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Lipids: Vegetable Oils

1. OILS SUBJECT TO A MONOGRAPH IN THE PHARMACOPOEIA (EUROPEAN 3r d EDITION, OR FRENCH, 10t h EDITION)

● Almond Oil

According to the 3rd edition of the European Pharmacopoeia, this oil is «the fatty oil obtained by cold expression from the ripe seeds of *Prunus dulcis* (Miller) D.A. Webb var. *dulcis* or *Prunus dulcis* (Miller) D.A. Webb var. *amara* (D.C.) Buchheim or a mixture of both varieties». The Pharmacopoeia also describes refined almond oil.

The Plant, the Drug. The almond tree is a Rosaceae with white or pinkish flowers very widely cultivated around the Mediterranean, including in Spain, Italy, Greece, Turkey, and North Africa, but also in Iran and in the western United States. The fruit is an oblong drupe with light green velvety epicarp; the seed is oval, flattened, and has a thin and wrinkly tegument that is easy to peel off. It tastes mild, oily, and slightly sweet. The seeds of the two varieties, *amara* and *dulcis*, are rich in oil (50-60%) and can only be distinguished by the occurrence in the *amara* variety of a cyanogenic glycoside, the gentiobioside of mandelonitrile: amygdalin. Its hydrolysis yields two molecules of glucose and, by decomposition of mandelonitrile, benzaldehyde and hydrocyanic acid.

Fatty acid composition * *of the oil* (major fatty acids, %, Eur. Ph., 3rd Ed.): shorter than C_{16}< 0.1; palmitic, 4-9; palmitoleic, <0.6; margaric, <0.2; stearic, <3; oleic, 62-86; linoleic, 20-30; linolenic, <0.4; arachidic, gadoleic, behenic, and erucic, <0.1.

The unsaponifiable matter (<0.7%) contains sitosterol, Δ^5-avenasterol (73-87% and >10% of total sterols, respectively); the cholesterol content is <0.7%, brassicasterol <0.3% (Eur. Ph.). α-Tocopherol is dominant: 92-99% of total tocopherols.

Tests. In addition to the common tests, the French Pharmacopoeia prescribes a search for persic oil or peach kernel oil (no color with nitric acid), as well as sesame oil (no blue-green color with a furfural solution in acetic anhydride in the presence of sulfuric acid [verification of the absence of sesamol]).

The composition of the sterol fraction and the fatty acid composition (and the absence of foreign fixed oils) are determined by GC.

* For official oils, the values listed in this chapter are from the pharmacopoeias. For non-official oils, the values are, unless otherwise indicated, from the handbook on fats by A.

Uses. Almond oil is mainly used in cosmetology and dermatology. It is often substituted for by hazelnut oil (*Corylus avellana* L.*, Corylaceae) which has a similar composition (the kernel contains 50-60% oil). The cosmetic industry also uses a fraction containing essentially low molecular-weight proteins associated with carbohydrates. This active fraction is said to relieve skin irritation and the sensation of heat (after-sun lotions, after-shaves, makeup removers, and so on).

Bitter almonds (but also other Rosaceae seeds, such as apricot kernels) are also used to produce essential or volatile oil of almonds. After elimination of the epicarp, the oil is extracted from the almonds of these various species, and the cattle cake undergoes steam extraction. The crude essential oil is treated with ferrous sulfate and calcium hydroxide to eliminate hydrocyanic acid, then submitted to another steam distillation. This essential oil of almonds, in competition with synthetic benzaldehyde **, is used as flavor, chiefly in food technology. Packaged under nitrogen, it must be stored protected from air to prevent the formation of benzoic acid. It can be stabilized by the addition of ethanol.

● Peanut Oil

Peanut oil (Eur. Ph., 3rd Ed.), one of the most consumed in the world, is obtained from the shelled seed of a Fabaceae, *Arachis hypogaea* L., the peanut, also called groundnut, earthnut, or arachis. This species, native to the South American tropics, has been used since early times: the culture of *tlacacahuatl* —later to become the French *cacahuète*—is documented in Peru during the third millennium B.C. Introduced in western Africa in the 16th century, then in Asia, it is now one of the oilseed crops most cultivated on the planet, including in China, India, western Africa (e.g., Nigeria, Senegal, Sudan, Congo), the United States, and Indonesia

The Plant, the Drug. Botanically we shall merely emphasize the peculiarity of this annual herb of modest size, which stands erect or lies down, a curiosity which is linked to its mode of fructification. First, the ovary of the flower is borne by a short support, the gynophore; after fertilization, the latter lengthens and lengthens, bows toward the earth, and gradually buries beneath it the fertilized ovary; there, the ovary

* Oleic acid: 66-83%, linoleic acid: 8-25%, triolein, 44-60%. The leaves of this indigenous shrub are also used for medicinal virtues. They are traditionally used [French Expl. Note, 1998]: for the subjective symptoms of the functional troubles of venous insufficiency, such as fullness or tiredness in the legs, and for hemorrhoids; for the symptomatic treatment of mild diarrhea; and locally (collutoria, lozenges) as antalgics in diseases of the buccal cavity and/or of the oropharynx. The composition of the drug is ill-known. It is known to contain proanthocyanidols; see Parcerisa, J., Richardson, D.G., Rafecas, M., Codony, R. and Boatella, J. (1997). Fatty Acid Distribution in Polar and Nonpolar Lipid Classes of Hazelnut Oil (*Corylus avellana* L.), *J. Agric. Food Chem.*, **45**, 3887-3890.

** The natural origin of this essential oil—FFPA, i.e., free from prussic acid—can be verified

OLEA EUROPAEA L.

turns into an indehiscent pod with bumps where it contains 1-3 seeds: this is the peanut. The seed consists of two oily cotyledons covered by a thin tegument of variable color. The oil content of the kernel may exceed 50% (in the industry, 100 kg of fruit yield 70 kg of seeds, which yield, by expression-extraction, 34 kg of oil). The cattle cake may be used as animal feed, as the protein content of the seed ranges from 20 to 50%.

Fatty acid composition of the oil (major fatty acids, %, Eur. Ph., 3rd Ed.): $<C_{16}$, <0.4; palmitic, 7-16; stearic, 1.3-6.5; oleic, 35-72; linoleic, 13-43; linolenic, <0.6; arachidic, 1-3; gadoleic, 0.5-2.1; behenic, 1-5; erucic, <0.5; lignoceric, 0.5-3. The wide ranges allowed by the Pharmacopoeia take into account the variability linked to the geographical origin, with the African oils—regardless of the botanical variety—containing far more oleic acid (48-66%) than the South American oils, which contain relatively more linoleic acid (35-41%).

The unsaponifiable matter (0.6-1%; <1% [Eur. Ph.]) contains β-sitosterol and campesterol (58-67% and 12-19% of total sterols, respectively), as well as α- and γ-tocopherol (42-65% and 30-52% of total tocopherols, respectively).

Tests, Uses. The tests are the classic ones for oils. They include verifying the absence of sesame oil (see almond oil) and that of semidrying oils, by saponification and determination of the solidification temperature.

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

Pharmaceutical technology also uses hydrogenated peanut oil (Eur. Ph., 3rd Ed. Add. 1998 [fatty acids, %]): $< C_{14} < 0.5$; myristic, < 0.5; palmitic, 7-16; stearic, 3-19; oleic and isomers, 54-78; linoleic and isomers, < 10; arachidic, 1-3; eicosenoic, < 2.1; behenic, 1-5; erucic and isomers, < 0.5; lignoceric, 0.5-3.

The peanut, as such or as derived products (meal, oil, butter), has an important place in the human diet. It 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). It is absolutely necessary for these patients to exclude peanut and its derived products from their diet, and this is difficult to achieve because food labels are often incomplete.

