The fruit of *Corema album* (L.) D. Don, a singular white berry with potential benefits in nutrition and health

Antonio J. León-González[1,2], Inmaculada Navarro[3], Nuria Acero[4], Dolores Muñoz-Mingarro[5], Carmen Martín-Cordero[1]*

[1]Department of Pharmacology, Faculty of Pharmacy, C/ P. García González, 2. 41012 Seville, Spain.

[2] Maimonides Biomedical Research Institute of Cordoba (IMIBIC), 14014 Córdoba, Spain.

[3]Department of Physical Chemistry, Faculty of Pharmacy, C/ P. García González, 2. 41012, Seville.

[4]Pharmaceutical and Health Science Department. Pharmacy Faculty. San Pablo-CEU University. CEU Universities. Campus Monteprincipe, 28668 Boadilla del Monte, Madrid, Spain.

[5]Chemistry and Biochemistry Department. Pharmacy Faculty. San Pablo-CEU University. CEU Universities. Campus Montepríncipe, 28668 Boadilla del Monte, Madrid, Spain.

* *Corresponding author: Prof. Dr. Carmen Martin-Cordero; Department of Pharmacology, Faculty of Pharmacy, University of Seville, Spain. (Ph) +34-954556723. (Fax) +34-954556074. E-mail: carmenmc@us.es*

Abstract

Corema album (L.) D. Don (Ericaceae) is an endemic bush that grows along the Atlantic littoral of the Iberian Peninsula. Its edible white berries (known as camarinas, camariñas, camarinhas, white crowberry, among other vernacular names) have been used in popular medicine as an antipyretic and are consumed in localised areas of Portugal and Spain as appetisers and in the preparation of juices and jams. The aim of the present review is to summarise the knowledge of the chemical composition and pharmacological studies performed with *C. album* fruit and extracts.

These berries are rich in phenolic compounds, including phenolic acids, stilbenes, flavonols, flavanones, prenylated flavanone, flavanols, and anthocyanins. The total phenolic content of various extracts of the pulp of these berries has been positively correlated with their antioxidant capacity. In this respect, the treatment with acetone, ethyl acetate, and aqueous extracts of this fruit has protected HepG2 cells against chemically induced oxidative stress. The chemoprotective effect of these extracts is mediated by preventing reactive oxygen species formation, reduced glutathione (GSH) depletion, antioxidant enzyme over-activity, and oxidative damage to proteins and lipids. Furthermore, the presence of pentacyclic triterpenes, such as ursolic and oleanolic acids, in *C. album* berries confers reflectance UV properties to this fruit and derived extracts.

In short, existing studies suggest that the development of *C. album* crops should be considered as a promising opportunity to obtain these remarkable berries. Moreover, further experiments should also be designed to evaluate their *in vivo* effect and to ascertain the underlying mechanism of action.

Keywords: *Corema album*, Ericaceae, berries, antioxidant, chemoprotection

Introduction

Corema album (L.) D. Don (Ericaceae) is a wild shrub endemic to the Atlantic coast of the Iberian Peninsula (Figure 1). This species grows in sandy coastal areas from the north of Galicia to Tarifa in the south, and in an isolated population along the south-eastern coast of Spain (Benidorm, Alicante). The fruit, acid-tasting white edible berries, has been traditionally consumed as an appetiser in these coastal areas, either served fresh or made into lemonades, jams, and liquors, and is employed in traditional medicine to treat fevers and pinworm infections (Font Quer 2016). Indeed, recent studies show archaeobotanical data that suggests the systematic gathering of *C. album* fruit for human consumption since the Upper Palaeolithic Age (Martínez-Varea et al. 2019). However, its current distribution remains very restricted and is even considered vulnerable or in danger in several regions due to the impact of the climate change and to the loss of its natural habitat (Blanca et al. 1999; Gil-López 2011).

This species is known under the guise of a variety of names (López-Dóriga 2018). The botanist Clusio, when studying the flora of Portugal, described this shrub for the first time and named it *Erica baccifera lusitanum*, since it reminded him of *Erica baccifera* (syn: *Empetrum hermaphroditum*, *Empetrum nigrum).* Tournefort later called it *Empetrum lusitanum* and from here the direct translation was made into the English vernacular name “Portuguese crowberry”, due to its similarity with the species *Empetrum nigrum* (“crowberry”). However, this name cannot be considered accurate, since *C. album* is not an exclusively Portuguese shrub, since it also grows along the entire Atlantic coast of the Iberian Peninsula (Martín Sarmiento 1974).

Currently, the accepted name is *Corema album* (L.) D. Don. The genus *Corema* refers to the Greek word *Korema*, which means broom, alluding to the growing form, but also to the use of this bush in making rustic brooms. On the other hand, *album* is due to the white colour of its fruit. *C. album* has been denoted in English as white crowberries, pearlberries, beachberries, and Atlantic pearls, and receives different vernacular names, depending on the geographic location: camarina, camariña, and camarinha, among others (Brás de Oliveira et al. 2016; López-Dóriga 2018; Barroca and Moreira da Silva 2021). There are various theories regarding the origin of the euphonic name of “camarina”, such as the fusion of the words erica and marina, being an *Ericaceae* that grows near the sea, or receiving the name of the nymph Kamarina, a Greek deity, the daughter of the god Ocean (Pindar and Sandys 1915).

This species is considered in high esteem in many populations on the Atlantic coast of Spain and Portugal, where these berries have traditionally formed part of their diet and life. Proof of this is that many streets and institutions (e.g., in Huelva, Almonte, Moguer) are called Camarina, and there are the Spanish towns of Camariñas and A Pobra do Caramiñal in La Coruña and Cape Camariñal in Cádiz (Gil-López 2011). Likewise, the Nobel Prize winner in Literature Juan Ramón Jiménez, a native of Moguer (Huelva), dedicates a chapter of "Platero and I" to the camarinas, or as he calls them, "those edible pearls that filled my entire childhood", since these berries have traditionally been considered a treat, especially by children. Moreover, a Portuguese legend relates that the *camarinhas* are the tears shed by Queen Saint Isabel of Portugal upon learning of the infidelity of her husband, King Dionisio I.

