Unravelling Potential Health-Beneficial Properties of Corema album Phenolic Compounds: A Systematic Review

Ana Sofia Cerquido 1, Martin Vojtek 1, Rita Ribeiro-Oliveira 1, Olga Viegas 2,3, Joana Beatriz Sousa 1,* , Isabel M. P. L. V. O. Ferreira 2,* and Carmen Diniz 1,*

1 LAQV/REQUIMTE, Laboratory of Pharmacology, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal
2 LAQV/REQUIMTE, Laboratory of Bromatology and Hydrology, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal
3 Faculty of Nutrition and Food Sciences, University of Porto, 4150-180 Porto, Portugal
* Correspondence: jbsousa@ff.up.pt (J.B.S.); isabel.ferreira@ff.up.pt (I.M.P.L.V.O.F.); cdiniz@ff.up.pt (C.D.)

Abstract: Corema (C.) album belongs to the family Ericaceae and can be found in the Iberian Peninsula, especially on the coastal areas facing the Atlantic coast. C. album berries have been used for centuries in traditional medicine. Recent studies have revealed that not only the berries but also the leaves have relevant antioxidant, antiproliferative, and anti-inflammatory properties, bringing this plant to the forefront of discussion. A systematic review of the literature was carried out to summarize the phenolic compounds and bioactive properties identified in C. album berries and leaves and to search for research gaps on this topic. The search was conducted in three electronic databases (PubMed, SCOPUS, and Web of Science) using PRISMA methodology. The inclusion criteria were the chemical compositions of the berries, leaves, or their extracts and their bioactive properties. The exclusion criteria were agronomic and archaeological research. The number of studies concerning phenolic compounds’ composition and the bioactive properties of C. album berries and leaves is still limited (11 articles). However, the variety of polyphenolic compounds identified make it possible to infer new insights into their putative mechanism of action towards the suppression of NF-kB transcription factor activation, the modulation of inflammatory mediators/enzymes, the induction of apoptosis, the modulation of mitogen activated protein kinase, cell cycle arrest, and the reduction of oxidative stress. These factors can be of major relevance concerning the future use of C. album as nutraceuticals, food supplements, or medicines. Nevertheless, more scientific evidence concerning C. album’s bioactivity is required.

Keywords: plant; natural products; camarinha; antioxidant; polyphenols; anticancer; anti-inflammatory

1. Introduction

Plants as natural medicinal agents have been used since ancient civilizations to treat diseases such as cancer, inflammation, fever, etc. Their value as sources of molecules with therapeutic potential has been recognized and, recently, they have gained much attention in the drug discovery field, since many drugs from natural sources have been emerging, currently constituting up to 50% of all drugs in the pharmaceutical industry [1].

Corema belongs to the family Ericaceae and includes two species: Corema conradii and Corema album. The first is native to the Northwest coast of the USA and the latter can be found in the Iberian Peninsula, especially on the coastal areas facing the Atlantic [2]. In addition, Corema conradii differs from Corema album mainly by its very small fruit that lacks fleshiness and is covered with oily appendages [3]. Both species are coastal shrubs with sexual dimorphism. Concerning Corema album, this plant is a densely branched and long-living shrub with evergreen leaves [4]. While male flowers are bigger and have reddish petals and stamens with red-purple anthers, female flowers are smaller with pink-reddish
petals [5]. Traditionally, the plant itself was also used in the Iberian Peninsula to make rustic brooms [6].

The berries from Corema album have been consumed for many centuries since the Islamic period (either fresh or in jams) and are employed in popular medicine [6,7]. In recent years, several reports have highlighted the health-beneficial properties of Corema album against several diseases, including cancer and neurodegenerative and cardiovascular diseases, and have ascribed most of their beneficial effects to their composition of phenolic compounds. Thus, this review is focused on unravelling the phenolic compounds already identified in Corema album with an emphasis on describing the biological mechanisms and signalling pathways related to their health-beneficial properties.

The species Corema album has two subspecies: Corema album azoricum, which is native to the islands of Azores, and Corema album album (C. album), which is more commonly found on the mainland [2]. The main difference between these two subspecies resides in its area of distribution: Corema album azoricum typically grows on volcanic lava or ash fields whereas C. album is characteristically found in coastal habitats [4].

C. album is an evergreen wild shrub that grows mainly on sandy soil over coastal dunes and cliffs, reaching a maximum height of 1 m, with numerous branches exhibiting leaves. Along the coast of Portugal, C. album is predominant on the southwest region from Sines to Troia and in the central-north region from Nazaré to Ovar [6]. The flowering of both female and male plants begins in early spring, from February to April [4]. The fruits are produced by the female plants and ripen in early summer (June and July) in the south and a little later (August and September) in the north [6]. The fruits are small, round berries coloured white or pink-white when ripe with an acidic flavour [8].

C. album has been used in traditional medicine and is one of the medicinal plants included in the herbarium of Francesc Bolóis (1773–1844) [9]. It has been described to exhibit beneficial properties against fever and intestinal pinworm infection [6,7], which is in accordance with the reported ability of C. album extracts to prevent oxidative damage [7]. Recently, the composition of each part of C. album has been studied by complementary Raman and infrared techniques, revealing vibrational signatures for the skin (outer and inner) and the seeds with distinct chemical compositions, specifically in its respective content in phenolic derivatives [10,11]. A systematic review of the literature was carried out to summarize the phenolic compounds and bioactive properties identified in C. album berries and leaves and to search for research gaps in this topic.

2. Methods
2.1. Search Strategy

PRISMA methodology was applied by performing a search for publications in three databases, namely, PubMed, SCOPUS, and Web of Science, using the following keywords: (“Corema album” AND (berries OR leaves)). The collection of papers was performed up to 15 June 2022. A total of 74 publications were identified after compiling all three databases. Duplicates, reviews, and opinion articles (n = 40) were removed.

2.2. Inclusion and Exclusion Criteria

The two authors of this publication independently screened the titles and abstracts of the 34 remaining articles. Inclusion criteria were studies focusing on chemical composition of berries, leaves, or their extracts and their bioactive properties. Exclusion criteria were agronomic and archaeological studies. Then, the full texts of eligible articles were carefully studied by all authors and the relevant data concerning phenolic compounds identified, C. album samples (berries, leaves, and extracts), and the bioactive properties studied were collected. In all steps, disagreements were resolved by meeting all authors and deciding on the inclusion or exclusion of the articles together.
3. Results

3.1. Literature Search Process

From the 74 records identified, only 34 remained for the title and abstract screening. The remaining reports were duplicated articles, reviews, or opinion articles (Figure 1). Then, 21 articles were excluded based on the title and abstract reviews because these studies involved agronomic or archaeological studies and did not include the chemical composition of the berries, leaves, or of the respective extracts. The remaining 13 papers proceeded to the full text review. From those, only 11 were about phenolic compounds’ identification in *C. album*; thus, they were considered eligible for the data extraction [7,10–19].

![Flowchart summarizing the literature selection process according to PRISMA methodology.](image-url)

3.2. Phenolic Compounds in Berries and Leaves from *C. album*

Both berries and leaves from *C. album* revealed a rich content in several phenolic compounds, which are summarized in Tables 1 and 2, respectively. The phenolic compounds were divided into three main groups, namely, phenolic acids, flavonoids, and stilbenes, according to their structural similarities. Phenolic acids are commonly divided into two groups: the benzoic acids (C6-C1) with seven carbon atoms and cinnamic acids (C6-C3) with nine carbon atoms. Usually, these compounds occur predominantly in their hydroxylated forms: hydroxybenzoic and cinnamic acids, respectively. Flavonoids present...
a basic structure with 15 carbon atoms distributed by two aromatic rings linked by a three-carbon chain (C₆-C₃-C₆). Stilbenes are known to display a structure with two aromatic rings linked by an ethene bridge.