• Corn Oil

Recall (see polysaccharide-containing drugs) 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

Pharmacopoeia (10th Ed.) specifies that the oil is obtained from the caryopsis, «with the major part of the cotyledon removed».

Fatty acid composition of the oil (major fatty acids, %): $<C_{16}$, <0.1; palmitic, 8-13; stearic, 1-4.5; oleic, 24-33; linoleic, 45-62; linolenic, 0.5-1.5; arachidic, gadoleic, and behenic, <0.5; erucic, <0.1.

The unsaponifiable matter (0.8-2%) contains β-sitosterol and campesterol (63-70% and 16-21% of total sterols, respectively), as well as γ- and α-tocopherol (68-89% and 8-22% of total tocopherols, respectively).

As far as tests are concerned, corn oil must pass those that are general for oils (various values, absence of foreign fixed oils, and so on). It must also be free of sesame (see almond oil), rapeseed, safflower, and sunflower oil. Verifying the absence of these oils entails GC analysis of the sterols, including brassicasterol quantitation in particular. Determination of the tocopherol level is also required (chromatography of the oil on a very selective adsorbent followed by colorimetric quantitation of the tocopherols [2,2'-bipyridine and ferric chloride]; level to be not less than 0.1%).

• Persic Oil

According to the French Pharmacopoeia, persic oil is the fixed oil obtained from the kernels of various species of *Prunus* by cold expression. The Pharmacopoeia also has a monograph for refined persic oil «obtained by refining and deodorizing» the crude oil.

The kernels that are used are those of apricots (*P. armeniaca* L.), peaches (*P. persica* Stokes), cherries * (*P. cerasus* L.), and plums (*P. domestica* L.).

Fatty acid composition of the oil (major fatty acids, %): $<C_{16}$, <0.1; palmitic, 4-9; stearic, <4; oleic, 58-80; linoleic, 10-32; linolenic, <0.1; arachidic and gadoleic, <0.2; erucic, <0.1.

Persic oil, which must not smell or taste like bitter almond, must pass the common tests for oils, and must not contain sunflower oil (as shown by GC of the sterols). The refined oil must fulfill stricter quality criteria (lower acid value and peroxide value—<0.5 instead of <2 and <10 instead of <15, respectively—, alkaline

* Note the use of cherry syrup for aromatization and note here a drug impossible to classify that has hardly been of any interest to phytochemists and pharmacologists—imagine that!—the «peduncle of the fruit of the morello cherry tree»; folk medicine merely refers to «cherry stems» and attributes to their infusions diuretic «virtues». The French Explanatory Note of 1998 did echo this reputation: «traditionally used to facilitate renal elimination and digestive functions, and to enhance the renal elimination of water». It is known, however, that the drug contain an isoflavone glycoside: Khalid, S.A., Gellert, M., Szendrei, K. and Duddeck, H. (1989). Prunetin 5-O-β-D-Glucopyranoside, an Isoflavone from the Peduncle of *Prunus avium* and *P. cerasus*. Phyto[illegible]

impurities); it must not be contaminated by sesame oil (as shown by the furfural reaction). It may be used as is almond oil.

• Olive Oil

Olive oil is the subject of two monographs: olive oil (Eur. Ph., 3rd Ed., 1998 add.) and refined olive oil for parenteral preparations (Fr. Ph., 10th Ed.). In its definition of olive oil, the French Pharmacopoeia specifies that it may be obtained from the «ripe drupes by cold expression or by any other appropriate mechanical means». In the case of the refined oil, the text is markedly different since the oil is «prepared from the fruit [...], by cold expression, by centrifugation, or by other recognized mechanical procedures».

The Drug. The olive tree is cultivated for its edible fruits, and secondarily for its leaves, which are used in phytotherapy (see p. 602). Olives are ellipsoid drupes (1-3 x 1-1.5 cm), and their thin and smooth epicarp gradually turns from green to blackish-purple during ripening. This epicarp surrounds a fleshy and oily mesocarp, which in turn surrounds a hard kernel with sclerified endocarp. The fruits, produced in the entire Mediterranean region (Italy, Spain, Greece, Turkey, Portugal, Morocco, Syria, and elsewhere) are harvested either green (for the canning industry) or at a more advanced state of maturity (for the food and oil industry, generally small fruit varieties).

Chemically, the fresh fruit is rich in water (40-45%), in carbohydrates (10-20%), and especially in lipids, which represent about 30% of the ripe fruit, as 50% of the pericarp and 35-40% of the almond (but the sclerified endocarp is the most important element by weight, as the almond only represents 15% of the weight of the kernel).

Fatty acid composition of the oil (major fatty acids, %, Eur. Ph., 3rd Ed.): $<C_{16}$, <0.1; palmitic, 7.5-20; palmitoleic, <3.5; stearic, 0.5-5; oleic, 56-85; linoleic, 3.5-20; linolenic, <1.2; arachidic, <0.7; eicosenoic, <0.4; gadoleic and lignoceric, <0.2 [these limits take into account the main variations observed between the oils of the «Italy-Spain»-type which are higher in oleic acid and those of the «Greece-Tunisia»-type which are higher in linoleic acid].

The unsaponifiable matter of virgin olive oil (<1.5%) contains sterols (see «tests» below), tocopherols (α-, 52-87%, β-, 10-25%, γ-, 7-23%), triterpenes, and pigments (carotenes, chlorophylls).

Production of Olive Oil. The sorted and quality-controlled olives must be treated as expeditiously as possible to limit the hydrolysis, and enzymatic and microbial lipolysis phenomena that are detrimental to the quality of the final product. Following a wash, the olives are crushed by millstone grinders or in disc mills, and

of continuous lipidic phase. The olive paste then undergoes a first expression (disc press, continuous screw press, or continuous roller press). Instead of expressing, it is possible to fluidize the paste moderately with lukewarm water and to centrifuge in order to separate the oil, the aqueous phase and the solids (the «foots»). The crude oil—a mixture of oil and water—is sieved then clarified by decantation or centrifugation: virgin oil is obtained, as used by the French Pharmacopoeia and as consumed as salad oil.

The residual paste may undergo a second expression and yield an oil that will require refining before becoming edible. The solvent extraction of the residual oil gives a product which may only be used industrially.

Tests. The tests include, in addition to the determinations classically carried out for fixed oils, a search for the absence of sesame oil (see almond oil) and a study of sterols (2.4.23). The European Pharmacopoeia monograph specifies limit percentages for five sterols: β-sitosterol >93%, cholesterol and Δ^7-stigmasterol <0.5%, stigmasterol <campesterol<4%. The absence of foreign oils must be verified by GC.

Uses. Official olive oil is traditionally used as choleretic or cholagogue [French Expl. Note, 1998]. 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. Later, we shall see proposals for uses of the leaves (see iridoids, p. 603).

• Castor Oil

«Castor oil is the fixed oil obtained by cold expression from the seeds of *Ricinus communis* L. » (Eur. Ph., 3rd Ed.).

The Plant, the Drug. Castor is a herbaceous or arborescent Euphorbiaceae which is annual or perennial, depending on the climatic conditions. The stem is branchy and bears large palmatilobate leaves (5-12 lobes), the petiole and underside of which are, in some varieties, purple. All of the flowers are grouped in racemes of cymes; the males flowers have numerous stamens with branched filaments; the female flowers have a carpellate ovary and long reddish styles. The fruit is a tricoccous capsule with multiple types of dehiscence, armed with spikes (although there are inerm varieties). The seed (8-12 [18] x 4-9 [12] mm), sometimes called castor bean, generally has a smooth and shiny tegument, most often gray marbled with red, black, or brown. A fleshy prominence, the caruncle, prolongs the top extremity; the raphe forms a very visible ridge on the ventral face. Do these characteristics make the castor bean look like a tick? In any event, that is the meaning of its Latin genus name (*ricinus*).

