

Review

Use of Strawberry Tree (*Arbutus unedo*) as a Source of Functional Fractions with Biological Activities

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Abstract: *Arbutus unedo*, commonly named ‘strawberry tree’ (ST), is a Mediterranean native plant that represents a relevant source of biologically active fractions and compounds. ST fruits, traditionally used with culinary and medicinal purposes, along with other components (leaves, roots, honeys, etc.), have been subjected to varied extraction procedures to obtain enriched and bioactive products. This work reviewed the scientific literature, searching for studies that evaluated the potential health implications of ST fractions and attending to the tested biological activities (antioxidant, antiproliferative, hypoglycemic, immune-modulatory, antihypertensive, antimicrobial, etc.), the part of the tree, the experimental model, the specific bioactive compounds and the selected extraction protocol. Furthermore, the strengths and weaknesses of the current state of the published evidence were critically analysed. Although in vitro results demonstrated the potential of ST fractions, further research is encouraged in order to obtain in vivo evidence (animal and clinical studies), assess additional activities (hypocholesterolemic, microbiome-modulatory), maximize the use of advanced extraction technologies, purify and isolate specific bioactive compounds and broaden the analysis investigating phenolic and non-phenolic molecules and their bioavailability.

Keywords: *Arbutus unedo*; strawberry tree; antioxidant; phenolic compounds; arbutin; antitumoral; hypoglycemic; antimicrobial



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1. Introduction

Arbutus genus belongs to the Ericaceae family and comprises 12 accepted species with different geographical distributions and interest (Table 1). Among them, *Arbutus unedo*, commonly named ‘strawberry tree’ (ST), is the most popular and investigated species due to its gastronomical and medicinal uses. ST (also called arbutus, strawberry madrone, Irish/Killarney ST) is an evergreen and flowering small tree or shrub whose fruits have been traditionally utilized in fermented and distilled beverages, jellies, jams, marmalades, sauces and vinegars and are even consumed fresh. This Mediterranean native plant can be found in Southern, Western and Central Europe, Canary Islands, Ireland, North-Eastern Africa and Western Asia, growing in regions with unusual intense dryness or frost [1,2].

Table 1. List of accepted *Arbutus* species, geographical distribution and main parts of interest.

| <i>Arbutus</i> Species | Geographical Distribution | Main Parts of Interest | References |
|------------------------|--|-------------------------------|------------|
| <i>A. unedo</i> | Europe (South, West, Central), Africa (North-East), Asia (East), Canary Islands, Ireland | Fruits, leaves, roots, honeys | [1,2] |
| <i>A. andrachne</i> | Europe (South-East, East), Asia (West) | Fruits, leaves | [3,4] |
| <i>A. canariensis</i> | Canary Islands | Fruits | [5] |
| <i>A. pavarii</i> | Lybia | Fruits, honeys, bark | [6] |

Table 1. Cont.

| <i>Arbutus</i> Species | Geographical Distribution | Main Parts of Interest | References |
|---|--|------------------------|------------|
| <i>A. arizonica</i> | USA, Mexico | Fruits | [2] |
| <i>A. madrensis</i> | Mexico | - | [2,7] |
| <i>A. menziesii</i> | USA, Mexico, Canada | Fruits | [8] |
| <i>A. occidentalis</i> | Mexico | - | [2] |
| <i>A. tessellata</i> | Mexico | - | [9] |
| <i>A. xalapensis</i> | USA, Mexico, Nicaragua, El Salvador, Guatemala, Honduras | Bark, wood | [10] |
| <i>Arbutus</i> × <i>andrachnoides</i> (<i>A. unedo</i> × <i>A. andrachne</i>) | Greece, Turkey, Cyprus | Fruits | [11] |
| <i>Arbutus</i> × <i>androsterilis</i> (<i>A. unedo</i> × <i>A. canariensis</i>) | Canary Islands | Fruits | [5] |

ST fruits are the most exploited for culinary purposes, and they show a high carbohydrate content (70–80% dry weight) with a relevant fiber fraction (10–30% dw), constituting an interesting source of vegetal protein (1–9% dw) and lipids (2–3% dw), these percentages being dependent on the ripeness stage, location and environmental conditions (temperature, humidity, soil, etc.) [12,13]. However, other ST parts such as leaves, roots, wood and honeys have also been valued not only because of their inclusion in food and beverage preparations but also because of their content in bioactive compounds (polyphenols, lipids, proteins, secondary metabolites, etc.) that are able to exert relevant biological activities that can contribute to reducing the incidence of varied disorders (Table 2) [1,13].

