

# Lipids

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Lipids are natural substances, esters of fatty acids and alcohols or polyols. The lipids, also called «fats» are hydrophobic substances soluble in apolar or barely polar organic solvents and non volatile. They are referred to as «**fixed oils**» as opposed to «**essential or volatile oils**».

Lipids are commonly distinguished :

- **Simple lipids**, esters of a fatty acid and of an alcohol that may be :
  1. Glycerol, constituent of triacylglycerols or triglycerides
  2. A high molecular-weight aliphatic alcohol, a constituent of waxy esters
- **Complex lipids** : Phospholipids, glycolipids (except for lecithins, they have no pharmaceutical or industrial applications).

# **TRIACYLGLYCEROLS (TRIGLYCERIDES)**

## Natural Occurrence

Triacylglycerols are practically nonexistent in vegetative organs (leaves). They are stored as oily inclusions called oleosomes, which arise from the endoplasmic reticulum, and at times gather in large piles in the cells of reserve tissues; this is partially true in **seeds** which they may represent over 50% of the dry weight. The triacylglycerol content of seeds increases during the maturation process whereas in parallel, the phospholipids and glycolipids of young seminal tissues disappear.

## Structure of Triacylglycerols

They are triesters of triol, glycerol, and of fatty acids, in other words aliphatic carboxylic acids of variable length which normally have an even number of carbon atoms.

**Nature of the fatty acids** : The vast majority of vegetable fatty acids falls into two groups : **saturated fatty acids** and **unsaturated fatty acids**. In both groups 18 or 16 carbon atoms are most common.

**Saturated fatty acids** : Fatty acids with less than 12 carbon atoms are rare in plants : they occur, especially those in  $C_8$  and  $C_{10}$ , in the triacyl glycerols of palm seeds. Up to  $C_{14}$ , fatty acids are rarely present in substantial quantity : examples are bay butter ( $C_{12}$ ) and nutmeg butter. Fatty acids with 20 or more carbon atoms are not common either, except in peanut oil.

**Palmitic acid is the major saturated constituent of vegetable oils.**

$C_{6:0}$	:	hexanoic acid	=	caproic acid
$C_{8:0}$	:	octanoic acid	=	caprylic acid
$C_{10:0}$	:	decanoic acid	=	capric acid
$C_{12:0}$	:	dodecanoic acid	=	lauric acid
$C_{14:0}$	:	tetradecanoic acid	=	myristic acid
$C_{16:0}$	:	hexadecanoic acid	=	<b>palmitic acid</b>
$C_{18:0}$	:	octadecanoic acid	=	stearic acid
$C_{20:0}$	:	eicosanoic acid	=	arachidic acid
$C_{22:0}$	:	docosanoic acid	=	behenic acid
$C_{24:0}$	:	tetracosanoic acid	=	lignoceric acid
$C_{26:0}$	:	hexacosanoic acid	=	cerotic acid
$C_{28:0}$	:	octacosanoic acid	=	montanic acid
$C_{30:0}$	:	triacontanoic acid	=	melissic acid

**Unsaturated Fatty Acids** : The most important ones are in the  $C_{18}$  series

$C_{18:1}$  : 9-octadecenoic acid = **oleic acid**

$C_{18:2}$  : 9,12-octadecadienoic acid = **linoleic acid**

$C_{18:3}$  : 9,12,15-octadecatrienoic acid =  **$\alpha$ -linolenic acid**



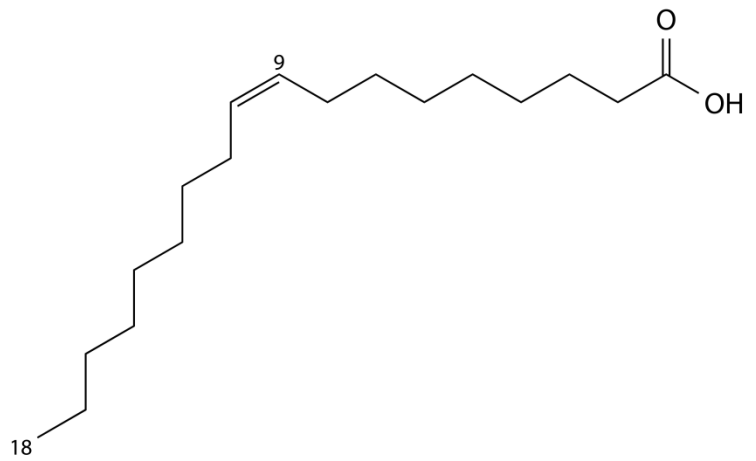
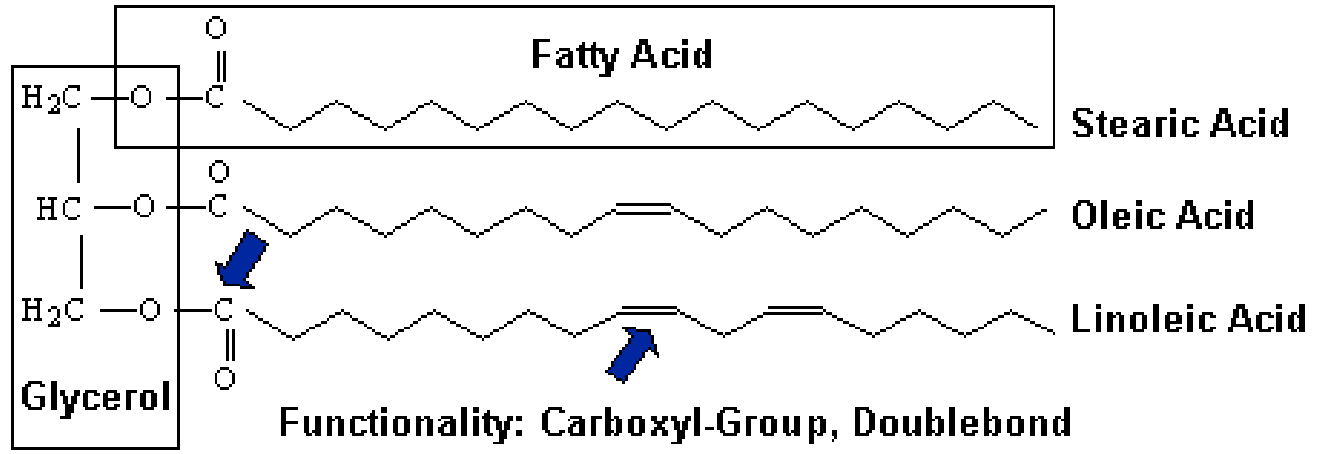
$C_{14:1}$ :	9-tetradecenoic acid	=	myristoleic acid
$C_{16:1}$ :	9-hexadecenoic acid	=	palmitoleic acid
$C_{20:1}$ :	9-eicosenoic acid	=	gadoleic acid
$C_{22:1}$ :	13-docosenoic acid	=	<b>erucic acid (toxic)</b>

