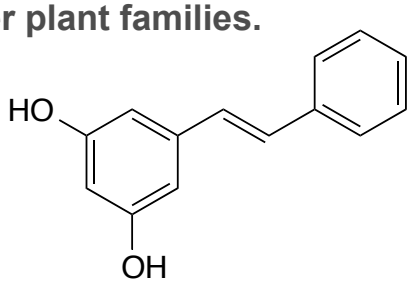
# PHARMACOGNOSY – 1
## Lecture 14

1. Phenylpropanoids and Stilbenoids
2. Diarylheptanoids and Arylalkanones
3. Lignans and Styrylpyrones



## Stilbenoids

- Stilbenoids are compounds that contain two aromatic ring systems connected with an ethane or ethylene chain.
- They were found as their glycosides as well as aglycones and in general stereochemisty of the ethylene chain is *trans (E)*.
- Stilbenoids widely distributed in higher plant families.
- These compound act as **phytoalexin*** or as a plant growth hormone.



**Pinosylvin**

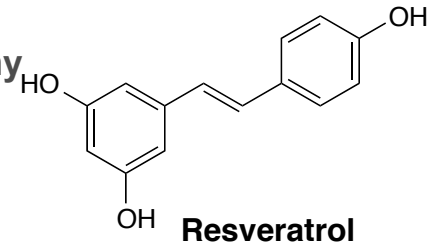
***Phytoalexin**; these compounds were produced by plants when a parasitic infestation occurs, phytoalexins inhibit the growth of parasites.

# Stilbenoids

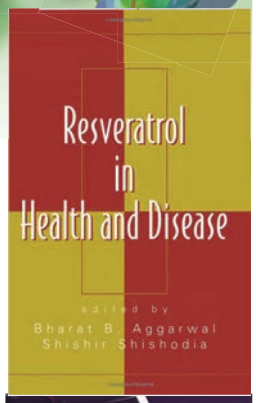
## Resveratrol

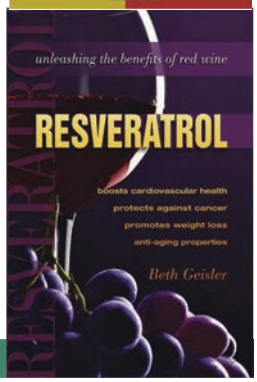
- Primarily found in ***Vitis vinifera***, also isolated from ***Polygonum, Cassia, Veratrum, Arachis*** and ***Eucalyptus*** species.

- **Resveratrol** has many biological activities:
  - Antioxidant
  - Anti-inflammation,
  - Anticancer,
  - Inhibition of platelet aggregation factor (PAF),
  - Neuro- and cardio-vascular system protective,
  - Antidiabetic,
  - Antifungal ve antibacterial



**Resveratrol**



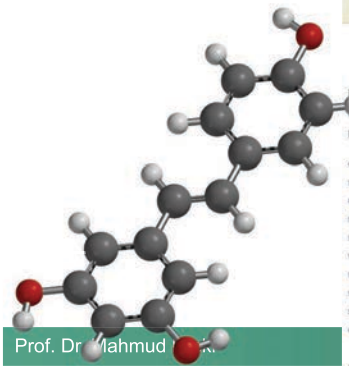



# Stilbenoids

## Resveratrol (contd.);

- Prolongs life of fruit flies and nematodes (*C. elegans*) by modulating activities of sirtuin enzymes.

- Probably most of the resveratrols biological activities were due to its effect on the regulation of genetic factors

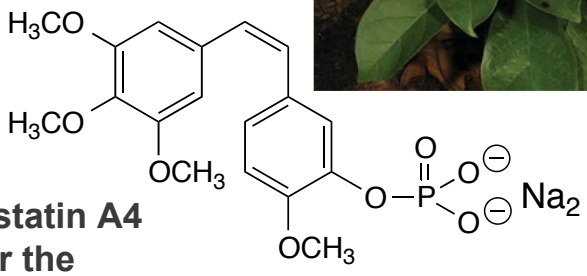



# Stilbenoids

## Combretastatins

- The extracts of ***Combretum caffre*** and ***C. molle*** (Combretaceae) were found to be active against P-388 lymphocytic leucemia, a bioactivity directed isolation study led to the isolation of combretastatins from these extracts.

