

# NOTESKARTS

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## PHARMACOGNOSY & PHYTOCHEMISTRY

### UNIT – 1 | COMPLETE NOTES

**B. Pharmacy | 5th Semester | Subject Code: BP501T**

#### **Unit 1: Metabolic Pathways in Higher Plants & Their Determination**

★ **Basic Metabolic Pathways & Secondary Metabolite Formation**

★ **Shikimic Acid Pathway**

★ **Acetate Pathways (Mevalonate & MEP/DXP Pathway)**

★ **Amino Acid Pathway**

★ **Radioactive Isotopes in Biogenetic Studies**

#### **UNIT 1 TOPICS**

- Brief study of basic metabolic pathways and formation of different secondary metabolites through these pathways
- Shikimic Acid Pathway – formation of aromatic amino acids, phenylpropanoids, lignins, tannins, flavonoids
- Acetate Pathways – Mevalonate Pathway (terpenoids, steroids) and MEP/DXP Pathway (monoterpenes, diterpenes, carotenoids)
- Amino Acid Pathway – formation of alkaloids via different precursor amino acids
- Study of utilization of radioactive isotopes in the investigation of biogenetic/biosynthetic pathways

# INTRODUCTION TO PLANT METABOLISM & SECONDARY METABOLITES

## PLANT METABOLISM – PRIMARY VS SECONDARY

### Primary vs. Secondary Metabolism

Plant metabolism is broadly classified into Primary Metabolism and Secondary Metabolism. Both are essential but serve different functions in the plant.

Feature	PRIMARY Metabolism vs SECONDARY Metabolism
Definition	PRIMARY: Metabolic processes essential for survival, growth, and reproduction   SECONDARY: Metabolic processes producing specialized compounds not directly needed for basic life functions
Products	PRIMARY: Carbohydrates, proteins, lipids, nucleic acids, chlorophyll   SECONDARY: Alkaloids, terpenoids, phenolics, flavonoids, tannins, glycosides
Distribution	PRIMARY: Universal – found in all living cells   SECONDARY: Often species-specific or tissue-specific
Functions	PRIMARY: Energy production, cell structure, genetic information   SECONDARY: Defense against herbivores/pathogens, attraction of pollinators/seed dispersers, UV protection, allelopathy
Pharmaceutical Importance	PRIMARY: Carbohydrates (excipients), fats (vehicles)   SECONDARY: Most pharmacologically active plant constituents (morphine, quinine, taxol, caffeine)
Intermediates	PRIMARY: Acetyl-CoA, pyruvate, amino acids, nucleotides   SECONDARY: Derived from primary metabolites – phenylpropanoids, terpene units (IPP), amino acid derivatives

### Secondary Metabolites – Classification




Class	Biosynthetic Pathway & Examples
PHENOLICS & PHENYLPROPANOIDS	Shikimic Acid Pathway → Simple phenols, Cinnamic acid derivatives, Coumarins, Lignans

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FLAVONOIDS	Shikimic Acid + Acetate-Malonate → Flavones, Flavonols, Anthocyanins, Isoflavones, Tannins
TANNINS	Shikimic Acid Pathway → Hydrolysable Tannins; Condensed Tannins (Proanthocyanidins)
TERPENOIDS (TERPENES)	Acetate (Mevalonate) Pathway & MEP/DXP Pathway → Mono-, Sesqui-, Di-, Tri-, Tetraterpenes
STEROIDS	Mevalonate Pathway → Cholesterol, cardiac glycoside aglycones, saponins, phytosterols
ALKALOIDS	Amino Acid Pathway → Morphine, Quinine, Reserpine, Caffeine, Nicotine, Colchicine
GLYCOSIDES	Various pathways → Cardiac glycosides, Anthraquinone glycosides, Cyanogenic glycosides, Saponins
FATTY ACIDS & POLYKETIDES	Acetate-Malonate Pathway → Fixed oils, Polyketide antibiotics (e.g., tetracyclines)

## Overview of Metabolic Pathways

The three major biosynthetic pathways that produce secondary metabolites in higher plants are:

 SHIKIMIC ACID PATHWAY	 ACETATE PATHWAY	 AMINO ACID PATHWAY
<p><b>Precursor:</b> PEP + Erythrose-4-P</p> <p><b>Products:</b></p> <ul style="list-style-type: none"> <li>• Aromatic amino acids</li> <li>• Phenylpropanoids</li> <li>• Flavonoids</li> <li>• Lignins</li> <li>• Tannins</li> <li>• Coumarins</li> </ul>	<p><b>Precursor:</b> Acetyl-CoA</p> <p><b>Products:</b></p> <ul style="list-style-type: none"> <li>• Mono/Sesqui/Diterpenes</li> <li>• Steroids &amp; Sterols</li> <li>• Saponins</li> <li>• Carotenoids</li> <li>• Fixed oils</li> <li>• Polyketides</li> </ul>	<p><b>Precursor:</b> Amino acids</p> <p><b>Products:</b></p> <ul style="list-style-type: none"> <li>• Pyridine alkaloids</li> <li>• Tropane alkaloids</li> <li>• Isoquinoline alkaloids</li> <li>• Indole alkaloids</li> <li>• Imidazole alkaloids</li> <li>• Purine alkaloids</li> </ul>

## SHIKIMIC ACID PATHWAY

# SHIKIMIC ACID PATHWAY

### Introduction

The Shikimic Acid Pathway (also called Shikimate Pathway) is one of the most important biosynthetic routes in plants, microorganisms, and fungi. It does NOT occur in animals. This pathway is responsible for the biosynthesis of the aromatic amino acids (Phenylalanine, Tyrosine, Tryptophan) and, from these, a vast array of secondary metabolites including phenylpropanoids, flavonoids, lignins, tannins, and coumarins.

Points: The enzyme EPSPS (5-enolpyruvylshikimate-3-phosphate synthase) in this pathway is the target of the herbicide Glyphosate (Roundup®). Since animals lack this pathway, glyphosate is selectively toxic to plants and microbes.