Probably native to Ethiopia, castor is a species that spread very rapidly: it has adopted wild

former USSR, and from the Mediterranean to eastern Asia. The same naturalization phenomenon took place in the New World after its introduction, probably by African slaves. Wherever it is cultivated (India, China, Brazil), the dwarf varieties are exploited for the purpose of oil production following an annual cycle. In France, the culture of castor was investigated in the 1980s for large scale production .

Chemical Composition. Castor oil has a very peculiar composition, in that its major constituents (90%) are triacylglycerols containing an unsaturated and hydroxylated C18 fatty acid: (*R*)-(+)-12-hydroxy-*Z*-octadec-9-enoic acid, also known as ricinoleic acid*. The other castor oil fatty acids are also C_{18} compounds: oleic (3%) and linoleic (3-4%). The castor seed contains little water, 15-20% proteins, and 40-60% lipids. Other constituents have been described, including a toxic glycoproteinic lectin, ricin and a cyano derivative of pyridone, ricinine.

Properties and Uses. Known since remote times, used for lighting in India (2,000 B.C.?), as well as in Greece and the Rome of antiquity, castor oil also used to be prized for its laxative properties: it is a drastic cathartic, which must now be formally prescribed. Polyethoxylated castor oil (Eur. Ph., 3rd Ed.) and hydrogenated polyethoxylated castor oil (Eur. Ph., 3rd Ed.) are both used in pharmaceutical technology. The former is a vehicle for parenteral preparations: it has the disadvantage of having the potential to induce anaphylactic-like reactions.

Castor oil is a dense, viscous, and non-drying oil; it is miscible with alcohol and partially miscible with common organic solvents. It is above all an industrial product: it is used directly to manufacture resins and it can also be converted. Its hydrogenation product is a major constituent of lubricating greases (lithium 12-hydroxystearate). The «dehydrated» oil (dehydrated by acidic catalysis) is used to make resins. Castor oil is the source of undecylenic acid and heptanal (a starting material for textile polyamides [Rilsan®] and polyol esters [aviation turbine oils]). In addition, it is used to obtain surfactants, waxes, varnishes, inks, resins, and

* Because the hydroxylated fatty acids are of industrial interest, if need be, another oil could have similar applications, namely the oil of *Lesquerella fendleri* (A. Gray) S. Watson, an annual Brassicaceae of North America whose black seeds contain 25% of an oil high (55%) in lesquerolic acid (= [11*Z*]-14-hydroxy-eicosenoic) and unsaturated fatty acids.

Among the oil crops that are good candidates for agronomic development and that are currently undergoing thorough investigations is *Vernonia galamensis* (Cass.) Less. (Asteraceae): its seed oil is rich in an epoxidized fatty acid, vernolic acid, which may be a good replacement for the polluting diluents used in the paint industry. There are also many species of *Cuphea* (Lythraceae) whose seeds specifically contain medium or short chain triacylglycerols. They have the potential for being a steady source of acids currently obtained from Palmae (e.g., C_{10} acids, widely used in the industry [plastics, lubricants]). Also worth watching are *Calendula officinalis* L. and *Dimorphotheca pluvialis* (L.) Moench (Asteraceae, [9*S*-hydroxy-18:2(10*E*,12*Z*)]), *Limnanthes alba* Hartweg ex Benth. (Limnanthaceae), and

electrical insulation coatings, as well as for the preparation of various synthetic intermediates. Undecylenic acid has been used as an antifungal agent and may be used as a preservative in cosmetic formulations. The other castor oil cracking product, *n*-heptanal, is used only after reduction (*n*-heptanol) or oxidation (*n*-heptanoic acid).

Castor: a Toxic Plant. Ricin is an extremely dangerous toxin. It is a glycoprotein consisting of two subunits, A and B. First, subunit B links the toxin to cell membranes sites that have galactosyl residues, then the A chain, an enzyme, can enter the cell by endocytosis and inactivate the 28S subunit of ribosomes, thereby blocking protein synthesis. Parenteral administration of a few tens of micrograms of ricin can kill (LD50 [mouse, IP] = 0.1 μg). Although ricin seems far less toxic per os, the ingestion of seeds can cause gastrointestinal symptoms, the severity of which varies mainly as a function of the number of seeds ingested and whether or not they were chewed (in two of the three case reports published in 1997 about adult patients, 10 to 15 seeds were chewed). If the digestive troubles (vomiting, diarrhea) persist, they can lead to dehydration with subsequent onset of neurological symptoms. Although mortality is lower than what older texts suggest—death is exceptional—intoxication by castor beans, especially in young children, makes hospitalization absolutely necessary (toxin removal, control of electrolytes). In industrial settings, it is important to clean up, at every procedural step, the dusts that are carriers of the allergenic principles.

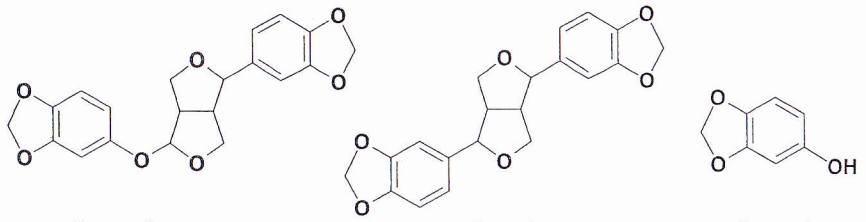
● Sesame Oil

«Sesame oil is obtained from the ripe seeds of *Sesamum indicum* L. by expression or extraction and subsequent refining [...] (it) may contain a suitable antioxidant» (Eur. Ph., 3rd Ed., 1998).

The Plant, the Drug. Sesame is a very rugged Pedaliaceae dispersed very early on from Africa to India and Asia. An annual herb of modest size (0.6-1 m), sesame has flowers with a white or pinkish bilabiate corolla (Pedaliaceae are classified close to Scrophulariaceae), whose bilocular ovary leads to a capsule with four locules containing numerous small oval seeds (<3 mm) which escape spontaneously at maturity (some think that this is the origin of Ali Baba's «Open, Sesame» in The Arabian Nights).

Cultivated for at least four millennia in Mesopotamia, documented somewhat later in India and China, sesame was introduced on the South American continent by the Portuguese. It is currently a largely exploited oil crop but its consumption remains local: only a small part of the world production (2.7 million metric tons of seeds [1997]) is shipped on the international market and the exportation of the oil is practically non-existent. The major producers are Asian (China, India, Mynamar), African (Sudan), or American (Mexico).

Chemical Composition. Sesame seeds contain 40-50% lipids, 20% carbohydrates, and 20-25% proteins. The unsaponifiable matter contains diarylfuranofuranic lignans, including sesamin and sesamolin (up to 0.5% of each). During industrial refining, sesamolin readily 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.



Sesamolin Sesamin Sesamol

Fatty acid composition of the oil (major fatty acids, %, Eur. Ph., 1997): $<C_{16}$: <0.5; palmitic, 7-12; stearic, 3.5-6; oleic, 35-50; linoleic, 35-50; linolenic and arachidic, <1; behenic and gadoleic, <0.5; erucic, <0.1.

The unsaponifiable matter (1-1.5%; <2% [Eur. Ph., 1998]) contains, in addition to the lignans described above, sterols (campesterol [18-19%], stigmasterol [6-7%], β-sitosterol [59-62%], Δ^5-avenasterol [10-11%]), and tocopherols (γ-tocopherol and δ-tocopherol [83% and 11% of total tocopherols, respectively]).

Tests. The identity of the oil is verified by TLC, by its refractive index, and by its triglyceride composition. In addition to determining the common values, the assay includes verifying the absence of cotton oil and determining the triglyceride composition by HPLC. Major triglycerides (%, Eur, Ph., 1998 add.): LLL (7-19), OLL (13-30), PLL (5-9), OOL (14-25), POL (8-16), OOO (5-14), SOL (2-8), POO (2-10); L= linoleic, O = oleic, P= palmitic, S = stearic.