Some isomers are rare

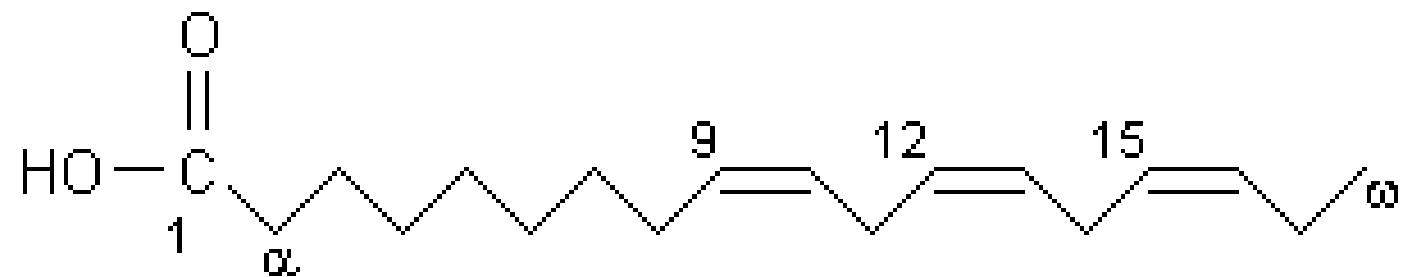
$C_{18:1}$ :	6-octadecenoic acid	=	petroselinic acid
$C_{18:1}$ :	11-octadecenoic acid	=	cis-vaccenic acid
$C_{18:3}$ :	6,9,12-octadecatrienoic acid	=	<b><math>\gamma</math>-linolenic acid</b>

Exceptional

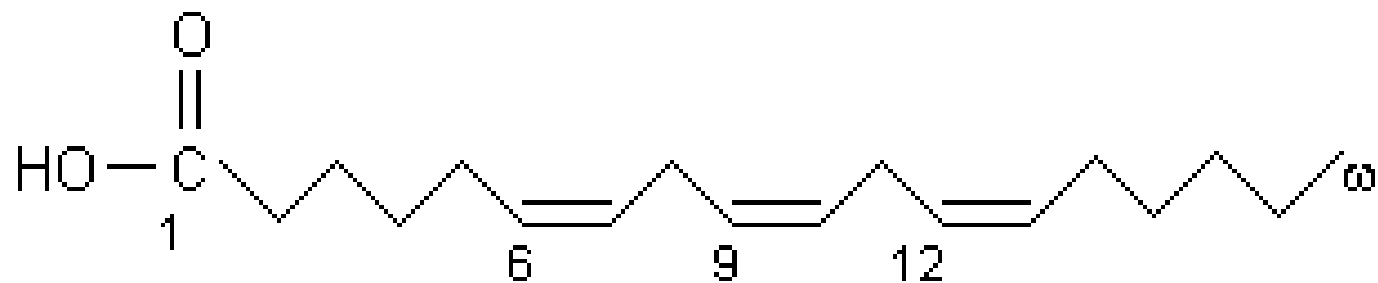
$C_{20:4}$ :	5,8,11,14-octadecatetraenoic acid	=	<b>arachidonic acid</b>
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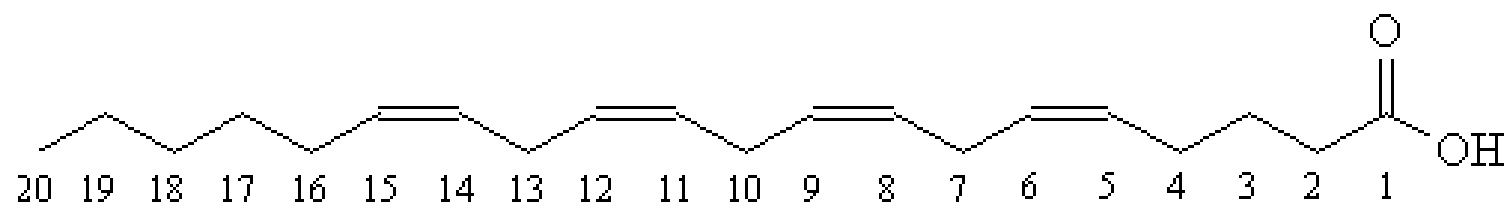
**Oleic acid**