### Table 1. Phenolic compounds identified in *C. album* Berries.

| Group                  | Sub-Group                   | Compound                      | General Structure | Ref. |
|------------------------|-----------------------------|--------------------------------|------------------|------|
| PHENOLIC ACIDS         |                             | Benzoic acid                   | ![Benzoic acid](image) | [12] |
|                        |                             | Salicilic acid                 | ![Salicilic acid](image) | [12] |
|                        |                             | Tannic acid                    | ![Tannic acid](image) | [13] |
|                        | Hydroxibenzoic acids        | p-hydroxybenzoic acid (R₁=R₂=R₃=H) and derivatives | ![p-hydroxybenzoic acid](image) | [7,10–12,14] |
|                        |                             | Vanillic acid (R₁=R₂=H; R₃=OCH₃) | ![Vanillic acid](image) |      |
|                        |                             | Protocatechuic acid (R₁=H; R₂=OH) | ![Protocatechuic acid](image) |      |
|                        |                             | Syringic acid (R=H; R₁=R₂=OCH₃) | ![Syringic acid](image) |      |
|                        |                             | Gallic acid (R=H; R₁=R₂=OH)    | ![Gallic acid](image) |      |
|                        | Hydroxicinnamic acids       | p-coumaric acid (R₁=R₂=H)      | ![p-coumaric acid](image) | [7,12,14] |
|                        |                             | Sinapic acid (R₁=R₂=OCH₃)      | ![Sinapic acid](image) |      |
|                        |                             | Ferulic acid (R₁=R₂=H; R₃=OCH₃) and derivatives (R₁=R₂=H; R₃=OHexose) | ![Ferulic acid](image) |      |
|                        |                             | Caffeic acid and derivatives    | ![Caffeic acid](image) |      |
|                        |                             | Chlorogenic acid (R₁=R₂=H; R₃=Caffeic acid) | ![Chlorogenic acid](image) | [7,14–16] |
|                        |                             | Neochlorogenic acid (R₁=R₂=H; R₃=Caffeic acid) | ![Neochlorogenic acid](image) |      |
|                        |                             | Cryptochlorogenic acid (R₁=R₂=R₃=H; R₄=Caffeic acid) | ![Cryptochlorogenic acid](image) |      |
### Table 1. Cont.

| Group       | Sub-Group | Compound | General Structure | Ref.       |
|-------------|-----------|----------|-------------------|------------|
| Phenolic    |           | Kaempferol (R₁=R₂=R₃=R₄=OH; R₅=R₆=H) and derivatives: | ![Kaempferol](image) | [7,14-16] |
|             |           | - i.e., Kaempferol 3-O-galactoside (R₅=galactose) | ![Kaempferol 3-O-galactoside](image) |             |
|             |           | - i.e., Kaempferol 3-O-glucoside (R₅=glucose) | ![Kaempferol 3-O-glucoside](image) |             |
|             |           | Quercetin (R=R₁=R₂=R₃=OH; R₄=R₅=H) and derivatives: | ![Quercetin](image) | [7,15,16] |
|             |           | - i.e., Quercetin 3-O-glucoside (R₅=glucose) | ![Quercetin 3-O-glucoside](image) |             |
|             |           | - i.e., Quercetin 3-O-arabinoside (R₅=arabinose) | ![Quercetin 3-O-arabinoside](image) |             |
|             |           | - i.e., Quercetin 3-O-galactoside (R₅=galactose) | ![Quercetin 3-O-galactoside](image) |             |
|             |           | - i.e., Quercetin 3-O-rhamnoside (R₅=rhamnose) | ![Quercetin 3-O-rhamnoside](image) |             |
|             |           | Rutin (R₊R₁=R₂=R₃=OH; R₄=H; R₅=glucopyranose) | ![Rutin](image) |             |
|             |           | Myricetin (R=R₁=R₂=R₃=OH; R₄=H; R₅=OH) and derivatives: | ![Myricetin](image) | [7,15,16] |
|             |           | - i.e., Myricetin 3-O-arabinoside | ![Myricetin 3-O-arabinoside](image) |             |
|             |           | - i.e., Myricetin 3-O-glucoside (R=R₁=R₂=R₃=OH; R₄=H; R₅=O-glucose) | ![Myricetin 3-O-glucoside](image) |             |
|             |           | Catechin (R=R₁=R₂=R₃=R₄=R₅=OH) and derivatives | ![Catechin](image) | [15] |
|             |           | Procyanidin (R=H, n=1) and derivatives: | ![Procyanidin](image) | [15] |
|             |           | - i.e., Procyanidin Dimer type A (R=H, n=2) | ![Procyanidin Dimer type A](image) |             |
|             |           | pinocembrin | ![Pinocembrin](image) | [7] |
|             |           | 6-geranylnaringenin | ![6-Geranylnaringenin](image) | [7] |
|             |           | Cyanidin (R₁=R₂=OH; R₃=R₄=R₅=R₆=H) and derivatives | ![Cyanidin](image) | [7] |
|             |           | - i.e., Cyanidin 3-O-glucoside (R₅=glucose) | ![Cyanidin 3-O-glucoside](image) |             |
|             |           | - i.e., Cyanidin 3-O-arabinoside (R₅=arabinose) | ![Cyanidin 3-O-arabinoside](image) |             |
|             |           | Delphinidin (R₁=R₂=R₃=R₄=OH; R₅=H) and derivatives: | ![Delphinidin](image) | [7] |
|             |           | - i.e., Delphinidin 3-O-glucoside (R₅=glucose) | ![Delphinidin 3-O-glucoside](image) |             |
|             |           | Anthocyanins | | |
|             |           | Resveratrol (R₁=R₂=H) and derivatives: | ![Resveratrol](image) | [7,15] |
|             |           | - i.e., Pterostilbene (R₁=R₂=CH₃) | ![Pterostilbene](image) |             |
|             |           | - i.e., Stilbene Hexoside (R₂=Hexose) | ![Stilbene Hexoside](image) |             |
### Table 2. Phenolic compounds identified in C. album leaves.

| Group            | Sub-Group                  | Compound | General Structure | Ref. |
|------------------|----------------------------|----------|-------------------|------|
| **PHENOLIC ACIDS** | Hydroxycinnamic acids      | Coumaric acid (R=R$_1$=R$_2$=H) and derivatives: - i.e., Coumaroyl Glucose (R=Glucose) | ![Coumaric acid](image) | [15,16] |
|                  |                            | Catechin (R=R$_1$=R$_2$=R$_3$=R$_4$=R$_5$=OH) and derivatives: - i.e., Catechin 3-O-glucose (R$_3$=Glucose) | ![Catechin](image) | [15,16] |
|                  |                            | Epicatechin (R=R$_1$=R$_2$=OH; R$_3$=R$_4$=H) | ![Epicatechin](image) | [15,16] |
| **FLAVONOIDS**   | Flavanols                  | Myricetin (R=R$_1$=R$_2$=R$_3$=R$_4$=OH; R$_5$=H) and derivatives: - i.e., Myricetin 3-O-galactoside (R$_5$=O-galactose) | ![Myricetin](image) | [15,16] |
|                  |                            | Myricetin 3-O-glucoside (R$_5$=O-glucose) | ![Myricetin glucoside](image) | [15,16] |
|                  |                            | Myricetin 3-O-xyllose (R$_5$=O-xyllose) | ![Myricetin xyllose](image) | [15,16] |
|                  |                            | Myricetin Rhamnosyl Hexoside (R$_5$=O-rhamnose) | ![Myricetin rhamnose](image) | [15,16] |
|                  |                            | Myricetin Methyl ether Hexoside | ![Myricetin methyl ether](image) | [15,16] |
|                  |                            | Kaempferol (R=R$_1$=R$_2$=OH; R$_3$=R$_4$=R$_5$=H) and derivatives: - i.e., Kaempferol Hexoside (R$_5$=Hexose) | ![Kaempferol](image) | [15] |
|                  |                            | Rhamnetin (R=OCH$_3$; R$_1$=R$_2$=R$_3$=OH; R$_4$=R$_5$=H) and derivatives: - i.e., Rhamnetin Hexoside (R$_5$=Hexose) | ![Rhamnetin](image) | [16] |
|                  | Flavones or Flavonols      | Quercetin (R=R$_1$=R$_2$=R$_3$=OH; R$_4$=R$_5$=H) and derivatives: - i.e., Quercetin 3-O-glucoside (R$_5$=glucose) | ![Quercetin glucoside](image) | [15,16] |
|                  |                            | Quercetin 3-O-galactoside (R$_5$=galactose) | ![Quercetin galactose](image) | [15,16] |
|                  |                            | Quercetin Rhamnosyl Hexoside (R$_5$=Rhamnosyl Hexose) | ![Quercetin rhamnose](image) | [15,16] |
|                  |                            | Methyl-quercetin hexoside (R$_5$=Hexose) | ![Methyl-quercetin hexoside](image) | [15,16] |
|                  |                            | Rutin (R= R$_1$= R$_2$=R$_3$=OH; R$_4$=H; R$_5$=glucopyranose) | ![Rutin](image) | [15,16] |
|                  |                            | Pinocembrin | ![Pinocembrin](image) | [18] |
|                  | Stilbenes and derivatives  |          | ![Stilbenes](image) | [15,16] |
Moreover, and in accordance with previously described features [20], natural phenolic acids, free or conjugated, can also appear as amides or esters whereas natural flavonoids, free or conjugated, are often esterified to one or two sugar molecules (by one or more hydroxyl groups).

