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→ Means Using Medicine to fight Against Free Radical.

Unit-5

Cause of Disease.

Etiology. Pathogenesis → Development of Disease.

Free radicals Pharmacology-

Generation of free radicals, role of free radicals in etiopathology of various diseases

such as diabetes, neurodegenerative diseases and cancer.

Protective activity of certain important antioxidant

Recent Advances in Treatment:

Alzheimer's disease, Parkinson's disease, Cancer, Diabetes mellitus

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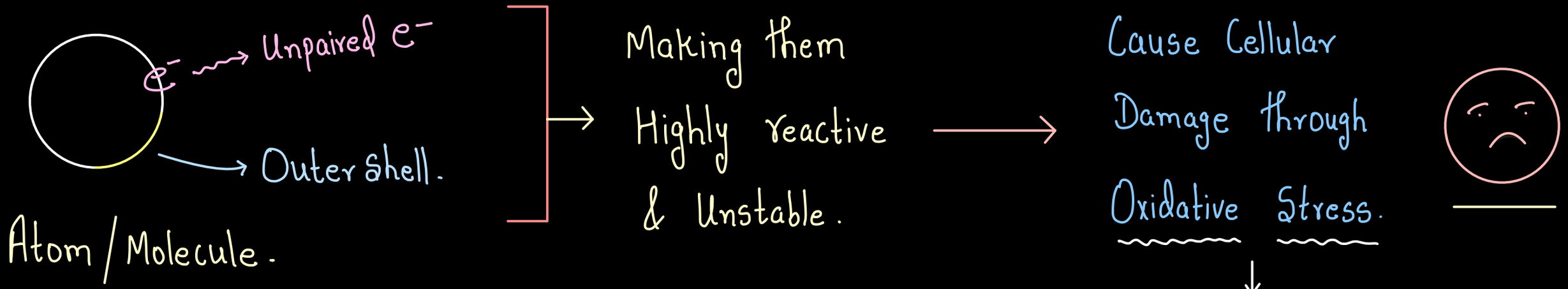
→ Oxidative Stress → Imbalance b/w Free Radicle & Anti-Oxidant.

Free Radical -

*Free radicals are atoms or molecules that have one or more unpaired electrons in their outer shell, making them highly reactive and unstable.



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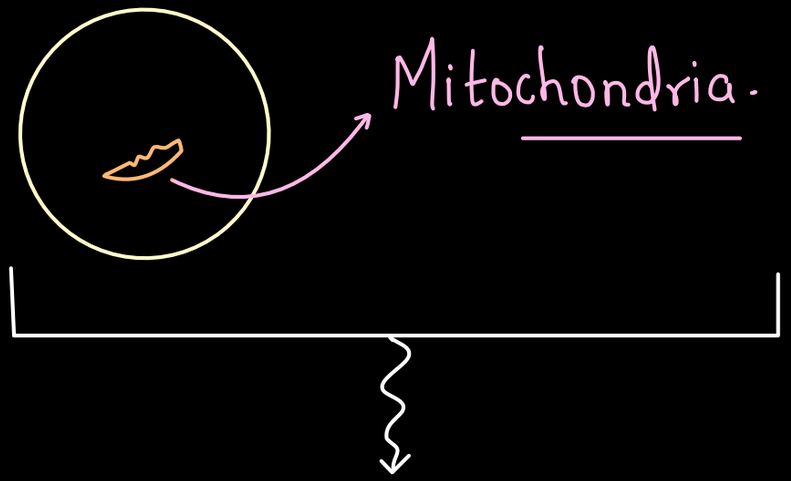
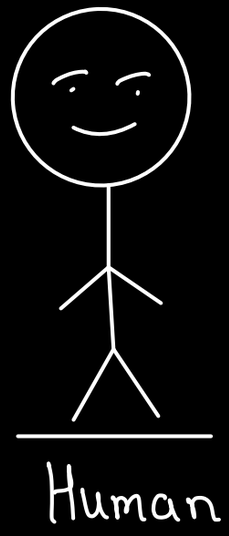


Radicals are primarily generated during Normal Cellular Metabolism. especially in Mitochondria.

- Cell Signalling
- Immune defense

Apoptosis.



Pollution
Smoking
Radiation.

Enviromental factor.

Free Radical Generate.

excess Accumlation.

Lead to Oxidative Damage to Lipid, Protein, DNA.

