Food Chemistry 423 (2023) 136275

Contents lists available at ScienceDirect

Food Chemistry

journal homepage: www.elsevier.com/locate/foodchem

Review

The wide spectrum of industrial applications for cultivated cardoon (*Cynara cardunculus* L. var. *Altilis* DC.): A review

Filipa Mandim[a,b,c], Celestino Santos-Buelga[c], Isabel C.F.R. Ferreira[a,b], Spyridon A. Petropoulos[d], Lillian Barros[a,b,*]

[a] *Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Campus de Santa Apolónia, 5300-253 Bragança, Portugal*
[b] *Laboratório Associado para a Sustentabilidade e Tecnologia em Regiões de Montanha (SusTEC), Instituto Politécnico de Bragança. Campus de Santa Apolónia, 5300-253 Bragança, Portugal*
[c] *Grupo de Investigación em Polifenoles (GIP-USAL), Facultad de Farmacia, Universidad de Salamanca, Campus Miguel de Unamuno, 37007 Salamanca, Spain*
[d] *University of Thessaly, Department of Agriculture, Crop Production and Rural Environment, 38446 N. Ionia, Volos, Greece*

ARTICLE INFO

Keywords:
Cynara cardunculus L.
Industrial applications
Biological properties
Bioactive compounds
Circular economy
Bioenergetic culture

ABSTRACT

Cynara cardunculus L. var. *altilis* DC. belongs to the Asteraceae family and is widely used. This species is integrated into the Mediterranean diet and has broad applicability due to its rich chemical composition. Its flowers, used as a vegetable coagulant for gourmet cheese production, are rich in aspartic proteases. Leaves are rich in sesquiterpene lactones, the most abundant being cynaropicrin, while stems present a higher abundance of hydroxycinnamic acids. Both classes of compounds exhibit a wide range of bioactive properties. Its chemical composition makes it applicable in other industrial sectors, such as energy (e.g., manufacturing of biodiesel and biofuel) or paper pulp production, among other biotechnological applications. In the last decade, cardoon has been identified as a competitive energy crop, constituting an opportunity for the economic recovery and development of the rural areas of the Mediterranean basin. This article reviews the chemical composition, bioactive properties, and multifaceted industrial applications of cardoon.

1. Introduction

The world population is constantly growing. Despite the enormous scientific evolution over the last decades, mankind is still facing serious developmental challenges. The scarcity of resources, global warming, and growing environmental awareness call for an increase in the search for alternatives to commonly used raw materials. The proper use and application of resources, as well as the development of environmentally friendly strategies and sustainable methodologies, are being encouraged (Williamson et al., 2020).

Plant species have been used in traditional medicine since ancient times for the treatment of various pathologies and conditions (Aware et al., 2022). Over time and with increasing knowledge, plant species have been explored and recognized as a source of bioactive compounds of interest and with enormous potential for the discovery of new therapeutic compounds, as well as for applications in the most varied industrial sectors. Higher plants may synthesize through their primary and secondary metabolism a wide variety of chemical compounds with unique characteristics. Endowed with high potential, those compounds can be used for the development of drugs, novel nutraceuticals, functional foods, and cosmetics, resulting in more accessible and efficient products with fewer adverse effects (Aware et al., 2022; Williamson et al., 2020). The recovery of biomass and its application to obtain energy, animal feed, and paper pulp, among others, has been explored as an attempt to reduce the impact on the climate and environment and advance the concept of circular economy (Kumar & Verma, 2021; Kumar et al., 2022). Out of more than 422,000 plant species documented worldwide, only a few have been explored and characterized regarding their pharmacological potential (Aware et al., 2022). Furthermore, their chemical composition affects their therapeutic and energetic values, being influenced by several external factors (Aware et al., 2022). Despite the high potential that has been demonstrated, the isolation and characterization of bioactive compounds of interest in plants can be a challenge, since their isolation may result in modified

---

[*] Corresponding author at: Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Campus de Santa Apolónia, 5300-253 Bragança, Portugal; Laboratório Associado para a Sustentabilidade e Tecnologia em Regiões de Montanha (SusTEC), Instituto Politécnico de Bragança. Campus de Santa Apolónia, 5300-253 Bragança, Portugal.

E-mail address: lillian@ipb.pt (L. Barros).

https://doi.org/10.1016/j.foodchem.2023.136275
Received 6 November 2022; Received in revised form 28 March 2023; Accepted 27 April 2023

bioactivities due to synergistic and/or antagonistic effects among compounds commonly present in natural matrices (Aware et al., 2022).

Cardoon, both cultivated and wild, is a plant species that has been attracting great interest from several industrial sectors over the last decade. This species has low requirements in agronomic inputs and can establish itself in areas with adverse environmental conditions and infertile soils. Cardoon has a high concentration of bioactive compounds, as well as a high biomass yield per harvested area (Pandino, Lombardo, & Mauromicale, 2013a). In this study, a systematic literature search was followed using scientific databases and keywords related to the issue. The selected keywords were "*Cynara cardunculus* L.", "cardoon", "chemical composition", "biological properties", "industrial applications", "cosmetic", "energy crop", and "paper pulp". The above keywords were used individually and in combination to search Science Direct, Google Scholar, and Scopus databases. Given a large number of scientific literature (more than 1200 articles), preference was given to those published in the last five years. However, when required information wasn't available within this time period, the search was extended to the last decade. This review aims to summarize the most relevant data published regarding the multifaceted potential exhibited by cardoon. Its chemical composition, biological properties, and energetic and food applications are further described. We also intend to identify the main future challenges associated with each of the applications described.

2. Botanical description

2.1. *Asteraceae family*

The Asteraceae family, also known as the Compositae, is one of the largest families of flowering plants in the plant kingdom. It is a cosmopolitan family widespread in all continents except Antarctica (Lopes et al., 2021). The Asteraceae family comprises more than 1700 genera and 25,000 species (Lopes et al., 2021; Michel et al., 2020; Rolnik & Olas, 2021). They have been used since ancient times because of their sundry medicinal benefits, namely as a laxative, astringent, anti-inflammatory, and hepatoprotective. They are also employed for relieving pain, treating wounds, hemorrhoids, flatulence, and other disorders (Garcia-Oliveira et al., 2021). The chemical composition and biochemical potential have been widely studied and molecules of high bioactive significance such as inulin, sesquiterpenoids, phenolic acids, and flavonoids were identified (Garcia-Oliveira et al., 2021; Rolnik & Olas, 2021). Besides that, various medicinal properties (e.g., antimicrobial, antioxidant, anti-inflammatory, or hepatoprotective activities), as well as applications in sectors such as food, cosmetics, and pharmaceutical industries have been described. These features, associated with the urgent need for the discovery and development of innovative drugs, are the main reasons for the high interest that have been shown for these species (Garcia-Oliveira et al., 2021; Rolnik & Olas, 2021).

2.2. *Cynara cardunculus L.*

C. cardunculus L. is a species belonging to the Asteraceae family. It is native to the Mediterranean basin and comprises three different taxa: cultivated cardoon (*C. cardunculus* L. var. *altilis* DC.), wild cardoon (*C. cardunculus* L. var. *sylvestris* (Lamk) Fiori), and globe artichoke (*C. cardunculus* L. var. *scolymus* L. Fiori) (Silva et al., 2022). The three taxa are sexually compatible which allows cross-pollination. Many studies have shown that the wild variety is the ancestor of cultivated cardoon and artichoke (Conceição et al., 2018).

Cardoon is a diploid herbaceous species with an annual growth cycle. This species has nine developmental phenological stages (principal growth stages (PGS) comprise between 1 and 9) according to the Biologische Bundesanstalt, Bundesssortenamt, CHemische Industrie (BBCH) scale. The main characteristics of each phenological stage of the species are provided as Supplementary Material. The crop grows and develops vegetative organs between autumn and spring, while at the end of summer the growth cycle is complete. The harvest time is influenced by the type of application and plant organs of interest (Gominho et al., 2018). Moreover, in scientific studies regarding small-scale and large-scale cardoon cultivation, its applicability and effectiveness are supported. The obtained results validate its exploitation for both whole plant harvesting, as also for achenes recuperation. Cardoon stalks correspond to the largest amount of total biomass, followed by the capitulum (Gominho et al., 2011, Gominho et al., 2014). Its morphology is influenced by the growth cycle, environmental conditions, and variety (Barracosa et al., 2019; Gominho et al., 2018). This plant fully adapts to the adverse environmental conditions of the Mediterranean basin countries, in which rainfall is low and irregular, with higher frequency in autumn and winter, and a large temperature fluctuation, ranging from 7 °C to 40 °C. In the period of extreme drought, the aerial parts dry up and the new growth cycle only initializes at the beginning of autumn. In this season, the environmental conditions are more favorable due to rainfalls that induce sprouting of dormant buds and the regeneration of new shoots. In addition to its high tolerance to abiotic stressors, its cultivation has a positive effect on soil fertility (Mauromicale et al., 2014; Rossi et al., 2022). The reduction of soil weeds, as well as an increase in some beneficial soil bacteria and the organic matter, exchangeable potassium, total nitrogen, organic carbon, and assimilable phosphorus pentoxide were also described in the literature (Mauromicale et al., 2014; Scavo et al., 2019a).

Cardoon is a robust plant, reaching more than 2 m tall (Gominho et al., 2018; Silva et al., 2022). Its perennial root develops annually and can persist for more than ten years. This root system is branched and deep when it reaches maturity and can be used strategically as a land-stabilizing crop and to increase soil fertility, due to its potential to prevent ground degradation (Rossi et al., 2022). The achenes (cypselas) are smooth and can have a gray, black, or brown color, depending on the genotype. At the top of each achene, feathery bristles of pappus (modified calyx) are easily recognizable and detached. Generally, achenes germination occurs under favorable humidity and temperature conditions, normally in the first weeks of autumn. The leaves are gradually formed, maintaining the leaf rosette state throughout winter and early spring. After this period, the stems begin to elongate giving rise to a branched inflorescence, constituted by several capitula. The basal leaves can reach 120 cm in length and 30 cm in width, while the upper leaves are smaller, about 10 cm to 50 cm long. They are gray-green and are covered with dense hairs. Their tips usually have yellow-orange spines measuring 5 mm to 20 mm long, although the presence and density of spines is a genotype dependent on character. The capitula, or heads, are 1 cm to 6 cm long and consist of bluish or purple flowers, distributed in a fleshy receptacle, and surrounded by several bracts. After the flowering stage, the achenes ripen and, during the summer, the aerial biomass dries out. In the first years of harvest, the amount of aerial biomass is lower, due to the gradual development of the root system (Barbosa et al., 2020; Conceição et al., 2018; Gominho et al., 2018; Pesce & Mauromicale, 2019; Silva et al., 2022). This system works as a plant storage organ, accumulating large amounts of carbohydrates, including inulin, to assure the necessary compounds for the beginning of a new growth cycle in the next autumn (Conceição et al., 2018; Silva et al., 2022).

Cultivated and wild cardoon production is more concentrated in southern European countries, namely Portugal, Greece, Spain, Italy, and France (Conceição et al., 2018). The different plant organs have a multifaceted potential, presenting a wide range of applications. Its flowers are widely known due to their high content of aspartic proteases, and the consequent use as vegetable coagulants in the production of different Protected Designation of Origin (PDO) cheeses (Barracosa et al., 2018a; Conceição et al., 2018). Its lignocellulosic fraction has the potential as a solid biofuel and in bioethanol and biogas production. Stalks and capitulum can be also used to produce pulp fibers. The achenes are used to obtain oil for human consumption or biodiesel. In addition, several pharmacological and nutraceutical properties have been proven (Gominho et al., 2018; Silva et al., 2022; Zayed et al., 2020). These applications will be explored throughout this systematic review and are summarized in Fig. 1.

3. Chemical composition

3.1. Nutritional value

Cardoon is widely consumed in the Mediterranean diet, being used in soups and salads. The edible part consists of its fleshy stems, as well as the immature heads or inflorescences, inner bracts, and the upper part of the receptacle. They can be used fresh, frozen, or canned (Barbosa et al., 2020; Silva et al., 2022). It can be considered a functional food due to its high nutritional value associated with the content of proteins, fatty acids, organic acids, amino acids, minerals, vitamins, carbohydrates including fiber and sugars, and phytochemicals (Mandim et al., 2020a; Petropoulos et al., 2018a; Silva et al., 2022). Silva et al. (2022) recently presented a systematic review regarding this subject and the cardoon effect as a promoting agent in metabolic disorders.

Most studies concerning the lipid content of cardoon are related to its achenes. They are widely explored due to their multifaceted potential and applicability in various industrial sectors (Mandim et al., 2020a; Mandim et al., 2022a; Petropoulos et al., 2019), which will be discussed in the following sections. The lipidic content of the remaining plant organs (heads, bracts, petioles, blades, and stalks) has also been studied, and variations between samples, as well as in phenotypic characteristics have been described (Mandim et al., 2020a; Mandim et al., 2020b; Mandim et al., 2020c; Mandim et al., 2022a; Mandim et al., 2022b, 2022c; Petropoulos et al., 2018a). In general, palmitic and oleic acids are the fatty acids detected in high quantities in cardoon organs, namely achenes, heads, bracts, petioles, and blades (Mandim et al., 2020a; 2020b; 2020c; Mandim et al., 2022a, 2022b, 2022c; Petropoulos et al., 2018a; Petropoulos et al., 2018b). Cardoon achenes reveal a higher abundance of unsaturated fatty acids (Mandim et al., 2020a; Mandim et al., 2022a; Petropoulos et al., 2018a; Petropoulos et al., 2018b) compared to other organs, while in heads, bracts, petioles, and blades the levels of saturated fatty acids stand out (Mandim et al., 2020b; Mandim et al., 2020c; Mandim et al., 2022b; Mandim et al., 2022d; Petropoulos et al., 2018a). Authors justify the observed differences with temperature oscillation. Those alterations influence the production of fatty acid desaturates, that are the enzymes responsible for unsaturating C18 saturated fatty acids (Mandim et al., 2022a; 2022b). Tocopherols are a group of lipophilic compounds with important antioxidant capacity. The α-, β-, γ-, and δ-tocopherol isoforms were all identified in the different plant organs of cardoon (Mandim et al., 2020a; 2020b; 2020c; Mandim et al., 2022a; 2022b; 2022c; Petropoulos et al., 2019). Several studies described an increase in their concentration in more advanced stages of maturation. This fact has been justified by higher exposure to adverse environmental conditions, namely dry periods and higher light exposure. Those conditions induce oxidative stress situations, that lead to an increase in the content of compounds with antioxidant capacity (Mandim et al., 2022b; Rey et al., 2021). Moreover, fruit ripening stimulates the tocopherol biosynthesis coding genes, which is further diminished by darkness (Mandim et al., 2022b).

Cynara cardunculus is considered one of the main sources of inulin, a fructose-based polysaccharide that makes part of the dietary fiber, commonly used in the food industry due to its nutraceutical and technological properties (Melilli et al., 2021; Pari et al., 2021). Inulin accumulates in underground organs as a source of energy, being involved in several adaptive mechanisms when the plant is subjected to stress conditions. Several authors identified cardoon roots as important sources of inulin (Melilli et al., 2021; Pari et al., 2021). From a technological point of view, inulin and derived oligosaccharides are used as fat substitutes and/or sugar. It also has beneficial health properties, due to its prebiotic effect, helping to control intestinal transit, improving intestinal microbiota composition, and triglycerides and cholesterol levels in blood (Melilli et al., 2021). Inulin applications in food products such as ice creams, cheeses, and beverages have already been explored (Melilli et al., 2021). For a competitive inulin recovery, optimization of extraction methodologies is needed. Rheological, sensorial, and stability characteristics of the products supplemented with inulin seem to be important research areas to complement the existing studies. Besides inulin, sugars such as fructose, glucose, sucrose, trehalose, raffinose, rhamnose, galactose, mannose, arabinose, and xylose have also been reported in cardoon (Amira et al., 2018; Mandim et al., 2020a; 2020b; 2020c; Mandim, et al., 2022a; 2022b, 2022c; Pari et al., 2021; Petropoulos et al., 2018a). Sucrose is the most commonly described sugar and the one present in the highest concentrations (Mandim et al., 2020a; 2020b; 2020c; Mandim et al., 2022a; 2022b; 2022c; Petropoulos et al., 2018a). Cardoon has a low protein content (0.7 g per 100 g dw), with achenes being the organ with the highest content (Petropoulos et al., 2019).

