

# ROS and Detoxification Mechanisms

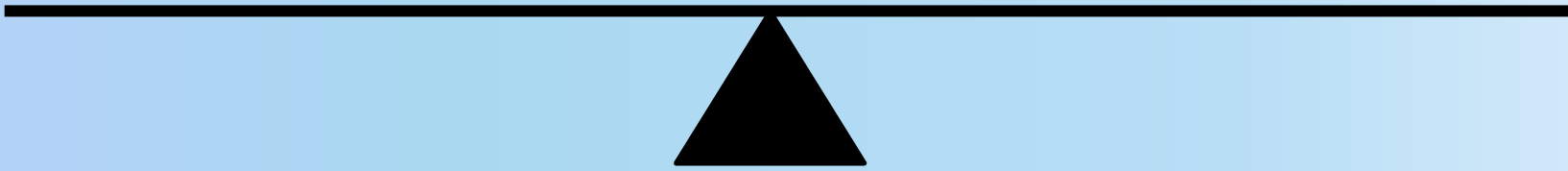
Melissa Cartwright

# Overview

- What are Reactive Oxygen Species?
- Sources of ROS
- ROS Defense Mechanisms
- ROS Cellular Damage
- Clinical Correlation: Ischemia Reperfusion Injury
  
- What are Xenobiotics?
- Body's Defense Mechanisms
- Phase I Reactions
- CYP450
- Phase II Reactions
- Clinical Correlation: Acetaminophen Metabolism

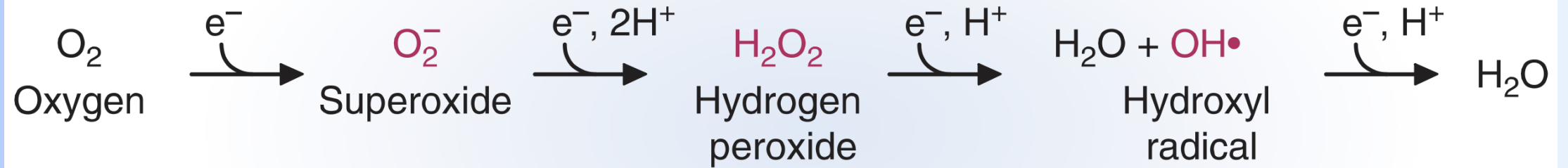
ROS

Antioxidants



Healthy Cell

# What are Reactive Oxygen Species (ROS)?



- ROS are generated when oxygen undergoes **partial reduction**
- **Hydroxyl radical** is the most reactive

Partially Reduced Oxygen = Dangerous Oxygen

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# Where do ROS come from?

## Endogenous Sources

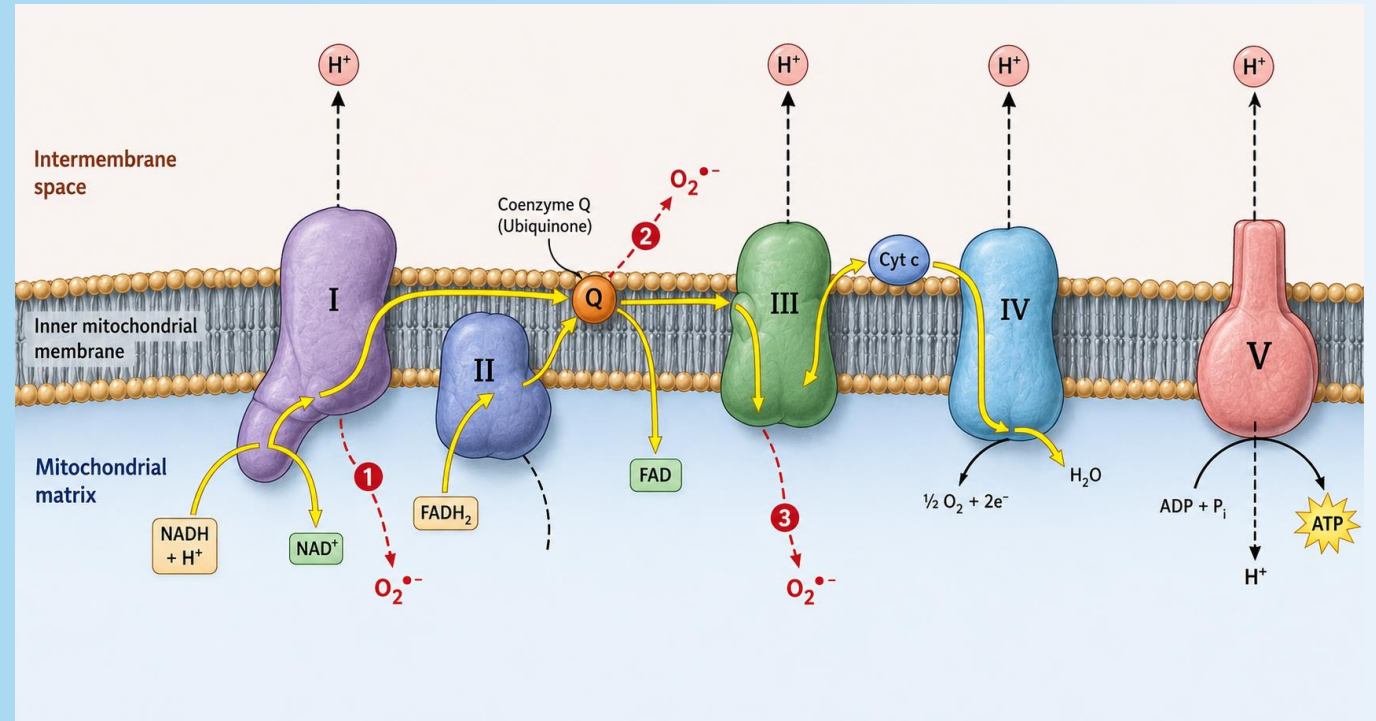
- Electron Transport Chain (ETC)
- Oxidases, Oxygenases, and Peroxidases
- Cytochrome P450 enzymes

## Exogenous Sources

- UV radiation
- Pollution
- Smoking
- Ionizing radiation

# Mitochondria: Superoxide Formation

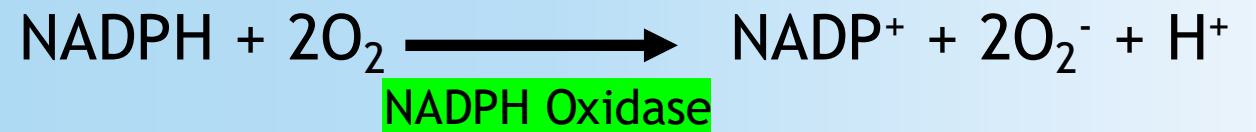
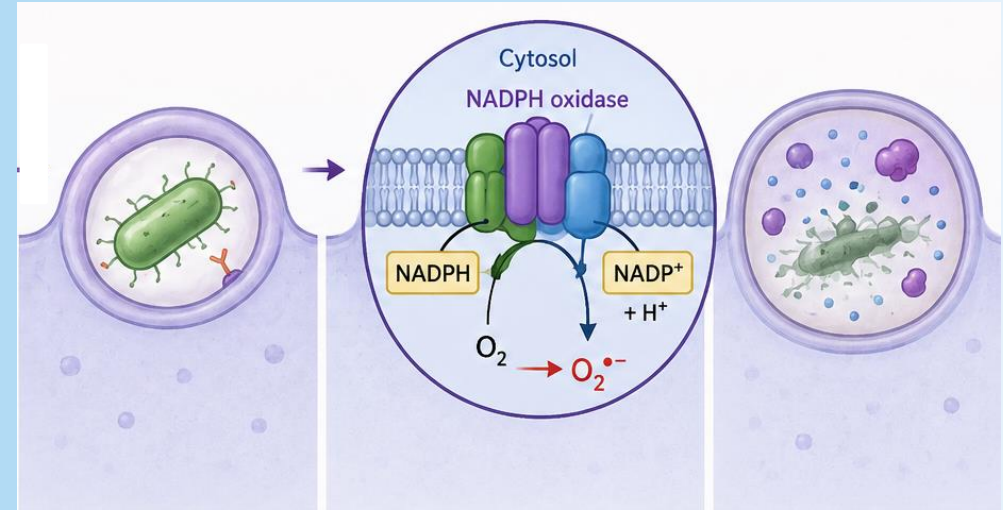
- Mitochondria are the primary endogenous source of ROS
- Electron leakage can occur during **oxidative phosphorylation**
- **Coenzyme Q, Complex I and III** may accidentally transfer electrons to oxygen