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These radicals are primarily generated during normal cellular metabolism, especially in the mitochondria, but can also arise due to environmental factors such as pollution, radiation, smoking, and exposure to toxic chemicals.

Although free radicals play essential physiological roles in cell signaling, immune defense, and apoptosis, an excess accumulation leads to oxidative damage to lipids, proteins, and DNA.

This oxidative stress has been implicated in the pathogenesis of numerous chronic diseases, including cancer, cardiovascular disorders, neurodegenerative diseases (like Alzheimer's and Parkinson's), diabetes mellitus, and aging-related degeneration.

Generation of Free Radicals

[A.] Endogenous Sources (Inside the Body)-

These are normal processes in our body that accidentally generate free radicals:

1. Mitochondria (Cell's Powerhouse)-

During ATP (energy) production, oxygen is used.
Sometimes, oxygen is partially reduced forming:
Superoxide anion (O_2^-)
This is one of the first steps in free radical generation.

ATP formation.
⇝ में
O_2 is Used.
⇝
Sometime O_2 is partially reduced & forming $[O_2^-]$

2. Enzymatic Reactions-

Some enzymes produce free radicals as part of their function:

Xanthine oxidase
Cytochrome P450 enzymes
Cyclooxygenase (COX)
Lipoxygenase (LOX)

→ These are involved in metabolism and inflammation.

3. Immune Cells (Neutrophils, Macrophages)-

During infections, white blood cells produce free radicals to kill bacteria.

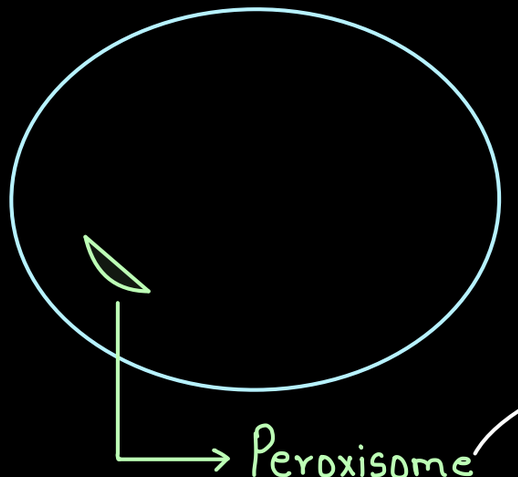
Example: NADPH oxidase generates superoxide during phagocytosis.

O_2^-

4. Peroxisomes-

These cell structures help in fat breakdown (β-oxidation).

In the process, hydrogen peroxide (H_2O_2) is produced



Peroxisome

Break Fatty Acid & Amino Acid.

& Produce H_2O_2

May Generate OH^- free Radical.

5. Transition Metals (Iron, Copper)-

These metals can catalyze Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {\bullet}OH + OH^-$$

→ Produces hydroxyl radicals which are highly reactive.

B. Exogenous Sources (Outside the Body)-

These sources are environmental and increase oxidative stress:

1. Radiation (UV light, X-rays, Gamma rays) ⟶

Break water molecules in the body to form:
Hydroxyl radicals (•OH)
Hydrogen radicals (H•)

$H_2O \longrightarrow H^{\bullet}$ & $OH^{\bullet}$

2. Pollutants & Chemicals ⟶

Cigarette smoke, pesticides, industrial smoke contain harmful chemicals that generate free radicals.

