Rare fatty acids and lipids in plant oilseeds: occurrence and bioactivity

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Abstract Lipids are biomolecules which are present in plants as general metabolites with different functions such as structural, protective and also as storage material. Plants produce a high number of different fatty acids: the most common structural types are long linear hydrocarbon chains, saturated or unsaturated with an even number of carbon atoms. In addition, plants accumulate rare fatty acids with reference to their occurrence and to their structures such as number and arrangement of unsaturated bonds, chain branches, type of functional groups, cyclic structures and halogenation. Their presence is limited in plant leaves, roots or stems, while they are mostly found as components of storage seed oils. The present review aims to describe the structural features of selected unusual rare fatty acids occurring in plants, their bioactivity and applications as pharmaceutical, cosmetic, food and non-food industrial products. Cyanolipids, a group of rare natural lipids containing a cyanogenic group in the molecule and only found in seed oils of a few plant species are also commented.

Keywords Rare fatty acids · Lipid chemistry · Cyanolipids · Biological activity · Seed oil

Introduction

Lipids are lipophilic or amphophilic biomolecules which naturally are present in plants as structural constituents of cell membranes, as protective tegumental coatings such as waxes and cutin and also as storage reserve in seeds (Avato 1987; Cassim et al. 2019; Cahoon and Li-Beisson 2020).

Based on their backbone structures, they can be classified into non-saponifiable and saponifiable lipids. Non saponifiable lipids do not contain ester groups in their molecule and can not be saponified, (such as sterols, prostaglandins, vitamin D etc.), while saponifiable lipids contain ester linkage which can undergo saponification. These latter can be divided in two groups: simple lipids, that are esters of fatty acids and alcohols or polyols, and complex lipids, which often occur combined either covalently or through weak bonds with other biomolecules to form hybrid structures. Among simple lipids of plant origin, triacylglycerols and waxes are the most represented compounds, while complex lipids include phosphoglycerides and sphingolipids that are characterized by the presence of phosphate, amino alcohols or carbohydrates in their structures. Cyanolipids are another class of natural lipids of plant origin in which

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a cyanogenic group is included in the molecule. This last group of lipids is considered an uncommon class of compounds as their occurrence is limited only to the seed oils of a few plant species.

The presence of different reactive chemical groups in lipid structures contributes to originate a great diversity of plant-derived compounds. The variety of lipids is also related to the high number of different fatty acids which are produced in plants. The most common structural types are long linear hydrocarbon chains, saturated or unsaturated, with a terminal carboxyl group and an even number of carbon atoms. In addition, plants accumulate fatty acids, the so called *unusual* or *rare* fatty acids, that are characterized by structural variations such as number and arrangement of unsaturated bonds, chain branches, type of functional groups (hydroxyls, ketones, epoxyls, etc.), cyclic structures and halogenation. In addition they are rare in reference to their distribution in the various plant species. In total, over 450 different fatty acids structures have been reported to occur exclusively in vascular plants, although it is estimated that many plant families still remain to be explored for their fatty acid composition possibly allow to discover many other novel structural types (Ohlrogge et al. 2018).

Rare fatty acids are frequently found in plants as components of storage seed oils; only a small number has been reported as present in leaves or other plant tissues such as roots and stems. They show a plant family specific distribution (Smith 1971; Badami and Patil, 1980; Spitzer 1999): thus for example cyclic fatty acids have been identified in the Malvaceae; epoxy acids are common in the Asteraceae and Cruciferae; fatty acids with the uncommon unsaturation in the 6:7 position of the C₁₈ fatty acid chain have been identified in the Apiaceae plant family; acetylenic fatty acids are widespread in the families of Santalaceae, Olacaceae, Asteraceae and Caesalpiniaceae; rare hydroxy fatty acids are present in the seed oil of some Euphorbiaceae and cyanolipids are restricted to only a few plant families such as the Boraginaceae, the Hippocastanaceae and the Sapindaceae (Møller and Siegler 1999).

Unusual natural fatty acids and lipids have been considered worth of studying for several reasons. Their presence mostly in seed oils suggest a functional role as defense metabolites to protect the plant from pathogen attacks and their ecological

importance against herbivory or insects has been studied (Rani and Rajasekharreddy 2010; Diaz and Rossini 2012; Van de Loo et al. 2018). Moreover, their specific occurrence in some plant families has encouraged chemotaxonomic investigations (Smith 1971; Avato et al. 2003; Ohlrogge et al. 2018). In fact, presence or absence of specific unusual fatty acids have in some cases suggested a close or less close botanical relationship between plant species. Their unusual structural features have in addition contributed to highlight new mechanisms involved in plant lipid biochemistry (Napier 2007; Cahoon and Schmid 2008; Aznar-Moreno and Durrett 2017). Finally, many of these rare fatty acids have shown important biological and pharmacological properties and may represent valuable industrial products (Murphy 2005).

The present review aims to describe selected unusual plant derived fatty compounds, such as rare fatty acids and cyanolipids underlying their structural features, occurrence in plants, bioactivity and applications.

Structural types

Non oxygenated

Non-conjugated ethylenic fatty acids

Fatty acids classified in this group are characterized by the presence of a variable number of non-conjugated double bonds, from one bond such as in petroselinic, erucic and nervonic acids, up to three or four bonds such as in γ -linolenic and arachidonic acids (Fig. 1). The characteristic of monounsaturated fatty acids belonging to this group is the position of the double bond in the chain, that is in a specific and unique position compared to the most common monounsaturated fatty acids.

The polyunsaturated fatty acids belonging to this class are typically characterized by a methylene-interrupted pattern in which double bonds are alternated with methylene units to form a chain ($-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}-$) with *cis*-double bonds usually placed at the 9-, 12- and 15-positions in the common C₁₈ series of polyunsaturated fatty acids (Smith 1971). Petroselinic, γ -linolenic, arachidonic, erucic (Fig. 1) and nervonic acids are some of the

Non conjugated ethylenic fatty acids

Conjugated ethylenic fatty acids

Non conjugated acetylenic fatty acids

Conjugated acetylenic fatty acids

Fig. 1 Chemical structure of the most representative non oxygenated unusual fatty acids: conjugated and non-conjugated ethylenic and acetylenic fatty acids

most representative rare fatty acids belonging to this structural group and found in plant oils.

Coniugated ethylenic fatty acids

A number of conjugated C₁₈-trienoic acids from plants are known (Smith 1971; Badami and Patil 1980; Gunstone et al. 2007). The three double bonds

characterizing these fatty acids are primarily at 9-, 11-, 13- and 8-, 10- 12- positions and they exist in both *cis* and *trans* geometrical isomers. A species specific distribution of isomer types usually occur due to the fact that each plant has a specific conjugase enzyme which catalyzes conversion of linoleic acid into conjugated linolenic acids thus allowing the accumulation of only one isomer. α-Eleostearic acid

(*cis,trans,trans*-9,11,13-octadecatrienoic acid, α -ESA) is the most widespread (Rao et al. 1991; Sbihi et al. 2014) often occurring together with its isomer β -eleostearic acid (*trans,trans,trans*-9,11,13-octadecatrienoic acid) (Fig. 1). Other geometrical isomers found in seed oils from *Punica* and *Catalpa* species, respectively, include *cis,trans,cis*-9,11,13-octadecatrienoic acid (punicic acid), *trans,trans,cis*-9,11,13-octadecatrienoic acid (catalpic acid) (Fig. 1). In addition, the two positional isomers *trans,trans,cis*-8,10,12-octadecatrienoic acid (calendic acid) and *cis,trans,cis*-8,10,12-octadecatrienoic acid (jacaric acid) (Fig. 1) have been identified in some *Calendula* and *Jacaranda* species (Chisholm and Hopkins 1965; 1967; Dulf et al. 2013; Nguyen et al. 2017).

Non-conjugated acetylenic fatty acids

This chemical group only includes two monoynoic fatty acids: tariric (octadec-6-ynoic) acid, firstly isolated from seed oils of some *Picramnia* species, where it can amount up to 95% of total fatty acids, and stearolic (octadec-9-ynoic) acid (Fig. 1), the acetylenic analogue of oleic acid, characterizing some Santalaceae and Oleaceae, although present in low amount (Spencer et al. 1970; Stuhlfauth et al. 1985).

In addition, crepenynic acid (*cis*-9-octadecen-12-ynoic acid) (Fig. 1), an acetylenic analogue of linoleic acid, should also be included among these structural types. It is distributed in some *Crepis* species (on average 40–70% of total fatty acids) and it has been also isolated from different plant parts of *Afzelia cuanzensis* Welw. (Gunstone et al. 1967, 2007). Moreover, recently it has been identified in the rhizome of the two species *Atractylodes lancea* Thunb. and *A. macrocephala* Koidz. (Sun et al. 2017).

Conjugated acetylenic fatty acids

These fatty acids are characterized by a conjugated system which begins at the 9-position with one or more triple bond and ends with one or more double bond, *cis* or *trans*. Some of these structural types have a terminal double bond (Smith 1971; Okada et al. 2013). Conjugated acetylenic fatty acids have been mainly isolated from two plant families, the Santalaceae and Olacaceae.

Conjugated enynoic fatty acids include ximenynic acid (*trans*-11-octadecen-9-ynoic acid) also known as santalbic acid (Fig. 1), which is the simplest isolated conjugated acetylenic acid and the structural analogue, pyrullic acid (*trans*-10-heptadecen-8-ynoic acid). The less common, dehydrocrepenynic acid (*cis,cis*-9,14-octadecadien-12-ynoic acid) with a double and triple bond in conjugation also belongs to this series of compounds.

