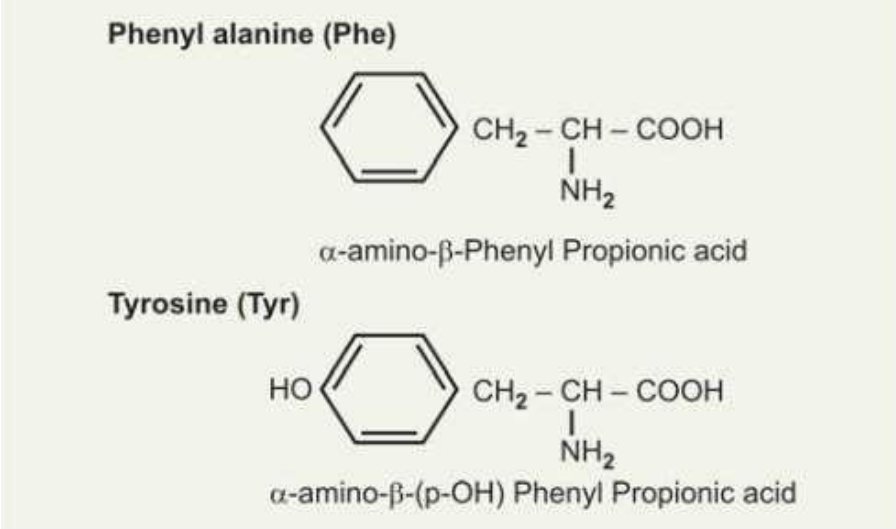
CATABOLISM OF PHENYLALANINE AND TYROSINE THEIR METABOLIC DISORDERS

Tyrosine possesses an extra –OH group at para position of benzene ring



PHENYLALANINE

- ✓ Aromatic & essential amino acid
- ✓ Both Glucogenic & Ketogenic.
- ✓ Phenylalanine is converted to tyrosine.
- ✓ The need for phenylalanine becomes minimal, if adequate tyrosine is supplied in the food.
- ✓ This is called the sparing action of tyrosine on phenylalanine.
- ✓ Predominant metabolism of phenylalanine occurs through tyrosine and incorporated into various biologically important compounds.
- ✓ Epinephrine, norepinephrine, dopamine, thyroid hormones & the pigment melanin.
- ✓ Phenylalanine (Phe) is specified by the codons UUU and UUC

Conversion of phenyl alanine to tyrosine

Reaction involves hydroxylation of phenyl alanine at p- position in benzene ring

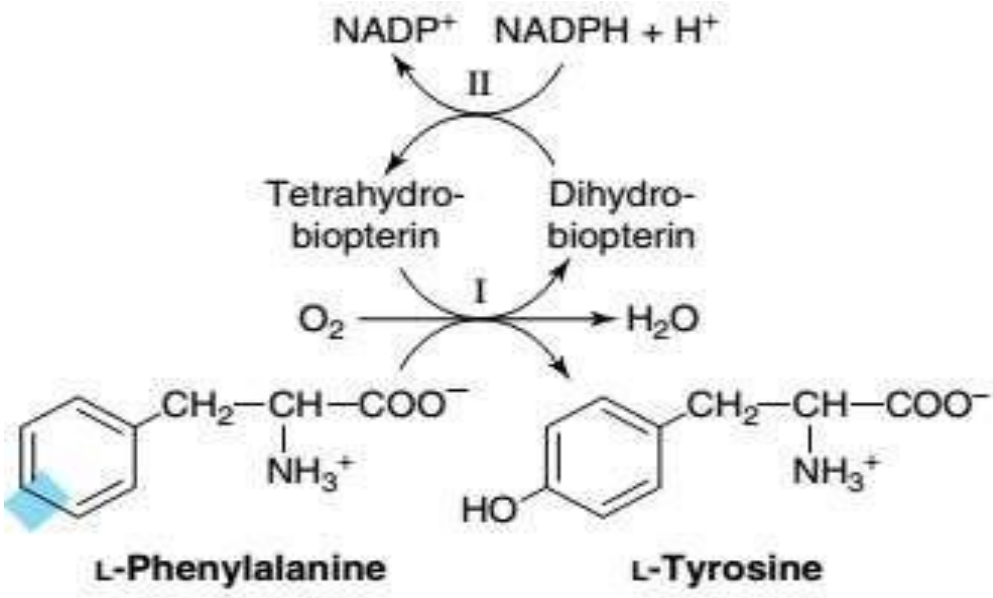
Enzyme: Phenyl alanine hydroxylase.

