CHAPTER 112

Purple Viper's Bugloss (*Echium plantagineum*) Seed Oil in Human Health

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CHAPTER OUTLINE

LIST OF ABBREVIATIONS

ALA,α-linolenic acid (18:3n-3)
CVD, dardiovascular disease
DGLA, dihomo γ-linolenic acid (20:3n-6)
DHA, docosahexaenoic acid (22:6n-3)
ESO, echium seed oil
EPA, eicosapentaenoic acid (20:5n-3)
ETA, eicosatetraenoic acid (20:4n-3)
GLA, γ-linolenic acid (18:3n-3)
LA, linoleic acid (18:2n-6)
n-3 LC PUFA, omega-3 long-chain ($\geq C_{20}$) polyunsaturated fatty acid
n-6 LC PUFA, omega-6 long-chain polyunsaturated fatty acid
RDI, recommended daily intake
PA, pyrrolizidine alkaloid
SDA, stearidonic acid (18:4n-3)
TAG, triacylglycerol

Nuts & Seeds in Health and Disease Prevention. DOI: 10.1016/B978-0-12-375688-6.10112-4

INTRODUCTION

The word *Echium* originated from the ancient Greek word *echis* (ϵχισ), which means "viper," due to its claimed use to cure viper's bite, or the resemblance of its nutlets to a viper's head, or both (Klemow *et al.*, 2002). The genus *Echium* encompasses over 50 species that belong to the *Boraginaceae* (borage family). Echium originated in the Mediterranean region, but many species are now found throughout Europe, North America, and Australia. This chapter is limited to the species known as purple viper bugloss, or Paterson's curse (*E. plantagineum)*. Echium is a very interesting herb, because it is either admired for its spectacular floral colors and its medicinal value, or condemned as a noxious weed of incredible persistence. We summarize the agronomic description, health benefits, and toxicity associated with the use of echium seeds for human health.

BOTANICAL DESCRIPTION

The biology of *E. plantagineum* is very well described by Piggin (1982), and the following is a summary taken from that source. Echium is a bristly annual or biennial herb or shrub, varying in stature and floral colors. It stands 20–60 cm tall, and has a floral color dominated by purple. It exhibits thickened, short stems, with hairy rosette leaves that are 5–20 cm long and 1.5–10 cm wide (Figure 112.1). Mature plants can produce 1–20 branching flowering stems with a sparsely branched taproot system, which can extend up to a meter below ground. The fruits (nutlets) are gray and pyramidal, with a pointed tip and flat base which bears an attachment scar (Figure 112.1). The seeds inside have an embryo, a cotyledon, a conical radicle, and a seed coat (no endosperm). In laboratory conditions, seeds have maintained viability for up to 6 years. Figure 112.1 shows *E. Plantagineum* in its reproductive stage, both as an opportunistic plant occupying roadside verges and as a sown crop.

HISTORICAL CULTIVATION AND USAGE

Early medicinal uses included as a remedy for bites of serpents and stings of scorpions. Other herbal medicine applications include treatments for colds, coughs, fever, headache, water retention, kidney stones, inflammation, skin boils, and melancholia, and applications for pain relief and the promotion of wound healing (Klemow *et al.*, 2002). The cultivation history is largely for use as a garden and/or border plant, and its opportunistic invasion of marginal lands and sand dunes.

PRESENT-DAY CULTIVATION AND USAGE

Experimental plot studies have shown that seedling emergence is severely limited if seeds are buried 7.6 cm or deeper (Piggin, 1982). The seed yield per plant can be 60–260 (Piggin, 1982). Seed dispersal is by herbivores and other opportunistic means (e.g., runoff). Berti *et al.* (2007) reported on the agronomic performance of echium as a sown crop. Seed oil content was 272–298 g per kg, biomass yields ranged from 3 to 11 t/ha, and seed yields ranged from 63 to 425 kg/ha. They estimated oil yield per ha at 116 kg. For comparison, typical oil yields expressed per 100 kg seed and per ha for some common vegetable oils are given in Table 112.1.

Echium seed oil (ESO) yield per unit area is much inferior to that of other vegetable oils (Table 112.1). We could not find any historical or current data on the global area of land devoted to commercial cultivation of Echium.