In *C. album* leaves, another three predominant compounds were identified: 2′,4′-dihydroxydihydrochalcone, 2′-methoxy-4′-hydroxydihydrochalcone [17], and 2′,4′-dihydroxychalcone [18] (Figure 2). These compounds are chalcones, which are intermediates in the biosynthesis of flavonoids and isoflavonoids [19].

![Figure 2](image-url)

**Figure 2.** Structure of identified chalcones in *C. album*: (A) R = OH, 2′,4′-dihydroxydihydrochalcone, R = OCH₃, 2′-methoxy-4′-hydroxydihydrochalcone; (B) 2′,4′-dihydroxychalcone.

Both the berries and leaves from *C. album* revealed interesting bioactive properties, which are summarized in Figure 3. Scientific information regarding *C. album*’s bioactive activities is very scarce and is mostly focused on the beneficial healthy properties of its berries. *C. album* berries were described to have antimicrobial [11] and antioxidant activities [7,11,14,15]. Moreover, this antioxidant activity seems to be increased after simulated digestion [13] and can protect against oxidative stress (yeast: [13]). *C. album* berries have also been described as having cytotoxic effects in Caco-2 cells when the concentration of the extract exceeds 8% [14]. There is also evidence that these berries are able to inhibit lipid peroxidation and acetylcholinesterase activation [11].

![Figure 3](image-url)

**Figure 3.** Summary of bioactive properties found in the literature for *C. album* berries, leaves, or their extracts.

The bioactivity of *C. album* leaves has been studied regarding its cytotoxicity in yeast [15,20]; colon carcinoma cells (HT-29 cells: [17]), an effect that seems to be mediated through G2/M cell cycle arrest [18,21]; and apoptosis [18]. The cytotoxicity observed was reported to be triggered by the pro-oxidant activity of at least two different hydroxydihydrochalcones found in these leaves [17]. In contrast, a study using an enriched fraction of polyphenols from *C. album* leaves claimed that this extract has promising cytoprotective effects, modulating key events in Parkinson’s disease pathogenesis. Some other reports also describe *C. album* leaves as having antioxidant effects [15,20].
4. Discussion

A wide variety of phenolic compounds were identified in the berries and leaves from <i>C. album</i>, but few studies explore the biological activities and signalling events triggered by their extracts. Nevertheless, their physical–chemical profile and high phenolic content supports a potential market expansion [22]. In particular, their enriched composition in phenolic compounds, both in the berries and leaves, bring valuable insights into their putative mechanism of action. Currently, it is well accepted that phenolic compounds can modulate the activity of several enzymes, kinases, and transcriptional factors involved in the modulation of biological processes such as oxidative stress, inflammation, cell proliferation, apoptosis, and cell death [21,23]. In accordance, the phenolic compounds previously identified in <i>C. album</i> berries and leaves are known to present a modulatory capability in several signalling pathways, signal mediators or enzymes, and/or kinases (Tables 3 and 4). Thus, these mechanisms can be indirectly associated with <i>C. album</i>.

| Compound                  | Protective Mechanisms (s)                                                                 | Experimental Model                  | Ref. |
|---------------------------|-----------------------------------------------------------------------------------------|-------------------------------------|------|
| <p>-hydroxybenzoic acid   | • Inhibits iNOS/NO and COX-2/PGE₂ production.                                            | Mouse macrophages                   | [24] |
|                           | • Suppresses MAPKs, IKK, IκB, and p65 phosphorylation; and p65 nuclear translocation.   |                                     |      |
|                           | • Inhibits IL-1β, IL-6, and TNF-α production.                                            |                                     |      |
|                           | • Downregulates iNOS and COX-2 expression.                                              |                                     |      |
| <p>-coumaric acid         | • Suppresses apoptosis via modulation of MAPK signalling pathway.                       | - Human epithelial cells            |      |
|                           | • Suppresses IL-6 and TNF-α levels                                                    | - Animal models: rheumatoid arthritis rats | [25,26] |
| Ferulic acid              | • Reduces UV-B radiation-induced oxidation.                                             | - Human lymphocytes                 |      |
|                           | • Suppresses NF-κB and MAPK pathways.                                                   | - Bovine endometrial epithelial cells | [27–29] |
|                           | • Inhibits H₂O₂-induced MAPK activation via ROS pathway                                  | - Rat vascular smooth muscle cells  |      |
| Caffeic acid and          | • Reduces mRNA and protein synthesis of TNF-α, IL-6, IL-1β cytokines.                  | - Human cancer cells fibrosarcoma   |      |
| derivatives               | • Induces apoptosis.                                                                     | - Animal model: albino mice (BALB/c) | [30,31] |
| Chlorogenic acid          | • Downregulates LPS-induced COX-2 up-expression.                                        | - Mouse macrophages                 | [32–36] |
|                           | • Inhibits PGE₂, NF-κB, JNK/AP-1 signalling pathway activation.                         |                                     |      |
|                           | • Inhibits production of TNF-α, IL-6, IL-1β, IFN-γ, MIP-1α.                             |                                     |      |
| Neochlorogenic acid       | • Reduces production of TNF-α, IL-1β, IL-6 and NO.                                      | - Human cancer cells: lung          | [37–40] |
|                           | • Inhibits NF-κB activation and blocks MAPK signalling pathway phosphorylation.         | Mouse macrophages                   |      |
|                           | • Increases HO-1 expression via AMPK/Nrf2 signalling pathway activation.                 |                                     |      |
|                           | • Reduces CM-activated IκB/NFκB, STAT3 expression, and Akt/mTOR pathways.                |                                     |      |
| Kaempherol and derivatives| • Upregulates caspase-3 activity.                                                       | - Human cancer cells: brain, breast, stomach, liver, QBC939 (human cholangiocarcinoma) | [41–45] |
|                           | • Induces apoptosis.                                                                    | - HCCC9810 (mice) and (human)       |      |
|                           | • Inhibits cell growth.                                                                  |                                     |      |
|                           | • Induces Cell-cycle arrest at G2/M                                                     |                                     |      |
| Quercetin and             | • Increases apoptosis.                                                                  | - Human cancer cells: breast, liver | [46–50] |
| derivatives               | • Increases cell cycle progression.                                                     |                                     |      |
| Rutin                     | • Inhibits P-glycoprotein expression.                                                   | - Human cancer cells: neuroblastoma | [51–54] |
|                           | • Upregulates p53 and BAX expression.                                                   | - Animal models: Calf lung and muscle cells; |      |
|                           | • Downregulates PDK, PKC, COX-2 and ROS expression.                                     | Albino rats of Wistar strain.        |      |
|                           | • Downregulates hypoxia-induced Nox4.                                                   |                                     |      |
|                           | • Inhibits xanthine oxidase.                                                            |                                     |      |
|                           | • Inhibits lipid peroxidation.                                                          |                                     |      |
|                           | • Induces G2/M cell cycle arrest.                                                       |                                     |      |
|                           | • Increases apoptosis.                                                                  |                                     |      |
Table 3. Cont.

| Compound                  | Protective Mechanisms (s)                                                                                                                                   | Experimental Model                        | Ref.          |
|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|--------------|
| Myricetin and derivatives | • Increases apoptosis through reduction in Bcl-2 and pro-caspase-3 levels and increase in BAX and cleaved caspase-3 levels.  
• Decreases cell proliferation through stimulation of phosphorylation and degradation of YAP.  
• Increases cell cycle arrest.  
• Reduces metastasis. | - Human cancer cells: esophagus, ovary, and liver | [55–58] |
| Cyanidin and derivatives  | • Reduces cell proliferation.  
• Reduces IL-3 and IL-4 by GATA-3 inhibition.  
• Increases apoptosis.  
• Decreases mucin 4 expression.  
• Increases fatty acid oxidation and AMPK activity. | - Human cancer cells: breast, liver, colon, prostate and ovarian.  
- Animal model: Murine thymoma | [59–62] |
| Delphinidin and derivatives | • Inhibits BAX and caspase 3.  
• Increases Bcl-2 protein.  
• Inhibits intracellular ROS generation and Nox1 protein.  
• Normalizes the enzyme activity of SOD, CAT, GSH-PX and MDA levels via increase in nuclear Nrf2 protein.  
• Increases NF-κB and Nrf2 pathways antioxidant response.  
• Inhibits activation of PI3K/Akt/mTOR components and secretion of proinflammatory cytokines and chemokines. | - Human cells (normal): eye, keratinocytes  
- Transformed cell line: human chondrocyte | [63–65] |

