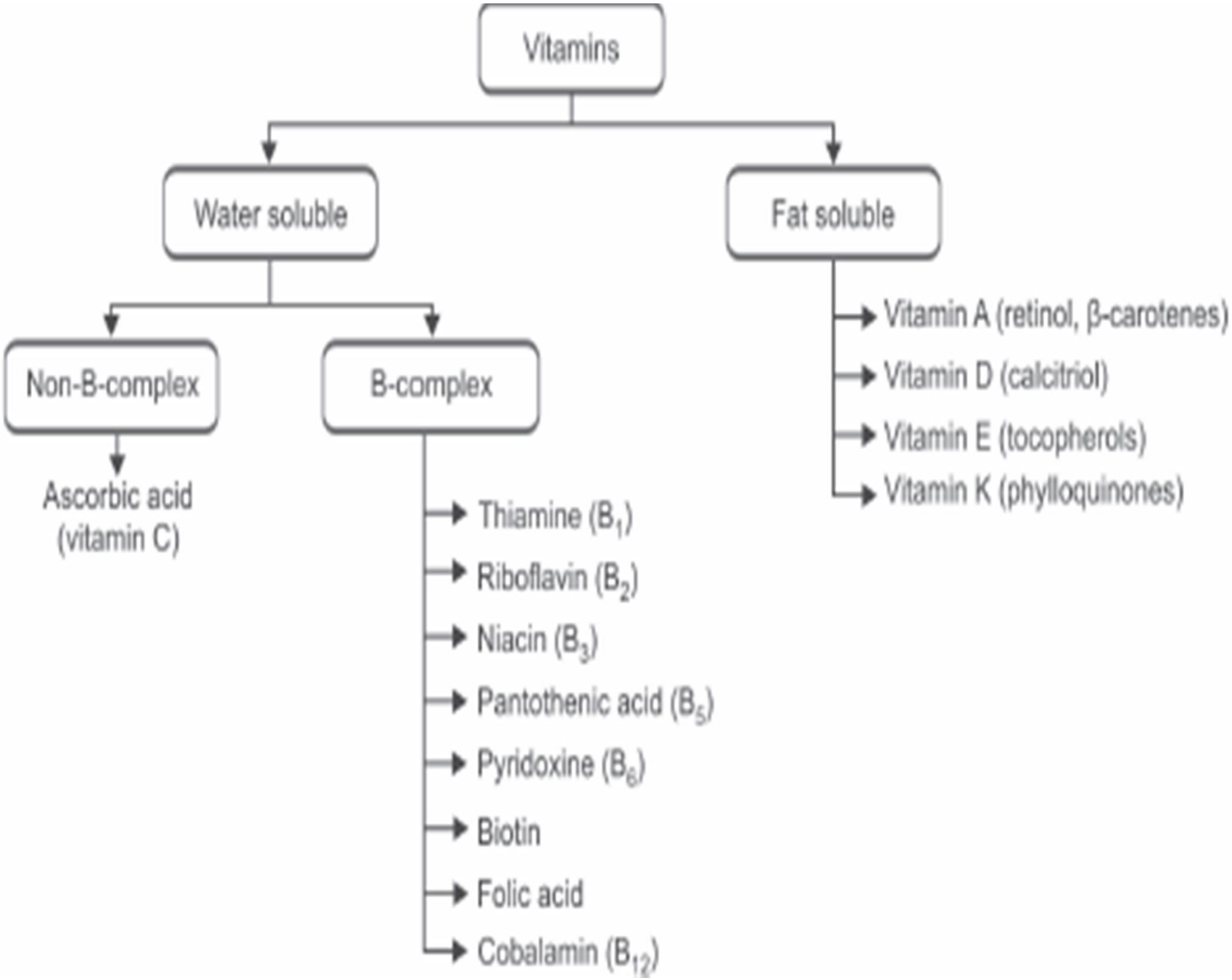
Vitamins

organic substances, required in very small amounts, for optimum growth and health, but cannot be synthesized in our body (except vitamin D and niacin).