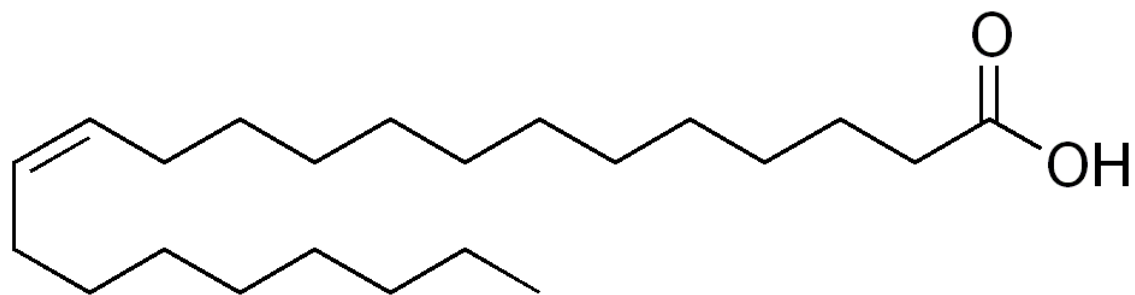
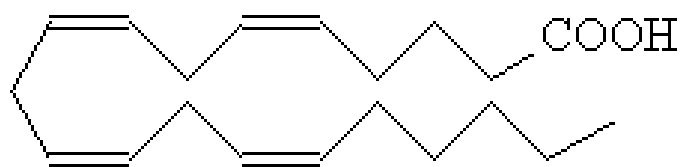
**α-linolenic acid**



**γ-linolenic acid**



Arachidonic acid  
5,8,11,14-eicosatetraenoic acid



Erucic acid

**Properties of Glycerides and Fatty Acids** : Triacylglycerols are soluble in organic solvents, including acetone, and this differentiates them from phospholipids. On treatment by an alkaline hydroxide, they release one molecule of glycerol and three molecules of fatty acid : the saponification value determined by this method provides information on the average chain length. Unsaturated fatty acid-containing triacylglycerols become rancid : when exposed to air they develop foul smells more or less rapidly. This phenomenon is linked to peroxidation of unsaturated fatty acids : the resulting peroxides may polymerize. They may also be cleaved and yield aldehydes, ketones, and acids of unpleasant odor.

In general, acylglycerols involving saturated fatty acids are solid and those of unsaturated acids are liquids. They are all insoluble in water and soluble in organic solvents. As acids they form salts : this is the basis of the soap and detergent industry (alkaline salts, organic base salts). As acids they may be esterified : the volatility of their methyl esters is greater than that of the acids and makes them amenable to GC analysis.

## **OIL PRODUCTION**

**Extraction by Expression** : Expression of the starting material yields the oil directly.

**Extraction by Solvents** : The solvent is generally hexane (bp 65°C).

## **REFINING THE CRUDE OIL:**

Crude oils obtained by distillation of the miscella may contain water, free fatty acids, lecithins, resins, pigments, (carotene, chlorophyll), sterols, waxes, substances with odors and tastes. Refining includes the following sequence :

**Degumming** (mucilage removal): Its role is to eliminate lecithins, proteins, and other constituents present in the oil in colloidal suspension. To accomplish this the hot oil is hydrated, where upon the colloids form a dense gel which separates from the lighter oil. The gel is discarded and the oil dried under vacuum.

**Neutralization** : The free fatty acids, always present in the crude oil, are neutralized by dilute sodium hydroxide. The soap (soap stock) adsorbs part of the impurities : coloring matter, phenols, sterols, wax esters. The excess soap and sodium hydroxide are removed by washing with hot water.

**Bleaching** : This is done by passing the oil through diatomaceous earth or activated charcoal. The bleaching agent is removed by filtration.

**Wax removal** : The crude oils rich in waxes (sunflower, corn, cotton) are freed from those by cooling (winterization): the crystallized waxes are removed by filtration.