Abbreviations: AKT—Protein kinase B; AP-1—Activator protein 1; BAX—Bcl-2-like protein 4; Bcl-2—B-cell lymphoma-2; CAT—Catalase; CM—conditioned medium; COX-2—Cylooxygenase-2; GSH-PX—Glutathione peroxidase; H₂O₂—hydrogen peroxide; HO-1—Heme oxygenase 1; IFN-γ—Interferon γ; IL—Interleukin; iNOS—Inducible nitric oxide synthase; IkB—NF-κB inhibitor; IKK—IkB kinase; JNK—c-Jun N-terminal kinase; IncRNA-MALAT1—Long non-coding RNAs of metastasis associated lung adenocarcinoma transcript 1; LPS—Lipopolysaccharide; MAPK—Mitogen-activated protein kinase; MDA—Malondialdehyde; MIP-1α—Macrophage inflammatory protein-1; mRNA—messenger RNA (ribonucleic acid); mTOR—mammalian target of rapamycin; NF-κB—Nuclear factor kappa-light-chain-enhancer of activated B-cells; NO—Nitric oxide; Nox1—NADPH (nicotinamide adenine dinucleotide phosphate) oxidase 1; Nox4—NADPH (nicotinamide adenine dinucleotide phosphate) oxidase 4; Nrf2—Nuclear factor erythroid factor 2-related factor 2; p53—Tumor protein p53; p65—Nuclear translocation of p65 subunit of NF-κB and NF-κB DNA binding activity; PGE₂—Prostaglandin E2; PI3K—Phosphatidylinositol-3-kinase; PKC—Protein kinase C; ROS—Reactive oxygen species; SOD—Superoxide dismutase; STAT3—Signal transducer and activator of transcription 3; TNF-α—Tumor necrosis factor α; UV-B—Ultraviolet B; YAP—Yes-associated protein.

Note that the phenolic compounds may exert their biological effects through signalling pathways separately or in a sequential way. Moreover, a putative crosstalk between these pathways should not be overlooked.

4.1. Suppression of NF-κB Transcription Factor Activation

The nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) is a transcription factor involved in the regulation of the expression of several genes that are associated with inflammation and carcinogenesis. NF-κB, in the cytosol, is inactive since it is bound to inhibitor kB (IkB) [83]. When IkB is phosphorylated, NF-κB is free to be translocated to the nucleus and can activate genes such as p53, Myc, and other cellular genes [21,83]. Present in C. album berries, neochlorogenic [37,39,40], p-hydroxybenzoic [24], and ferulic [28,29] acids seem to be able to inhibit NF-κB activation. In addition, several flavonols such as catechins [66–69], quercetin rhamnosyl hexose [78–80], myricetin [74,75], procyanidins [72,73] and kaempherol hexoside [76], identified in C. album leaves have been shown to suppress NF-κB transcriptional activity and, thus, can prevent inflammation and carcinogenesis.
Table 4. Protective mechanisms ascribed to phenolic compounds identified in *C. album* leaves.

| Compound                  | Protective Mechanisms (s)                                                                                       | Experimental Model                                                                 | Ref.                  |
|---------------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------|
| Catechin and derivatives  | • Inhibits NF-κB and AP-1.                                                                                      | - Animal studies: mice and rats.                                                    | [66–69]               |
| Epicatechin               | • Inhibits “pro-oxidant” enzymes and induces antioxidant enzymes.                                                | - Animal model: experimental autoimmune myocarditis rats, mouse fibroblasts          |                      |
|                           | • Suppresses inflammatory factors including NF-κB, cytokines and adhesion molecules.                             |                                      |                      |
|                           | • Reduces IL-6, IL-12, IL-1α and IL-1β mRNA expression induced by TNF-α.                                          |                                      |                      |
| Procyanidin and derivatives| • Upregulates expression and activity of antioxidant enzymes via ERK, JNK and p38 MAPK pathways.                | - Human cancer cells: liver                                                         | [70–73]               |
|                           | • Upregulates Nfr2 expression and activates Nfr2 antioxidant response element-mediated transcription via p38 MAPK and PI3K/Akt pathways. |                                      |                      |
|                           | • Downregulates mRNA expression of proinflammatory cytokines such as TNF-α, IL-1β and inflammatory molecules of COX-2. |                                      |                      |
|                           | • Upregulates mRNA expression of IL-10                                                                          |                                      |                      |
|                           | • Suppresses MAPK, AP-1 and NF-κB pathways.                                                                       |                                      |                      |
| Myricetin and derivatives | • Inhibits production of pro-inflammatory mediators (NO, iNOS, PGE2, and COX-2).                                 | - Animal model: mouse macrophage, diabetic cardiomyopathy mice                       | [74,75]               |
|                           | • Decreases NO, iNOS, TNF-α, IL-6 and IL-12 production.                                                           |                                      |                      |
|                           | • Decreases NF-κB activation (suppresses degradation of IkBα, nuclear translocation of p65 subunit of NF-κB and NF-κB DNA-binding activity). |                                      |                      |
|                           | • Attenuates phosphorylation of STAT1 and IFN-β production.                                                       |                                      |                      |
|                           | • Upregulates HO-1 expression through Nrf2 translocation.                                                          |                                      |                      |
| Kaempherol and derivatives| • Suppresses NF-κB pathway by targeting protein-docking sites.                                                    | - Human cancer cells: leukemia                                                      | [76,77]               |
|                           | • Modulates expression of inflammatory cytokines (TNF-α, IL-6, IL-1β and PGE2).                                   |                                      |                      |
|                           | • Modulates phosphorylation of IκBβ and p65.                                                                      |                                      |                      |
|                           | • Inhibits phosphorylation of p38, ERK and JNK                                                                    |                                      |                      |
| Quercetin and derivatives | • Downregulates the expressions of iNOS and IFN-γ                                                               | - Animal model: HFD-induced inflammatory mice, mouse macrophages, male C57BL/6 mice, periodontitis mice | [78–82]               |
|                           | • Attenuates NF-κB-mediated inflammation. (Scavenges ROS, necessary for NF-κB activation, or blocks TNF-α-dependent commencement of nuclear translocation of NF-κB) |                                      |                      |
|                           | • Suppresses MIP-1α-mediated migration/activation of macrophages through downregulation of CCR1/CCR5 production and inhibition of inflammatory signalling activation in macrophages. |                                      |                      |
|                           | • Inhibits MAPKs (ERK and JNK) and transcription factors (NF-κB and AP-1).                                         |                                      |                      |
|                           | • Downregulates mRNA and protein levels of TNF-α, IL-1β, IL-6, iNOS and MIP-1α                                    |                                      |                      |
|                           | • Downregulates microRNA 155 levels, inhibiting NF-κB activation.                                                  |                                      |                      |
|                           | • Reduces IL-1β, TNF-α, IL-17 and intercellular adhesion molecule 1 production                                    |                                      |                      |

Abbreviations: AKT—Protein kinase B; AP-1—Activator protein 1; CCR1—C-C chemokine receptor type 1; CCR5—C-C chemokine receptor type 5; COX-2—Cyclooxygenase-2; ERK—Extracellular signal-regulated kinase; HO-1—Heme oxygenase 1; IFN-β—Interferon β; IFN-γ—Interferon γ; IL—Interleukin; iNOS—Inducible nitric oxide synthase; IκBα—NF-κB inhibitor α; IκBβ—NF-κB inhibitor β; JNK—c-Jun N-terminal kinase; MAPK—Mitogen-activated protein kinase; MIP-1α—Macrophage inflammatory protein-1; mRNA—messenger RNA (ribonucleic acid); NF-κB—Nuclear factor kappa-light-chain-enhancer of activated B-cell; NO—Nitric oxide; Nfr2—Nuclear factor erythroid factor 2-related factor 2; p65—Nuclear translocation of p65 subunit of NF-κB and NF-κB DNA binding activity; PGE2—Prostaglandin E2; PI3K—Phosphatidylinositol-3-kinase; ROS—Reactive oxygen species; STAT1—Signal transducer and activator of transcription 1; TNF-α—Tumor necrosis factor α.
4.2. Modulation of Inflammatory Mediators/Enzymes

All the phenolic acids identified in *C. album* berries present anti-inflammatory properties since they inhibit the production of several interleukins (IL-1β and IL-6) and TNF-α (Table 3). The following activities were reported in the leaves of *C. album*: some polyphenols, such as catechins, were shown to inhibit IL-6, IL-12, and IL-1α; IL-1β, TNF-α production [67,68]; procyanidins, shown to inhibit IL-1β and TNF-α expression [72]; quercetin rhamnosyl hexoside, which decreased the expression of TNF-α, IL-1β, IL-6, and IL-17 [78,81,82]; kaempferol hexoside, which suppressed TNF-α, IL-1β, and IL-6 generation [77]; myricetin, which reduced TNF-α, IL-12, and IL-6 expression [74]; and rhamnetin, which reduced TNF-α, IL-1β, IL-6, and IL-8 generation [84]. In addition, other compounds were identified in the leaves such as chalcone derivatives that inhibited the production of cytokines [85]; isoliquiritigenin and butein that inhibited lipopolysaccharide (LPS)-induced inducible nitric oxide synthase (iNOS); and cyclooxygenase-2 (COX-2) expression [86], contributing to the modulation of inflammation.