- Combretastatins and their semi-synthetic derivatives currently being developed for the treatment of various type of cancer tumors.



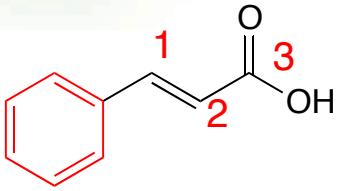

- Phosphate ester of Combretastatin A4 has been approved by FDA for the treatment of thyroid cancer.

Kombretastatin A4 Phosphate Sodyum Tuzu



# Simple Phenylpropanoids

- Simple **phenylpropanoids** contain an aromatic ring that has a propane chain attached.

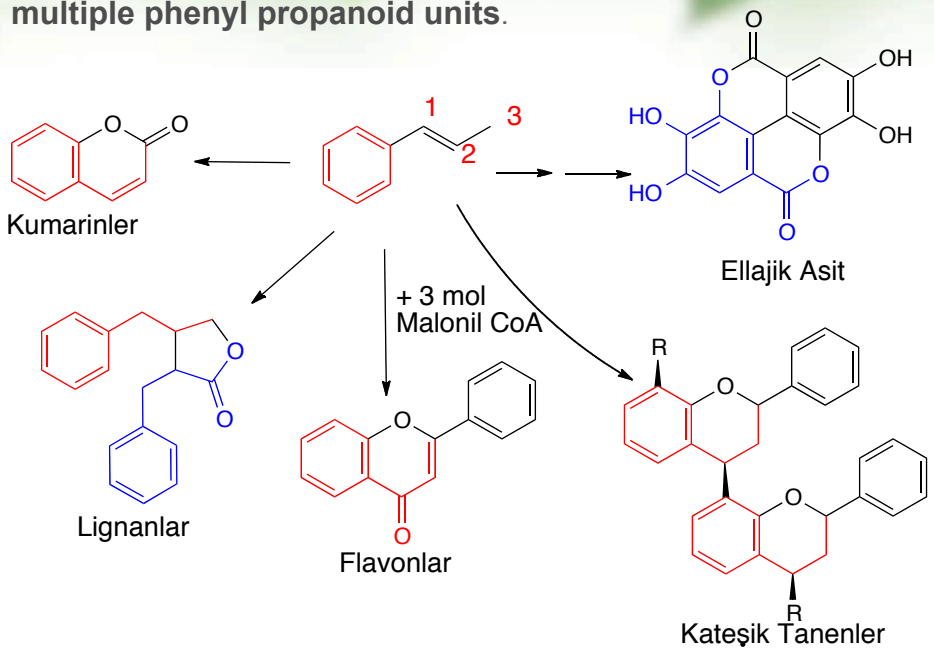



Sinnamik Asit

- The aromatic ring portion usually contains phenolic hydroxyl group(s), they can be found in all plant families and forms the simplest phenolic compounds class.
- Biosynthetically phenylpropanoids derive from the shikimmic acid pathway.

# Simple Phenylpropanoids

❖ **Most of the complex phenolic compounds were consist of multiple phenyl propanoid units.**






# Simple Phenylpropanoids

**Drugs containing Caffeic acid derivatives;**

**Cynarae folium, Artichoke leaves**

❖ **Drug obtained from the basal leaves of *Cynara scolymus* L. (Asteraceae)**

❖ ***C. scolymus*** is a perennial cultivated plant, it's capitulum (composite flower head) develops in the second year of plant growth.