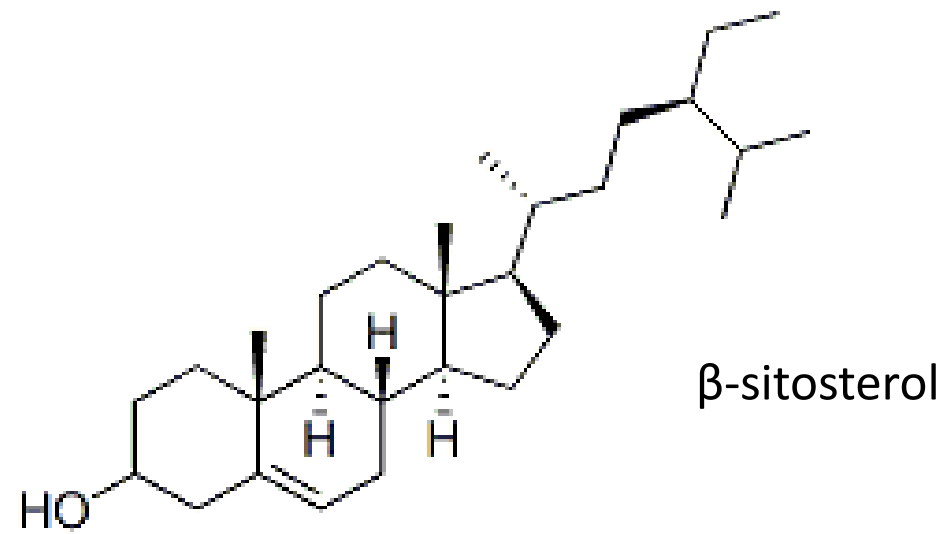
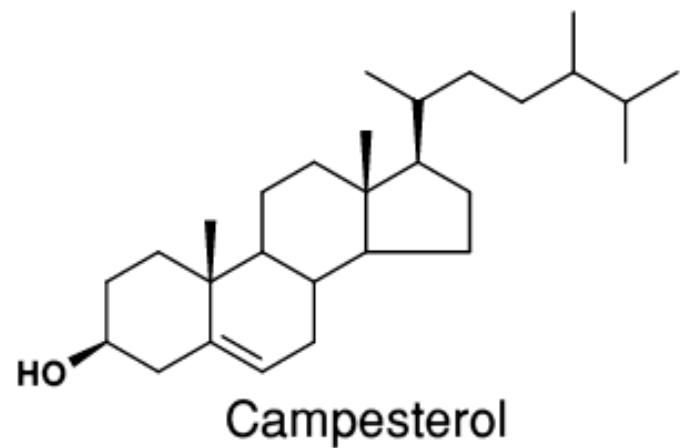
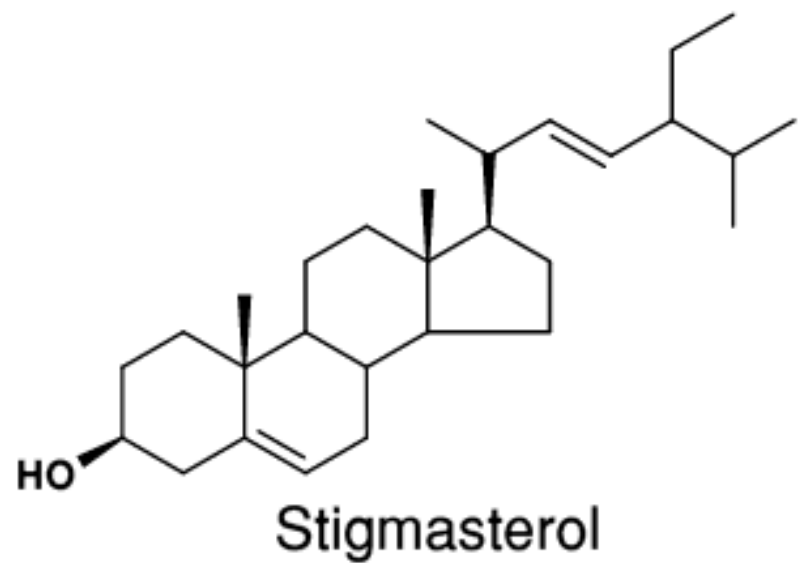
**Deodorizing** : The aldehydes and ketones responsible for the unpleasant odor of crude oil are eliminated by injecting steam into the very hot oil under high vacuum.



# QUALITY CONTROL FOR LIPID-CONTAINING DRUGS : TESTS FOR FIXED OILS

- Determining the fatty acid composition is easy : it is carried out on methyl esters obtained by methylation subsequent to saponification or, more directly, by alkaline methanolysis. This method is by far the most often used for fat analysis. After methylation the composition will be identified mostly by GC (Gas chromatography).
- The main constituents of the unsaponifiable matter are saturated and unsaturated, aliphatic or tetraterpenoid hydrocarbons (carotenes), sterols, triterpenoid alcohols, fatty alcohols, vitamins (tocopherols, tocotrienols). **The sterols are, from the analytical point of view, the most interesting constituents of the unsaponifiable matter.**

They are generally represented by two to five major sterols that are commonly  $\Delta^5$ -sterols (sitosterol, campesterol, stigmasterol). Sterols are analyzed generally and tocopherols occasionally. In both cases, preliminary extraction of the unsaponifiable matter is necessary (with diethyl ether or hexane), and so is separation, which is straight forward by preparative TLC. The recover sterol fraction is analyzed directly by GC.



## **European Pharmacopoeia and Fixed Oils**

Quality control of fixed oils listed in the European Pharmacopoeia includes common assays and, tests specific to the oil under consideration. For each fixed oil will be determined :

**Specific gravity**

**Acid value**

**Peroxide value**

**Unsaponifiable matter**

**Foreign oils in fixed oils**

**Amygdalae oleum**

**Almond oil**

**Badem yağı**

***Prunis dulcis = Prunus amygdalus***

**Rosaceae**

According to the 3. edition of the European Pharmacopoeia, amygdalae oleum is the fatty oil obtained by cold expression from the ripe seeds of *Prunus dulcis* var. *dulcis* or sometimes of *Prunus dulcis* var. *amara* (*Prunus amygdala*).

**Fatty acid Composition of the oil** : major acids are, oleic acid (62-86%), linoleic acid (20-30%), palmitic acid (4-9%).

The unsaponifiable part is rich in sitosterol and avanasterol.

The composition of the sterol fraction and the fatty acid composition are determined by GC.

**Uses :** Almond oil is mainly used in cosmetology and dermatology. It is said to relieve **skin irritation** and the sensation of heat (after-sun lotions, after-shaves, makeup removers...). Bitter almonds are also used to produce essential oils. After elimination of the epicarp, the oil is extracted from the almonds .

**Arachidis oleum**  
*Arachis hypogea*

**Peanut oil**  
**Fabaceae**

**Yer fıstığı yağı**



Arachidis oleum is obtained from the shelled seed of *Arachis hypogea*. Fatty acid composition of the oil : Major acids are oleic (35-72%), linoleic (13-43%), palmitic (7-16%) and stearic (1.3-6.5%) acids. The unsaponifiable part contains  $\beta$ -sitosterol, campesterol,  $\alpha$ - and  $\gamma$ -tocopherol.

**Uses** : In pharmacy, this oil is an oily excipient. When it is intended for the preparation of parenteral formulations, it must contain not more than 0.3% water and its acid value must not be more than 0.5%.