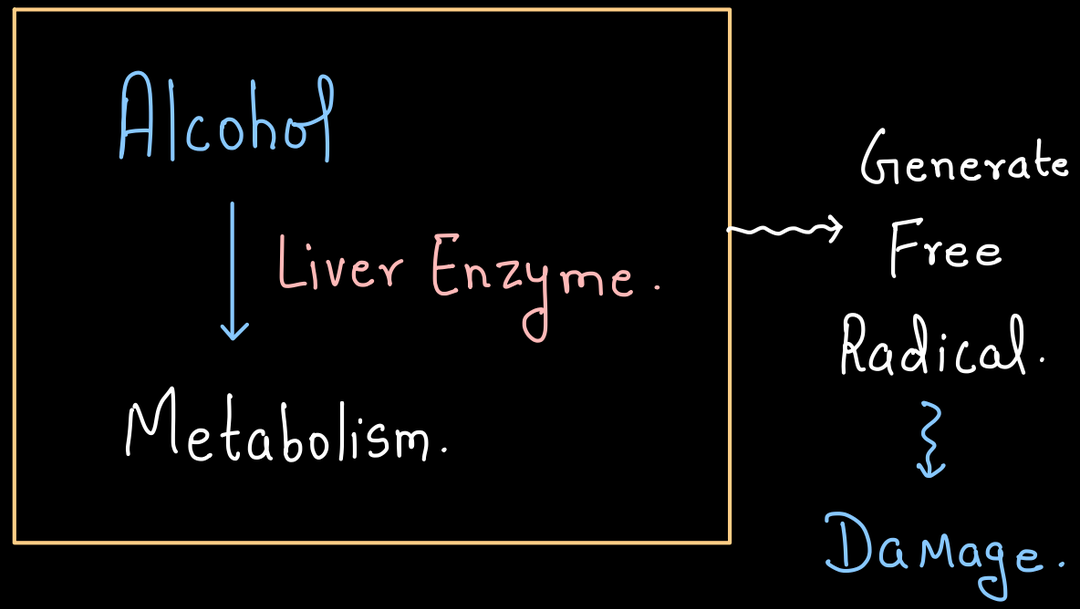
3. Drugs and Toxins-

Some drugs (like doxorubicin) undergo redox cycling, generating ROS.

4. Alcohol and Poor Diet-

Alcohol metabolism (via CYP2E1) generates free radicals.

Deficiency in antioxidants (Vitamin E, C, glutathione) increases the damage.



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Source Type	Key Processes	Free Radicals Produced
Mitochondria	ATP production	$O_2^{-}\bullet$ (superoxide)
Immune Cells	Killing pathogens	$O_2^{-}\bullet$, $NO\bullet$
Radiation	Water breakdown	$\bullet OH$, $H\bullet$
Drugs/Pollutants	Redox reactions	$O_2^{-}\bullet$, H_2O_2
Metals	Fenton reaction	$\bullet OH$

Role in Etiopathology (Disease Development)-

Free radicals contribute to the initiation, progression, and complications of many diseases through oxidative stress (imbalance between free radicals and antioxidants).

* Free Radical → Contribute to Initiation, Progression & Complication. of Many disease through Oxidative Stress.

Protective activity of certain important antioxidant

-Antioxidants are molecules that protect the body by neutralizing free radicals and preventing oxidative stress.

-They donate an electron to stabilize free radicals

Mechanism of Action of Antioxidants:

Free radical scavenging – Antioxidants donate electrons to stabilize ROS.

Metal chelation – They bind to metals (like Fe^{2+}, Cu^{2+}) to stop the Fenton reaction.

Enzyme activation – Enhance action of enzymes like SOD, catalase, glutathione peroxidase.

Repair of damaged molecules – Some antioxidants repair oxidized proteins or lipids.

📌 Types of Antioxidants & Their Examples

Type	Examples	Role
Enzymatic Antioxidants	Superoxide Dismutase (SOD), Catalase, Glutathione Peroxidase	Convert ROS to water or oxygen
Non-Enzymatic (Nutrient)	Vitamin C, Vitamin E, β-carotene, Selenium	Scavenge free radicals directly
Endogenous (Produced in body)	Glutathione (GSH), Coenzyme Q10, Uric acid	Maintain redox balance
Phytochemicals	Curcumin, Resveratrol, Flavonoids	Modulate inflammation & oxidative damage

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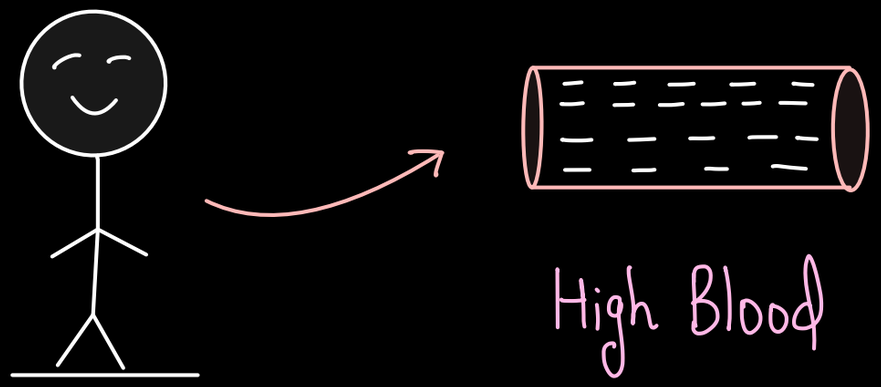
1. Diabetes-



High Blood Glucose ↑↑

↓

More Stress to Body

More Free Radical Generate.