A high fruit intake has been related with a decrease in the risk of cardiovascular disease, cancer, and all-cause mortality (Aune et al. 2017). Along these lines, berries are considered one of the most widely researched fruits due to their chemical composition and health-promoting properties. Under the term berries are commonly included soft fruits with multiple seeds, such as strawberries, raspberries, blueberries, currants, and blackberries. In recent years, there has been a growth in the number of scientific publications and conferences to study these fruits in depth. Apart from the traditional benefits attributed to berries (urinary antiseptic, source of vitamins and minerals, etc.), researchers are increasingly exploring other aspects, such as the prevention of degenerative neurological and cardiovascular diseases, the modulation of inflammatory response, and cancer prevention (Kristo et al. 2016; Kowalska and Olejnik 2016; Lavefve et al. 2020).

In contrast with other berries, the knowledge available regarding *C. album* berries remains very limited, except in very restricted coastal areas. Consequently, the aim of the present review is to contribute towards divulging the interest of this singular berry, by providing its botanical, phytochemical, and pharmacological overview.

Botanical description

C. album is a perennial dioecious shrub, although a few individuals are hermaphrodites (Zunzunegui et al. 2006). It is up to 1 m tall, and highly branched. The lower branches are glabrous and with numerous foliar scars, while those of recent years are densely tomentose, with slightly wavy hairs and a greyish colour. It has thick, creeping, and gnarled roots, similar to those of heather. Many brittle, dark-brown erect shoots emerge from these roots. The leaves are xeromorphic, adapted to a dry climate and measure approximately 5-6 mm long and 1-2 mm wide. The male flowers appear gathered in terminal cymes, rarely intercalary, with reddish petals and stamens; the female flowers are gathered in groups of 3 to 6, in terminal or intercalary cymes, with reddish petals and a very sparsely tomentose ovary, with a long-stemmed style and three patent stigmatic branches. The fruit is considered a berry, *lato sensu*, although its strict botanical classification would be a drupe. It is a spherical white or pink fruit, with a diameter of 5-10 mm, which contains inside three seeds with a flat face and another convex and rough. The fruit can be observed on the plant, at different points of ripening, from April to September (Figure 2) (Cabezudo 1987; Villar 1993).

Phytochemical analysis

~~*Corema*~~ C. *album* is a wild shrub whose fruit was eaten and sold in coastal Atlantic villages until the end of the 1950s, when consecutive clearing of the vegetation in favour of bushes presenting a better economic situation caused the end of this activity (Gil-López 2011). Due to its comparatively low level of use, studies into the chemical composition of the plant have been few and far between. Table 1 summarises the main compounds found from berries and methods used for their analysis.

The ripe fruit is pearly white with a strong skin, which protects it from dehydration in July and August, a period of high temperatures, absence of rainfall, and from strong solar radiations, especially on the exposed areas of coastal dunes. The proportion of water in this berry is significant with a percentage average of 83.41% to 97.66% (León-González et al. 2013b; Martínez-Varea et al. 2019).

The mineral content is similar to those observed in other berries. In comparison with cranberry (*Vaccinium macrocarpum*), *C. album* fruit presents a lower content of phosphorus and iron, but higher concentrations of the remaining minerals (K, Ca, Mg, Cu, Zn).

Organic acids are good indicators of fruit acidity. Citric and malic acids have been detected by GC/MS in camarinhas, resulting a fruit acidity of 10.7±0.1, expressed as g citric acid/100 g (Andrade et al. 2017a). Levels of vitamin C quantified by potentiometry in *C. album* plants from Doñana (Huelva, Spain) were particularly high (97 mg/100 g of fresh weight (FW)) (Martínez-Varea et al. 2019), related to those values reported in plants from the Comporta region (Portugal) (5.4 mg/100 g FW) quantified by LC/DAD (Pimpão et al. 2013). Camarinas have higher vitamin C concentrations than *Vaccinium* berry species (Cocetta et al. 2012) and other popular edible berries (Häkkinen et al. 1999; Pantelidis et al. 2007).

The total content of reducing sugars was 41.24±1.74 % of dry weight (DW) (Andrade et al. 2017). Specifically, glucose, fructose, and sucrose, which are considered as indicators of sweetness, were detected by GC/MS (León-González, 2012a). These results indicated that *Corema* fruit is less sweet and more acidic than the other berries studied (Andrade et al. 2017a).

The total phenolic content of this berries berry was determined by the Folin–Ciocalteu method and resulted on 1214.4±122.7 mg of gallic acid equivalents per kg of FW (GAE/kg FW) or 7318.6±739.6 mg GAE/kg DW. *C. album* fruit phenolic content was lower than that of other berry values reported in the literature (Marhuenda et al. 2016). The high proportion of the weight of the seeds (54.97% of DW) also indicates that this fruit has lower edible pulp than other berries (Pantelidis et al. 2007).

The main phenolic compounds are phenolic acids, with 3753.7 µg/g DW or 623.53 µg/g FW. These kinds of compounds occur mainly in combined forms as esters, of which the most important are esters of caffeoylquinic acid, 5-*O*-caffeoylquinic acid (chlorogenic acid), 4-*O*-caffeoylquinic acid (cryptochlorogenic acid), and 3-*O*-caffeoylquinic acid (neochlorogenic acid). The ester fraction represented 87.1% (3271.5 µg/g DW) of the total phenolic acid content, while the free fraction supposed only 12.85% (482.4 µg/g DW). In this respect, it can be concluded that free forms failed to make a significant contribution to the composition of the total phenolic acids in these berries. Twelve compounds have been identified in this fraction, where caffeic, benzoic, *p*-hydroxybenzoic, and ferulic acids presented the highest concentrations (252.5 µg/g DW, 70.8 µg/g DW, 50.2 µg/g DW, and 49.4µg/g DW, respectively) (Table 1).