Classification

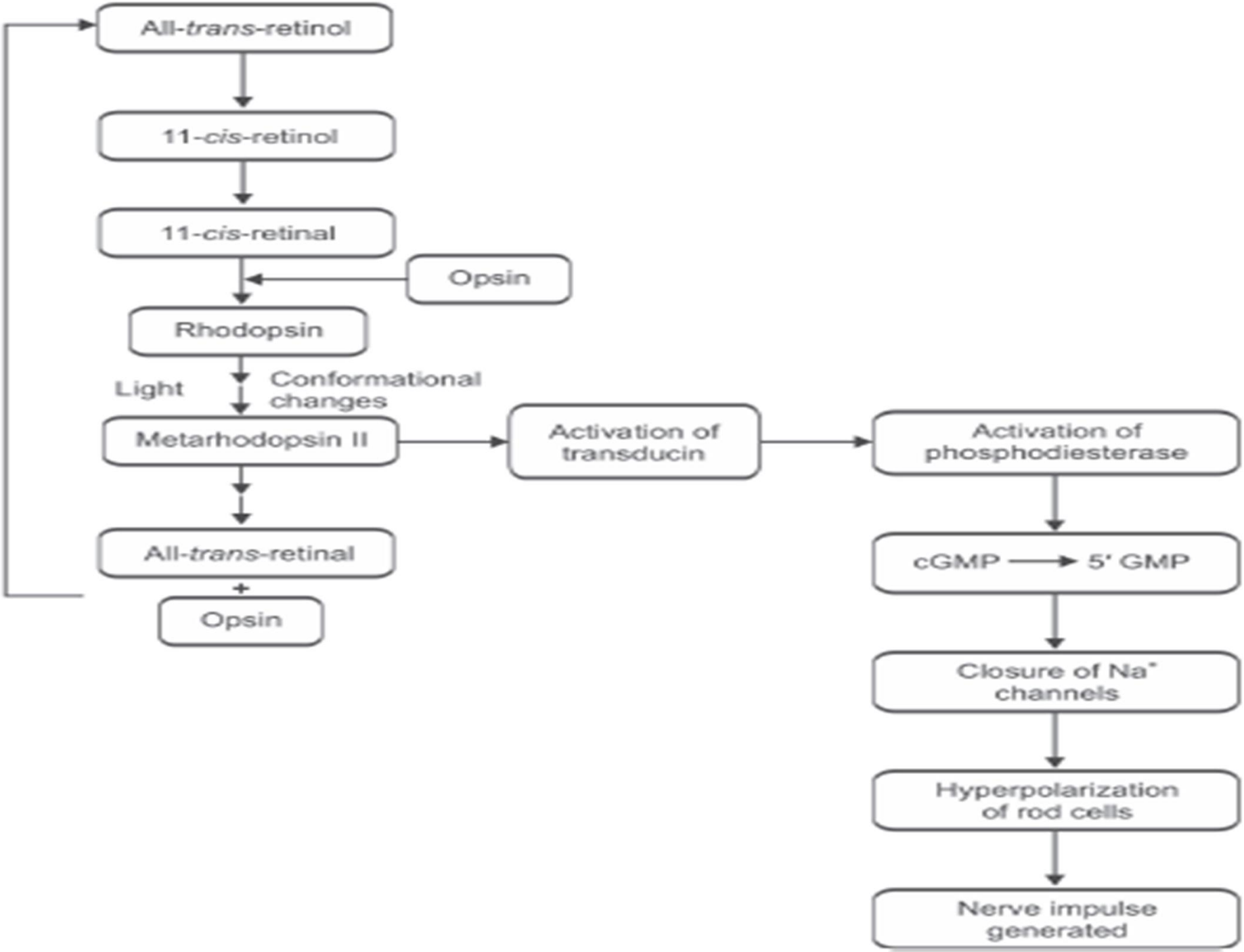
i. Fat-soluble vitamins.
ii. Water-soluble vitamins


Vitamins
Water soluble
Fat soluble
Non-B-complex
B-complex
Ascorbic acid
(vitamin C)
Thiamine (B_1)
Riboflavin (B_2)
Niacin (B_3)
Pantothenic acid (B_5)
Pyridoxine (B_6)
Biotin
Folic acid
Cobalamin (B_{12})
Vitamin A (retinol, β-carotenes)
Vitamin D (calcitriol)
Vitamin E (tocopherols)
Vitamin K (phylloquinones)

Vitamin A

RDA	Sources	Functions
750 µg of vitamin A	Animal sources: liver, egg yolk, fish liver oil, milk Plant sources (carotene): carrot, mango, papaya, green vegetables	• Vision • Growth, development and tissue differentiation • For normal reproduction • Maintain integrity of epithelial cells • Synthesis of glycoproteins • Antioxidant

Deficiency symptoms	Toxic manifestations [MN: HALT]
Vision: Loss of sensitivity to green light, increased dark adaptation time, night blindness, xerophthalmia, Bitot's spots, keratomalacia, blindness	Headache, hepatomegaly, hypercalcemia Alopecia
Others: Follicular hyperkeratosis, increased susceptibility to infection, anemia	Hyperlipidemia Teratogenicity


All-*trans*-retinol
11-*cis*-retinol
11-*cis*-retinal
Opsin
Rhodopsin
Light
Conformational changes
Metarhodopsin II
Activation of transducin
Activation of phosphodiesterase
cGMP → 5' GMP
Closure of Na+ channels
Hyperpolarization of rod cells
Nerve impulse generated
All-*trans*-retinal
+
Opsin

Vitamin D

Vitamin D forms	RDA and sources
Cholecalciferol/ergocalciferol/ calcitriol	5–15 µg or 400 IU Fish liver oil, egg yolk