In the inflammatory process, enzymes such as COX-2 and xanthine oxidase (XO) play a key role, and their levels of expression are modulated during the inflammation’s progression. The polyphenols identified in the berries of *C. album* were shown to be capable of suppressing/reducing the activity of XO and/or COX-2: through phenolic acids such as chlorogenic [37] or p-hydroxybenzoic [24] acids or by flavonols such as quercetin-3-O-hexoside [48].

4.3. Induction of Apoptosis

Apoptotic regulation involves numerous proteins such as families of p53, bcl-2-like protein 4 (BAX), and caspases [23]. Several flavonols identified in *C. album* berries seem to be able to induce apoptosis: anthocyanins, such as delphinidin-3-O-hexoside can induce apoptosis by modifying BAX, caspase 3, and Bcl-2 proteins [64]; quercetin-3-O-hexoside seems to be able to promote apoptosis, enhancing the expression of p53 and BAX proteins [46]; and kaempferol-3-O-hexoside was associated with the induction of apoptosis through the upregulation of caspase 3 and the downregulation of Bcl-2 [41,43,44]. Another flavonoid identified in *C. album* leaves, pinocembrin, was reported to be able to induce apoptosis in many different types of cancer cells [87].

4.4. Modulation of Mitogen Activated Protein Kinase

Since mitogen-activated protein kinase (MAPK) pathways are a convergent avenue involved in numerous biological processes, changes in MAPK activity are of utmost importance. *p*-coumaric acid has been demonstrated to have both antioxidant and anti-inflammatory properties since it is capable of preventing oxidative stress-induced apoptosis in human epithelial cells through the modulation of the MAPK signalling pathway [88]. Other phenolic acids identified in *C. album* berries, such as ferulic acid [28,29], p-hydroxybenzoic acid [24], and neochlorogenic acid [36,40], can also prevent MAPK activation. In the leaves, some polyphenols have also been reported to exert modulatory effects on MAPK pathways, including quercetin rhamnosyl hexoside [79] and procyanidins [73].

4.5. Cell Cycle Arrest

The deregulation of the cell cycle is associated with carcinogenesis and phenolic compounds are known to be capable of inhibiting, in a variety of cell types, different cell phases (G1, S, S/G2, and G2) [21,89]. *C. album* flavonols, identified in the berries, are capable of changing the cell cycle; kaempferol-O-hexoside causes cell cycle arrest at G2 [43,45] while rutin (a quercetin derivative) induces G2/M cell cycle arrest [54].

4.6. Reduction of Oxidative Stress

The antioxidant properties ascribed to *C. album* seem to be mediated by an upregulation of glutathione and cellularly antioxidant enzymes, as well as by the suppression of reactive oxygen species (ROS) generation [90,91]. Indeed, berries usually exhibit an
enriched content of phenolic compounds commonly associated with their high antioxidant properties [15]. Such properties are also exhibited by C. album berries since they have an anthocyanin content that can inhibit the intracellular content of ROS [63–65]. In these berries, gallic acid, chlorogenic acid derivatives, and flavonols have also been identified as having antioxidant properties [15,24,51,53].

Some compounds identified in the leaves of C. album also have antioxidant properties: myricetin derivatives [74,75], reported as a modulator of nitric oxide (NO) generation and of iNOS activity; stilbene derivatives [92]; and prenylated chalcone glycoside, which showed radical scavenging activity [93].

5. Conclusions and Future Perspectives

Although a wide variety of phenolic compounds have been identified in the berries and leaves from C. album, at the time of this review (15th Jun 2022), there are scarce scientific data regarding the potential health benefits exerted by C. album. Only nine studies have evaluated the biological properties of the berries, leaves, or respective extracts of this plant. Nevertheless, the discussion section evidences that their rich composition in phenolic compounds is promising when considering their health benefits and therapeutic potential. The phenolic compounds identified in C. album leaves and berries can modulate several pathophysiological processes, namely, inflammation, oxidative stress, carcinogenesis, etc., and this plant may also be attractive to the pharmaceutical industry with respect to generating new drug(s), nutraceuticals, or supplements, but more scientific evidence concerning C. album’s bioactivity is required.

Author Contributions: Conceptualization: C.D., M.V., R.R.-O. and J.B.S.; writing—original draft preparation, C.D., M.V., A.S.C. and O.V.; writing—review and editing, C.D., M.V., J.B.S., A.S.C., R.R.-O. and I.M.P.L.V.O.F.; funding acquisition, I.M.P.L.V.O.F. and C.D. All authors have read and agreed to the published version of the manuscript.

Funding: The Portuguese Foundation for Science and Technology (FCT) is acknowledged for UIDB/QUI/50006/2020, and Portugal 2020—POCI-01-0145-FEDER-029305, IDEAS4life—Novos IngrediEntes Alimentares de Plantas Marítimas (jointly financed by the European Community Fund and FEDER).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing not applicable.

Acknowledgments: Martin Vojtek thanks the Portuguese Foundation for Science and Technology (FCT) and the PhD Program in Medicines and Pharmaceutical Innovation (i3DU) for PhD Grant PD/BD/135460/2017, funded by the European Social Fund of the European Union and national funds FCT/MCTES. Rita Ribeiro–Oliveira thanks the Portuguese Foundation for Science and Technology (FCT) for PhD Grant SFRH/BD/146243/2019 funded by the European Social Fund of the European Union and national funds FCT/MCTES through the Norte’s Regional Operational Programme. The authors thank Maria do Céu Pereira e Mónica Caldas for their technical assistance.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Newman, D.J.; Cragg, G.M. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J. Nat. Prod. 2012, 75, 311–335. [CrossRef] [PubMed]
2. Andrade, S.C.; Gonçalves, F.; Guiné, R. Contribution for the physical-chemical characterization of Portuguese Crowberry (Corema album). Int. J. Food Sci. Nutr. 2017, 2, 9–14.
3. Martine, C.T.; Lubertazzi, D.; Dubrul, A. The biology of Corema conradii: Natural history, reproduction, and observations of a post-fire seedling recruitment. Northeast. Nat. 2005, 12, 267–286. [CrossRef]
4. Guitián, P.; Medrano, M.; Rodríguez, M. Reproductive biology of Corema album (L.) D. Don (Empetraceae) in the northwest Iberian Peninsula. Acta Bot. Gall. 1997, 144, 119–128. [CrossRef]
5. Zunzunegui, M.; Barradas, M.D.; Clavijo, A.; Cansino, L.A.; Lhout, F.A.; Novo, F.G. Ecophysiology, growth timing and reproductive effort of three sexual forms of Corema album (Empetraceae). Plant Ecol. 2006, 183, 35–46. [CrossRef]
6. de Oliveira, P.B.; Dale, A. Corema album (L.) D. Don, the white crowberry—A new crop. J. Berry Res. 2012, 2, 123–133. [CrossRef]

7. León-González, A.J.; Mateos, R.; Ramos, S.; Martín, M.A.; Sarriá, B.; Martín-Cordero, C.; López-Lázaro, M.; Bravo, L.; Goya, L. Chemo-protective activity and characterization of phenolic extracts from Corema album. Food Res. Int. 2012, 49, 726–738. [CrossRef]

8. López-Dorría, I.I. The archaeobotany and ethnobotany of Portuguese or white crowberry (Corema album (L.) D. Don). Ethnobiol. Lett. 2018, 9, 19–32. [CrossRef]

9. Gras, A.; Garnatje, T.; Ibáñez, N.; López-Pujol, J.; Nualart, N.; Vallés, J. Medicinal plant uses and names from the herbarium of Francesc Boïós (1773-1844). J. Ethnopharmacol. 2017, 204, 142–168. [CrossRef]

10. Martin, D.; Marques, J.; Amado, A.M.; Barroca, M.J.; Moreira da Silva, A.; Batista de Carvalho, L.A.E.; Marques, M.P.M. Shedding light into the health-beneficial properties of Corema album—a vibrational spectroscopy study. J. Raman Spectrosc. 2020, 51, 313–322. [CrossRef]