The pterostilbene (Figure 3) content (45.9 µg/g DW) in *C. album* berries was higher than that in *Vaccinium* spp. (0.099 µg to 0.520 µg/g DW) (Rimando et al. 2004).

The main flavonoids detected in *C. album* berries were flavonols, flavanones, and flavanols. The main detected flavonol was quercetin 3-*O*-hexoside (320.4 µg/g DW), followed by rutin (quercetin 3-*O*-rutinoside) (52.8 µg/g DW) and myricetin-3-*O*-glucoside (47.4 µg/g DW) (Table 1). The total flavonols content (472.6 µg/g DW or 78 µg/g FW) was higher than in the results reported by Häkkinen et al. (1999) in different berries of the genera *Vaccinium, Ribes, Fragaria, Rubus, Empetrum, Hyppophae.* The flavanones, pinocembrin, and 6-geranylnaringenin were detected for the first time in any edible berries (Figure 3). The

Formatted: Font: Italic

Formatted: Font: Italic

Formatted: Font: Italic

prenylated flavanone, 6-geranylnaringenin, is a relatively unknown flavonoid occurring in hop and beer (Venturelli et al. 2016).

The flavonol, (-)-epicatechin, has also been isolated in *Vitis vinifera* (grape wine), *Camellia sinensis* (tea), and *Theobroma cacao* (cocoa), and is a component of proanthocyanidin chemical structure.

C. album berries are white or pinkish-white berries that have very low amounts of anthocyanins (6.4 µg/g DW), which represent a main contribution in total polyphenol content in coloured berries from *Vaccinium* spp., *Fragaria* spp., and *Ribes* spp. (Jakobek et al. 2007).

The ~~P~~pentacyclic triterpenes ~~and~~ ursolic and oleanolic acids were isolated together by column chromatography ~~on silica gel 60 from 6-10 fractions (30 mg)~~ and identified through gas chromatography/mass spectrometry (Diaz-Barradas et al. 2016).

Pharmacological activities

In recent years, there has been a growing interest in the health-promoting activities of *C. album* extracts and phytochemicals, especially in those related with the prevention of oxidative stress-related diseases, such as cancer, and neurodegenerative and cardiovascular diseases.

The content of phenolic compounds has been positively correlated with the antioxidant activity of the pulp and seeds of the fruit by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) methods (Andrade et al. 2017b). Although the phenolic content of *C. album* berries is lower than that in coloured berries, various studies showed considerable antioxidant activity, expressed in micromoles of Trolox equivalents per gram of dry pulp weight (µmol TE/g DW). The substantial variability of the antioxidant capacity deserves mention, since it depends on the geographical origin of the fruit and the methodological conditions. The values of Andrade et al. (2017b) ranged from 39 to 42 µmol TE/g, assessed by DPPH assay and from 72 to 80 µmol TE/g by ABTS , whereas Brito et al. (2021) showed a lower antioxidant capacity of dry pulp, with values of 7.7 ± 0.3, 9.1 ± 0.1, and 11.9 ± 0.5 µmol TE/g, depending on which test was conducted: ABTS, FRAP (ferric-reducing antioxidant power), or DPPH, respectively (Brito et al. 2021). Otherwise, the oxygen radical-scavenging capacity (ORAC) of the fruit was 956.19 ± 54.46 µmol TE/g DW (Macedo et al. 2015). Nevertheless, when the antioxidant capacity was referred to in terms of per total phenol content (µmol TE/mg GAE), then the values were more consistent, ranging from 48.73 ± 2.4 to 60.48 ± 3.09 µmol TE/mg GAE (Macedo et al. 2015; Jardim et al. 2017).

On the other hand, the *in vitro* antioxidant and chemoprotective activity of three phenolic-rich extracts of the fruit of *C. album* (i.e., aqueous, acetone, and ethyl acetate) was evaluated in HepG2 cells. This human hepatocellular carcinoma cell line is considered as a model that reproduces the human hepatocyte and has been widely used for the evaluation of the effects of different compounds of natural origin (Goya et al. 2009). No significant damage to HepG2 cells was observed when cells were treated with 1-40 µg/mL of the three extracts for 20 h. Furthermore, in this same range of concentrations of the three extracts, there was a dose-dependent reduction in the production of reactive oxygen species (ROS). This is in accordance with the data that indicates that hydroxycinnamic acids, which are the major phenolic acids in the fruit of *C. album*, are effective chemical reducers and antioxidants in cell cultures (Lee et al. 2020; Ruwizhi and Aderibigbe 2020).

In addition to the regulation of ROS levels, the treatment with *C. album* extracts produced a significant increase in cellular GSH values, the main non-enzymatic antioxidant within the cell, which constitutes a preparation against potential oxidative damage for the cell. In line with this result, the treatment of HepG2 cells with quercetin (Wang et al. 2020) epicatechin (Martín et al. 2010), kushenol C (Cho et al. 2021), 5-caffeoylquinic acid (Chen et al. 2020), and phlorotannin-rich extracts of seaweed (Quéguineur et al. 2012) also led to an increase in basal GSH concentrations. This has been attributed to certain phytochemicals which stimulate glutathione synthesis by inducing the enzyme γ-glutamylcysteine synthetase (Scharf et al. 2003).

Furthermore, the three tested extracts unequivocally showed their protective activity against chemically induced oxidative stress damage by the potent pro-oxidant tert-butyl hydroperoxide (t-BOOH), thereby not only reducing the formation of ROS, lipid peroxidation, and oxidative damage to proteins, but also modulating cellular antioxidant defence systems, such as GSH and glutathione reductase and glutathione peroxidase enzymes. This study suggested that the cells treated with extracts are in a more favourable condition to face the aggression of an oxidising agent, since they decrease the ROS production, and modulate the activity of antioxidant enzymes, thereby promoting a rapid recovery of redox homeostasis and limiting lipid and protein damage (León-González 2012).