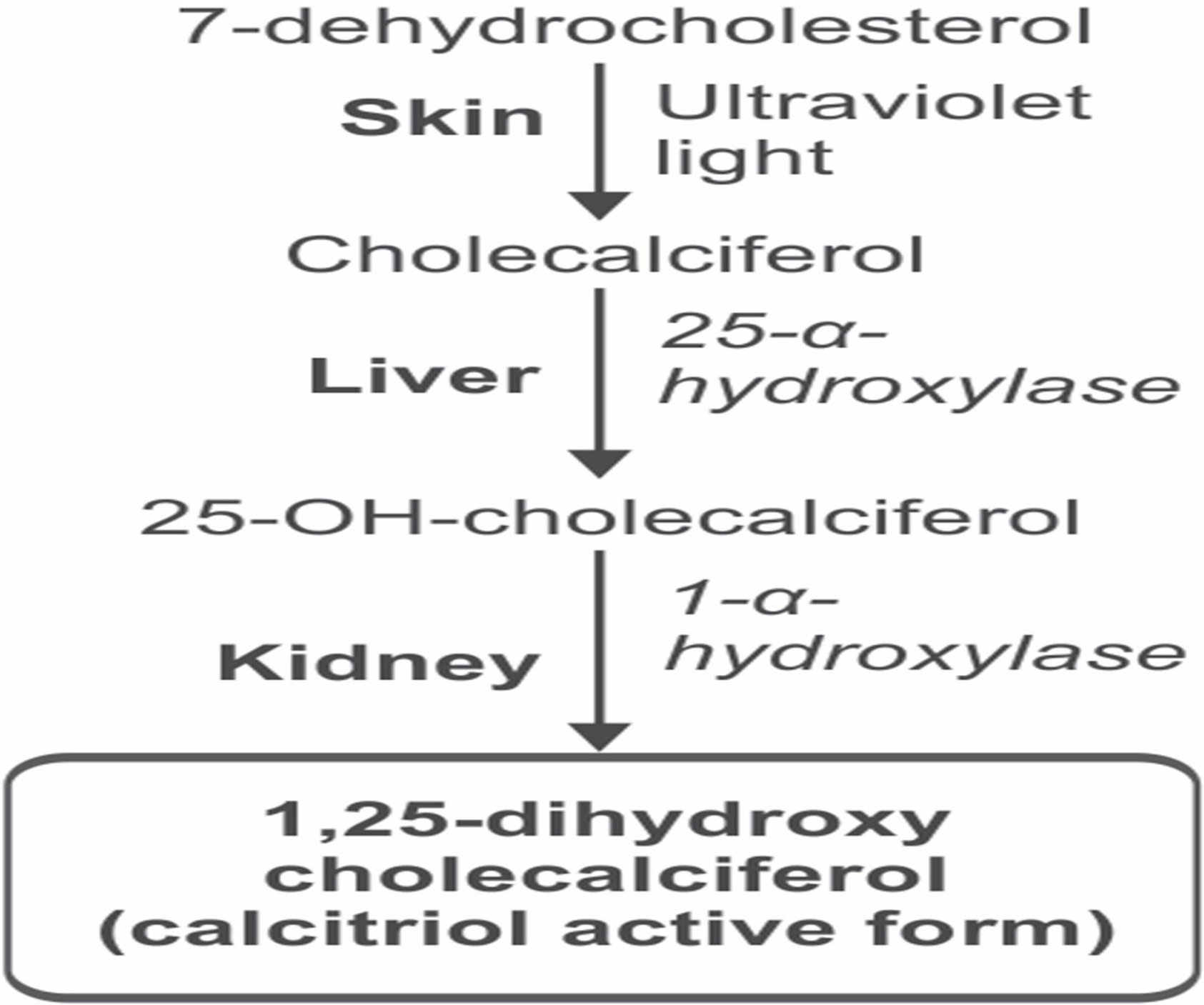
Metabolic Functions of Vitamin D

Maintains serum calcium and phosphorus levels by acting on bone, kidney and intestine.

- **Bone:** Causes mobilization of calcium and phosphate from the bone and promotes bone mineralization
- **Kidney:** Promotes reabsorption of calcium and phosphorus → decreases excretion of calcium and phosphorus
- **Intestine:** Increases absorption of calcium (via calbindin) and phosphorus

Causes of Deficiency

- Inadequate dietary intake
- Lack of exposure to sunlight
- Impaired absorption
- Liver and kidney diseases


7-dehydrocholesterol
Skin
Ultraviolet light
Cholecalciferol
Liver
25-α-hydroxylase
25-OH-cholecalciferol
Kidney
1-α-hydroxylase
1,25-dihydroxy cholecalciferol (calcitriol active form)

Transporter for vitamin D: Vitamin D2 and D3 are absorbed from the intestine and transported to the liver bound to a specific vitamin D-binding protein.

1-α-hydroxylase: It is present in the proximal convoluted tubules of the kidneys, bone and placenta.

Mechanism of action of calcitriol is similar to steroid hormones: Upon entering the nucleus of a cell, calcitriol functions as a steroid hormone and associates with the vitamin D receptor (VDR) and promotes its association with the retinoic acid X receptor (RXR), which binds to the gene and modulates transcription of calbindin in the intestine.

Hereditary rickets: It is an inherited form of the disease—the kidneys are unable to retain phosphate.