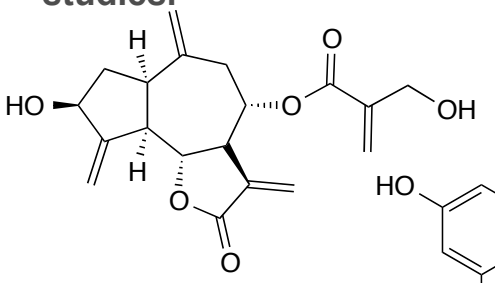
❖ Drug: the basal rosette leaves that form on the first year of plant growth were used as the **Cynarae folium.**

❖ **Chemical composition; Chlorogenic acid, cynarin, flavonoids and sesquiterpene lactones (cynaropicrin and derivatives)**

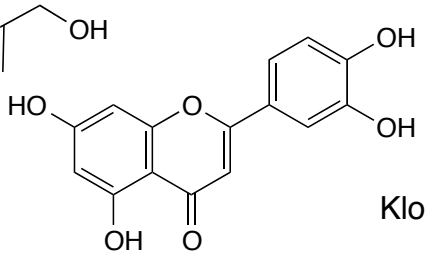
# Simple Phenylpropanoids

**Cynarae folium, Artichoke leaves (contd.);**

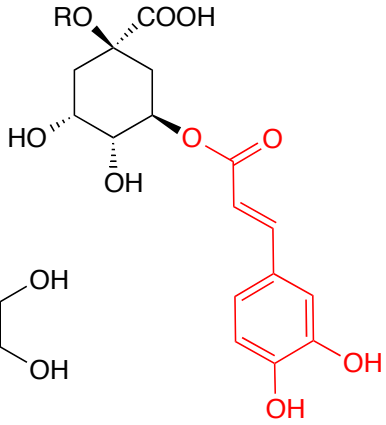
- **Uses; Choleretic (promoting bile secretion), antioxidant, hypocholesterolemia**
- **Antidiabetic activity of chlorogenic acid has been shown by limited clinical studies.**



Sinaropikrin



Luteolin



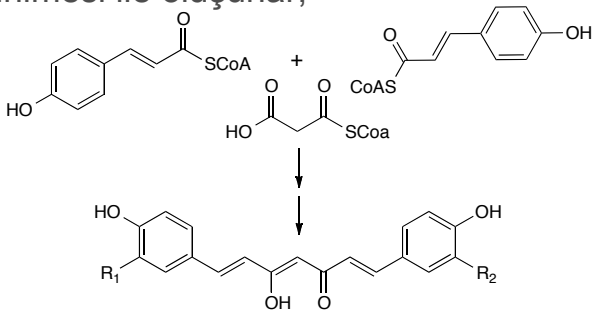
Klorojenik Asit; R = H

Sinarin; R = Kafeik Asit



# Diarylheptanoids and Arylalkanones

- Bu bileşikler **Zingiberaceae** familyasına has maddelerdir.
- **Zerdaçal'a (*Curcuma longa* L.)** turuncu rengini veren ve **zencefil'e (*Zingiber officinalis* Roscoe)** bitkisinin kokulu-yakıcı tadını veren bileşiklerdir.
- Biyosentetik oluşumları sinnamik asit'ten türeyen fenilpropanoidlere malonil koenzim A ünitelerinin katılması (zencefil'in bileşikleri; gingeroller) ya da iki sinnamik asit turevinin bir malonil koenzim A ünitesi köprüsü (kurkuminoidler) ile birleştirilmesi ile oluşurlar;



Kurkuminoidler

# Diarylheptanoids

## Curcumae longae rhizoma, Turmeric

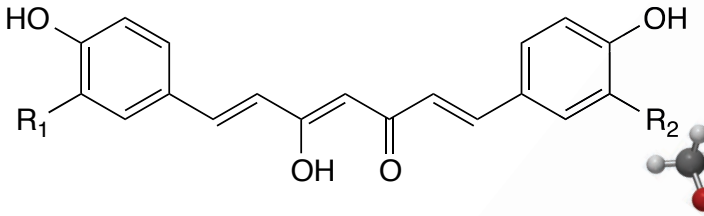
- Drug: The rhizome of *Curcuma longa* L.
- Chemical composition; %2.5 - 6 essential oil (contain mono- and sesquiterpenes) and curcuminoids (diarylheptanoid compounds).
- Curcuminoids produce the orange color of drug and their amount could reach up to %8.
- Curcumin is the major constituent of curcuminoids, desmethoxycurcumin and bisdesmethoxycurcumin were the other pigments found in the rhizome.

