2.3.3 Pentose phosphate pathway

Hexose monophosphate shunt (HMP) or pentose phosphate pathway or phosphogluconate pathway is an alternative pathway for glucose oxidation. The enzymes of HMP shunt are located in the cytosol. Hexose monophosphate shunt has two primary functions:

1. To provide NADPH for reductive biosynthesis and
2. To provide ribose 5-phosphate for nucleotide and nucleic acid biosynthesis.

The sequence of reactions of HMP shunt is divided into two phases-oxidative and non-oxidative phase.

Oxidative phase (irreversible) — Glucose 6-phosphate dehydrogenase (G6PD) is an NADP-dependent enzyme that converts glucose 6-phosphate to 6 phosphogluconolactone. The latter is then hydrolysed by the gluconolactonase to 6-phosphogluconate. The next reaction involving the synthesis of NADPH is catalyzed by 6-phosphogluconate dehydrogenase to produce 3-keto 6-phosphogluconate which then undergoes decarboxylation to give ribulose 5-phosphate. The net result of the oxidative phase is generation of 2 moles of NADPH, oxidation of one carbon to CO_2 and synthesis of 1 mole of pentose phosphate.

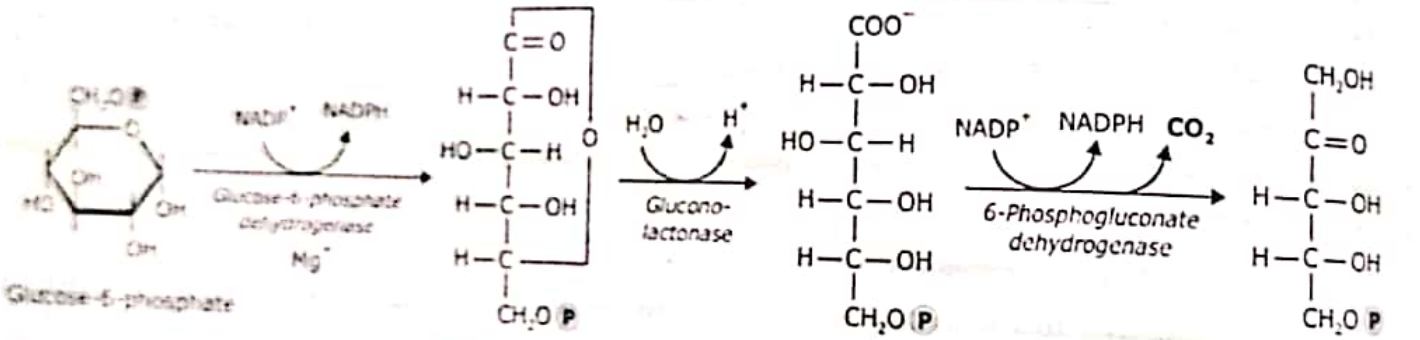
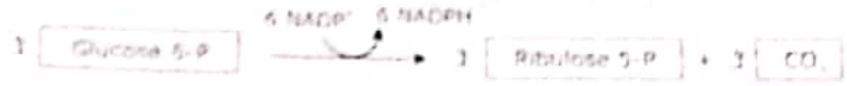


Figure 2.20 : Oxidative phase of the pentose phosphate pathway. The three reactions of the oxidative phase include two oxidations, which produce NADPH.

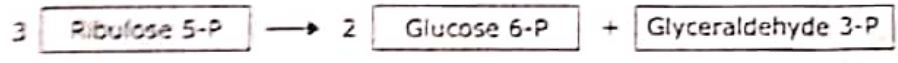


Note : In pentose phosphate pathway, oxidation of glucose-6-Phosphate utilizes $NADP^+$ rather than NAD^+ and produces CO_2. Whereas glycolytic process utilizes NAD^+ and does not produce CO_2. Similarly no ATP is generated in the pentose phosphate pathway, whereas it is a major product of glycolysis.

Non-oxidative phase (Reversible)

In oxidative phase, three molecules of glucose-6-phosphate (G6P) give rise to three molecules of CO_2 and three five carbon sugars. These are rearranged to regenerate two molecules of glucose-6-phosphate and one molecule of glyceraldehyde-3-phosonate (G3P) in non-oxidative phase.