### Starting Materials / Precursors

#### PRECURSORS OF SHIKIMIC ACID PATHWAY

- Phosphoenolpyruvate (PEP) – a 3-carbon compound derived from glycolysis
- Erythrose-4-phosphate (E4P) – a 4-carbon compound derived from the Pentose Phosphate Pathway (Calvin cycle in plants)
- Both precursors are products of primary metabolism (carbohydrate metabolism)
- These combine to ultimately form Shikimic acid (a cyclohexane carboxylic acid with 7 carbons)

### Biosynthetic Steps of the Shikimic Acid Pathway

#### ◆ STAGE 1 – Formation of Shikimic Acid

This stage involves the condensation of PEP and Erythrose-4-phosphate and subsequent modifications:

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### STAGE 1: SHIKIMIC ACID FORMATION

**Phosphoenolpyruvate (PEP) + Erythrose-4-Phosphate (E4P)**



**3-Deoxy-D-arabino-heptulosonate-7-phosphate (DAHP)**

↓ [*DAHP Synthase (3 isoforms, each regulated by Phe/Tyr/Trp)*]

**3-Dehydroquinic acid (DHQ)**

↓ [*DHQ Synthase*]

**3-Dehydroshikimic acid (DHS)**

↓ [*Dehydroquinase Dehydratase*]

**Shikimic acid**

↓ [*Shikimate Dehydrogenase*]

**Shikimate-3-phosphate**

↓ [*Shikimate Kinase*]

**5-Enolpyruvylshikimate-3-phosphate (EPSP)**

↓ [*EPSPS [Target of Glyphosate herbicide]*]

**Chorismic acid ← BRANCH POINT**

↓ [*Chorismate Synthase*]

### ◆ STAGE 2 – From Chorismic Acid: Branch Points

Chorismic acid is the critical branch point of the shikimate pathway. From chorismate, two major branches diverge:

Branch	Products & Details
BRANCH 1 → Prephenate Route	Via Prephenate → Phenylalanine and Tyrosine (aromatic amino acids); these then enter the Phenylpropanoid pathway
BRANCH 2 → Anthranilate Route	Via Anthranilic acid → Tryptophan (aromatic amino acid); Tryptophan is the precursor for indole alkaloids
BRANCH 3 → p- Hydroxybenzoate	Via Chorismate → p-Hydroxybenzoate → Ubiquinone (Coenzyme Q) biosynthesis
BRANCH 4 → Isochorismate	Via Isochorismate → Salicylic acid (defense signal), Menaquinone (Vitamin K2)

### ◆ STAGE 3 – Phenylpropanoid Pathway (Extension of Shikimate Pathway)

Phenylalanine (from Stage 2) enters the Phenylpropanoid Pathway – the most important secondary metabolite pathway in plants:

### PHENYLPROPANOID PATHWAY

#### L-Phenylalanine



#### trans-Cinnamic acid

↓ [*Phenylalanine Ammonia Lyase (PAL)* —regulatory enzyme]

#### p-Coumaric acid (4-hydroxycinnamic acid)

↓ [*Cinnamate 4-Hydroxylase (C4H)*]

#### p-Coumaroyl-CoA

↓ [*4-Coumarate-CoA Ligase (4CL)*]

#### ✓ BRANCH POINT ✎

↓ [*Multiple downstream enzymes*]

[1] Monolignols → Lignins | [2] + Malonyl-CoA → Chalcones →

Flavonoids/Anthocyanins | [3] Coumarins | [4] Caffeic acid, Ferulic acid

## Products of Shikimic Acid Pathway

### ◆ A. Aromatic Amino Acids

Amino Acid	Details & Secondary Metabolite Connections
L-Phenylalanine (Phe)	Most abundant aromatic AA in plants; precursor of all phenylpropanoids, lignin, most flavonoids, stilbenes, coumarins
L-Tyrosine (Tyr)	Precursor of isoquinoline alkaloids (morphine, codeine, berberine), tocopherols (Vitamin E), plastoquinones
L-Tryptophan (Trp)	Precursor of indole alkaloids (vinblastine, vincristine, reserpine, strychnine), serotonin, melatonin, auxin (IAA)

### ◆ B. Phenylpropanoids & Related Compounds

#### PHENYLPROPANOIDS – PRODUCTS & IMPORTANCE

- **SIMPLE PHENOLS:** Vanillin (vanilla flavor), Caffeic acid, Ferulic acid (antioxidant)
- **COUMARINS:** Coumarin (from Cinnamomum), Umbelliferone, Bergapten, Psoralen (from Psoralea corylifolia – Bakuchi); used as anticoagulants, photosensitizers
- **LIGNANS:** Podophyllotoxin (from Podophyllum peltatum – anti-cancer precursor); Secoisolariciresinol
- **LIGNINS:** Structural polymers of cell walls; made from coniferyl, sinapyl, p-coumaryl alcohols; second most abundant organic compound on Earth

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- STILBENES: Resveratrol (from grapes/peanuts – cardioprotective, antioxidant)
- PHENYLPROPANOIDS: Anethole (anise), Eugenol (clove), Safrole (sassafras)

### ◆ C. Flavonoids

Flavonoids are a large and diverse group of plant secondary metabolites formed by the combination of the Phenylpropanoid pathway (Shikimate origin – ring B and C-3 unit) and the Acetate-Malonate pathway (3 acetate units form ring A). This is called the MIXED BIOSYNTHETIC ORIGIN.

#### FLAVONOID BIOSYNTHESIS – OVERVIEW

- PRECURSORS: p-Coumaroyl-CoA (from Shikimate pathway) + 3 × Malonyl-CoA (from Acetate pathway)
- ENZYME: Chalcone Synthase (CHS) → forms Chalcone (the first flavonoid)
- Chalcone → Flavanone (Naringenin) → Multiple branches:
  - BRANCH 1: Flavones (e.g., Apigenin, Luteolin) – anti-inflammatory
  - BRANCH 2: Flavonols (e.g., Quercetin, Kaempferol, Rutin) – antioxidants, widely distributed
  - BRANCH 3: Anthocyanidins (e.g., Cyanidin, Pelargonidin) – flower/fruit colors
  - BRANCH 4: Isoflavones (e.g., Genistein, Daidzein) – phytoestrogens; from legumes
  - BRANCH 5: Condensed Tannins (Proanthocyanidins) – astringents
  - BRANCH 6: Catechins (e.g., EGCG from green tea) – antioxidant, anticancer

### ◆ D. Tannins

Type	Biosynthetic Origin & Examples
HYDROLYSABLE TANNINS	Derived from Shikimate pathway: Gallic acid + Glucose → Gallotannins (e.g., Tannic acid from oak galls) OR Ellagic acid + Glucose → Ellagitannins (e.g., Pomegranate peel)
CONDENSED TANNINS (Proanthocyanidins)	Derived from Flavonoid pathway; polymerized flavan-3-ols; e.g., Catechin polymers in Acacia (Katha), Catechu
Uses	Astringents, anti-diarrhoeal, protein precipitants, wound healing; in Pharmacognosy: Catechu, Gambier, Galls, Myrobalan