Table 2. Traditional uses, biological activities and potential health implications (related disorders whose risk may be reduced) of the main parts of *Arbutus unedo*.

| Part | Main/Traditional Uses | Tested Biological Activities | Potential Health Implications | References |
|-----------|---------------------------------------|---|---|------------|
| Fruit | Food, beverages, medicinal | Antioxidant, hypoglycemic, antimicrobial, antiproliferative | Diabetes, hypertension, metabolic syndrome, cancer | [14,15] |
| Leaves | Infusions, medicinal | Antioxidant, anti-inflammatory, hypoglycemic, antimicrobial, antiviral, antiproliferative, antihypertensive, anti-urolithiasis, antileishmanial | Diabetes, hypertension, metabolic syndrome, viral infections (papilloma virus), urolithiasis, leishmaniasis | [16,17] |
| Flower | Medicinal | Antioxidant | Oxidative stress-related disorders | [18] |
| Honey | Food, medicinal | Antioxidant, anti-inflammatory, antimicrobial, antiproliferative, antihypertensive | Hypertension, metabolic syndrome, cancer | [19–22] |
| Bark/wood | Firewood, tools, ornamental | Antioxidant | Oxidative stress-related disorders | [23] |
| Root | Medicinal, red dye (textile industry) | Antioxidant, hypoglycemic, antimicrobial, antihypertensive | Diabetes, hypertension, metabolic syndrome | [24–27] |

Targeting the aforementioned molecules, most of the efforts carried out by food scientists and technologists have been focused on applying extraction methods to obtain functional fractions using ST raw materials (Table 3) [28].

Table 3. Biological activities of *Arbutus unedo* extracts tested in different experimental models.

| Activity | Raw Material | Experimental Model | Bioactive Compound(s) | Extraction Method | Reference | |
|---|--------------------|--|---|---|--|----------|
| Antioxidant | Fruits | Radical scavenging assays | Phenolic compounds | Delipidation + Ultrasound-assisted extraction (Ethyl acetate; 80% methanol) | [29] | |
| | | | | 80% ethanol; 80% methanol extraction | [30] | |
| | | | | 80% methanol extraction | [31] | |
| | | | | 80 and 100% methanol extraction | [32] | |
| | | | | - | [33] | |
| | | Radical scavenging and β -carotene bleaching assays | Phenolic compounds (gallic acid, cyanidin 3-glucoside), ascorbic acid | - | [33] | |
| | | | Phenolic compounds, fatty acids, α -tocopherol | 96% ethanol extraction | [34] | |
| | | Radical scavenging and β -carotene bleaching assays | Galloyl hexoside, 5-O-galloylquinic acid | Supercritical-CO ₂ extraction (40, 55, 70 °C) | [35] | |
| | | | Phenolic compounds, ascorbic acid | Ethanol extraction | [36] | |
| | | Radical scavenging and β -carotene bleaching assays | Phenolic compounds (galocatechol, catechin) | Ethanol extraction (Ultra-turrax homogeneization, 25 °C) | [37] | |
| | | | Phenolic compounds, ascorbic acids, tocopherols, carotenoids | - | [38] | |
| | | Radical scavenging, β -carotene bleaching and lipid peroxidation inhibition assays | Phenolic compounds, carbohydrates | Phenolic compounds, carbohydrates | Maceration (20–90 °C), microwave- (50–145 °C) and ultrasound-assisted (30–35 °C) extraction (ethanol–water mixtures) | [28] |
| | | | | | Radical scavenging, β -carotene bleaching and lipid peroxidation inhibition assays (bread fortification) | Catechin |
| | | Radical scavenging assays (yoghurt fortification) | Anthocyanins | Acidified water extraction | [14] | |
| | | Radical scavenging assays (cheese fortification) | Phenolic compounds | Water infusion | [40] | |
| Radical scavenging assays (wafers fortification) | Anthocyanins | 80% acidified ethanol (90 °C) | [41] | | | |
| Food oxidative stability (sausages fortification) | Phenolic compounds | Ethanol extraction | [42] | | | |
| Lipid oxidation (limpet pâté) | | Water extraction | [15] | | | |