3.2. Phytochemical composition

Cardoon chemical composition has been extensively explored. A wide variety of bioactive compounds has been identified (Table 1). Organic acids have a strong influence on the organoleptic characteristics of plant species and are highly concentrated in fruits and vegetables. Oxalic, quinic, malic, citric, and fumaric acids have been described in cardoon plant organs (Mandim et al., 2020a; 2020b; 2020c; Mandim

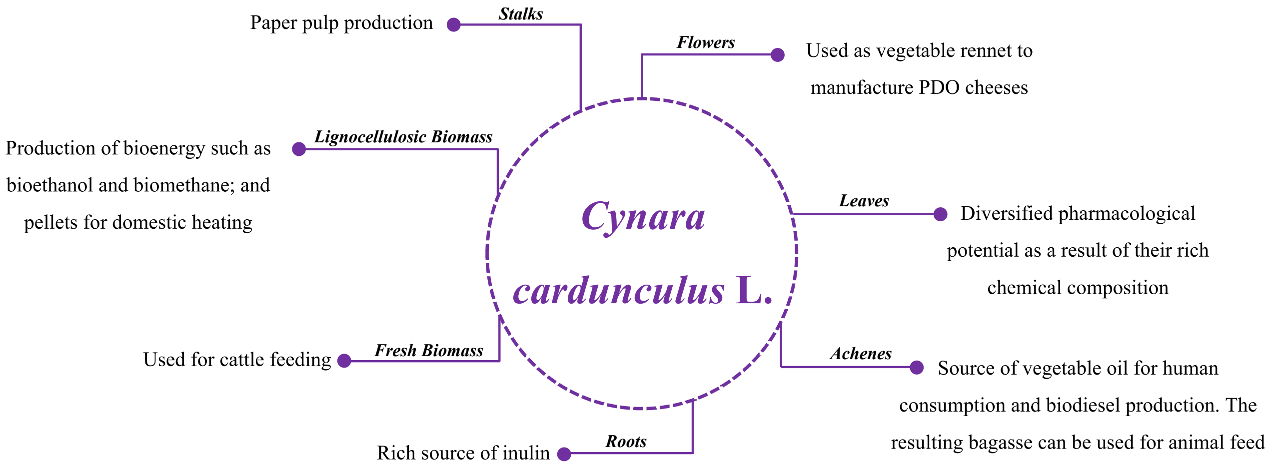

Fig. 1. Applications of cultivated and wild cardoons vegetable organs. *Self-authored scheme.*

Table 1
Phytochemicals identified in *C. cardunculus* L. organs.

Phytochemical Composition	Vegetable organ	Reference
Phenolic acids		
1-*O*-Caffeoylquinic acid	Petioles, leaves, stalks, heads	Ferioli & D'Antuono, 2022; Pandino et al., 2022; Ramos et al., 2014
3-*O*-Caffeoylquinic acid (neochlorogenic acid)	Blades, inflorescences, petioles, stalks, capitula, leaves	Dias et al., 2018; Ferioli & D'Antuono, 2022; Mandim et al., 2021b, 2022d; Ramos et al., 2014
cis 3-*O*-caffeoylquinic acid	Leaf midribs and petioles	Petropoulos, Pereira, et al., 2018a
trans 3-*O*-caffeoylquinic acid	Heads, leaf midribs and petioles, leaf blades	Petropoulos, Pereira, et al., 2018a
4-*O*-Caffeoylquinic acid (cryptochlorogenic acid)	Blades, petioles	Mandim et al., 2021b, Mandim et al., 2022d
5-*O*-Caffeoylquinic acid (chlorogenic acid)	Capitula, bracts, leaves, leaf blades, leaf midribs and petioles, achenes, stalks	Ferioli & D'Antuono, 2022; Huarte, Juániz, et al., 2021a; Juániz et al., 2017; Mandim et al., 2020a, 2020d, 2021a; Pandino et al., 2022; Petropoulos et al., 2018b, 2019; Ramos et al., 2014; Scavo et al., 2018
cis 5-*O*-Caffeoylquinic acid	Bracts, petioles, achenes	Mandim et al., 2021b, Mandim et al., 2022a, Mandim et al., 2022d
trans 5-*O*-Caffeoylquinic acid	Blades, achenes	Mandim et al., 2022a; Mandim et al., 2022d
Tri-*O*-caffeoylquinic acid	Heads	Mandim et al., 2020d
Caffeoylquinic acid derivative	Blades	Mandim et al., 2022d
Caffeic acid hexoside	Leaf blades	Petropoulos, Pereira, et al., 2018a
O-Dicaffeoylquinic acid	Petioles	Mandim et al., 2021b
1,3-*O*-Dicaffeoylquinic acid (cynarine)	Blades, petioles, stalks, capitula, leaves, inflorescences, leaf midribs	Dias et al., 2018; Huarte, Juániz, et al., 2021a; Mandim et al., 2021b, 2022d; Pandino et al., 2022; Petropoulos, Pereira, et al., 2018a; Ramos et al., 2014
cis 1,3-*O*-Dicaffeoylquinic acid	Blades, achenes	Mandim et al., 2022a, Mandim et al., 2022d
trans 1,3-*O*-Dicaffeoylquinic acid	Achenes	Mandim et al., 2022a
1,4-*O*-Dicaffeoylquinic acid	Petioles, stalks, capitula, leaves	Ferioli & D'Antuono, 2022; Huarte, Juániz, et al., 2021a; Ramos et al., 2014
1,5-*O*-Dicaffeoylquinic acid	Inflorescences, petioles, stalks, capitula, leaves	Ferioli & D'Antuono, 2022; Mandim et al., 2021b, 2022d; Ramos et al., 2014
cis 1,5-*O*-Dicaffeoylquinic acid	Blades	Mandim et al., 2022d
trans 1,5-*O*-Dicaffeoylquinic acid	Blades	Mandim et al., 2022d
3,4-*O*-Dicaffeoylquinic acid	Petioles, achenes, stalks	Ferioli & D'Antuono, 2022; Huarte, Juániz, et al., 2021a; Mandim et al., 2021b, Mandim et al., 2022a
cis 3,4-*O*-Dicaffeoylquinic acid	Blades, heads, leaf midribs, petioles	Mandim et al., 2022d; Petropoulos, Pereira, et al., 2018a
trans 3,4-*O*-Dicaffeoylquinic acid	Blades, heads	Mandim et al., 2022d; Petropoulos, Pereira, et al., 2018a
3,5-*O*-Dicaffeoylquinic acid	Bracts, petioles, inflorescences, heads, leaves, achenes, stalks	Dias et al., 2018; Ferioli & D'Antuono, 2022; Huarte et al., 2021a; Mandim et al., 2020a, 2020d, 2022a, 2021a, 2021b; Pandino et al., 2022; Petropoulos et al., 2019
cis 3,5-*O*-Dicaffeoylquinic acid	Blades, leaf midribs, petioles	Mandim et al., 2022d; Petropoulos, Pereira, et al., 2018a
trans 3,5-*O*-Dicaffeoylquinic acid	Blades, heads, leaf blades, leaf midribs, petioles, achenes	Mandim et al., 2020d, 2022d; Petropoulos et al., 2018a
4,5-*O*-Dicaffeoylquinic acid	Petioles, stalks	Ferioli & D'Antuono, 2022; Huarte, Juániz, et al., 2021a
Protocatechuic acid	Blades, petioles, stalks	Juániz et al., 2017; Mandim et al., 2021b, Mandim et al., 2022d
Monosuccinyldicaffeoylquinic acid	Leaves	Pandino et al., 2022; Scavo et al., 2018
Dicaffeoyldisuccinoylquinic acid isomer	Stalks, capitula, leaves	Ramos et al., 2014
1,5-*O*-Dicaffeoylsuccinoylquinic acid	Stalks, capitula, leaves	Ramos et al., 2014
1,5-*O*-Dicaffeoylsuccinoylquinic acid isomer	Stalks, capitula, leaves	Ramos et al., 2014
1,5-*O*-Dicaffeoyl-3-*O*-succinylquinic acid	Petioles	Ferioli & D'Antuono, 2022
1,5-*O*-Dicaffeoyl-4-*O*-succinylquinic acid	Petioles	Ferioli & D'Antuono, 2022
1,5-*O*-Dicaffeoyl-3,4-di-*O*-succinylquinic acid	Petioles	Ferioli & D'Antuono, 2022
4-Acyl-*O*-dicaffeoylsuccinoylquinic acid isomer	Stalks, capitula, leaves	Ramos et al., 2014
4-Acyl-*O*-dicaffeoylquinic acid isomer	Stalks, capitula, leaves	Ramos et al., 2014
Coumaric acid	Stalks	Juániz et al., 2017
Coumaroylquinic acid	Stalks	Juániz et al., 2017
p-Coumaric acid hexoside	Heads, bracts, leaf blades	Mandim et al., 2021a, 2020d; Petropoulos, Pereira, et al., 2018b
3-*p*-Coumaroylquinic acid	Inflorescences	Dias et al., 2018
Gallic acid	Inflorescences	Dias et al., 2018
5-*O*-Feruloylquinic acid	Bracts, leaf blades	Mandim et al., 2021a; Petropoulos, Pereira, et al., 2018a
Coumarins		
Scopolin isomer	Stalks, capitula, leaves	Ramos et al., 2014
Flavonoids – Flavones		
Apigenin	Stalks, capitula, leaves	Pandino et al., 2022; Ramos et al., 2014; Scavo et al., 2018
Apigenin acetyl-hexoside	Inflorescences, stalks, capitula, leaves	Dias et al., 2018; Ramos et al., 2014
Apigenin-*O*-glucuronide-*O*-hexoside	Capitula	Mandim et al., 2020d
Apigenin glucuronide	Stalks, capitula, leaves	Ramos et al., 2014
Apigenin-7-*O*-glucoside	Inflorescences, stalks, capitula, leaves	Dias et al., 2018; Ramos et al., 2014; Scavo et al., 2018
Apigenin-7-*O*-rutinoside	Inflorescences, stalks, capitula, leaves	Dias et al., 2018; Mandim et al., 2020d; Ramos et al., 2014
Apigenin-7-*O*-glucuronide	Heads, inflorescences, blades, leaves	Dias et al., 2018; Mandim et al., 2020d, 2022d; Scavo et al., 2018
Apigenin-*O*-malonyl-hexoside	Heads, bracts	Mandim et al., 2021a, Mandim et al., 2020d
Apigenin malonylglucoside	Leaves	Pandino et al., 2022; Scavo et al., 2018
Luteolin	Leaves, stalks	Juániz et al., 2017; Pandino et al., 2022; Ramos et al., 2014; Scavo et al., 2018
Luteolin-7-*O*-glucuronide	Inflorescences, heads, leaves, leaf blades	Dias et al., 2018; Mandim et al., 2020d;

(*continued on next page*)

Table 1 (*continued*)

Phytochemical Composition	Vegetable organ	Reference
		Petropoulos, Pereira, et al., 2018b; Scavo et al., 2018
Luteolin 7-*O*-malonylglucoside	Leaves	Scavo et al., 2018
Luteolin-*O*-glucuronide	Heads, bracts	Mandim et al., 2020d, 2021a
Luteolin-*O*-hexoside	Bracts, blades	Mandim et al., 2021a, Mandim et al., 2022d
Luteolin-*O*-malonyl-hexoside	Inflorescences, bracts, petioles, blades	Dias et al., 2018; Mandim et al., 2021a, Mandim et al., 2021b, Mandim et al., 2022d
Luteolin-*O*-hexuronoside	Blades, petioles	Mandim et al., 2021b, Mandim et al., 2022d
Luteolin-*O*-hexoside-*O*-glucuronide	Inflorescences	Dias et al., 2018
Luteolin-*O*-acetylglucuronide	Heads	Petropoulos, Pereira, et al., 2018b
Luteolin-7-*O*-rutinoside	Leaves, leaf midribs and petioles, inflorescences	Dias et al., 2018; Pandino et al., 2022; Petropoulos, Pereira, et al., 2018b
Luteolin-7-*O*-glucoside (cynaroside)	Leaf blades, leaf midribs and petioles, stalks, capitula, leaves	Pandino et al., 2022; Petropoulos, Pereira, et al., 2018a; Ramos et al., 2014
Luteolin 7-*O*-glucuronide	Leaves	Pandino et al., 2022
Luteolin malonyl glucoside	Leaves	Pandino et al., 2022
Luteolin acetyl-hexoside	Stalks, capitula, leaves	Ramos et al., 2014
Chrysoeriol isomer	Stalks, capitula, leaves	Ramos et al., 2014
Chrysoeriol hexoside isomer	Stalks, capitula, leaves	Ramos et al., 2014
Flavonoids - Flavanones		
Eriodyctiol-*O*-glucuronide	Inflorescences, bracts, leaf midribs and petioles	Dias et al., 2018; Mandim et al., 2021a; Petropoulos, Pereira, et al., 2018b
Eriodictyol-*O*-hexuronoside	Blades, petioles	Mandim et al., 2021b, Mandim et al., 2022d
Eriodictyol hexoside	Stalks, capitula, leaves	Ramos et al., 2014
Naringenin	Stalks, capitula, leaves	Ramos et al., 2014
Naringenin-7-*O*-glucoside	Stalks, capitula, leaves	Ramos et al., 2014
Naringenin rutinoside	Stalks, capitula, leaves	Ramos et al., 2014
Flavonoids - Flavonols		
Kaempferol-3-*O*-rutinoside	Bracts	Mandim et al., 2021a
Flavonoids - Anthocyanins		
Cyanidin-malonyl-hexoside	Inflorescences	Dias et al., 2018
Triterpenoids		
Cynaropicrin	Leaves	Ferro et al., 2018; Scavo et al., 2018
Aguerin B	Leaves	Scavo et al., 2019c
Grosheimin	Leaves	Scavo et al., 2019c
Cynaratriol	Leaves	Scavo et al., 2019c
Deacylcynaropicrin	Leaves	Scavo et al., 2019c
11,13-dihydroxy-8-deoxygrosheimin	Leaves	Scavo et al., 2019c
11,13-dihydrodeacylcynaropicrin	Leaves	Scavo et al., 2019c
β-Amyrin	Leaves	Ferro et al., 2018
Lupeol	Leaves	Ferro et al., 2018
Taraxasterol	Leaves	Ferro et al., 2018
Taraxasteryl acetate	Leaves	Ferro et al., 2018
ψ-Taraxasterol	Leaves	Ferro et al., 2018
ψ-Taraxasteryl acetate	Leaves	Ferro et al., 2018
Alfa-Amirin acetate	Leaves	Ferro et al., 2018
Lignans		
Pinoresinol-4-*O*-hexoside	Leaf blades	Petropoulos, Pereira, et al., 2018a

et al., 2022a; 2022b; 2022c). The aerial parts of the plant have a very similar composition, although the organic acids profile is influenced by several factors, such as the phenological stage of development and environmental conditions. Samples at intermediate stages of maturation exhibit higher amounts of organic acids (Mandim et al., 2020a; 2020b; 2020c; Mandim, et al., 2022a; 2022c), except for petioles, for which they stand out at more advanced maturation states (samples at principal growth stage (PGS) 8/9) (Mandim et al., 2022b). The differences in organic acids composition between cardoon vegetable organs are related to their inherent functions. The incomplete oxidation of photosynthetic products is linked to the production of organic acids, which act as stores of fixed carbon storage (Mandim 2022b).