## Pharmaceutical Importance of Shikimic Acid Pathway Products

Compound	Source Plant	Pathway	Therapeutic Use
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Morphine & Codeine	Papaver somniferum	Shikimic (Tyr) → Isoquinoline	Analgesic, Antitussive
Resveratrol	Vitis vinifera (grapes)	Shikimic → Stilbene	Cardioprotective, Antioxidant
Rutin (Quercetin-3-O-rutinoside)	Buckwheat, Citrus	Shikimic → Flavonol	Capillary strengthening, Antioxidant
Podophyllotoxin	Podophyllum peltatum	Shikimic → Lignan	Anticancer precursor (Etoposide)
Psoralen	Psoralea corylifolia	Shikimic → Coumarin	Vitiligo, Psoriasis (PUVA therapy)
Shikimic acid itself	Star anise (Illicium verum)	Direct extraction	Precursor for Oseltamivir (Tamiflu)
Eugenol	Syzygium aromaticum (Clove)	Shikimic → Phenylpropanoid	Dental anaesthetic, Antiseptic
Caffeic acid	Widely distributed	Shikimic → Phenolic acid	Antioxidant, Anti-inflammatory

## ACETATE PATHWAYS – MEVALONATE & MEP/DXP PATHWAYS

### ACETATE PATHWAYS

#### Introduction to the Acetate Pathways

The Acetate Pathways use Acetyl-CoA (derived from acetate) as the fundamental building block for biosynthesis of a large variety of secondary metabolites. In plants, two major acetate-derived pathways operate:

Pathway	Location & Products
ACETATE-MALONATE PATHWAY (Polyketide Pathway)	Cytosol; produces: Fatty acids, Fixed oils, Polyketides, waxes; contributes to flavonoid ring A
MEVALONATE (MVA) PATHWAY	Cytosol / Endoplasmic Reticulum; produces: Sesquiterpenes, Triterpenes (steroids, saponins), Polyterpenes
MEP/DXP (METHYLERYTHRITOL PHOSPHATE) PATHWAY	Plastids (chloroplasts); produces: Monoterpenes, Diterpenes, Tetraterpenes (carotenoids); also provides IPP for plastidic terpenes

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## The Isoprene Rule & Terpene Classification

All terpenoids are built from the 5-carbon isoprene unit (C<sub>5</sub>): Isopentenyl Pyrophosphate (IPP) and its isomer Dimethylallyl Pyrophosphate (DMAPP). This is called the 'Isoprene Rule' proposed by Leopold Ruzicka.

Number of Isoprene Units (C <sub>5</sub> ) Terpene Class	Examples
1 unit (C <sub>5</sub> ) Hemiterpenes	Isoprene itself; Prenol
2 units (C <sub>10</sub> ) Monoterpenes	Menthol, Camphor, Geraniol, Limonene, Thymol, Borneol
3 units (C <sub>15</sub> ) Sesquiterpenes	Artemisinin, Farnesol, Bisabolol, Sesquiterpene lactones
4 units (C <sub>20</sub> ) Diterpenes	Taxol (Paclitaxel), Gibberellins, Retinoids, Phytol
5 units (C <sub>25</sub> ) Sesterterpenes	Relatively rare; found in marine organisms
6 units (C <sub>30</sub> ) Triterpenes	Steroids, Squalene, Oleanolic acid, Ursolic acid, Glycyrrhizin
8 units (C <sub>40</sub> ) Tetraterpenes	Carotenoids (β-Carotene, Lycopene, Lutein, Zeaxanthin)
9 units (C <sub>5n</sub> ) Polyterpenes	Rubber ( <i>Hevea brasiliensis</i> ), Gutta-percha

## The Mevalonate (MVA) Pathway

The Mevalonate pathway occurs in the cytosol and is the predominant route for terpenoid synthesis in animals and for sesqui-, tri-, and polyterpenes in plants.

### ◆ Step-by-Step Mevalonate Pathway

#### MEVALONATE PATHWAY – COMPLETE STEPS

**Acetyl-CoA (C<sub>2</sub>)**



**Acetoacetyl-CoA (C<sub>4</sub>)**



**HMG-CoA (3-Hydroxy-3-methylglutaryl-CoA) (C<sub>6</sub>)**



**Mevalonic Acid (MVA) (C<sub>6</sub>) ← RATE-LIMITING STEP**



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### Mevalonate-5-phosphate

↓ [*Mevalonate Kinase*]

### Mevalonate-5-pyrophosphate

↓ [*Phosphomevalonate Kinase*]

### Isopentenyl Pyrophosphate (IPP) – C5 ← ACTIVE ISOPRENE UNIT

↓ [*Mevalonate Pyrophosphate Decarboxylase*]

### Dimethylallyl Pyrophosphate (DMAPP) – C5 ← ISOMER

↓ [*IPP Isomerase (reversible)*]

### IPP + DMAPP → Geranyl Pyrophosphate (GPP) – C10 → MONOTERPENES

↓ [*Geranyl Pyrophosphate Synthase (GPPS)*]

### GPP + IPP → Farnesyl Pyrophosphate (FPP) – C15 → SESQUITERPENES

↓ [*Farnesyl Pyrophosphate Synthase (FPPS)*]

### FPP + FPP → Squalene (C30) → TRITERPENES & STEROIDS

↓ [*Squalene Synthase*]

## ◆ Products of Mevalonate Pathway – Details

### ● (i) Monoterpenes (C10) – from GPP

#### MONOTERPENES

- Formed from Geranyl Pyrophosphate (GPP) (C10) via various cyclizations and modifications
- **ACYCLIC:** Geraniol (rose), Linalool (lavender – *Lavandula* spp.), Citral (lemon)
- **MONOCYCLIC:** Menthol (*Mentha piperita* – peppermint), Limonene (citrus), Terpeneol, Thymol (*Thymus vulgaris*), Carvacrol
- **BICYCLIC:** Camphor (*Cinnamomum camphora*), Borneol, Pinene (turpentine), Fenchone (fennel)
- **IRIDOIDS:** Aucubin, Loganin – important in indole alkaloid biosynthesis as secologanin precursor
- **Pharmaceutical Uses:** Essential oil components; antiseptic (Thymol), carminative (Menthol), rubefacient (Camphor), antifungal (Terpeneol)

### ● (ii) Sesquiterpenes (C15) – from FPP

#### SESQUITERPENES

- Formed from Farnesyl Pyrophosphate (FPP) (C15)
- **ACYCLIC:** Farnesol (anti-fungal, pheromone)
- **MONOCYCLIC:** Bisabolol (*Matricaria chamomilla* – German chamomile; anti-inflammatory)
- **BICYCLIC:** Guaiol (*Bulnesia sarmientoi* – Guaiac wood), Artabsin (*Artemisia*)
- **TRICYCLIC:** Copaene

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- **SESQUITERPENE LACTONES:** Artemisinin (*Artemisia annua* – antimalarial), Parthenolide (*Tanacetum parthenium* – migraine), Absinthin
- **Pharmaceutical Uses:** Artemisinin is the basis for artemisinin-based combination therapy (ACT) for malaria

### • (iii) Triterpenes & Steroids (C30) – from Squalene

Two farnesyl pyrophosphate (FPP) units combine tail-to-tail to form Squalene (C30), which is then cyclized to form steroids and other triterpenes.