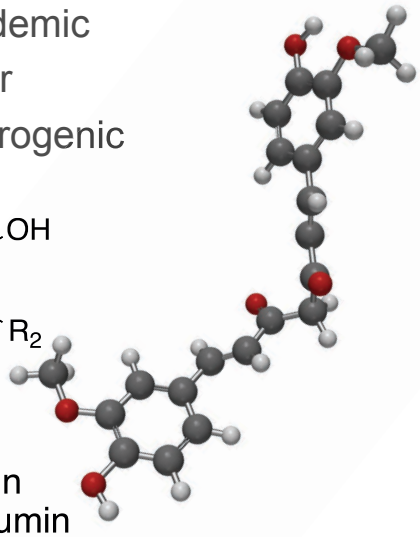


# Diarylheptanoids

## Curcumae longae rhizoma (contd.);

- Pharmacological activities of curcuminoids;
  - Anti-inflammation
  - Antimutagenic
  - Antioxydant
  - Choleretic
  - Hypolipidemic
  - Antitumor
  - Anti-ulcerogenic



$R_1 = R_2 = OCH_3$, Kurkumin
$R_1 = H$, $R_2 = OCH_3$, Dezmetoksikurkumin
$R_1 = R_2 = H$, Bisdezmetoksikurkumin

# Diarylheptanoids

## Curcumae longae rhizoma (contd.);

- Medical uses;
  - Choleretic and cholagogue
  - Functional dyspepsia (due to the liver problems)
  - Appetizer
- Recent investigations on the curcuminoids have shown many potential medical uses of these compounds including their anticancer activities.
- However, poor water solubility of curcuminoids diminish their potential medical applications.
- Cyclodextrins can be used to prepare highly bioavailable formulations of curcuminoinds.



# Arylalkanones

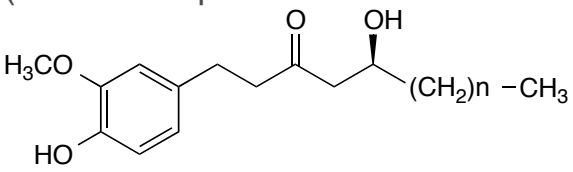
## Zingiberis rhizoma, Ginger

- Drug; The rhizome of *Zingiber officinalis* Roscoe
- Chemical constituents; Essential oil (%1 - 2.5), starch (60%), protein, fat and resin.
- The pungent compounds of drug were gingerols. These compounds were aromatic compounds with 7-10, 12, 14 or 16 carbon chains that contain ketone and alcohol groups.
- In addition, labdane diterpenes were also isolated from the rhizome.

# Arylalkanones

**Zingiberis rhizoma (contd.);**

- **Pharmacological activities; the drug has been used in India and China since ancient times.**
  - Liver protective and hypocholesterolemia activities of the extracts of rhizome has been proven
  - Antiemetic activity
  - Has positive effect on GERD (gastroesophageal reflux disease)
- **Medical Uses;**
  - Treatment of motion sickness (cars, aeroplanes) due to the antiemetic activity
  - Digestive system stimulant (increase in peristalsis and stomach secretion)
  - Positive inotropic activity