Caffeoylquinic and dicaffeoylquinic acids, flavones, anthocyanins, and terpenoids, are some of the phytochemical classes most frequently described (Barracosa et al., 2019; Mandim et al., 2022a; Pandino et al., 2022; Silva et al., 2022). Cardoon's rich chemical composition is considered the key factor for its biological, nutraceutical, industrial, and pharmaceutical properties (Barbosa et al., 2020; Conceição et al., 2018; Silva et al., 2022). This fact also supports its use since antiquity in various pathological treatments.

Cardoon account for approximately 60% of the wasted plant material (Barbosa et al., 2020). They are the most studied plant organ, due to their richness in compounds with pharmacological interest, namely caffeoylquinic and dicaffeoylquinic acids derivatives (Pandino et al., 2022; Scavo et al., 2018), flavonoids (luteolin and apigenin derivatives) (Pandino et al., 2022; Scavo et al., 2018), as well as sesquiterpene lactones (Ferro et al., 2018; Scavo et al., 2018). Cardoon bracts are also considered an important by-product and present a large variety of phenolic acids and flavonoids (Mandim et al., 2021a; Petropoulos et al., 2018a). The petioles also possess a range of phenolic acids and flavonoid glycosides (Ferioli & D'Antuono, 2022; Mandim et al., 2021b; Petropoulos et al., 2018a), while achenes are rich in caffeoylquinic and dicaffeoylquinic acids derivatives (Mandim et al., 2020a; Mandim et al., 2022a; Petropoulos et al., 2019). Finally, hydroxycinnamic acids and luteolin derivatives are predominant in stalks and apigenin derivatives in florets (Pandino et al., 2013b; Silva et al., 2022).

The most well-known and explored bioactive compounds of cardoon are chlorogenic acid (5-*O*-caffeoylquinic acid) and the sesquiterpene lactone cynaropicrin. The latter has great bioactive potential, namely anti-inflammatory, antimicrobial, and antitumoral (Barbosa et al., 2020; Brás, Neves, et al., 2020a). This sesquiterpene lactone is considered a major contributor to the bioactive properties demonstrated by cardoon organs, (Barbosa et al., 2020; Scavo et al., 2020a). Conventional extraction methodologies require the use of organic solvents, long extraction times, and high temperatures. Those conditions favor the degradation of those compounds limiting their use on an industrial scale (Brás, Neves, et al., 2020a). Due to the important biological value of the sesquiterpene lactones group, research has been focusing on the extraction solvent used, methodologies optimization, and also on compounds identification (Brás et al., 2023). The cynaropicrin extraction process has been optimized by several authors in order to establish efficient and cost-effective industrial extraction methodologies. Soxhlet, ultrasound-assisted extraction, maceration, pressurized and ionic liquids, and microwave extraction have already been explored (Brás et al., 2020a; 2020b; de Faria et al., 2018). According to the finding described in several studies, better results were obtained by ultrasonic extraction, for which shorter extraction times, energy consumption, and higher yields have been optimized (Brás et al., 2020a; 2020b). As above mentioned, better extraction results have been obtained through non-conventional methods. Their application on a large scale is still to be established. In this sense, and in order to make these methodologies feasible, the integrated design of the process would need to take into account several variables, namely solvents, methods, sustainability, biomass, cost, and bioactivity (Brás et al., 2023).

Cardoon antioxidant, anti-obesity, hepatoprotective, chemopreventive, and antimicrobial activities are factors that have gained the attention of pharmaceutical, nutraceutical, and cosmetic industries regarding the species (Borroni et al., 2021). Given the high biomass yield associated with this crop, Borroni et al. (2021) explored its potential as a feedstock for chlorogenic acid extraction and identified it as a promising alternative to the currently raw materials used, namely coffee and chicory. However, it is still not an economically competitive feedstock when compared to the regular industrial practices (Borroni et al., 2021).

The presence of the aforementioned bioactive compounds is strongly influenced by factors such as genotype (Dias et al., 2018; Ferioli & D'Antuono, 2022), growth cycle (Mandim et al., 2020a; Mandim et al., 2021a; Mandim et al., 2020c; Mandim et al., 2022c; Mandim et al., 2022b), plant organ (Petropoulos et al., 2018a), environmental conditions (Pandino et al., 2022; Pappalardo et al., 2020), and growing season (Pandino et al., 2015). Pandino et al. (2022) observed that supplying 100% of the plant's water requirement increases the content of total polyphenols in cardoon by about 26%, caffeoylquinic acids by 28%, and luteolin by 27%, compared to plants under water stress. The authors further observed that 24 h cycle of light increases the biosynthesis of total polyphenols, caffeoylquinic acids, and luteolin by 129, 119, and 273% respectively, when compared with a 0 h supply of light. This finding could be used for the standardization and extraction optimization of these compounds of interest, allowing a better use in different industrial sectors. On the other hand, biosynthesis of chlorogenic acid is known to be boosted during stressful conditions caused by fungi, bacteria, and insects, as well as wound damage and exposure to ultraviolet radiation (Borroni et al., 2021; Naveed et al., 2018).

The influence of the growth cycle on the plant organs of cardoon showed oscillations along the different stages of development. The achenes phenolic compounds content increased with the maturation stage (Mandim et al., 2022a), while heads and bracts showed higher levels in PGS 5 (Mandim et al., 2021a; Mandim et al., 2020d). However, in petioles and blades, higher content of polyphenols was recorded in younger stages (PGS 1) (Mandim et al., 2021b; Mandim et al., 2022d). Contrarily to these, Pandino et al., (2020) obtained higher polyphenols concentrations in leaves collected during the spring time. Even so, it has also been demonstrated that growth stage and harvest time, both influence the flavonoids, caffeoylquinic acids, and cynaropicrin contents.

The chemical richness found in the plant organs of this species is evident. An adequate characterization is fundamental to determine which characteristics are most profitable. The obtainment of these compounds of interest, the development of isolation techniques, and the transfer of all this knowledge to the different industrial sectors are the main challenges.

4. Bioactive properties

Cardoon is widely consumed in traditional medicine because of its multiple medicinal properties. Infusions are traditionally used as a liver protector, due to their choleretic, anti-hemorrhagic, cardiotonic, and anti-diabetic actions, and also for their properties against arterial hypertension and atherosclerosis (Barracosa et al., 2019; Castro et al., 2021; Conceição et al., 2018; Silva et al., 2022; Zayed et al., 2020). Its bioactive potential has been extensively studied and a rich variety of compounds of interest has been described so far. Several studies have proven various pharmacological properties for which cardoon has been widely used in traditional medicine. In recent years, the influence of external factors on composition and the identification of the molecules responsible for the bioactivities have been explored aiming to identify natural compounds with health beneficial effects. A scheme with the main compounds associated to distinct bioactive properties in cardoon is shown in Fig. 2.

4.1. *Antioxidant activity*

The diversity of benefits associated to antioxidants in human health have put the study of these compounds in focus of interest. Antioxidant activity is one of the most studied bioactive properties of cardoon. Over the last decade, research was carried out on the influence of different factors on this biological potential. Assays such as thiobarbituric acid reactive substances (TBARS), oxidative hemolysis inhibition (OxHLIA), *β*-carotene bleaching, Trolox equivalent antioxidant capacity (TEAC), ferric reducing-antioxidant power (FRAP), reducing power, and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging have been applied for this purpose. The studies described in the literature and their main conclusions are summarized in Table 2.

The assessment throughout the growth cycle allowed to characterize the oscillations on the antioxidant potential caused by the different stages of development. For example, immature samples of petioles and blades (PGS 1) demonstrated higher capacity to inhibit lipid peroxidation than later growth stages (Mandim et al., 2021b; Mandim et al., 2022d). Contrarily, bracts and heads showed higher potential in intermediate stages of maturation (PGS 5 and 6/7, respectively) (Mandim et al., 2021a; Mandim et al., 2020d), whereas achenes exhibited better

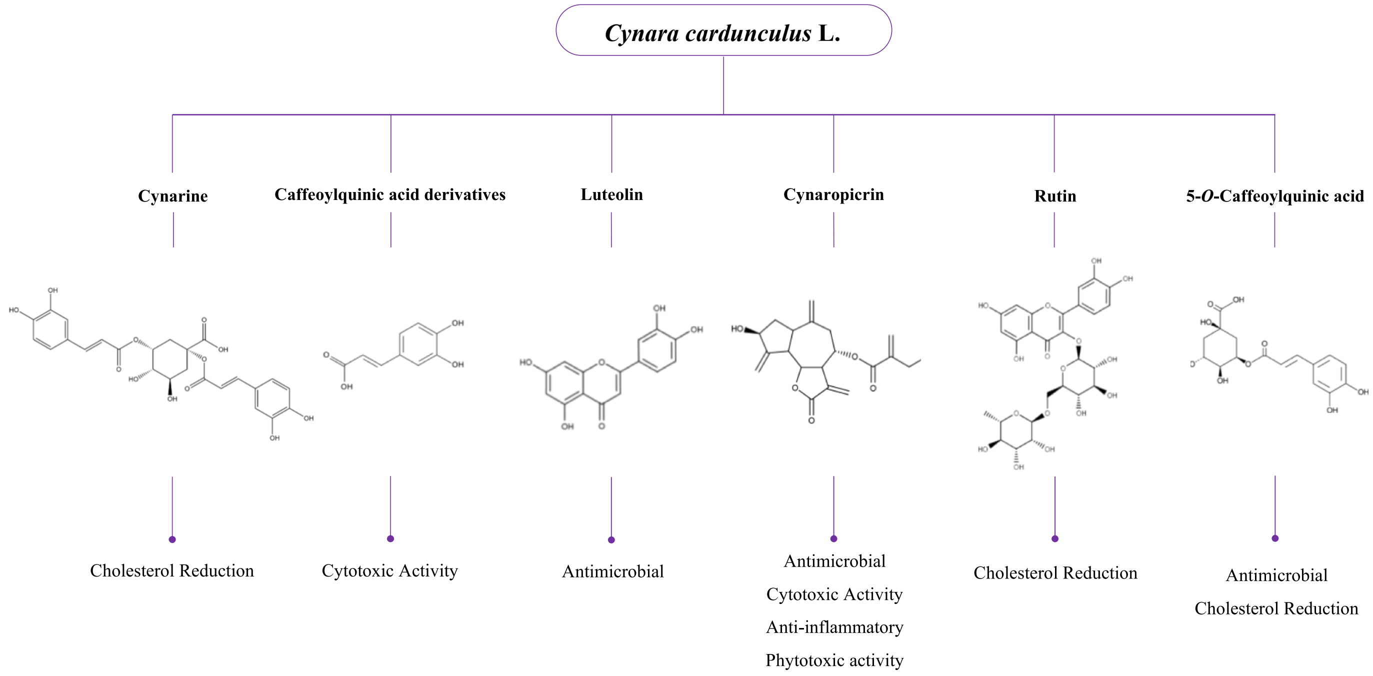

Fig. 2. Some described relationships between the *C. cardunculus* chemical composition and the observed bioactivities. *Self-authored scheme.*

Table 2
Synopsis of assays on the antioxidant and cytotoxic capacity of *C. cardunculus*.

Part Used	Extract	Assay	Main Results	Reference
Antioxidant capacity				
Petioles	EtOH/H_2O, 80:20	TBARS and OxHLIA	Petioles at early maturity (PGS 1) exhibited the highest antioxidant activity for TBARS assays, samples with PGS 5 were more effective for the OxHLIA assay.	Mandim et al., 2021b
Blades	EtOH/H_2O, 80:20	TBARS and OxHLIA	Immature blade exhibited the highest capacity to inhibit the TBARS formation and samples at more advanced maturation stages a higher capacity to inhibit oxidative hemolysis. Authors suggest a positive correlation with the phenolic compounds.	Mandim et al., 2022d
Bracts	EtOH/H_2O, 80:20	TBARS and OxHLIA	Extract with PGS 5 demonstrated higher capacity for the TBARS assays, yeasted bracts with PGS 8/9 were more effective for the OxHLIA assay. Authors suggest a positive correlation with the phenolic compounds.	Mandim et al., 2021a
Capitula	EtOH/H_2O, 80:20	TBARS and OxHLIA	Sample with PGS 6/7 demonstrated the higher antioxidant potential. Samples with higher maturity (PGS 7) grade exhibited the lower effectiveness.	Mandim et al., 2020d
Achenes	EtOH/H_2O, 80:20	TBARS and OxHLIA	Samples with higher maturity grade (PGS 7/8) demonstrated the higher potential.	Mandim et al., 2022a
Achenes	MeOH/H_2O, 80:20	TBARS and OxHLIA	Viable achenes demonstrated higher activity. The authors suggest a positive correlation with the phenolic compounds.	Mandim et al., 2020a
Stalks, capitula, and leaves	Dichloromethane	DPPH	Stalk's outer part, capitula receptacle, and bracts were the most effective to scavenge DPPH free radicals. Authors considered that activity is correlated with total phenols content.	Ramos et al., 2014
Blades, petioles, and midribs	MeOH/H_2O, 80:20	DPPH, reduction power, β-carotene, and TBARS	Leaf blades and achenes exhibited the highest potency for all the tested assays. Authors considered that activity is correlated with total phenols content.	Petropoulos et al., 2018a
Achenes	MeOH/H_2O, 80:20	DPPH, reduction power, β-carotene TBARS, and bleaching inhibition	The authors observed differences between the tested genotypes.	Petropoulos et al., 2019
Inflorescences	MeOH/H_2O, 80:20	DPPH and reduction power	Although the activity has been proven, the genotype has been shown to influence the demonstrated potential.	Dias et al., 2018
Capitula, bracts, and stems	Ultrasound-assisted extraction and classic extraction	DPPH and TEAC	Cardoon's heads extract exhibited the highest radical scavenging activity. The extraction technique exhibited influence, with the ultrasound-assisted extractions with better results.	Kollia et al., 2017
Stalks	EtOH/H_2O, 80:20	ABTS and DPPH	The cooking heat treatments increase the antioxidant potential, authors suggests that the heat treatment destroyed the cell walls and favor the release of phenolic compounds.	Juániz et al., 2017
Stalks	EtOH/H_2O, 80:20	ABTS and DPPH	Blenching and frying cardoon stalks cause a decrease in ABTS antioxidant capacity and doesn't significantly affect the DPPH activity.	Huarte, Juániz, et al., 2021a
Achenes, leaves, hypocotyls, cotyledons	EtOH/H_2O, 50:50	ABTS, DPPH, and FRAP	Significant differences between the tested genotypes were observed, with achenes showing better activity.	Graziani et al., 2020
Achenes oils, achenes, and seed cakes	MeOH/H_2O, 80:20; seed oil with MeOH	DPPH, reduction power, β-carotene, and TBARS	The authors observed differences between the seed oils extracted with different methods and between the growing years. The by-product seed cakes exhibited the highest antioxidant potential.	Petropoulos et al., 2018b
Leaves	EtOH/H_2O, 70:30	DPPH	Salinity improves the observed antioxidant potential.	Colla et al., 2012
Achenes	No information	ABTS, DPPH, and TEAC	Head orders do not interfere with the antioxidant potential.	Piluzza et al., 2019
Cytotoxic activity				
Achenes	MeOH/H_2O, 80:20	Assay: Sulforhodamine B Cell lines: MCF-7, NCI-H460, HeLa, HepG2, PLP2	Did not reveal cytotoxic potential (GI_{50} > 400 μg/mL).	Mandim et al., 2020a
Heads	EtOH/H_2O, 80:20	Assay: Sulforhodamine B Cell lines: MCF-7, NCI-H460, HeLa, HepG2, PLP2	Immature heads revealed the highest cytotoxic activity against the tumor cells tested (GI_{50} between 69 and 268 μg/mL).	Mandim et al., 2020d
Achenes, achenes oil, and seedcakes	Different methodologies	Assay: Sulforhodamine B Cell lines: PLP2	No toxicity for the PLP2 non-tumor cells was observed (GI_{50} > 400 μg/mL).	Petropoulos et al., 2018b
Achenes	MeOH/H_2O, 80:20	Assay: Sulforhodamine B Cell lines: HeLa, HepG2, MCF-7, NCI-H460, PLP2	Genotypes AS1 and AS9 were the most effective in the inhibition of the tumor cells proliferation ((GI_{50} between 212 and 323 μg/mL).	Petropoulos et al., 2019
Bracts	EtOH/H_2O, 80:20	Assay: Sulforhodamine B Cell lines: MCF-7, NCI-H460, HeLa, HepG2, PLP2	Bracts collected at early maturation stages demonstrated the highest capacity to inhibit the tumor cells proliferation (GI_{50} between 30 and 79 μg/mL).	Mandim et al., 2021a
Achenes	EtOH/H_2O, 80:20	Assay: Sulforhodamine B Cell lines: MCF-7, NCI-H460, HeLa, HepG2, PLP2	Mature achenes demonstrated the highest cytotoxic potential (GI_{50} between 97 and 216 μg/mL).	Mandim et al., 2022a
Petioles	EtOH/H_2O, 80:20	Assay: Sulforhodamine B Cell lines: MCF-7, NCI-H460, HeLa, HepG2, PLP2	Petioles collected at intermediate maturation stages showed higher cytotoxic activity (GI_{50} between 11.1 and 16 μg/mL).	Mandim et al., 2021b
Blades	EtOH/H_2O, 80:20	Assay: Sulforhodamine B Cell lines: MCF-7, NCI-H460, HeLa, HepG2, PLP2	Samples at more advanced maturation stages demonstrated higher cytotoxic potential (GI_{50} between 7.1 and 17 μg/mL).	Mandim et al., 2022d

