



Herbal compounds

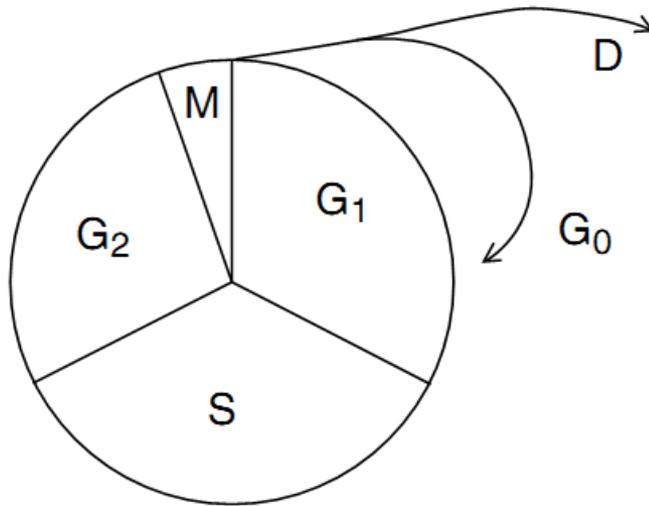
MODES OF ACTION

Modes of action at Target Sites

- Cell Life Cycle and Cancer Treatment
- Transmembrane Signaling
- Immunomodulation
- Toxic Effect:
 - Teratogenesis
 - Carcinogenesis
 - toxicity
- Molecular mechanism at target sites (Cyt)

Cell life cycle and cancer

treatment

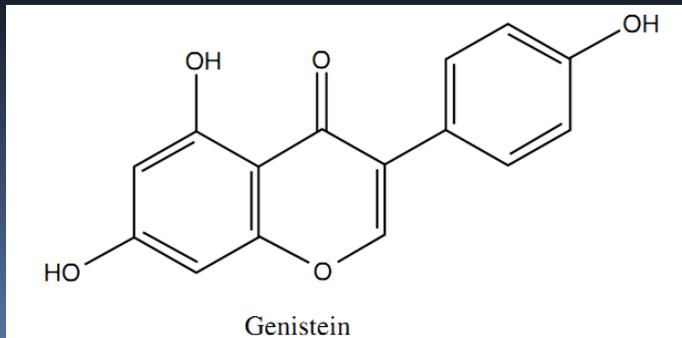


G₀ = Resting
G₁ = Synthesis of purines and pyrimidines
S = Synthesis of DNA
G₂ = Synthesis of components for mitosis
M = Mitosis
D = Differentiation

1. Genistein
2. Mistletoe and Apoptosis
3. Rhein and Necrosis
4. Homoharringtonine and Protein Synthesis
5. Taxoids and Vinca Alkaloids