#### SQUALENE TO STEROIDS

2 × Farnesyl Pyrophosphate (FPP) – C15 each

↓

**Squalene (C30) – acyclic**

↓ [*Squalene Synthase (tail-to-tail condensation)*]

**Squalene-2,3-oxide (epoxidation)**

↓ [*Squalene Epoxidase*]

**Lanosterol (C30, tetracyclic) ← ANIMALS & FUNGI**

↓ [*Oxidosqualene Cyclase (Lanosterol Synthase)*]

**Cycloartenol (C30, tetracyclic) ← PLANTS**

↓ [*Oxidosqualene Cyclase (Cycloartenol Synthase)*]

↓ **Multiple steps**

↓

**Phytosterols (Sitosterol, Stigmasterol, Campesterol) / Saponin aglycones / Cardiac glycoside aglycones**

#### TRITERPENE / STEROID PRODUCTS

- **PHYTOSTEROLS:** β-Sitosterol (most abundant plant sterol; cholesterol-lowering), Stigmasterol, Campesterol
- **STEROIDAL SAPONINS:** Diosgenin (from *Dioscorea* – precursor for steroid hormone synthesis), Hecogenin
- **CARDIAC GLYCOSIDE AGLYCONES:** Digitoxigenin (*Digitalis purpurea*), Digoxigenin (*Digitalis lanata*), Strophanthidin
- **PENTACYCLIC TRITERPENES:** Oleanolic acid, Ursolic acid, Betulinic acid (anti-HIV), Glycyrrhizin (*Glycyrrhiza glabra* – liquorice; anti-ulcer, anti-inflammatory)
- **CUCURBITACINS:** Bitter principles of cucurbits; anticancer
- **DAMMARANE TRITERPENES:** Ginsenosides (*Panax ginseng* – adaptogenic)

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## The MEP/DXP Pathway (Non-Mevalonate Pathway)

The 2-C-methyl-D-erythritol-4-phosphate (MEP) pathway, also called the DXP (1-deoxy-D-xylulose-5-phosphate) pathway or Non-Mevalonate pathway, operates in the plastids (chloroplasts) of plants. It was discovered relatively recently (1990s) and is responsible for monoterpene, diterpene, and carotenoid biosynthesis in plant plastids.

### MEP/DXP PATHWAY –STEPS

**Pyruvate + Glyceraldehyde-3-phosphate (G3P)**

↓

**1-Deoxy-D-xylulose-5-phosphate (DXP/DOXP) ← pathway named after this**

↓ [*DXP Synthase (DXS) – requires TPP (Thiamine pyrophosphate)*]

**2-C-Methyl-D-erythritol-4-phosphate (MEP) ← pathway named after this**

↓ [*DXP Reductoisomerase (DXR) [Target of antibiotic Fosmidomycin]*]

**CDP-ME → CDP-ME-2P → ME-cPP → HMBPP**

↓ [*Multiple steps*]

**IPP + DMAPP (in PLASTIDS)**

↓ [*HMBPP Reductase (IspH)*]

**GPP (C10) → Monoterpenes | GGPP (C20) → Diterpenes, Carotenoids | Phytol**

### MEP PATHWAY PRODUCTS

- **MONOTERPENES:** Menthol, Camphor, Geraniol, Limonene, Thymol (same as MVA – both contribute)
- **DITERPENES (C20, from GGPP):** Taxol/Paclitaxel (*Taxus brevifolia* – anticancer), Gibberellins (plant hormones), Casbene, Phytol (side chain of chlorophyll and Vitamin K)
- **CAROTENOIDS/TETRATERPENES (C40):** β-Carotene (pro-Vitamin A), Lycopene (antioxidant, tomato), Lutein, Zeaxanthin (macular protection), Astaxanthin
- **Isoprene (volatile C5 compound emitted by plants – climate significance)**
- **CROSS-TALK:** IPP and DMAPP can be exchanged between plastid (MEP) and cytosol (MVA) pathways to some extent

## Acetate-Malonate Pathway (Polyketide Pathway)

This pathway produces fatty acids and polyketides using Acetyl-CoA as a starter unit and Malonyl-CoA as the chain-extender. The enzyme complex Fatty Acid Synthase (FAS) or Polyketide Synthase (PKS) catalyzes repeated condensations.

### ACETATE-MALONATE PATHWAY – PRODUCTS

- **FATTY ACIDS:** Palmitic acid (C16), Stearic acid (C18), Oleic acid (C18:1), Linoleic acid (C18:2) – components of fixed oils
- **FIXED OILS:** Castor oil, Olive oil, Coconut oil, Arachis oil – used as pharmaceutical excipients, vehicles
- **ANTHRAQUINONES (via Polyketide route):** Emodin, Rhein, Sennoside (Cassia senna – laxative), Hypericin (St. John's Wort)
- **FLAVONOID RING A:** Three Malonyl-CoA units contribute to ring A of all flavonoids (mixed Shikimate-Acetate origin)
- **PHENOLIC ACIDS:** Orsellinic acid and related compounds
- **WAXES:** Cuticular waxes on plant surfaces (mixture of long-chain fatty acids, alcohols, esters)

## AMINO ACID PATHWAY – ALKALOID BIOSYNTHESIS

# AMINO ACID PATHWAY – ALKALOID BIOSYNTHESIS

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### Introduction to Alkaloids

Alkaloids are nitrogen-containing secondary metabolites derived primarily from amino acids (the Amino Acid Pathway). They are basic in nature (due to the nitrogen), often pharmacologically active, bitter in taste, and precipitate with heavy metal salts and alkaloid reagents. The term 'alkaloid' was first used by W. Meissner (1819). There are over 12,000 known alkaloids.