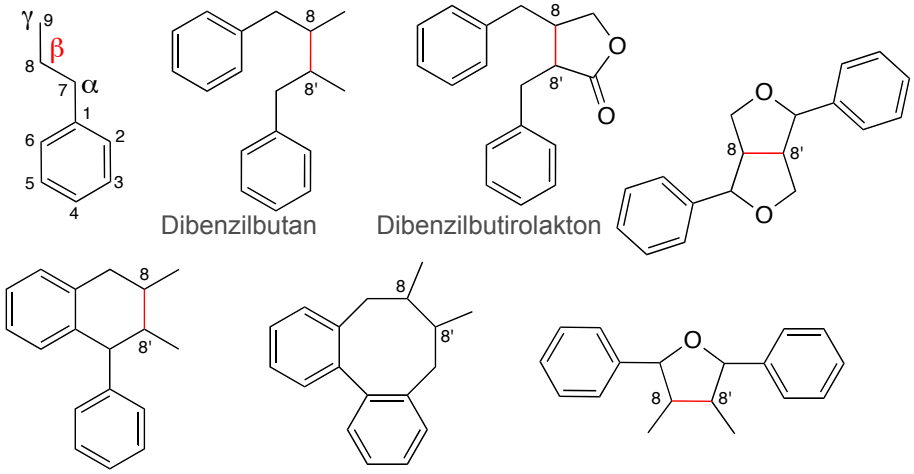



Gingeroller (n = 1-4, 6, 8, 10)



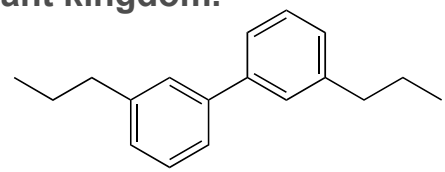
# Lignans

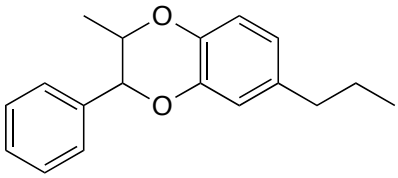
- **Lignans are dimeric compounds that form by connection of two phenylpropanoid units through their β carbon by the formation of C-C bond.**
- **Lignans are found in ca. 70 plant families.**
- **Lignans have several structural classes:**

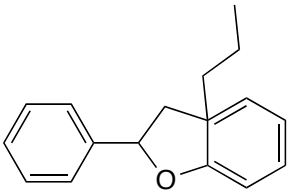


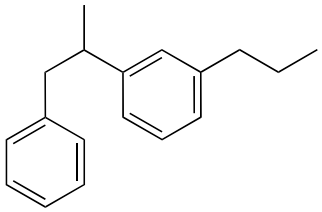
# Lignans

- In stead of β carbons if phenylpropanoid units were connected through the other atoms to form a lignan, this type of lignans were named as neolignans. Neolignans are less common comparing with the regular lignans and are mostly found in Piperales and Magnoliales orders of the plant kingdom.





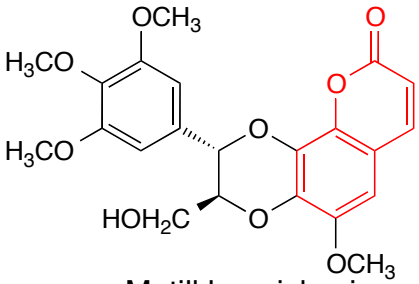




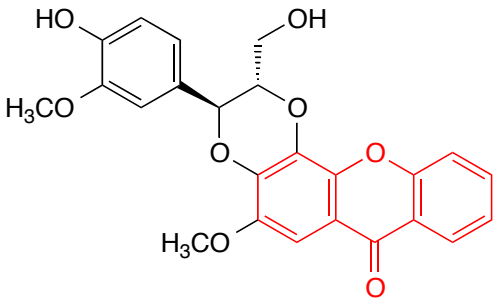


# Lignans

- Sometimes a phenylpropanoid unit joins with a coumarin, xanthone or flavonoid structure to form a hybrid lignan, depending on the type of non-phenylpropanoid part of the hybrid molecule they are named as coumarinolignan, xantholignan or flavonolignan.



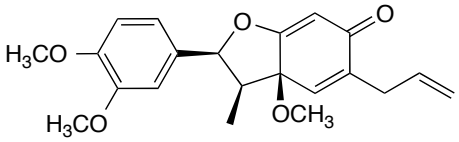
Metilkleomiskosin
(Kumarinolignan)



Kielkorin
(Ksantolignan)

# Lignans

- **Biological Activities of Lignans;**
  - Plants use lignans for their antibacterial, antifungal and insecticidal activities to protect themselves.
  - Most of the arylnaphtalen ve dibenzocyclo-octane derivative lignans have antimitotic and cytotoxic activities, nevertheless only podophyllotoxin derivetives were used as anticancer agents.
  - Many lignan and neolignan derivatives have enzyme inhibitor activities. For example, Chinese medicinal plant *Piper futokadsura* has antiallergic and anti-rheumatoid activities. **Kadsurenon**, a neolignan isolated from this plant, shows antiallergic and anti-inflammation activity by inhibition of the **P**latelet **A**ctivation **F**actor (**PAF**).