Pharmaceutical technology also uses hydrogenated peanut oil. The peanut, as such or as derived products (meal, oil, butter), has an important place in the human diet.

**Peanut is also one of the major causes of food allergy. Sometimes fatal, this allergy is most often severe : respiratory difficulties, edema of the larynx, eczema, and gastrointestinal symptoms. Immediate medical attention is crucial to the survival of many susceptible patients (adrenalin, corticosteroids).**

**Maydis oleum**  
*Zea mays*

**Corn oil**  
**Poaceae**

**Mısır yağı**

Recall the uses of this cereal for its styles in phytotherapy, and especially for starch and its derivatives, which are largely exploited by pharmaceutical technology. During the starch preparation process, the steeped grains are separated from the germs prior to fine milling : the germs are recovered, and may contain up to 20% lipids (dried germs).

The major fatty acids are linoleic (45-62%), oleic (24-33%), palmitic (8-13%) and stearic (1-4.5%) acids.

**Olivae oleum**  
*Olea europea*

**Olive oil**

**Oleaceae**

**Zeytin yağı**

Olivae oleum may be obtained from the «ripe drupes by cold expression or by any other appropriate mechanical means».

The major fatty acids in the oil are : oleic acid (58-85%), linoleic acid (3.5-20%), palmitic acid (7.5-20%), stearic acid (0.5-5%).

The unsaponifiable part is rich in tocopherols, triterpenes and pigments (carotenes, chlorophylls).

Official olive oil is traditionally used as choleric and cholagogue.

Some authors believe that it has mild laxative properties. **Externally, it is a demulcent and emollient. It is a good solvent for drugs. Once refined, it is a solvent for parenteral preparations.**

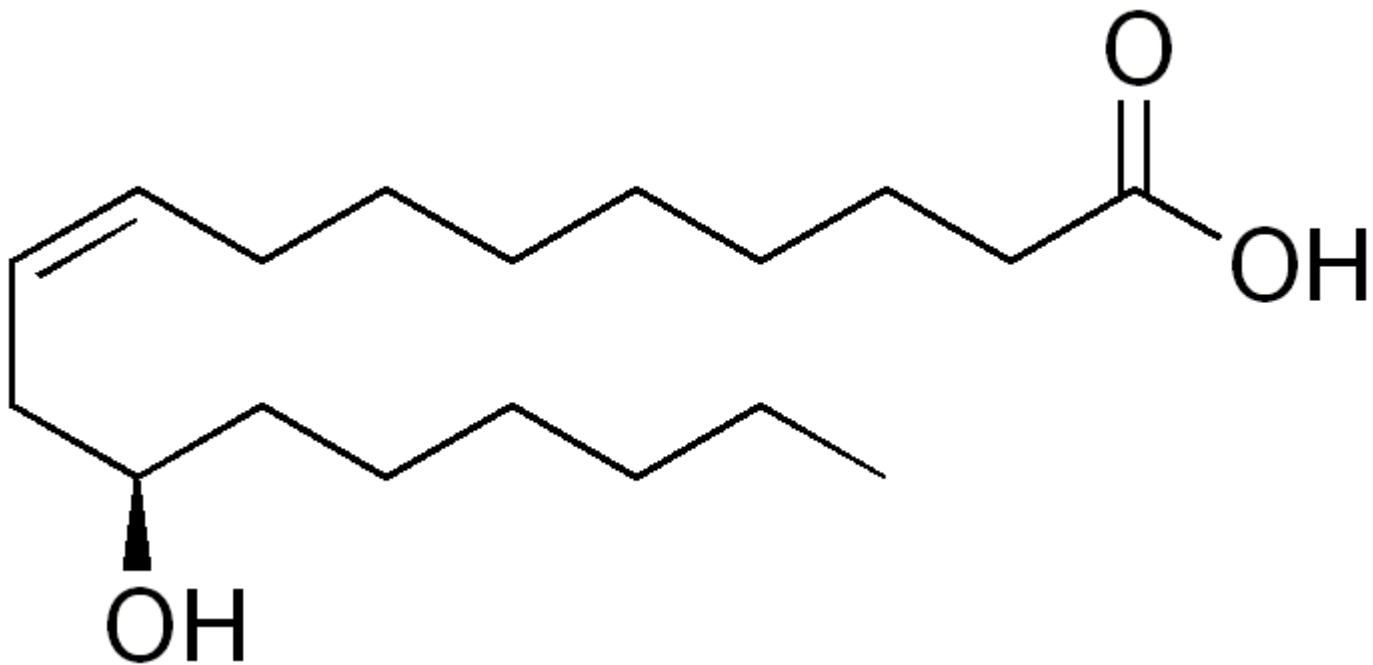
**Ricini oleum**  
*Ricinus communis*

**Castor oil**  
**Euphorbiaceae**

**Hint yağı**

Castor oil is the fixed oil obtained by cold expression from the seeds of *Ricinus communis*.

**Chemical composition** : Ricini oleum has a very peculiar composition, in that its major constituents (90%) are triacylglycerols containing an unsaturated and hydroxylated C 18 fatty acid :  
(R)-(+)-12-hydroxy-Z-octadec-9-enoic acid = Ricinoleic acid





The other castor oil fatty acids are also C<sub>18</sub> compounds oleic (3%) and linoleic (3-4%) acids. Other constituents have been described, including **a toxic glycoprotein lectin:ricin**, and a cyano derivative of pyridone : ricinine.

**Properties and Uses : Known since remote times, used for lighting in India, as well as in Greece and the Rome of antiquity, castor oil also used to be prized for its laxative properties : it is drastic cathartic**, which must now be formally prescribed.