↓

[Organ Damage Start.]

Natural Defense of Free Radical.

Anti-Oxidant

Can't Control Free Radicle.

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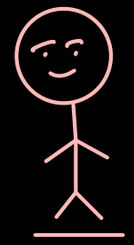

High ⟶ • High Energy Production.

• Glucose ↑

NADPH ⟶ Also, Used to Make

Sorbitol ↑

Glutathione ↓↓

≀

Strong Antioxidant.

2. Polyol pathway-

1. Mitochondria Leakage

e^- Leakage from Mitochondria.

e^- e^- e^- e^-

Lead to formation of Superoxide (O_2^-).

Free Radical.

3. AGEs (Advanced Glycation End-products):

- Glucose + Bind with Protein ⟶ Advanced Glycation End Product. [•AGE]

Activate NADPH Oxidase.

More ROS.

4. PKC (Protein Kinase C) Activation:

High Glucose ↑

Oxidative Stress ↑

Inflammation

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Damage Caused by Free Radicals in Diabetes:

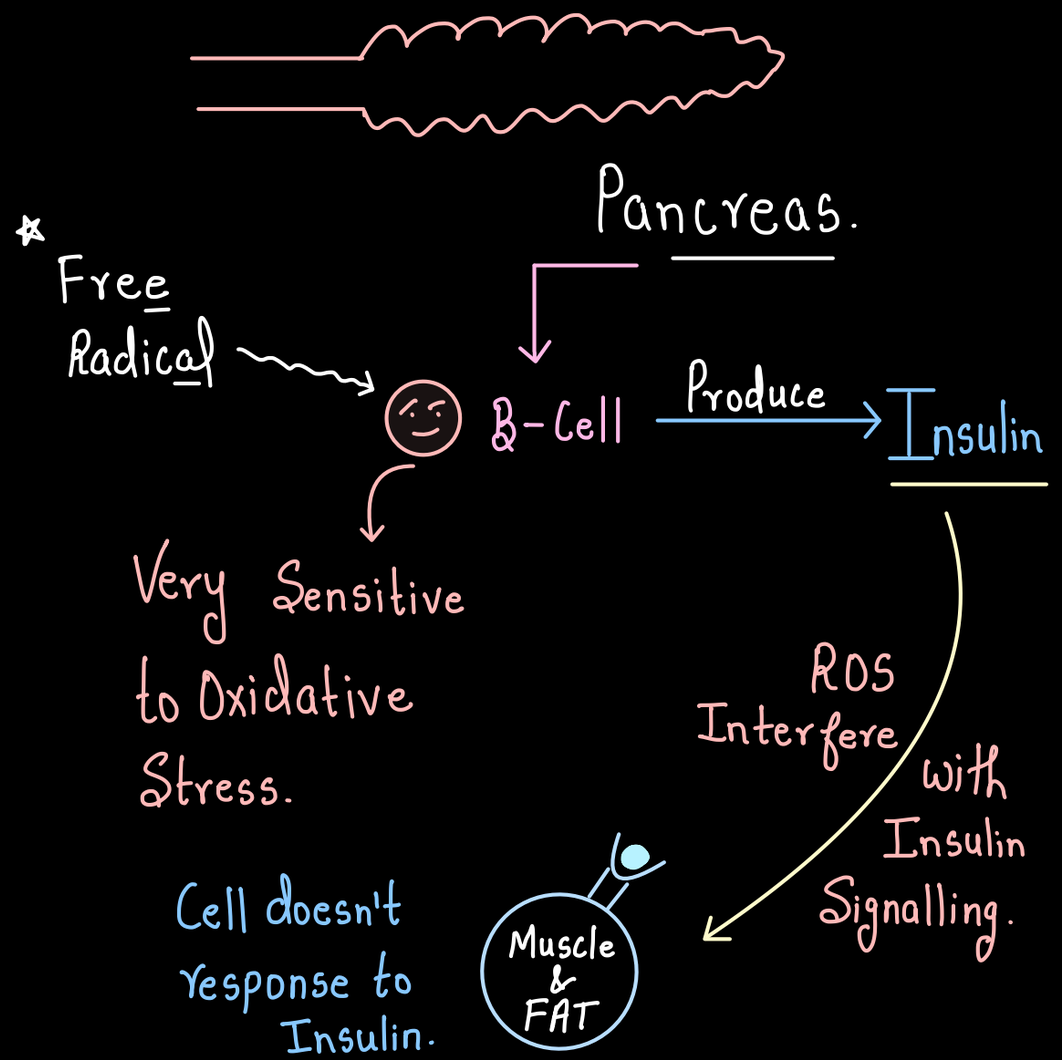
➤ 1. Pancreatic β-cell Damage:

β-cells make insulin but are very sensitive to oxidative stress

Free radicals damage them → less insulin produced

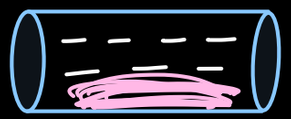
➤ 2. Insulin Resistance:

ROS interfere with insulin signaling in muscles and fat → cells don't respond well to insulin



➤ 3. Vascular Damage (Chronic Complications):

Complication	Free Radical Effect
Retinopathy	Damages blood vessels in eyes → vision loss
Nephropathy	Damages kidney filtration → protein loss in urine
Neuropathy	Damages nerves → numbness, tingling
Atherosclerosis	Damages blood vessels → heart disease, stroke



Plaque.

🩸 B. Antioxidants in Diabetes Mellitus

🧬 Problem:

- High blood sugar → more ROS → damage to β-cells and insulin resistance.

✅ Protective Role:

Antioxidant	Protective Function
Vitamin C & E	Scavenge ROS, reduce vascular damage
Alpha-Lipoic Acid (ALA)	Improves insulin sensitivity, reduces neuropathy
Glutathione	Detoxifies ROS, protects β-cells
Selenium	Boosts glutathione peroxidase activity
Zinc	Stabilizes insulin, supports antioxidant enzymes

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🧪 Recent Advances in Treatment:

Treatment Type	Examples	Action
SGLT2 Inhibitors	Empagliflozin, Dapagliflozin	Reduce blood glucose via urine
GLP-1 Agonists	Semaglutide, Liraglutide	Increase insulin secretion, weight loss
DPP-4 Inhibitors	Sitagliptin, Vildagliptin	Prolong GLP-1 action
Antioxidant Therapy	Alpha-lipoic acid, Vitamin C, NAC	Reduce oxidative stress in β-cells
Artificial Pancreas	Closed-loop insulin pumps	Auto-adjusts insulin in real time
Islet Cell Transplantation	Experimental	Restore natural insulin production

2. Neurodegenerative Disease -

[Alzheimer's Disease (AD), Parkinson's Disease (PD)].

Free radicals, especially Reactive Oxygen Species (ROS), play a major role in damaging neurons by:

1. Oxidative Damage:

Neurons use high oxygen and have high lipid content → highly sensitive to ROS.

ROS attack:

Lipids → lipid peroxidation

Proteins → misfolding, aggregation

DNA → mutations, apoptosis

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2. Mitochondrial Dysfunction:

ROS impair mitochondrial function → ↓ ATP → ↑ ROS → cell death cycle.

3. Neuroinflammation:

Free radicals activate microglia (brain immune cells) → release inflammatory cytokines → more damage.

4. Excitotoxicity:

Excess glutamate → overactivation of NMDA receptors → Ca^{2+} overload → ROS production → neuron death

Protective Role of Antioxidants in Neurodegeneration

Antioxidant	Mechanism of Protection
Vitamin E	Stops lipid peroxidation in brain cells
Curcumin	Inhibits amyloid aggregation, anti-inflammatory
Coenzyme Q10	Stabilizes mitochondria, reduces neuron loss
Resveratrol	Activates SIRT1, promotes neuron survival
N-Acetyl Cysteine (NAC)	Boosts glutathione, reduces oxidative stress

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📌 Parkinson's Disease:

Treatment	Action
Levodopa + Carbidopa	Replaces dopamine
MAO-B inhibitors (Selegiline, Rasagiline)	Reduce dopamine breakdown
Coenzyme Q10	Mitochondrial support, delays disease
Deep Brain Stimulation (DBS)	Improves motor symptoms
Stem cell therapy	Dopaminergic neuron replacement (experimental)
Gene therapy	AAV2-GDNF gene delivery in clinical trials

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📌 Alzheimer's Disease:

Treatment	Action
Lecanemab (2023 FDA approved)	Removes amyloid-β plaques
Cholinesterase inhibitors (e.g. Donepezil)	Improve memory and learning
Tau inhibitors (under research)	Block tau aggregation
Gene therapy	Targets BDNF (brain-derived neurotrophic factor)
Antioxidants	Curcumin, Vitamin E in trials for reducing progression

3. Cancer-

Cancer is a group of diseases involving uncontrolled growth and spread of abnormal cells.
If not controlled, it can invade nearby tissues or spread (metastasize) to other parts of the body.