**1-Q-3 Spill the Tea**

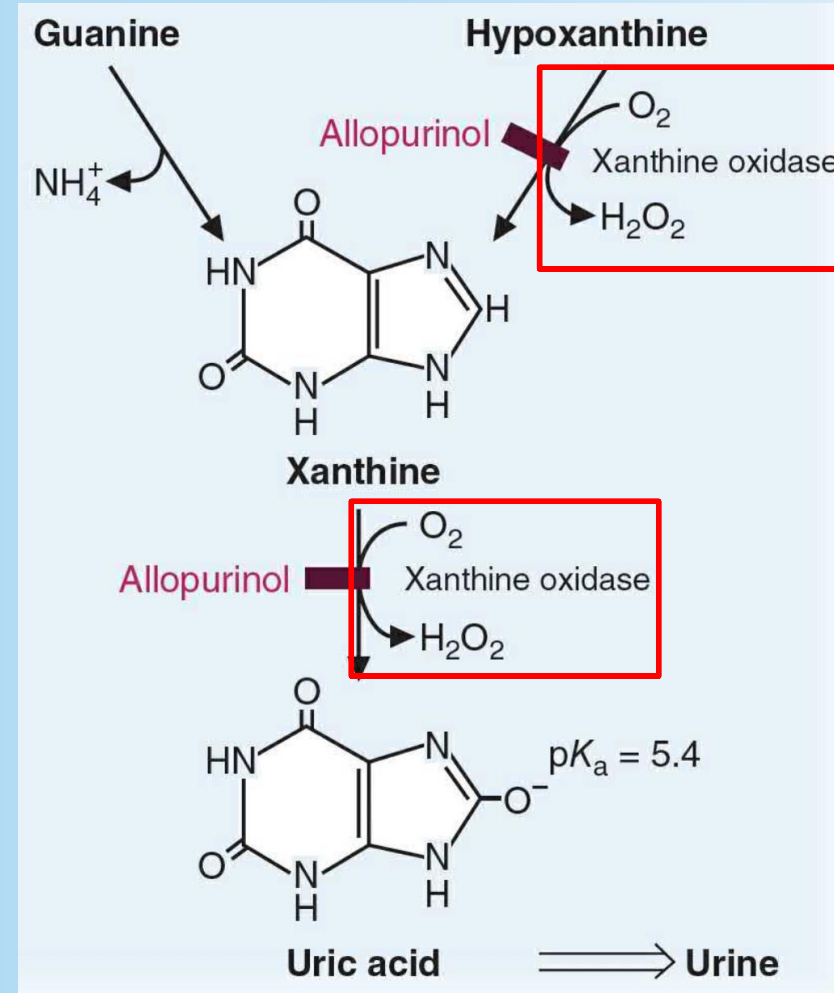
# Immune Cells: NADPH Oxidase

- ROS production can also be intentional
- **Respiratory burst** can occur during phagocytosis of bacteria
- NADPH oxidase transfers electrons from **NADPH** to **Oxygen**
- Superoxide production helps destroy pathogens



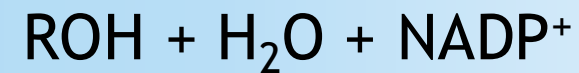
# Xanthine Oxidase

- Functions in **purine degradation**
- Produces **superoxide** and **hydrogen peroxide**
- Major contributor to ischemia-reperfusion injury