Table 3. Cont.

| Activity | Raw Material | Experimental Model | Bioactive Compound(s) | Extraction Method | Reference |
|----------|-----------------|---|--|--|-----------|
| | | Lipid oxidation (pork burgers) | - | Ethanol extraction | [43] |
| | | Protein oxidation (pork burgers) | - | Ethanol extraction | [44] |
| | | | | 80% methanol extraction | [45] |
| | | | | Ultrasound-assisted extraction (70% ethanol) | [46] |
| | Fruits, leaves | Radical scavenging assays | Phenolic compounds | Ultrasound-assisted extraction (80% methanol) | [47] |
| | | | Phenolic compounds, ascorbic acid, β -carotene | 80% ethanol | [48] |
| | | Human erythrocytes | | Water infusion (100 °C) | [49] |
| | Fruits, flowers | Radical scavenging and β -carotene bleaching assays | | Water, ethanol and methanol extraction | [18] |
| | | | | Delipidation + hot 80% ethanol extraction or water infusion (100 °C) | [50] |
| | | | Phenolic compounds | Ultrasound-assisted extraction (50% methanol) | [51] |
| | | Radical scavenging assays | | Ethanol, methanol, diethyl ether extraction | [34] |
| | | | | Delipidation + methanol extraction | [52] |
| | | | | Water infusion (100 °C) | [53] |
| | | | Arbutin, phenolic compounds (hydroquinone) | Ethanol, water extraction (50 °C) | [54] |
| | | | - | Ethanol maceration | [17] |
| | Leaves | Radical scavenging and β -carotene bleaching assays | Phenolic compounds, iridoids | Maceration, Soxhlet and ultrasound-assisted extraction (ethanol) | [55] |
| | | Radical scavenging assays and inhibition of β -carotene peroxidation | | Water maceration | [56] |
| | | Radical scavenging assays, <i>Saccharomyces cerevisiae</i> strains | | 50% Ethanol extraction, in vitro digestion | [57] |
| | | Radical scavenging, crocin-bleaching and liposome-accelerated oxidation assays (teas) | | Addition of boiling water (decoction) (100 °C) | [58] |
| | | Human peripheral blood lymphocytes | Phenolic compounds (galloylquinic acid derivatives and myricitrin) | Ultrasound-assisted extraction (water) | [59] |

Table 3. Cont.

| Activity | Raw Material | Experimental Model | Bioactive Compound(s) | Extraction Method | Reference |
|-----------------------------------|--|--|--|--|---------------------------------|
| Antiproliferative/ antitumoral | Honeys | Radical scavenging assays | Phenolic compounds | - | [60] |
| | | | Phenolic compounds (arbutin) | Amberlite resin purification and methanol extraction | [21] |
| | | Radical scavenging, cholesterol, liposome oxidation assays | Homogentistic acid | - | [61] |
| | | | Phenolic compounds | 60% acetone, 95% ethanol extraction | [23] |
| | Wood, stalks, leaves | Radical scavenging assays | Phenolic compounds (catechin) | Ethyl acetate or methanol extraction (100 °C) | [63] |
| | Roots | | Phenolic compounds (flavonoids) | High-pressure solvent extraction (water, methanol, ethyl acetate, dichloromethane) | [26] |
| | | | Fruits | Human breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460), colon carcinoma (HCT-15), cervical carcinoma (HeLa) and hepatocellular carcinoma (HepG2) cells | 80 and 100% methanol extraction |
| | Fruit residues (after fermentation and distillation) | Human colorectal adenocarcinoma (HT29) | Phenolic compounds, fatty acids esters, terpenes | Supercritical-CO ₂ extraction (35, 45, 55 °C), 50% ethanol extraction, Soxhlet extraction (hexane) | [64] |
| | | | Proteins (lectins) | Protein extraction | [65] |
| | | Human epithelial carcinoma cells (KB) | - | Hot water extraction (80 °C) | [66] |
| Leaves | | Human cervical epithelial carcinoma (HeLa), human epidermoid carcinoma (A431), human malignant melanoma (A375) cells | - | Ethanol maceration | [17] |
| | Human embryonal rhabdomyosarcoma cancerous cells (RD), rat embryonal rhabdomyosarcoma cancerous cells (L20B), monkey kidney cancerous cells (Vero) | Phenolic compounds | Hexane, ethanol and methanol extraction | [67] | |