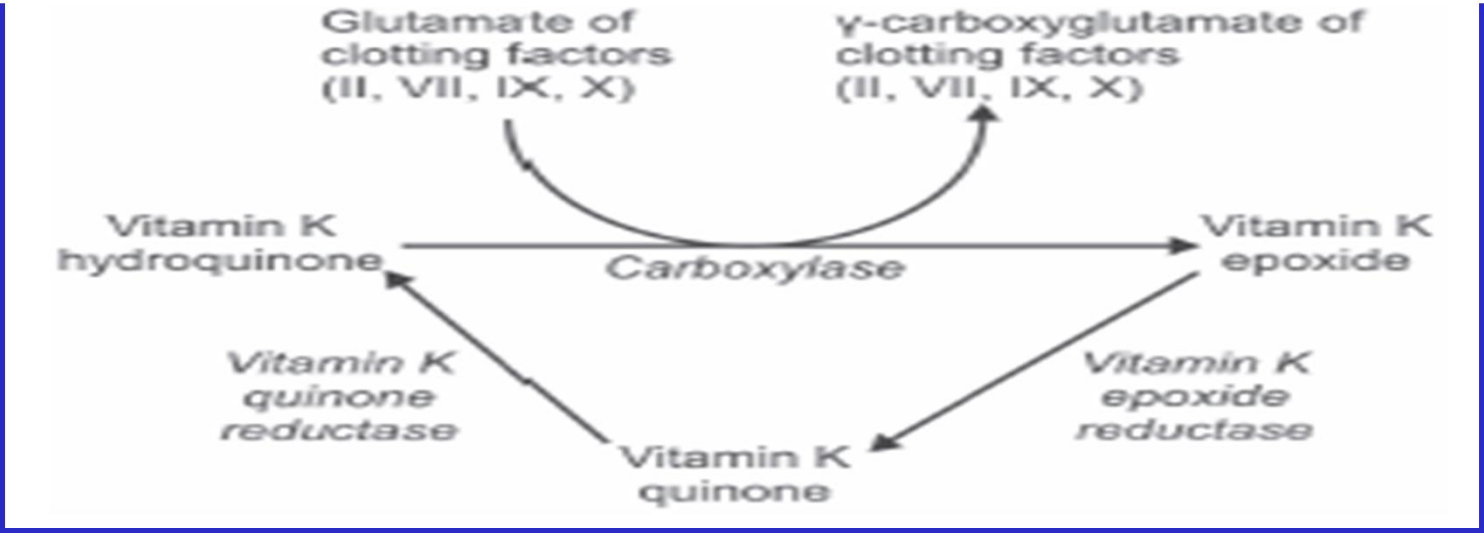
Fanconi syndrome: Disease of the proximal renal tubules of the kidney in which phosphate is passed into urine, instead of being reabsorbed.

Anticonvulsants like phenobarbital: Can cause hypocalcaemia, as it induces a microsomal enzyme (cytochrome P450), which inactivates vitamin D.

Vitamin K

Forms of vitamin K: Phylloquinone (K1), menaquinone (K2) and menadione (K3).
Recommended daily allowance (RDA) of vitamin K is 70–140 μg.

Sources	Functions
Green vegetables: cabbage, cauliflower, spinach (K_1); formed by intestinal bacteria, egg yolk, meat, liver (K_2); water soluble, synthetic form (K_3)	• Cofactor for synthesis of γ-carboxyglutamic acid (Gla) (Fig. 10.5) • Formation of Gla is a post-translational modification required for activation of clotting factors II, VII, IX and X. Gla helps these proteins to trap calcium • Other Gla proteins: osteocalcin and matrix Gla-protein (MGP) of bone



Causes for deficiency	Manifestations
Prolonged antibiotic treatment: Kills intestinal flora (which forms vitamin K in adults) Obstructive jaundice: No bile salt enters into the intestine, which is necessary for absorption of fat-soluble vitamins Malabsorption syndrome Newborn (premature): Their gut is sterile and mother's milk is not a good source of vitamin K Anticonvulsant treatment: They interfere with absorption of vitamin K	• Easy bruising, ecchymosis, bleeding • Increased prothrombin time

Differentiating features of vitamin K and vitamin C deficiency:

In contrast to vitamin K deficiency,

vitamin C deficiency will have increased bleeding time, but prothrombin time will be normal. Also, there will be gum hyperplasia, inflammation, skeletal deformity and poor wound healing.

Warfarin and dicumarol

Structural analogues of vitamin K, competitively inhibit the enzyme epoxide reductase and vitamin K quinone reductase. They are used as anticoagulants.

Toxic manifestations of vitamin K

In premature babies, menadione →↑ hemolysis →↑ serum unconjugated bilirubin → kernicterus.

Vitamin E

Mention the sources, RDA and functions of vitamin E.

The RDA, sources and functions of vitamin E are mentioned in Table

Active form	RDA and sources	Functions
α-tocopherol	RDA: 8–10 mg Wheat germ oil (richest source), oils from nuts and seeds	• **Antioxidant:** Prevents peroxidation of polyunsaturated fatty acids and plasma lipoproteins • **Prevention of atherosclerosis, cancer and aging:** by reducing oxidative stress • May have a role in cell signaling

Vitamin E deficiency

Deficiency in humans is very rare. The major symptoms are increased red blood cell (RBC) fragility due to peroxidation.