Additionally, Brito et al. (2021) also observed that the incubation of Caco-2 cells (a human intestinal epithelium model) with up to 4% (w/v) of dry pulp in DEMEM culture medium (i.e., 23.8 µg GAE/mL) did not affect the cell viability, measured by means of an MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) assay.

Related to cardiovascular diseases, the protective effect of a berry-enriched diet including *C. album* berries was evaluated in a chronic salt-sensitive Dahl rat model. The daily consumption of berries promoted animal survival, normalised body weight, and protected renal and cardiovascular function against salt-induced hypertension. Subsequent to the left ventricle proteomics analysis, a key protein involved in myocyte cytoarchitecture, cysteine- and glycine-rich protein 3 (CSRP3), was identified as the target of the phenolic metabolites, via an impact on tissue cohesion maintenance and hypertrophy (Oudot et al. 2019). Moreover, this cardioprotective effect was accompanied with the ability of phenolic compound metabolites to modify the gut microbiota (Gomes et al. 2019).

Regarding the potential of this fruit as a photoprotector, Diaz-Barradas et al. (2016) studied the reflectance of the fruit, the aqueous and ethyl acetate extracts, and the triterpene compound ursolic and oleanolic acids. The most relevant optical characteristics of this white fruit involve the elevated brightness and UV reflectance. In addition to the ecological implications (i.e., the fruit is more visible to seed dispersers in a sunny environment), the presence of ursolic and oleanolic acids confers a photoprotective capacity to the extracts that could be of particular interest in the formulation of a natural sunscreen.

In addition to the fruit, the leaves of *C. album* also constitute a source of bioactive phytochemicals, such as the flavonol myricetin, catechin derivatives, and proanthocyanidins (Macedo et al. 2015). Indeed, the polyphenol-rich extract obtained from the leaves exerted a greater protective effect from α-synuclein (a presynaptic protein whose aggregation has been correlated with Parkinson's disease) toxicity than that of the fruit extract. This cytoprotective effect was mediated *in vitro* by the inhibition of α-synuclein fibrillization, the reduction of induced oxidative stress, and by promoting the clearance of this toxic substance via autophagy.

Several studies have also described the *in vitro* anticancer effect of *C. album* leaf extract in colon adenocarcinoma cell lines. Early studies by León-González et al. (2013a) identified cytotoxic chalcones, such as 2',4'-dihydroxychalcone, whereas Oliveira et al. (2019) observed that the lectins from leaf protein extract were involved in the cell proliferation and migration of HT-29 cells.

Future perspectives and Conclusions

C. album fruit continues to be highly appreciated in those regions where this plant grows. However, unlike other berries, studies into this fruit have been few and far between, probably due to their restricted geographical distribution and the difficulty of harvesting their crop. However, according to traditional medicine, they have high therapeutic potential. The results of the studies presented in this article demonstrate a significant antioxidant activity, as a free radical scavenger both *in vitro* and in cell culture, which guarantees its use in the prevention of cancer, and degenerative and cardiovascular diseases. These results present high nutraceutical potential; consequently the inclusion of this berry in the diet can contribute towards the protective effect offered by other fruits and beverages of plant origin against disorders in which oxidative stress is involved.

In this respect, the chemical composition in phenolic compounds of *C. album* fruit, rich in chlorogenic acid, makes them interesting candidates for cell chemoprotection. As mentioned above, there are interesting singularities in the composition of these berries. The high pterostilbene content gives the consumption of this fruit beneficial effects, such as anti-aging, a reduction in inflammation, cell senescence, and in oxidative damage, ~~and,~~and consequently helps in the maintenance of health and lifespan (Li et al. 2018). Furthermore, this phenol is able to cross the blood-brain barrier, thereby preventing and treating dementia more effectively than resveratrol, since it is a more lipophilic compound (Lange and Li 2018). This molecule hepatoprotective, oncostatic, and cardioprotective ability has already been studied (Song et al. 2019; Ma et al. 2019; Kang et al. 2019). Together with pterostilbene, pinocembrin also exerts cardioprotective actions, since it is able to attenuate acute ischemic myocardial injury and to decrease susceptibility to ventricular fibrillation (Sangweni et al. 2020; Zheng et al. 2020; Ye et al. 2020). Pinocembrin induces apoptosis in several lines of human cancer cells: HepG2 (hepathocarcinoma), SHSY5Y (neuroblastome), HT-29 (colon adenocarcinoma), PC-3 (prostate), and MCF7 (mammary gland adenocarcinoma)(Gao et al. 2008; Kumar et al. 2019; Carullo et al. 2020). And finally, other camarin~~h~~a components, such as oleanolic and ursolic acids, possess major bioactivity features, such as nephroprotective, anti-diabetic, anti-tumour, antioxidant, and anti-inflammatory characteristics, and also cardio and hepatoprotective properties (Silva et al. 2016).

The phytochemical composition of camarin~~h~~as justifies their nutraceutical properties, but it must be borne in mind that the biological effects of phenolic compounds are also dependent on their bioavailability. Further research is therefore needed in order to perform *in vivo* analyses of these berries to better ascertain their pharmaceutical and nutraceutical properties.

Authorship

AJLG and CMC conceived the idea; AJLG, DM, IN, NA, and CMC performed the review of papers; AJLG, NA, and CMC wrote the first draft of the manuscript. All authors made meaningful contributions to the final manuscript and approved the manuscript for final submission.

Conflict of interest

The authors declare there to be no conflict of interest.