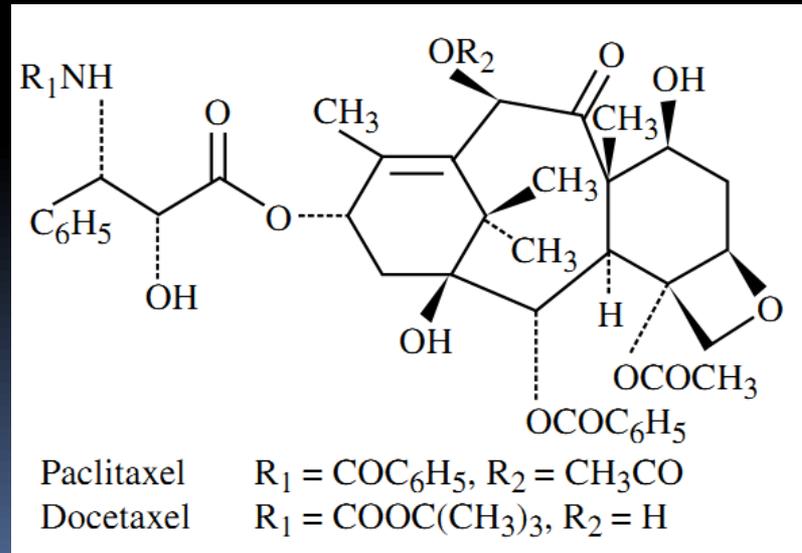
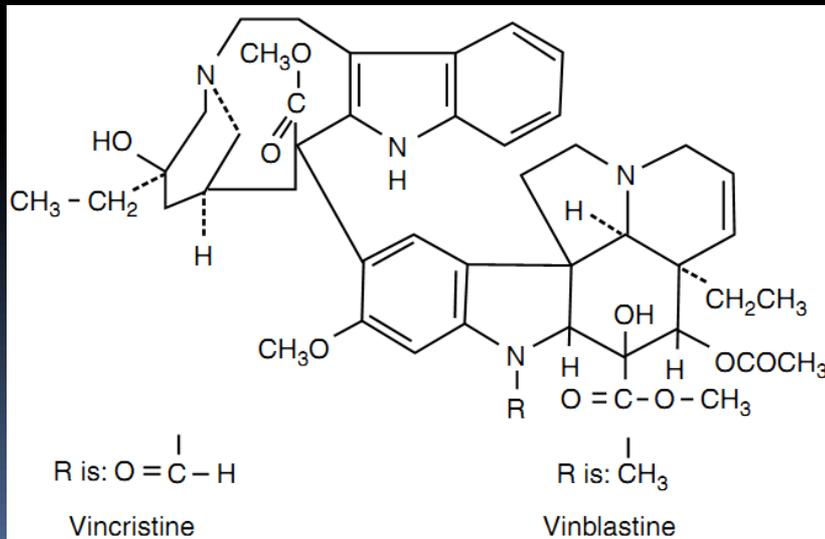
Genistein

- Genistein is an isoflavone found in high quantities in soybean products
- inhibition of angiogenesis
- interaction with steroid hormone receptors
- inhibition of tyrosine kinase
- inhibition of reactive oxygen species (ROS) formation
- interaction with topoisomerase



Taxoids and Vinca Alkaloids

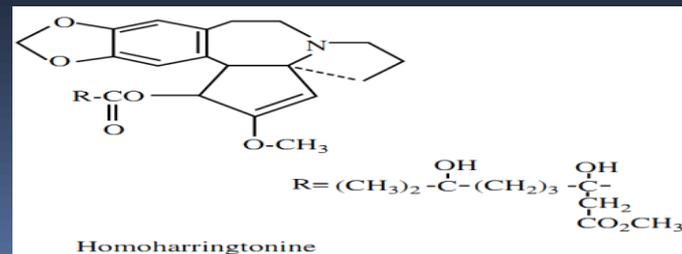
- target site for the taxoids and the well-known Vinca alkaloids is microtubule formation
- The Vinca alkaloids (vinblastine and vincristine), are derived from the periwinkle (*Catharanthus roseus*) inhibit cancer cell reproduction by promoting micro-tubule disassembly.
- The taxoids, paclitaxel (Taxol®) provided by plants Pacific yew (*Taxus brevifolia*), and Docetaxel (*Taxus baccata* L.) induce assembly of micro-tubules and stabilize microtubule networks.



Homoharringtonine and Protein

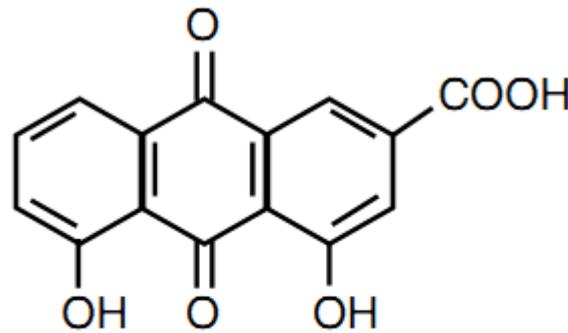
Synthesis

- Homoharringtonine (HHT) is the most active of the alkaloids.
- HHT has its cytotoxic effects in the G₁ and G₂ phases of the cell cycle
- HHT inhibits the elongation step, by competitively inhibiting the enzyme, peptidyl transferase,
- detaching ribosomes from endoplasmic reticulum,
- degrading ribosomes,
- inhibiting release of completed proteins from ribosomes,
- inhibiting glycosylation of completed proteins
- HHT may induce both apoptosis and differentiation of cancer cells



Rhein and Necrosis

- Rhein is an anthraquinone found in rhubarb (*Rheum* spp.)
- it exerts an effect on the membrane level, distort and disrupt the membranes of mitochondria and cells.