Present in liver and the conversion occurs in Liver

The reaction is complex and takes place in two activity -

I. Reduction of O2 to H2O and conversion of phenylalanine to tyrosine. Tertahydrobiopterin acts as H-donor to the molecular O2

II. Reduction of dihydrobiopterin, FH2 by NADPH, catalysed by the enzyme Dihydrobiopterin reductase.



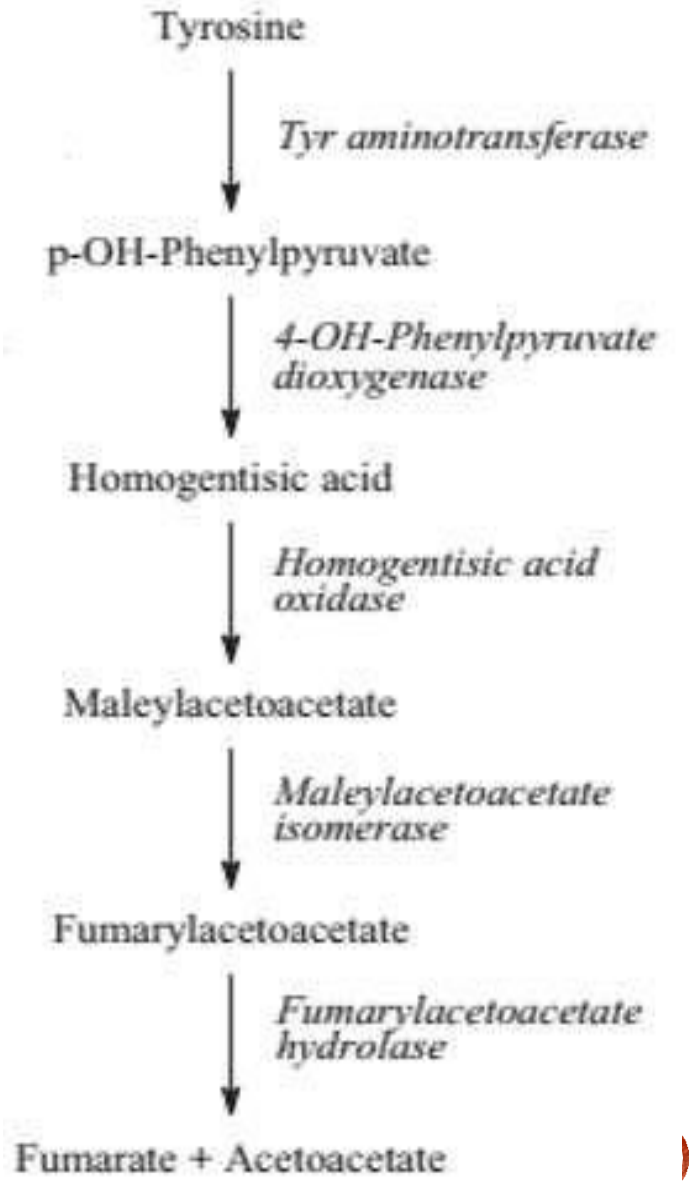
TYROSINE

It is aromatic amino acid

It is synthesized from phenylalanine, and so is a non- essential amino acid

Tyrosine is degraded to produce as end products 'Fumarate' and 'acetoacetate'. Fumarate is glucogenic, whereas acetoacetate is ketogenic

Tyrosine is specified by the codons UAU and UAC, Degradation of tyrosine occurs mostly in liver.