11. Marques, J.; Martin, D.; Amado, A.M.; Lysenko, V.; Osório, N.; Batista de Carvalho, L.A.E.; Marques, M.P.M.; Barroca, M.J.; Moreira da Silva, A. Novel Insights into Corema album Berries: Vibrational Profile and Biological Activity. Plants 2021, 10, 1761. [CrossRef] [PubMed]

12. León-González, A.J.; Truchado, P.; Tomás-Barberán, F.A.; López-Lázaro, M.; Barradas, M.C.D.; Martín-Cordero, C. Phenolic acids, flavonols and anthocyanins in Corema album (L.) D. Don berries. J. Food Compos. Anal. 2013, 29, 58–63. [CrossRef]

13. Andrade, S.C.; Guiné, R.P.F.; Gonçalves, F.J.A. Evaluation of phenolic compounds, antioxidant activity and bioaccessibility in white crowberry (Corema album). J. Food Meas. Charact. 2017, 11, 1936–1946. [CrossRef]

14. Brito, C.; Bertotti, T.; Primitivo, M.J.; Neves, M.; Pieres, C.L.; Cruz, P.F.; Martins, P.A.T.; Rodrigues, A.C.; Moreno, M.J.; Brito, R.M.M.; et al. Corema album spp: Edible wild crowberries with a high content in minerals and organic acids. Food Chem. 2021, 345, 128372. [CrossRef] [PubMed]

15. Macedo, D.; Tavares, L.; McDougall, G.J.; Vicente Miranda, H.; Stewart, D.; Ferreira, R.B.; Tenreiro, S.; Outeiro, T.F.; Santos, C.N. (Poly)phenols protect from α-synuclein toxicity by reducing oxidative stress and promoting autophagy. Hum. Mol. Genet. 2015, 24, 1717–1732. [CrossRef] [PubMed]

16. Jardin, C.; Macedo, D.; Figueira, I.; Dobson, G.; McDougall, G.J.; Stewart, D.; Ferreira, R.B.; Menezes, R.; Santos, C.N. (Poly)phenol metabolites from Arbutus unedo leaves protect yeast from oxidative injury by activation of antioxidant and protein clearance pathways. J. Funct. Foods 2017, 32, 333–346. [CrossRef]

17. León-González, A.J.; López-Lázaro, M.; Espartero, J.L.; Martín-Cordero, C. Cytotoxic Activity of Dihydrochalcones Isolated from Corema album Leaves against HT-29 Colon Cancer Cells. Nat. Prod. Commun. 2013, 8, 1934578X1300800. [CrossRef]

18. León-González, A.J.; Manso, M.M.; Lopez-Lazaro, M.; Navarro, I.; Martín-Cordero, C. Induction of apoptosis and cell cycle arrest in human colon carcinoma cells by Corema album leaves. Nat. Prod. Commun. 2014, 9, 1934578X1400900117. [CrossRef]

19. Wong, E. The role of chalcones and flavanones in flavonoid biosynthesis. Phytochemistry 1968, 7, 1751–1758. [CrossRef]

20. Sánchez-Pícó, À.; León-González, A.J.; Martín-Cordero, C.; Daga, R.R. Screening for natural anticancer agents using a fission yeast bioassay. Phytochem. Lett. 2014, 8, 184–189. [CrossRef] [PubMed]

21. Fresco, P.; Borges, F.; DINIZ, C.; Marques, M. New insights on the anticancer properties of dietary polyphenols. Med. Res. Rev. 2006, 26, 747–766. [CrossRef]

22. Jacinto, J.; Giovannetti, M.; Oliveira, P.B.; Valdiviesso, T.; Mágicas, C.; Alegria, C. Quality attributes of cultivated white crowberries (Corema album (L.) D. Don) from a multi-origin clonal field. Euphytica 2021, 217, 40. [CrossRef]

23. Fresco, P.; Borges, F.; Marques, M.P.; DINIZ, C. The anticancer properties of dietary polyphenols and its relation with apoptosis. Curr. Pharm. Des. 2010, 16, 114–134. [CrossRef]

24. Lee, J.; Ha, S.J.; Lee, H.J.; Kim, M.J.; Kim, J.H.; Kim, Y.T.; Song, K.M.; Kim, Y.J.; Kim, H.K.; Jung, S.K. Protective effect of Tremella fuciformis Berk extract on LPS-induced acute inflammation via inhibition of the NF-κB and MAPK pathways. Food Funct. 2016, 7, 3263–3272. [CrossRef] [PubMed]

25. Peng, J.; Zheng, T.; Liang, Y.; Duan, L.; Zhang, Y.; Wang, L.-J.; He, G.; Xiao, H. P-Coumaric Acid Protects Human Lens Epithelial Cells Against Oxidative Stress-Induced Apoptosis by MAPK signaling. Oxidative Med. Cell. Longev. 2018, 2018, 8549052. [CrossRef] [PubMed]

26. Zhu, H.; Liang, Q.H.; Xiong, X.G.; Wang, Y.; Zhang, Z.H.; Sun, M.J.; Lu, X.; Wu, D. Anti-Inflammatory Effects of p-Coumaric Acid, a Natural Compound of Oldenlandia diffusa, on Arthritis Model Rats. Evid. Based Complement. Altern. Med. 2018, 2018, 5198594. [CrossRef] [PubMed]

27. Prasad, N.R.; Ramachandran, S.; Pugalendhi, K.V.; Menon, V.P. Ferulic acid inhibits UV-B–induced oxidative stress in human lymphocytes. Nutr. Res. 2007, 27, 559–564. [CrossRef]

28. Yin, P.; Zhang, Z.; Li, J.; Shi, Y.; Jin, N.; Zou, W.; Gao, Q.; Wang, W.; Liu, F. Ferulic acid inhibits bovine endometrial epithelial cells against LPS-induced inflammation via suppressing NF-κB and MAPK pathway. Res. Vet. Sci. 2019, 126, 164–169. [CrossRef]

29. Cao, Y.; Zhang, Y.; Qi, J.; Liu, R.; Zhang, H.; He, L. Ferulic acid inhibits H2O2-induced oxidative stress and inflammation in rat vascular smooth muscle cells via inhibition of the NADPH oxidase and NF-κB pathway. Int. Immunopharmacol. 2015, 28, 1018–1025. [CrossRef]

30. Zhang, M.; Zhou, J.; Wang, L.; Li, B.; Guo, J.; Guan, X.; Han, Q.; Zhang, H. Caffeic acid reduces cutaneous tumor necrosis factor alpha (TNF-alpha), IL-6 and IL-1beta levels and ameliorates skin edema in acute and chronic model of cutaneous inflammation in mice. Biol. Pharm. Bull. 2014, 37, 347–354. [CrossRef] [PubMed]
31. Prasad, N.R.; Karthikeyan, A.; Karthikeyan, S.; Reddy, B.V.J.M.; Biochemistry. C. Inhibitory effect of caffeic acid on cancer cell proliferation by oxidative mechanism in human HT-1080 fibrosarcoma cell line. *Mol. Cell. Biochem.* 2011, 349, 11–19. [CrossRef]

32. Shan, J.; Fu, J.; Zhao, Z.; Kong, X.; Huang, H.; Luo, L.; Yin, Z. Cholorogenic acid inhibits lipopolysaccharide-induced cyclooxygenase-2 expression in RAW264.7 cells through suppressing NF-kappaB and JNK/AP-1 activation. *Int. Immunopharmacol.* 2009, 9, 1042–1048. [CrossRef] [PubMed]

33. Zheng, Z.; Sheng, Y.; Lu, B.; Ji, L. The therapeutic detoxification of chlorogenic acid against acetaminophen-induced liver injury by ameliorating hepatic inflammation. *Chem. Biol. Interact.* 2015, 238, 93–101. [CrossRef] [PubMed]

34. Kang, T.Y.; Yang, H.R.; Zhang, J.; Li, D.; Lin, J.; Wang, L.; Xu, X. The studies of chlorogenic Acid antitumor mechanism by gene chip detection: The immune pathway gene expression. *J. Anal. Methods Chem.* 2013, 2013, 617243. [CrossRef] [PubMed]

35. Bufalo, M.C.; Ferreira, I.; Costa, G.; Francisco, V.; Liberal, J.; Cruz, M.T.; Lopes, M.C.; Batista, M.T.; Sforcin, J.M. Propolis and its constituent caffeic acid suppress LPS-activated pro-inflammatory response by blocking NF-κB and MAPK activation in macrophages. *J. Ethnopharmacol.* 2013, 149, 84–92. [CrossRef]