Water-Soluble Vitamins

Thiamine (Vitamin B1)

Coenzyme form	Sources and RDA	Functions
Thiamine pyrophosphate (TPP)	Unrefined grains, legumes (e.g. beans), nuts and yeast RDA: 1.0–1.5 mg (directly proportional to amount of carbohydrates in the diet)	• Coenzyme for pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, branched chain α-ketoacid dehydrogenase and transketolase • Nerve conduction

Deficiency disease: (Fig. 10.6)

Dry beriberi (mainly neurological features)

- Peripheral neuropathy—diminished sensation and weakness in the legs and arms
- Muscle pain and tenderness, and difficulty in rising from a squatting position

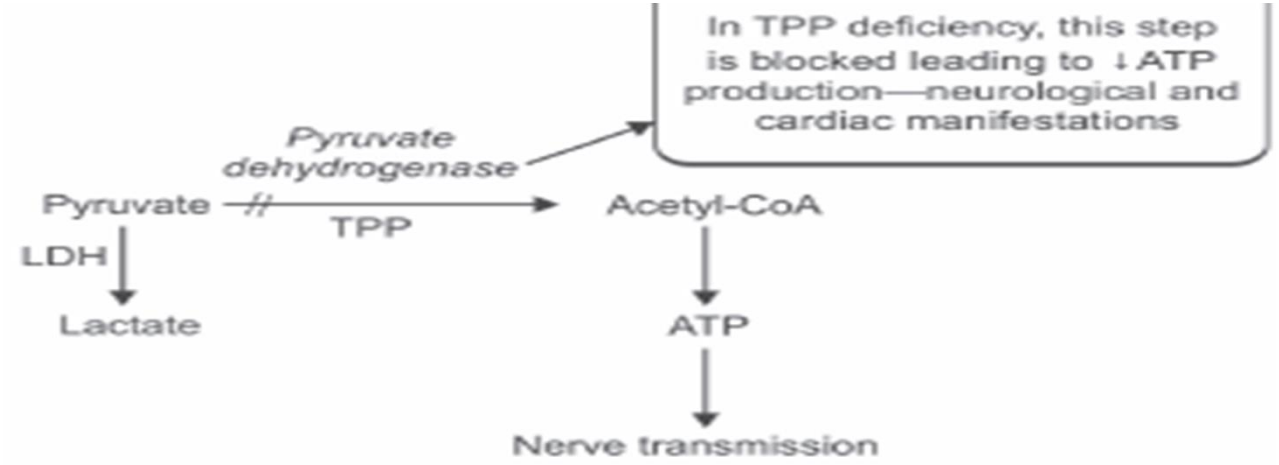
Wet (cardiac) beriberi

- Edema, difficulty in breathing and ultimately congestive heart failure

Wernicke's encephalopathy and Korsakoff's psychosis: Seen in alcoholics and manifests as:

- Abnormal eye movements
- Abnormal gait
- Dementia
- Psychosis

Infantile beriberi: Occurs in children born to mother with thiamine deficiency. It presents with tachycardia, convulsions, etc.



: Consequences of thiamine deficiency (TPP, thiamine pyrophosphate; ATP, adenosine triphosphate; LDH, lactate dehydrogenase; // = blocked)

Requirement of B1 increases when a person is placed on high-carbohydrate diet: This is due to increase in TPP-mediated reactions (e.g. pyruvate to acetyl-CoA, α-ketoglutarate to succinyl-CoA, etc.) in carbohydrate metabolism.

Antithiamine factors: Certain raw freshwater fish, raw shellfish, ferns (they contain thiaminases, which destroys thiamine).

Thiamine pyrophosphotransferase: Converts thiamine to its active form TPP in the brain and liver.

Transketolase activity: in RBCs is used to measure the thiamine status in an individual.

Riboflavin (Vitamin B2)

Coenzyme forms	RDA and sources	Functions
Flavin mononucleotide (FMN) Flavin adenine dinucleotide (FAD)	RDA: 1.2–1.7 mg Milk and dairy products, egg, whole cereals, green leafy vegetables	Flavin coenzymes are involved in mitochondrial respiratory chain, fatty acid and amino acid oxidation, and citric acid cycle. They play a role in the metabolism of drugs and toxins (cytochrome P450) **FMN-dependent enzymes** • L-amino acid oxidase • NADH dehydrogenase (electron transport chain) **FAD-dependent enzymes** • Pyruvate dehydrogenase • α-ketoglutarate dehydrogenase • Glycerol-3-phosphate dehydrogenase (shuttle transport in electron transport chain) • Acyl-CoA dehydrogenase • Xanthine oxidase

Deficiency manifestations of riboflavin:
Glossitis, angular stomatitis, cheilosis.