APPLICATIONS TO HEALTH PROMOTION AND DISEASE PREVENTION

The modern use of ESO relates to its essential n-3 and n-6 fatty acids. These polyunsaturated fatty acids (PUFAs) are termed essential fatty acids because the human body is unable to synthesize adequate amounts endogenously, and therefore they must be obtained by dietary

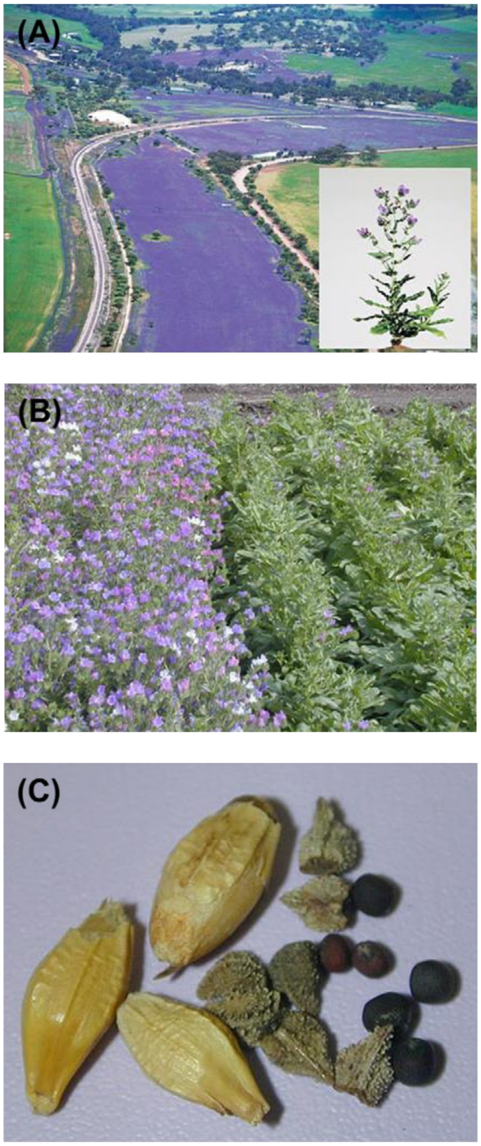

FIGURE 112.1
(A) *Echium plantagineum* in rural western Australia, and a close-up on a pot plant; (B) sown *Echium plantagineum* stands in North Dakota at the onset of flowering and at full bloom; and (C) Echium seeds compared to barley (*Hordeum vulgare* L.) (left) and canola (*Brassica napus* L.) (right). (A) Reprinted courtesy of the Department of Agriculture and Food, Western Australia, Australia. *(B) & (C) Reprinted with permission from* Berti et al. *(2007), in J. Janick & A. Whipkey (eds),* Proceedings of the 6th National New Crops Symposium — Issues in New Crops and New Uses, San Diego, October 14—18, 2007. *Alexandria, VA: ASHS Press.*

TABLE 112.1 Typical Oil Yields per Hectare and per Unit Weight of Seeds for Common Oilseeds

Oilseed	kg per 100 kg Seeds	Litres per ha
Rapeseed[a]	37	1190
Linseed[a]	35	478
Soybean[a]	14	446
Echium[b]	27	116

[a]*Extracted from Journey to Forever (www.journeytofoever.org/biodiesel_yield.html), accessed December 30, 2009.*
[b]*Approximation from* Berti et al. *(2007).*

means. In n-3 PUFAs, the first unsaturation occurs at the third carbon, counting from the methyl (omega) end of the fatty acid (Figure 112.2A), whilst in n-6 PUFAs, the first double bond appears in the sixth position. The first fatty acid in the n-3 PUFA series is α-linolenic acid (ALA, 18:3n-3). For n-6 PUFAs, the essential precursor is linoleic acid (LA, 18:2n-6). The first step in the n-3 biosynthetic pathway is stearidonic acid (SDA, 18:4n-3) through the enzyme Δ-6 desaturase (Figure 112.2B). This is thought to be the rate-limiting step. In lower marine organisms, the pathway directly culminates in the production of DHA. In mammals, the Δ-4 desaturase has not been isolated. Sprecher and colleagues (1995) proposed the side reaction which involves elongation to a C_{24} LC-PUFA followed by peroxisomal β-oxidation to create DHA.

Echium seed oil has two main distinguishing features from other vegetable oils (Table 112.2): (1) it is naturally rich in SDA (Figure 112.2B), and (2) its n-6 fatty acid content includes GLA (18:3n-6). The latter is thought to lead to production of anti-inflammatory eicosanoids similar to that of eicosapentaenoic acid (see below). The typical fatty acid profile of ESO derived from *E. plantagineum* and marketed by Croda (Croda Australia, Villawood, NSW 2163, Australia) together with profiles of other common vegetable oils are compared in Table 112.2. ESO is the only oil that is naturally rich in SDA.