CATABOLISM OF TYROSINE

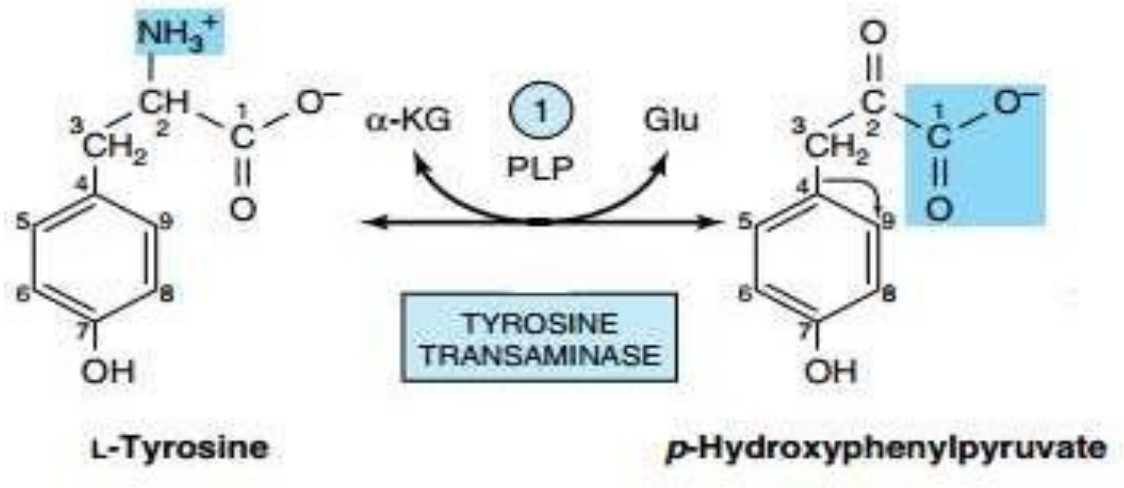
- Transamination
- Production of homogentisic acid
- Cleavage of aromatic ring
- Isomerization
- Hydrolysis

1. TRANSAMINATION

Tyrosine first undergoes transamination to P-hydroxyphenyl pyruvate, catalyzed by tyrosine transaminase

It is pyridoxal phosphate dependent.

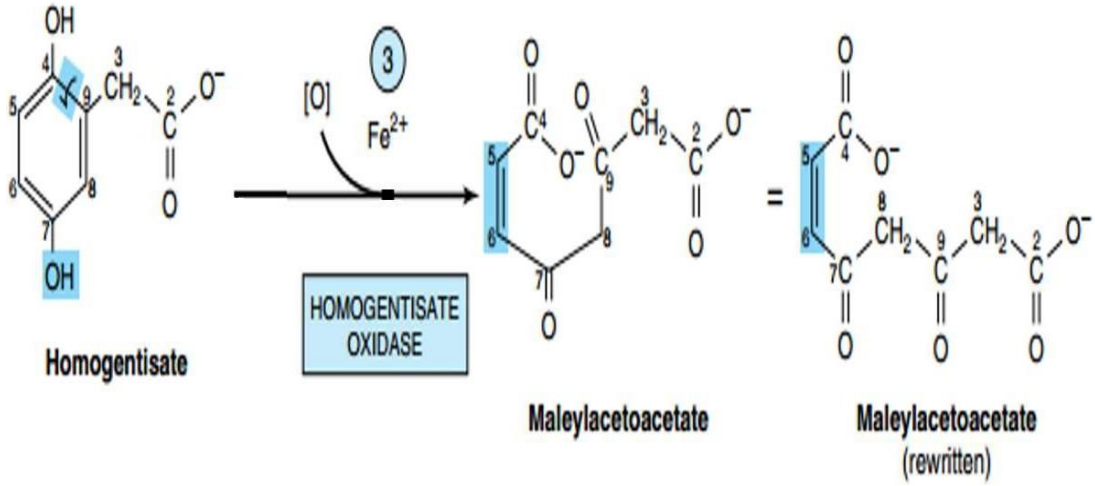
It is induced by glucocorticoids.