(*continued on next page*)

Table 2 (*continued*)

Part Used	Extract	Assay	Main Results	Reference
Leaves	Ultrasound assisted extraction	Assay: Live-cell imaging Cell lines: HCT116 with different core-clock genes (BMAL1, PER2, NR1D1)	The extract causes a direct effect on the circadian phenotype, inhibited the cell proliferation and induced toxicity and apoptosis.	Fuhr et al., 2022
Leaves	Dichloromethane	Assay: MTT Cell lines: MDA-MB-231	Efficiency in decreasing the ability of cell proliferation has been proven. Cynaropicrin showed a highly antiproliferative potential.	Ferro et al., 2018
Aerial parts	MeOH/H_2O, 70:30	Assay: MTT Cell lines: K562 CML and K562 IMAR	The viability of both cell lines tested was affected.	Russo et al., 2017
Leaves, florets, and their major compounds	Dichloromethane	Assay: MTT Cell lines: MDA-MB-231 and MCF-10A	Leaves showed higher antiproliferative potential. The authors considered that cynaropicrin is the most probably component responsible for the observed potential.	Ramos et al., 2017

TBARS – thiobarbituric acid reactive substances; OxHLIA – oxidative haemolysis; DPPH – 2,2,-Diphenyl-1-picrylhydrazyl; FRAP – ferric-reducing antioxidant power; TEAC – Trolox equivalent antioxidant capacity; GI_{50} – concentration responsible for 50% of cell growth inhibition.

activity at more advanced growth (PGS 8) (Mandim et al., 2022a). When the antioxidant activity was assessed using the oxidative hemolysis inhibition assay, different results were observed. Better activities were observed by petioles and heads in lower maturation stage (PGS 2 and PGS 4/5, respectively), as contrast to bracts and achenes with higher potential in more advanced stages of maturation (PGS between 5 and 8) (Mandim et al., 2021a; Mandim et al., 2021b; Mandim et al., 2020d; Mandim et al., 2022a). Achenes extracts were those with lowest IC_{50} values, therefore higher antioxidant potential, compared to the other plant organs studied, namely bracts, capitula, petioles, and blades (Mandim et al., 2022a).

Petropoulos et al. (2018a) reported a promising activity for achenes extracts compared to other plant organs, namely flowers and leaf blades. Mandim et al. (2020a) separated cardoon achenes into viable and non-viable through “float-testing”, showing that the viable achenes exhibited higher antioxidant potential when compared to non-viable ones (Mandim et al., 2020a). Significant differences between achenes (Mandim et al., 2022a) and inflorescences (Dias et al., 2018) were also reported. Ramos et al. (2014) evaluated the different constituents of the cardoon heads and described higher activities for the receptacle and bracts. These observations revealed the antioxidant potential of different cardoon plant organs, especially its achenes. Exploration of the bioactive compounds responsible for the activities observed would be an important area of future investigation aiming to unveil the mechanisms involved.

Also, genotypes have been shown to influence the antioxidant potential of the species. Their proper characterization allows the selection of the most promising samples (Dias et al., 2018). Extraction methodologies also showed an influence on the antioxidant potential. Cardoon head extracts obtained by ultrasound-assisted extraction (UAE) demonstrated higher DPPH (IC_{50} = 0.91 mg/mL) and ABTS radical scavenging activity (2.08 mg Trolox equivalents/g fw), in comparison to infusion (Kollia et al., 2017). The influence of thermal cooking on the cardoon stalks was also reported. Juániz et al. (2017) observed an increase in DPPH radical scavenging activity in samples subjected to thermal processes (*i.e.*, frying and griddling). The authors suggested that heat treatment destroys the cell walls, favoring the release of phenolic compounds and consequently increasing the antioxidant activity. In contrast, Huarte et al. (2021a) did not detect significant differences in DPPH antioxidant capacity in blanched and fried cardoon stalks compared to non-treated samples, although they observed a decrease in ABTS antioxidant capacity. The described studies showed that many factors may affect the antioxidant potential of *C. cardunculus*. Exploration and optimization of procedures and variables to determine which conditions ensure the highest potential is extremely important.

Most studies suggested the existence of a positive correlation between antioxidant activity and phenolic compounds content. Many authors described higher activity for samples with higher content of phenolic compounds (Dias et al., 2018; Mandim et al., 2020a; Mandim et al., 2021a; Mandim et al., 2022c; Petropoulos et al., 2018a). Contrarily to what was reported in the literature, a negative correlation was described for petioles samples by Mandim et al. (2021b), suggesting that other molecules could be involved in the observed activity.

4.2. Antimicrobial activity

The number of microorganisms that are multi-resistant to existing therapies is increasing, resulting in infections with limited therapeutic possibilities. This problem causes concern and a higher demand for novel molecules with antimicrobial activity. The composition of plants contains an infinite number of bioactive compounds. If properly explored, they can be used as a source of molecules with antimicrobial capacity and attain an excellent strategy to solve this public health problem (Chang et al., 2022).

Cardoon has proved to be a promising source of compounds capable of inhibiting bacteria and fungi growth (Dias et al., 2018; Ferro et al., 2018; Mandim et al., 2022d; Petropoulos et al., 2018b). As shown in Table 3, the different plant organs of cardoon, as well as the achenes oil, have demonstrated the ability to inhibit the growth of microorganisms, even though this capacity can be determined by different conditions. Mandim et al. (2020a) evaluated the influence of achenes viability and found that non-viable ones had higher antibacterial potential, with values of minimum inhibitory concentrations (MIC) similar to the positive control used, sodium benzoate. This finding suggested that cardoon achenes could be a promising source of compounds for this specific purpose. The state of maturation has a significant influence on the antimicrobial potential of cardoon. Organs such as heads, achenes, bracts, and blades with PGS between 5 and 8 exhibited higher antibacterial and antifungal potential (Mandim et al., 2021a; Mandim et al., 2020d; Mandim et al., 2022a; Mandim et al., 2022c). On the other hand, petioles showed higher antibacterial potential for samples harvested at PGS 2, however, none of the tested samples demonstrated a significative antifungal activity (Mandim et al., 2021b). Scavo et al. (2018) tested aqueous, methanolic, and ethanolic extracts of cardoon leaves against eleven Gram-positive and Gram-negative bacteria, with the ethanolic extract exhibiting the best results. Significant activities were also described by Petropoulos et al. (2019) who studied the methanolic extracts of achenes from different cardoon genotypes. The assayed extracts had higher or similar antibacterial activity than control compounds (streptomycin and ampicillin).

Compounds such as phenolic acids, flavonoids, and tannins play plant defense functions against invading agents such as microorganisms, pathogens, and insects (Noman et al., 2021). Thus, several authors have associated the antimicrobial potential of cardoon with its phenolic composition, especially luteolin and 5-*O*-caffeoylquinic acid content (Fig. 2) (Barbosa et al., 2020; Ferraz et al., 2022; Mandim et al., 2022b). However, so far this relationship has not been fully proven, and further studies are needed. The antimicrobial activity of cynaropicrin was also studied. Its potential to inhibit the growth of *Bacillus cereus*, *Pseudomonas aeruginosa*, and methicillin-resistant *Staphylococcus aureus*

Table 3
List of the microorganisms tested with *C. cardunculus* extracts.

Part used	Extract	Microorganism	Main results		Reference
			Disc diffusion (cm)	MIC (mg/mL)	
Inflorescences	MeOH/H_2O, 80:20	*Escherichia coli* ESBL		20 – >20	Dias et al., 2018
		Escherichia coli		20 – >20	
		Klebsiella pneumoniae		20 – >20	
		Klebsiella pneumoniae ESBL		20 – >20	
		Morganella morganii		10 – >20	
		Pseudomonas aeruginosa		10 – >20	
		Enterococcus faecalis		10 – 20	
		Listeria monocytogenes		2.5 – 10	
		MRSA		10 – >20	
		MSSA		5 – >20	
Achenes	MeOH/H_2O, 80:20	*Bacillus cereus*		0.01 – 0.01	Petropoulos et al., 2019
		Staphylococcus aureus		0.015 – 0.20	
		Listeria monocytogenes		0.075 – 0.20	
		Escherichia coli		0.075 – 0.30	
		Enterobacter cloacae		0.075 – 0.20	
		Salmonella Typhimurium		0.075 – 0.45	
		Aspergillus fumigatus		0.05 – 0.30	
		Aspergillus ochraceus		0.075 – 0.20	
		Aspergillus niger		0.10 – 0.30	
		Penicillium funiculosum		0.075 – 0.30	
		Penicillium ochrochloron		0.04 – 0.45	
		Penicillium verrucosum var. *cyclopium*		0.05 – 0.45	
Achenes	MeOH/H_2O, 80:20	*Staphylococcus aureus*		2 – 4	Mandim et al., 2020a
		Bacillus cereus		0.5 – 2	
		Listeria monocytoegenes		1	
		Escherichia coli		1 – 2	
		Salmonella enterica ser. Thyphimurium		2 – 4	
		Enterobacter cloacae		2	
		Aspergillus niger		4	
		Aspergillus versicolor		4	
		Penicillium funiculosum		4	
		Penicillium aurantiogriseum		8 – >8	
		Penicillium ochrochloron		8	
		Trichoderma viride		4	
Capitula	EtOH/H_2O, 80:20	*Bacillus cereus*		0.38 – 1.75	Mandim et al., 2020d
		Staphylococcus aureus		0.59 – 3.49	
		Listeria monocytogenes		1–17 – 3.49	
		Enterobacter cloacae		0.59 – 3.49	
		Escherichia coli		1.18 – 3.075	
		Salmonella Typhimurium		0.59 – 3.49	
		Aspergillus fumigatus		0.51 – 4.08	
		Aspergillus versicolor		0.26 – 6.03	
		Aspergillus niger		0.51 – 9.32	
		Penicillium funiculosum		0.51 – 6.03	
		Penicillium ochrochloron		0.51 – 1.51	
		Penicillium verrucosum var. *cyclopium*		0.51 – 6.03	
Bracts	EtOH/H_2O, 80:20	*Bacillus cereus*		0.81 – 3.37	Mandim et al., 2021a
		Staphylococcus aureus		1.58 – 4.73	
		Listeria monocytogenes		1.61 – 3.37	
		Enterobacter cloacae		1.61 – 4.73	
		Escherichia coli		0.87 – 3.22	
		Salmonella Typhimurium		1.58 – 4.73	
		Aspergillus fumigatus		0.52 – 4.22	
		Aspergillus versicolor		0.26 – 1.75	
		Aspergillus niger		0.525 – >9	
		Penicillium funiculosum		0.27 – 6.24	
		Penicillium ochrochloron		0.52 – 1.75	
		Penicillium verrucosum var. *cyclopium*		0.27 – 6.24	
Achenes	EtOH/H_2O, 80:20	*Bacillus cereus*		0.80 – 1.60	Mandim et al., 2022a
		Staphylococcus aureus		0.80 – 3.21	
		Listeria monocytogenes		1.60 – 3.21	
		Enterobacter cloacae		0.80 – 3.21	
		Escherichia coli		0.80 – 3.21	
		Salmonella Typhimurium		0.80 – 3.21	
		Aspergillus fumigatus		0.51 – 0.89	
		Aspergillus versicolor		0.27 – 0.89	
		Aspergillus niger		1.02 – 1.77	
		Penicillium funiculosum		0.51 – 1.06	
		Penicillium ochrochloron		0.51 – 1.77	
		Penicillium verrucosum var. *cyclopium*		0.51 – 3.55	
Petioles	EtOH/H_2O, 80:20	*Bacillus cereus*		0.75 – 2.39	Mandim et al., 2021b
		Staphylococcus aureus		1.51 – 6.84	
		Listeria monocytogenes		1.51 – 4.78	

(*continued on next page*)

Table 3 (*continued*)

Part used	Extract	Microorganism	Main results		Reference
			Disc diffusion (cm)	MIC (mg/mL)	
Blades	EtOH/H_2O, 80:20	*Enterobacter cloacae*		1.15 – 4.61	Mandim et al., 2022d
		Escherichia coli		0.75 – 4.61	
		Salmonella Typhimurium		1.51 – 6.75	
		Aspergillus fumigatus		0.28 – 3.71	
		Aspergillus versicolor		0.50 – 1.86	
		Aspergillus niger		0.54 – >9.12	
		Penicillium funiculosum		0.52 – >9	
		Penicillium ochrochloron		0.52 – 5.62	
		Penicillium verrucosum var. *cyclopium*		0.30 – >8.05	
		Bacillus cereus		0.43 – 3.57	
		Staphylococcus aureus		0.77 – 3.27	
		Listeria monocytogenes		0.58 – 3.63	
		Enterobacter cloacae		0.81 – 3.63	
		Escherichia coli		0.77 – 3.48	
		Salmonella Typhimurium		0.77 – 3.55	
		Aspergillus fumigatus		0.54 – 4.84	
		Aspergillus versicolor		0.39 – 3.69	
		Aspergillus niger		0.58 – >9.68	
		Penicillium funiculosum		0.39 – 1.83	
		Penicillium ochrochloron		0.3 – 1.92	
		Penicillium verrucosum var. *cyclopium*		0.51 – 1.86	
Leaves	Dichloromethane	*Bacillus cereus*		256 – 2048	Ferro et al., 2018
		Pseudomonas aeruginosa		2048	
		MRSA		256–2048	
Leaves	H_2O, MeOH, EtOH	*Bacillus cereus*	0.7 – 1.3		Scavo et al., 2018
		Bacillus megaterium	0.8 – 2.3		
		Bacillus subtilis	0.4 – 0.8		
		Escherichia coli	No inhibition		
		Listeria innocua	0.8 – 1.2		
		Pseudomonas fluorescens	0.7		
		Pseudomonas syringae pv. *tomato*	0.6 – 1.2		
		Rhodoccoccus fascians	0.6 – 1.2		
		Salmonella enterica	No inhibition		
		Staphylococcs aureus	0.7 – 1.1		
		Xanthomonas perforans	0.4 – 1.5		
Achenes oil	*n*-Hexane	*Staphylococcus aureus*	1.5		Khaldi et al., 2021
		Enterococcus faecalis	1.6		
		Escherichia coli	1.0		
Leaves	H_2O extract in silver nanoparticles	*Escherichia coli*	0.77		Ruíz-Baltazar et al., 2018
		Staphylococcus aureus	0.81		

(MRSA) bacteria was demonstrated at concentrations of 256, 2048, and 256 μg/mL, respectively (Ferro et al., 2018). Ruíz-Baltazar et al. (2018) prepared silver nanoparticles by a green biosynthetic procedure where the reduction of silver ions was performed using an aqueous extract of cardoon leaves. The obtained nanoparticles were tested against *S. aureus* and *Escherichia coli* and remarkable antibacterial responses were found. The authors concluded that cardoon leaves has a high potential for the synthesis of silver nanoparticles through biological routes and also a potential application in biomedicine (Ruíz-Baltazar et al., 2018).