36. Yun, N.; Kang, J.W.; Lee, S.M. Protective effects of chlorogenic acid against ischemia/reperfusion injury in rat liver: Molecular evidence of its antioxidant and anti-inflammatory properties. *J. Nutr. Biochem.* 2012, 23, 1249–1255. [CrossRef]

37. Gao, X.H.; Zhang, S.D.; Wang, L.T.; Yu, L.; Zhao, X.L.; Ni, H.Y.; Wang, Y.Q.; Wang, J.D.; Shan, C.H.; Fu, Y.J. Anti-Inflammatory Effects of Neochlorogenic Acid Extract from Mulberry Leaf (Morus alba L.) Against LPS-Stimulated Inflammatory Response through Mediating the AMPK/Nrf2 Signaling Pathway in A549 Cells. *Molecules* 2020, 25, 1385. [CrossRef]

38. Kim, M.; Choi, S.Y.; Lee, P.; Hur, J. Neochlorogenic Acid Inhibits Lipopolysaccharide-Induced Activation and Pro-inflammatory Responses in BV2 Microglial Cells. *Neurochem. Res.* 2015, 40, 1792–1798. [CrossRef]

39. Chang, C.H.; Chang, Y.T.; Tseng, T.H.; Wang, C.J. Mulberry leaf extract inhibit hepatocellular carcinoma cell proliferation via depressing IL-6 and TNF-alpha derived from adipocyte. *J. Food Drug. Anal.* 2018, 26, 1024–1032. [CrossRef]

40. Park, S.Y.; Jin, M.L.; Yi, E.H.; Kim, Y.; Park, G. Neochlorogenic acid inhibits against LPS-activated inflammatory responses through up-regulation of Nrf2/HO-1 and involving AMPK pathway. *Environ. Toxicol. Pharmacol.* 2018, 62, 1–10. [CrossRef]

41. Colombo, M.; Figueiró, F.; de Fraga Dias, A.; Teixeira, H.F.; Battastini, A.M.O.; Koester, L.S. Kaempferol-loaded mucoadhesive nanoemulsion for intranasal administration reduces glioma growth in vitro. *Int. J. Pharm.* 2018, 543, 214–223. [CrossRef] [PubMed]

42. Yi, X.; Zuo, J.; Tan, C.; Xian, S.; Luo, C.; Chen, S.; Yu, L.; Luo, Y. Kaempferol, a Flavonoid Compound from Gynura Medica Induced Apoptosis and Growth Inhibition in Mcf-7 Breast Cancer Cell. *Afr. J. Tradit. Complement. Altern. Med.* 2016, 13, 210–215. [CrossRef] [PubMed]

43. Song, H.; Bao, J.; Wei, Y.; Chen, Y.; Mao, X.; Li, J.; Yang, Z.; Xue, Y. Kaempferol inhibits gastric cancer tumor growth: An in vitro and in vivo study. *Oncol. Rep.* 2015, 33, 868–874. [CrossRef] [PubMed]

44. Qin, Y.; Cui, W.; Yang, X.; Tong, B. Kaempferol inhibits the growth and metastasis of cholangiocarcinoma in vitro and in vivo. *Acta Biochim. Et Biophys. Sin.* 2016, 48, 238–245. [CrossRef] [PubMed]

45. Imran, M.; Salehi, B.; Sharifi-Rad, J.; Aslam Gondal, T.; Saeed, F.; Imran, A.; Shahbaz, M.; Tsouh Fokou, P.; Umair Arshad, M.; Kostić, D.A.; Dimitrijević, D.S.; Stojanović, G.S.; Palić, I.R.; Đorđević, A.S.; Ickovski, J.D. Xanthine Oxidase: Isolation, Assays of Activity, and Inhibition. *Chem. Biol. Interact.* 2019, 2016, 238–245. [CrossRef] [PubMed]

46. Li, Q.; Qiu, Y.; Mao, M.; Lv, J.; Zhang, L.; Li, S.; Li, X.; Zheng, X. Antioxidant mechanism of Rutin on hypoxia-induced pulmonary macrophages. *Int. J. Oncol.* 2013, 47, 1494–1502. [CrossRef] [PubMed]

47. Huang, H.; Chen, A.Y.; Ye, X.; Li, B.; Rojasanakul, Y.; Rankin, G.O.; Chen, Y.C. Myricetin inhibits proliferation of cisplatin-resistant cancer cells through a p53-dependent apoptotic pathway. *Int. J. Oncol.* 2015, 47, 1494–1502. [CrossRef] [PubMed]
56. Zang, W.; Wang, T.; Wang, Y.; Li, M.; Xuan, X.; Ma, Y.; Du, Y.; Liu, K.; Dong, Z.; Zhao, G. Myricetin exerts anti-proliferative, anti-invasive, and pro-apoptotic effects on esophageal carcinoma EC9706 and KYSE30 cells via RSK2. *Tumour. Biol.* **2014**, *35*, 12583–12592. [CrossRef]

57. Li, M.; Chen, J.; Yu, X.; Xu, S.; Li, D.; Zheng, Q.; Yin, Y. Myricetin Suppresses the Propagation of Hepatocellular Carcinoma via Down-Regulating Expression of YAP. *Cells* **2019**, *8*, 358. [CrossRef]

58. Jiang, M.; Zhu, M.; Wang, L.; Yu, S. Anti-tumor effects and associated molecular mechanisms of myricetin. *Biomed. Pharmacother.* **2019**, *120*, 109506. [CrossRef]

59. Urias-Lugo, D.A.; Heredia, J.B.; Muy-Rangel, M.D.; Valdez-Torres, J.B.; Serna-Saldívar, S.O.; Gutiérrez-Uribé, J.A. Anthocyanins and Phenolic Acids of Hybrid and Native Blue Maize (*Zea mays* L.) Extracts and Their Antiproliferative Activity in Mammary (MCF7), Liver (HepG2), Colon (Caco2 and HT29) and Prostate (PC3) Cancer Cells. *Plant Foods Hum. Nutr.* **2015**, *70*, 193–199. [CrossRef]

60. Pyo, M.Y.; Yoon, S.J.; Yu, Y.; Park, S.; Jin, M. Cyanidin-3-glucoside suppresses Th2 cytokines and GATA-3 transcription factor in EL-4 T cells. *Biosci. Biotechnol. Biochem.* **2014**, *78*, 1037–1043. [CrossRef]

61. Zeng, L.; Gao, J.; Zhang, R. Study on anti-tumor effect of cyanidin-3-glucoside on ovarian cancer. *Zhongguo Zhong Yao Za Zhi* **2012**, *37*, 1651–1654. [PubMed]

62. Guo, H.; Liu, G.; Zhong, R.; Wang, Y.; Wang, D.; Xia, M. Cyanidin-3-O-beta-glucoside regulates fatty acid metabolism via an AMP-activated protein kinase-dependent signaling pathway in human HepG2 cells. *Lipids Health Dis.* **2012**, *11*, 10. [CrossRef]

63. Ni, T.; Yang, W.; Xing, Y. Protective effects of delphinidin against H2O2-induced oxidative injuries in human retinal pigment epithelial cells. *Biosci. Rep.* **2019**, *39*, BSR20190689. [CrossRef]

64. Lee, D.-Y.; Park, Y.-J.; Song, M.-G.; Kim, D.R.; Zada, S.; Kim, D.-H. Cytoprotective Effects of Delphinidin for Human Chondrocytes with Oxidative Stress. *Antioxid. Redox Signal.* **2017**, *26*, 49–69. [CrossRef]

65. Bhardwaj, P.; Khanna, D. Green tea catechins: Defensive role in cardiovascular disorders. *Chin. J. Nat. Med.* **2013**, *11*, 345–353. [CrossRef]

66. Suzuki, J.; Ogawa, M.; Futamatsu, H.; Kosuge, H.; Sagesaka, Y.M.; Isobe, M. Tea catechins improve left ventricular dysfunction, suppress myocardial inflammation and fibrosis, and alter cytokine expression in rat autoimmune myocarditis. *Eur. J. Heart Fail.* **2007**, *9*, 152–159. [CrossRef]

67. Cheng, A.W.; Tan, X.; Sun, J.Y.; Gu, C.M.; Liu, C.; Guo, X. Catechin attenuates TNF-alpha induced inflammatory response via AMPK-SIRT1 pathway in 3T3-L1 adipocytes. *PLoS ONE* **2019**, *14*, e0217090. [CrossRef]

68. Frei, B.; Higdon, J.V. Antioxidant activity of tea polyphenols in vivo: Evidence from animal studies. *J. Nutr.* **2003**, *133*, 3275S–3284S. [CrossRef]