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

● Soybean Oil

The 3rd edition of the European Pharmacopoeia defines «soya-bean oil» as «the refined fatty oil obtained from seeds of *Glycine soja* Sieb. & Zucc. and *Glycine max* (L.) Merr. (*G. hispida* (Moench) Maxim)». In the 1998 addendum, this pharmacopoeia describes the characteristics of and the assay for hydrogenated soybean oil.

The Plant and Its Products. Soybean, *Glycine max* (L.) Merr., is a Fabaceae which only exists in culture; it is very close to *G. soja* Siebold & Zucc. which is probably its wild ancestor. It is a small herbaceous annual plant, with trifoliolate leaves, with oval and pubescent folioles. The fruit is a pod; brown, bumpy, and very fuzzy, it contains 1-4 ovoid to spherical seeds of variable color.

Where does soybean come from? According to several authors, it did not originate in China, but rather from the Australian continent from where migratory birds introduced it into China. It has undoubtedly been used for a long time in Asia, especially as «milk» (*tonyu*) obtained by steeping and grinding the seeds, followed by boiling and sieving, and as tofu, a kind of «cheese» arising from the coagulation, draining, and pressing of *tonyu* (traditionally; the industrial preparation entails ultrafiltration and in-line coagulation). Tofu is consumed fresh, cooked (fried), or fermented (*sufu*); it can be sterilized (UHT or ultra high temperature) or pasteurized. The Orientals also consume fermentation products obtained by inoculating pounded seeds (*tempeh, miso, natto*) as well as «sauces» such as *shoyu*, which are protein hydrolysates rich in glutamic acid.

Soybean became known rather late in Europe and its culture in the United States started at the beginning of the twentieth century. The market for this oil crop—the most important one in the world—is largely dominated by the United States (74 million t in 1997); Brazil, China, and Argentina are also major producers, far ahead of India and Canada. Initiated in France in the late 1970s after lengthy studies, soybean culture is progressing: production approched 250,000 metric tons in 1996-97 on 90,000 hectares * (about 20% of the production of the European Union). In France, "soyfoods" have made rapid progress since 1985; the French definitely have a sweet tooth (desserts, flavored beverages, yogurts).

The soybean seed contains 15-35% carbohydrates (mainly insoluble fibers), 35-40% proteins containing a fair amount of essential aminoacids, and 15-20% lipids (2-3% phospholipids). Note the occurrence of saponin glycosides with a triterpenoid aglycone, of thermolabile antitrypsic factors, and of phytic acid at a high concentration.

Fatty acid composition of the oil (major fatty acids, %, Eur. Ph., 3rd Ed.): shorter than C_{14}< 0.1; myristic, <0.2; palmitic, 9-13; palmitoleic, <0.3; stearic, 3-5; oleic, 17-30; linoleic, 48-58; linolenic, 5-11; arachidic, gadoleic and behenic, <1.

The unsaponifiable matter contains sterols: β–sitosterol (47-59%), stigmasterol (17-19%), campesterol (19-23%), Δ^5-avenasterol (2-4%), Δ^7-sterols (2-4%), as well as tocopherols: γ- (44-60%), δ- (30-43%), α- (5-10%), β- (2-3%).

Tests. The assay per se includes the determination of the customary values, unsaponifiable matter (<1.5%), and brassicasterol by GC (<0.3%).

* For comparison, sunflower represented—also in 1996—800,000 hectares and about 2 million t. Reference: SIGMA. http://www.sigma-grain.fr/stats. The FAO provides similar

Uses of the oil. In pharmacy, refined soybean oil is used for parenteral feeding (for caloric intake and essential fatty acid intake). The formulation is a 10 or 20% O/W emulsion which provides 1,100 or 2,000 kcal/L; the administration must be by slow infusion under medical observation; the adult posology is 1-3 g/kg/day. Soybean oil can be hydrogenated, in which case it becomes a white mass (MP 66-72 °C) mostly composed of triglycerides of saturated fatty acids: stearic acid (79-89%) and palmitic acid (9-16%). The main use of soybean oil is, of course, dietary.

Soybean Proteins. Soybean is an important source of proteins: the cattle cake is used massively (for animal feeding), and so are meals (protein content = 45 to 65%), concentrates (65 to 90%), and isolates (over 90%), which are becoming more common as meat substitutes (vegetable protein hamburgers). This use of soybean proteins has healthful benefits: it has long been known—a meta-analysis published in 1995 clearly demonstrated it—that substituting soybean proteins for animal proteins (average consumption 47 g/day) induces a decrease in triglycerides (–10.5%), total cholesterol (–9.3%), and LDL-cholesterol (–12.9%), without altering HDL-cholesterol. Because of a 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. This advice is well accepted because proteins incorporated in «classic» foods do not have the peculiar taste and bitterness that are hard for western consumers to accept. (See p. 350, isoflavones from this legume.)

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 (Eur. id. code E322), including the industry of margarine (20 g/kg), chocolate, cooked cereals, and instant products (a lecithin film allows rapid and lump-free reconstitution of a dehydrated product rich in lipids); it is also a good lubricating agent (faciliates removal of food from a mold).

Some countries authorize the use of artificial lecithin obtained by glyceride hydrolysis of hydrogenated rapeseed oil and subsequent phosphorylation and neutralization by ammonia.

Other Emulsifiers

Monoglycerides. These amphophilic compounds are prepared by trans-

sodium hydroxide. The starting materials are cottonseed oil and sunflower oil, as well as hydrogenated animal fats. Distillation of the reaction mixture under vacuum separates the more volatile monoglycerides.

Fatty acid mono- and diglycerides are used directly (Eur. id. code E471), or as esters (acetate, lactate, citrate, and so on: E472a-f), as ester sugars (E473), as glyceride sugars (E474), as polyglyceric esters (E475), and so forth.

Also used are monostearates and the monooleate of sorbitan (Spans®), as well as their polyethoxylated derivatives (Tweens®).

Highly esterified ***ester sugars*** (hexa- to octaesters) are a possible substitute for fats in low-fat foods (Olestra®).

2. COMMON DIETARY OILS

Although these oils are scarcely used in pharmacy (parenteral feeding), their presence in our daily diet and the use of some of their derivatives in pharmaceutical technology justify covering them briefly, whether they are salad oils (rapeseed, soybean) or cooking and salad oils (sunflower).

• Rapeseed Oil

Rapeseed, *Brassica napus* L., var. *oleifera* (Brassicaceae) is the natural (amphidiploid) hybrid of two cabbages (*B. campestris* x *B. oleracea* L.); it is a herbaceous annual plant with ramified stems, waxy leaves, racemes of tetramerous yellow flowers, and dehiscent siliques. Essentially all cultivated varieties are winter forms with long rosette phase (cycle from September to July).

Normally, the oil obtained from the seeds contains about 45% of a C_{22} unsaturated fatty acid, erucic acid ($C_{22:1(13)}$). Since animal experiments have indicated a potential for myocardial toxicity for this acid, breeders have optimized varieties devoid of it, and also devoid of glucosinolates—these impart to cattle cake some undesirable properties for non-ruminants—or, more precisely, fulfilling European standards. Effective in 1990, these standards set the maximum erucic acid concentration in the oil at 2% and the maximum glucosinolate concentration in the defatted cattle cake at 35 µM/g; the latter limit was later lowered. These varieties are known as «double low»; they meet criteria that are very close to the Canadian Canola standards (2% erucic acid [oil], 30 µM/g glucosinolate [cattle cake]).

The oil is extracted by expression after hulling and cooking. The residual cattle cake oil is recovered by hexane extraction. Solvent removal from the cattle cake (by steam) eliminates the volatile products of glucosinolate decomposition. The yield is approximately 40 kg of crude oil/100 kg of seeds. The production of rapeseed (and rapeseed oil) increased substantially in France in the late 1990s (major producers: China, India, Canada, France, Germany, United Kingdom).