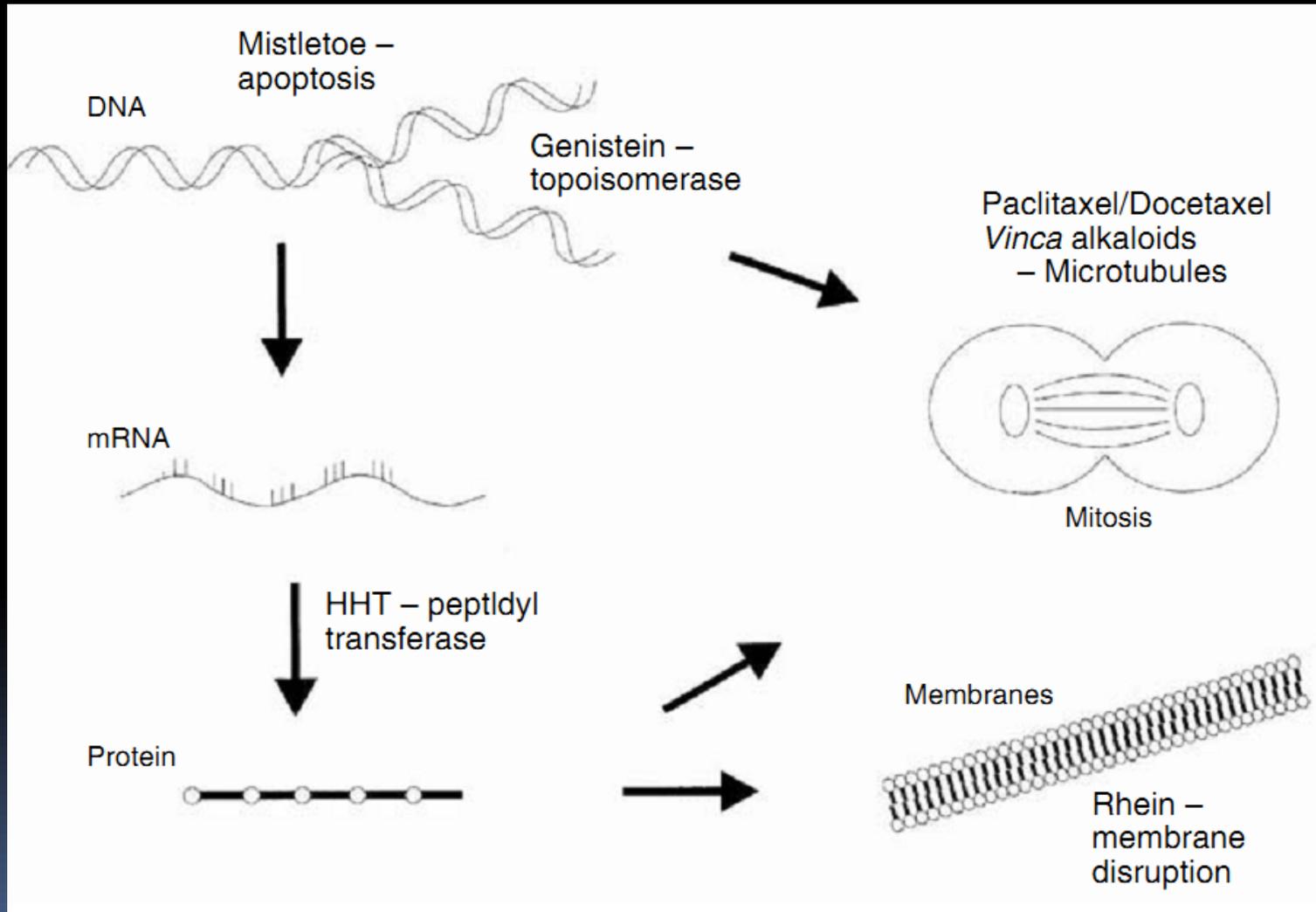
Rhein anthraquinone



Mistletoe and Apoptosis

- Aqueous extracts of *Viscum album* L.
 - the lectin portion of mistletoe extract inhibit tumor growth induce the DNA in these cells is fragmented, as would be expected in apoptosis.
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Anticancer mechanisms.