The non-oxidative reactions are concerned with the interconversion of three, four, five and seven carbon monosaccharides. Ribulose 5-phosphate (Ru5P) is acted upon by an **epimerase** to produce xylulose 5-phosphate (Xu5P) while phosphopentose isomerase converts ribulose 5-phosphate to ribose 5- phosphate (R5P). Two enzymes unique to the pentose phosphate pathway act in interconversions of three, four, five and seven carbon monosaccharides: *transketolase* and *transaldolase*. Transketolase and transaldolase catalyze transfer of 2-C and 3-C molecular fragments respectively, in each case from a ketose donor to an aldose acceptor. However the names of these enzymes should be changed, since transketolase (alternative name glycoaldehyde transferase) actually transfers an aldol moiety and transaldolase actually transfers a ketol moiety. However the traditional enzyme names are used here. Transketolase employs thiamine pyrophosphate as a coenzyme.



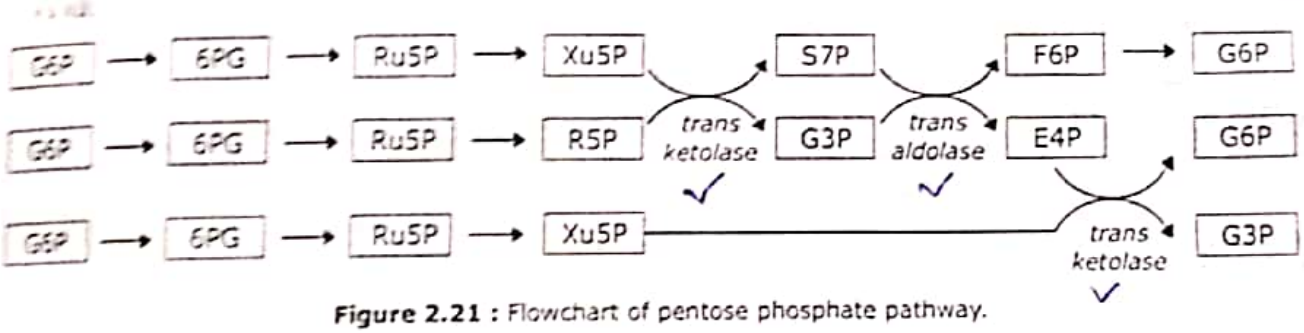


Figure 2.21 : Flowchart of pentose phosphate pathway.

G6P (Glucose 6-phosphate), 6PG (6-Phosphogluconate), Ru5P (Ribulose-5-phosphate) Xu5P (Xylulose 5-phosphate), R5P (Ribose 5-phosphate), G3P (Glyceraldehyde 3-phosphate), E4P (Erythrose 4-phosphate), S7P (sedoheptulose 7-phosphate)

Function of pentose phosphate pathways

1. NADPH from the pentose phosphate pathway serves as a source of electrons for the reduction of molecules during biosynthesis.
2. The pathway synthesizes four- and five-carbon sugars for a variety of purposes. The four-carbon sugar erythrose 4-phosphate is used to synthesize aromatic amino acids and vitamin B_6 (pyridoxal). The pentose ribose 5-phosphate is a major component of nucleic acids, and ribulose 1,5-bisphosphate is the primary CO_2 acceptor in photosynthesis.
3. Intermediates in the pentose phosphate pathway may be used to produce ATP. Glyceraldehyde 3-phosphate from the pathway can enter the three-carbon stage of the glycolytic pathway and be converted to ATP and pyruvate.

Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency

G6PD deficiency is an X-linked recessive disease. G6PD deficiency impairs the ability to form NADPH. NADPH is required for several reductive processes in addition to lipid biosynthesis. For example, erythrocyte membrane integrity requires a plentiful supply of reduced glutathione (GSH), a *Cys*-containing tripeptide (γ-glutamyl-cysteinylglycine). A major function of GSH in the erythrocyte is to eliminate H_2O_2 and organic hydroperoxides. H_2O_2, a toxic product of various oxidative processes, reacts with double bonds in the fatty acid residues of the erythrocyte cell membrane to form organic hydroperoxides. These, in turn, results in membrane cell lysis. Peroxides are eliminated through the action of glutathione peroxidase, yielding glutathione disulfide (GSSG). So, G6PD deficiency results in hemolytic anemia caused by the inability to detoxify oxidizing agents.

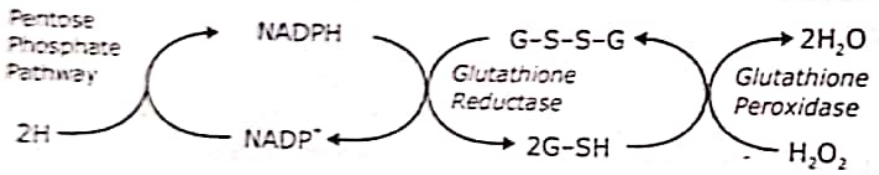


Figure 2.22 : Role of the pentose phosphate pathway in the reduction of oxidized glutathione.