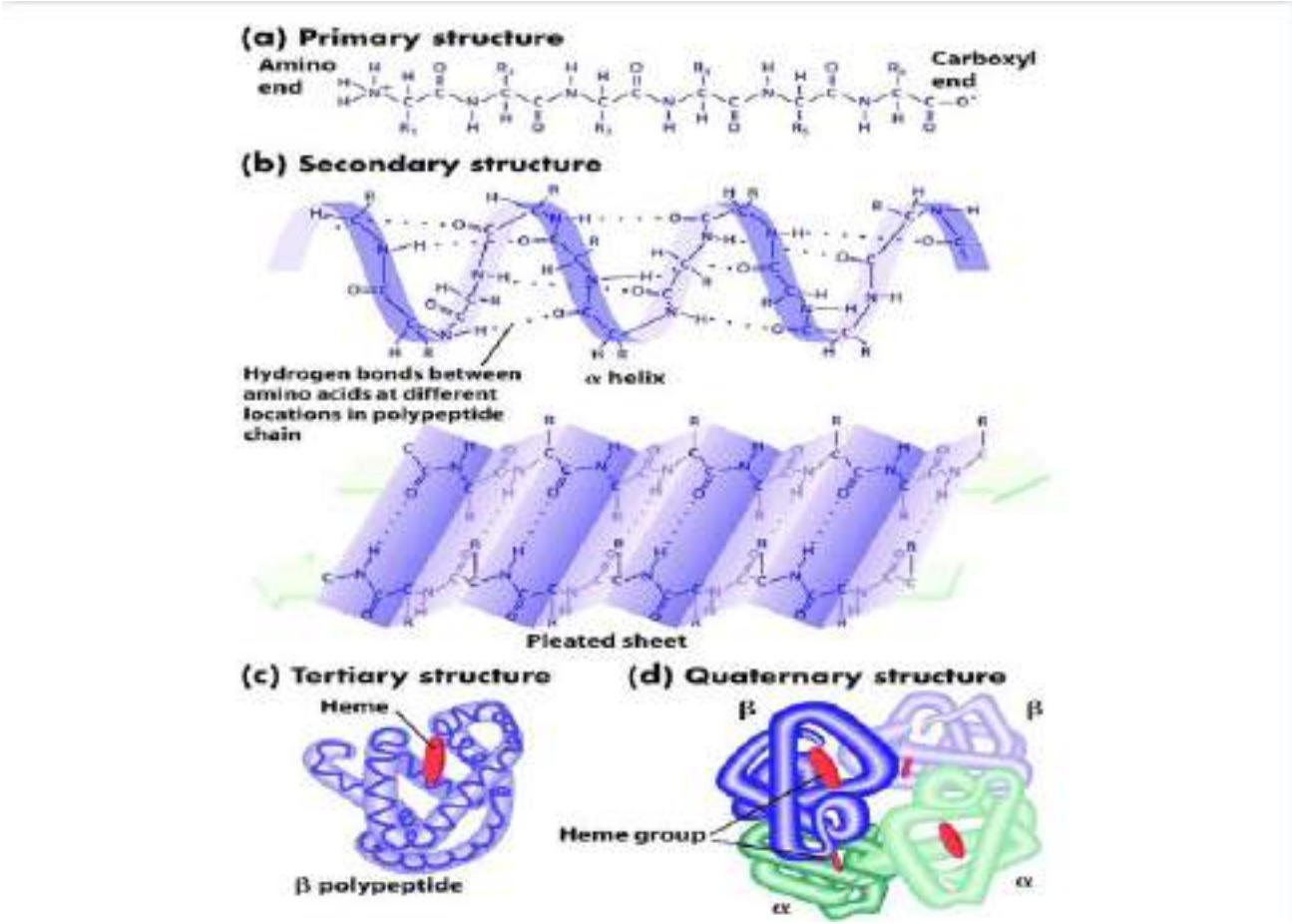
Hemoglobin is an example of the quaternary structure of a protein