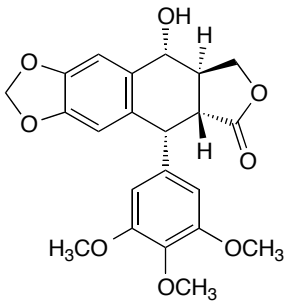

Kadsurenon



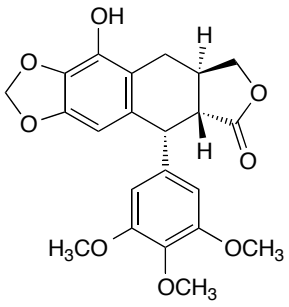
# Lignan Drugs

## Podophyllin

- **Drug**: Podophyllin is a resin obtained from the rhizome of ***Podophyllum peltatum* L.** (Berberidaceae. The rhizome contains ca. % 3-6 of resin.
- **Active compounds; 1-aryltetrahydronaphtalen derivative lignans: Podophyllotoxin (% 20), α-peltatin (% 5), β-peltatin (% 10) and related derivatives.**




Podofillotoksin

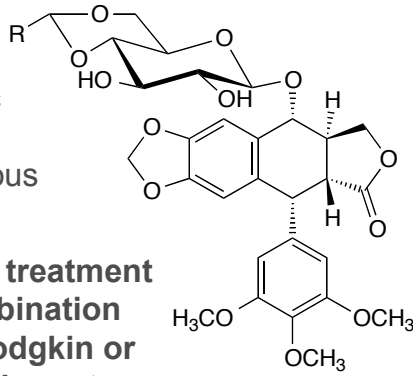



α-Peltatin

# Lignan Drugs

## Podophyllin (contd.);

- **Medical uses;** Podophyllin previously used as laxative and cholagouge, howerver, due to its extreme toxicity podophyllin is no longer used for these purposes. **Podophyllotoxin is an antimitotic substance, it stops tubulin polymerization and prevents cell division. Externally used for the treatment of condyloma (genital wart).**
- Currently **podophyllin** mainly used for the production of **podophyllotoxin.** Semi-synthetic derivatives of podophyllotoxin; **etoposide** and **teniposide** were used for the treatment of various cancer types.
- **Teniposide and etoposide were used for the treatment of various cancer diseases (alone or in combination with the other cancer medicines) such as Hodgkin or non-Hodgkin lymphoma, brain, bladder and breast cancer tumors.**



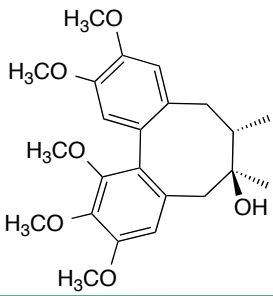

R = $CH_3$, Etopozit
R = Tiyenil, Tenipozit



# Lignan Drugs

## Schizandra, Wuweizi

- Drug: Fruits of ***Schizandra chinensis*** (Turcz.) Bailon (Schizandraceae).
- **Medical uses; Drug is used as tonic, cough suppressant and CNS stimulant in traditional Chinese medicine.**
- **Active compounds; More than 30 dibenzo-cyclooctane derivative neolignans were isolated from the seeds of this plant. Hepatoprotective effect of the alcoholic extract of seed kernels were shown. The antioxidant activity of neolignans were responsible for this activity.**