ORCID

AJLG 0000-0003-2668-8205; CMC 0000-0002-2821-6327; NA 0000-0001-9307-3839; IN 0000-0002-1536-6473; DMM 0000-0003-0195-9849

References

Andrade SC, Gonçalves FJA, Guiné RPF (2015) Physiscal-chemical properties of *Corema album* (white crowberry or camarinha). In: proceedings of ICEUBI2015-International Conference on Engineering 2015. Covilhã, Portugal, pp 1–8

Andrade S, Gonçalves F, Guiné RPF (2017a) Contribution for the physical-chemical characterization of Portuguese Crowberry (*Corema album*). Int J Food Sci Nutr 2:9–14

Andrade SC, Guiné RPF, Gonçalves FJA (2017b) Evaluation of phenolic compounds, antioxidant activity and bioaccessibility in white crowberry (*Corema album*). J Food Meas Charact 11:1936-1946. https://doi.org/10.1007/s11694-017-9576-4

Aune D, Giovannucci E, Boffetta P et al (2017) Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality—a systematic review and dose-response meta-analysis of prospective studies. Int J Epidemiol 46:1029-1056. https://doi.org/10.1093/ije/dyw319

Barroca MJ, Moreira da Silva A (2021) From folklore to the nutraceutical world: the C*orema album* potential. In: Galanakis CM (ed) Gastronomy and Food Science. Elsevier, London

Blanca G, Cabezudo B, Hernández-Bermejo JE, et al (1999) Libro rojo de la flora silvestre amenazada de Andalucía. I. Especies en peligro de extinción. Junta de Andalucía

Brás de Oliveira P, Valdiviesso T, Trindade CS et al (2016) Os primeiros passos na investigaçao em *Corema album* (camarinha). Vida Rural 29–31

Brito C, Bertotti T, Primitivo MJ, et al (2021) *Corema album* spp: Edible wild crowberries with a high content in minerals and organic acids. Food Chem 345:128732. https://doi.org/10.1016/j.foodchem.2020.128732

Cabezudo B (1987) Flora Vascular de Andalucía Occidental. Ketres S. A., Barcelona

Carullo G, Mazzotta S, Koch A et al (2020) New Oleoyl Hybrids of Natural Antioxidants: Synthesis and *In Vitro* Evaluation as Inducers of Apoptosis in Colorectal Cancer Cells. Antioxidants 9(11):1077. https://doi.org/10.3390/antiox9111077

Chen X, Yang JH, Cho SS et al (2020) 5-Caffeoylquinic acid ameliorates oxidative stress-mediated cell death via Nrf2 activation in hepatocytes. Pharm Biol 58(1):999-1005. https://doi.org/10.1080/13880209.2020.1818791

Cho BO, Kim JH, Che DN et al (2021) Kushenol C Prevents Tert-Butyl Hydroperoxide and Acetaminophen-Induced Liver Injury. Molecules 26(6):1635. https://doi.org/10.3390/molecules26061635

Cocetta G, Karppinen K, Suokas M et al (2012) Ascorbic acid metabolism during bilberry (*Vaccinium myrtillus* L.) fruit development. J Plant Physiol 169:1059-1065. https://doi.org/10.1016/j.jplph.2012.03.010

Diaz-Barradas MC, Costa C, Correia O et al (2016) Pentacyclic triterpenes responsible for photoprotection of *Corema album* (L.) D.Don white berries. Biochem Syst Ecol 67:103-109. https://doi.org/10.1016/j.bse.2016.05.009

Font Quer P (2016) Plantas medicinales: el Dioscórides renovado, 12th ed. Ediciones Península

Gao M, Zhang W, Liu Q et al (2008) Pinocembrin prevents glutamate-induced apoptosis in SH-SY5Y neuronal cells via decrease of bax/bcl-2 ratio. Eur J Pharmacol 591:73-79. https://doi.org/10.1016/j.ejphar.2008.06.071

Gil-López MJ (2011) Etnobotánica de la camarina (*Corema album*, Empetraceae) en Cádiz. Ethnobotany of *Corema album* (Empetraceae) in Cadiz. Acta Bot Malac 36:137-144. https://doi.org/10.24310/abm.v36i1.2784

Gomes A, Oudot C, Macià A et al (2019) Berry-Enriched Diet in Salt-Sensitive Hypertensive Rats: Metabolic Fate of (Poly)Phenols and the Role of Gut Microbiota. Nutrients 11:2364. https://doi.org/10.3390/nu11112634

Goya L, Martin M, Ramos S et al (2009) A Cell Culture Model for the Assessment of the Chemopreventive Potential of Dietary Compounds. Curr Nutr Food Sci 5:56–64. https://doi.org/10.2174/157340109787314721

Häkkinen SH, Kärenlampi SO, Heinonen IM et al (1999) Content of the Flavonols Quercetin, Myricetin, and Kaempferol in 25 Edible Berries. J Agr Food Chem 47:2274-2279. https://doi.org/10.1021/jf9811065

Jakobek L, Šeruga M, Medvidović-Kosanović M, Novak I (2007) Anthocyanin content and antioxidant activity of variousred fruit juices. Dtsch Lebensmitt Rundsch 103:58–64

Jardim C, Macedo D, Figueira I et al (2017) (Poly)phenol metabolites from *Arbutus unedo* leaves protect yeast from oxidative injury by activation of antioxidant and protein clearance pathways. J Funct Foods 32:333-346. https://doi.org/10.1016/j.jff.2017.03.010

Kang LL, Zhang D-M, Jiao RQ et al (2019) Pterostilbene Attenuates Fructose-Induced Myocardial Fibrosis by Inhibiting ROS-Driven Pitx2c/miR-15b Pathway. Oxid Med Cell Longev 2019: 1243215. https://doi.org/10.1155/2019/1243215

Kowalska K, Olejnik A (2016) Current evidence on the health-beneficial effects of berry fruits in the prevention and treatment of metabolic syndrome. Curr Opin Clin Nutr Metab Care 19:446-452. https://doi.org/10.1097/MCO.0000000000000322