Fatty acid composition of the oil (major fatty acids, %): palmitic, 2.5-6; stearic, 0.9-2.1; oleic, 50-66; linoleic, 18-28; linolenic, 6-14; other fatty acids: gadoleic, <1.5; erucic, <0.5.

The unsaponifiable matter of rapeseed oil is rich in sterols (530-790 mg/100 g, in major part β-sitosterol and campesterol) and in tocopherols (up to 90 mg/100 g, γ- and α-tocopherol, 2/3-1/3).

High Erucic (Acid) Rapeseed. This term designates rapeseed varieties rich in erucic acid (50% of the oil). This oil and erucic acid are used to prepare additives (plastics industry), detergents, lubricants stable at high temperature, and more. Rapeseed is not the only Brassicaceae to produce an oil containing erucic acid: this acid can represent over 55% of the seed oil from *Crambe abyssinica* Hochst. Ex R.E. Fr. It also occurs in the seeds of nasturtium.

Rapeseed and Diester. As shown by several experiments, treating rapeseed oil with methanol yields a product, the diester, which may be incorporated in fuel oil industry products. Since its combustion releases less carbon monoxide, less smoke, no sulfur-containing products and *does not increase* global carbon dioxide (the combustion merely restitutes the CO_2 captured by photosynthesis), this biological fuel might be a partial response to increasing pollution and to land fallowing. The problems to be solved are mainly political (land fallowing is subsidized) and economic (fuels are taxed). Note that these fuels are being used experimentally in public transportation vehicles in several major French cities, and that they are scheduled to be incorporated into farm equipment fuel in 1994. Similar trials are in progress in the United States (Illinois) with analogous products from soybean oil transesterification («Soydiesel»).

• Sunflower Oil

The sunflower, *Helianthus annuus* L., is an Asteraceae * from North America. Around the time of arrival of the first Europeans, it was commonly cultivated and the seeds, which contain 20 to 30% oil, were consumed toasted, or after having been turned into a meal. Introduced in Europe in the sixteenth century as an ornamental species, it was improved (the oil content was doubled), then later reintroduced to the United States, which remains one of the chief world producers (far behind Argentina, Russia, Ukraine, and France [1996 world production: 25 million t]).

* Another Asteraceae is also used, dyer's saffron, *Carthamus tinctorius* L., which has been prized since antiquity for the oil contained in its akenes but also for the dye principles of its flowers (carthamin). Its world production, without being negligible, is far from approaching that of the major oil crops. Producers include India (45% of the world production, i.e., 430,000 t in 1997 [FAO]), Mexico, the United States, Ethiopia, and Australia. This is an

Characterized by its large capitulums, whose receptacle may bear 2,000 tubular flowers, by its large cordate leaves, and by its angular akenes, the sunflower was cultivated in Russia in the nineteenth century. Since then it has continually been optimized: the oil content in the varieties currently cultivated reaches 50%; selection also favored single-stalk plants (wild sunflower is ramified) and those with akenes with a thin hull.

Fatty acid composition of the oil (main fatty acids*, %): palmitic, 3-10; stearic, 1-10; oleic, 14-35; linoleic, 55-75; linolenic, <0.3. Trilinoleate (LLL) and oleodilinolein (OLL) each represent about 1/3 of the triacylglycerols.

The unsaponifiable matter is characterized by many sterols: β-sitosterol is by far the major one (60%), alongside Δ^7-stigmasterol (7-14%) and Δ^5-avenasterol (4-6%). Tocopherols are almost exclusively represented by α-tocopherol.

Under the heading of uses other than in the oil industry, note the use of the meal obtained after defatting (aleurone meal) in the formulation of dietetic products.

3. OTHER DIETARY OILS **

Considering their limited interest in pharmacy, we shall describe these oils only briefly. Some (walnut and cottonseed oils) have been described elsewhere in this text.

* Also cultivated are «oleic-type sunflowers», the triglycerides of which contain not less than 80% oleic acid. Their dietary oil is more heat-resistant than the classic «linoleic-type» sunflower oil. These sunflowers have the potential for being an industrial source of oleic acid easier to process than animal fats.
Oleic-type sunflower oil (Oleisol®) currently enters in the composition of oily mixtures available to the consumer concerned about «balancing his/her lipidic diet»; one example includes sunflower oil, Oleisol®, soybean oil, and that of grape seeds for a final composition of $C_{18:1}$ (40%), $C_{18:2}$ (45%), and $C_{18:3}$ (1.2%).
Grapeseed oil is produced from the seeds of the grape, by expression; it is a plentiful by-product in the wine-producing countries of the Mediterranean rim; its composition is palmitic, 5.5-11; stearic, 3-6; oleic, 12-28; linoleic, 58-78; linolenic, <1. The unsaponifiable matter contains tocotrienols (α- and γ-tocotrienol).

** Dietary oils could also be classified as a function of their heat resistance. In fact, in France, two criteria are used to distinguish oils on the basis of their α-linolenic acid content. If the oil contains more than 2% α-linolenic acid, its label must include the wording «vegetable salad oil»; if it is not more than 2% α-linolenic acid, the label must include the wording «vegetable salad and cooking oil». This distinction (French decree or *décret* of December 2, 1973) was introduced to address the toxicity attributed to degradation products formed upon heating oils. In fact - according to the relevant professional organizations - it appears that, contrary to currently accepted ideas, the quantity of products formed is practically the same regardless of the polyunsaturated fatty acid content. The most important is probably the manner in which the oil is used: moderate temperature, frequent renewal of the frying oil... Only those oils obtained by mechanical pressure without refining or chemical treatment [illegible]

• PALM OILS

The fruits of several species of Palmae are used as sources of oil. Although some oils are of limited use (such as Babassu oil*), others, such as coconut oil and palm oil, hold a place of choice on the world oil market.

- COCONUT PALM, *Cocos nucifera* L.

The coconut palm is a lignified plant with the habit of a tree: its straight stipe bears a spiral rosette of leaves that only appear compound (they are in fact divided into segments through tearing). The fruit is a large drupe with hard endocarp and fibrous pericarp. The seed and its endocarp are the commercial «coconut». The seed albumen is in part liquid—hence its name, coconut milk—and in part solid—this is copra. Dry copra contains about 65% lipids. In temperate regions, copra oil is a «concrete oil»: below 25-27 °C it forms a white, tasteless, and odorless mass.

Used in pharmacy to obtain semisynthetic glycerides, copra is a dietary product (Végétaline® in France) and an industrial product: it is extensively used to produce detergents of the lauryl-sulfate type. In countries where coconut palms are cultivated (Africa, southeast Asia) they yield many other products: cattle cake, palm wine, vegetable charcoal, and the fibrous pericarp called *coïr* made into brooms, brushes, rugs, ropes, and more.

Medium-chain Triglycerides. According to the European Pharmacopoeia (3rd Ed.), these triglycerides are «obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. or from the dried endosperm of *Elaeis guineensis* Jacq. They consist of a mixture of triglycerides of saturated fatty acids [...] They contain not less than 95 per cent of saturated fatty acids with 8 and 10 carbon atoms.» The composition, as defined by the assay section of the monograph, is the following: caproic acid, <2%; caprylic acid, 50-80%; capric acid, 20-50%; lauric acid, <3%; myristic acid, <1%.