Several di- and polyacetylenic fatty acids have been isolated from the *Onguekoa gore* Engler seed oil, commonly known as boleko or isano oil (Badami and Gunstone 1963; Miller et al. 1977). Among them, isanic (or erythrogenic) acid (17-octadecen-9,11-diynoic), bolekiic acid (*cis*-13-octadecen-9,11-diynoic), *cis*-13,17-octadecadien-9,11-diynoic acid and the ene-diynoic exocarpic acid (*trans*-13-octadecen-9,11-diynoic acid) (Fig. 1) plus five analogues should also be mentioned (Miller et al. 1977; Naidoo et al. 1992; El-Jaber et al. 2003; Koch et al. 2009).

Allenic fatty acids

Fatty acids belonging to this group are mainly found as fungal metabolites (Kenar et al. 2017). In higher plants the three compounds, laballenic acid ((*R*)-5,6-octadecadienoic acid), lamnallenic acid ((*R*)-octadeca-5,6-*trans*-16-trienoic acid) (Fig. 2) and phlomic acid (7,8-eicosadienoic acid) are the major components of seed oils. They are easily detectable, in that their allenic group is not a part of a conjugated system and, due to their structural feature, have a strong optical activity.

Allenic fatty acids have mainly being detected in some Lamiaceae species where they can account for up to about 30% of the oil (Dembitsky and Maoka 2007; Kenar et al. 2017). Laballenic acid (16–28% of total fatty acids) is extracted, mostly as free acid, from the seed oil of *Leonotis nepetaefolia* (L.) R.Br., *Leucas urticifolia* (Vahl) Sm. (24% of total fatty acids) and *Leucas cephalotes* (Roth) Speng. (28% of total fatty acids); it has been also isolated from a Compositae plant (*Macledium zeyheri* (Sond.) S. Ortiz) together with its methyl ester. If esterified, its distribution in triacylglycerols appears to be specifically at the *sn*-3 position. Lamnallenic acid (16% of total fatty acids) (Fig. 2) has been detected in *Lamium purpureum* L., while phlomic acid is widely distributed in several genera within the Lamiaceae,

Allenic fatty acids

Cyclic fatty acids

Fig. 2 Chemical structure of the most representative non oxygenated unusual fatty acids: allenic and cyclic fatty acids

subfamily Lamioideae, such as *Lamium*, *Phlomis*, *Galeopsis*, *Stachys* and *Leonurus*. The latter seems to derive by elongation of laballenic acid and it is often present in plant seed oils with the unusual gadoleic (*cis*-9-eicosenoic acid) or gondoic (*cis*-11-eicosenoic acid) fatty acid suggesting a biosynthetic relationships among them (Dembitsky and Maoka 2007).

Cyclic fatty acids

A number of cyclopropene fatty acids have been isolated from the seed oils of species belonging to the Sterculiaceae, Malvaceae, Tiliaceae and Bombacaceae botanical families (Bohannon and Kleiman 1978; Bao et al. 2002; Ahmad et al. 2017). Among them, sterculic acid (8-(2-octyl-cyclopropen-1-yl)-octanoic acid) (Fig. 2), a thermal unstable component which was firstly detected in the kernel oil from *Sterculia foetida* L. and malvalic acid (7-(2-octyl-cyclopropen-1-yl)-heptanoic acid), a homologue of sterculic acid with one-less carbon in its structure, which also occurs in edible oils from some *Gossypium* species. In a specific study it has been demonstrated that seed oils from *S. foetida* contain four types of triacylglycerols in the ratio of 6:41:33:20. The first type does not have cyclopropene fatty acids, while the other three contain one, two and

three of them, respectively, with sterculic acid preferentially esterified at the *sn*-2 position and malvalic acid at *sn*-1,3 position (Pasha and Ahmad, 1992). These two unusual fatty acids often co-occur in the same seed oil (up to 60% of the total, depending on the plant species) and are often present with smaller amounts of the two biosynthetically related cyclopropanoic acids, dihydrosterculic and dihydromalvalic.

The cyclopropenoid 2-hydroxysterculic acid, involved in the bio-conversion of sterculic to malvalic acid has also been described as a component of oils from *Bombacopsis glabra* (Pasq.) A. Robyns (Chaves et al. 2012).

Sterculynic acid, 7-[2-(8-nonyl)-cyclopropen-1-yl]-heptanoic acid) (Fig. 2) from the seed oil of *Sterculia alata* Roxb. represents another unusual structural type of this series, containing both a terminal acetylene and a cyclopropene group (Jevans and Hopkins, 1968).

Among cyclic fatty acids, three unique cyclopentenyl types with a terminal cyclopent-2-enyl ring have been isolated from the so called “chaulmoogra oil”, obtained from the seeds of some *Hydnocarpus* species (Flacourtiaceae). Namely they are: hydnocarpic acid (11-cyclopent-2-enyl-undecanoic acid), chaulmoorgic acid (13-(cyclopent-2-enyl)-

tridecanoic acid) (Fig. 2) and gorlic acid (13-(cyclopent-2-enyl)-tridec-6-enoic acid). They all have the (*R*)-(+)) stereochemistry at carbon 1 of the ring.

Oxygenated

Epoxy fatty acids

These include (+)vernolic acid (*cis*-12,13-epoxy-*cis*-9-octadecenoic acid) (Fig. 3) and its enantiomer (–)vernolic acid with the epoxy group in the 12*S*, 13*R* configuration. Very interestingly, the first has been characterized in some *Vernonia* (Asteraceae) species as well as in some other botanical families systematically widely distant such as the Euphorbiaceae, Dipsacaceae, Onagraceae and Valerianaceae. In contrast, (–)vernolic acid seems to be present only in the seed oils of some Malvaceae (Smith 1971; Spitzer et al. 1996; Tsevegsuren et al. 2004; Gasparetto et al. 2012).

A positional isomer of vernolic acid, the *cis*-9,10-epoxy-*cis*-12-octadecenoic acid, known as coronaric acid (Fig. 3), has been identified in the *Glebionia coronaria* (L.) Cass. ex Spach (Asteraceae). In addition, the *cis*-15,16-epoxy-*cis*,*cis*-9,12-octadecadienoic acid and the *cis*-9,10-epoxyoctadecanoic acid have been isolated, as minor components, from seed oils of other Asteraceae (Smith 1971; Badami and Patil 1981; PlantFAdb 2016).

Hydroxy fatty acids

This class of unusual fatty acids, includes non-conjugated monohydroxy and polyhydroxy fatty acids distributed in various botanical families. Among them, ricinoleic acid (12-hydroxy-*cis*-9-octadecenoic acid) (Fig. 3), reaching up to 90% in castor oil from *Ricinus communis* L. (Euphorbiaceae) seeds, is one of the most known of this type (McKeon 2016). Its isomer, isoricinoleic acid (9-hydroxy-*cis*-

Fig. 3 Chemical structure of the most representative oxygenated unusual fatty acids grouped according to their chemical characteristics

12-octadecenoic acid) is common in the genus *Strophanthus* (Apocynaceae).

The genus *Lesquerella* (Cruciferae) produces typical seed oils containing hydroxy olefinic fatty acids (Smith 1971; Kleiman et al. 1972) such as: lesquerolic acid (14-hydroxy-*cis*-11-eicosenoic acid), a homologue of ricinoleic acid with two more methylene groups between the carboxyl group and the double bond; densipolic acid (12-hydroxy-*cis,cis*-9,15-octadecadienoic acid) and auricollic acid (14-hydroxy-*cis,cis*-11,17-eicosadienoic acid). Other examples are represented by 15-hydroxylinoleate (avenoleic acid) identified in the seeds of *Avena sativa* L. (Graminaceae), nebraskanic acid (7,18-dihydroxy-*cis*-15-tetracosenoic acid) and its isomer, wuhanic acid (7,18-dihydroxy-*cis,cis*-15,21-tetracosadienoic acid) (Fig. 3), with an additional double bond at 21 position, detected in the seed oil of *Orychophragmus violaceus* (L.) Schultz, Cruciferae (Leonova et al. 2008; PlantFAdb 2016; Li et al. 2018).

A number of rare C₁₈ conjugated oxygen-containing dienoic fatty acids have also been isolated from plants (Chisholm and Hopkins 1966; Smith et al. 1960). Examples are: the conjugated trienoic acid α -kamlolenic acid (18-hydroxy-*cis,trans,cis*-9,11,13-octadecatrienoic acid) which has been isolated from the seed oil of some Euphorbiaceae; dimorphecolic acid (9-hydroxy-*trans,trans*-10,12-octadecadienoic acid) and its geometrical isomer 9-hydroxy-*trans,cis*-10,12-octadecadienoic acid, which have been identified, from the two Compositae, *Dimorphotheca sinuata* D.C. and *Calendula officinalis* L., respectively. Further examples of hydroxy fatty acids to be mentioned are coriolic acid (13-hydroxy-*cis,trans*-9,11-octadecadienoic acid), ximenynolic acid (8-hydroxy-*trans*-11-octadecen-9-ynoic acid) and isanolic acid (8-hydroxy-17-octadecen-9,11-dienoic acid). Moreover, a series of dihydroxy and trihydroxy fatty acids have been characterized such as the 9,10-dihydroxy-octadecanoic acid and some higher homologues, phloionolic acid ((+)-*threo*-9,10,18-trihydroxyoctadecanoic acid) and the related (+)-*threo*-9,10,18-trihydroxy-*cis*-12-octadecenoic acid (PlantFAdb 2016; Uzzan 1961; Mikolajczak and Smith 1967). They are esterified to the glycerol backbone: in the dihydroxy fatty acids one of the hydroxyls of each dihydroxy acid moiety is acetylated, while in the trihydroxy fatty acids, two of the

hydroxyls of each trihydroxy moiety is acetylated with acetic acid or other fatty acids.