Kristo A, Klimis-Zacas D, Sikalidis A (2016) Protective Role of Dietary Berries in Cancer. Antioxidants 5:37. https://doi.org/10.3390/antiox5040037

Kumar N, Shrungeswara AH, Mallik SB et al (2019) Pinocembrin-Enriched Fractions of *Elytranthe parasitica* (L.) Danser Modulates Apoptotic and MAPK Cellular Signaling in HepG2 Cells. Anti-Cancer Agent Me 18:1563-1572. https://doi.org/10.2174/1871520618666180911112127

Lange KW, Li S (2018) Resveratrol, pterostilbene, and dementia. BioFactors 44:83-90. https://doi.org/10.1002/biof.1396

Lavefve L, Howard LR, Carbonero F (2020) Berry polyphenols metabolism and impact on human gut microbiota and health. Food Funct 11:45-65. https://doi.org/10.1039/C9FO01634A

Lee SM, Zheng LW, Jung Y et al (2020) Effects of hydroxycinnamic acids on the reduction of furan and α-dicarbonyl compounds. Food Chem 312:12685. https://doi.org/10.1016/j.foodchem.2019.126085

León-González AJ (2012a) Actividad antitumoral de plantas de Andalucía. aislamiento de principios activos de *Corema album* (L.) D.Don. Thesis. Department of Pharmacology Faculty of Farmacy. Seville University

León-González AJ, Mateos R, Ramos S, et al (2012b) Chemo-protective activity and characterization of phenolic extracts from Corema album. Food Res Int 49:728-738. https://doi.org/10.1016/j.foodres.2012.09.016

León-González AJ, López-Lázaro M, Espartero JL, Martín-Cordero C (2013a) Cytotoxic activity of dihydrochalcones isolated from *Corema album* leaves against HT-29 colon cancer cells. Nat Prod Commun 8:1255–1256

León-González AJ, Truchado P, Tomás-Barberán FA, et al (2013b) Phenolic acids, flavonols and anthocyanins in Corema album (L.) D. Don berries. J Food Compos Anal 29:58-63. https://doi.org/10.1016/j.jfca.2012.10.003

León-González AJ, López-Lázaro M, Navarro I, Martín-Cordero C (2014) Induction of apoptosis and cell cycle arrest in human colon carcinoma cells by *Corema album* leaves. Nat Prod Commun 9:55–56

Li YR, Li S, Lin CC (2018) Effect of resveratrol and pterostilbene on aging and longevity. BioFactors 44:69-82. https://doi.org/10.1002/biof.1400

López-Dóriga I (2018) The Archaeobotany and Ethnobotany of Portuguese or White Crowberry (*Corema album*). Ethnobiol Lett 9:19-32. https://doi.org/10.14237/ebl.9.2.2018.1069

Ma Z, Zhang X, Xu L et al (2019) Pterostilbene: Mechanisms of its action as oncostatic agent in cell models and *in vivo* studies. Pharmacol Res 145:104265. https://doi.org/10.1016/j.phrs.2019.104265

Macedo D, Tavares L, McDougall GJ, et al (2015) (Poly)phenols protect from α-synuclein toxicity by reducing oxidative stress and promoting autophagy. Hum Mol Genet 24:1717-1732. https://doi.org/10.1093/hmg/ddu585

Marhuenda J, Alemán MD, Gironés-Vilaplana A et al (2016) Phenolic Composition, Antioxidant Activity, and *In Vitro* Availability of Four Different Berries. J Chem 2016:5134301. https://doi.org/10.1155/2016/5194901

Martín MA, Ramos S, Mateos R et al (2010) Protection of human HepG2 cells against oxidative stress by the flavonoid epicatechin. Phytother Res 24:503-509. https://doi.org/10.1002/ptr.2961

Martín Sarmiento J de S (1974) Opúsculos lingüísticos gallegos del siglo XVIII. J Pensado (ed.). Galaxia, Vigo

Martínez-Varea CM, Ferrer-Gallego PP, Raigón MD et al (2019) *Corema album* archaeobotanical remains in western Mediterranean basin. Assessing fruit consumption during Upper Palaeolithic in Cova de les Cendres (Alicante, Spain). Quat Sci Rev 207:1-12. https://doi.org/10.1016/j.quascirev.2019.01.004

Oliveira I, Nunes A, Lima A et al (2019) New Lectins from Mediterranean Flora. Activity against HT29 Colon Cancer Cells. Int J Mol Sci 20:3059. https://doi.org/10.3390/ijms20123059

Oudot C, Gomes A, Nicolas V et al (2019) CSRP3 mediates polyphenols-induced cardioprotection in hypertension. J Nutr Biochem 66:29-42. https://doi.org/10.1016/j.jnutbio.2019.01.001

Pantelidis G, Vasilakakis M, Manganaris G, Diamantidis G (2007) Antioxidant capacity, phenol, anthocyanin and ascorbic acid contents in raspberries, blackberries, red currants, gooseberries and Cornelian cherries. Food Chem 102:777-783. https://doi.org/10.1016/j.foodchem.2006.06.021

Pimpão RC, Dew T, Oliveira PB et al (2013) Analysis of Phenolic Compounds in Portuguese Wild and Commercial Berries after Multienzyme Hydrolysis. J Agric Food Chem 61:4053-4062. https://doi.org/10.1021/jf305498j

Pindar, Sandys JE (1915) The Odes of Pindar. Including the principal fragments. Traslation by Sandys, J. London. W. HeinemannThe Macmillan Co., New York

Quéguineur B, Goya L, Ramos S et al (2012) Phloroglucinol: Antioxidant properties and effects on cellular oxidative markers in human HepG2 cell line. Food Chem Toxicol 50:2886-2893. https://doi.org/10.1016/j.fct.2012.05.026

Rimando AM, Kalt W, Magee JB et al (2004) Resveratrol, Pterostilbene, and Piceatannol in *Vaccinium* Berries. J Agr Food Chem 52:4713-4719. https://doi.org/10.1021/jf040095e