In general, Gram-positive bacteria demonstrated higher susceptibility to cardoon extracts when compared to Gram-negative ones. This difference could be due to the characteristics of bacterial membranes. Gram-negative bacteria have a cell wall of lipopolysaccharides that can protect against the penetration and accumulation of the compounds in the membranes of target cells (Dias et al., 2018; Mandim et al., 2020a; Mandim et al., 2020d).

More recently, this species has been explored as a food preservative in active food packaging. Mazzaglia et al. (2018) evaluated its effect on microbiological reduction and increased shelf life of eggplant-based burgers and found a significant reduction in bacterial growth in burgers with 3% cardoon.

4.3. Cytotoxicity

The cytotoxicity of cardoon has been evaluated by several authors and is compiled in Table 2. Various studies have described that cardoon did not present toxicity to non-tumor cells (Mandim et al., 2020d; Mandim et al., 2022a; Petropoulos et al., 2018b). On the contrary, for tumor cell lines cytotoxicity potential was demonstrated; genotype (Petropoulos et al., 2019), stage of maturation, and plant organ (Mandim et al., 2022d) seemed to influence this potential. According to literature data, heads, bracts, blades and petioles at intermediate stages of maturation (PGS between 5 and 6/7) (Mandim et al., 2021a; Mandim et al., 2020b, Mandim et al., 2021b; Mandim et al., 2022d), and achenes of more advanced ones (PGS 8) (Mandim et al., 2022a) are those with the highest cytotoxic potential. Ethanol extracts from bracts and petioles stood out with lower cell growth inhibition (GI$_{50}$) values, and therefore superior cytotoxic potential, against the cervical carcinoma cell line (HeLa) (Mandim et al., 2021a; Mandim et al., 2021b). On the other hand, cardoon heads showed a higher ability to inhibit cell proliferation of lung cancer cell line (NCI-H460), with GI$_{50}$ values of 69 μg/mL (Mandim, Petropoulos, Giannoulis, Dias, et al., 2020d). For their part, the achenes presented a higher capacity to inhibit hepatocellular carcinoma (HepG2) the blades were more effective against breast carcinoma (MCF-7), with GI$_{50}$ of 97 and 8 μg/mL, respectively (Mandim et al., 2022a; Mandim et al., 2022d). Recently, Fuhr et al. (2022) reported cytotoxic and apoptotic properties for extracts from cardoon leaves, finding that they directly affected the circadian clock of colorectal cancer cells (HCT116). Thus, a lipophilic extract of cardoon leaves interfered with the central clock of gene expression, circadian oscillations, and genes involved in cancer proliferation and metastasis.

Cynaropicrin has been in the focus of scientific interest because of its multiple bioactive properties, including anti-tumor activity (Ferro et al., 2018; Lepore et al., 2019). Russo et al. (2017) evaluated the effect of a hydro methanolic extract of the aerial parts of cardoon on leukemic K562 cells viability. They identified cynaropicrin as the compound responsible for the downregulation of oncoprotein kinase ($p210^{BCR/ABL}$), involved in the gene translation associated with chronic myeloid leukemia. Its antiproliferative potential was also evidenced by Ferro et al. (2018) testing it against a human breast cancer cell line (MDA-MB-123) and obtained an IC_{50} value of 4.89 μg/mL. Still lower values were obtained for the flower's lipophilic extracts (ranging 9.91 and 27.54 μg/mL). Antiproliferative potential of lipophilic extracts from leaves and florets of cardoon, as well as cynaropicrin and taraxasteryl acetate were tested (Ramos et al., 2017). Leaves showed greater ability to inhibit cell proliferation and together with cynaropicrin increased the expression of G2 mitosis checkpoint proteins. The results pointed to cynaropicrin as the compound responsible for the observed antiproliferative activity, although further studies are required to better understand if other molecules are also involved in this effect (Ramos et al., 2017).

Cardoon organs are equally rich in caffeoylquinic acids. Pandino et al. (2013a) stated that this class of bioactive compounds has a great ability to prevent tumor formation due to its capacity to inhibit the formation of reactive oxygen species (ROS). Several authors have tried to correlate the cytotoxic activities observed with the chemical composition, but more studies are needed to ascertain whether a correlation exists.

4.4. Anti-inflammatory

The inflammatory process is the immune system's response to various types of stimuli, namely toxic compounds, external agents such as pathogens, and damaged cells. An uncontrolled inflammatory process can lead to the development of chronic inflammatory diseases. Research has been carried out in order to identify substances that can minimize the expression of inflammatory mediators like nitric oxide (NO), prostaglandin E2 (PGE 2), tumor necrosis factor (TNF-α), and interleukins (IL 1β, IL-6, IL-8) [65]. Cardoon's anti-inflammatory potential has been demonstrated in several studies and through different methodologies. The study of the influence of the maturation stage showed that the capitula (Mandim et al., 2020d), bracts (Mandim et al., 2021a), and petioles (Mandim et al., 2021b) at PGS 5 demonstrated higher ability to inhibit NO formation in RAW 264.7 murine macrophages cells stimulated with lipopolysaccharide (LPS). On the other hand, blades and achenes presented higher potential at more advanced stages of maturation, PGS 7/8 and 8, respectively (Mandim et al., 2022a; Mandim et al., 2022d). An aqueous extract of the dried leaves was applied in a model of colitis induced by 2,4,6-trinitrobenzenesulfonic acid in mice in the search for new pharmacological approaches for the inflammatory bowel disease treatment. The authors proved the extract's ability to reduce the TNF-α levels and extraintestinal manifestations related to it (Mateus et al., 2021). These results are in agreement with those reported by Speciale et al. (2022) that evaluated the *in vitro* potential of an extract of cardoon leaves against acute intestinal inflammation induced by TNF-α in Caco-2 cells. The extract was found to counteract pro-inflammatory effects, suppressing NF-κB and activating Nrf2 pathways. The authors pointed chlorogenic acid as the compound responsible for the observed effects (Speciale et al., 2022). However, other studies suggested cynaropicrin as the anti-inflammatory agent responsible for the anti-inflammatory effect, namely through its ability to suppress the pro-inflammatory NF-κB pathway (Elsebai et al., 2016).

Huarte et al. (2021b) evaluated the anti-inflammatory activity of raw and cooked *sous-vide* cardoon on intestinal (differentiated CaCo-2) and colon (HT-29) cell lines. Raw cardoon exhibited capacity to inhibit inflammation caused by lipopolysaccharides in differentiated CaCo-2 cells, while *sous-vide* cooked caused pro-inflammatory effects. The authors considered that these differences could be related to a higher bioaccessibility and absorption of polyphenols in *sous-vide* cooked when compared to raw cardoon. No anti-inflammatory activity on HT-29 cells was, however, observed for any of these preparations (Huarte et al., 2021b).

Chitosan films enriched with a leaves 5% ethanolic extract, obtained by ultrasonic-assisted extraction, showed a reduction of 86% in IL-6 cytokine levels in normal human skin fibroblasts (Bj5-ta cells) stimulated with LPS compared to non-treated cells; an effect that was attributed to cynaropicrin (Brás et al., 2020c). Based on the obtained results, the authors suggested the possibility of incorporation of these extracts into wound dressings for healing of chronic lesions.

Despite the existing studies, to the best of the authors' knowledge, the actual bioactive compounds and mechanisms involved in the anti-inflammatory potential of cardoon have not yet been adequately established, so that further research is required to ascertain these effects.

4.5. Other relevant bioactivities

In addition to the bioactivities described above, more recent studies have demonstrated properties such as antidiabetic, anti-HIV, anti-hemorrhoidal, cardiotonic, and choleretic (Conceição et al., 2018; Kollia et al., 2017; Ramos et al., 2017; Silva et al., 2022). Cardoons' wide variety of bioactive compounds is making it a promising raw material able to open new areas of investigation and permit the exploration of new bioactivities.

Cardoon infusions demonstrated anti-diabetic activity, with anti-glucose, anti-hyperglycemic, and anti-glycation effects in diabetic rats (Kuczmannová et al., 2016). Although the mechanism associated with these effects remains unknown, consumption of cardoon preparations as supplements has been suggested for patients with diabetes. Falé et al. (2014) reported a decrease in cholesterol levels in persons ingesting cardoon infusions. The evaluation of these infusions through *in vitro* assays demonstrated their ability to inhibit the activity of HMG-CoA reductase. The dicaffeoylquinic acid cynarine, rutin, and chlorogenic acid have been proposed as the potential compounds responsible for this activity (Falé et al., 2014). The antithrombotic activity of lipophilic extracts from cardoon leaves was also evaluated (Ferro et al., 2018). Although the ability to inhibit thrombin has been proven, the results obtained were very variable, which suggest a possible influence of the genetic information of the species (Ferro et al., 2018). Cardoon also showed potential as a bioherbicide (Scavo, Pandino, et al., 2019b). Scavo et al. (2020b) evaluated the phytotoxicity of ethanol extracts from cardoon leaves, finding that they complete inhibit seed germination of four weeds common in the Mediterranean Basin, *i.e.*, *Amaranthus retroflexus* L., *Portulaca oleracea* L., *Stellaria media* (L.) Vill., and *Anagallis arvensis* L.

5. Food and feed applications

5.1. Food

Cardoon is widely used in regional dishes in Mediterranean countries. This crop is used in various soup and salad recipes (Conceição et al., 2018; Gominho et al., 2018). Several authors emphasized its rich chemical composition and considered cardoon as a functional food. Considering its nutritional and therapeutic potential, together with its high adaptability and production yield, its proper exploitation and application would be of extreme importance to consumers (Elsebai et al., 2016; Gominho et al., 2018; Ierna et al., 2020). One of the best-known applications of cardoon is its use in goat and sheep cheese production. Its flowers have been used since ancient times as vegetable rennet which gives cheeses a creamy consistency, a characteristic aroma, and a slightly spicy flavor. Such cheeses are typically produced on an artisanal scale and marketed under the protected designation of origin (PDO) status (Conceição et al., 2018; Gominho et al., 2018). Some examples are the PDO cheeses of Azeitão, Évora, Nisa, Serra da Estrela, and Serpa, produced in Portugal; Flor de Guía, La Serena, Los Ibores, Los Pedroches, Torta del Casar, or Casar de Cáceres from Spain, and Cacioiore, Cacioricota, Cacio Fiore, or Fiore Sardo in Italy (Almeida & Simões, 2018; Conceição et al., 2018).

Cardoon flowers have a rich composition in coagulating enzymes with activity similar to mammal chymosin and pepsin, enzymes commercially used in the cheese industry. Aspartic proteinases such as cardosins A-H, kinarase, and cyprosins 1–3 have been identified (Conceição et al., 2018). Cardosins A and B are the main enzymes responsible for the observed clotting activity, demonstrating similar activity and specificity compared to the commercially used ones (Almeida & Simões, 2018; Barbosa et al., 2020). Cardosin A is responsible for the hydrolysis of k-casein, and cardosin B for proteolysis (Barbosa et al., 2020; Gominho et al., 2018). These coagulation enzymes are extracted from dried styles and stigmas using water in a mortar during a variable extraction time (Conceição et al., 2018). The enzymatic coagulation of milk is one of the most crucial steps in cheese production. This process can be divided into two steps: the enzymatic phase, with the neutralization of milk proteins, formed by casein micelles with a negatively charged end, kappa-casein; and the micellar aggregation phase with the casein micelles forming aggregates and generating a three-dimensional gel network, resulting in the curd formation (Fig. 3) (Almeida & Simões, 2018; Conceição et al., 2018).

Although cardoon flowers have been used as coagulants since ancient times, their properties and influence on cheese's characteristics have been subject of study recently. Thus, cardoon flower enzymatic extracts have been extensively assessed for their impact on biochemical, sensory, and texture features of cheese products, and their activities compared with other coagulant agents. Sensorial properties of cheeses produced with cardoon have been associated to the more pronounced proteolysis when compared to animal rennet (Almeida & Simões, 2018). The coagulant activity of the plant, production yield, and cheese characteristics are influenced by factors such as genotype, maturation stage, moisture content, and drying time (Almeida & Simões, 2018; Amira et al., 2018; Barracosa et al., 2018b; Barracosa et al., 2018a; Gomes et al., 2019). Different cardosin profiles were observed for samples from different ecotypes, leading to the production of cheeses with different sensorial attributes (Barracosa et al., 2018b; Barracosa et al., 2018a). Characteristics such as proteolytic (PA) and milk clotting (MCA) capacities are essential to obtain cheese with appropriate sensorial and rheological features (Gomes et al., 2019). Different enzymes demonstrate different proteolytic activity and selectivity to peptide bonds. According to Amira et al. (2017a) this could be attributed to the presence of only four cardosins (A, E, G, and H) in flowers collected in Tunisia. The authors suggest that the absence of other types of cardosins reduces the release and accumulation of peptides and therefore the excessive proteolytic activity. This excessive activity is responsible for bitter taste and defects in cheese texture (Amira et al., 2017a). Manufacturing conditions (*i.e.,* temperature, pH, and thermal stability) also influence final product features (Amira et al., 2017b). Amira et al. (2017c) varied the pH of the rennet between 3 and 6 and observed an increase in the MCA/PA ratio for a pH value of 3. The complete characterization of the enzymatic activity of cardoon flowers is important for cardosin profile standardization and to obtain cheeses with higher acceptance characteristics. The optimization of the application on an industrial scale is an important area of research since it would contribute to increasing the economic value of the species and the income of the producing countries.

Despite the great attention given to cardoon in cheese production, several authors have praised the potential of its by-products as green fodder for animal feed. It has been reported that this green forage has a high nutritional value with high protein, fiber, and energy contents, as well as a high digestibility coefficient (Barbosa et al., 2020). Furthermore, several studies have reported that the harvest of cardoon rosettes of leaves in winter did not interfere with the growth cycle of the plant species (Barracosa et al., 2019). The solid residue resultant from the oil achenes extraction was also pointed out as promising for animal feed (Cabiddu et al., 2019; Gominho et al., 2018; Zumbo et al., 2022). Petropoulos et al. (2018b) described this by-product as a high-value one and a valuable source of fatty acids and bioactive compounds. The seed cake exhibited higher antioxidant capacity and also higher total phenol content when compared with the achenes and achenes oil (Petropoulos, Fernandes, et al., 2018b). Zumbo et al. (2022) included press cake cardoon in pigs' diets and observed a decrease in intra-muscular fat and lower monounsaturated fatty acid content, while the untreated pigs presented higher contents of polyunsaturated fatty acids. Although the information is scarce, some studies describe this by-product as suitable for animal feed in order to obtain quality products with potential health benefits for consumers, owing to the reduction of unsaturated fatty acids content and phenolic compounds significant concentration (Cabiddu et al., 2019).

The use of achenes oil cakes in biodegradable and edible plastics production for application in the food and agricultural industries have also been investigated as a strategy to replace petroleum-based plastics (Mirpoor et al., 2021). The exploitation of cardoon in this sense would be extremely interesting and an additional way of valuing the crop, while contributing to the circular economy and to new environmentally friendly technologies development. Despite the diverse potential that has been demonstrated, further studies are needed to assess the effectiveness of the above-expressed applications, as well as the environmental impacts associated with their exploitation for livestock applications (Barbosa et al., 2020; Gominho et al., 2018).

