“Within the infant rind of this weak flower
Poison hath residence and medicine power”
W. Shakespeare,
“Romeo and Juliet”, II, ii.
Geraniol from *Rosa centifolia*

Story of Aspirin

- Before the Christian era, preparations from various barks were used for treatment of pain, fluid retention and gout. Clay tablets from the Sumerian period describe the use of willow leaves in the treatment of rheumatism. Egyptians also knew the pain-relieving effects of potions made from willow and myrtle leaves. However, because of St. Augustine’s dictum that all diseases of Christians were due to punishment by demons, physicians in the Middle Ages were reluctant to interfere with God’s will.
- In the late 18th Century, Edward Stone in England, believing in old wives’ tales that willow trees grow in moist places and therefore must contain remedies to pains caused by moisture ("The cause of a disease offers a clue to its treatment"), powdered and dissolved in water the barks of willow trees, and cured rheumatism pains.
- In 1826 the active component, salicylic acid, was isolated. In 1859, Adolph Kolbe, a professor of chemistry, identified and synthesized salicylic acid, in the laboratory at the Bayer Company. This allowed salicylic acid to be produced at industrial scale and sold at a tenth of the price of the material extracted from the willow bark.
- Felix Hoffmann was a junior chemist at the Bayer laboratory. His father was suffering from severe rheumatoid arthritis. The new synthetic drug cured his pains but was irritating to the stomach. Hoffmann set out to modify salicylic acid so that it would be more soluble in stomach acids. The more soluble form would pass through the stomach more rapidly causing less irritation. He prepared derivatives of salicylic acid and tested them on his father. The acetyl derivative proved miraculous.
- Bayer took the patent and marketed aspirin in 1899. "A" stands for acetyl and "spirin" for spirea, the willow tree *Salix spirea*. It has low toxicity. Aspirin is the most successful medicine in history and Bayer sells 11 billion tablets a year.

Aspirin is analgesic (pain-killer), antipyretic (reduces fever), an anti-inflammatory agent (reduces swelling), and a uricosuric (relieves symptoms of arthritis and gout). It has also proven to be effective against heart attack.

Synthetic drugs with similar structures to aspirin

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Thyleanol</th>
<th>Phenacetin</th>
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<tbody>
<tr>
<td><strong>Active</strong></td>
<td>antipyretic</td>
<td>analgesic</td>
<td>analgesic</td>
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<tr>
<td><strong>Formula</strong></td>
<td>( \text{CH}_3\text{COO} )</td>
<td>( \text{CH}_3\text{CONH} )</td>
<td>( \text{CH}_3\text{CONH} )</td>
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<tr>
<td><strong>Structure</strong></td>
<td><img src="https://example.com/aspirin.png" alt="Aspirin Structure" /></td>
<td><img src="https://example.com/thyleanol.png" alt="Thyleanol Structure" /></td>
<td><img src="https://example.com/phenacetin.png" alt="Phenacetin Structure" /></td>
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</table>
Menthol from *Mentha piperita* L. peppermint

Camphor from *Cinnamomum camphora*

Nicotine from *Nicotina tabacum*

Morphine, R1=R2=H
Codeine, R1=Me, R2=H
from *Papaver somniferum*

Heroin, R1=R2=MeCO
Cannabis sativa

Tetrahydrocannabinol

Quinine

Cloroquine

coniine

Cocaine

Novocaine
10/04/2014

Atropine

\[
\text{Atropine} = \text{N} - \text{O} - \text{C} \cdot \text{CH} - \text{Ph} \quad \text{CH}_2\text{OH}
\]

Taxol

from *Taxus brevifolia*

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**Story of Taxol**

- Taxol has been isolated from the yew tree. The tree was known to be very poisonous even in the old ages. In the first century Pliny wrote that wine kept in yew barrels had been poisoned.
- Taxol was isolated in the late 1960s from the bark of the Pacific yew tree, *Taxus brevifolia*, which grows in North West America, as a result of a random screening of 110,000 samples from 35,000 plant species. The drug discovery program was led by the US National Cancer Institute.
- Samples were tested *in vitro*, using human tumor cell lines. Taxol has proved to be the most effective drug against ovarian and breast cancer.

- Taxol works by stopping cell division. It interferes with the processing of microtubules, promotes their formation, but stops their demolition so the cell becomes clogged up and dies.
- The yew tree has a long lifetime. It lives about 600-1000 years. 2.5 kg Taxol has been isolated from about 1200 yew trees. The annual dose for one person requires the bark of up to six, sixty-year-old, trees. Removing the bark kills the tree. If about 100,000 people are to be treated, 600,000 trees are necessary per year. This poses an ecological problem.
- There are efforts all over the world to obtain more of the compound. Structural analogues have not been found as effective as Taxol. Total synthesis has proven to be very hard.
- Another approach is partial synthesis. It has been observed that the needles of the European yew tree, *Taxus baccata*, contain the compound 10-deacetylbaccatin III, which can be converted to Taxol in a few steps. As the needles grow back after harvesting, this approach offers a way to isolate the compound without harming the tree. Now this route supplies the clinical demand.
- Another attempt to obtain the compound has been growing yew cells in the laboratory, as nature already knows how to synthesize the compound.
WHAT DO NATURAL PRODUCTS CHEMISTS DO?

- Literature or field research for:
  - Traditional medicinal plants
  - Physiologically active plant groups
- Collaborate with botanists who identify and collect the plants

- Dry, to avoid decomposition
- Extract with different solvents
- Distill off the solvent

Hexane extract, Chloroform extract, Water extract

Each one contains hundreds of organic compounds

COLUMN CHROMATOGRAPHY

- Solvent
- Extract
- Stationary phase

Thin layer chromatography

- Identify the purified components by spectroscopy: UV, IR, NMR, MASS
- New? Physiological activity?

THIN LAYER CHROMATOGRAPHY

Identify the purified components by spectroscopy: UV, IR, NMR, MASS

New? Physiological activity?
Isolation and Identification of the Sesquiterpene Lactone Constituents of
Centaurea Cheirolopha and Centaurea Cuneifolia

*Centaurea plant species are rich in terpenoids, especially sesquiterpene lactones.

*Sesquiterpene lactones are a special group of compounds that have received considerable attention because of their biological activities. They have been used in crude preparations in folk medicine. For example, α-santonin is widely used in the Far East to combat intestinal worms. Artemisia annua is an antimalarial drug. Parthenolide from the herb feverfew is an antimigraine compound. Antitumor, antibacterial, diuretic, and allergenic activities have also been related to various sesquiterpene lactones.

*The α-methylene-γ-lactone moiety has been shown to be responsible for the physiological activity of these compounds. This moiety functions as an enzyme-alkylating agent.

SESQUITERPENE LACTONES

*One of the Largest Classes of Natural Products

*Chemotaxonomically Important

*Pharmacologically Active

*Bitter Flavoring Agents

*Crystalline

Basic Sesquiterpene Lactone Skeletons

Guaianolide

Pseudo-guaianolide

Eudesmanolide

Germacranolide

Sesquiterpene Lactones Isolated from Centaurea cheirolopha

R = H

Sesquiterpene Lactones Isolated from Centaurea cuneifolia

R = H