TUGAS

Pelajari dan fahami jurnal dengan link di bawah ini:

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0013536>

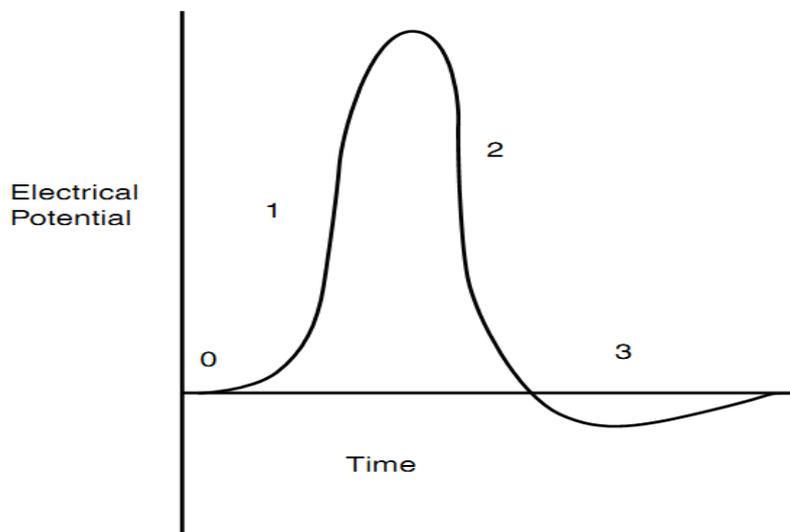


Transmembrane Signaling

- Two types of signaling:
 - ligand-gated ion channels and
 - G-protein/second messenger,
- are particularly relevant to the function of nerves and muscles

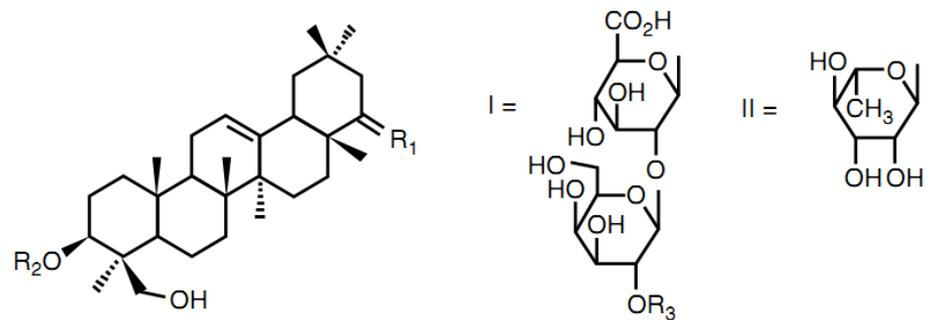
Ligand-Gated Ion Channels

- ❖ Ion channels regulate the flow of sodium, potassium, and calcium across the cell membrane
- ❖ In Ghana, *Desmodium adscendens* is used to treat asthma.
- ❖ The symptoms of asthma can be modified by inhibiting the contraction of smooth muscles lining the airways.
- ❖ Three triterpenoid glycosides were isolated from *D. adscendens*., increase the probability that calcium-dependent potassium channels of bovine tracheal smooth muscle will be open, the cell will hyperpolarize.



Cellular Electrical Events

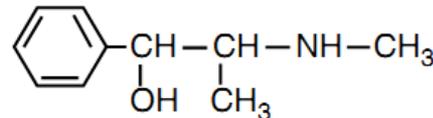
- 0 = Resting phase
- 1 = Depolarization
- 2 = Repolarization
- 3 = Hyperpolarization



Compound	R ₁	R ₂	R ₃
Soyasaponin I	H, OH	I	II
Dehydrosoyasaponin I	O	I	II
Soyasaponin III	H, OH	I	H
Soyasapogenol B	H, OH	H	-