Finally, although they are abundant in animal tissues and found as components of plant sphingolipids, some structurally peculiar 2-hydroxy fatty acids have been identified in the seed oils of some Lamiaceae, that is 2-hydroxy-octadeca-9,12,15-trienoate in *Thymus vulgaris* L. and 2-hydroxyoleic and hydroxylinoleic acids in *Salvia nilotica* Juss ex Jacq (Smith and Wolff 1969; Smith 1971; Bohannon and Kleiman 1975; Galliard 1978).

Halogenated

Examples of fatty acids or their derivatives having carbon-halogen covalent bonds in their structure have been identified in living organisms including microorganisms, plants, marine organisms and animals. The common halogen contained in these molecules are fluorine, chlorine and bromine. While, to the best of our knowledge, no chlorinated fatty acids have been found in plants until now, a few examples of fluorinated and brominated fatty acids have been reported as components of higher plants seed oils (Dembitsky and Srebnik 2002).

Fluorinated fatty acids

Fluorinated compounds have been rarely identified in plants and microorganisms, while, to the best of our knowledge, none has been identified in animals or marine organisms (Dembitsky and Srebnik 2002). The low number of fluorinated compounds found in nature has been related to the physicochemical property of fluorine compared to the other halogens, that is fluorine has a small steric bulk but it has a very high electronegativity forming the strongest single bond to carbon which results in a strong polarization of the C-F bond on electron withdrawing. This pronounced electronic effect also influences the biosynthetic pathway to fluorine natural products and their reactivity towards enzyme nucleophilic centers (Harper and O'Hagan 1994).

Fluorinated structural types have been specifically isolated from species within the *Dichapetalum* genus (Dichapetaleaceae), tropical climbing shrubs growing in Africa, Asia, Australia and South America which can be deadly toxic to cattle for the presence of fluoracetate in their aerial parts (Msami 1999).

A series of ω -fluoro fatty acids (totally amounting up to 1800 $\mu\text{g g}^{-1}$ of dried seeds) have been isolated from the seeds oil of *D. toxicarum* (G. Don) Baill. They include ω -fluorooleic (80% of total fatty acids), ω -fluoropalmitoleic, ω -fluorostearic, ω -fluorolinoleic, ω -fluoroarachidic, ω -fluoroeicosenoic, ω -fluorocapric and ω -fluoromyristic acids. In addition the seed oil from the same species was reported to contain low amounts of 18-fluoro-9,10-epoxy-octadecanoic acid and *threo*-18-fluoro-9,10-dihydroxy-octadecanoic acid, the latter possibly formed from ω -fluorooleic via the related 9,10-epoxide (Hamilton and Harper 1997; Harper et al. 2003). Moreover, chemical studies allowed to establish that ω -fluoropalmitoleic and ω -fluoroarachidic acids were both present as two isomers with the unsaturation at the 7- or 9-positions and at the 9- or 11-positions respectively (Harper et al. 2003).

In plants, compositional profile of ω -fluoro acids containing triglycerides was shown to be similar to that of non-fluorinated triglycerides in terms of chain length and degree of unsaturation of esterified fatty acids, suggesting that fatty acid synthetase is equally able to utilize fluoroacetyl-CoA and acetyl-CoA in the early steps of fatty acid synthesis. Nevertheless, it has been observed that, in these fatty acids, fluorine is always confined to the terminal position of the chain suggesting enzymic constraints on the use of fluorinated intermediates in the subsequent steps of fatty acyl-chain elongation (Harper et al. 2003).

Brominated fatty acids

Brominated fatty acids are also unusual in plants (Dembitsky and Srebnik 2002). To the best of our knowledge only a few of these types have been detected until now, namely 9,19-dibromooctadecanoic and 9,10,12,13-tetrabromo octadecanoic which was found in the seed oil of *Eremostachys molucelloides* Bunge (Lamiaceae).

Cyanolipids

Cyanolipids represent an unusual class of lipids co-occurring in the seed oil of a limited number of plant families, such as for example the Sapindaceae, the Hippocastanaceae and the Boraginaceae (Møller et al. 1999), together with the more common acylglycerols (Mikolajczak 1977; Avato et al. 2003, 2005, 2006).

Their basic structure includes the same branched five-carbon nitrile skeleton with variations in the number and position of the hydroxyl groups and double bonds.

Most of the information on these phytochemicals comes from chemical studies on several Sapindaceae species (*Paullinia* sp., *Allophylus* sp., *Nephelium* sp., *Sapindus* sp., etc.). Four major structural types have been detected until now in these species (Spitzer 1995; Hopkins and Swingle 1967; Avato et al. 2003, 2005, 2006) having the fatty acids esterified to either a mono- or a di-hydroxynitrile moiety. According to their structure they have been classified as: type I, 1-cyano-2-hydroxymethylprop-2-en-1-ol-diester; type II, 1-cyano-2-methylprop-1-en-3-ol-ester; type III, 1-cyano-2-hydroxymethylprop-1-en-3-ol-diester; and type IV, 1-cyano-2-methylprop-2-en-1-ol-ester (Fig. 4). On enzymatic hydrolysis, cyanolipids of type I and IV release cyanohydrins which spontaneously decompose forming hydrogen cyanide, the other two types instead are not cyanogenic.

In addition, compositional studies on cyanogenic lipids from different Sapindaceae species have shown that they contain high amounts of eicosanoic and eicosenoic fatty acids and that two rare vaccenic acid (*cis*-11-octadecenoic acid) and paullinic acid (*cis*-13-eicosenoic acid), which are usually present in low amounts in plant seed oils, are the most abundant esterified fatty acids accounting for up to 50% of total cyanolipids in some of these plant species (Spitzer 1995; Hopkins and Swingle 1967; Avato et al. 2003, 2005). Moreover, a specific study (Tava and Avato 2014) have indicated that cyanolipids occur in Sapindaceae seed oils as different isomers deriving by the combination of the various fatty acid esterified to the hydroxynitrile moiety.

Bioactivity and industrial uses of selected rare fatty acids

Due to their peculiar structures, unusual fatty acids from plant seed oils are a diverse and important group of phytochemicals with special chemical-physical properties such as for example high reactivity, viscosity and surfactant features which allow to use them as renewable sources of industrial chemicals including waxes, nylons, plastics, resins, paintings, detergents, biodiesel, etc.. (Sommerville and Bonatta 2001; Cahoon and Kinney 2005; Metzger and

Fig. 4 Chemical structure of cyanolipids types I-IV; R=fatty acyl

Bornscheuer 2006; Dyer et al. 2008; Field et al. 2009; Rus 2010; Montero de Espinosa and Meier 2011; Lee et al. 2015). Nevertheless, it has been found that some of them have interesting physiological and pharmacological properties and may be employed in human health (Damude and Kinney 2008; Dyer et al. 2008; Msanne et al. 2020).

Selected examples of rare fatty acids of economic importance are reviewed in the following paragraphs.

Petroselinic acid

Petroselinic acid (*cis*-6-octadecenoic acid, C_{18:1ω12}) (Fig. 1) is a positional isomer of oleic acid (*cis*-9-octadecenoic acid, C_{18:1ω9}) and the two acids are often present together in the same plant oil. The location of the unsaturation at the 6,7-position in petroselinic acid is rare among octadecenoic acids and besides influencing the chemical-physical properties such as its melting point (30 °C), also allows to produce unique derivatives from this molecule.

Occurrence of petroselinic acid has been reported in seven species of Geraniaceae, with *Geranium sanguineum* L. showing the highest content (48% of

total fatty acids) and in three species within the Picramiaceae family, with *Picramnia quassioides* Benn. producing 77% of total fatty acids. Only two Asteraceae and four Lamiaceae species have been reported to contain petroselinic acid with *Madia sativa* Molina (62% of total fatty acids) and *Eremostachys lehmannii* (Bunge) Kuntze (66% of total fatty acids) having the highest yield, respectively in the two plant families. Among the Garryaceae, only five species have been detected to contain petroselinic acid, which was mainly found in some *Garrya* species with a maximal yield of about 80% of total fatty acids (Tsevergsuren et al. 2004; Ohlrogge et al. 2018; Plant FadFAdb 2016).

The Apiales plant order includes the highest number of species which synthesize petroselinic acid. Only nineteen Araliaceae species have been reported to produce oils containing this unusual fatty acid, while petroselinic acid has been detected in over three hundred species within the Apiaceae plant family (PlantFAdb 2016; Sayed-Ahmad et al. 2017; Ohlrogge et al. 2018; Ušjak et al. 2019). Some species such as *Anethum graveolens* L., *Bifora testiculata* (L.) Spreng, *Deverra aphylla* (Cham. & Schltdl.) DC, *Peucedanum*

capense (Thunb.) Sond., *Apium leptophyllum* (Pers.) Benth. and *Torillis leptophylla* (L.) Rechb.f. have the highest content (82–87% of total fatty acids) of this uncommon fatty acid (Smith 1971; Kleiman and Spencer 1982; PlantFAdb 2016).