# Cytochrome P450

- Transfers single electrons to oxygen
- Can accidentally leak ROS intermediates

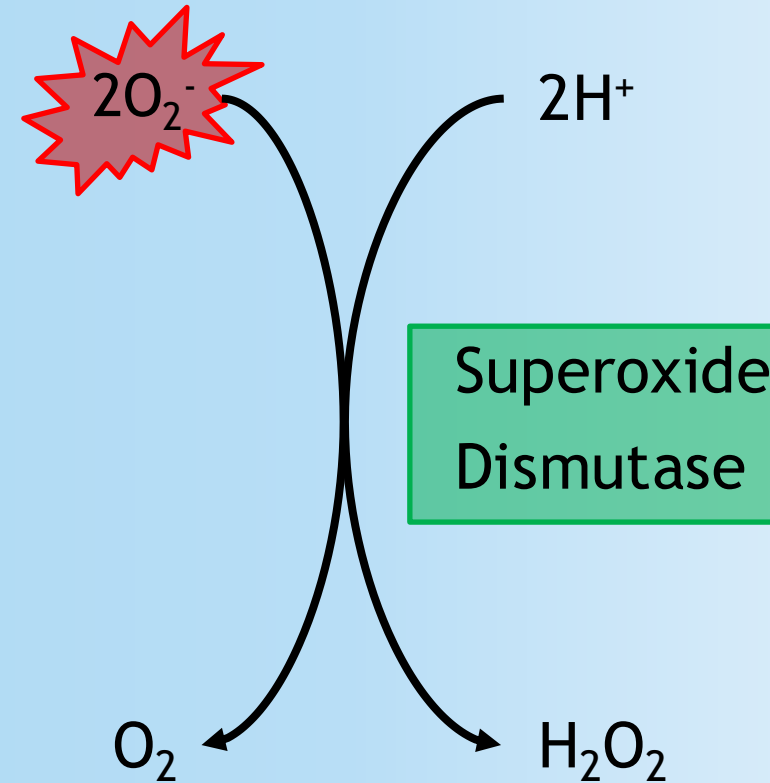


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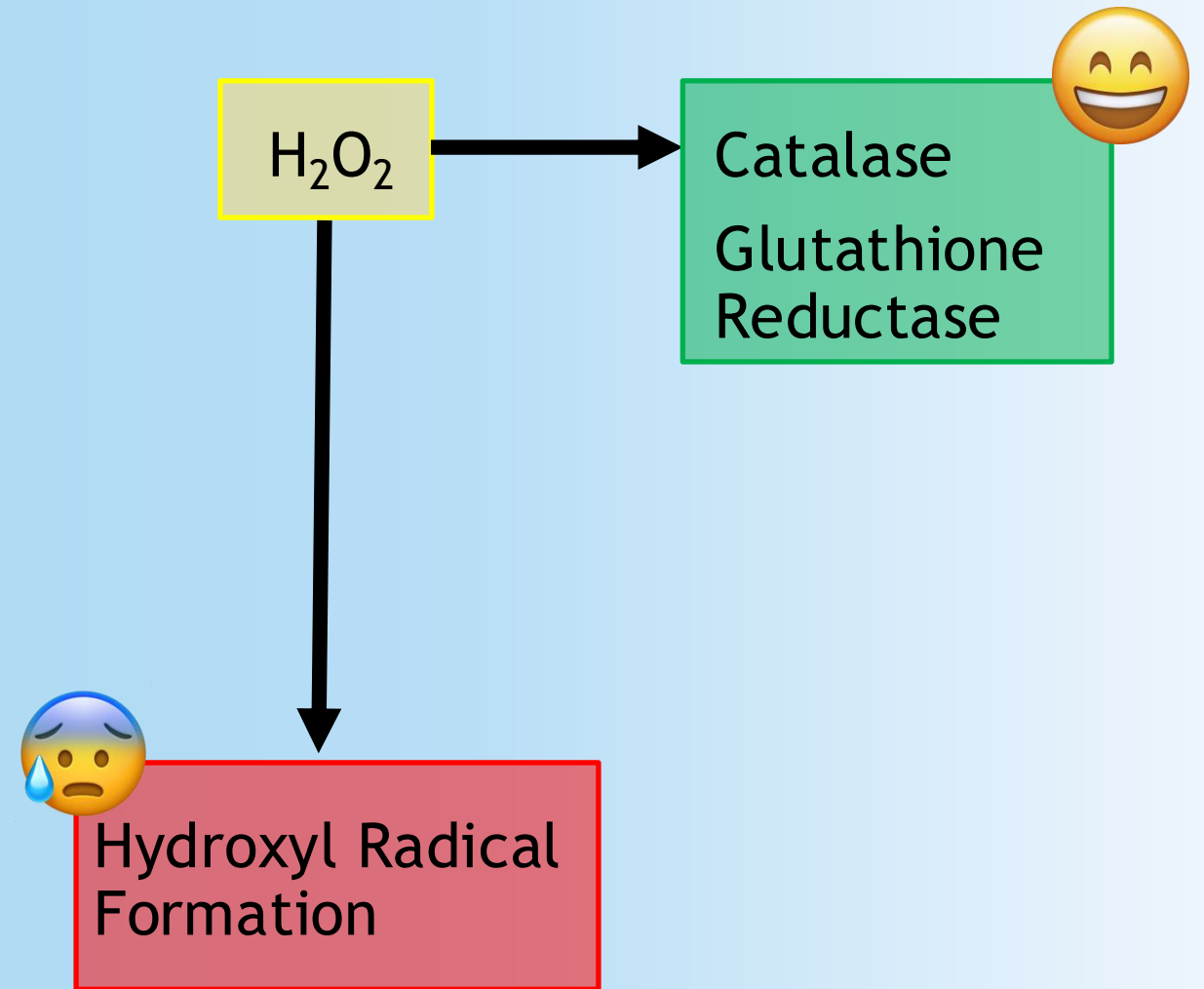
# Defense Mechanisms: SOD

- SOD: Superoxide Dismutase
- Removes **superoxide radicals**
- Catalyzes dismutation reaction
- Produces **hydrogen peroxide** and **oxygen**



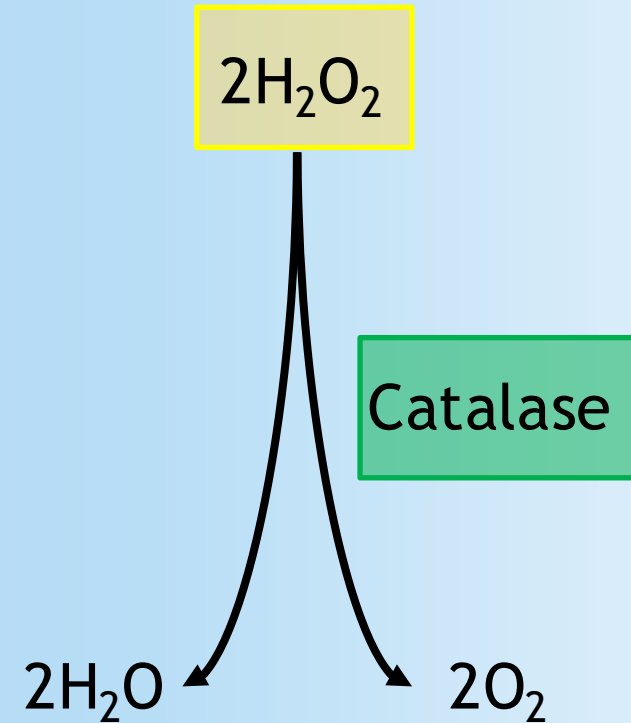
# Hydrogen Peroxide: Control Point

- Weak oxidizing agent
  - Considered a reactive oxygen species, but not necessarily considered a free radical
- Can be detoxified safely
- Can form **hydroxyl radicals** if not removed



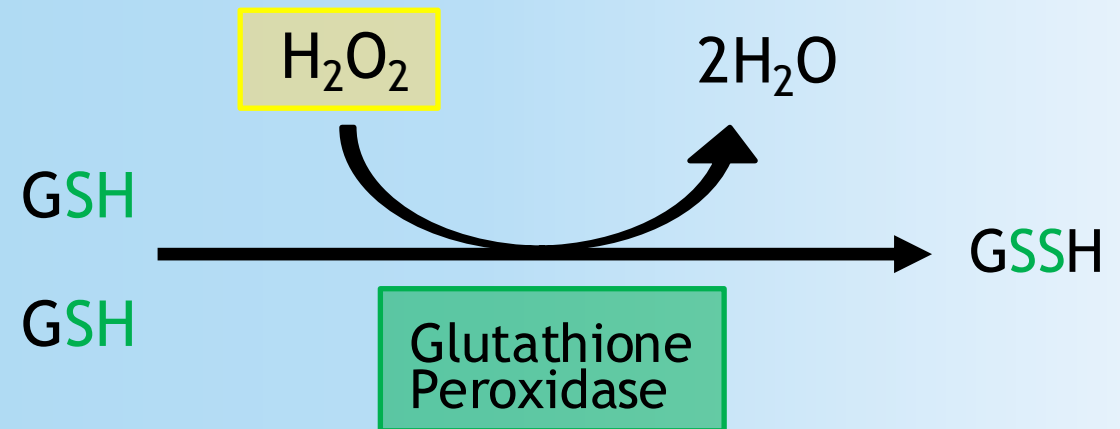
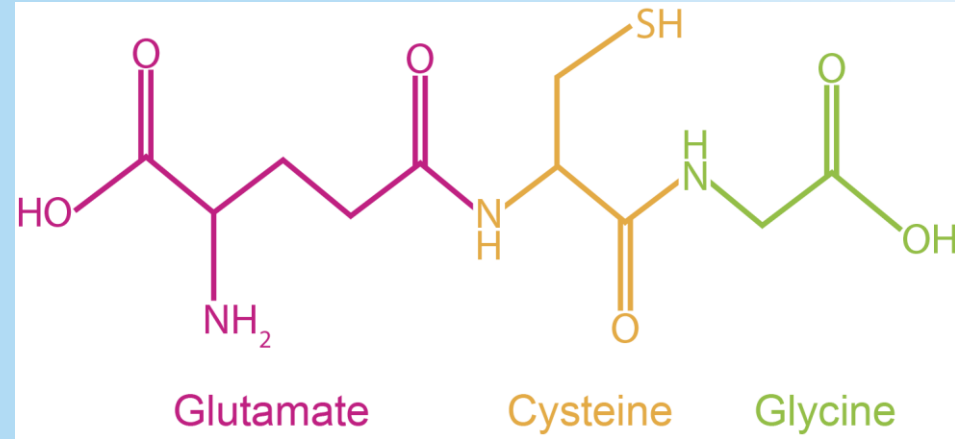
# Defense Mechanisms: Catalase

- Found mainly in **peroxisomes**
- Rapidly detoxifies hydrogen peroxide
- Prevents hydroxyl radical formation
- Converts **hydrogen peroxide** into **water and oxygen**