**Castor : a toxic plant : Ricin is an extremely dangerous toxin. If the digestive troubles (vomiting, diarrhea) persist, they can lead to dehydration with subsequent onset on neurological symptoms. Although mortality is lower than what older texts suggest, intoxication by castor beans, especially in young children, makes hospitalization necessary (toxin removal, control of electrolytes).**

**Sesami oleum**

***Sesamum indicum***

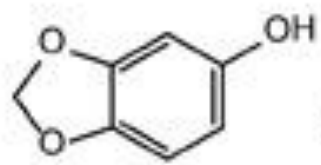
**Sesame oil**

**Pedaliaceae**

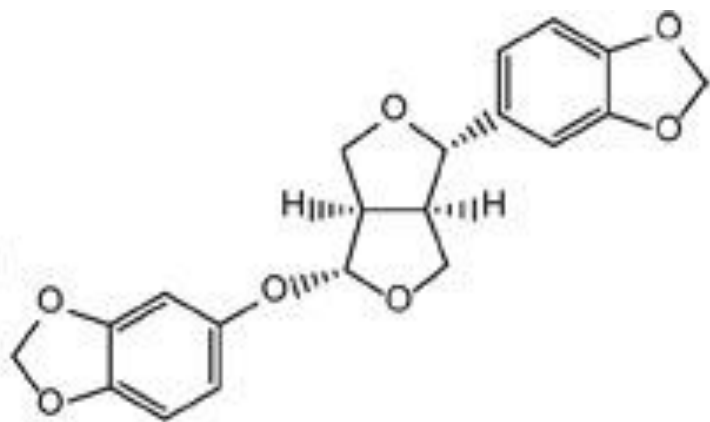
**Susam yağı**

Sesame oil is obtained from the ripe seeds of *Sesamum indicum* by expression or extraction and subsequent refining.

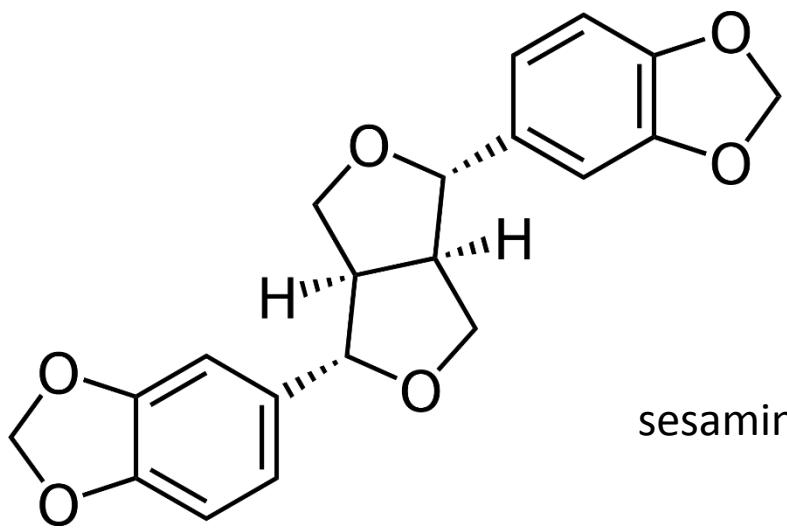
Sesame seeds (Sesami semen) contain 40-50% lipids, 20% carbohydrates and 20-25% proteins. The unsaponifiable matter contains diarylfuranofuranic lignans, including sesamin and sesamolin (up to 5%, each). During industrial refining, sesamolin yields antioxidant phenols, sesamol and in smaller quantities sesamolinol. Sesamol allows the detection of sesame oil in other oils because it gives a color reaction with furfural in acidic medium.



sesamol



sesamolin



sesamin

Major fatty acids in Sesami oleum are oleic and linoleic acids (35-50%, each) and also palmitic acid (7-12%), stearic acid (3.5-6%). The unsaponifiable matter contains, in addition to the lignans especially  $\beta$ -sitosterol and campesterol in high amounts.

Uses : A mild laxative, sesame oil is stable in storage; it may be used as a drug solvent. The cosmetics industry uses an extract enriched in unsaponifiable matter (lignans, especially sesamin) as an antioxidant and radical scavenger.

**Sojae oleum**  
*Glycine max*

**Soybean oil**  
Fabaceae

**Soya yağı**

The third edition of the European Pharmacopoeia defines «soybean oil» as the «refined fatty oil obtained from the seeds of *Glycine max* = *Glycine soja*).

Sojae oleum contains linoleic (48-58%), oleic (17-30%), palmitic (9-13%), and linolenic (5-11%) acids.

The unsaponifiable matter contains in high amounts  $\beta$ -sitosterol and tocopherols.

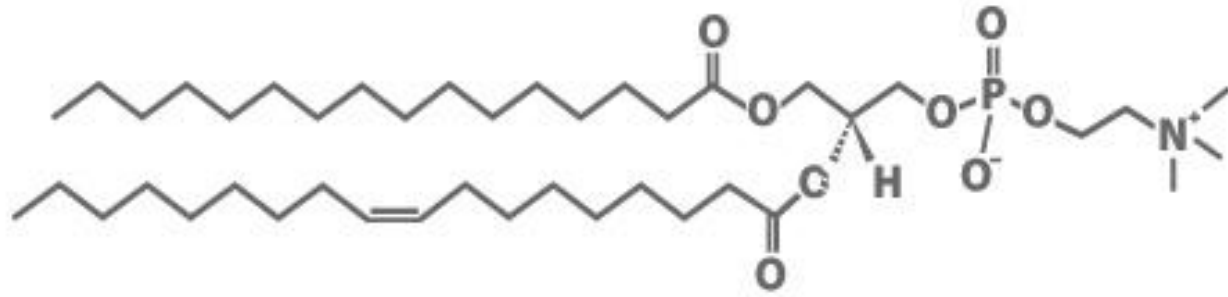
**Uses** : In pharmacy, refined soybean oil is used for parenteral feeding (for caloric intake and essential fatty acid intake). The administration must be by slow infusion under medical observation; the adult posology is 1-3 g/kg/day. The main use of soybean oil is, of course, dietary.