2.PRODUCTION OF HOMOGENTISATE

Reaction catalyzed by the enzyme p-Hydroxyphenylpyruvate oxidase,a copper-containing enzyme.

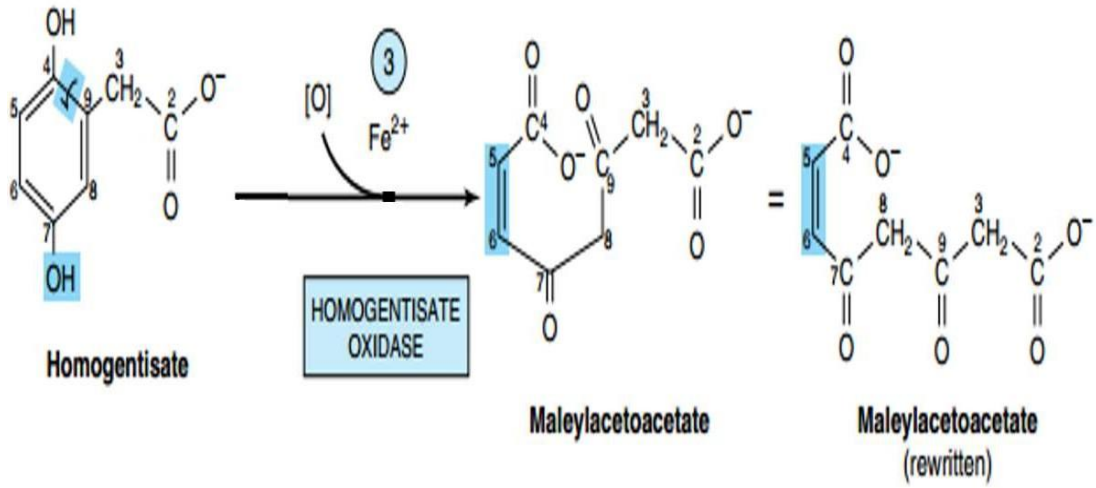
It catalyzes oxidative decarboxylation as well as hydroxylation of the phenyl ring of p-hydroxyl phenyl pyruvate to produce homogentisate. It requires ascorbic acid (Vit. C) and Vit. B12



3.CLEAVAGE OF AROMATIC RING

Homogentisate oxidase (iron metallo- protein) cleaves the benzene ring of homogentisate to form 4-maleylacetoacetate.Molecular oxygen is required for this reaction to break the aromatic ring.