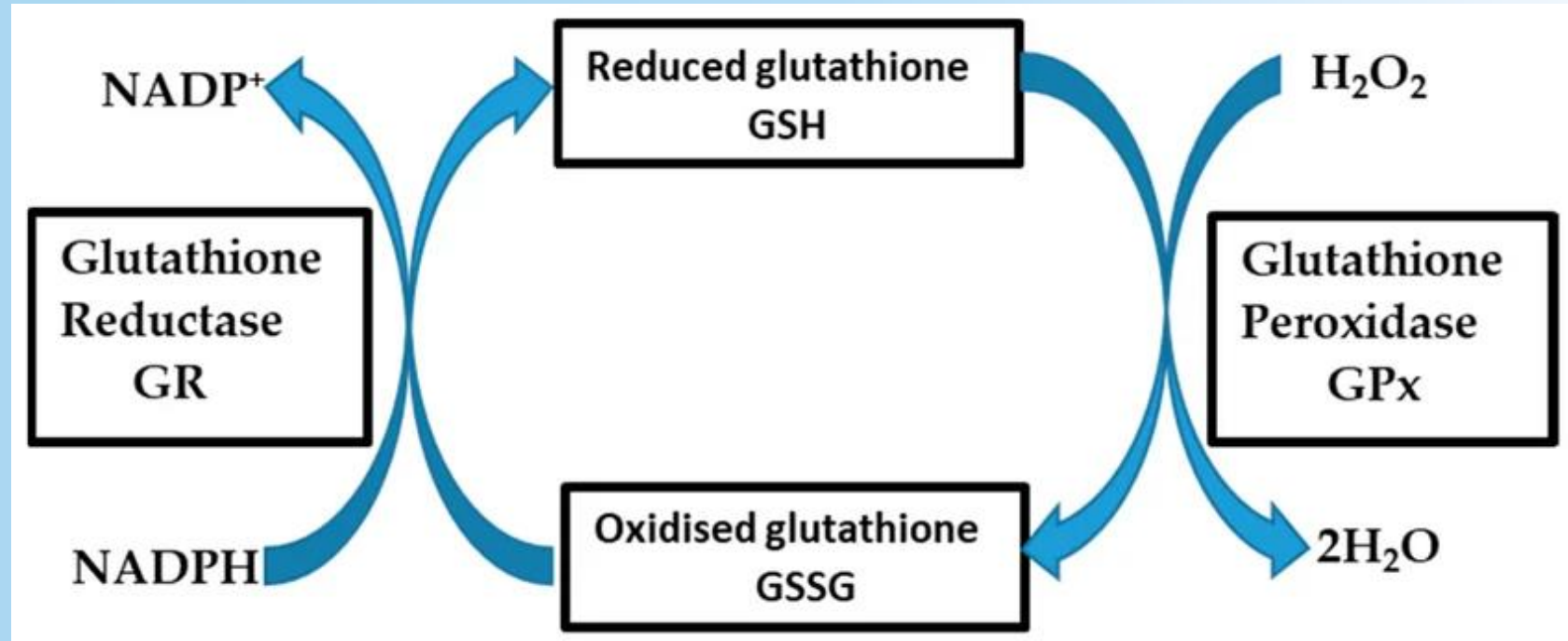
# Defense Mechanisms: Glutathione System

- Glutathione = Tripeptide
  - Glutamate
  - Cysteine
  - Glycine
- Glutathione peroxidase uses GSH
- Reduced glutathione (GSH) detoxifies hydrogen peroxide
  - **GSH = Guardian Shield**



# Defense Mechanisms: Glutathione System

- **Glutathione peroxidase** uses GSH to detoxify Hydrogen Peroxide
- **Glutathione reductase** regenerates GSH using NADPH



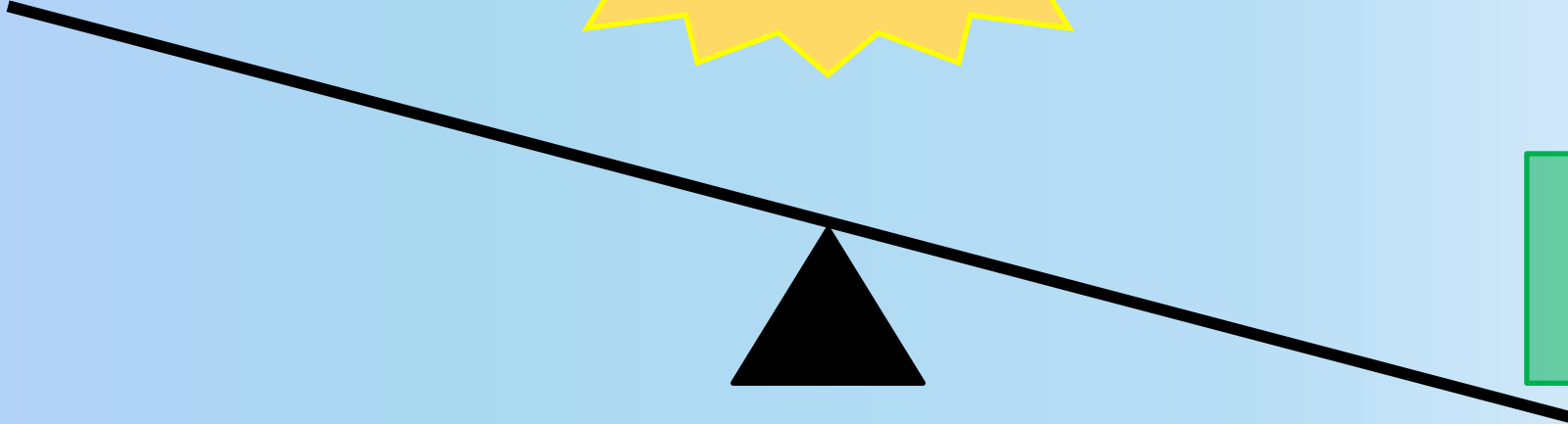
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ROS