5.2. Pharmaceutic and cosmetic potential

Cardoon-based preparations have been used in traditional medicine since the 4th century (Conceição et al., 2018). This specie demonstrates

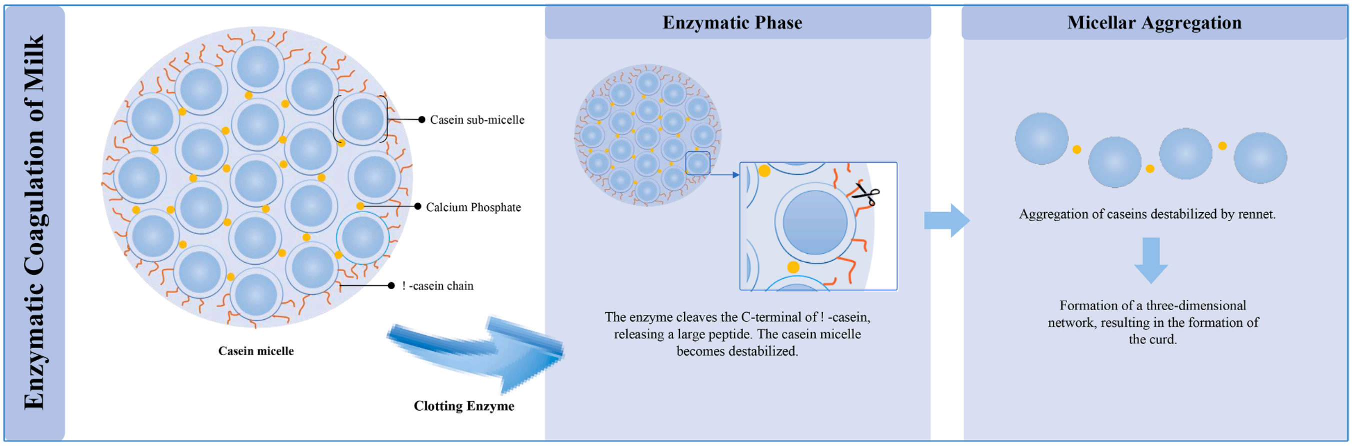

Fig. 3. Scheme of the enzymatic coagulation of milk. *Self-authored scheme.*

cardiotonic, antidiabetic, choleretic, and antihemorrhagic effects (Conceição et al., 2018; Silva et al., 2022; Zayed et al., 2020). Cardoon leaves are the most popular and explored part of the plant. Despite the wide variety of compounds with pharmacological properties of interest, their appropriate exploration and application are still very scarce (Conceição et al., 2018). Implementing and optimizing environmentally friendly extraction and purification processes, reducing costs, and ensuring the obtainment of compounds of interest are important areas of study (Brás et al., 2020b; Vergara et al., 2018). Given the close relationship between the *altilis* and *scolymus* varieties, an overlap of information exists regarding their usage (Conceição et al., 2018; Zayed et al., 2020). Actually, the majority of the preparations found in the market are based on globe artichoke. Cardoon, in turn, has been used as a supplement constituent to improve liver function (Borroni et al., 2021). The proper pharmaceutical exploitation of this species is still a lowly explored area but with significant potential.

The search for new cosmeceutical ingredients with specific pharmacological properties (*i.e.*, antioxidants, anti-inflammatory, anti-cancer, anti-hyperpigmentation, and ultraviolet protectors) is also a current area of research (Yahya et al., 2018). Despite the information regarding the cosmetic application of cardoon being very scarce (Barbosa et al., 2020), its achenes oil has been used in the cosmetic industry, namely to produce body oils and creams. To the best of the authors' knowledge, the cosmetic potential of cardoon has not yet been properly explored. Taking into account the above reported findings, the possible exploitation of cardoon as a source of compounds of cosmeceutical interest is becoming an important and promising alternative.

5.3. *Bioenergy*

One of the current challenges for Europe and the world is to increase renewable energy sources and reduce greenhouse gas emissions (Mauromicale et al., 2019). This has been of crucial importance resulting in an increase in the number of studies on applications of plant species in the energy sector. In addition to all the known uses and potentials associated with *C. cardunculus* L., the low maintenance cost, large-scale availability, and high yield in lignocellulosic biomass have enhanced its consideration as an interesting raw material for energy production (Mauromicale et al., 2019). This species produces a significant amount of biomass from the second year. Studies that have been carried out described different yields, strongly influenced by the soil and climatic conditions (Gominho et al., 2018). Ierna et al., (2020) verified that higher biomass yields was obtained in hilly areas. The available studies were mainly developed in Portugal, Spain, and Italy and describe yields between 10 t ha^{-1} and 30 t ha^{-1}. Associated with its production yield, chemical composition, bioactive properties, and applicability in several industrial sectors are crucial factors for the growing interest for the species. Studies carried out in recent decades have shown the high commercial potential of cardoon as an energy crop, boosting the industrial interest associated with this species (Barracosa et al., 2019). The evaluation of their production costs compared to other herbaceous species showed lower cultivation cost per hectare and better crop performance (Mehmood et al., 2017). Applications including direct combustion and bioethanol, biomethane, and bio-oil production have already been explored (Gominho et al., 2018; Mauromicale et al., 2019).

Besides its high productivity, low moisture, high lignocellulosic contents, and high heat capacity make this species suitable for its application as a solid fuel. Similarly, characteristics such as the high content of polysaccharides and the low content of lignin are making cardoon a good raw material for the production of biomethane through anaerobic digestion (Gominho et al., 2018). Menna et al. (2016) did not observe significant differences in biomethane productivity by using pretreatment with catalytic enzymes but just a marginal saving in terms of feedstock consumption. However, the treatment with NaOH and the decrease in biomass size seemed to have a positive effect on the production yield. Pesce et al. (2017) reinforced the importance of *C. cardunculus* for biomethane production by comparing the yields of *altilis* and *sylvestris* varieties. The latter was less productive both in terms of biomass (11.8 t dry matter per hectare per year compared to 16.8 and 19.1 for the varieties 'Altilis 41′ and 'Bianco Avorio', respectively), and the amount of biomethane produced (2867 Nm^3 compared to 4074 and 4162 Nm^3 for the 'Altilis 41′ and 'Bianco Avorio' varieties, respectively) (Pesce et al., 2017).

Cardoon biomass has also been exploited for bioethanol production. Bioethanol seems a suitable alternative to oil-based liquid fuels, but the costs are still higher than those of non-renewable energy resources. Lignocellulosic biomass consists of cell walls, containing cellulose and hemicellulose structures combined with lignin, proteins, starch, and inorganic compounds (Espada et al., 2021; Mauromicale et al., 2019). Different pre-treatment methodologies can be applied to release those constituents. Temperature, pH, and biomass concentrations are some variables that could influence the process. The reason why its optimization to obtain better results and yields is important (Fernandes et al., 2018). Although steam explosion and dilute acid hydrolysis pretreatments resulted in increased accessibility of polysaccharides to enzymatic hydrolysis and therefore higher fermentation efficiency, bioethanol fermentation with simultaneous saccharification still provides better results (Fernandes et al., 2018). Studies concerning the influence of the pretreatment processes are still scarce. As so the environmental impact associated with those processes should be taken into consideration and further studied (Espada et al., 2021). Recently, Espada et al. (2021) explored the efficiency of three different biomass pretreatments (*i.e.*, dilute acid, steam explosion, and steam explosion combined with alkaline extraction) on bioethanol production from cardoon, concluding that steam explosion provided the best results in terms of reduction of the environmental impact, lower energy demands and greenhouse gas emissions.

Although cardoon seed oil can be used for human consumption, its application in biodiesel production has also been explored. Its transesterification results in biodiesel with characteristics that meet those defined by European standards (EN14214), except for the content of fatty acid metallic esters (FAME) and cetane number (Martínez et al., 2014). According to Alexandre et al. (2012), the transesterification process through two synthesis reactions improves the FAME content into values accepted by the EN14214 standard, as well as the biodiesel yield (from 21% to 50%). Despite the great potential that cardoon has demonstrated as a bioenergy crop, the authors report that several conditions can interfere with the yield associated with their application as a bioenergetic crop. Variables such as climatic and cultivation conditions, as well as genotype can influence yield and bioenergetic properties (Gominho et al., 2018; Mauromicale et al., 2019).

5.4. *Paper pulp*

The pulp and paper industries mostly use woody plants, which contributes significantly to the large wood consumption. Non-woody fibrous plants have been explored as sources of cellulose fibers. Cardoon biomass has a rigid structure and is widely known for its cellulose microfibers, protected by a lignin and hemicellulose network. As a result of its high fiber composition, cardoon has been widely used in the production of pulp and paper (Gominho et al., 2018; Vergara et al., 2018). The existing studies are based on the implementation and optimization of efficient, and profitable delignification methodologies, making cellulose accessible and removing lignin and hemicellulose. Most of these described studies use stems with or without leaves. Gominho et al. (2009) also evaluated the potential of hair and pappi, obtaining high pulp yields, 63% and 48%, respectively. Their high cellulose content makes them a promising raw material for fiber and pulp products. To reduce dispersion and recover pappi, an approach has been explored and wetting has been suggested as a strategy, since about 52.8 kg/ha of pappi could be recovered from the soil (Pari et al., 2017).

Abrantes et al. (2007) studied several delignification processes, namely conventional kraft, kraft-anthraquinone (AQ), and soda-AQ, and obtained promising results for the kraft-AQ process using 20% AQ, in terms of better degree of delignification, pulp viscosity, and sieved yield. The obtained cardoon fibers exhibited similar characteristics to eucalyptus fibers, used as a reference, demonstrating suitable characteristics for the manufacture of paper (Abrantes et al., 2007). For their part, Vergara et al. (2018) optimized the ethanol–water method, through a Taguchi experimental design, for the fractionation of cardoon, and observed that temperature was the only statistically significant variable. They obtained the highest yields for an extraction time of 60 min, with a solid/liquid ratio of 20 L/Kg, ethanol at 0.25 L/L, and a temperature of 190 °C. Pre-hydrolysis with sulfuric acid (1.28%) and stem explosion before cooking were also tested as a way to stimulate the disruption of parenchyma cells (Lourenço et al., 2017). Despite the different methodologies and conditions that have been studied so far, the pulps obtained by the distinct approaches exhibited the appropriate properties for the paper industry. More studies should be, however, explored in order to implement more efficient and environmentally friendly methodologies.

6. Conclusions

The main purpose of this review was to update the recent progresses about chemical composition of cardoon and its bioactive and industrial potential. In addition to its well-known characteristics as a perennial crop, fully adapted to adverse environmental conditions, high yield, applicability, and low cultivation costs, further knowledge on its characterization and exploitation are subjects of great interest. Cardoon has shown massive potential both for its rich chemical composition and nutritional value and its applicability in the energy, cosmetic, and pharmacological sectors. One of the main challenges associated with the vast potential demonstrated by cardoon is to study in more detail the influence that different factors may have on its yield, chemical composition and, consequently, applicability. The transfer of knowledge to several industrial sectors will allow the full exploitation of the multifaceted potential associated with this species. Further studies about the influence that aspects such as geographic location, stage of maturation, environmental conditions, and genetic information, among others, may have on its potential are extremely important. The acquired knowledge will be crucial for this crop proper application, and economical valorization.

CRediT authorship contribution statement

Filipa Mandim: Writing – original draft. **Celestino Santos-Buelga:** Writing – review & editing. **Isabel C.F.R. Ferreira:** Writing – review & editing. **Spyridon A. Petropoulos:** Writing – review & editing. **Lillian Barros:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

The authors are grateful to the Foundation for Science and Technology (FCT; Portugal) for financial support through national funds FCT/MCTES (PIDDAC) to CIMO (UIDB/00690/2020 and UIDP/00690/2020) and SusTEC (LA/P/0007/2021), for the F. Mandim PhD grant (SFRH/BD/146614/2019) and L. Barros contracts through individual and institutional scientific employment program contracts. GIP-USAL is funded by Junta de Castilla y León (Spain) through Project SA093P20 and the Strategic Research Program for Units of Excellence (ref. CLU-2018-04).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodchem.2023.136275.

References

Abrantes, S., Amaral, M. E., Costa, A. P., & Duarte, A. P. (2007). *Cynara cardunculus* L. alkaline pulps: Alternatives fibres for paper and paperboard production. *Bioresource Technology, 98*(15), 2873–2878. https://doi.org/10.1016/j.biortech.2006.09.052

Alexandre, A. M. R. C., Dias, A. M. A., Seabra, I. J., Portugal, A. A. T. G., de Sousa, H. C., & Braga, M. E. M. (2012). Biodiesel obtained from supercritical carbon dioxide oil of *Cynara cardunculus* L. *The Journal of Supercritical Fluids, 68*, 52–63. https://doi.org/10.1016/j.supflu.2012.03.012

Almeida, C. M., & Simões, I. (2018). Cardoon-based rennets for cheese production. *Applied Microbiology and Biotechnology, 102*(11), 4675–4686. https://doi.org/10.1007/s00253-018-9032-3

Amira, A. B., Bauwens, J., De Pauw, E., Besbes, S., Attia, H., Francis, F., & Blecker, C. (2017a). Identification of proteins from wild cardoon flowers (*Cynara cardunculus* L.) by a proteomic approach. *Journal of Chemical Biology, 10*(1), 25–33. https://doi.org/10.1007/s12154-016-0161-9

Amira, A. B., Blecker, C., Richel, A., Arias, A. A., Fickers, P., Francis, F., … Attia, H. (2018). Influence of the ripening stage and the lyophilization of wild cardoon flowers on their chemical composition, enzymatic activities of extracts and technological properties of cheese curds. *Food Chemistry, 245*, 919–925. https://doi.org/10.1016/j.foodchem.2017.11.082

Amira, A. B., Makhlouf, I., Flaviu Petrut, R., Francis, F., Bauwens, J., Attia, H., … Blecker, C. (2017c). Effect of extraction pH on techno-functional properties of crude extracts from wild cardoon (*Cynara cardunculus* L.) flowers. *Food Chemistry, 225*, 258–266. https://doi.org/10.1016/j.foodchem.2017.01.040

Amira, B. A., Besbes, S., Attia, H., & Blecker, C. (2017b). Milk-clotting properties of plant rennets and their enzymatic, rheological, and sensory role in cheese making: A review. *International Journal of Food Properties, 20*, S76–S93. https://doi.org/10.1080/10942912.2017.1289959

Aware, C. B., Patil, D. N., Suryawanshi, S. S., Mali, P. R., Rane, M. R., Gurav, R. G., & Jadhav, J. P. (2022). Natural bioactive products as promising therapeutics: A review of natural product-based drug development. *South African Journal of Botany, 1–17*. https://doi.org/10.1016/j.sajb.2022.05.028

Barbosa, C. H., Andrade, M. A., Vilarinho, F., Castanheira, I., Fernando, A. L., Loizzo, M. R., & Sanches Silva, A. (2020). A new insight on cardoon: Exploring new uses besides cheese making with a view to zero waste. *Foods, 9*(5), Article 564. https://doi.org/10.3390/foods9050564

Barracosa, P., Barracosa, M., & Pires, E. (2019). Cardoon as a sustainable crop for biomass and bioactive compounds production. *Chemistry & Biodiversity, 16*(12), Article e1900498.

Barracosa, P., Oliveira, J., Barros, M., & Pires, E. (2018b). Morphological evaluation of cardoon (*Cynara cardunculus* L.): Assessing biodiversity for applications based on tradition, innovation and sustainability. *Genetic Resources and Crop Evolution, 65*(1), 17–28. https://doi.org/10.1007/s10722-017-0579-0

Barracosa, P., Rosa, N., Barros, M., & Pires, E. (2018a). Selected cardoon (*Cynara cardunculus* L.) genotypes suitable for PDO cheeses in mediterranean regions. *Chemistry & Biodiversity, 15*(7), e1800110.