# Soybean Lecithins

Soybean is currently the chief source of lecithins used in food technology. Since crude lecithin from degumming generally contains 60-70% lecithins and 30-40% soybean oil, products are preferred that have undergone one or several treatments : purification, defatting (low viscosity products), modifications (to obtain more hydrophilic products), fractionation or hydrogenation.

In pharmacy, lecithin yields liposomes and can help formulate stable emulsions. Its main outlet is food technology.





structure of lecithin (phosphatidilcolin) molecule

**Soybean Proteins** : Soybean is an important source of proteins. The use of soybean proteins has healthful benefits : it has long been known that substituting soybean proteins for animal proteins induces a decrease in triglycerides (-10.5%), total cholesterol (-9.3%) and LDL cholesterol (-12.9%), without altering HDL cholesterol. Because of good biological value and because the absence of toxicity has been documented by secular use of soybean products in Asia, many experts recommend blending these proteins into diets designed to control hypercholesterolemia.

# Oils with $\gamma$ -linolenic acid

Fats are required nutrients, and it is generally accepted that they must constitute 30 to 35% of the daily caloric intake in a normal diet. Although fats provide a substantial amount of energy in a small volume, it must be noted that all the fatty acids that constitute them do not have the same role or the same worth. Some polyunsaturated fatty acids are in fact indispensable : they are called essential (**essential fatty acids = EFA**) because they are not synthesized by the human body (for example linolenic acid), or are synthesized in sufficient amounts only by the young and healthy body (arachidonic acid).

EFAs have an important biological role : as constituents of the phospholipids of cell membranes, they may contribute to ensuring their fluidity ; they are also precursors of eicosanoids (prostaglandins, leukotrienes, and thromboxanes), which have multiple known functions as intra- and intercellular mediators, and as agents in platelet aggregation or in the inflammatory process.

Thus linolenic acid is necessary regardless of age or health status, and the need is estimated at about 6-8% of the caloric ration and is satisfied by the consumption of vegetable fats. Linolenic acid deficiency manifests itself by dermatological signs (such as eczema, lesions, impetigo, and erythema), delayed growth, hypertension, and poor platelet aggregation.

Certain factors may lead to a marked decrease in  $\Delta^6$ -**desaturase activity** : stress, aging, alcoholism, nicotine addiction, hepatic insufficiency, and diabetes mellitus, among others. Diet must fulfill the needs in polyunsaturated fatty acids, especially in **arachidonic acid**, present in eggs and livers; but absent in vegetable oils.

$\alpha$ -Linolenic acid is present in most vegetable oils, but  **$\gamma$ -linolenic acid** is much more rare. The most interesting sources appear to be evening primrose seeds and borage seeds.

**Oenotherae oleum**  
*Oenothera biennis*

**Evening primrose oil**  
**Onagraceae**

**onethera yağı**

The drug is rich in unsaturated fatty acids  $\gamma$ -linolenic acid (8-14%), linoleic acid (65-80%), oleic acid (6-11%). The oil is extracted by cold expression, and like all other highly unsaturated oils, it is very difficult to preserve. Evening primrose oil is used in the formulation of cosmetic products and toiletries. This products are said to have the potential for preserving skin elasticity and preventing wrinkle formation. Several studies have attempted to support various indications for evening primrose oil by the oral route : breast pain, premenstrual syndrome, hypercholesterolemia, eczema, cirrhosis, rheumatoid arthritis, psoriasis, and more.

The plant is cultivated in the United Kingdom for the production of seeds.



**Borago oleum**

***Borago officinalis***

**Borago oil**

**Hodan yağı**

**Boraginaceae**

Borage is also cultivated for the production of the oil seeds contained in its dehiscent akenes. The oil content varies from 13 to 33% depending on the mode of extraction and the degree of ripeness. This is an unsaturated fatty acid-containing oil, with linoleic acid (30-40%),  $\gamma$ -linolenic acid (18-25%) and oleic acid (15-19%). The uses of this unstable oil are the same as those of evening primrose oil.

# **Unsaponifiable Matter and Related Compounds**

The unsaponifiable matter, composed of the non-glyceride constituents of oil, represents from 0.3 to 2% of the weight of the oil. The composition of the unsaponifiable matter is often complex ; the most common constituents are hydrocarbons, carotenoids, sterols, (sitosterol, stigmasterol,  $\Delta^7$ -sterols), tocopherols, high molecular weight-aliphatic alcohols and terpenoid alcohols.