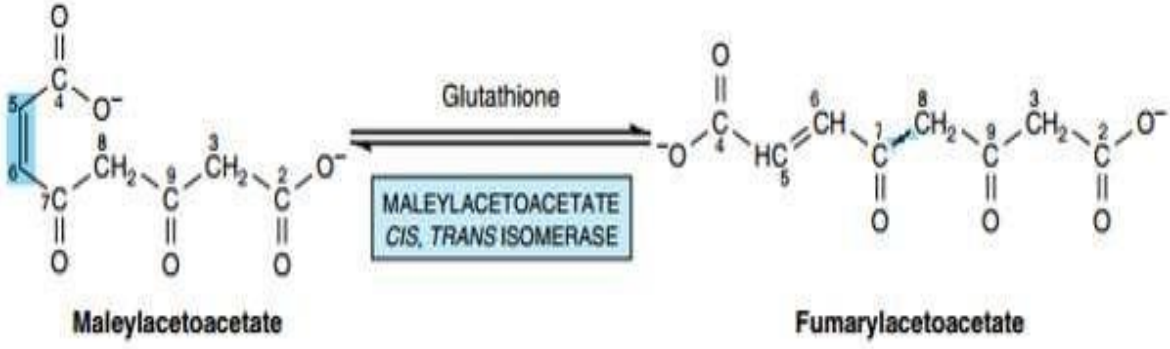
Inhibitor : α-α'-dipyridil



4.ISOMERISATION

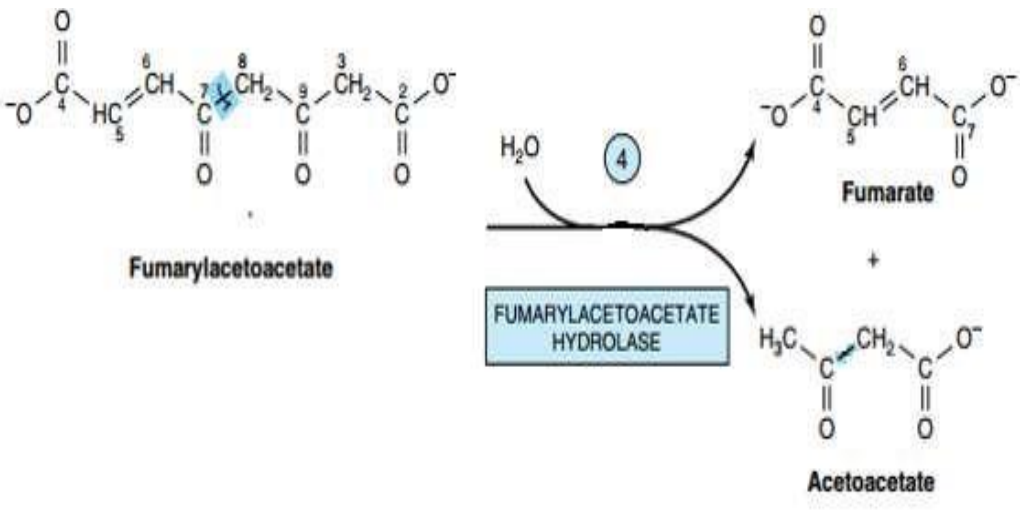
4-Maleylacetoacetate undergoes isomerization to form 4- fumaryl acetoacetate.

Catalyzed by maleylacetoacetate isomerase



5. HYDROLYSIS

Fumaryl acetoacetase (fumaryl acetoacetate hydrolase) brings about the hydrolysis of fumaryl acetoacetate to liberate fumarate (glucogenic product) & acetoacetate (ketone body). Hence, phenylalanine and tyrosine are partly glucogenic and partly ketogenic.



DISORDERSOF PHENYLALANINE AND TYROSINE METABOLISM

- Phenylketonuria (PKU)
- Tyrosinemia type II
- Neonatal tyrosinemia (Tyrosinemia type III)
- Alkaptonuria
- Tyrosinemia type I
- Albinism

PHENYLKETONURIA (PKU)

INTRODUCTION:

- Most common metabolic disorder in amino acid metabolism
- Type I Hyper phenylalaninemia
- Autosomal recessive with Incidence of PKU is 1 in 10,000 births
- Due to deficiency of the hepatic enzymes, phenylalanine hydroxylase, encoded by the PAH gene
- Defect in dihydrobiopterin reductase is also reported
- PKU primarily causes the accumulation of phenylalanine in tissues and blood & excretion in urine

Biochemical manifestation:

1.Effect on CNS

Mental retardation, failure to walk or talk, failure of growth, seizures and tremor

Hypotyrosinemia:low[tyrosine],low neurotransmitters (loss of biogenic amines at critical stages in postnatal brain maturation)

Defective brain myelination (chronic and irreversible)

2.Effect on pigmentation

Melanin is the pigment synthesized from tyrosine by tyrosinase

Accumulation of phenylalanine competitively inhibits tyrosinase and impairs melanin formation The result is hypopigmentation that causes light skin color, fair hair, blue eyes

2. Elevated levels of phenylalnine, phenylpyruvate, phenylactate and phenylacetate are found in plasma & urine giving mousey odor

ALBUNISM (Albino – white)

INTRODUCTION

- ✓ Inborn error due to lack of synthesis of the melanin pigment
- ✓ Defect in tyrosinase enzyme
- ✓ Autosomal recessive disorder with 1 in 20,000

Biochemical basis:

- ✓ Deficiency or lack of the enzyme tyrosinase
- ✓ Decrease in melanosomes of melanocytes
- ✓ Impairment in melanin polymerization
- ✓ Limitation of substrate (tyrosine) availability
- ✓ Lack of protein matrix in melanosomes

Types of Albinism

Oculocutaneous albinism:

Decreased pigmentation of skin and eyes.