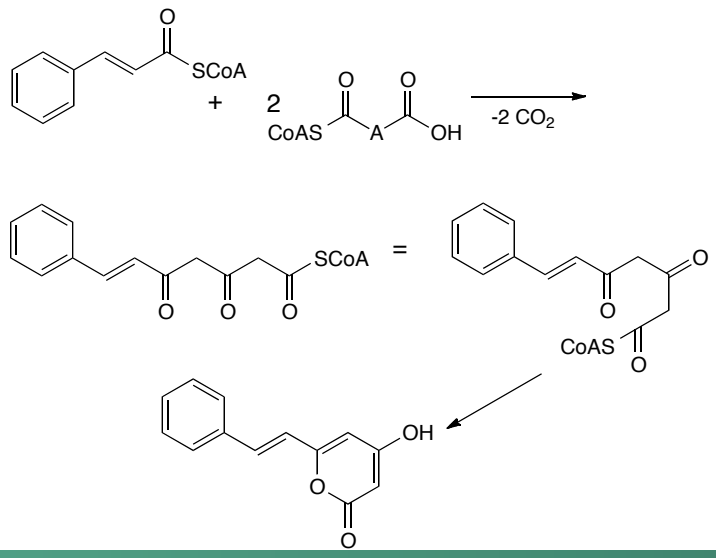



Şizandrin

# Styrylpyrones

**Chemical structure of styrylpyrones is a styryl group substituted (from the C-6) 4-hydroxy-α-pyrone compounds.**

Stirilpironların Biyosentetik Yolakları:






# Styrylpyrone Drug

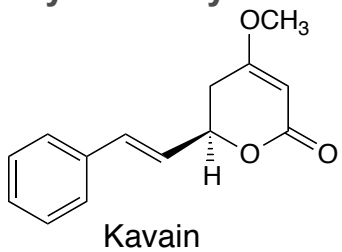
## Kava

- **Drug: A special drink prepared from the rhizome and root pieces of *Piper methysticum* Forst. (Piperaceae) (kava, kava-kava).**
- ***Piper methysticum***: Is a *Piper* species indigenous to Pacific islands, 14 varieties of this plant were used by **Polynesian**, **Micronesian** and **Melanesian** people.

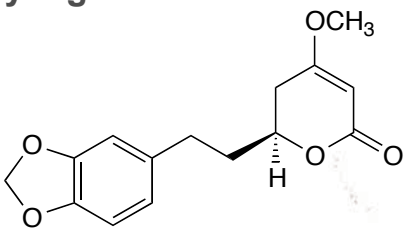
# Styrylpyrone Drug

## Kava

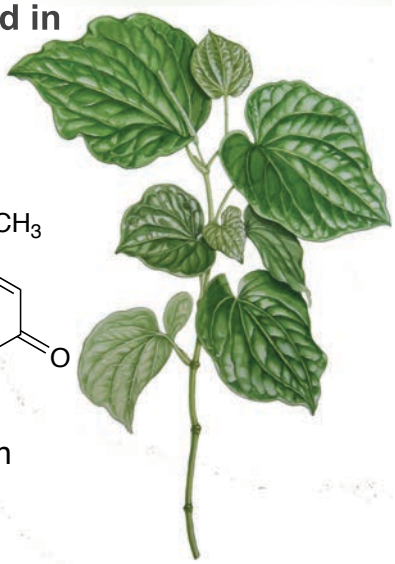
- Active compounds of the plant were styryl (phenylethyl)-α-pyrone derivatives, they are mainly found in the resin produced by the rhizome of *P. methysticum*. Major compounds were kawain, dihydrokawain, methysticin, dihydromethysticin ve yangonindir.




Kavain




Dihidrometistisin





# Styrylpyrone Drug

## Kava (contd.);

- Pharmacological activities of Kava, extracts of the *P. methysticum* rhizome (especially lipophyllic fractions), dihydrokawain and dihydromethysticin were investigated extensively.
- These compounds have sedative, sleep inducing, anticonvulsant, muscle relaxant activities.
- Phytopharmaceuticals containing these compounds were used as anxiolytic, sedative and for the treatment of insomnia.
- However, due to their hepatotoxic activity in certain people, use of these preparations were temporarily stopped in certain countries.