69. Bak, M.J.; Jun, M.; Jeong, W.S. Procyanidins from wild grape (*Vitis amurensis*) seeds regulate ARE-mediated enzyme expression via Nrf2 coupled with p38 and PI3K/Akt pathway in HepG2 cells. *Int. J. Mol. Sci.* **2012**, *13*, 801–818. [CrossRef] [PubMed]

70. Bak, M.J.; Truong, V.L.; Ko, S.Y.; Nguyen, X.N.; Ingkasupart, P.; Jun, M.; Shin, J.Y.; Jeong, W.S. Antioxidant and Hepatoprotective Effects of Procyanidins from Wild Grape (*Vitis amurensis*) Seeds in Ethanol-Induced Cells and Rats. *Int. J. Mol. Sci.* **2016**, *17*, 758. [CrossRef] [PubMed]

71. Chu, H.; Tang, Q.; Huang, H.; Hao, W.; Wei, X. Grape-seed proanthocyanidins inhibit the lipopolysaccharide-induced inflammatory mediator expression in RAW264.7 macrophages by suppressing MAPK and NF-kappaB signal pathways. *Environ. Toxicol. Pharmac.* **2016**, *41*, 159–166. [CrossRef] [PubMed]

72. Limtrakul, P.; Yodkeeree, S.; Pitchakarn, P.; Punfa, W. Anti-inflammatory effects of proanthocyanidin-rich red rice extract via suppression of MAPK, AP-1 and NF-kB pathways in Raw 264.7 macrophages. *Nutr. Res. Pract.* **2016**, *10*, 251. [CrossRef]

73. Cho, B.O.; Yin, H.H.; Park, S.H.; Byun, E.B.; Ha, H.Y.; Jang, S.I. Anti-inflammatory activity of myricetin from Diospyros lotus through suppression of NF-kB and STAT1 activation and Nrf2-mediated HO-1 induction in lipopolysaccharide-stimulated RAW264.7 macrophages. *Biosci. Biotechnol. Biochem.* **2016**, *80*, 1520–1530. [CrossRef] [PubMed]

74. Liao, H.-H.; Zhu, J.-X.; Feng, H.; Ni, J.; Zhang, N.; Chen, S.; Liu, H.-J.; Yang, Z.; Deng, W.; Tang, Q.-Z. Myricetin Possesses Potential Protective Effects on Diabetic Cardiomyopathy through Inhibiting IkBalpha/NF-kappaB and Enhancing Nrf2/HO-1. *Oxidative Med. Cell. Longev.* **2017**, *2017*, 1–14. [CrossRef] [PubMed]

75. Kadioglu, O.; Nass, J.; Saeed, M.E.; Schuler, B.; Effertth, T. Kaempferol Is an Anti-Inflammatory Compound with Activity towards NF-kB Pathway Proteins. *Anticancer Res.* **2015**, *35*, 2645–2650. [PubMed]

76. Sun, Z.; Li, Q.; Hou, R.; Sun, H.; Tang, Q.; Wang, H.; Hao, Z.; Kang, S.; Xu, T.; Wu, S. Kaempferol-3-O-gluco-rhamnoside inhibits inflammatory responses via MAPK and NF-kappaB pathways in vitro and in vivo. *Toxicol. Appl. Pharm.* **2019**, *364*, 22–28. [CrossRef] [PubMed]

77. Das, N.; Sikder, K.; Bhattacharjee, S.; Majumdar, S.B.; Ghosh, S.; Majumdar, S.; Dey, S. Quercetin alleviates inflammation after short-term treatment in high-fat-fed mice. *Food Funct.* **2013**, *4*, 889–898. [CrossRef] [PubMed]
79. Noh, H.J.; Kim, C.S.; Kang, J.H.; Park, J.Y.; Choe, S.Y.; Hong, S.M.; Yoo, H.; Park, T.; Yu, R. Quercetin suppresses MIP-1alpha-induced adipose inflammation by downregulating its receptors CCR1/CCR5 and inhibiting inflammatory signaling. *J. Med. Food* **2014**, *17*, 550–557. [CrossRef] [PubMed]

80. Hämäläinen, M.; Nieminen, R.; Vuorela, P.; Heinonen, M.; Moilanen, E. Anti-inflammatory effects of flavonoids: Genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-kappaB activations, whereas flavone, isorhamnetin, naringenin, and pelargonicid inhibit only NF-kappaB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. *Mediat. Inflamm.* **2007**, *2007*, 45673. [CrossRef]

81. Chang, Y.C.; Tsai, M.H.; Sheu, W.H.; Hsieh, S.C.; Chiang, A.N. The therapeutic potential and mechanisms of action of quercetin in relation to lipopolysaccharide-induced sepsis in vitro and in vivo. *PLoS ONE* **2013**, *8*, e80744. [CrossRef] [PubMed]

82. Napimoga, M.H.; Clemente-Napimoga, J.T.; Macedo, C.G.; Freitas, F.F.; Stipp, R.N.; Pinho-Ribeiro, F.A.; Casagrande, R.; Verri, W.A., Jr. Quercetin inhibits inflammatory bone resorption in a mouse periodontitis model. *J. Nat. Prod.* **2013**, *76*, 2316–2321. [CrossRef] [PubMed]

83. Xia, Y.; Shen, S.; Verma, I.M. NF-kB, an active player in human cancers. *Cancer Immunol. Res.* **2014**, *2*, 823–830. [CrossRef]

84. Zhang, W.; Li, B.; Guo, Y.; Bai, Y.; Wang, T.; Fu, K.; Sun, G. Rhamnetin attenuates cognitive deficit and inhibits hippocampal inflammatory response and oxidative stress in rats with traumatic brain injury. *Cent. Eur. J. Immunol.* **2015**, *40*, 35–41. [CrossRef]

85. Hirai, S.; Kim, Y.I.; Goto, T.; Kang, M.S.; Yoshimura, M.; Obata, A.; Yu, R.; Kawada, T. Inhibitory effect of naringenin chalcone on inflammatory changes in the interaction between adipocytes and macrophages. *Life Sci.* **2007**, *81*, 1272–1279. [CrossRef]

86. Rammohan, A.; Reddy, J.S.; Sravya, G.; Rao, C.N.; Zyryanov, G.V. Chalcone synthesis, properties and medicinal applications: A review. *Environ. Chem. Lett.* **2020**, *18*, 433–458. [CrossRef]

87. Rasul, A.; Millimouno, F.M.; Ali Eltayb, W.; Ali, M.; Li, J.; Li, X. Pinocembrin: A novel natural compound with versatile pharmacological and biological activities. *BioMed Res. Int.* **2013**, *2013*, 379850. [CrossRef]

88. Gagliotti Vigil de Mello, S.V.; Frode, T.S. In Vitro and In Vivo Experimental Model-based Approaches for Investigating Anti-inflammatory Properties of Coumarins. *Curr. Med. Chem.* **2018**, *25*, 1446–1476. [CrossRef]

89. Shin, S.Y.; Yoon, H.; Ahn, S.; Kim, D.W.; Bae, D.H.; Koh, D.; Lee, Y.H.; Lim, Y. Structural properties of polyphenols causing cell cycle arrest at G1 phase in HCT116 human colorectal cancer cell lines. *Int. J. Mol. Sci.* **2013**, *14*, 16970–16985. [CrossRef]

90. Feng, R.; Lu, Y.; Bowman, L.L.; Qian, Y.; Castranova, V.; Ding, M. Inhibition of activator protein-1, NF-kappaB, and MAPKs and induction of phase 2 detoxifying enzyme activity by chlorogenic acid. *J. Biol. Chem.* **2005**, *280*, 27888–27895. [CrossRef]

91. Granado-Serrano, A.B.; Angeles Martin, M.; Goya, L.; Bravo, L.; Ramos, S. Time-course regulation of survival pathways by epicatechin on HepG2 cells. *J. Nutr. Biochem.* **2009**, *20*, 115–124. [CrossRef] [PubMed]

92. Malik, S.A.; Acharya, J.D.; Mehendale, N.K.; Mat, S.S.; Ghaskadbi, S.S. Pterostilbene reverses palmitic acid mediated insulin resistance in HepG2 cells by reducing oxidative stress and triglyceride accumulation. *Free Radic. Res.* **2019**, *53*, 815–827. [CrossRef] [PubMed]

93. Cioffi, G.; Morales Escobar, L.; Braca, A.; De Tommasi, N. Antioxidant chalcone glycosides and flavanones from Maclura (Chlorophora) tinctoria. *J. Nat. Prod.* **2003**, *66*, 1061–1064. [CrossRef] [PubMed]