- OIL PALM, *Elaeis guineensis* Jacq., *E.oleifera* (Kunth) Cortés

This species is a tall palm (15-30 m) with reddish fruits gathered into ovoid «bunches» of 1,000 to 2,000 plum-size drupes; it is cultivated in southeast Asia (Indonesia, Malaysia), as well as in Africa (Nigeria, Zaïre, Cameroon), and in South America (Brazil). The ripe fruits are expressed to yield palm oil (the mesocarp contains 65 to 70% lipids). The kernel is also used: the fruits are dried and freed of

* Babassu palm (*Orbignya phalerata* Mart.) is grown in Brazil. The almond of the seed gives an oil high in medium-chain fatty acids (lauric [50%], myristic [20%]). It is used mostly locally. It is also used in cosmetic formulation. See Pinheiro, C.U.B. and Frazão, J.M.F. (1995) [illegible] Processing of Babassu Palm (*Orbignya phalerata*, Arecaceae) Fruits:

RICINUS COMMUNIS L.

the pericarp, and the nut, in other words the seed surrounded by the endocarp, is pressed or extracted with solvents to give palm kernel oil.

These oils, like copra, are solid in temperate climates; the presence of carotenoids explains the deep color of palm oil, sometimes called «red oil».

The main uses of palm oil are in the margarine and soap industries.

Chemical composition (major fatty acids, %):

1- *copra*					
caprylic :	5-10	capric :	4.5-8	lauric :	43-51
myristic :	16-21	palmitic :	7.5-10	oleic :	5-10
2- *palm kernel oil*					
caprylic :	2.4-6.2	capric :	2.6-5	lauric :	41-55
myristic :	14-18	palmitic :	6.5-10	oleic :	12-19
3- *palm oil*					
myristic :	0.5-2	palmitic :	41-47	oleic :	36-44
linoleic :	6.5-12	stearic :	5.5-6		

The unsaponifiable matter of palm oil is high in carotenes (0.5-0.7 g/kg of oil) and its tocopherol fraction contains over 80% tocotrienols. These tocotrienols are also characteristic of the unsaponifiable matter of copra oil.

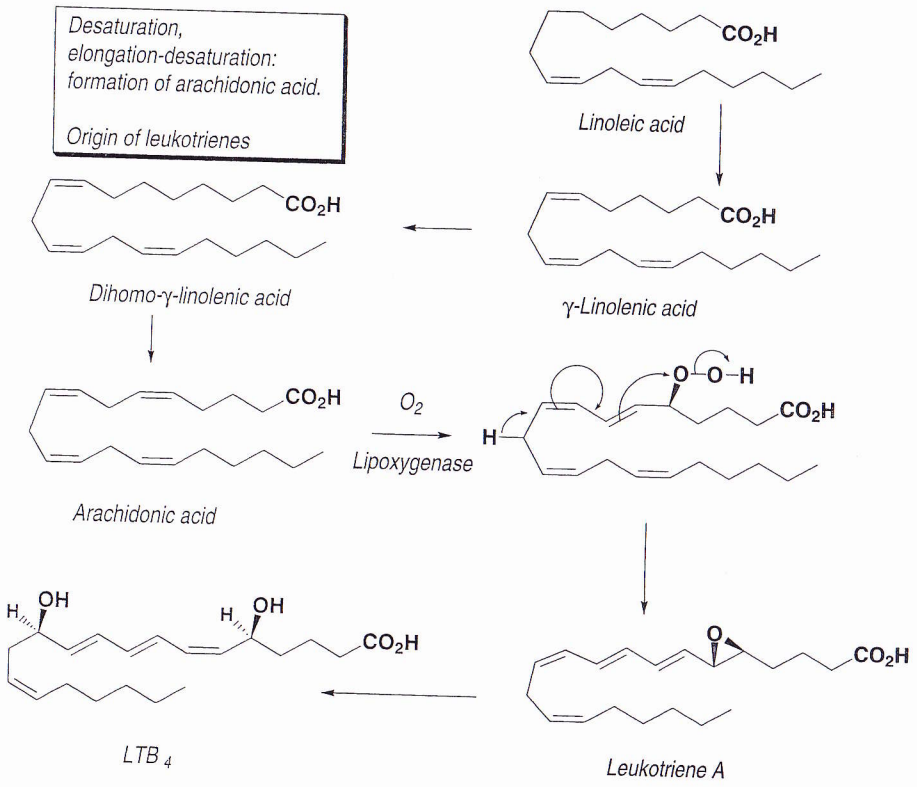
4. MISCELLANEOUS OILS

A. Oils with γ-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 acid* = 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 the 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. The biosynthesis of these compounds involves arachidonic acid, which normally arises from the desaturation

desaturation leading to arachidonic acid ($C_{20:4}$). It is this acid which is the substrate upon which cyclooxygenase and lipoxygenase will act to form eicosanoids. Thus, linoleic 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. The same applies to the 0.5-1% of the caloric ration in α-linolenic acid indispensable for a balance155d diet*. Linolenic acid deficiency manifests itself by dermatological signs (such as eczema lesions, impetigo, and erythema), delayed growth, hypertension, and poor platelet aggregation.



* A diet based on a decrease in animal proteins (red meat) consumption, an increased consumption of fruits and vegetables, and the replacement of saturated fats by products high in oleic and α-linolenic acid is effective in preventing coronary disease. See de Lorgeril, M., Renaud, S., Mamelle, N., Salen, P., Martin, J.-L., Monjaud, I., Guidollet, J., Touboul, P. and Delaye, J. (1994). Mediterranean Alpha-linolenic Acid-rich Diet in Secondary Prevention of Coronary Heart Disease, *Lancet*, **343**, 1454-1459. Polyunsaturated n-3 fatty acids also appear to provide protection against colon carcinogenesis (on the contrary, the cancer-promoting effect of an excess of lipids is well accepted, despite the fact that half the published studies fail to confirm it): Corbet, D.E. and Gerber, M. (1997). Alimentation méditerranéenne et santé, partie 1. Caractéristiques. Maladies cardiovasculaires et autres affections. *Med. Nut.* 4

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

α-Linolenic acid is present in most vegetable oils, but γ-linolenic acid is much more rare: it is found in Onagraceae (*Œnothera*), in Saxifragaceae (for example *Ribes nigrum* L. and *R. rubrum* L.), in various species of the genera *Anchusa, Borago, Cynoglossum, Onosma, Onosmodium* and *Symphytum*, of the Boraginaceae, but also in some species of *Anemone* and in *Cannabis* seeds. The most interesting sources appear to be black currant seeds, evening primrose seeds, and borage seeds.

• Evening Primrose, *Œnothera biennis* L., Onagraceae

The evening primrose is easy to identify by its large ephemeral flowers with four yellow emarginate petals, which bloom at night, hence the name (*Nachtkerze* in German). Originally from North America, this species is common in Mediterranean, as well as Atlantic coastal regions. It is cultivated in the United Kingdom for the production of seeds.

The drug—it consists of the seed, small (1-2 x 0.5-1 mm) and angular—contains up to 25% of an oil rich in unsaturated fatty acids: γ-linolenic acid (8-14%), linoleic acid (65-80%), and 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. These 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. Various authors believe that evening primrose oil can relieve the mild mastodynia of premenstrual syndrome. Yet placebo-controlled clinical trials conducted with strict inclusion criteria showed that although most of the symptoms were improved, the difference was not significant. Whether evening primrose oil is of interest for oral administration in the treatment of atopic eczema is just as controversial: some authors think that it is efficacious, others that it is potentially useful, and rigorous clinical trials indicate no activity beyond that of a placebo. Other proposed uses are based, at best, on contradictory and fragmented data.