A joint FAO/WHO expert consultation on fats and fatty acids in human nutrition has collated a number of elegant reviews on the health benefits of n-3 PUFAs in lowering the risk of CVD, modulating inflammation and immune responses, development of brain and visual acuity in infants, ameliorating age-related degenerative diseases, and modulating depression and mood disorders into a special issue of *Annals of Nutrition and Metabolism* (FAO/WHO, 2009). It is generally agreed that EPA and DHA lower the risk of CVD. It is also generally accepted that the role of vegetable oil-based n-3 PUFAs such as ALA is as a precursor for EPA and DHA (Figure 112.2B for pathway). Recent reviews on bioconversion of ALA to EPA and DHA in humans have shown that the very low activity of this conversion does not enable humans to get their recommended daily intake (RDI) of EPA and DHA from this precursor fatty acid (Brenna *et al.*, 2009). Due to low seafood intake, the per capita consumption of EPA and DHA in many developed nations is considerably below the RDI, which is generally set at around 500 mg EPA plus DHA per day. As shown in Figure 112.2B, the SDA-containing oils, such as

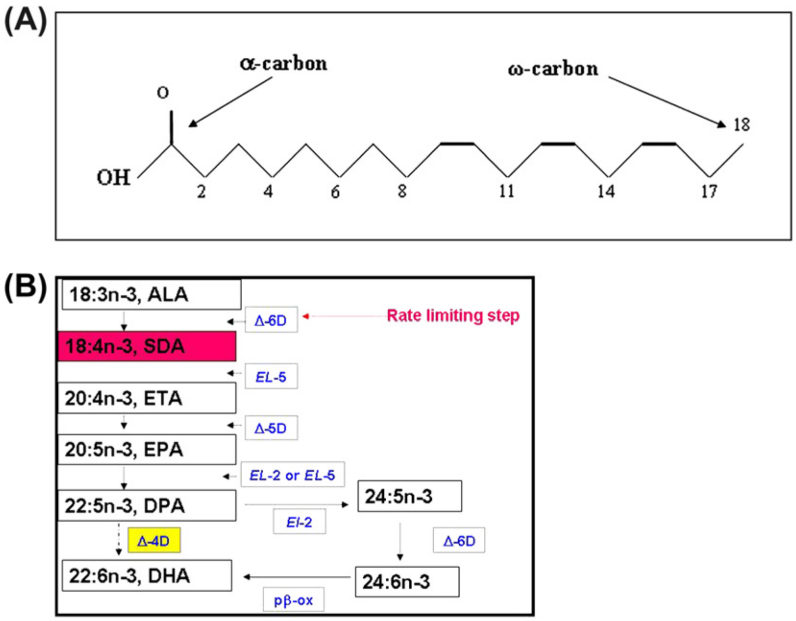

FIGURE 112.2
(A) Linear structure of α-linolenic acid (ALA, 18:3 n-3); (b) Biosynthesis of n-3 long-chain polyunsaturated fatty acids from α-linolenic acid (ALA). ALA, α-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; ETA, eicosatetraenoic acid; SDA, stearidonic acid. Elongases extend chain lenght, EL-2 and EL-5; elongases extend chain length; desaturases add double bonds (Δ-4, Δ-5, and Δ-6); peroxisomal β-oxidation removes carbons (pβ-ox). DHA synthesis through Δ-4 desaturase is only applicable in lower marine organisms, not mammals.

TABLE 112.2 Fatty Acid Composition (g/100 g Total Fatty Acids) of Vegetable Oils

Fatty Acid	Canola Oil[a]	Soybean Oil[a]	Linseed Oil[a]	Blackcurrant Oil[b]	Echium Oil[c]
Palmitic (16:0)	4.80	11.0	6.40	7.4	6.60
Stearic (18:0)	1.90	3.80	3.10	0.8	3.50
Oleic (18:1 *cis*-9)	58.5	23.3	20.1	10.4	17.1
Linoleic (18:2 n-6)	23.0	54.5	18.2	48.1	19.4
γ-linolenic acid (GLA, 18:3 n-6)	–	–	–	17.1	9.94
α-linolenic acid (ALA, 18:3 n-3)	7.70	5.90	51.4	12.7	29.8
Stearidonic acid (SDA, 18:4 n-3)	–	–	–	2.6	13.2

[a]Chouinard et al. (2001);
[b]Crozier et al. (1989);
[c]Kitessa & Young (2009).