Niacin (Vitamin B3)

Coenzyme form	RDA and sources	Functions
Nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate ($NADP^+$)	RDA: 10–15 mg Yeast, meat, poultry, fish, cereals, legumes	Coenzyme in oxidation-reduction (redox) reactions • NAD^+ is involved in the catabolism of carbohydrates, fats, proteins and alcohol to produce energy • For example: α-ketoglutarate → succinyl-CoA; Succinate → fumarate • $NADP^+$ functions more often in biosynthetic (anabolic) reactions, such as in the synthesis of fatty acids and cholesterol • NAD^+ is source of ADP-ribose for ADP-ribosylation of proteins

Carcinoid syndrome and pellagra:

Normally 1%–2% of tryptophan is converted to serotonin in argentaffin cells of gastrointestinal tract (GIT) and the rest is converted to niacin. But in carcinoid syndrome (tumor of argentaffin cells), more than 60% of tryptophan is diverted for serotonin, so less is available for niacin synthesis leading to pellagra.

Hartnup disease and pellagra:

Tryptophan and other neutral amino acids are not absorbed from intestine and also from kidneys, thus depleting amino acid tryptophan. This in turn leads to niacin deficiency (pellagra).

Pyridoxine and pellagra:

Synthesis of nicotinamide from tryptophan is pyridoxal phosphate (PLP) dependent; so in its deficiency, this pathway will not proceed and may lead to pellagra.

Pharmacologic doses of nicotinic acid have been known to reduce serum cholesterol.

Pyridoxine (Vitamin B6)

Coenzyme form	RDA and sources	Functions
Pyridoxal phosphate (PLP)	RDA: 1.4–2.0 mg Whole grain cereals, eggs, legumes, milk	PLP acts as a coenzyme for: • Transamination: Aspartate + α-ketoglutarate → glutamate + oxaloacetate • Deamination: Serine → pyruvate • Transsulfuration: Formation of cysteine from methionine • Cystathionine synthase, cystathionase, kynureninase • Heme synthesis: Aminolevulinic acid (ALA) synthase • Decarboxylation reactions of amino acids • Ceramide synthesis (palmitoyl-CoA + serine) • Glycogenolysis

Tuberculosis: The antitubercular drug isoniazid, competes with pyridoxine kinase and blocks the formation of PLP. Thus, long-term treatment with isoniazid can result in pyridoxine deficiency, which manifests as peripheral neuropathy; so pyridoxine is given along with isoniazid in tuberculosis patients.

Treatment of microcytic anemia: Along with iron and other supplements, pyridoxine is given, which helps in heme synthesis [aminolevulinic acid (ALA) synthase reaction].

In infants, pyridoxine deficiency can predispose to seizures: This may be due to decreased formation of γ-aminobutyric acid (GABA) from glutamic acid (decarboxylation reaction). GABA is an inhibitory neurotransmitter, so its decreased concentration can lead to seizures.

Deficiency manifestations of B6: Irritability, depression, confusion, glossitis, stomatitis.
Cycloserine, penicillamine: Form complexes with vitamin B6, creating a functional deficiency.
Parkinsonism treated with levodopa: Administration of pyridoxine will facilitate the peripheral decarboxylation of levodopa to dopamine; treatment becomes less effective as less of levodopa is available to cross into the brain.

Dietary requirement of B6 increases when a person is placed on high-protein diet: Pyridoxine has significant role in protein metabolism (transamination, decarboxylation, deamination and condensation reactions). So, its requirement is directly proportional to protein intake.

Folic Acid (Vitamin B9)

Coenzyme form	RDA and sources	Functions
Tetrahydrofolic acid (THFA)	RDA: 200 µg Green leafy vegetables (foliage), legumes and fortified cereals	• Carry and transfer various forms of one carbon units during biosynthetic reactions; one carbon donors are Glycine, Histidine, Odd chain fatty acids, Serine, Tryptophan **[MN: GHOST]** • Required for biosynthesis of serine, methionine, glycine, choline, purine nucleotides and thymidylate (dTMP) • Conversion of homocysteine to methionine

Causes of deficiency	Manifestations of folate deficiency
Dietary deficiency: alcoholics and overcooking of food **Impaired absorption:** tropical sprue, celiac disease **Increased demand:** pregnancy, lactation **Anticancer drugs:** methotrexate	↓ DNA synthesis during erythrocyte maturation → ↓ DNA replication + uninhibited protein synthesis → bigger than normal RBCs **(megaloblasts)** **Homocystinemia:** Folic acid is required (with B_{12} and B_6) for synthesis of methionine from homocysteine. So, folic acid deficiency leads to homocystinemia **Neural tube defect:** Since folate is required for nucleic acid synthesis, lack of this vitamin leads to neural tube defects in newborn. Hence, every pregnant woman is administered folic acid in the first trimester **Predisposition to cancer**

Inhibit some drug

Names	Uses
Methotrexate	Inhibits dihydrofolate reductase. Used as an anticancer drug
Trimethoprim	Inhibits bacterial dihydrofolate reductase. Used as an antimicrobial agent
Pyrimethamine	Antimalarial agent
Sulfonamide	Antibacterial agent

Folinic acid (leucovorin or citrovorum factor):

It is administered before giving methotrexate to prevent its systemic toxicity; methotrexate blocks the conversion of dihydrofolate to THFA. Folinic acid (N5 formyl-THFA) is the active coenzyme form and minimizes toxic effect of methotrexate on normal cells; this is leucovorin rescue.