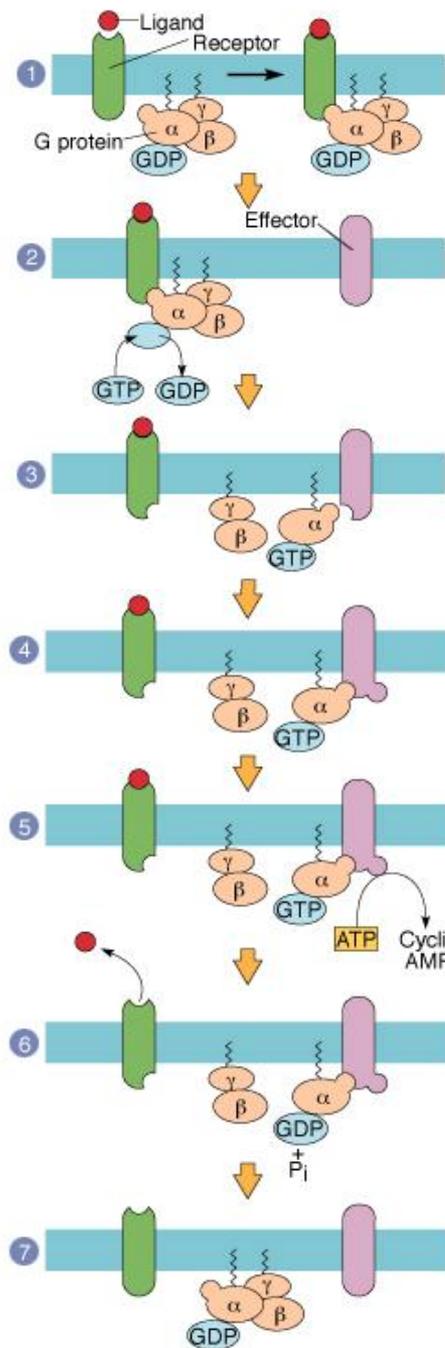
G-Protein and Second Messengers

- ❖ Catecholamines, of which there are many analogs found in natural products, act on the sympathetic nervous system effector organs through two basic types of receptors, alpha and beta.
- ❖ Ma huang or ephedra (*Ephedra sinica* or *E. equisetina*) has been used for thousands of years in China for promote sweating and urination.
- ❖ Ephedrine and pseudoephedrine from the stems of *E. sinica*
- ❖ Ephedrine directly stimulates β -receptors to dilate bronchioles in the lung
- ❖ ephedrine crosses the blood–brain barrier and causes central nervous system stimulation and appetite suppression.
- ❖ ephedrine and pseudoephedrine increase heart rate and the force of heart contractions. This leads to increased blood flow to the kidneys and increased urine formation. Actions on α -receptors cause increased sweating and the constriction of blood vessels in the nasal mucosa. The latter effect decongests the nose, relieving the symptoms of the common cold.
- ❖ These may also cause harm: Heart attacks



Ephedrine

G-protein coupled receptor



Ligand binding, receptor activation, interaction w/ heterotrimeric G protein

Nucleotide exchange. Picks up GTP for GDP.

G proteins activated & leave GPCR

activated subunit binds to effector

Effector (in this case) turns on and amplifies signal

Hydrolysis of GTP inactivates G protein

G protein stops stimulating effector, waits for next signal



immunomodulation

Immunomodulation

- aqueous extracts of *E. Purpurea* : polysaccharides , cell-wall-derived arabinogalactan and two fucogalactoxyloglucans.
- this polysaccharide fraction stimulates macrophages to produce signal molecules, TNF- α , IL-1, and IL-6 (interferon).
- These signals activate other parts of the immune system and promote the migration of other effector cells, such as neutrophils, from the bone marrow to the blood.
- The activated macrophages produce more ROS, phagocytize more, and are more cytotoxic to tumor cells.
- Overall, there is a higher rate of killing of *Listeria monocytogenes* bacteria and *Candida albicans* yeast,



Immunomodulation

- acetylated mannan, acemannan, extracted from Aloe vera, was shown to have immune-system modulating effects.
- This appears to be mediated through macrophages that synthesize and release nitric oxide, IL-1, and TNF- α when activated by acemannan (Peng et al., 1991; Karaca et al., 1995).
- The activated macrophages and other immune cells are then able to respond to viral or cancer cells.