ESO, bypass the first rate-limiting step. Hence, a number of human and animal studies have considered the potential of SDA-containing oils as precursors of EPA and DHA (Whelan, 2009). In the following section we will consider the benefits of ESO for human health from two angles: (1) the indirect use of ESO in enriching animal-derived foods from livestock and aquaculture species with EPA and DHA to increase population access to n-3 PUFAs; and (2) the direct use of ESO as a nutritional supplement, and its health benefits in humans.

ESO in aquaculture and livestock diets

The aquaculture industry relies on fish oil as an ingredient in aquafeeds for growth and to maintain the health benefits of fish. The use of vegetable oils in aquafeeds is hampered by the very limited conversion of ALA to EPA and DHA. Miller *et al.* (2008) showed limited conversion of SDA to EPA, and in particular DHA, in Atlantic salmon smolt (seawater phase); the authors noted that the ability of salmon and other species to digest, accumulate, and biosynthesize SDA into EPA and DHA needs to be further assessed before it can be considered as an ingredient in aquafeeds. We also propose that, for the benefits of SDA-containing oils in aquafeeds to be maximized, the n-3:n-6 ratio may need to be considerably higher than occurs in ESO.

Enrichment of meat and milk from livestock with EPA and DHA has been pursued by various groups, although the use of vegetable oils in livestock feed to increase EPA and DHA in meat and milk has also been limited by the inefficient conversion of ALA into EPA and DHA. In poultry, Kitessa and Young (2009) showed that the amounts of EPA + DHA per 100 g thigh muscle were 32 and 49 mg for rapeseed oil- and ESO-supplemented broilers, respectively. Hence, there is some evidence that ESO has the potential to improve the n-3 PUFA content of animal-derived foods for better health outcomes for the consumer.

Despite this, the current supply of ESO is so limited and expensive that it is presently neither practical nor commercially viable to use it in livestock and aquafeeds. Biotechnology companies have already launched high-SDA oils through the insertion of Δ-6 desaturase into traditional oilseeds like soybean (Bernal-Santos *et al.*, 2010). Such approaches have the potential to overcome the yield limitations as well as the toxins and allergens associated with echium, and possibly the capacity to improve the n-3 : n-6 ratio mentioned earlier.

ESO in human nutrition

Anti-inflammatory relief can be considered the basis of both the herbal medicine and modern use of ESO as an essential oil and nutritional supplement. Regarding the latter, there is now a consensus on the mechanisms by which n-3 and n-6 PUFAs are involved in inflammatory processes in the body. The major diseases and conditions with an inflammatory component include acute cardiovascular events, acute respiratory distress syndrome, allergic diseases, asthma (childhood and adult), atherosclerosis, cancer cachexia, chronic obstructive pulmonary disease, cystic fibrosis, inflammatory bowel disease (Crohn's disease, ulcerative colitis), lupus, multiple sclerosis, neurodegenerative disease of aging, obesity, and psoriasis, rheumatoid arthritis; systemic inflammatory response to surgery, trauma, and critical illness; and type 1 and type 2 diabetes (Calder, 2006). In addition to the well-recognized benefits against CVD, conditions and diseases where the evidences of n-3 PUFAs are considered to be greater are asthma, inflammatory bowel disease, and rheumatoid arthritis (Calder, 2006). Figure 112.3 presents the production of pro- and anti-inflammatory compounds from n-3 and n-6 PUFAs. The presence of significant quantities of ALA, SDA, and GLA in ESO (Table 112.2) enables it to play a potentially valuable anti-inflammatory role in the body through the supply of anti-inflammatory mediators arising from both its n-6 and, to a larger extent, n-3 PUFAs (Figure 112.3). Consequently, ESO has an added advantage over other vegetable oils, because it has an n-3 PUFA with an advanced step in the biosynthetic pathway as well as an n-6 PUFA which is atypically a precursor of anti-inflammatory eicosanoids.

Studies in mice have shown decreases in plasma TAG and very low density lipoprotein concentrations, and decreases in hepatic liver TAG content in mice supplemented with ESO (Zhang *et al.*, 2008). In humans, Miles *et al.* (2004) showed enhanced EPA levels in blood lipids of healthy young male volunteers when supplemented with SDA from ESO. Similarly, Surette *et al.* (2004) reported increases in plasma n-3 PUFAs and a 21% reduction in serum TAG in hypertriglyceridemic subjects supplemented with 15 g of ESO per day for 4 weeks. These studies have shown that ESO, as a source of n-3 PUFAs, can play a pivotal role in the prevention of chronic diseases. Recently, Harris *et al.* (2008) reported that SDA-enriched GM soybean oil increased the omega-3 index (an emerging CVD risk marker) in a study with human volunteers.