In addition, a specific study on the isolation and chemical identification of the lipid constituents from the fruits of different wild species of *Thapsia* has shown that triacylglycerols from *T. garganica* L., *T. villosa* L., *T. laciniata* Rouy, *T. minor* Hoffmanns & Link and *T. maxima* Mill. contain 80–90% of tripetroselinin (Avato et al. 2001).

Common spices such as fennel (*Foeniculum vulgare* L.), coriander (*Coriandrum sativum* L.) and caraway (*Carum carvi* L.) have also been reported to contain high amounts of petroselinic acid as the major storage fatty acid (Smith 1971; Badami and Patil 1981; Sahib et al. 2013; Uitterhaegen et al. 2016; Nguyen et al. 2020).

Although it has been described that the common distribution of petroselinic acid is of chemotaxonomic relevance, thus contributing to support a phylogenetic relationship between closely related plant families such as for example Apiaceae and Araliaceae (Bageci 2007; Rasmussen and Avato 1998), this fatty acid is especially recognized as a high-added-value compound for its several potential industrial uses as oleochemical raw material in cosmetics, pharmaceutical or food applications (Placek 1963; Kleiman and Spencer 1982; Murphy, 2005; Sahib et al. 2013; Sayed et al. 2017). Attempts to genetically engineer oilseed crops with high yield of petroselinic acid to meet industrial requests have been only partially successful due the complexity of the biosynthetic pathway (Cahoon et al. 1992; Cahoon and Ohlrogge 1994; Ohlrogge and Browse 1995; Thelen and Ohlrogge 2002; Cahoon and Schmid, 2008), thus plants naturally producing petroselinic acid still represent the preferred source.

The oxidative cleavage of the $\Delta 6$ double bond in the molecule gives a mixture of adipic ($C_{6:0}$) and lauric ($C_{12:0}$) acids which are utilized in the manufacture of plastics and soaps (Murphy 2005). In particular, adipic acid is used in the production of nylon 6,6 and softeners, while lauric acid is the starting material for the production of softeners, emulsifiers and detergents.

Being a structural isomer of oleic acid, petroselinic acid has been effectively employed in the synthesis of

innovative sophorolipids, biosurfactant glycolipid compounds which are produced by fermentation of renewable resources with a number of different non-pathogenic yeasts strains, and have been shown to possess several biological activities such as anticancer, antimicrobial, immunoregulatory and antiviral (de Oliveira et al. 2015; Delbeke et al. 2016, 2019).

In addition, sophorolipids feature self-assembly properties which result in the formation of nanostructures with supramolecular chirality. Thus fermentation of petroselinic acid with *Starmerella bombicola* allowed the synthesis of a new petroselinic acid based diacetylated sophorolipid lactone with high potential for self-assembly applications (Delbeke et al. 2016). Moreover, from microbiologically produced sophorolipids based on petroselinic acid, a series of new quaternary ammonium sophorolipids with antimicrobial and transfection activities have been also synthesized (Delbeke et al. 2019).

Petroselinic acid also proved to be a suitable substrate for the synthesis of estolide esters with acceptable properties as biobased lubricants, greases and printing ink (Erhan et al. 1992; Erhan and Asadauskas 2000; Cermak et al. 2011).

Additionally, several studies have shown that petroselinic acid may be used to benefit human health and wellbeing. Namely, it has been demonstrated by in vitro studies that triacylglycerols containing this unusual lipid as acid moiety become hydrolyzed by pancreatic lipase at much lower rate than triglycerides containing oleic acid suggesting a possible use of these oils in low-fat diets (Weber et al. 1995). In addition, it has been shown that the compound is able to reduce the accumulation of arachidonic acid in heart and liver tissues in rats by inhibiting desaturation/chain elongation of linoleic acid (Weber et al. 1997, 1999).

Moreover, a quite recent study has shown the efficacy of petroselinic acid, as well as of erucic acid, against some *Borrelia* sp., the causative zoonotic bacteria of Lyme disease. It was suggested that the bactericidal activity showed by petroselinic acid might be due to a surfactant-type action increasing cell membranes fluidity (Goc et al. 2019). Similarly, the molecule has been shown to inhibit the growth of *Burkholderia cenocepacia* K56-2, an opportunistic pathogen which causes multiresistant lung infections in patients with cystic fibrosis (Mil-Homens et al. 2012).

In vitro experiments have also highlighted the inhibitory effect of petroselinic acid on both topoisomerases I and II (Suzuki et al. 2000). It has been suggested that the fatty acid acts in a non-competitive manner directly on the two enzymes before the formation of the enzymes-DNA cleavable complexes, thus inhibiting the DNA breaking and rejoining reactions.

This rare fatty acid is also included in cosmetic products as a moisturizing, anti-aging and as a skin-irritation reducing agent in cosmetic formulations containing α -hydroxy acids (Wienkauf et al. 2000; Delbeke et al. 2016). Petroselinic acid has been in fact experimentally recognized to enhance epidermal cell differentiation, to reduce skin-inflammation and to improve skin photodamage being a potent activator of PPARs- α , involved in skin homeostasis (Alaluf and Rawlings 2002; Rawlings 2005).

Finally, it should be remarked that plant oils containing high amount of petroselinic acid have been explored for their use as functional foods and nutraceuticals (Sahib et al. 2013). Some years ago, coriander seed oil rich in petroselinic acid has been authorised by the European Commission as a novel food ingredient intended to be marketed as a food supplement for healthy adults (EFSA 2013).

γ -Linolenic acid

γ -Linolenic acid, also known as gamolenic acid, is an ω -6 fatty acid ($C_{18:3\omega6}$) having three *cis*-double bonds at position 6, 9 and 12 (*cis,cis,cis*-6,9,12-octadecatrienoic acid) (Fig. 1). It derives from linoleic acid ($C_{18:2\omega6}$) as an intermediate in the biosynthesis of arachidonic acid through a desaturation process which involves a specific $\Delta 6$ -desaturase. The resulting γ -linolenic is then rapidly elongated to give *dihomo*- γ -linolenic acid ($C_{20:3\omega6}$) converted into arachidonic acid ($C_{24:3\omega6}$) by a $\Delta 5$ -desaturase.

Usually, α -linolenic acid (*cis,cis,cis*-9,12,15-octadecatrienoic acid; $C_{18:3\omega3}$) is formed from linoleic acid by a $\Delta 15$ -desaturase, thus plant lipids containing high amounts of γ -linolenic acid are considered to be quite unusual.

Plant species belonging to the Onagraceae (e.g. *Oenothera biennis* L., evening primrose), Boraginaceae (*Borago officinalis* L., borage), Grossulariaceae (*Ribes nigrum* L. black currant), Malvaceae (*Durio graveolens* Becc.), Cannabaceae

(*Cannabis sativa* L., hemp) produce substantial amounts (7–20%) of this fatty acid as a constituent of their seed oils (PlantFAdb 2016; Guil-Guerrero et al. 2001; Alonso-Esteban et al. 2020; Kapoor and Nair 2020). In addition to higher plant species, γ -linolenic acid has been also detected in animals, protozoa, fungi, algae and mosses.

Plant triacylglycerols incorporating γ -linolenic acid show distinct stereospecific structures which characterize each plant oil, thus for example γ -linolenic acid is esterified at the *sn*-3 in the seed oils of *O. biennis* and *R. nigrum*, while it is present in the *sn*-2 position in the seed oils of *B. officinalis* (Lawson and Hughes 1988).

γ -Linolenic acid is classified as a “conditionally essential fatty acid”, because it becomes essential to humans in some specific health conditions. Several scientific studies have demonstrated that a high intake of ω -6 fatty acids such as γ -linolenic acid is beneficial to human health since its endogenous formation in the human body is low or impaired in some pathological conditions including diabetes, atopic dermatitis, cardiovascular disease, rheumatoid arthritis and cancer (Fan and Chapkin 1998; Belch and Hill 2000; Kapoor and Huang 2006; Kawamura et al. 2011; Simon et al. 2014; Kapoor and Nair 2020). Reduction of the synthesis of γ -linolenic acid also limits the physiological production of *dihomo*- γ -linolenic and arachidonic acids with the consequent decrease in the formation of eicosanoids (prostaglandins, prostanooids and prostacyclins), important cell signalling molecules involved in several physiological and pathological processes.

Although there are only few clinical evidences, there are numerous in vitro and in vivo animal model studies which have shown that supplementation of γ -linolenic acid or plant seed oils rich in this fatty acid can attenuate the symptoms of various inflammatory conditions (Sergeant et al. 2016, 2020).

γ -Linolenic acid enriched supplements given in combination with ω -3 long chain polyunsaturated fatty acids from marine organisms have for example been shown to potentiate anti-inflammatory effects by reducing the expression of genes for pro-inflammatory cytokines and leukotriene production. Consistently, it has been shown that such combinations of long chain polyunsaturated fatty acids enhance the conversion of dietary γ -linolenic acid into *dihomo*- γ -linolenic acid but inhibit its further

conversion to arachidonic acid thus reducing the production of active prostaglandins and leukotrienes (Barham et al. 2000; Veselinovic et al. 2017).

Supplementation of γ -linolenic acid to diabetic rats (Coste et al. 1999) indicated its beneficial effects also on diabetic neuropathy, a complication of diabetes characterized by a decrease of nerve conduction as a consequence of the inhibition of $\Delta 6$ -desaturase.