Ruwizhi N, Aderibigbe BA (2020) Cinnamic Acid Derivatives and Their Biological Efficacy. Int J Mol Sci 21:5712. https://doi.org/10.3390/ijms21165712

Sangweni NF, Moremane M, Riedel S et al (2020) The Prophylactic Effect of Pinocembrin Against Doxorubicin-Induced Cardiotoxicity in an *In Vitro* H9c2 Cell Model. Front Pharmacol 11: 1172. https://doi.org/10.3389/fphar.2020.01172

Scharf G, Prustomersky S, Knasmüller S et al (2003) Enhancement of Glutathione and γ-Glutamylcysteine Synthetase, the Rate Limiting Enzyme of Glutathione Synthesis, by Chemoprotective Plant-Derived Food and Beverage Components in the Human Hepatoma Cell Line HepG2. Nutr Cancer 45:74-83. https://doi.org/10.1207/S15327914NC4501_9

Silva FSG, Oliveira PJ, Duarte MF (2016) Oleanolic, Ursolic, and Betulinic Acids as Food Supplements or Pharmaceutical Agents for Type 2 Diabetes: Promise or Illusion? J Agr Food Chem 64:2991-3008. https://doi.org/10.1021/acs.jafc.5b06021

Song L, Chen T, Zhao X et al (2019) Pterostilbene prevents hepatocyte epithelial-mesenchymal transition in fructose-induced liver fibrosis through suppressing miR-34a/Sirt1/p53 and TGF-β1/Smads signalling. Br J of Pharmacol 176:1619-1634. https://doi.org/10.1111/bph.14573

Venturelli S, Burkard M, Biendl M et al (2016) Prenylated chalcones and flavonoids for the prevention and treatment of cancer. Nutrition 32:1171-1178. https://doi.org/10.1016/j.nut.2016.03.020

Villar L (1993) Corema D. Don. In: Castroviejo S, Aedom C., Gómez Campo C, et al. (eds) Flora Iberica. Real Jardín Botánico CSIC, Madrid, pp 524–526

Wang D, Jiang Y, Sun-Waterhouse D et al (2020) MicroRNA-based regulatory mechanisms underlying the synergistic antioxidant action of quercetin and catechin in H_2O_2-stimulated HepG2 cells: Roles of BACH1 in Nrf2-dependent pathways. Free Radic Bio Med 153:122-131. https://doi.org/10.1016/j.freeradbiomed.2020.04.018

Ye T, Zhang C, Wu G et al (2020) Pinocembrin Decreases Ventricular Fibrillation Susceptibility in a Rat Model of Depression. Front Pharmacol 11:547966. https://doi.org/10.3389/fphar.2020.547966

Zheng Y, Wan G, Yang B et al (2020) Cardioprotective Natural Compound Pinocembrin Attenuates Acute Ischemic Myocardial Injury via Enhancing Glycolysis. Oxid Med Cell Longev 2020:4850328. https://doi.org/10.1155/2020/4850328

Zunzunegui M, Díaz Barradas MC, Clavijo A et al (2006) Ecophysiology, growth timing and reproductive effort of three sexual foms of *Corema album* (Empetraceae). Plant Ecol 183:35-46. https://doi.org/10.1007/s11258-005-9004-4

Figure 1. Geographical distribution of *Corema album* in the Iberian Peninsula.

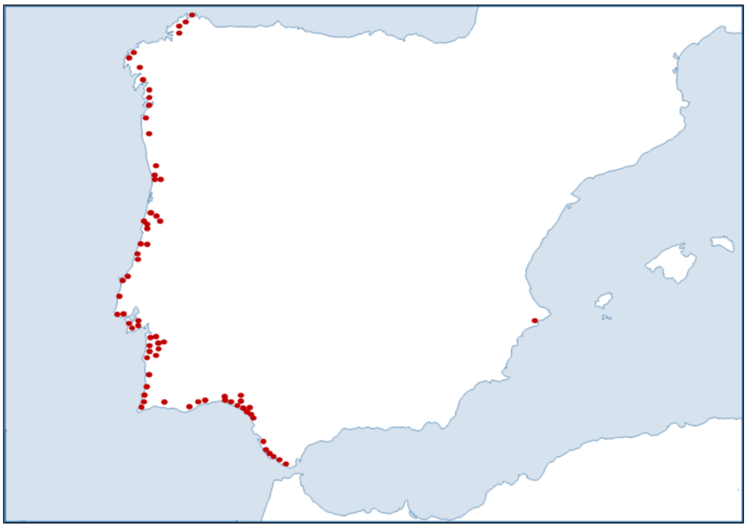
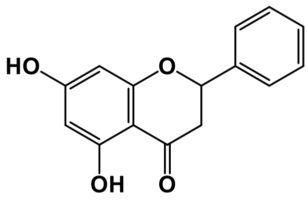
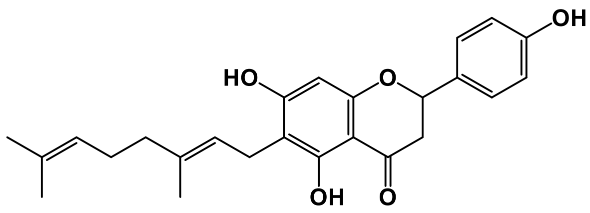


Figure 2. *Corema album* (L.) D. Don. (a) Lithography from Flora Forestal Española, 1885; (b) Bush in Doñana National Park, Spain (Photo: M.J. Cartes); (c) Collected berries (from https://www.canthecan.net); (d) Detail of white berries in the bush.

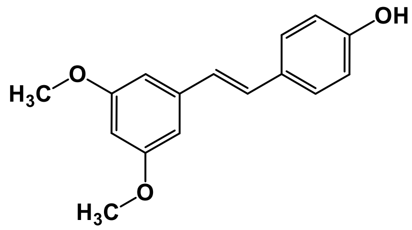
Figure 3. Flavanones and pterostilbene identified in *Corema album* edible berries



Pinocembrin



6-geranylnaringenin



Pterostilbene

Table 1. Compounds identified in *Corema album* berries.