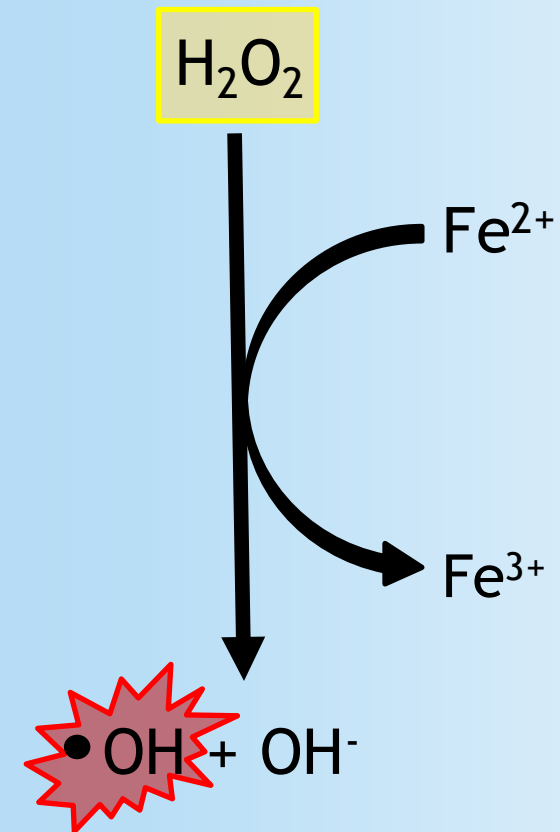
Oxidative Stress

Antioxidants



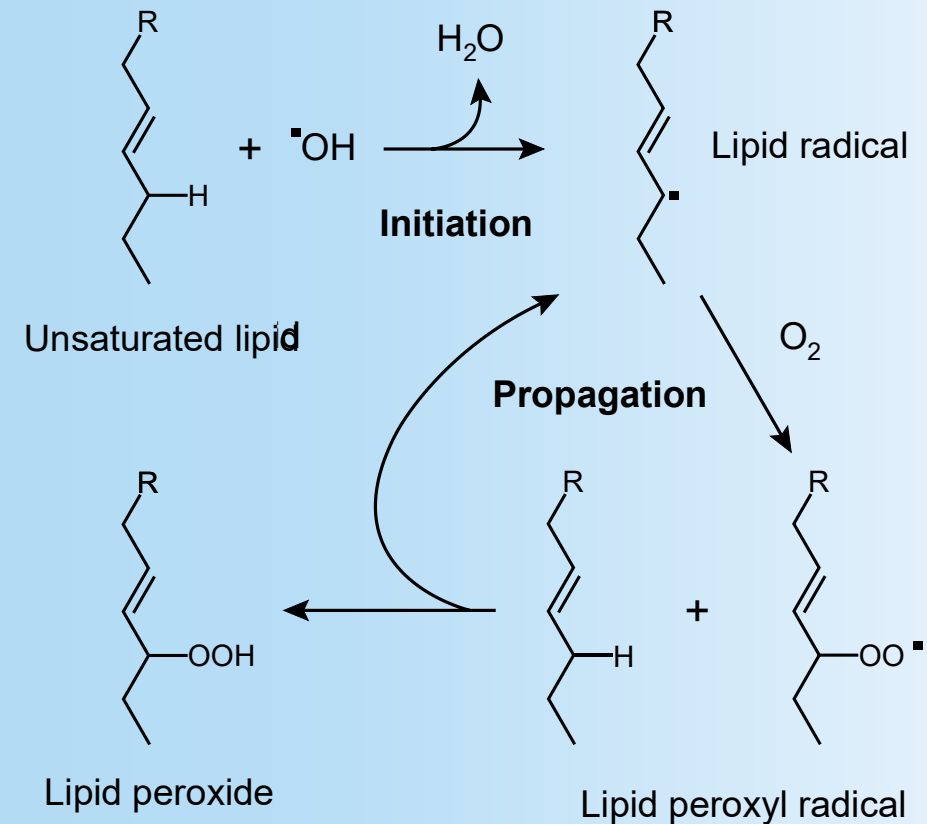
# Fenton Reaction

- Non-enzymatic reaction
- Hydrogen peroxide reacts with  $\text{Fe}^{2+}$  or  $\text{Cu}^+$
- Fenton reaction generates hydroxyl radical
  - **Fenton = Fire**
- Hydroxyl radical is extremely reactive
- Causes widespread cellular damage



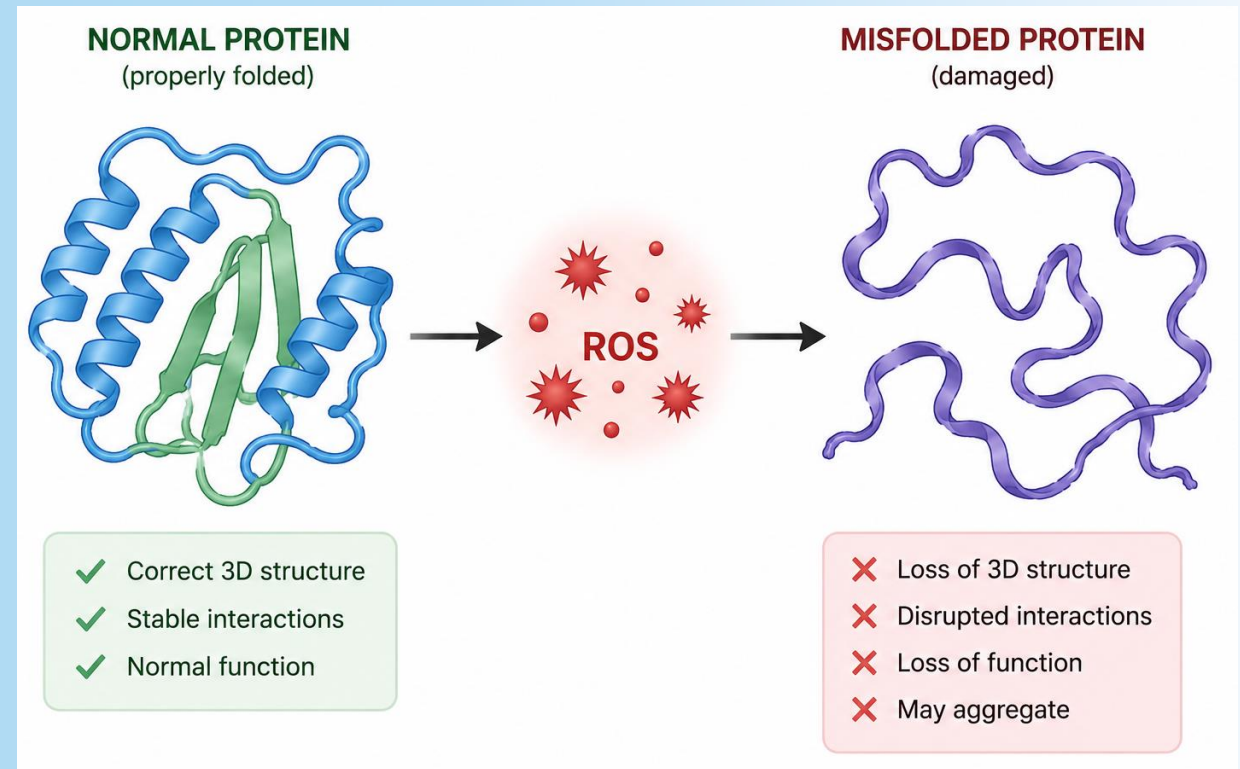
# Lipid Damage

- **Hydroxyl radicals** attack membrane lipids
- **Polyunsaturated fatty acids** are especially vulnerable
- Lipid peroxidation creates chain reactions
- Membrane integrity is lost



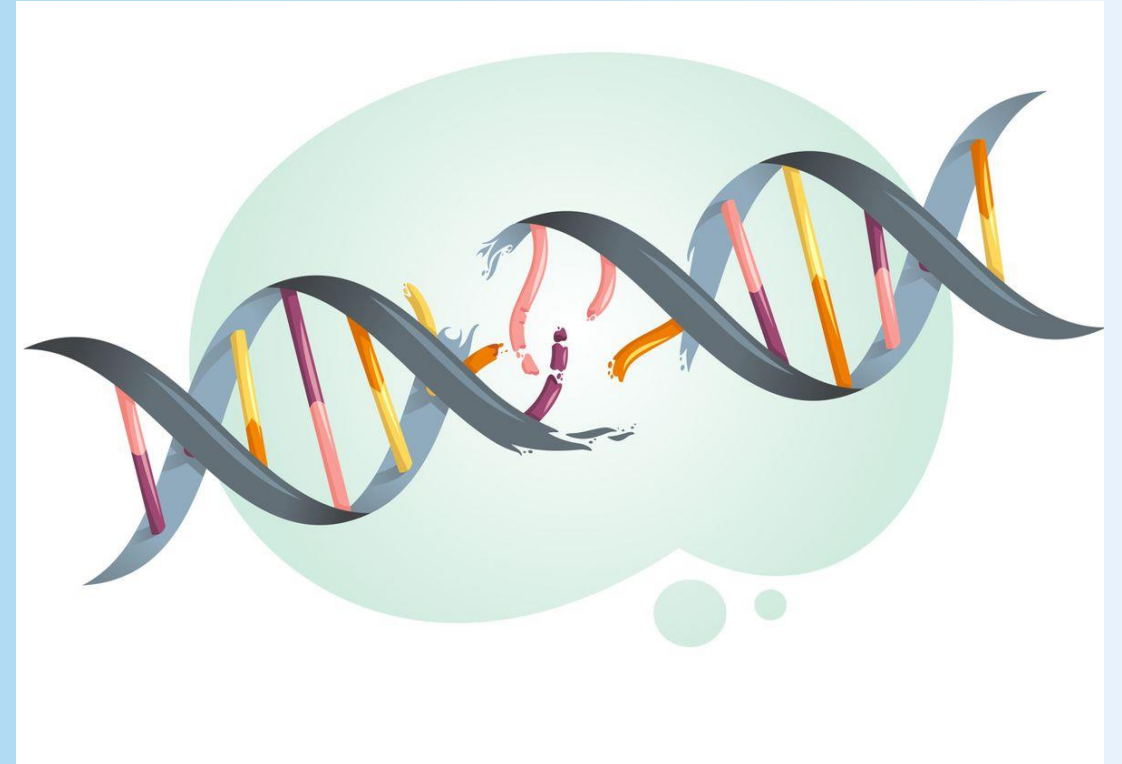
# Protein Damage

- ROS oxidize amino acid residues
- Sensitive amino acids:
  - Cysteine
  - Methionine
  - Histidine
  - Arginine
  - Proline
- Proteins may fragment or cross-link
- Structural changes cause loss of function