Formiminoglutamate (FIGLU) excretion test:

It is done to detect folic acid deficiency. In folic acid deficiency, increased excretion of FIGLU is observed after a load, due to impaired conversion of FIGLU to glutamate.

Cobalamin (Vitamin B12)

Coenzyme form	RDA and sources	Functions
5-deoxyadenosylcobalamin, Methylcobalamin	RDA: 1 μg Only bacteria can synthesize vitamin B_{12} Animal products such as meat, eggs, fish No plant source	• **Methylcobalamin:** Required for enzyme methionine synthase (homocysteine → methionine) • **5-deoxyadenosylcobalamin:** Required for enzyme methylmalonyl-CoA mutase (propionyl-CoA → succinyl-CoA)

Causes of deficiency	Deficiency manifestations
Decreased intake: Strict vegetarians and alcoholics **Impaired absorption:** Due to lack of intrinsic factor (pernicious anemia); atrophic gastritis **Increased demand:** Pregnancy	**Megaloblastic anemia:** Due to folate trap, folate is unavailable to participate in DNA synthesis resulting in formation of megaloblasts leading to anemia **Homocysteinemia:** Vitamin B_{12} is required (with folic acid and B_6) for synthesis of methionine from homocysteine ↓ Vitamin B_{12} → ↑ homocysteine → ↑ risk of cardiovascular disease **Methylmalonic acidemia:** Due to block in the conversion of methyl malonic acid to succinyl-CoA **Neurological symptoms:** Demyelination due to vitamin B_{12} deficiency—peripheral neuropathy, ataxia, both sensory and motor fibers are affected

Absorption of B12: Vitamin B12 binds to intrinsic factor (IF), a glycoprotein secreted by parietal cells of stomach. Receptors on the surface of the ileum take up the IF-B12 complex in the presence of calcium. It is bound to transcobalamin II and transported to the liver.
Vitamin B12: Only water-soluble vitamin stored in the liver (sufficient for upto 6 years).

Subacute combined degeneration of spinal cord (SACD): Group of neurologic symptoms—peripheral neuropathy, tingling, numbness, weakness, mental disturbances and ataxia seen in cobalamin deficiency.

Folate trap: In vitamin B12 deficiency, conversion of methyltetrahydrofolate (methyl-FH4) to tetrahydrofolate (FH4) is affected and results in accumulation of methyl TH4. Thus, deficiency of vitamin B12 can cause secondary folate deficiency.

Cyanocobalamin, mehylcobalamin (oral) and hydroxocobalamin (parenteral/injectable): Are commercially available forms of cobalamin.
Schilling test: This is a test used to detect pernicious anemia (or to detect cause of megaloblastic anemia). The patient is first given a saturating dose of vitamin B12 by injection and then given radiolabeled B12 orally. If after sometime, there is no appearance of radioactivity in urine, it means oral B12 is not absorbed. Then, oral radiolabeled vitamin B12 is given along with intrinsic factor and
urine radioactivity is checked after some time. If it appears in urine, it indicates the person has perniciousanemia. If there is still no radioactivity in urine, the person has malabsorption syndrome.

Biotin (Vitamin B7)

RDA and sources	Functions	Deficiency manifestations
RDA: 30–100 µg Egg yolk, liver, yeast, intestinal flora	Required for carboxylation reactions in fatty acid synthesis and gluconeogenesis • Acetyl-CoA carboxylase • Pyruvate carboxylase • Propionyl-CoA carboxylase	Dermatitis, hair loss (deficiency is rare)

Biotinidase:
Shown to catalyze the biotinylation of histones, suggesting that biotin may play a role in DNA replication and transcription.

Consumption of raw egg white for a prolonged period may cause biotin deficiency as it contains a protein avidin, which strongly binds biotin and prevents its absorption.

Pantothenic Acid (Vitamin B5)

Coenzyme form	RDA and Sources	Functions	Deficiency manifestations
Coenzyme A (CoASH)	RDA: 10 mg Liver, yeast, egg yolk, intestinal flora	• Tricarboxylic acid (TCA) cycle and gluconeogenesis • For synthesis of fatty acid, cholesterol and steroid hormones • Acetylcholine, melatonin synthesis • Heme synthesis • Ketone body synthesis and utilization	Deficiency is rare • Burning foot syndrome: Numbness and tingling of hands and feet

Ascorbic Acid (Vitamin C)

RDA and sources	Functions
RDA: 75 mg Amla, guava, citrus fruits, green vegetables	• Hydroxylation of proline and lysine residues in collagen • Antioxidant: protects proteins, lipids, carbohydrates and nucleic acids from damage by free radicals • Synthesis of norepinephrine, carnitine • Involved in the conversion of cholesterol to bile acid • Role in tryptophan and tyrosine metabolism

Scurvy

Deficiency of vitamin C leads to scurvy: There is poor hydroxylation of proline and lysine residues of collagen.