How Free Radicals Contribute to Cancer:

Free radicals, especially Reactive Oxygen Species (ROS), play a major role in the initiation, promotion, and progression of cancer:

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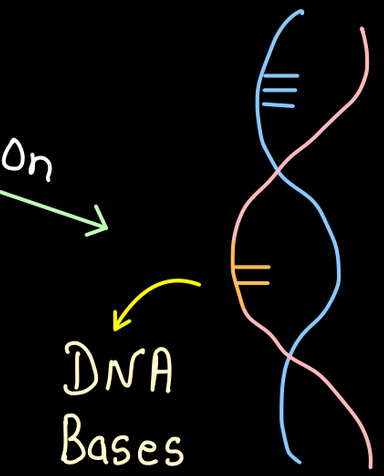
1.

ROS · Attack on DNA.



→ Lead to Mutation.

→ Damage Tumor [P-53 Supressor Gene.

→ Activation of Oncogenes.

↓

Uncontrolled Cell Growth.

↓

· Stimulate Cell Proliferation & Block Apoptosis.

· ROS promote Angiogenesis → formation of New Blood Vessel for Tumor.

↓

· Help Tumor Cell Invade New Tissue [Metastasis].

Example ROS Involved-

Superoxide anion ($O_2^{-\bullet}$)
Hydrogen peroxide (H_2O_2)
Hydroxyl radical ($\bullet OH$)

Protective Role of Antioxidants in Cancer Prevention-

How Antioxidants Help:

-Neutralize ROS and prevent DNA mutations.

-Inhibit inflammation and tumor-promoting signaling pathways.

-Enhance DNA repair and apoptosis of damaged cells.

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🧾 Examples of Key Antioxidants:

Antioxidant	Protective Action
Vitamin C	Neutralizes ROS, blocks nitrosamine (carcinogen) formation
Vitamin E	Prevents lipid peroxidation in cell membranes
Carotenoids (β-carotene, Lycopene)	Trap singlet oxygen, reduce tumor risk
Curcumin	Blocks NF-κB, reduces inflammation
Flavonoids	Modulate detox enzymes, antioxidant gene expression
Selenium	Cofactor for antioxidant enzyme glutathione peroxidase

⚠️ Note: In some cancer patients, excessive antioxidant supplementation may interfere with chemotherapy or radiotherapy — must be used cautiously.

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#Recent Advances in Cancer Treatment-

Modern treatments focus on targeted therapy, immune therapy, gene editing, and personalized medicine:

🔬 1. Targeted Therapy

- Drugs that **specifically block cancer cell signals** without harming normal cells.

Examples	Target
Imatinib	BCR-ABL (CML)
Trastuzumab	HER2 receptor (breast cancer)
Gefitinib	EGFR (lung cancer)
Olaparib	PARP (BRCA-mutated cancers)

🧪 2. Immunotherapy

- Uses the body's immune system to **identify and destroy** cancer cells.

Examples	Mechanism
Checkpoint inhibitors (e.g. Pembrolizumab, Nivolumab)	Block PD-1/PD-L1 → activate T cells
CAR-T Cell Therapy	Genetically engineered T cells attack cancer

↓

Modified Patient Own T-Cell.

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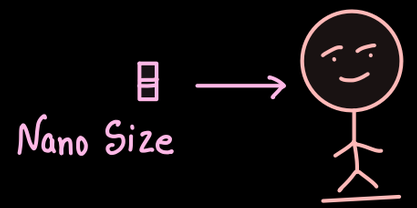
3. Gene Therapy & CRISPR-

Gene editing tools (like CRISPR/Cas9) to target oncogenes or repair mutations.
Still experimental but showing promise.

4. Nanotechnology-



- Nano-sized carriers used to deliver chemotherapy directly to tumors, minimizing side effects.

5. Combination Therapies-

- Combining chemotherapy + immunotherapy + antioxidants for better outcomes.