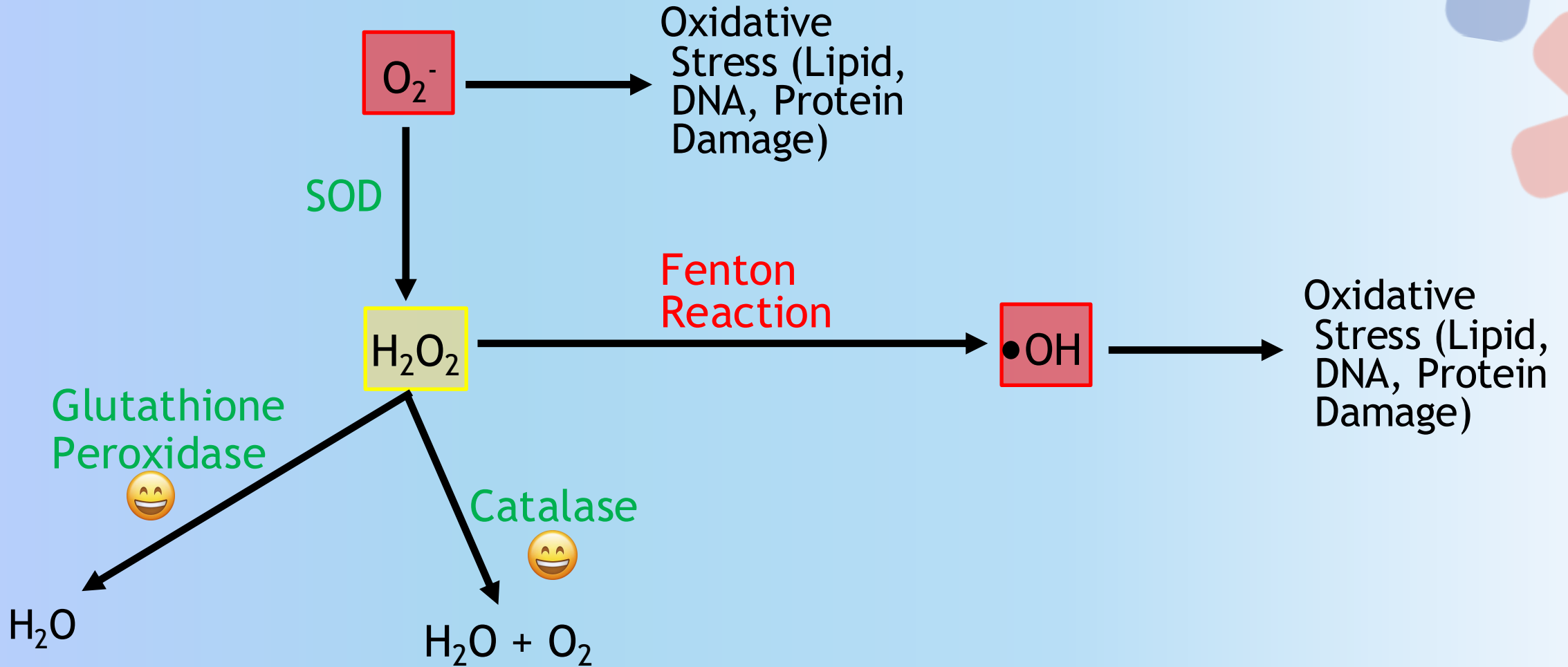


# DNA Damage

- ROS attack the **deoxyribose backbone**
- **DNA strand breaks** may occur
- Oxidative mutations accumulate
- Contributes to aging and disease



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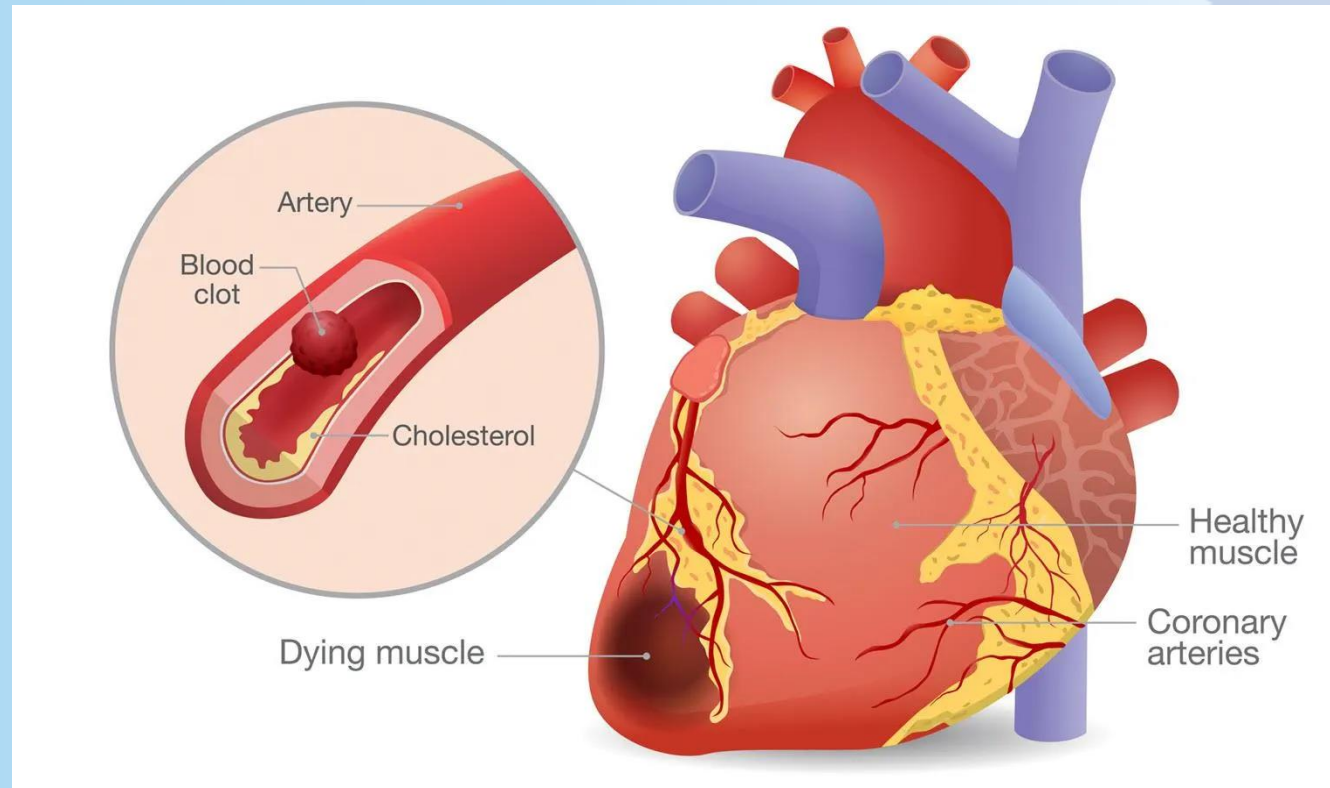


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# Clinical Correlation: Ischemia Reperfusion Injury

1. **Ischemia:** ETC slows → reduced mitochondria (NADH, succinate ↑)
2. **Reoxygenation:** Sudden  $O_2$  restarts electron transport
3. **Electron leak:** Complex I + Complex III and CoQ release electrons to  $O_2$
4. **ROS formation:** Superoxide ( $O_2 \cdot^-$ ) →  $H_2O_2$  →  $\cdot OH$
5. **Oxidative damage:** Lipids, proteins, DNA are injured



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# What are Xenobiotics?