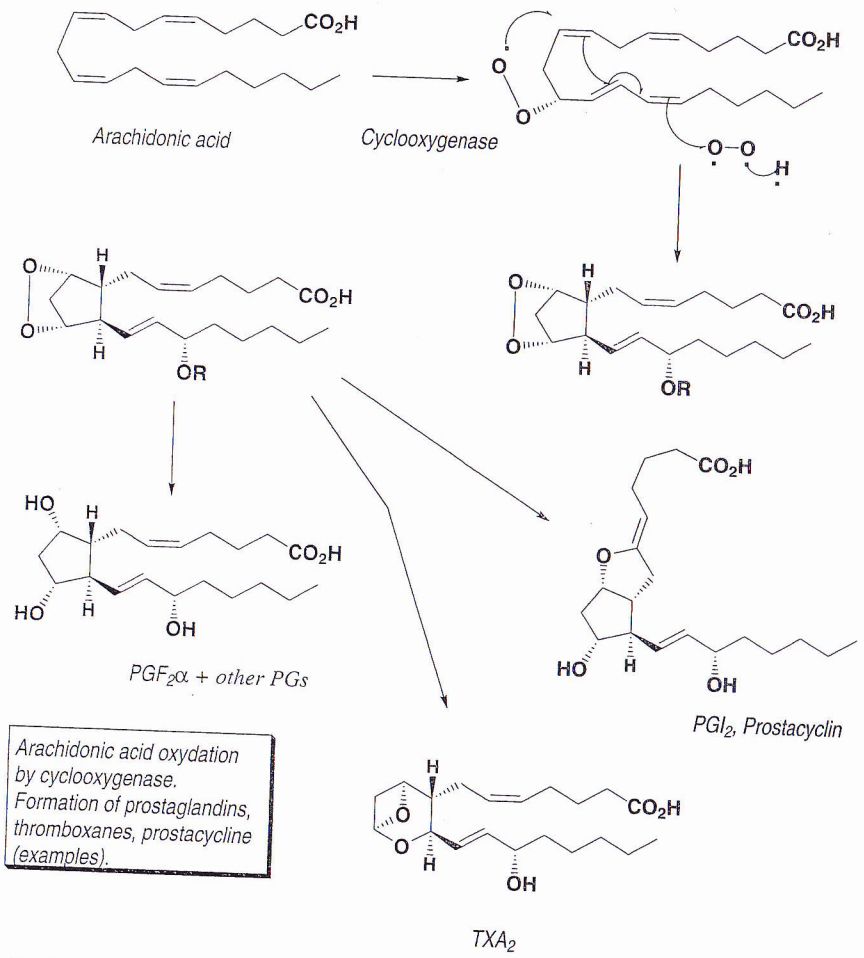
Modest results may justify its use for cyclic breast pains, but the other proposed uses rely on contradictory and fragmented data.

• Borage, *Borago officinalis* L., Boraginaceae

Its flowers and flowering tops are official in France (see p. 838), and borage is

although the yield from the seeds is uncertain: blooming is not synchronized, therefore seed maturation is not uniform, and ripe seeds fall on the ground before and during the harvest.

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%), oleic acid (15-19%), and γ-linolenic acid (18-25%) dominating. The uses of this unstable oil are the same as those of evening primrose oil; its efficacy in the indications that are claimed are just as controversial.



Arachidonic acid oxydation by cyclooxygenase. Formation of prostaglandins, thromboxanes, prostacycline (examples).

B. Sapotaceae Oils

Argan Oil. The *argan tree* (*Argania spinosa* [L.] Skeels) is a thorny Sapotaceae species from the Moroccan southwest. Its fleshy fruit is traditionally used to feed cattle. The seeds yield a clearly unsaturated oil (oleic acid 46-52%, linolic

sterols derived from cycloartane, but no sitosterol. The cattle cake contains saponins which are bidesmosides of polyhydroxylated acids from the oleanane series. Argan oil is used in cosmetic formulation.

Karite nut butter or shea butter is the fat obtained from the seeds of a plant grown mainly in Nigeria, Mali, Burkina, and Ghana. The pericarp of the fruit of this species, *Vitellaria paradoxa* Gaertner *f.* (= *Butyrospermum parkii* Kotschy.) is edible. Its composition is stearic acid (28-45%), oleic acid (42-59%), linoleic acid (3-9%); the unsaponifiable matter (7-10%) contains a specific hydrocarbon (20-30 g/kg). Market outlets are limited to cosmetology, and the formulation of a few healing and protective ointments (sunblocks, skin protectors).

Macassar Oil. This oil, used in the formulation of cosmetic and personal hygiene products (e.g., shampoos), is obtained from the seeds of the Ceylon oak, *Schleichera oleosa* (Lour) Oken (= *S. trijuga*).

The oily seeds of **other Sapotaceae** have local dietary uses, e.g., *Madhuca longifolia* (Koenig) Macbr. or illipe nuts, which give illipe butter and illipe oil (and must not be confused with the seeds of the *Shorea* of Borneo [Dipterocarpaceae], also known as illipe nuts).

5. UNSAPONIFIABLE MATTER AND RELATED COMPOUNDS

The unsaponifiable matter, composed of the non-glyceride constituents of oils, 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, Δ^7-sterols), tocopherols, high molecular weight-aliphatic alcohols, and terpenoid alcohols.

A. Unsaponifiable Matter - Avocado

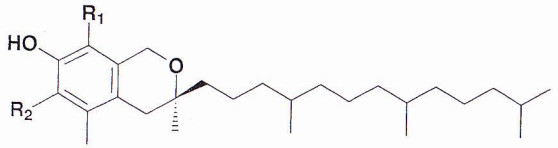
The avocado tree, *Persea americana* Miller, is a Lauraceae from South America. Cultivated in Africa, in America (Mexico, United States, Brazil), and in Israel, it is a tree with pear-shaped fruits - the avocados - with voluminous seeds. The fleshy mesocarp of this fruit yields a viscous, brownish-green oil with a fruity odor. The oil content and its composition depend on the variety, and include palmitic acid (17-29%), palmitoleic acid (6-12%), oleic acid (42-63%), linoleic acid (9-16), and linolenic acid (<1%). Branched hydrocarbons account for half of the unsaponifiable matter, the level of which may reach 1%; it contains 20% sterols and unidentified, highly reducing triols.

In rats, the combination of unsaponifiable materials from avocado and soybean

basic treatment for periodontitis, and used in rheumatology as an adjunctive therapy for arthritis pain.

B. Tocopherols

Tocopherols are prenylated derivatives of benzodihydropyran. Tocopherols and tocotrienols are distinguished by their lateral chain, which is either saturated or unsaturated, respectively; in either series the position and the nature of the substituents define four different compounds (α, β, γ, δ). Biosynthetically, tocopherols are derived from homogentisic acid.



$R_1 = R_2 = CH_3$: α-*Tocopherol* ; $R_1 = CH_3$, $R_2 = H$: β-*Tocopherol*
$R_1 = H$, $R_2 = CH_3$: γ-*Tocopherol* ; $R_1 = R_2 = H$: 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. Oxidized vitamin E is then reduced by ascorbic acid. The normal consumption of oils, margarines, and cereals easily fulfill the daily needs (10-12 mg/day). Although the basis for supraphysiological intake has not been demonstrated, at least it is apparently harmless (except in subjects deficient in vitamin K, either as a result of poor absorption or as a side effect of treatment with anticoagulants). A maximum safe dose is recommended by the *Conseil supérieur d'hygiène publique de France* : 40 mg/day.

Because 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. To date, the results of placebo-controlled prevention trials have been either negative or not significant (in primary prevention), or divergent (in secondary prevention). Vitamin E intake also has no impact on degenerative diseases such as Huntington's chorea. It is possible that vitamin E has a protective effect during the early phases of carcinogenesis induction (digestive tract, lungs), but the formal proof of such an activity remains to be established.

α-Tocopherol acetate is indicated for the treatment and prevention of vitamin E deficiency. It is proposed by some authors: 1. for the treatment of urinary incontinence in women and of progressive myopia; 2. as an adjunct in the dietary regimen of patients with high blood lipoproteins who are not eligible for treatment to

lower blood lipids, a proposal which other authors have good reasons to find debatable. It is also found, but in small doses, in dozens of proprietary drugs, over-the-counter drugs, and dietary supplements, in combination with other vitamins, flavonoids, fish oil, minerals, and more. It is frequently incorporated in dietetic preparations.