**Avocado fructus**

***Persea americana***

**Avocado fruit**

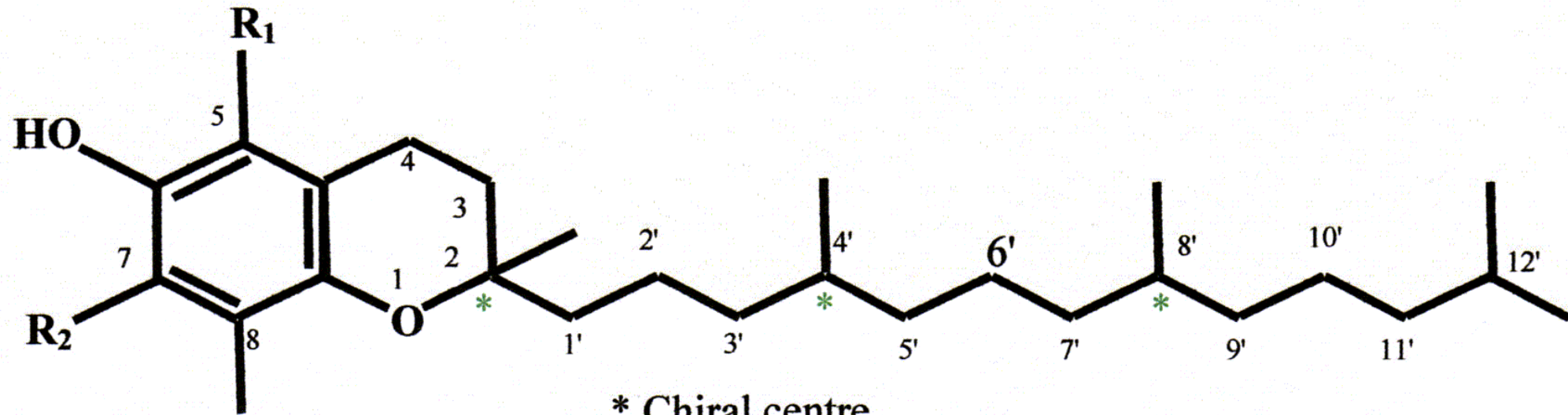
**Lauraceae**

**Avokado meyvesi**

The fleshy mesocarp of the fruit yields a viscous, brownish green oil with a fruity odor. The major fatty acids of this oil are oleic (42-63%), palmitic (17-29%), linoleic (9-16%) and palmitoleic (6-12%) acids. Branched hydrocarbons account for half of the unsaponifiable matter, the level of which may reach 1%, it contains 20% sterols and highly reducing triols. The unsaponifiable matter of avocado is proposed in stomatology as the basic treatment for periodontitis, and used in rheumatology as an adjunctive therapy for arthritis pain.

# Tocopherols

Tocopherols are prenylated derivatives of benzohydropyran.



\* Chiral centre

R<sub>1</sub> = R<sub>2</sub> = CH<sub>3</sub>:

α-Tocopherol

R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = H:

β-Tocopherol

R<sub>1</sub> = H, R<sub>2</sub> = CH<sub>3</sub>:

γ-Tocopherol

R<sub>1</sub> = R<sub>2</sub> = H:

δ-Tocopherol

The tocopherols constitute what some call vitamin E, a natural antioxidant especially for fatty acids : the tocopherols are highly oxidizable, form an epoxide first, then by opening and dehydration, a p-quinone. The normal consumption of oils, margarines, and cereals easily fulfill the daily needs (10-12 mg/day). Because of lipoprotein oxidation might play a role in atherogenesis, many studies have attempted to show a possible protective effect of vitamin E against cardiovascular disease. These studies suggest that a diet rich in vitamin E has a protective effect, but they are not without bias, therefore they fail to show a significant correlation between vitamin E intake and the risk of coronary disease.



**Pruni africanae cortex**      **African plum bark**  
*Prunus africana* = *Pygeum africanum*

**Afrika eriği gövde kabuğu**  
**Rosaceae**

The drug consist of the bark : red or dark brown, it smells weakly of hydrocyanic acid. The product most commonly used is lipid and sterol extract obtained by organic solvent extraction.

Analysis of the extract shows that it contains a lipid fraction ( $C_{12-24}$  fatty acids), phytosterols (free and conjugated  $\beta$ -sitosterol, campesterol), triterpenoid pentacyclic acids (ursolic, oleanolic.....), and linear aliphatic alcohols.

**Uses :** *Prunus africana* extract is used orally (100 mg/day in 6-8 week cycles) for the following indication : to treat moderate bladder outlet obstruction symptoms due to benign prostatic hyperplasia (BPH).

**Sabalıs serrulati fructus**

***Sabal serrulata = Serenoa repens***

**Saw palmetto fruit**

**Palmaceae**

**Cüce palmiye meyvesi**

The fruit constitutes the drug . The species grows wild in sandy soils of the southern United States .

Fruits and seeds are rich in a triacylglycerol-containing oil, with nearly 50% of the fatty acids containing 14 or fewer carbon atoms. These fatty acids, especially lauric acid, are present in the commercial lipid and sterol hexane extract. The extract is rich in phytosterols (sitosterol, campesterol, and sitosterol derivatives).

Uses : The lipidosterolic extract of the saw palmetto is marketed with the following indication (320 mg/day, per os) : treatment of moderate bladder outlet obstruction symptoms linked to benign prostatic hyperplasia.

**Cucurbitae peponis semen**  
*Cucurbita pepo*

**kabak çekirdeği**  
**Cucurbitaceae**

**Urticae radix**  
*Urtica species*

**ısırgan kökü**  
**Urticaceae**

**Both drugs contain same constituents and have same usage with *Sabalıs serrulati fructus*.**

## Other oils

### Common dietary oils

Brassicae napi oleum = Rapeseed oil = Kolza yağı

*Brassica napus var. oleifera*

Helianthi oleum = Sunflower oil = Ayçiçeği yağı

*Helianthus annuus*

Cocos nuciferae oleum = Coconut palm oil = Hindistan cevizi yağı  
*Cocos nucifera*

Elaeis oleum = Palm oil = Palmiye yağı *Elaeis guinensis*

# An oil important for Cosmetology

**Arganiae oleum = Argan oil = Argan yağı    *Argania spinosa***

## **Reference Books :**

### **Main Book**

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