- Xenobiotics refers to any **exogenous substance** that provides **no nutritional value** and can be potentially toxic
- Some examples: Medications, Environmental Pollutants, Food preservatives, pesticides

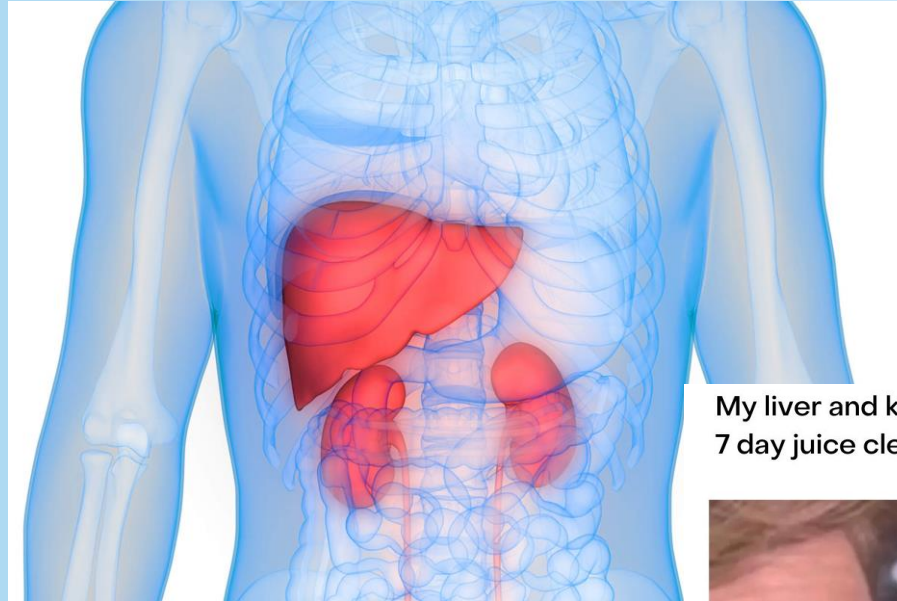


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# The Body's Defense System

- Liver is the major detoxification organ
  - Phase I and II processes
- Kidneys eliminate waste
  - Filter, reabsorb and secrete **water soluble** substances
- Lungs, intestines and skin also contribute

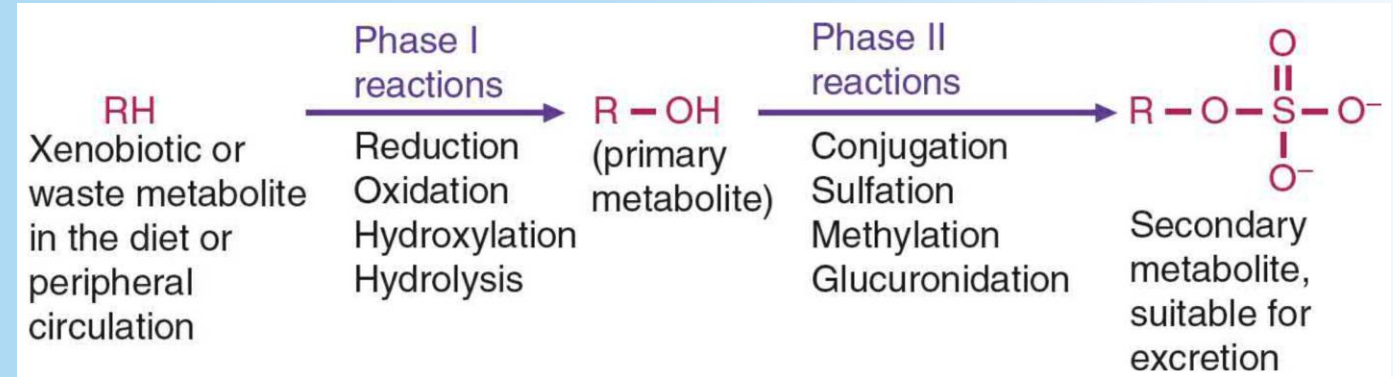


My liver and kidneys when I spend \$300+ on a 7 day juice cleanse



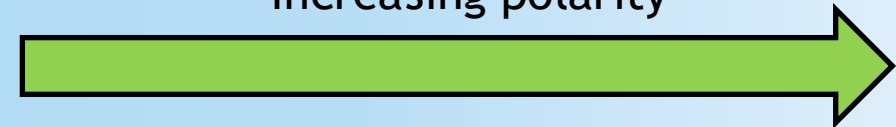
# Overview Detoxification Processes

- Many Xenobiotics are **lipophilic** (fat soluble)
- Goal: **Make xenobiotics more hydrophilic** so that they can be excreted
- **Phase I: Modification**
- **Phase II: Conjugation**



Lipophilic

Increasing polarity



Hydrophilic

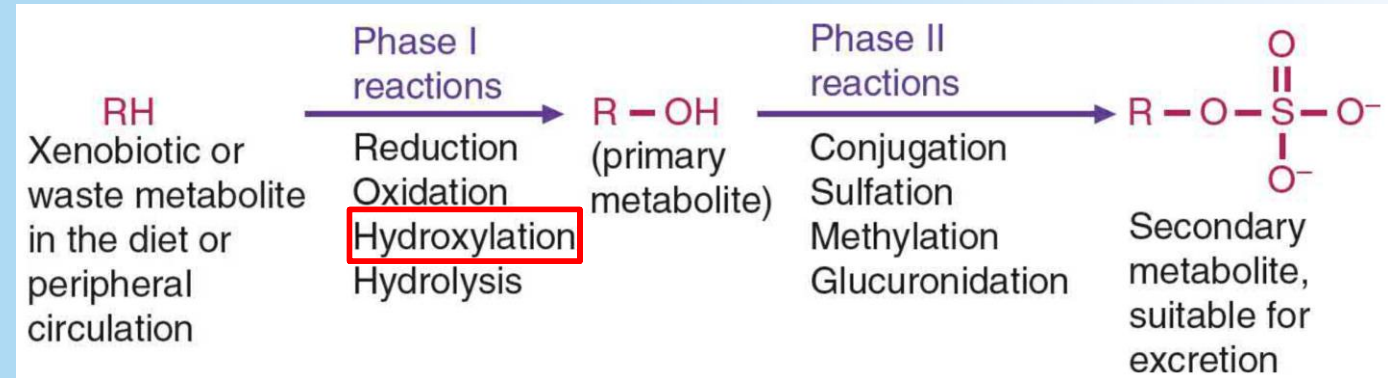
Phase I Exposes; Phase II Disposes

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# Phase I Reactions

- Introduces **reactive groups** such as hydroxyl groups
- Phase I reactions are mainly performed by **cytochrome P450** enzymes
- Primary types of reactions:
  - Oxidation
  - Reduction
  - Hydrolysis
  - Hydroxylation



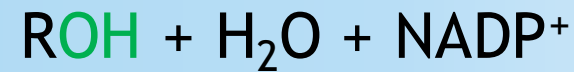
Phase I adds the hook

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# CYP450

- Large enzyme superfamily
- Located mainly in smooth ER of liver cells
- Requires:
  - Oxygen
  - NADPH (Electron Donor)
- **CYP3A4** most common CYP450 enzyme, metabolizes many drugs
- CYP enzymes have overlapping specificity