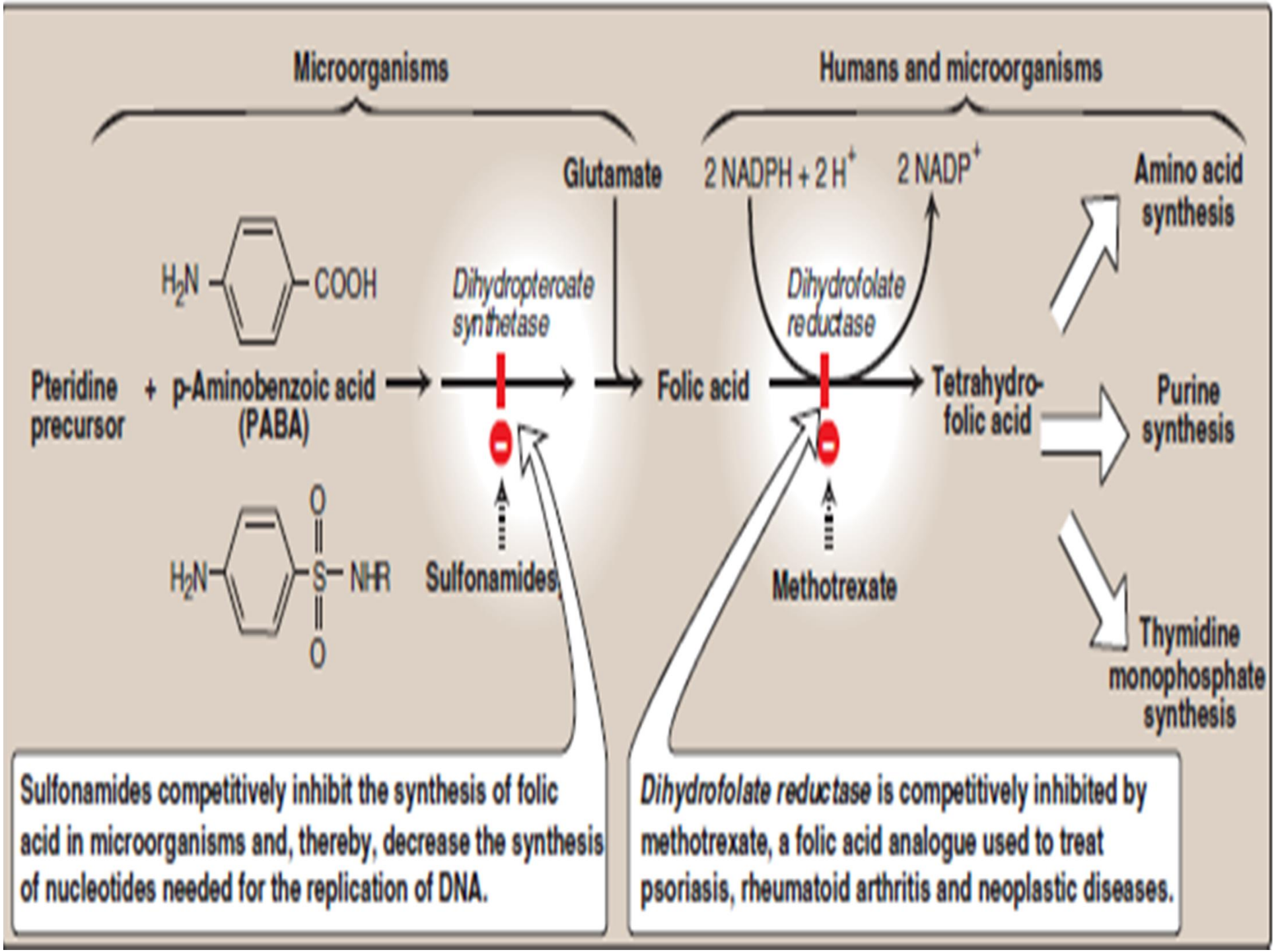
Symptoms: Bleeding and easy bruising, hair and tooth loss, joint pain and swelling, poor wound healing, etc.

Treatment: Vitamin C supplementation.

High doses of vitamin C predisposes to renal stone:
Vitamin C is metabolized to oxalic acid and it is capable of precipitating calcium as calcium oxalate in the urine.
Vitamin C cannot be synthesized in humans:
Because they lack the enzyme, L-gulonolactone oxidase.

Lipoic acid: Acts as coenzyme for oxidation-reduction reactions (pyruvate dehydrogenase and α-ketoglutarate dehydrogenase) and has antioxidant functions.

Choline: Lipotropic factor and prevents fatty liver.


Microorganisms
Humans and microorganisms
Glutamate
2 NADPH + 2 H+
2 NADP+
Amino acid synthesis
H2N
COOH
Dihydropteroate synthetase
Dihydrofolate reductase
Pteridine precursor
+ p-Aminobenzoic acid (PABA)
Folic acid
Tetrahydro-folic acid
Purine synthesis
O
H2N
S
NHR
O
Sulfonamides
Methotrexate
Thymidine monophosphate synthesis
Sulfonamides competitively inhibit the synthesis of folic acid in microorganisms and, thereby, decrease the synthesis of nucleotides needed for the replication of DNA.
Dihydrofolate reductase is competitively inhibited by methotrexate, a folic acid analogue used to treat psoriasis, rheumatoid arthritis and neoplastic diseases.