In food technology, tocopherols are authorized antioxidants, whether they are natural extracts from edible vegetable oils rich in tocopherols (Eur. id. code E306) or synthetic tocopherols (α, γ, δ, i.e., E307-9). Pharmaceutical technology also finds uses for the antioxidant properties of these molecules, often in synergy with ascorbic acid.

C. Compounds Related to the Unsaponifiable Matter

• *PRUNUS AFRICANA*, Kalkm., Rosaceae

The Plant, the Drug. Still often (erroneously) referred to as *Pygeum africanum* Hook., called «African plum tree», this African forest species grows mostly in mountain areas with heavy rainfall. It is a tall tree, which may reach 30 m, with elliptic, weakly acuminate, thick, and coriaceous leaves. The flowers are small, white, and pentamerous. The fruit is a tough red akene with a depression at the top. The drug consists of the bark: red or dark brown, it smells weakly of hydrocyanic acid. The product most commonly used is a lipid and sterol extract obtained by organic solvent extraction.

Chemical Composition. Analysis of the extract shows that it contains a lipid fraction (C_{12-24} fatty acids), phytosterols (free and conjugated β-sitosterol, campesterol), triterpenoid pentacyclic acids (ursolic, oleanolic, and their homologs di- or trihydroxylated at C-2, C-3, and/or C-24, sometimes acylated by ferulic acid), and linear aliphatic alcohols: *n*-tetracosanol and *n*-docosanol, which seem to occur in the extract as ferulic acid esters.

Pharmacological Activity. The mechanism of action of the extract of *P. africana* has not been elucidated completely. There may be several factors, particularly the inhibition of 5-lipoxygenase in the polymorphonuclear leucocytes that infiltrate prostatic tissue (the extract is an anti-inflammatory). Interaction with testosterone metabolism is excluded by most published studies, although a 1996 publication showed, *in vitro*, a partial inhibition of 5α-reductase and of aromatase, therefore the possibility of an action on tissues whose growth is hormone-dependent. It is also known that the extract regenerates the prostatic epithelium in rats and dogs. More recently, it was shown on cell cultures of rat prostatic fibroblasts that the extract inhibits the cell proliferation induced by the main growth factors responsible for the normal and pathological development of prostatic tissue: EGF (*Epidermal Growth Factor*, CI_{50} = 4.5 µg/mL), bFGF (*basic Fibroblast Growth Factor*), IGF-1 (*Insulin-*

the absence of stimulation, and with cells stimulated by a protein kinase C activator, TPA (see p. 654). No cytotoxicity is associated with the *P. africana* extract. Other studies in rabbits showed that at high doses, it prevents the functional problems with bladder contractility and metabolism that are induced by a partial obstruction of the urethra, but does not decrease the compensatory bladder hypertrophy (a consequence of the increase in bFGF).

Clinical trials * that have been published for the extract state a significant difference from a placebo for nocturnal pollakiuria and other symptoms of benign prostatic hyperplasia (post-voiding residual volume, maximum urinary flow rate) as well as for subjective symptoms; it has no action on the volume of the adenoma. Other trials show that the activity is, in similar conditions, comparable to that of *Serenoa repens* fruit extracts.

Uses. *P. 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). The treatment is no dispensation from having a physician monitor the BPH. Ongoing research is taking into account the international recommendations and will help determine if this drug is of interest (International Prostate Symptom Score = I-PSS).

• Saw Palmetto,
Serenoa repens (Bartr.) Small
= *Sabal serrulata* Rohm. & Schult., Palmae

The Plant, the Drug. The saw palmetto or dwarf American palm is a palm with «fan-shaped leaves» with a fairly short single stipe (0.5-2 m), with bluish-green, deeply split leaves, borne by a petiole lined on the edge by small sharp needles, with small flowers gathered into a spadix (raceme-like panicle). The fruit constitutes the drug and is globose (2-3 x 1.5 cm), monoseeded, and bluish to black at maturity. The species grows wild in sandy soils of the southern United States where it often forms impenetrable groves.

Chemical Composition. There is not much literature on the chemical composition of the drug. 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, which also contains linear alkanes (C_9-C_{28}), aliphatic alcohols (hexacosanol [C_{26}], octacosanol [C_{28}], triacontanol [C_{30}], and their esters) and monounsaturated

* Recall that the WHO experts were highly critical of the quality of the clinical trials conducted with most of the products that are widely proposed to treat benign prostatic hyperplasia. Twice, they emphasized that the efficacy had not been clearly established.

alkenes (C_{12}, C_{13}, and C_{24}), phytosterols (sitosterol, campesterol, cycloartenol, and sitosterol derivatives: 3-*O*-glycoside, 3-*O*-palmitate, 3-*O*-myristate, 6'-*O*-acyl-3-*O*-glucosyl, and others), and polyprenols.

Pharmacological Activity. The pharmacology of the hexane extract has been studied extensively. In the mouse and the castrated rat, it exerts a peripheral anti-androgenic effect, a consequence of its complex interaction with the metabolism and the mode of action of testosterone in the prostate. *In vitro* (cell culture), it inhibits steroid 5α-reductase and 3α-reductase; *in vitro* and *in vivo* (rat), it decreases the binding between dihydrotestosterone (DHT) and cytosolic and nuclear androgen receptors. Contradictory data were obtained from other studies: the inhibition of the 5α-reductase and of the binding of androgens to their receptors would in fact be due to the use of very high doses, therefore the mechanism would be nonspecific (on the same model, the IC_{50} of the saw palmetto extract is 5.6 mg/L whereas that of finasteride is 1 µg/L). Other authors distinguish the effects on both type 1 and type 2 isoforms of 5α-reductase. The anti-androgen activity should lead to a decrease in the prostate volume; but again the published results seem contradictory. The acidic lipophilic fraction of a supercritical carbon dioxide extract inhibits cyclooxygenase and lipoxygenase *in vitro*, an effect which might explain the antiinflammatory and antiedema activity that is attributed to the saw palmetto extract. A spasmolytic activity and inhibitory effects on growth factor-induced prostatic cell proliferation have also been considered.

The daily, short- or long-term administration of saw palmetto lipidosterolic extract (320 mg/day) does not significantly alter plasma levels of DHT; it also has no effect on plasma levels of prostate-specific antigen (PSA). Long-term use apparently results in a decrease in hormonal receptors in the prostate.

Alongside many uncontrolled trials, a few clinical trials that were controlled, but did not use normalized inclusion criteria, attempted to determine whether *Serenoa repens* is of clinical interest for benign prostatic hyperplasia. Overall, their results are convergent, and show that 1 to 3 months of treatment (320-480 mg/day) lead to an increase in urinary flow rate, a marked decrease in post-voiding residual urine, and more generally, to an improvement of the symptoms. As noted by several authors, the key question raised by these trials is undoubtedly why, with one exception, the clinical trial subjects treated with a placebo do not report a significant improvement of their symptoms, while it is well accepted that at least 30-50% of BPH patients report an improvement of their symptoms after treatment with a placebo, and that the percentage is about the same after simple monitoring *. Only one study—recent, but not placebo-controlled—quantitates the symptoms with a normalized questionnaire (I-PSS); it reveals a decrease of 35% of the initial score after 3 months of treatment. Another study, controlled and including a large number of patients, showed an

* Monitoring 282 untreated patients (for β-5 years) revealed a spontaneous decrease in subjective symptoms in 38 % of the patients and an improvement of the objective parameters in 22 % of

efficacy similar to that of finasteride, at least in terms of I-PSS score and quality of life score.

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. The product is very well tolerated in the vast majority of cases (administration on an empty stomach can cause nausea).

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