# CYP Induction and Inhibition

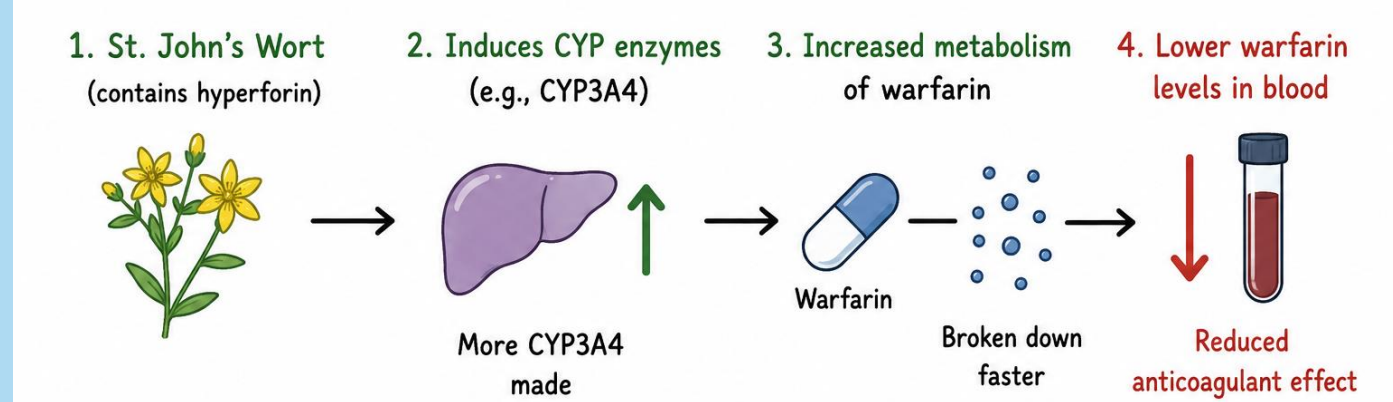
- Inhibitors

- Decrease CYP activity
- Increase drug concentration
- Example: Grapefruit juice inhibits CYP3A4



- Inducers

- Increase CYP activity
- Increases metabolism of the drug (decreasing concentration)
- Example: St. John's Wort induces CYP3A4

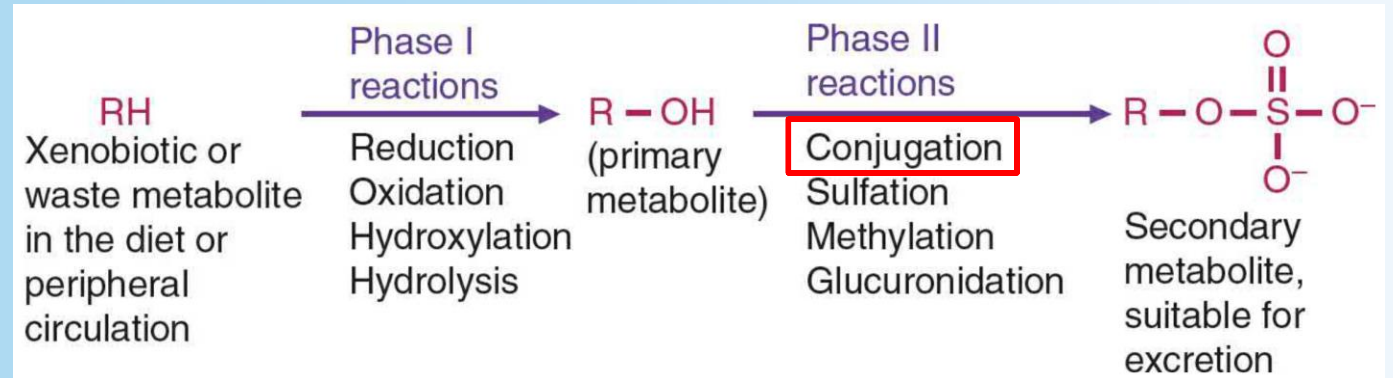


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# Phase II Reactions

- Conjugation reactions
- Adds negatively charged groups
- Increases water solubility (increases polarity)
- Major reactions:
  - Sulfation (adds sulfate group)
  - Glucuronidation (adds Glucuronic acid)
  - Glutathione (GSH) conjugation
  - Glycine conjugation



Phase II Tows the car away

# Overview

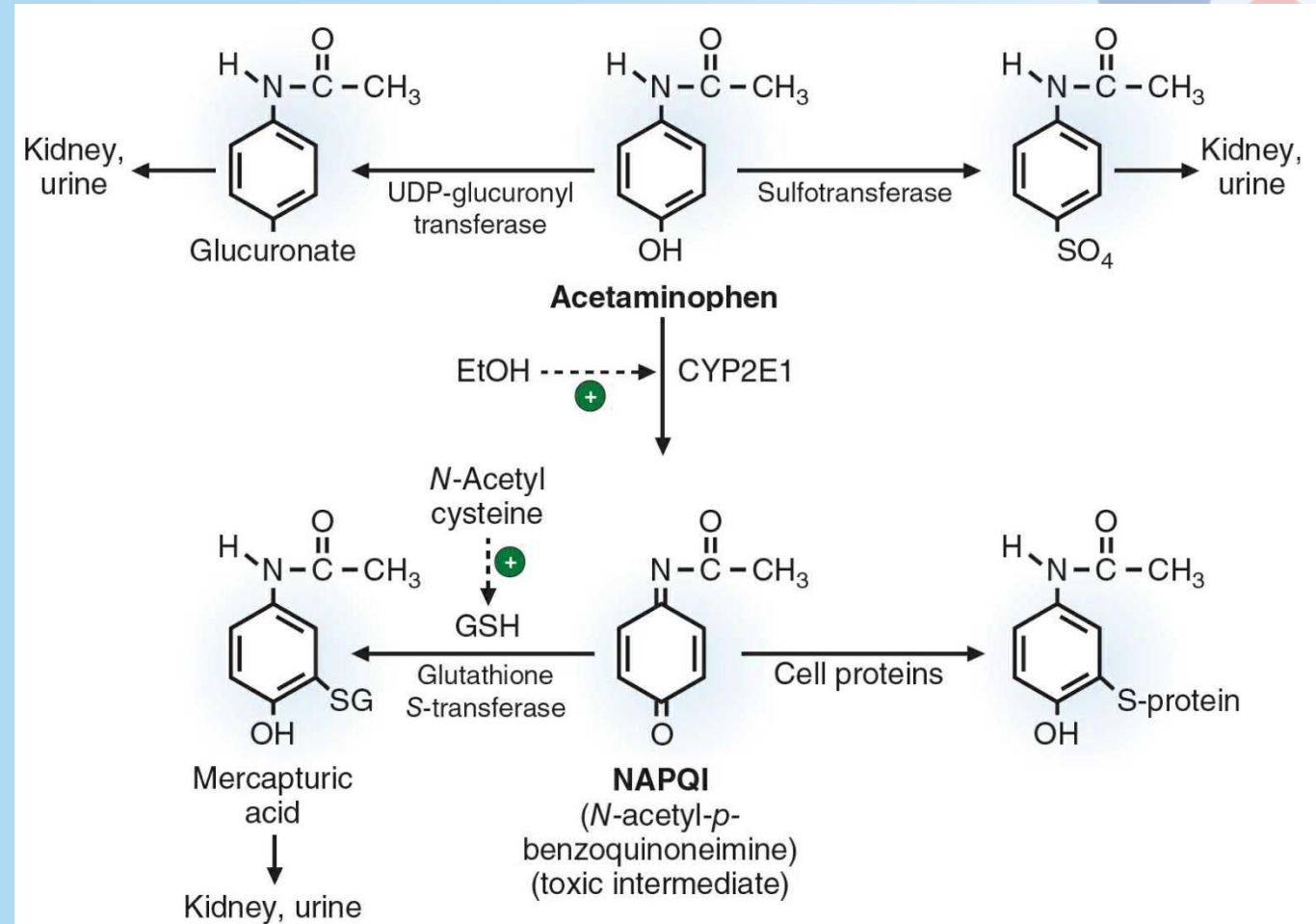
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# Acetaminophen Metabolism



- Normally detoxified by:
  - Glucuronidation
  - Sulfation
- Normally, small amount converted to **NAPQI** by **CYP2E1**
- **NAPQI** detoxified by **glutathione**
- Overdose **depletes glutathione** and can lead to liver damage
- **N-Acetyl Cysteine** can help increase glutathione production



Thank you :)

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