Compound	Quantity	Methodology	References
WATER	83.41% 87.89% 97.66%	Lyophilization Dehydration 120 °C Dehydration	(León-González et al. 201[illegible]; Andrade et al. 2015; Martínez-Varea et al. 2019)
MINERALS			
Phosphorus	3.75 mg/100g FW	Spectrometry UV/Vis	(Martínez-Varea et al. 20[illegible]
Potassium	121.3 mg/100g FW	Flame photometry	(Martínez-Varea et al. 2019)
Calcium	21.36 mg/100g FW	Atomic absorption spectrophotometry	(Martínez-Varea et al. 2019)
Magnesium	4.78 mg/100g FW	Atomic absorption spectrophotometry	(Martínez-Varea et al. 2019)
Iron	0.29 mg/100g FW	Atomic absorption spectrophotometry	(Martínez-Varea et al. 2019)
Copper	0.19 mg/100g FW	Atomic absorption spectrophotometry	(Martínez-Varea et al. 2019)
Zinc	0.22 mg/100g FW	Atomic absorption spectrophotometry	(Martínez-Varea et al. 2019)
ORGANIC ACIDS			
Ascorbic acid (Vitamin C)	5.4 mg/100g FW 97 mg/100g FW	LC–DAD Potentiometry	(Pimpão et al. 2013; Martínez-Varea et al. 2019)
Citric acid	n.q.	CG/MS	(León-González 2012)
Malic acid	n.q.	CG/MS	(León-González 2012)
CARBOHYDRATES			
Glucose	n.q.	CG/MS	(León-González 2012)
Fructose	n.q.	CG/MS	(León-González 2012)
Sucrose	n.q.	CG/MS	(León-González 2012)
~~Ascorbic acid (Vitamin C)~~	~~5.4 mg/100g FW~~ ~~97 mg/100g FW~~	~~LC–DAD~~ ~~Potentiometry~~	~~(Pimpão et al. 2013; Martí[illegible] Varea et al. 2019)~~
PHENOLIC COMPOUNDS			

Formatted: Font: Bold, English (United States)
Formatted: English (United States)
Formatted: Font: Italic, English (United States)
Formatted: Font: Ialic
Formatted: English (United States)
Formatted Table
Formatted Table
Formatted Table
Formatted Table
Formatted: Spanish (Spain)

Phenolic acids			
Benzoic and hydroxybenzoic acids			
~~Ascorbic acid (Vitamin C)~~	~~5.4 mg/100g FW 97 mg/100g FW~~	~~LC–DAD Potentiometry~~	~~(Pimpão et al. 2013; Martínez-Varea et al. 2019)~~
Benzoic acid	70.8 µg/g DW	GC/MS	(León-González et al. 2013
Salicylic	0.6 µg/g DW	GC/MS	(León-González et al. 2013b)
p-Hydroxybenzoic acid	50.2 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2013b)
Protocatechuic acid	13.2 µg/g DW	LC-DAD-MS/MS	(Pimpão et al. 2013)
Vanillic acid	21.3 µg/g DW	GC/MS	(León-González et al. 2013b)
Syringic acid	1.3 µg/g DW	GC/MS	(León-González et al. 2013b)
Gallic acid	4.8 µg/g DW	GC/MS	(León-González et al. 2013b)
Cinnamic and Hydroxycinnamic acids			
t-Cinnamic acid	1.9 µg/g DW	GC/MS	(León-González et al. 2013
p-Coumaric acid	11.8 µg/g DW	LC–DAD–MS/MS	(León-González 2012)
Ferulic acid	49.4 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2013b)
Sinapic acid	4.6 µg/g DW	GC/MS	(León-González et al. 2013b)
Caffeic acid	252.5 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012)
Caffeic acid-*O*-hexoside	242.3 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2013
3-*O*-caffeoylquinic acid (chlorogenic acid)	3005.9 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012
4-*O*-caffeoylquinic acid (cryptochlorogenic acid)	128.3 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012
5-*O*-caffeoylquinic acid (neochlorogenic acid)	137.3 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012
Total Phenolic acids	*3753.7 µg/g DW 623,53 µg/g FW*		
Stilbenes			
Pterostilbene	45.9 µg/g DW	LC-DAD-MS/MS	(Pimpão et al. 2013)
Flavonols			
Quercetin 3-*O*-glucoside	320.4 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012
Quercetin 3-*O*-arabinoside	19.9 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012)

Rutin	52.8 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012)
Myricetin-3-*O*-glucoside	47.4 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012)
Kaempferol-3-*O*-glucoside	19.2 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012)
Kaempferol-3-*O*-galactoside	12.9 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012)
Total flavonols	*472.6 µg/g DW* *78 µg/g FW*		
Flavanones			
Pinocembrin	46 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012)
6-geranylnaringenin	22.6 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012)
Flavanols			
(-)-Epicatechin	18.3 µg/g DW	LC-DAD-MS/MS	(Pimpão et al. 2013)
Anthocyanins			
Cyanidin-3-*O*-glucoside	2.7 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012)
Cyanidin-3-*O*-arabinoside	1.4 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012)
Delphinidin-3-*O*-glucoside	2.3 µg/g DW	LC–DAD–MS/MS	(León-González et al. 2012)
Total Anthocyanins	*6.4 µg/g DW* *1.0 µg/g FW*		
TERPENES			
Pentacyclic triterpenes			
Ursolic acid	n.q.	GC/MS	(Diaz-Barradas et al. 2016)
Oleanolic acid	n.q.	GC/MS	(Diaz-Barradas et al. 2016)

n.q.: not quantifed, DW: Dry Weight, FW: Fresh Weight