Hemoglubin

The four structures of protein has shown in figure below



Lipoproteins

1-High Density Lipoprotein-Cholesterol (HDL-C)

Transports cholesterol from cells to the liver

2-Low Density Lipoprotein (LDL)

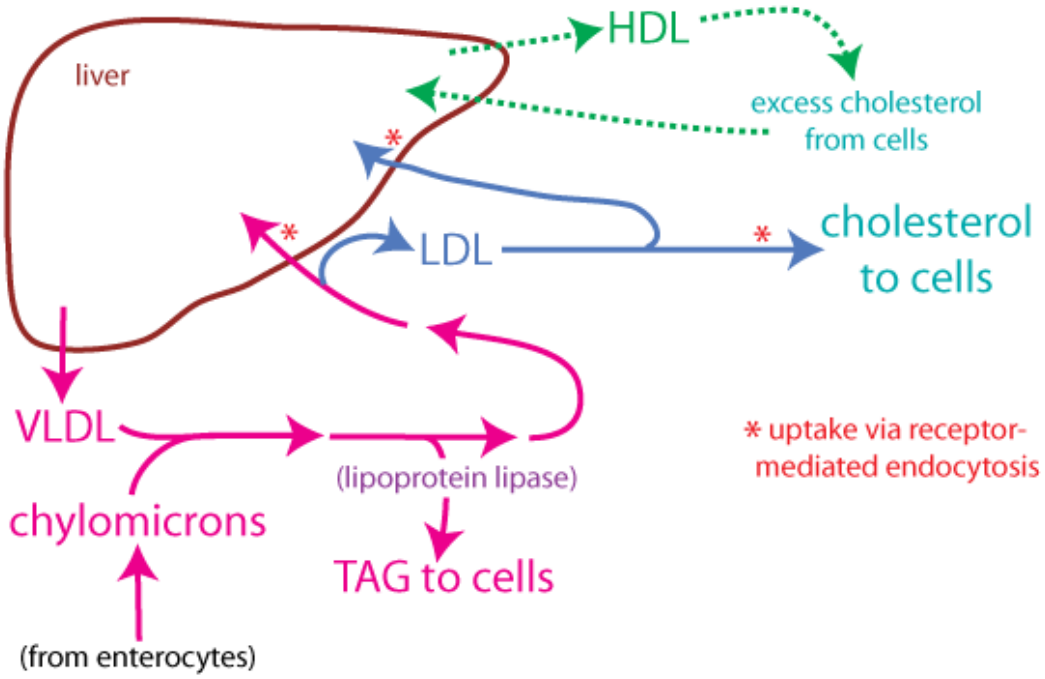
Transports cholesterol from liver to the cells

3-Very Low Density Lipoprotein-Cholesterol (VLDL-C)

Transport Triglycerides from liver to the cells

4- Chylomicrons

Transporting dietary triglycerides and cholesterol absorbed by intestinal epithelia



Denaturation of proteins

Denaturation is a process in which proteins or nucleic acids lose the quaternary structure, tertiary structure, and secondary structure which is present in their native state, by application of:

1-**some external stress**

2-**compound such as a strong acid or base**

3-**concentrated inorganic salt**

4-**Organic solvent** (e.g., alcohol or chloroform)

5-**Radiation or Ultra sound**

6-**Change in pH or heat.**

Denatured proteins can exhibit a wide range of characteristics, from conformational change and loss of solubility to aggregation due to the exposure of hydrophobic groups. Denatured proteins lose their 3D structure and therefore cannot function.

When a protein is denatured, secondary and tertiary structures are altered but the peptide bonds of the primary structure between the amino acids are left intact.

Most biological substrates lose their biological function when denatured. For example, enzymes lose their activity, because the substrates can no longer bind to the active site, and because amino acid residues involved in stabilizing substrates' transition states are no longer positioned to be able to do so.