The existing evidence from animal and human studies, although based on short-term observations, points to comparative improvements from using ESO in tissue deposition of n-3 PUFAs and some biomarkers of CVD over other vegetable oils. However, there are indications that ESO will be superseded by the development of oils with greater SDA content and higher n-3:n-6 ratios through plant biotechnology. For instance, the SDA-enhanced oil from

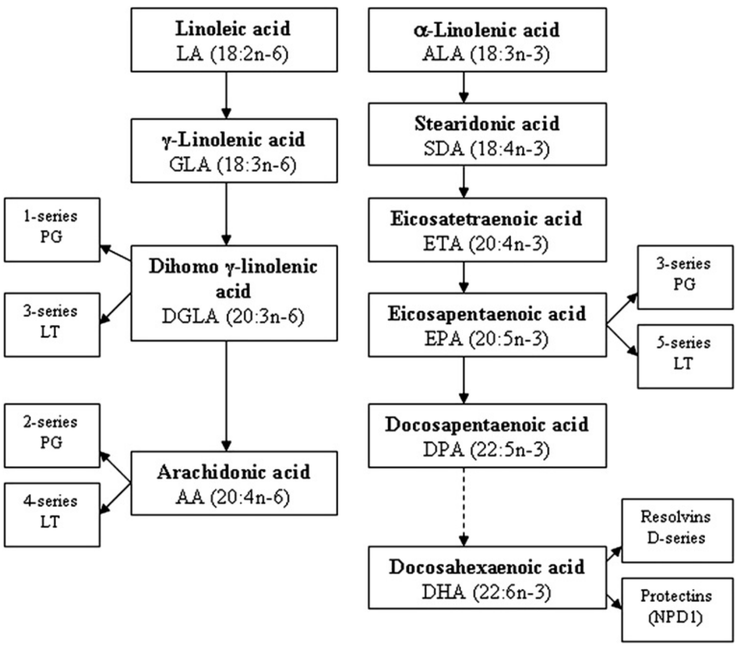

FIGURE 112.3
A schematic representation of the production pathways for anti-inflammatory mediators (1, 3, and 5 series PG and LT; resolvins and protectins) and pro-inflammatory mediators (2 and 4 series PG and LT) from n-3 and n-6 PUFAs. PG, prostaglandins; LT, leukotrienes; NPD1, neuroprotectin D1. *Adapted from Calder (2006).*

genetically modified soybeans used in the Bernal-Santos *et al.* (2010) dairy study had twice the SDA content – about 27% SDA in total fatty acids. Selection and breeding programs are needed to improve the oil yield per ha and SDA concentrations, and to decrease the anti-nutritional factors mentioned below.

ADVERSE EFFECTS AND REACTIONS (ALLERGIES AND TOXICITY)

Echium plants produce alkaloids as a chemical defense mechanism. The specific echium alkaloids are called pyrrolizidine alkaloids (PAs). PAs are hepatotoxic, and cause liver damage (Cheeke, 1988). In Australia, echium poisoning has been reported in sheep, cattle, horses, swine, and poultry (Cheeke, 1988). For humans, it is suggested that PA levels in herbal products of proven health benefit should be 1 μg per day for oral and 100 μg per day for external use, for a period of no more than 6 weeks in a year (Edgar *et al.*, 2002). The use of PA-containing herbal products in pregnant and lactating women is prohibited. Culvenor *et al.* (1981) reported 0.950 μg of PA per g of honey from *E. plantagineum*; hence, caution should be exercised in using honey from an area where bees largely rely on echium pollens and nectars to produce honey. With respect to ESO itself, the alkaloids are removed during extraction, and the PA content of echium seeds does not limit their use for the supply of n-3 oil.

SUMMARY POINTS

- *Echium* has a long history of use as a garden plant with some herbal medicine applications.
- ESO has a combination of specific n-3 and n-6 PUFAs that makes it unique among other vegetable oils.
- ESO is naturally rich (12–15%) in SDA, which is a superior precursor of EPA than ALA.
- Animal experiments and direct human supplementation studies show that ESO can bring about beneficial changes in biomarkers of chronic diseases, such as lowering TAG in plasma and tissue.
- ESO production is currently a niche activity, and widespread use is therefore limited by supply and cost.
- Selection and breeding programs are needed to move the role of echium in human health beyond niche-product status.

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