Table 3. Cont.

| Activity | Raw Material | Experimental Model | Bioactive Compound(s) | Extraction Method | Reference | |
|-------------------------------------|---------------------------------|--|--|---|---|------|
| Hypoglycemic | Honeys | Human colon carcinoma (HCT-116) and LoVo cells | Phenolic compounds, proteins | - | [19] | |
| | | | Phenolic compounds (phenolic acids, flavonols) | | [68] | |
| | | | Phenolic compounds | | [19,69] | |
| | Axillary buds, leaves fragments | Murine B6-F10 melanoma cells | Anthocyanins | Cell culture (MS medium, B5 medium) | [70] | |
| | Whole plant | Human osteosarcoma cells (U2OS) | Phenolic compounds (arbutin) | Ultrasound-assisted extraction (50% methanol) | [71] | |
| | Fruits | α -glucosidase inhibition test | Phenolic compounds | 80% methanol extraction | [31] | |
| | Fruits, leaves | α -glucosidase and α -amylase inhibition tests | Phenolic compounds, iridoids | Maceration, Soxhlet and ultrasound-assisted extraction (ethanol) | [55] | |
| | Roots | C57BL/6J mice, Sprague–Dawley rats | Wistar rats | - | Hot water extraction (100 °C) | [25] |
| | | | | | [72] | |
| | | | | | [73] | |
| Catechin | | | | | Pressurized liquid extraction (water, 100 °C, 10 MPa) | [74] |
| Anti-inflammatory/immune-modulatory | Leaves | Human red blood cells | Phenolic compounds | Water maceration | [56] | |
| | | Human alveolar epithelial (A549/8) cells, human leukemia monocytes (THP-1) and CD mice | | Methanol extraction | [75] | |
| | | Human breast cancer (MDA-MB-231) cells and human fibroblasts | | [76] | | |
| | Honeys | Hyaluronidase inhibition assay | Phenolic compounds (arbutin) | Amberlite resin-purification and methanol extraction | [21] | |
| Antihypertensive/vasodilatory | Leaves | Aorta isolation from Wistar rats | Tannins and catechin gallate | Water and methanol extraction; tannins precipitation by caffeine addition | [77] | |
| | | Platelet aggregation | Tannins | Hot water (100 °C), methanol and ethyl acetate extraction; tannins precipitation by caffeine addition | [78] | |
| | Roots | Aorta isolation from Wistar rats | - | Hot water (100 °C), diethyl ether, ethyl acetate extraction | [79] | |
| | | | | Hot water extraction (100 °C) | [27] | |

Table 3. Cont.