#### GENERAL CHARACTERISTICS OF ALKALOIDS

- Nitrogen is usually derived from an amino acid precursor
- Most are basic in nature (react with acids to form salts)
- Usually optically active (exist as L-isomers in nature)
- Mostly bitter in taste; some are coloured (berberine – yellow; sanguinarine – orange)
- React with alkaloid precipitant reagents: Mayer's, Dragendorff's, Wagner's, Hager's
- Found mainly in angiosperms; some in microorganisms (ergot alkaloids) and animals (batrachotoxin in frogs)

### Classification of Alkaloids by Amino Acid Precursor

#### ◆ A. From ORNITHINE (and ARGININE) → Pyrrolidine & Tropane Alkaloids

Ornithine is a non-protein amino acid; it is the direct precursor of the pyrrolidine ring system.

#### ORNITHINE → PYRROLIDINE → TROPANE ALKALOIDS

**L-Ornithine (C5 amino acid)**

↓

**Putrescine (1,4-diaminobutane)**

↓ [*Ornithine Decarboxylase (ODC)*]

**N-Methylputrescine**

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↓ [*Putrescine N-Methyltransferase*]

### 4-Methylaminobutanal

↓ [*Methylputrescine Oxidase*]

**N-Methyl- $\Delta^1$ -pyrrolinium cation (pyrrolidine ring) ← RING CLOSURE**

↓

**Hygrine → [+ Acetoacetic acid] → Tropinone**

↓ [*Spontaneous condensation / Tropinone synthase*]

**Tropine (Reduction) ← [or] → Pseudotropine**

↓ [*Tropinone Reductase I/II*]

**Tropine + Tropic acid → (-)-Hyoscyamine**

↓ [*Hyoscyamine/Littorine synthase*]

**(-)-Hyoscyamine → ( $\pm$ )-Atropine | or → Scopolamine (Hyoscine)**

↓ [*Hyoscyamine 6 $\beta$ -Hydroxylase*]

## ORNITHINE-DERIVED ALKALOIDS –EXAMPLES

- PYRROLIDINE ALKALOIDS: Hygrine (Coca plant), Cuscohygrine
- TROPANE ALKALOIDS: Atropine (*Atropa belladonna* – anticholinergic, mydriatic), Hyoscine/Scopolamine (*Datura* – antiemetic, antispasmodic), Cocaine (*Erythroxylum coca* – local anaesthetic, CNS stimulant)
- NICOTINE: Derived from Ornithine (pyrrolidine ring) + Nicotinic acid (pyridine ring); found in *Nicotiana tabacum*
- Pharmaceutical significance: Atropine – preanaesthetic medication, antidote for organophosphate poisoning, pupil dilation

## ◆ B. From LYSINE → Piperidine & Quinolizidine Alkaloids

### LYSINE → PIPERIDINE ALKALOIDS

**L-Lysine (C6 diamine amino acid)**

↓

**Cadaverine (1,5-diaminopentane)**

↓ [*Lysine Decarboxylase*]

**$\Delta^1$ -Piperideine (piperidine ring) ← RING CLOSURE**

↓ [*Oxidation*]

**Pipecoline → Lobeline → or Sedamine (piperidine alkaloids)**

## LYSINE-DERIVED ALKALOIDS –EXAMPLES

- PIPERIDINE ALKALOIDS: Piperine (*Piper nigrum* – black pepper; flavoring, insecticidal), Lobeline (*Lobelia inflata* – respiratory stimulant, smoking cessation)
- QUINOLIZIDINE ALKALOIDS: Lupinine, Sparteine (*Lupinus* spp. – antiarrhythmic)

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- **INDOLIZIDINE ALKALOIDS:** Swainsonine (from locoweeds – neurological toxin)

### ◆ C. From TYROSINE (& DOPA) → Isoquinoline Alkaloids

Tyrosine is the most prolific amino acid precursor of alkaloids. It gives rise to the important isoquinoline skeleton.

#### TYROSINE → ISOQUINOLINE → MORPHINE PATHWAY

##### L-Tyrosine

↓

##### Dopamine (via DOPA)

↓ [*Tyrosine Hydroxylase + DOPA Decarboxylase*]

##### 4-Hydroxyphenylacetaldehyde (from Tyrosine)

↓ [*Tyrosine Aminotransferase*]

##### (S)-Norcoclaurine (first isoquinoline) ← PICTET-SPENGLER CONDENSATION

↓ [*Norcoclaurine Synthase (NCS)*]

##### (S)-Cocclaurine → (S)-N-Methylcocclaurine → (S)-3'-Hydroxy-N-methylcocclaurine

↓ [*Various O-methyltransferases, N-methyltransferases*]

##### (S)-Reticuline ← BRANCH POINT

↓ [*CYP80B1*]

##### BRANCH 1: (R)-Reticuline → Salutaridine → Thebaine → Codeine → Morphine

↓ [*Salutaridine Synthase → SalR → SalAT → etc.*]

##### BRANCH 2: (S)-Reticuline → Scoulerine → Tetrahydrocolumbamine → Berberine

↓ [*Berberine Bridge Enzyme (BBE) → Various*]

#### TYROSINE/ISOQUINOLINE-DERIVED ALKALOIDS

- **BENZYLISOQUINOLINE:** Papaverine (Papaver somniferum – antispasmodic), Noscapine (antitussive)
- **MORPHINAN ALKALOIDS:** Morphine (analgesic), Codeine (antitussive, analgesic), Thebaine (precursor for oxycodone, naloxone)
- **PROTOBERBERINE:** Berberine (Berberis spp. – antibacterial, antidiarrhoeal, bright yellow), Coptisine
- **APORPHINE:** Cephaeline, Emetine (Psychotria ipecacuanha – Ipecac; expectorant, emetic)
- **COLCHICINE:** From Colchicum autumnale – treats gout (though mixed biosynthetic origin via Tyrosine + phenethylamine)

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- **PHENETHYLISOQUINOLINES:** Colchicine; Homoaporphines

### ◆ D. From TRYPTOPHAN → Indole Alkaloids

Tryptophan (from Shikimate pathway) is the precursor of the indole alkaloids – the largest and most complex group of alkaloids.