Furthermore, it has been described that patients with rheumatoid arthritis treated with γ -linolenic acid showed progressive improvements of the symptoms suggesting a possible use of the compound as an adjunctive therapy to synthetic anti-inflammatory drugs (Fan and Chapkin 1988). In animal models, dietary γ -linolenic acid also proved to reduce atherosclerosis lesions thus helping to control the development of the pathology (Fan et al. 1999, 2001).

Moreover, the efficacy of dietary intake of seed oils with high levels of γ -linolenic acid or γ -linolenic acid supplementation has been shown to correlate with the clinical improvement of symptoms of atopic dermatitis, an inflammatory skin disorder which is partly due to a deficiency of $\Delta 6$ -desaturase resulting in the synthesis of low levels of γ -linolenic acid (Callaway et al. 2005; Simon et al. 2014).

Cytotoxicity of γ -linolenic acid has been indicated by several studies as well as its specific antineoplastic activity against some types of tumors (Das 1990; Begin et al. 1988; Robbins et al. 1999). Among these, γ -linolenic acid has been described to inhibit the growth of brain tumors, both in animal models and human clinical studies (Bakshi et al. 2003; Andreoli Miyake et al. 2009). The inhibitory effect of γ -linolenic acid was found to be selective towards cancer cells while sparing astroglia cells and improving the radiotherapy response (Vartak et al. 1998).

In vivo and in vitro bioassays proved the safety and suitability of γ -linolenic acid and borage seed oil. It was shown that they are not-toxic, not-genotoxic or antimutagenic, making their dietary supplementation reasonable safe. Borage seed oils resulted to be less toxic than γ -linolenic acid to affect *D. melanogaster* life cycle, while both showed similar positive genotoxic/anti-genotoxic effects (Tasset-Cuevas et al. 2013). Nevertheless, long-term human feeding trials have demonstrated that supplementation of γ -linolenic acid is well tolerated up to a dose of 2.8 g (Fan and Chapkin 1988).

Large-scale production of γ -linolenic acid to satisfy the high demand for industrial applications has been achieved with genetically engineered plant sources such as *Brassica napus* L., *B. juncea* L., *Perilla frutescens* L. and *Carthamus tinctorius* L. varieties expressing the genes for $\Delta 12$ and $\Delta 6$ desaturases thus driving the synthesis of fatty oils containing 30–40% γ -linolenic acid (Hong et al. 2002; Nykiforuk et al. 2012; Lee et al. 2019).

Erucic acid

Erucic acid (*cis*-13-docosenoic acid, C_{22:1 ω 9}) (Fig. 1), is a long chain fatty acid occurring in high concentrations (up to 40% of total fatty acids) in the oil rich seeds of several Brassicaceae (PlantFadb 2016; Avato and Argentieri 2015; Lu et al. 2020), such as rapeseed (*Brassica napus* L. var. *oleifera* D.C.), mustard (*B. juncea* (L.) Czern & Coss) and turnip (*B. rapa* L.).

Plant oils with a high content of erucic acid are very useful for industrial non-food applications (Issariyakul and Dalai 2010; Madankar et al. 2013). Brassica oils with a moderate/high content of erucic acid are in fact excellent lubricants and represent a competitive renewable source for biofuel and biodiesel production. Nowadays, some improved crops from different brassicas either containing a low content of erucic acid (< 0.5% of total fatty acids) in the seed oil (the so called canola oil, “Canadian oil low in acid”) as well as with very high amounts (nearly 50%) of erucic acid have been developed and are commercially available for industrial applications (Dupont et al. 1989; McVetty and Duncan 2015).

EFSA (2016) has delivered a scientific opinion on the risk for human and animal health related to the presence of erucic acid in food and feed. Experiments on animal models have documented that the heart is the principal target organ for toxic effects due to dietary erucic acid. Adverse effects of this fatty acid, mainly present in the form of triacylglycerols in seed oils or derived food, consist in the onset of myocardial lipidosis and heart lesions. Although erucic acid induced lipidosis has not been described in humans, EFSA has established a Tolerable Daily Intake-TDI for humans equal to 7 mg of erucic acid per kg of body weight per day. In addition, in Europe a maximum content of 5% of erucic acid is allowed in rapeseed oil used in food.

Nevertheless, erucic acid has been investigated for potential therapeutic uses (Kumar and Sharma 2020). Triglycerides of erucic and oleic acid are components of the so called “Lorenzo’s oil”, a dietary formulation which has been experimented for the treatment of adrenoleukodystrophy, a pathology of dietary origin, characterized by abnormal high levels of very long chain fatty acids (C_{22} – C_{26}) in the brain possibly due to the bad functioning of fatty acid-CoA-synthase. This formulation was found to reduce the endogenous synthesis of long chain fatty acid by the inhibition of acyl chain elongation process (Moser 1977).

Modulation of fatty acid metabolism has been recognized of therapeutic importance to control the progression of other neurodegenerative disorders such as multiple sclerosis, Alzheimer’s and Parkinson’s diseases (Altinoz et al. 2019; Kumar and Sharma 2020). Thus, erucic acid has been shown to be an important ligand for the neuroprotective transcription factor PPAR δ , involved in suppressing inflammation, stimulating myelination and reducing the neurotoxicity of β -amyloid. It has also been found that it can directly affect lipid peroxidation and activate catalase, a potent antioxidant enzyme. In addition, it is known that erucic acid can be elongated by human hepatocytes to nervonic acid ($C_{24:1\omega9}$), a major component of myelin, thus promoting remyelination in neurological disorders (Altinoz et al. 2019).

Moreover, a very recent study (Liang et al. 2020) has highlighted the potential therapeutic use of erucic acid in the treatment of influenza. The fatty acid has been proved to be efficacious in vitro against several viral strains of human influenza. In vitro and in vivo experiments demonstrated that treatment of influenza with erucic acid suppressed the transcriptional activities of the viral polymerase complex by inactivation of the NF- κ B and p38 MAPK signalling pathway, thereby causing the inhibition of virus replication. Erucic acid was also shown to reduce the pro-inflammatory response induced by the influenza viruses.

Fatty oils from plants are often employed for topical cosmetic or medical skin applications. Oil free fatty acids, such as the ω -9 erucic, oleic, gondoic and nervonic acids may alter the skin lipid and protein structure and act as permeability enhancers for active components with beneficial physiological effects (Moore et al. 2020). In a specific study, it was shown that the enhancement of skin permeability by the

above mentioned *cis*-unsaturated fatty acids was dependent on their different alkyl chain lengths and double bond position, being nervonic acid the less active (Taguchi et al. 1999).

Despite of its implication on health, the industrial use of erucic acid has considerably increased during the last ten years. The main application is in the production of erucamide, an anti-blocking and slip agent in the plastic manufacture. Additionally, erucic acid is used as starting material to produce behenic acid ($C_{22:0}$) and derivatives which are utilized as pour point depressants and to obtain caprenin, a reduced-calorie substitute (Temple-Heald 2004).

α -Eleostearic acid

α -Eleostearic acid (α -ESA, $C_{18:3\omega5}$) (Fig. 1) is the most abundant natural conjugated linolenic acid in food plants. It is the major fatty acid obtained by pressing the seeds of *Vernicia fordii* (Hemsl.) Airy Shaw, the tung tree, that gives the so called “tung oil” or “China wood oil”, which upon exposure to air polymerizes becoming harder and transparent thus allowing its use to protect wood and for dyes or ink formulations (Zhang et al. 2020). α -ESA also represents the major (61%) fatty acid in the seed oil obtained from *Momordica charantia* L. (Cucurbitaceae), the bittermelon or bitter ground, a tropical crop native to Asia (Chisholm and Hopkins 1964; Yoshime et al. 2016; Jia et al. 2017). Similarly, *Gymnostemna pentaphyllum* (Thunb.) Makino, also belonging to the Cucurbitaceae plant family, produces a seed oil rich in conjugated linolenic acids including catalpic, α - and β -eleostearic acids (Zou et al. 2016). Among them, α -ESA is the most abundant both in diploid (57%) and tetraploid (63%) seeds. Moreover, discrete amounts (on average 30–47%) of α -eleostearic acid have been reported in the seed oils from *Schinziophyton rautanenii* (Schinz) Radcl.-Sm. (Euphorbiaceae), *Ricinocarpus tuberculatus* Muell. Arg. (Euphorbiaceae), *Parinari montana* Aubl. (Chrysobalanaceae) and *Prunus mahaleb* L. (Çavdar 2019).

α -Eleostearic acid has shown important biological activities which have been attributed to its specific chemical structure with a *cis* double bond at carbon 9 and a *trans* double bond at carbon 11 of the acyl chain (Churrua et al. 2009). Due to its structural features α -ESA is in fact less efficiently oxidized than

its *trans*-10, *cis*-12 isomer and has important antioxidant/pro-oxidant properties which also accounts for its pharmacological activity.