They can be differentiated by clinical presentation and biochemical and other features.

Such 'albinos' can be biochemically of two types:

'Tyrosinase' negative albinos

'Tyrosinase' positive albinos

Ocular albinism:

Affects only eye and not the skin.

Occurs both as autosomal recessive and as an X- linked trait

Ocular albunism

Oculocutaneous albunism

ALKAPTONURIA

INTRODUCTION

- It is First described by Lusitanus in 1649
- Autosomal recessive disorder with 1 in 25,000 births
- Defective enzyme: homogentisate oxidase in tyrosine metabolism
- Homogentisate accumulates in tissues and blood and is excreted into urine
- On standing, Homogentisate gets oxidized to corresponding quinones, which polymerize to give black or brown color
- Urine resembles coke in color

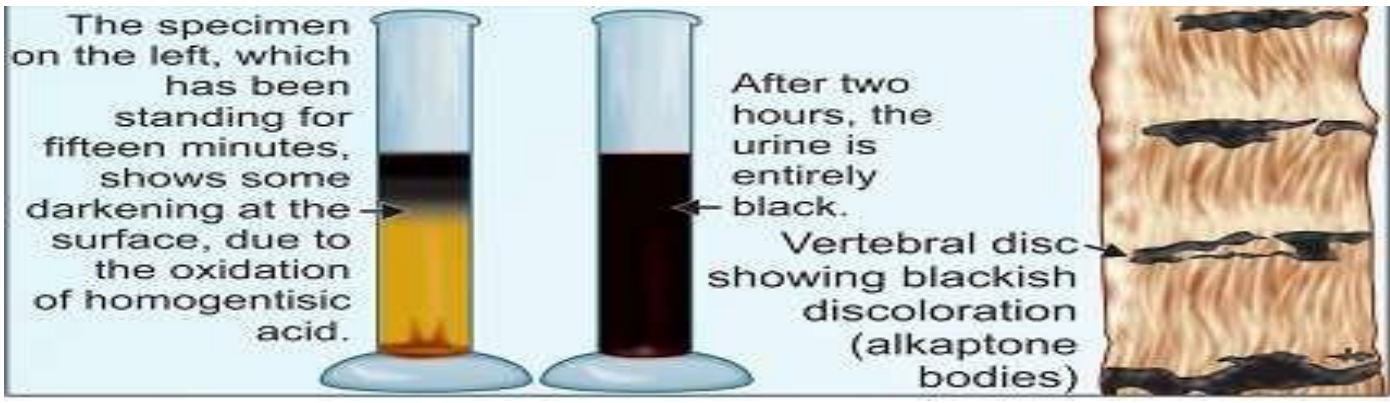
BIOCHEMICAL MANIFESTATION

Homogentisate gets oxidized by polyphenol oxidase to benzoquinone acetate which undergoes polymerization to produce a pigment called alkapton

Deposition occurs in connective tissue, bones and various organs (nose, ear) resulting in a condition known as ochronosis

Arthritis; due to deposition of pigment alkaptons in the joints

Treatment by consumption of protein diet with relatively low phenylalanine content



TYROSINEMIA TYPE I

- ✓ Due to deficiency of the enzymes: fumarylacetoacetate hydroxylase
- ✓ Rare but serious disorder
- ✓ Causes liver failure, rickets, renal tubular dysfunction and polyneuropathy
- ✓ Tyrosine and its metabolites are excreted in urine
- ✓ In acute tyrosinosis, the infant exhibits diarrhea, vomiting and cabbage-like odor
- ✓ Death may seen due to liver failure within 1 year

TYROSINEMIA TYPE II

- ➢ Defect in enzyme tyrosine transaminase
- ➢ Results in blockage in the routine degradative pathway of tyrosine
- ➢ Characterized by skin and eye lesions as well as neurologic problems