#### TRYPTOPHAN → INDOLE ALKALOIDS (MONOTERPENOID INDOLE ALKALOIDS – MIAs)

##### L-Tryptophan



##### Tryptamine

↓ [*Tryptophan Decarboxylase (TDC)*]

##### Tryptamine + Secologanin (iridoid monoterpene from MEP pathway)

↓ [*Strictosidine Synthase (STR) – Pictet-Spenglerase*]

##### Strictosidine ← UNIVERSAL PRECURSOR of all MIAs



##### Cathenamine → Ajmalicine (Rauwolfia) | OR



##### Geissoschizine → Strychnine (Strychnos nux-vomica) | OR



##### Tabersonine → Vindoline + Catharanthine → Vinblastine/Vincristine (Catharanthus roseus)



##### BRANCH: Secologanin + Tryptamine → Reserpine / Ajmaline pathway

#### TRYPTOPHAN-DERIVED INDOLE ALKALOIDS

- **ERGOT ALKALOIDS:** Ergotamine, Ergometrine (from *Claviceps purpurea* – ergot fungus; oxytocic, antimigraine, vasoconstrictor)
- **MONOTERPENOID INDOLE ALKALOIDS (MIAs):** Vinblastine, Vincristine (*Catharanthus roseus* – vinca alkaloids; anticancer – mitotic spindle inhibitors)
- **RESERPINE:** *Rauwolfia serpentina* – antihypertensive, tranquilizer; first antihypertensive in clinical use
- **STRYCHNINE & BRUCINE:** *Strychnos nux-vomica* – CNS stimulant (strychnine), fatal convulsant; brucine – less toxic
- **AJMALINE:** *Rauwolfia* – antiarrhythmic
- **PHYSOSTIGMINE (Eserine):** *Physostigma venenosum* (Calabar bean) – acetylcholinesterase inhibitor; used in glaucoma
- **PILOCARPINE:** *Pilocarpus jaborandi* – muscarinic agonist; glaucoma treatment (not indole, imidazole)

## ◆ E. From ANTHRANILIC ACID → Quinoline & Acridone Alkaloids

### ANTHRANILIC ACID-DERIVED ALKALOIDS

- QUINOLINE ALKALOIDS: Quinine, Quinidine, Cinchonine, Cinchonidine (from *Cinchona officinalis*/bark – antimalarial, antiarrhythmic); biosynthesis combines anthranilic acid with tryptophan-derived unit
- ACRIDONE ALKALOIDS: Acronycine (*Acronychia baueri* – anticancer)
- BENZOXAZINOIDs: Cyclic hydroxamic acids in grasses (defense compounds)

## ◆ F. From HISTIDINE → Imidazole Alkaloids

### HISTIDINE-DERIVED ALKALOIDS

- IMIDAZOLE ALKALOIDS: Pilocarpine (*Pilocarpus jaborandi* – parasympathomimetic; glaucoma, Sjögren's syndrome), Pilocosine
- PURINE ALKALOIDS (via Xanthine, structurally related): Caffeine, Theophylline (*Camellia sinensis* – tea), Theobromine (*Theobroma cacao* – cocoa); these are formed via adenine/xanthine pathway rather than directly from histidine

## RADIOACTIVE ISOTOPES IN BIOGENETIC STUDIES

## UTILIZATION OF RADIOACTIVE ISOTOPES IN BIOGENETIC STUDIES

### Introduction

Biogenetic studies (also called Biosynthetic studies or Tracer studies) involve the investigation of metabolic pathways in living organisms to understand how secondary metabolites are synthesized from simple precursors. Radioactive isotopes (radiolabeled compounds) are used as tracers to follow the fate of specific atoms through a biosynthetic pathway. This technique has been fundamental in elucidating the biogenetic origins of alkaloids, terpenoids, phenolics, and other plant natural products.

### What are Radioactive Isotopes (Radioisotopes)?

Radioisotopes are unstable isotopes of elements that emit radiation (alpha, beta, or gamma) as they undergo radioactive decay to a more stable form. In biosynthetic

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studies, specific atoms in a precursor molecule are replaced by their radioactive isotope. This 'labeled' precursor is then administered to the organism, and the radioactivity is tracked into the final product.

Radioisotope	Symbol
Carbon-14	$^{14}\text{C}$
Tritium (Hydrogen-3)	$^3\text{H}$
Nitrogen-15	$^{15}\text{N}$
Oxygen-18	$^{18}\text{O}$
Phosphorus-32	$^{32}\text{P}$
Deuterium	$^2\text{H}$ (D)

## Principles of Radiotracer Technique

### PRINCIPLES OF TRACER TECHNIQUE IN BIOGENETIC STUDIES

- **ISOTOPE DILUTION PRINCIPLE:** The labeled precursor is mixed with normal (unlabeled) precursor and fed to the plant; both are incorporated into the same metabolic pool
- **SPECIFIC ACTIVITY:** The ratio of radioactive to non-radioactive molecules; expressed as disintegrations per minute (dpm) per mole; used to calculate incorporation efficiency
- **INCORPORATION %:** Percentage of administered radioactivity that appears in the isolated product; usually 0.01–5%
- **ISOTOPE DILUTION:** If a precursor is closely related to the metabolite, incorporation % is high; if more distant, lower
- **NO METABOLIC DISRUPTION:** The labeled compound must behave exactly as its non-labeled analog (isotope effect is usually negligible for  $^{14}\text{C}$ )
- **DEGRADATION STUDIES:** After isolation of labeled product, chemical or enzymatic degradation is performed to determine which specific carbon/atom is labeled → reveals biosynthetic route

## Methodology of Isotope Tracer Experiments

Step	Details
STEP 1: HYPOTHESIS	Based on chemical structural analysis, a hypothesis is formed about the likely precursor(s). E.g., morphine is suspected to arise from tyrosine based on structural similarity

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STEP 2: PREPARATION OF LABELED PRECURSOR	The suspected precursor is synthesized with a specific $^{14}\text{C}$ or $^3\text{H}$ label at a defined position. E.g., $[1-^{14}\text{C}]$ -Tyrosine, $[2-^{14}\text{C}]$ -Acetate, $[1-^{13}\text{C}]$ -Phenylalanine
STEP 3: ADMINISTRATION TO PLANT	The labeled compound is administered to the plant/cell culture by: (a) Injection into stem/leaf, (b) Root absorption from solution, (c) Feeding to excised plant parts, (d) In vitro cell-free system or cell cultures
STEP 4: INCUBATION	Allow sufficient time for the plant to metabolize the precursor and incorporate it into the final product (hours to days)
STEP 5: ISOLATION OF PRODUCT	Extract and purify the secondary metabolite using standard pharmacognostical extraction techniques (steam distillation, solvent extraction, chromatography)
STEP 6: MEASUREMENT OF RADIOACTIVITY	Measure radioactivity of the isolated product using: (a) Geiger-Müller counter (b) Scintillation counter (liquid scintillation counting – LSC, most common) (c) Autoradiography for $^3\text{H}$
STEP 7: CALCULATION OF INCORPORATION	$\% \text{ Incorporation} = (\text{Radioactivity in product} / \text{Total radioactivity administered}) \times 100$
STEP 8: DEGRADATION & LOCALIZATION	Chemical/enzymatic degradation of the labeled product to identify WHICH carbon(s)/atom(s) are labeled → confirms biosynthetic route and stereochemistry