Immunomodulation

- Immediate contact dermatitis occurs when skin previously sensitized is reexposed to the offending agent.
- In some people, strawberries, kiwifruit, tomato, castor bean, and others trigger a type I hypersensitivity response typified by redness, swelling, and itching (Juckett, 1996).
- On first exposure, the plant antigens stimulate B lymphocytes to produce immunoglobulin E (IgE) antibodies that then bind mast cells. No reaction is apparent. At the second exposure, when antigen cross-links the antibodies on the mast cell, there is an influx of calcium ions into the cell. This causes release of preformed mediators, such as histamine, heparin, enzymes, and chemotactic and activating factors, and stimulates the formation of longer-acting mediators, such as prostaglandins and leukotrienes

Toxic Effects

- Teratogenic
 - alkaloids from angiosperms (flowering plants), such as colchicine, reserpine, tubocurarine, caffeine, nicotine, and quinine
 - Ethyl alcohol derived from fermentation of grapes or grains is a commonly ingested plant product with recognized teratogenic effects
- Carcinogenesis
 - Tobacco aromatic hydrocarbons may be complete carcinogenic agents in that they are sufficient to cause tumors without a promoter. The betel nut alone causes tumors in 38% of hamster cheek pouches, but when combined with tobacco, the number rises to 78%
- Toxicity
 - Neurotoxicity can occur when the plant molecule acts as a blocker to neurotransmission: The atropine-like substances, hyoscyamine and scopolamine
 - Comfrey (*Symphytum officinale*) contain pyrrolizidine alkaloids that can cause liver toxicity, as well as carcinogenesis and teratogenesis



Molecular Mechanisms at Target Sites

- how specific enzymes, such as cytochrome P₄₅₀ enzymes, can chemically alter drugs once they enter the body, and how these enzymes are controlled by additional induction and inhibition mechanisms;
- how natural products can interact with receptor proteins to trigger specific responses that govern downstream gene and enzyme activity; and
- how some plant compounds can be affected by environmental “stimulants,” such as light, to change the activity within the body at a molecular level

Effects of Plant Natural Products on Human Cytochrome P450 Enzymes

- The body regards drugs as foreign substances, not produced naturally.
- Sometimes such substances are referred to as “xenobiotics”
- Body has “goal” of removing such xenobiotics from system by excretion in the urine
- The kidney is set up to allow polar substances to escape in the urine, so the body tries to chemically transform the drugs into more polar structures.

Interactions of Plant Natural Products with Nuclear Receptors That Regulate CYP450 Activity

- The St. John's wort constituent, hyperforin, binds to the ligand binding domain of PXR.
- PXR then binds to the CYP₃A₄ promoter region and induces CYP₃A₄ transcription.
- PXR is an orphan nuclear receptor and a highly promiscuous molecule that binds to diverse drugs and toxins. Examples include the antibiotic drug rifampicin, the anticancer drug paclitaxel (Taxol[®])
- PXR binds to DNA and regulates a large array of genes in the liver and intestine that participate in the metabolism and excretion of potentially harmful xenobiotics, including genes encoding phase I, II, and III enzymes

Photodynamic Therapy (PDT) and the Anticancer Action of Hypericin in St. John's Wort (*Hypericum perforatum*)

- Most photosensitizers are porphyrin derivatives, such as hematoporphyrin or chlorins.
- It has a porphyrin ring in which one of the exo-pyrrole double bonds is hydrogenated; this structure results in intense absorption of wavelengths greater than 650 nm. When the photosensitizer absorbs a photon of red light that is delivered to the target tissue, the porphyrin molecule enters an excited state called the triplet state.
- The triplet state photosensitizer can then react with biomolecules by means of two different reactions:
 - The type I reaction involves electron/hydrogen transfer directly from the photosensitizer, producing ions or electron/hydrogen abstraction with a substrate biomolecule to form free radicals. These free radicals then react rapidly, usually with oxygen, to form highly reactive oxygen species (ROS), such as super-oxide and peroxide ions, which attack cellular targets such as cancer cells.
 - The type II reaction produces an electronically excited and highly reactive state of oxygen called singlet oxygen, which may be converted to the triplet state; or by the emission of a photon, it will return to the ground state.