Borroni, M., Pozzi, C. M., Daniotti, S., Gatto, F., & Re, I. (2021). Multi-criteria decision-making approach for nutraceuticals greener applications: The *Cynara cardunculus* case study. *Sustainability, 13*(23), Article 23. https://doi.org/10.3390/su132313483

Brás, T., Neves, L. A., Crespo, J. G., & Duarte, M. F. (2020a). Effect of extraction methodologies and solvent selection upon cynaropicrin extraction from *Cynara cardunculus* leaves. *Separation and Purification Technology, 236*, Article 116283. https://doi.org/10.1016/j.seppur.2019.11628

Brás, T., Neves, L. A., Crespo, J. G., & Duarte, M. F. (2023). Advances in sesquiterpene lactones extraction. *TrAC Trends in Analytical Chemistry, 158*, Article 116838. https://doi.org/10.1016/j.trac.2022.116838

Brás, T., Paulino, A. F. C., Neves, L. A., Crespo, J. G., & Duarte, M. F. (2020b). Ultrasound assisted extraction of cynaropicrin from *Cynara cardunculus* leaves: Optimization using the response surface methodology and the effect of pulse mode. *Industrial Crops and Products, 150*, Article 112395. https://doi.org/10.1016/j.indcrop.2020.112395

Brás, T., Rosa, D., Gonçalves, A. C., Gomes, A. C., Alves, V. D., Crespo, J. G., … Neves, L. A. (2020c). Development of bioactive films based on chitosan and *Cynara cardunculus* leaves extracts for wound dressings. *International Journal of Biological Macromolecules, 163*, 1707–1718. https://doi.org/10.1016/j.ijbiomac.2020.09.109

Cabiddu, A., Contini, S., Gallo, A., Lucini, L., Bani, P., Decandia, M., … Sulas, L. (2019). *In vitro* fermentation of cardoon seed press cake—A valuable byproduct from biorefinery as a novel supplement for small ruminants. *Industrial Crops and Products, 130*, 420–427. https://doi.org/10.1016/j.indcrop.2018.12.095

Castro, M. M., Rosa, D., Ferro, A. M., Faustino, A., Paulino, A., Brás, T., … Marum, L. (2021). Genetic diversity and population structure of *Cynara cardunculus* L. Southern Portugal. *PLOS ONE, 16*(6), Article e0252792.

Chang, R. Y. K., Nang, S. C., Chan, H.-K., & Li, J. (2022). Novel antimicrobial agents for combating antibiotic-resistant bacteria. *Advanced Drug Delivery Reviews, 187*, Article 114378. https://doi.org/10.1016/j.addr.2022.114378

Colla, G., Rouphael, Y., Cardarelli, M., Svecova, E., Rea, E., & Lucini, L. (2012). Effects of saline stress on mineral composition, phenolic acids and flavonoids in leaves of artichoke and cardoon genotypes grown in floating system. *Journal of the Science of Food and Agriculture, 93*(5), 1119–1127. https://doi.org/10.1002/jsfa.5861

Conceição, C., Martins, P., Alvarenga, N., Dias, J., Lamy, E., Garrido, L., Gomes, S., Freitas, S., Belo, A., Brás, T., Paulino, A., & Duarte, M. F. (2018). *Cynara cardunculus*: Use in Cheesemaking and Pharmaceutical Applications. In N. Koca (Ed.), *Technological Approaches for Novel Applications in Dairy Processing*. InTech. https://doi.org/10.5772/intechopen.76530.

de Faria, E. L. P., Gomes, M. V., Cláudio, A. F. M., Freire, C. S. R., Silvestre, A. J. D., & Freire, M. G. (2018). Extraction and recovery processes for cynaropicrin from *Cynara cardunculus* L. using aqueous solutions of surface-active ionic liquids. *Biophysical Reviews, 10*(3), 915–925. https://doi.org/10.1007/s12551-017-0387-y

Dias, M. I., Barros, L., Barreira, J. C. M., Alves, M. J., Barracosa, P., & Ferreira, I. C. F. R. (2018). Phenolic profile and bioactivity of cardoon (*Cynara cardunculus* L.) inflorescence parts: Selecting the best genotype for food applications. *Food Chemistry, 268*, 196–202. https://doi.org/10.1016/j.foodchem.2018.06.081

Elsebai, M., Mocan, A., & Atanasov, A. (2016). Cynaropicrin: A comprehensive research review and therapeutic potential as an anti-hepatitis C virus agent. *Frontiers in Pharmacology, 7*. https://www.frontiersin.org/articles/10.3389/fphar.2016.00472.

Espada, J. J., Villalobos, H., & Rodríguez, R. (2021). Environmental assessment of different technologies for bioethanol production from *Cynara cardunculus*: A life cycle assessment study. *Biomass and Bioenergy, 144*, Article 105910. https://doi.org/10.1016/j.biombioe.2020.105910

Falé, P., Ferreira, C., Rodrigues, A. M., Frazão, F. N., & Serralheiro, M. L. M. (2014). Studies on the molecular mechanism of cholesterol reduction by *Fraxinus angustifolia*, *Peumus boldus*, *Cynara cardunculus* and *Pterospartum tridentatum* infusions. *Journal of Medicinal Plants Research, 8*(1), 9–17. https://doi.org/10.5897/JMPR2013.5273

Ferioli, F., & D'Antuono, L. F. (2022). Phenolic compounds in local Italian types of cultivated cardoon (*Cynara cardunculus* L. var. *altilis* DC) stalks and artichoke (*Cynara cardunculus* L. var. *scolymus* L.) edible sprouts. *Journal of Food Composition and Analysis*, *106*, 104342. https://doi.org/10.1016/j.jfca.2021.104342.

Fernandes, M. C., Ferro, M. D., Paulino, A. F. C., Chaves, H. T., Evtuguin, D. V., & Xavier, A. M. R. B. (2018). Comparative study on hydrolysis and bioethanol production from cardoon and rockrose pretreated by dilute acid hydrolysis. *Industrial Crops and Products, 111*, 633–641. https://doi.org/10.1016/j.indcrop.2017.11.037

Ferraz, A. R., Pintado, C. M. B. S., & Serralheiro, M. L. (2022). Influence of *Cynara cardunculus* L. Phenolic compounds on *Pseudomonas putida* isolated from the dairy industry: Growth and melanin bioproduction. *Applied Sciences, 12*(7), Article 7. https://doi.org/10.3390/app12073629

Ferro, A. M., Ramos, P., Guerra, Â., Parreira, P., Brás, T., Guerreiro, O., … Gonçalves, S. (2018). Haplotype analysis of the germacrene A synthase gene and association with cynaropicrin content and biological activities in *Cynara cardunculus*. *Molecular Genetics and Genomics, 293*(2), 417–433. https://doi.org/10.1007/s00438-017-1388-z

Fuhr, L., Basti, A., Brás, T. S., Duarte, M. F., & Relógio, A. (2022). Antiproliferative Effects of *Cynara Cardunculus* in colorectal cancer cells are modulated by the circadian clock. *International Journal of Molecular Sciences, 23*(16), Article 16. https://doi.org/10.3390/ijms23169130

Garcia-Oliveira, P., Barral, M., Carpena, M., Gullón, P., Fraga-Corral, M., Otero, P., … Simal-Gandara, J. (2021). Traditional plants from Asteraceae family as potential candidates for functional food industry. *Food & Function, 12*(7), 2850–2873. https://doi.org/10.1039/D0FO03433A

Gomes, S., Belo, A. T., Alvarenga, N., Dias, J., Lage, P., Pinheiro, C., … Martins, A. P. L. (2019). Characterization of *Cynara cardunculus* L. flower from Alentejo as a coagulant agent for cheesemaking. *International Dairy Journal, 91*, 178–184. https://doi.org/10.1016/j.idairyj.2018.09.010

Gominho, J., Curt, M. D., Lourenço, A., Fernández, J., & Pereira, H. (2018). *Cynara cardunculus* L. as a biomass and multi-purpose crop: A review of 30 years of research. *Biomass and Bioenergy, 109*, 257–275. https://doi.org/10.1016/j.biombioe.2018.01.001

Gominho, J., Lourenço, A., Curt, M., Fernández, J., & Pereira, H. (2009). Characterization of hairs and pappi from *Cynara cardunculus* capitula and their suitability for paper production. *Industrial Crops and Products, 29*(1), 116–125. https://doi.org/10.1016/j.indcrop.2008.04.022

Gominho, J., Lourenço, A., Curt, M., Fernández, J., & Pereira, H. (2014). *Cynara cardunculus* in large scale cultivation. A case study in Portugal. *Chemical Engineering Transactions, 37*, 529–534. https://doi.org/10.3303/CET1437089

Gominho, J., Lourenço, A., Palma, P., Lourenço, M. E., Curt, M. D., Fernández, J., & Pereira, H. (2011). Large scale cultivation of *Cynara cardunculus* L. for biomass production—A case study. *Industrial Crops and Products, 33*(1), 1–6. https://doi.org/10.1016/j.indcrop.2010.09.011

Graziani, G., Docimo, T., Palma, M. D., Sparvoli, F., Izzo, L., Tucci, M., & Ritieni, A. (2020). Changes in phenolics and fatty acids composition and related gene expression during the development from seed to leaves of three cultivated Cardoon genotypes. *Antioxidants, 9*(11), E1096. https://doi.org/10.3390/antiox9111096

Huarte, E., Juániz, I., Cid, C., & de Peña, M.-P. (2021a). Impact of blanching and frying heating rate/time on the antioxidant capacity and (poly)phenols of cardoon stalks (*Cynara cardunculus* L. var. *altilis* DC). *International Journal of Gastronomy and Food. Science, 26*, Article 100415. https://doi.org/10.1016/j.ijgfs.2021.100415

Huarte, E., Serra, G., Monteagudo-Mera, A., Spencer, J., Cid, C., & de Peña, M.-P. (2021b). Raw and *Sous-Vide*-cooked red Cardoon stalks (*Cynara cardunculus* L. var. *altilis* DC): (Poly)phenol bioaccessibility, anti-inflammatory activity in the gastrointestinal tract, and prebiotic activity. *Journal of Agricultural and Food Chemistry, 69*(32), 9270–9286. https://doi.org/10.1021/acs.jafc.1c03014

Ierna, A., Sortino, O., & Mauromicale, G. (2020). Biomass, seed and energy yield of *Cynara cardunculus* L. as affected by environment and season. *Agronomy, 10*(10), 1548. https://doi.org/10.3390/agronomy10101548

Juániz, I., Ludwig, I. A., Bresciani, L., Dall'Asta, M., Mena, P., Del Rio, D., Cid, C., & de Peña, M.-P. (2017). Bioaccessibility of (poly)phenolic compounds of raw and cooked cardoon (*Cynara cardunculus* L.) after simulated gastrointestinal digestion and fermentation by human colonic microbiota. *Journal of Functional Foods, 32*, 195–207. https://doi.org/10.1016/j.jff.2017.02.033

Khaldi, S., Naouari, M., & Ben Jemaa, A. (2021). Cardoon (*Cynara cardunculus* L.) oil from cultivated and wild Tunisian populations and its antimicrobial activity. *Industrial Crops and Products, 171*, Article 113852. https://doi.org/10.1016/j.indcrop.2021.113852

Kollia, E., Markaki, P., Zoumpoulakis, P., & Proestos, C. (2017). Antioxidant activity of *Cynara scolymus* L. and *Cynara cardunculus* L. extracts obtained by different extraction techniques. *Natural Product Research, 31*(10), 1163–1167. https://doi.org/10.1080/14786419.2016.1219864

Kuczmannová, A., Balažová, A., Račanská, E., Kameníková, M., Fialová, S., Majerník, J., … Mučaji, P. (2016). *Agrimonia eupatoria* L. and *Cynara cardunculus* L. water infusions: Comparison of anti-diabetic activities. *Molecules, 21*(5), Article 5. https://doi.org/10.3390/molecules21050564

Kumar, B., & Verma, P. (2021). Biomass-based biorefineries: An important architype towards a circular economy. *Fuel, 288*, Article 119622. https://doi.org/10.1016/j.fuel.2020.119622

Kumar, V., Sharma, N., Umesh, M., Selvaraj, M., Al-Shehri, B. M., Chakraborty, P., … Maitra, S. S. (2022). Emerging challenges for the agro-industrial food waste utilization: A review on food waste biorefinery. *Bioresource Technology, 362*, Article 127790. https://doi.org/10.1016/j.biortech.2022.127790

Lepore, S. M., Maggisano, V., Lombardo, G. E., Maiuolo, J., Mollace, V., Bulotta, S., … Celano, M. (2019). Antiproliferative effects of cynaropicrin on anaplastic thyroid cancer cells. *Endocrine, Metabolic & Immune Disorders - Drug Targets, 19*(1), 59–66. https://doi.org/10.2174/1871530318666180928153241

Lopes, D. C. D. X. P., de Oliveira, T. B., Viçosa, A. L., Valverde, S. S., & Ricci Júnior, E. (2021). Anti-inflammatory activity of the compositae family and its therapeutic potential. *Planta Medica, 87*, 71–100. https://doi.org/10.1055/a-1178-5158

Lourenço, A., Gominho, J., Curt, M. D., Revilla, E., Villar, J. C., & Pereira, H. (2017). Steam explosion as a pretreatment of *Cynara cardunculus* prior to delignification. *Industrial & Engineering Chemistry Research, 56*(1), 424–433. https://doi.org/10.1021/acs.iecr.6b03854

Mandim, F., Dias, M. I., Pinela, J., Barracosa, P., Ivanov, M., Stojković, D., … Ferreira, I. C. F. R. (2020a). Chemical composition and *in vitro* biological activities of cardoon (*Cynara cardunculus* L. var. *altilis* DC.) seeds as influenced by viability. *Food Chemistry, 323*, Article 126838. https://doi.org/10.1016/j.foodchem.2020.126838

Mandim, F., Petropoulos, S. A., Dias, M. I., Pinela, J., Kostić, M., Soković, M., … Barros, L. (2021b). Phenolic composition and biological properties of *Cynara cardunculus* L. var. *altilis* petioles: Influence of the maturity stage. *Antioxidants, 10*(12), 1907. https://doi.org/10.3390/antiox10121907

Mandim, F., Petropoulos, S. A., Dias, M. I., Pinela, J., Kostic, M., Soković, M., … Barros, L. (2021a). Seasonal variation in bioactive properties and phenolic composition of cardoon (*Cynara cardunculus* var. *altilis*) bracts. *Food Chemistry, 336*, Article 127744. https://doi.org/10.1016/j.foodchem.2020.127744

Mandim, F., Petropoulos, S. A., Fernandes, Â., Santos-Buelga, C., Ferreira, I. C. F. R., & Barros, L. (2020b). Chemical composition of *Cynara Cardunculus* L. var. *altilis* heads: The impact of harvesting time. *Agronomy, 10*(8), 1088. https://doi.org/10.3390/agronomy10081088

Mandim, F., Petropoulos, S. A., Giannoulis, K. D., Dias, M. I., Fernandes, Â., Pinela, J., … Ferreira, I. C. F. R. (2020d). Seasonal variation of bioactive properties and phenolic composition of *Cynara cardunculus* var. *altilis*. *Food Research International, 134*, Article 109281. https://doi.org/10.1016/j.foodres.2020.109281

Mandim, F., Petropoulos, S. A., Giannoulis, K. D., Santos-Buelga, C., Ferreira, I. C. F. R., & Barros, L. (2020c). Chemical composition of *Cynara cardunculus* L. var. *altilis* bracts cultivated in central Greece: The Impact of Harvesting Time. *Agronomy, 10*(12), 1976. https://doi.org/10.3390/agronomy10121976

Mandim, F., Petropoulos, S. A., Pinela, J., Dias, M. I., Giannoulis, K. D., Kostić, M., … Barros, L. (2022a). Chemical composition and biological activity of cardoon (*Cynara cardunculus* L. var. *altilis*) seeds harvested at different maturity stages. *Food Chemistry, 369*, Article 130875. https://doi.org/10.1016/j.foodchem.2021.130875

Mandim, F., Petropoulos, S. A., Pinela, J., Dias, M. I., Kostic, M., Soković, M., … Barros, L. (2022d). Phenolic composition and antioxidant, anti-inflammatory, cytotoxic, and antimicrobial activities of Cardoon blades at different growth stages. *Biology, 11*(5), 699. https://doi.org/10.3390/biology11050699

Mandim, F., Petropoulos, S. A., Santos-Buelga, C., Ferreira, I. C. F. R., & Barros, L. (2022b). Chemical composition of cardoon (*Cynara cardunculus* L. var. *altilis*) petioles as affected by plant growth stage. *Food Research International, 156*, Article 111330. https://doi.org/10.1016/j.foodres.2022.111330

Mandim, F., Petropoulos, S. A., Santos-Buelga, C., Ferreira, I. C. F. R., & Barros, L. (2022c). Effect of harvesting time on the chemical composition of *Cynara cardunculus* L. var. *altilis* blades. *Agronomy, 12*(7), 1705. https://doi.org/10.3390/agronomy12071705

Martínez, G., Sánchez, N., Encinar, J. M., & González, J. F. (2014). Fuel properties of biodiesel from vegetable oils and oil mixtures. Influence of methyl esters distribution. *Biomass and Bioenergy, 63*, 22–32. https://doi.org/10.1016/j.biombioe.2014.01.034

Mateus, V., Estarreja, J., Silva, I., Barracosa, P., Teixeira-Lemos, E., & Pinto, R. (2021). Effect of *Cynara cardunculus* L. var. *altilis* (DC) in Inflammatory Bowel Disease. *Applied Sciences, 11*(4), 1629. https://doi.org/10.3390/app11041629

Mauromicale, G., Pesce, G. R., Curt, M. D., Fernández, J., González, J., Gominho, J., … Portis, E. (2019). *Cynara cardunculus* as a multiuse crop. In E. Portis, A. Acquadro, & S. Lanteri (Eds.), *The Globe Artichoke Genome* (pp. 65–98). Springer International Publishing. https://doi.org/10.1007/978-3-030-20012-1_4.