## Detection Methods for Radioisotopes

### DETECTION METHODS

- **GEIGER-MÜLLER (GM) COUNTER:** Detects beta and gamma radiation; measures count rate (counts per minute, cpm); simple, robust; less sensitive than scintillation counting
- **LIQUID SCINTILLATION COUNTING (LSC):** Most widely used for  $^{14}\text{C}$  and  $^3\text{H}$ ; the sample is dissolved in a scintillation cocktail (liquid scintillator); radiation energy converted to light photons; detected by photomultiplier tube; extremely sensitive; can count both  $^{14}\text{C}$  and  $^3\text{H}$  in same sample
- **AUTORADIOGRAPHY:** Film-based method; the labeled compound is placed against X-ray film; radiation exposes the film; useful for localization of  $^3\text{H}$  in thin sections (e.g., plant tissues); used with TLC and paper chromatography to locate labeled spots
- **RADIOCHROMATOGRAPHY:** TLC or paper chromatography combined with radioactivity scanning to detect labeled intermediates in the pathway
- **MASS SPECTROMETRY (MS):** For stable isotopes ( $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^2\text{H}$ ,  $^{13}\text{C}$ ); measures mass differences between labeled and unlabeled molecules; NMR (Nuclear Magnetic Resonance) also used for  $^{13}\text{C}$
- **RADIOGAS CHROMATOGRAPHY:** For volatile  $^{14}\text{C}$ -labeled compounds

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## Classic Biogenetic Studies Using Radioisotopes

### ◆ A. Elucidation of Morphine Biosynthesis

The biosynthesis of morphine in *Papaver somniferum* was one of the landmark achievements of isotope tracer studies:

#### MORPHINE BIOSYNTHESIS STUDIES

- **PRECURSOR HYPOTHESIS:** Morphine was suspected to arise from Tyrosine based on structural analysis (two tyrosine-like units detected)
- **TRACER EXPERIMENTS:** [1-<sup>14</sup>C]-Tyrosine administered to *Papaver somniferum* plants
- **RESULTS:** <sup>14</sup>C was incorporated into morphine; degradation showed specific labeling in the ring carbons
- **FURTHER STUDIES:** [<sup>14</sup>C]-DOPA, [<sup>14</sup>C]-Dopamine, [<sup>14</sup>C]-Norlaudanoline all showed incorporation
- **CONCLUSION:** Morphine biosynthesis: Tyrosine → Dopamine + 4-Hydroxyphenylacetaldehyde → Norcoclaurine → ... → Reticuline → Salutaridine → Thebaine → Codeine → Morphine
- **Researchers:** Battersby, Barton, Zenk – pioneers in elucidating morphine/benzylisoquinoline alkaloid biosynthesis

### ◆ B. Elucidation of Cholesterol/Steroid Biosynthesis

#### STEROID BIOSYNTHESIS STUDIES (Konrad Bloch & Feodor Lynen – Nobel Prize 1964)

- **PRECURSOR HYPOTHESIS:** Steroids hypothesized to arise from acetate (Rittenberg & Schoenheimer, 1945)
- **TRACER EXPERIMENT:** [1-<sup>14</sup>C]-Acetate and [2-<sup>14</sup>C]-Acetate fed to liver slices and animals
- **RESULTS:** Both C1 and C2 of acetate incorporated into cholesterol in a specific pattern
- **DEGRADATION:** Chemical degradation of labeled cholesterol showed that C1 of acetate → specific carbons; C2 of acetate → other specific carbons
- **CONCLUSION:** All 27 carbons of cholesterol derived from acetate (C2 unit); 18 from C2 of acetate, 9 from C1 of acetate
- **Led to discovery of:** Acetyl-CoA → Mevalonate → IPP → Squalene → Lanosterol → Cholesterol pathway
- This work established the MEVALONATE PATHWAY and earned Nobel Prize in Physiology/Medicine 1964

## ◆ C. Elucidation of Penicillin Biosynthesis (Fungi)

### PENICILLIN BIOSYNTHESIS STUDIES

- **PRECURSOR STUDIES:**  $^{35}\text{S}$ -Cysteine incorporated into penicillin beta-lactam ring (detected by sulfur-35)
- $^{14}\text{C}$ -Valine incorporated into the thiazolidine ring
- **CONCLUSION:** Penicillin assembled from three amino acids:  $\alpha$ -aminoadipic acid + Cysteine + Valine  $\rightarrow$  Tripeptide ACV  $\rightarrow$   $\beta$ -lactam formation
- Demonstrated the power of radioisotope studies in proving biosynthetic origin of antibiotics

## ◆ D. Elucidation of Terpenoid Biosynthesis

### TERPENOID BIOSYNTHESIS STUDIES

- **ACETATE  $\rightarrow$  MEVALONATE PATHWAY:** [ $1\text{-}^{14}\text{C}$ ] and [ $2\text{-}^{14}\text{C}$ ] acetate incorporation into terpenoids showed alternating labeling pattern consistent with head-to-tail condensation of isoprene units
- **MEVALONATE LABELING:** [ $2\text{-}^{14}\text{C}$ ]-Mevalonate incorporated efficiently into monoterpenes, sesquiterpenes, diterpenes, steroids – confirming MVA is the universal terpenoid precursor
- **ISOPRENE RULE CONFIRMATION:** Radiolabeling confirmed that all terpenes are built from C5 isoprene units derived from mevalonate
- **MEP PATHWAY DISCOVERY:**  $^{13}\text{C}$  NMR and  $^{14}\text{C}$  studies in plastids showed that monoterpenes in chloroplasts are NOT exclusively from MVA  $\rightarrow$  led to discovery of MEP pathway (Rohmer, 1993)

## Advantages & Limitations of Radiotracer Method

ADVANTAGES	LIMITATIONS
High sensitivity – even traces (picomoles) of labeled compounds can be detected	Requires specialized equipment and radiation safety precautions
Does not disturb the metabolic system (isotopic effect minimal for $^{14}\text{C}$ )	Low % incorporation makes detection difficult for distant precursors
Specific position labeling allows precise determination of biosynthetic route	Expensive – radioisotope synthesis and scintillation counting equipment
Can study biosynthesis in intact living plants without homogenization	Regulatory restrictions on use of radioactive materials
Multiple isotopes ( $^{14}\text{C}$ and $^3\text{H}$ ) can be used	Disposal of radioactive waste requires strict protocols