Anti-carcinogenic effects of this phytochemical have been particularly studied in *in vitro* and *in vivo* systems (Grossmann et al. 2009; Yuan et al. 2014). Thus it has been shown that this rare fatty acid and its dihydroxy derivative are able to affect the growth of some cancer cell lines inducing apoptosis in promyelocytic HL60 leukemia and HT29 colon carcinoma cells (Kobori et al. 2008) and causing antiproliferation of transformed NIH-3T3 mouse fibroblasts and human monocytic leukemia cells (Suzuki et al. 2001a, b). Some other studies have in addition shown that α -ESA inhibits proliferation of both MDA-wt and MDA-ER α 7 breast cancer cell lines more efficiently than conjugated linoleic acids and that inhibition of tumorigenesis may involve an oxidation-dependent mechanism leading to cell death (Grossmann et al. 2009; Farooqi et al. 2018). Moreover, it has been demonstrated that α -ESA can contribute to breast cancer suppression also through the activation of AMPK, an enzyme which has a role in tumor inhibition.

In vivo studies on the antitumor activity of α -eleostearic acid have been mainly focused on colon cancer. Dietary supplement of an extract from bittermelon rich in α -ESA was able to significantly lower the incidence of AOM (azoxymethane)-induced colorectal cancer in rats. In addition, it has been evidenced that α -ESA inhibits colon adenocarcinoma induced by DLD-1 cell lines in immunodeficient nude mice and that the effects involve the increase of lipid peroxidation within cancer cells (Yuan et al. 2014).

Analysis of the anti-tumorigenic effects of different conjugated linolenic acids (*cis,trans,cis*-9,11,13; *trans,trans,cis*-9,11,13; *trans,trans,cis*-8,10,12), including α -eleostearic acid (*cis,trans,trans*-9,11,13), also highlighted the importance of bonds number, position and configuration on their pharmacological activity. That is, the isomers with double bonds at 9, 11, 13 displayed a higher cytotoxicity and all *trans* isomers had a greater inhibitory activity than partial *trans* isomers. Furthermore, when compared with conjugated linoleic acids, conjugated linolenic acid always had higher anti-carcinogenic effects (Hennessy et al. 2011).

Efficacy of α -ESA to fight oxidative stress and its ability to protect against adverse effects by environmental toxins has been further investigated in animal systems (Pal and Ghosh 2012; Saha and Ghosh 2010). Thus, a specific study established that α -eleostearic acid is able to reduce the oxidative stress induced by organic methyl-mercury in rat liver and kidney, by reducing lipid peroxidation and restoring the normal activity of antioxidant enzymes. It was also shown that this phytochemical has a protective effect against arsenite-induced renal oxidative stress in animal model. Administration of α -ESA to arsenite-treated rats caused amelioration of renal oxidative stress with restoration of the altered enzymatic parameters. Comparison of α -ESA and puniceic acid effects on arsenite treated rats indicated that the better antioxidant activity of α -ESA was consistent with its highly *trans* configuration. Both isomers showed however synergistic effect when administered together, possibly due to their contrasting *cis-trans* structure (Saha and Ghosh 2011; 2012).

In addition to its anti-tumorigenic property, α -eleostearic acid has been reported to have anti-adipogenic, anti-diabetic and anti-inflammatory activities (Yuan et al. 2014).

Although some positive evidences, the role of α -ESA on lipid metabolism appears still controversial. Some studies have indicated a significant capacity of α -ESA to lower total and high-density lipoprotein cholesterol in diabetic rats, while this effect was not confirmed in other studies. A possible role of α -ESA to control obesity has also been suggested and associated with delipidation, inflammation and browning of the white adipose tissue in diet-induced obese rats in some studies, while in other investigations weight of adipose tissue resulted not influenced by α -ESA dietary administration to mice (Yuan et al. 2014).

α -Eleostearic acid has been also identified as an agonist of PPAR γ , the receptor involved in the regulation of fat accumulation and glucose metabolism, thus possibly being effective in improving pathological conditions such as diabetes, inflammation and dyslipidemia (Lewis et al. 2011; Yan et al. 2014). Consistently, in a targeted study to identify novel therapeutic drugs for inflammatory bowel disease, α -ESA was shown to significantly ameliorate clinical signs of the pathology in mouse model with experimentally induced colitis.

Finally, α -ESA and oils rich in this phytochemical can be used in cosmetics. UV polymerization of α -eleostearic acid results in a protective film for skin or hair which has been exploited in the manufacturing of care products (Fischer et al. 2016). Similarly, *Momordica charantia* seed oil proved to be suitable for the production of organic antiseptic soaps beneficial in preventing skin aging, infections and inflammation (Zubair et al. 2018).

Despite of all its possible applications, the use of α -ESA as a drug is however limited by its high hydrophobicity which requires specific delivery systems to allow its administration in humans. Thus several studies have been also accomplished to engineer innovative formulations such as nanoemulsions to improve stability and enhance the bioavailability of the compound (Paul et al. 2015, 2019).

Punicic and catalpic acids

The trienoic punicic acid, also known as trichosanic acid ($C_{182:3\omega5}$) (Fig. 1) is an isomer of conjugated α -linolenic acid and it is an ω -5 polyunsaturated fatty acid. It is particularly abundant in the seed oil of pomegranate (*Punica granatum* L.) representing one of the major component up to 85% and it has been also isolated in higher amount from the seeds of some species of *Trichosantes* such as *T. kirilowii* Maxim (TK) and *T. anguina* L. (Hopkins and Chrisholm 1962a, 1962b; Joh et al. 1995; Pereira de Melo et al. 2014; Aruna et al. 2016; Hennessy et al. 2016). Experimental studies have shown that punicic acid has some important pharmacological and therapeutic properties against cancer, diabetes, coronary heart disease, and obesity (Grossmann et al. 2010; Aruna et al. 2016; Shabbir et al. 2017; Holic et al. 2018). Health benefits of natural conjugated trienoic fatty acids had, in the recent years, encouraged the production of genetically modified plants with high level of punicic acid. However, until now, only a genetically engineered rapeseed oil with a very low content of punic acid has been produced on an experimental basis (Koba et al. 2007).

In in vitro experiments it has been shown that punicic acid inhibits proliferation of human prostate carcinoma cancer PC-3 and DU 145 cell lines. In particular, it has been demonstrated that the trienoic fatty acid is able to inhibit some of the key enzymes

in hormone-dependent prostate cancer such as aromatase and 5- α -reductase. In addition, punicic acid was shown to induce apoptosis in androgen-sensitive human prostate adenocarcinoma cell lines through a caspase-dependent pathway (Gasmi et al. 2013; Aruna et al. 2016).

Anticancer activity of punicic acid has been also studied against human breast cancer cells (Grossmann et al. 2010). The trienoic fatty acid was able to inhibit proliferation of estrogen sensitive cancer cells by 92–96% and to induce cell death possibly involving lipid peroxidation and protein kinase C activation.

Antidiabetic and antiobesity properties of punicic acid have been studied in in vitro and in vivo experiments (Aruna et al. 2016; Shabbir et al. 2017). Administration with the diet of punicic acid to OLETF rats, a specific strain for studying obesity and diabetes, indicated that adipocytes undergo to cellular suicide and animals remain relatively lean. It has also been shown that punicic acid is able to prevent fat-induced obesity and insulin resistance (Arao et al. 2004; Aruna et al. 2016). Similarly, hypolipidemic and antidiabetic effects have also been observed in experiments with pomegranate seed oil containing high amounts of punicic acid highlighting a protective effect against diet-induced obesity and insulin resistance in mice (Aruna et al. 2016). Overall, these effects have been related to the capacity of punicic acid, as α -ESA, to activate PPARs thus producing an alteration of adiposity and a normalization of blood levels of glucose associated with the amelioration of intestinal inflammation (Viladomiu et al. 2013).

Punicic acid was shown to significantly reduce perirenal adipose tissue weight in rats in a dose-dependent manner and, very interestingly, it has been shown that reduction of adipose fat mass may also depend on the specific position of the fatty acid in the triacylglycerols. Thus it has been demonstrated that genetically engineered rapeseed oil with punicic acid exclusively in the *sn*-2 position of the glyceride backbone is more effective than pomegranate oil with punicic acid located in all positions of triacylglycerol molecule (Koba et al. 2007).

Punicic acid has been reported to have high anti-inflammatory effects and it has been proposed as a valid therapeutic agent against various inflammatory diseases involving oxidative stress (Aruna et al. 2016). Besides its capacity to activate PPARs,

punicic acid was also reported to inhibit COX and LOX activities in animal experimental models and to suppress NF- κ B and TNF- α expression in diabetic rats (Boussetta et al. 2009; Shabbir et al. 2017; Pererira de Melo et al. 2019). Its anti-inflammatory properties were also supported by the evaluation of the anti-inflammatory properties of a hydrophilic fraction from pomegranate seed oil, rich in the trienoic fatty acid, on breast cancer cells (Costantini et al. 2014). In this specific study a synergistic effect between anti-inflammatory, antioxidant and cytotoxic activity of punicic acid was evidenced.

Application of punicic acid in therapy however poses some questions: it is slowly absorbed and it is rapidly metabolized forming other conjugated isomeric linolenic fatty acids such as catalpic and α - and β -eleostearic acids. Alternatively, the use of appropriate formulations of pomegranate seed oil such as encapsulation into lipid-based carrier systems, nanoemulsion delivery systems or nanodispersions is being considered to protect the active fatty acids from degradation (Adu-Frimpong et al. 2018).

Catalpic acid represents another C_{18:3 ω 5} natural isomer and namely is the *trans,trans,cis*-9,11,13-octadecatrienoic acid (Fig. 1) isomer of punicic acid. It is the major component (> 40 g/100 g of oil) of triglycerides isolated from the seeds of *Catalpa ovata* G. Don, an endemic plant from China (Hopkins and Chisolm 1962a, 1962b; PlantFAdb 2016). In addition it is also present, together with α -ESA in the flesh of bitter melon (Suzuki et al. 2001a, b).