Mauromicale, G., Sortino, O., Pesce, G. R., Agnello, M., & Mauro, R. P. (2014). Suitability of cultivated and wild cardoon as a sustainable bioenergy crop for low input cultivation in low quality Mediterranean soils. *Industrial Crops and Products, 57*, 82–89. https://doi.org/10.1016/j.indcrop.2014.03.013

Mazzaglia, A., Licciardello, F., Aurelio, S., Muratore, G., Giovanni, M., & Restuccia, C. (2018). Effect of *Cynara cardunculus* extract on the shelf life of aubergine burgers. *Italian Journal of Food Science, 30*, 19–24.

Mehmood, M. A., Ibrahim, M., Rashid, U., Nawaz, M., Ali, S., Hussain, A., & Gull, M. (2017). Biomass production for bioenergy using marginal lands. *Sustainable Production and Consumption, 9*, 3–21. https://doi.org/10.1016/j.spc.2016.08.003

Melilli, M. G., Costa, C., Lucera, A., Padalino, L., Del Nobile, M. A., & Conte, A. (2021). Fiordilatte Cheese fortified with Inulin from *Cichorium intybus* or *Cynara cardunculus*. *Foods, 10(6), Article 6*. https://doi.org/10.3390/foods10061215

Menna, F. D., Malagnino, R., Vittuari, M., Molari, G., Seddaiu, G., Deligios, P., … Ledda, L. (2016). Potential biogas production from artichoke byproducts in Sardinia. *Italy. Energies, 9*(2), 92. https://doi.org/10.3390/en9020092

Michel, J., Abd Rani, N. Z., & Husain, K. (2020). A review on the potential use of medicinal plants from Asteraceae and Lamiaceae plant family in cardiovascular diseases. *Frontiers in Pharmacology, 11*. https://www.frontiersin.org/articles/10.3389/fphar.2020.00852.

Mirpoor, S. F., Giosafatto, C. V. L., & Porta, R. (2021). Biorefining of seed oil cakes as industrial co-streams for production of innovative bioplastics. A review. *Trends in Food Science & Technology, 109*, 259–270. https://doi.org/10.1016/j.tifs.2021.01.014

Naveed, M., Hejazi, V., Abbas, M., Kamboh, A. A., Khan, G. J., Shumzaid, M., … XiaoHui, Z. (2018). Chlorogenic acid (CGA): A pharmacological review and call for further research. *Biomedicine & Pharmacotherapy, 97*, 67–74. https://doi.org/10.1016/j.biopha.2017.10.064

Noman, A., Aqeel, M., Islam, W., Khalid, N., Akhtar, N., Qasim, M., … Al-sadi, A. (2021). Insects–plants-pathogens: Toxicity, dependence and defense dynamics. *Toxicon, 197*, 87–98. https://doi.org/10.1016/j.toxicon.2021.04.004

Pandino, G., Bonomo, A., Scavo, A., Mauromicale, G., & Lombardo, S. (2022). Caffeoylquinic acids and flavones profile in *Cynara cardunculus* L. seedlings under controlled conditions as affected by light and water-supply treatments. *Scientia Horticulturae, 302*, Article 111180.

Pandino, G., Gattesco, F., Bosisio, S., Lombardo, S., Russo, A., & Mauromicale, G. (2020). Cynaropicrin, total caffeoylquinic acids and flavonoids in leaves of *Cynara cardunculus* (cardoon) forms. *Acta Horticulturae, 1284*, 279–284. https://doi.org/10.17660/ActaHortic.2020.1284.37.

Pandino, G., Lombardo, S., & Mauromicale, G. (2013a). Globe artichoke leaves and floral stems as a source of bioactive compounds. *Industrial Crops and Products, 44*, 44–49. https://doi.org/10.1016/j.indcrop.2012.10.022

Pandino, G., Lombardo, S., Moglia, A., Portis, E., Lanteri, S., & Mauromicale, G. (2015). Leaf polyphenol profile and SSR-based fingerprinting of new segregant *Cynara cardunculus* genotypes. *Frontiers. Plant Science, 5*. https://www.frontiersin.org/articles/10.3389/fpls.2014.00800.

Pandino, G., Lombardo, S., Williamson, G., & Mauromicale, G. (2013b). Flavonoids content of *Cynara cardunculus L.* wild and cultivated germplasm accessions. *Acta Horticulturae, 983*, 81–86. https://doi.org/10.17660/ActaHortic.2013.983.9.

Pappalardo, H. D., Toscano, V., Puglia, G. D., Genovese, C., & Raccuia, S. A. (2020). *Cynara cardunculus* L. as a multipurpose crop for plant secondary metabolites production in marginal stressed lands. *Frontiers. Plant Science, 11*, 240. https://doi.org/10.3389/fpls.2020.00240

Pari, L., Alfano, V., Mattei, P., & Santangelo, E. (2017). Pappi of cardoon (*Cynara cardunculus* L.): The use of wetting during the harvesting aimed at recovering for the biorefinery. *Industrial Crops and Products, 108*, 722–728. https://doi.org/10.1016/j.indcrop.2017.07.037

Pari, L., Alfano, V., Stefanoni, W., Latterini, F., Liuzzi, F., De Bari, I., … Ciancolini, A. (2021). Inulin content in chipped and whole roots of cardoon after six months storage under natural conditions. *Sustainability, 13*(7), Article 7. https://doi.org/10.3390/su13073902

Pesce, G. R., & Mauromicale, G. (2019). *Cynara cardunculus* L.: Historical and economic importance, botanical descriptions, genetic resources and traditional uses. In E. Portis, A. Acquadro, & S. Lanteri (Eds.), *The Globe Artichoke Genome* (pp. 1–19). Springer International Publishing. https://doi.org/10.1007/978-3-030-20012-1_1.

Pesce, G. R., Negri, M., Bacenetti, J., & Mauromicale, G. (2017). The biomethane, silage and biomass yield obtainable from three accessions of *Cynara cardunculus*. *Industrial Crops and Products, 103*, 233–239. https://doi.org/10.1016/j.indcrop.2017.04.003

Petropoulos, S. A., Fernandes, Â., Calhelha, R. C., Danalatos, N., Barros, L., & Ferreira, I. C. F. R. (2018b). How extraction method affects yield, fatty acids composition and bioactive properties of cardoon seed oil? *Industrial Crops and Products, 124*, 459–465. https://doi.org/10.1016/j.indcrop.2018.08.027

Petropoulos, S. A., Pereira, C., Tzortzakis, N., Barros, L., & Ferreira, I. C. F. R. (2018a). Nutritional value and bioactive compounds characterization of plant parts from *Cynara cardunculus* L. (Asteraceae) cultivated in central Greece. *Frontiers. Plant Science, 9*, 459. https://doi.org/10.3389/fpls.2018.00459

Petropoulos, S., Fernandes, Â., Pereira, C., Tzortzakis, N., Vaz, J., Soković, M., … Ferreira, I. C. F. R. (2019). Bioactivities, chemical composition and nutritional value of *Cynara cardunculus* L. seeds. *Food Chemistry, 289*, 404–412. https://doi.org/10.1016/j.foodchem.2019.03.066

Piluzza, G., Molinu, M. G., Re, G. A., & Sulas, L. (2019). Phenolic compounds content and antioxidant capacity in cardoon achenes from different head orders. *Natural Product Research, 34*(14), 2071–2075. https://doi.org/10.1080/14786419.2019.1569009

Ramos, P. A. B., Santos, S. A. O., Guerra, Â. R., Guerreiro, O., Freire, C. S. R., Rocha, S. M., … Silvestre, A. J. D. (2014). Phenolic composition and antioxidant activity of different morphological parts of *Cynara cardunculus* L. var. *Altilis* (DC). *Industrial Crops and Products, 61*, 460–471. https://doi.org/10.1016/j.indcrop.2014.07.042

Ramos, P., Guerra, Â., Guerreiro, O., Santos, S., Oliveira, H., Freire, C., … Duarte, M. (2017). Antiproliferative effects of *Cynara cardunculus* L. var. *altilis* (DC) lipophilic extracts. *International Journal of Molecular Sciences, 18*(63). https://doi.org/10.3390/ijms18010063

Rolnik, A., & Olas, B. (2021). The plants of the *Asteraceae* family as agents in the protection of human health. *International Journal of Molecular Sciences, 22*(6), 3009. https://doi.org/10.3390/ijms22063009

Rossi, R., Picuno, P., Fagnano, M., & Amato, M. (2022). Soil reinforcement potential of cultivated cardoon (*Cynara cardunculus* L.): First data of root tensile strength and density. *Catena, 211*, Article 106016. https://doi.org/10.1016/j.catena.2022.106016

Ruíz-Baltazar, Á. de J., Reyes-López, S. Y., Mondragón-Sánchez, M. de L., Estevez, M., Hernández-Martinez, A. R., & Pérez, R. (2018). Biosynthesis of Ag nanoparticles using *Cynara cardunculus* leaf extract: Evaluation of their antibacterial and electrochemical activity. *Results in Physics, 11*, 1142–1149. https://doi.org/10.1016/j.rinp.2018.11.032

Russo, A., Perri, M., Cione, E., Di Gioia, M. L., Nardi, M., & Cristina Caroleo, M. (2017). Biochemical and chemical characterization of *Cynara cardunculus* L. extract and its potential use as co-adjuvant therapy of chronic myeloid leukemia. *Journal of Ethnopharmacology, 202*, 184–191. https://doi.org/10.1016/j.jep.2017.03.026

Scavo, A., Pandino, G., Restuccia, A., Lombardo, S., Pesce, G. R., & Mauromicale, G. (2019b). Allelopathic potential of leaf aqueous extracts from *Cynara cardunculus* L. on the seedling growth of two cosmopolitan weed species. *Italian Journal of Agronomy, 14*(2), Article 2. https://doi.org/10.4081/ija.2019.1373

Scavo, A., Pandino, G., Restuccia, A., & Mauromicale, G. (2020b). Leaf extracts of cultivated cardoon as potential bioherbicide. *Scientia Horticulturae, 261*, Article 109024. https://doi.org/10.1016/j.scienta.2019.109024

Scavo, A., Pandino, G., Restuccia, C., Parafati, L., Cirvilleri, G., & Mauromicale, G. (2018). Antimicrobial activity of cultivated cardoon (*Cynara cardunculus* L. var. *Altilis* DC.) leaf extracts against bacterial species of agricultural and food interest. *Industrial Crops and Products, 129*, 206–211. https://doi.org/10.1016/j.indcrop.2018.12.005

Scavo, A., Restuccia, A., Abbate, C., & Mauromicale, G. (2019a). Seeming field allelopathic activity of *Cynara cardunculus* L. reduces the soil weed seed bank. *Agronomy for Sustainable Development, 39*(4), 41. https://doi.org/10.1007/s13593-019-0580-4

Scavo, A., Rial, C., Molinillo, J. M. G., Varela, R. M., Mauromicale, G., & Macías, F. A.. (2020a). Effect of shading on the sesquiterpene lactone content and phytotoxicity of cultivated Cardoon leaf extracts. *Journal of Agricultural and Food Chemistry, 68*(43), 11946–11953. https://doi.org/10.1021/acs.jafc.0c03527

Scavo, A., Rial, C., Varela, R. M., Molinillo, J. M. G., Mauromicale, G., & Macias, F. A. (2019c). Influence of genotype and harvest time on the *Cynara cardunculus* L. sesquiterpene lactone profile. *Journal of Agricultural and Food Chemistry, 67*(23), 6487–6496. https://doi.org/10.1021/acs.jafc.9b02313

Silva, L. R., Jacinto, T. A., & Coutinho, P. (2022). Bioactive compounds from Cardoon as health promoters in metabolic disorders. *Foods, 11*(3), 336. https://doi.org/10.3390/foods11030336

Speciale, A., Muscarà, C., Molonia, M. S., Toscano, G., Cimino, F., & Saija, A. (2022). *In vitro* protective effects of a standardized extract from *Cynara cardunculus* L. leaves against TNF-α-Induced intestinal inflammation. *Frontiers in Pharmacology, 13*, Article 809938. https://doi.org/10.3389/fphar.2022.809938

Vergara, P., Ladero, M., García-Ochoa, F., & Villar, J. C. (2018). Valorization of *Cynara Cardunculus* crops by ethanol-water treatment: Optimization of operating conditions. *Industrial Crops and Products, 124*, 856–862. https://doi.org/10.1016/j.indcrop.2018.08.064

Williamson, E. M., Liu, X., & Izzo, A. A. (2020). Trends in use, pharmacology, and clinical applications of emerging herbal nutraceuticals. *British Journal of Pharmacology, 177* (6), 1227–1240. https://doi.org/10.1111/bph.14943

Yahya, N. A., Attan, N., & Wahab, R. A. (2018). An overview of cosmeceutically relevant plant extracts and strategies for extraction of plant-based bioactive compounds. *Food and Bioproducts Processing, 112*, 69–85. https://doi.org/10.1016/j.fbp.2018.09.002

Zayed, A., Serag, A., & Farag, M. A. (2020). *Cynara cardunculus* L.: Outgoing and potential trends of phytochemical, industrial, nutritive and medicinal merits. *Journal of Functional Foods, 69*, Article 103937. https://doi.org/10.1016/j.jff.2020.103937

Zumbo, A., Tardiolo, G., Genovese, C., Sutera, A. M., Raccuia, S. A., & D'Alessandro, E. (2022). Cardoon (*Cynara cardunculus* L. var. *altilis*) seeds presscake: A natural by-product for pigs feeding. *Natural Product Research.*. https://doi.org/10.1080/14786419.2021.1993218