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simultaneously to trace two positions	
Autoradiography allows visualization in tissue sections	Cannot distinguish true biosynthetic incorporation from non-specific binding

## Modern Alternatives to Radiotracer Studies

### MODERN METHODS IN BIOGENETIC INVESTIGATIONS

- STABLE ISOTOPE LABELING + NMR:  $^{13}\text{C}$ -labeled precursors detected by  $^{13}\text{C}$ -NMR spectroscopy; safer than radioactive isotopes; gives positional information
- STABLE ISOTOPE LABELING + MS:  $^2\text{H}$ ,  $^{13}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ -labeled compounds detected by mass spectrometry (LC-MS/GC-MS); very sensitive; determines exact labeled positions
- GENE KNOCKOUT/SILENCING (RNAi, CRISPR): Identify biosynthetic genes by blocking pathway at specific steps; genetic proof of enzyme function
- ENZYME ISOLATION & IN VITRO ASSAYS: Purify enzymes, incubate with substrate, identify product – direct proof of enzyme function
- HETEROLOGOUS EXPRESSION: Express plant genes in *E. coli* or yeast to produce the enzyme and confirm function
- METABOLOMICS + ISOTOPE LABELING: Combine stable isotope labeling with untargeted metabolomics to map entire pathway networks

## EXAM-ORIENTED MCQs – PHARMACOGNOSY & PHYTOCHEMISTRY UNIT 1

**Q1. The Shikimic Acid pathway does NOT occur in:**

- a) Plants b) Microorganisms c) Fungi d) Animals

✓ **Answer: d) Animals**

**Q2. The starting materials for the Shikimic Acid Pathway are:**

- a) Acetyl-CoA + Malonyl-CoA b) PEP + Erythrose-4-phosphate c) Pyruvate + G3P d) Phenylalanine + Tryptophan

✓ **Answer: b) PEP + Erythrose-4-phosphate**

**Q3. The enzyme EPSPS in the Shikimic Acid Pathway is inhibited by which herbicide?**

- a) Paraquat b) Atrazine c) Glyphosate d) 2,4-D

✓ **Answer: c) Glyphosate**

**Q4. Phenylalanine Ammonia Lyase (PAL) catalyzes conversion of Phenylalanine to:**

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- a) Tyrosine b) Cinnamic acid c) Shikimic acid d) Chorismate

✓ Answer: b) Cinnamic acid

**Q5. Chalcone Synthase (CHS) uses which two substrates to form Chalcone?**

- a) Shikimate + Pyruvate b) p-Coumaroyl-CoA + 3 × Malonyl-CoA c) Phenylalanine + Acetyl-CoA d) GPP + IPP

✓ Answer: b) p-Coumaroyl-CoA + 3 × Malonyl-CoA

**Q6. The rate-limiting enzyme of the Mevalonate pathway (and target of Statin drugs) is:**

- a) Squalene Synthase b) MVK (Mevalonate Kinase) c) HMG-CoA Reductase d) DAHP Synthase

✓ Answer: c) HMG-CoA Reductase

**Q7. The active isoprene unit in terpenoid biosynthesis is:**

- a) Geranyl Pyrophosphate (GPP) b) Isopentenyl Pyrophosphate (IPP) c) Farnesyl Pyrophosphate (FPP) d) Squalene

✓ Answer: b) Isopentenyl Pyrophosphate (IPP)

**Q8. Artemisinin is a \_\_\_\_\_ derived from the \_\_\_\_\_ pathway:**

- a) Diterpene; MEP b) Monoterpene; MVA c) Sesquiterpene; MVA d) Triterpene; MVA

✓ Answer: c) Sesquiterpene; MVA

**Q9. Taxol (Paclitaxel) is biosynthetically a:**

- a) Monoterpene b) Sesquiterpene c) Diterpene d) Triterpene

✓ Answer: c) Diterpene

**Q10. The MEP/DXP pathway is located in:**

- a) Cytosol b) Mitochondria c) Nucleus d) Plastids (Chloroplasts)

✓ Answer: d) Plastids (Chloroplasts)

**Q11. Morphine biosynthesis begins from the amino acid:**

- a) Tryptophan b) Phenylalanine c) Tyrosine d) Ornithine

✓ Answer: c) Tyrosine

**Q12. The universal precursor for all Monoterpenoid Indole Alkaloids (MIAs) formed from Tryptamine + Secologanin is:**

- a) Norcoclaurine b) Strictosidine c) Geissoschizine d) Reticuline

✓ Answer: b) Strictosidine

**Q13. Berberine is classified as which type of alkaloid?**

- a) Tropane b) Indole c) Protoberberine (Isoquinoline) d) Quinoline

✓ Answer: c) Protoberberine (Isoquinoline)

**Q14. Which radioisotope is most commonly used in biogenetic tracer studies due to its long half-life and ability to label carbon skeletons?**

- a)  $^3\text{H}$  (Tritium) b)  $^{32}\text{P}$  c)  $^{14}\text{C}$  (Carbon-14) d)  $^{35}\text{S}$

✓ Answer: c)  $^{14}\text{C}$  (Carbon-14)

**Q15. The Nobel Prize in Physiology/Medicine 1964 was awarded to Bloch and Lynen for elucidating:**

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- a) Morphine biosynthesis b) Sterol/cholesterol biosynthesis from acetate c) Shikimic acid pathway d) Flavonoid biosynthesis

✓ Answer: b) Sterol/cholesterol biosynthesis from acetate

**Q16. Liquid Scintillation Counting (LSC) is used to detect:**

- a) Stable isotopes b) X-rays c) Beta-emitting radioisotopes like  $^{14}\text{C}$  and  $^3\text{H}$  d) Alpha particles only

✓ Answer: c) Beta-emitting radioisotopes like  $^{14}\text{C}$  and  $^3\text{H}$

**Q17. Diosgenin (used as a precursor for steroidal contraceptives) is derived from which pathway?**

- a) Shikimic Acid Pathway b) MEP Pathway c) Mevalonate Pathway d) Amino Acid Pathway

✓ Answer: c) Mevalonate Pathway

**Q18. Shikimic acid (the direct precursor of Oseltamivir/Tamiflu) is obtained commercially from which plant?**

- a) Podophyllum peltatum b) Illicium verum (Star anise) c) Cinchona officinalis d) Papaver somniferum

✓ Answer: b) Illicium verum (Star anise)

**BEST OF LUCK FOR EXAMS!**

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