Experimental evidences have indicated that this fatty acid, similarly to α -ESA and punicic acid, has potential as cancer chemopreventive agent. In vivo studies have shown that dietary feeding with catalpa oil rich in catalpic acid causes a significant decrease in the multiplicity of colonic aberrant crypt foci in rats treated with azoxymethane and a significant increase of apoptotic cells (Suzuki et al. 2006). A cytotoxic effect of catalpic acid was also evidenced in some human cancer leukemia cell lines (Tanaka et al. 2011). In addition, this fatty acid was shown to have a strong dose-dependent cytotoxic effect on DLD-1 human adenocarcinoma cells via apoptosis and the ability to promote lipid peroxidation (Shinoara et al. 2012).

Jacaric and calendic acids

These two unconventional C_{18:3} fatty acids differ from punicic and catalpic acids for the position of the three conjugated double bonds which in jacaric and calendic acids are located in 8-, 10- and 12- positions. Jacaric acid, *cis,trans,cis*-8,10,12-octadecatrienoic acid, C_{18:3 ω 6} (Fig. 1) is abundant in the seed oil of some species of *Jacaranda* (Bignoniaceae), they are trees native to tropical and subtropical areas of South and Central America; the content of jacaric acid in the oil of these plants ranges from 30 to 36%, with *J. mimosifolia* D. Don producing the highest amount (Gunstone et al. 2007). Calendic acid, *trans,trans,cis*-8,10,12-octadecatrienoic acid, C_{18:3 ω 6} (Fig. 1), is abundant in *Calendula officinalis* L. seed oil (about 60%). The same fatty oil, also contains small amounts of the isomer β -calendic acid, *trans,trans,trans*-8,10,12-octadecatrienoic acid (Hopkins and Chisolm 1962a, b; Smith 1971; PlantFAdb 2016).

Jacaric acid has been proposed as an effective drug to prevent obesity and diabetes (Shinoara et al. 2012). The administration of this compound to ICR mice resulted in a decrease of the desaturation index (ratio of palmitoleic/palmitic acid and oleic/stearic acid) in liver and white adipose tissue, indicating that jacaric acid is able to inhibit stearoyl-CoA desaturase, an enzyme catalyzing the formation of monounsaturated fatty acids from saturated fatty acids and considered a key target in the control of obesity and diabetes.

As other isomeric trienoic fatty acids, jacaric acid has shown antiproliferative properties in vitro against various types of cancer, including prostate cancer. In a specific study (Gasmi and Sanderson 2013), jacaric and punicic acids, compared to their octadecatrienoic geometric isomers, proved to be the most cytotoxic and the most active in inducing apoptosis in hormone-dependent and hormone-independent human prostate cancer cell lines, without affecting the viability of normal cells. In the same study, a 3-D conformational analysis indicated that the double bonds in the *cis-trans-cis* conformation as in jacaric and punicic acids have a crucial role in the high cytotoxic activity of these two compounds.

Additionally, it has been shown that jacaric acid may be considered to be a good drug, with very low toxicity and fewer side effects, to treat immunological disorders (Liu and Leung 2015a). It has been found that the molecule has immunomodulatory effects

on murine peritoneal macrophages being able to enhance the endocytic and phagocytic activity of these specialized cells and to increase their capacity to release pro-inflammatory cytokines and produce intracellular reactive oxygen and nitrogen species. Moreover, jacaric acid was shown to markedly increase the murine peritoneal macrophages cytostatic activity on MBL-2 cell lines without being cytotoxic to the macrophages. In another study by Liu and Leung (2015b), it was also demonstrated to have anti-allergic properties when tested by in vitro on activated human mast cell lines. The suppression of the allergic response was associated with the reduction of inflammatory mediators secretion and with the modulation of the expression of the matrix metalloproteinases MMP-2, MMP-9 (decrease of their expression levels) and the metalloproteinase inhibitor TIMP-1 (increase of its expression) generally present in tissues in which inflammatory processes are active.

Both isomers α - and β -calendic acids have demonstrated anticancer properties in in vitro systems (Yuan et al. 2014; Dubey et al. 2019). It was shown that they both induce apoptosis in Caco-2 cells but the *trans* (β -calendic acid) isomer is more active than the *cis* isomer (α -calendic acid) in terms of growth inhibition of the cancer cells. In addition the two isomeric calendic acids have been shown to be cytotoxic to human choriocarcinoma cells with, again, β -calendic acid being more active. In general, calendic acid also resulted much less active than α -ESA, puniceic acid and catalpic acid on human leukemic and much less active than jacaric acid against DLD-1 cancer cells (Shinohara et al. 2012).

Finally, fatty oils from *C. officinalis* and *J. mimosifolia*, in association with other plant oils containing octadecatrienoic acids are ingredients of a patented topical cosmetic formulation (Spencer 2013) aimed to enhance production of skin collagen.

Ximenynic acid

This rare acetylenic fatty acid is typically found in the seed oils from the botanical genera of *Ximenia* (Olacaceae) and *Santalum* (Santalaceae) from which the common names ximenynic acid or santalbic acid are derived. It is also a component of the seed oils of some Opiliaceae. It represents one of the few acetylenic fatty acids present at high amounts in plant oils; quite often it can reach amounts above

70% and in certain species even levels up to 95% of the total seed oil fatty acids as in *S. album* (Aitzemüller 2012).

From a chemical point of view, ximenynic acid (*trans*-11-octadecen-9-ynoic acid) (Fig. 1) is characterized by a conjugated ene-yne functional group which makes it a very reactive molecule for industrial applications. The fatty acid is an approved cosmetic ingredient and is extensively employed in cosmetics as hair conditioner and in formulations to improve hair vitality by stimulating microvascular activity (Bombardelli et al. 1994). Nevertheless, ximenynic acid rich oils from plants are used as a skin cosmetic to improve skin hydration and elasticity and UV screen. It has been proved that it has anti-aging properties which can justify the skin protective effect of ximenynic acid rich fatty oils (Satoto et al. 2020; Shivatare et al. 2020). In addition, ximenynic acid and its ethyl ester have been reported to ameliorate blood circulation thus validating their use in the treatment of venous insufficiency cellulitis. Furthermore, this compound was reported to be antimicrobial specifically against Gram positive bacteria and some pathogenic fungi supporting its beneficial antiseptic use in cosmetics (Jones et al. 2008).

Other in vitro studies have demonstrated that ximenynic acid has anti-inflammatory properties acting as a potent inhibitor of the eicosanoids synthesis, specifically it was found that it is a COX-1 selective inhibitor. This inhibitory property of ximenynic acid has also been related with its anti-cancer activity on HepG2 human hepatoma cells (Cai et al. 2016).

Acetylenic fatty acids have been shown to inhibit some enzymes involved in the regulation of lipid metabolism. Thus it was shown that ximenynic acid can down-regulate the gene expression of stearoyl-CoA desaturase and fatty acid desaturase 1 and 2, as well as the expression of fatty acid desaturase 2 protein in HepG2 human hepatoma cells causing a significant decrease on *n*-3 polyunsaturated fatty acids, which are known to prevent and improve many chronic pathologies such as diabetes, cancer, inflammatory and cardiovascular diseases. (Cai et al. 2020).

Finally, based on its numerous biological activities, a series of concentrated blends containing ximenynic acid or its derivatives were invented for

application in food products (for example margarine, chocolate, ice cream, cheese, drinks, dry soup, etc.) or food supplements to enhance their physical properties, to have beneficial effect on satiety or to improve health claims (Koenen et al. 2004).

Sterculic acid

This cyclopropenoid fatty acid (Fig. 2), together with malvalic acid, is found as a component of seed oils produced by several plant families within the Malvales. The highest content (around 55%) of sterculic acid has been reported for *Sterculia foetida* seeds oil (Pasha et al. 1992; PlantFAdB 2016).

Due to the presence of the highly strained and reactive cyclopropene ring which contains a double bond in the 9 position, sterculic acid shows several biological activities. It can rapidly react with biological thiols and in general with sulfur containing compounds. Because of this peculiarity, it is a potent inhibitor both in vitro and in vivo of SH-containing enzymes, such as Δ^9 -desaturase, an important lipogenic enzyme which controls fatty acids desaturation. In particular, sterculic acid is able to control the biosynthesis of monounsaturated fatty acids, mainly oleate and palmitoleate by irreversible binding of the cyclopropene ring to the sulfhydryl groups of the enzyme stearoyl-CoA desaturase-1. Increase in the expression and/or activity of this enzyme is also related with obesity and its complications, thus the enzyme may represent a pharmacological target to treat obesity and improve insulin resistance (Ortinou et al. 2012). Consistently, some studies have shown that supplementation of sterculic acid to obese (ob/ob) mice reduces body weight and adiposity, improves glucose metabolism and insulin tolerance and attenuates hepatic inflammation (Ortinou et al. 2012; Major et al. 2008).

Besides to control obesity, sterculic acid resulted of interest to treat other pathologies such as atherosclerosis, liver disorders, cancer and neurodegenerative pathologies including Alzheimer's, multiple sclerosis, Parkinson's and others (Anderson et al. 2020; Peláez et al. 2020; Ramírez-Higuera et al. 2020) where stearoyl-CoA desaturase is also involved.

Recently, evidence has been gained for a role of sterculic acid in the treatment of ocular diseases such as age-related macular degeneration. The exact

mechanism of action is not clear yet, but it has been proposed that sterculic acid antagonizes pathological inflammation and cytotoxic responses induced by 7-ketocholesterol, a non-enzymatic oxidation product of cholesterol which promotes cellular oxidative stress and apoptosis in macrophages and represents an important component implicated in this pathology (Pariente et al. 2019, 2020). It has in fact been observed that treatment of retinal pigmented epithelium cells with sterculic acid caused a reduction of the expression of many genes involved in sterol biosynthesis thus influencing the intracellular metabolism of the oxysterol. In addition, sterculic acid was found to reduce cell death mediators and, due to its high binding affinity against PPAR γ (containing reactive cysteine residues) and TLR4 receptor, to induce a decrease of mediated inflammation and cytotoxicity (Pariente et al. 2020).

Sterculic acid has also been reported (Hao et al. 2016; Peláez et al. 2020) to inhibit the growth in vitro of the parasite *Toxoplasma gondii*, the etiological agent of toxoplasmosis. The fatty acid is able to reduce propagation of the parasite and the number of ruptured cells as well as to inhibit the replication of intracellular tachyzoites by targeting the synthesis of unsaturated fatty acids, essential for the reproduction and development of the parasite. Similarly, inhibition of the synthesis of oleic acid by sterculic acid and some structural analogues resulted in a parasitocidal effect against the asexual blood stage of *Plasmodium falciparum*, the parasite responsible for malaria. Moreover, it was also shown that sterculic acid affects the growth of *Mycobacterium tuberculosis*, the causative pathogen of tuberculosis (Gratraud et al. 2009; Peláez et al. 2020). Based on these evidences, sterculic acid is considered an effective candidate drug to treat the above mentioned pathologies.

Hydnocarpic acid and chaulmoogric acid

These rare cyclopentenyl fatty acids (Fig. 2) are typically found as components of the seed oil of some Flacurtiaceae plants together with gorlic acid. Already in the eighteenth century they have been described as the main therapeutic agents against leprosy (Hansen's disease) and the chaulmoogra oil, obtained from different species of *Hydnocarpus*, represented the common natural remedy against this infection during the 1920–1930s (Walker and

Sweeney, 1920; Santos dos et al. 2008). Since then, these compounds have been proposed for the treatment of other skin diseases, as anti-inflammatory and to treat tuberculosis (Sahoo et al. 2014; Almahli 2017). The causal organisms of leprosy are the bacteria *Mycobacterium leprae* and *M. lepromatosis*, whose multiplication was shown to be inhibited in *in vivo* and *in vitro* studies by hydnocarpic acid and chaulmoogra acids (Jacobsen and Levy 1973; Levy 1975). As indicated by the low/nil antimicrobial activity observed for saturated chaulmoogric acid, dihydrochaulmoogric acid and saturated straight-chain fatty acids, the cyclopentenyl ring in the structure is required to inhibit the growth of the mycobacteria with a unique mechanism of action involving the inhibition of the synthesis of biotin by the microbe, or of some biotin-requiring metabolic reactions essential for the reproduction of the bacteria (Jacobsen and Levy 1973).

The fixed oil obtained from some *Hydnocarpus* species was also shown to improve the healing of wounds in leprosy patients and in patients with diabetic ulcers when administrated topically or orally (Oommen et al. 1999) possibly by enhancing the synthesis and secretion of collagen from fibroblast cells thus promoting epithelization. Experiments on diabetic mice have also demonstrated that wound healing induced by *Hydnocarpus* extract is associated with an increase of inflammatory cytokines which are involved in the activation of vascular endothelial cells and fibroblast proliferation (Lee et al. 2010).

Another interesting biological activity has been highlighted for chaulmoogric acid which has been identified as an activator of protein phosphatase 5 (Cher et al. 2010), an important protein expressed in the central nervous system whose activity is decreased in patients with Alzheimer's disease. It has been shown that the cyclopentenyl fatty acid is able to bind specifically to a repeat domain of the protein causing a conformational change responsible of its activation.

First semisynthetic therapeutic products derived from chaulmoogric acid were already patented in 1941 (Orlando et al 1941); recently (Osorio et al. 2020), a series of novel triazole derivatives based on hydnocarpic acid conjugation have been synthesized showing promising antineoplastic activity against human cell lines from lung carcinoma. Furthermore, the chaulmoogra oil, rich in hydnocarpic acid, is an

ingredient in a patented cosmetic formulation for the treatment of depigmented or non-pigmented skin (Leconte and Leclere 2012).

Ricinoleic acid

Ricinoleic acid, 12-hydroxy-*cis*-9-octadecenoic acid (Fig. 3), is the major component of castor oil obtained by cold expression from the seeds of *Ricinus communis* L. (Euphorbiaceae). This fatty acid represents about 70–90% of the total triglycerides (triricinolein) forming the oil. It is an unsaturated ω -9 fatty acid characterized by the unique homoallylic hydroxy group at carbon-12 which contributes to the unusual physical and chemical properties of castor oil such as higher viscosity, lower cloud point, lower oxidative stability and higher flash point. Moreover, the presence of the hydroxyl functional group, which makes ricinoleic acid more polar than most other lipids, its carboxylic group and its long hydrocarbon chain confer a high reactivity to the molecule and/or castor oil that allow their employment as valuable renewable chemicals for several industrial applications such as the synthesis of biodegradable polymers, cosmetics, biofuels, lubricants and plastics (Teomim et al. 1999).

Additionally, ricinoleic acid has some potential applications in human health. Castor oil is an approved laxative agent (EMA 2016) for short term use in occasional constipation. Its laxative effects are mediated by ricinoleic acid; on ingestion, the oil is enzymatically hydrolyzed by intestinal lipases releasing the fatty acid. Ricinoleic acid acting as a local irritant promotes then intestine motility and increases mucosal permeability eliciting massive contractions in the colon which facilitate the intestinal physiological function. Castor oil use during pregnancy is however contraindicated due to the known capacity of ricinoleic acid to influence labour and shorten the course of delivery in animal models (EMA 2016). At the molecular level, these pharmacological effects have been related with the capacity of ricinoleic acid to activate the prostaglandin EP₃ receptor which mediates the activity of castor oil/ricinoleic acid on intestinal and uterine smooth-muscle cells (Tunaru et al. 2012). Interestingly, a strong structure–activity relationship for the *cis*-isomer (ricinoleic acid) compared to the *trans*-isomer (ricinelaidic acid) and oleic

acid (lacking the hydroxyl group) has been highlighted to support its bioactivity.

Furthermore, ricinoleic acid has also been found to have analgesic properties and to affect inflammatory responses in induced acute and subchronic experimental models of inflammation. It has been observed that ricinoleic acid possesses dual pro- and anti-inflammatory properties similarly to capsaicin. Unlike capsaicin it is devoid of algesic properties *in vivo* and it might be used as a capsaicin-like anti-inflammatory drug for peripheral applications (Vieira et al. 2000; 2001).

Studies on ricinoleic toxicity are limited; nevertheless several safety studies have been conducted on castor oil and these information are also considered to apply to ricinoleic acid which is the major constituent. Specific investigations and the well established medicinal use of castor oil (EMA 2016) allow to consider ricinoleic acid as a safe chemical for human use.

Finally, due to its unusual structure ricinoleic acid has been chemically or enzymatically used to produce a series of novel therapeutics which find applications as antifungal and antimicrobial with anti-biofilm properties, in drug delivery systems, as biodegradable carriers for antitumoral drugs, as bioadhesives and as wound dressing (Shikanov et al. 2004; Pabiś and Kula, 2016). Moreover some of these synthetic derivatives have shown potential as anti-inflammatory, antitumoral and anti-tubercular drugs (Boddu et al. 2015; Yamamoto et al. 2018). Interestingly, most of these bioactive derivatives still have the hydroxyl group in their structure and retain chirality with an unchanged configuration of the stereocenter thus confirming the structural requirements for the pharmacological effects (Pabiś and Kula 2016).

Concluding remarks

Plant lipids are major structural constituents of plant tissues and organs and they additionally represent an important storage material as components of plant seed oils. As described, many plant species produce unusual fatty acids with peculiar molecular features such as structural variations in the number and arrangement of unsaturated bonds, chain branches, type of functional groups, cyclic structures and

halogenation. In seed oils, they are commonly present as triacylglycerols, although their combination can form other types of lipids such as the unusual cyanolipids. As highlighted in this review, due to their chemical properties and reactivity they have a high economic value for several industrial uses, such as production of biofuels, plastics or dyes, and particularly for pharmaceutical applications. These structurally unique fatty acids represent in fact promising bioactive compounds showing a wide and diverse range of pharmacological activities. Based on the knowledge of these properties, several efforts have been accomplished to synthesize bioactive derivatives with improved biological activities and to explore new uses of rare fatty acids to the benefit of human health.

Several attempts to genetically modify oilseed crops with high concentration of selected unusual fatty acids to meet industrial requests have been carried out, but these crops with targeted modifications have been only partially successful due the complexity of the biosynthetic pathway. As reviewed here, occurrence of rare fatty acids and unusual lipids is restricted to a few plant families and they are often species-specifically synthesized. Limited success in obtaining genetic modified crops for their production indicates a constant need for exploring plant biodiversity as well as to preserve plant genetic resources.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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