| Activity | Raw Material | Experimental Model | Bioactive Compound(s) | Extraction Method | Reference | | |
|-------------------|--------------------------|---|---|---|---|--|------|
| Antimicrobial | Fruits | Microbiological analyses | Phenolic compounds | 80% ethanol extraction | [30] | | |
| | | Microbiological analyses (limpet pâté) | | Water extraction | [15] | | |
| | Leaves | Microbiological analyses | | Water infusion (100 °C) | [53] | | |
| | | | | Delipidation + methanol extraction | [52] | | |
| | | Microbiological analyses | | Ultrasound-assisted extraction (50% ethanol) | [80] | | |
| | | | | Phenolic compounds (hydroquinone, arbutin) | Ethanol, water extraction (50 °C) | [54] | |
| | | - | | Microbiological analyses (silver nanoparticles) | Ethanol and hot water extraction (100 °C) | [81] | |
| | | | | | Hot water extraction (100 °C) | [82] | |
| | | Roots | | Microbiological analyses | Phenolic compounds | Methanol and water extraction | [24] |
| | | | | | Phenolic compounds (flavonoids) | High-pressure solvent extraction (water, methanol, ethyl acetate, dichloromethane) | [26] |
| Honeys | Microbiological analyses | Phenolic compounds (flavonoids) | Amberlite resin purification and methanol extraction | [21] | | | |
| | | | Pentane, dichloromethane, butanol extraction | [20] | | | |
| Antiviral | Leaves | Anti-herpes simplex virus type-1 assay | - | Ethanol maceration | [17] | | |
| Antileishmanial | Leaves | Anti-promastigote activity assays | Phenolic compounds | Methanol, ethanol and hexane maceration | [16] | | |
| Anti-urolithiasis | Leaves | Inhibition of calcium oxalate's crystallization | Phenolic compounds, tannins, saponins, sterols, polyterpenes, alkaloids | Water and ethanol extraction (100 °C) | [50,83] | | |

The published works (Table 3) show that the most frequent techniques involved traditional solid–liquid extraction using different solvents—mainly, water, ethanol and methanol, but also ethyl acetate, acetone or hexane, in some cases [26,50]. In addition, advanced technologies more closely related to Green Chemistry principles have also been tested, e.g., supercritical fluid procedures or ultrasound- and microwave-assisted extractions. However, these sustainable alternatives represented a very minor percentage, and other novel approaches such as pulsed-electric fields, ionic liquids or deep eutectic solvents have not been considered yet for ST [28,35,64].

Among the investigated compounds and bioactivities, phenolics have attracted the greatest attention, particularly associated with antioxidant properties (with health and technological implications) but also with antiproliferative, hypoglycemic, anti-inflammatory, antihypertensive and antimicrobial actions [17,22,26,30,39,71]. While >90% of the works

highlighted polyphenols as target compounds, a significantly lower number of publications were focused on the presence of other biologically active molecules such as ascorbic acid, tocopherols, carotenoids, fatty acids, lectins and other proteins, carbohydrates, etc. These non-phenolic compounds were particularly effective as antioxidant and antiproliferative or cytoprotective agents, and the reported activities encourage further investigation to broaden the spectrum of possibilities and efficiently exploit the versatility of ST composition [28,38,64,65].

Nevertheless, despite the promising *in vitro* results, just a few *in vivo* experiments have been carried out so far to validate the real impact of ST fractions on health. Among them, the hypoglycemic effect of roots extracts was confirmed in different rodent models [25,72,73], as well as the safety of leaf extracts administration in rats [84] and the anti-inflammatory and immune-modulatory effects in CD mice [75], but most of the activities have not been assayed in animals, and no clinical trials have been registered to date testing ST parts, extracts or isolated molecules. This lack of animal and human studies must be considered as a key point for the future to be able to formulate novel healthy products based on ST components.

In this article, the scientific literature was reviewed with the aim of identifying the recent insights into the obtention of functional fractions from ST, investigating the relevance of the different ST parts as raw materials, the described biological activities, the utilized experimental models and extraction methods (conventional and advanced) and the identification of the active molecules as well as the potential effects on human health in spite of the absence of clinical interventions.

2. Antioxidant Activity

When the production and accumulation of oxygen reactive species cannot be alleviated by the action of biological mechanisms in cells and tissues, the resultant imbalance is called 'oxidative stress', and the related damage may lead to cancer, cardiovascular, neurological, respiratory and renal diseases, among others [85]. Since the use of dietary antioxidants has been demonstrated to be effective in preventing the disturbances or restoring the balance, vegetal sources have been exhaustively investigated during recent decades to obtain potent antioxidant fractions [86,87].

ST components, particularly fruits and leaves, have been subjected to numerous and varied extraction procedures to obtain phenolics-rich fractions with high antioxidant power (Table 3). In general, solid-liquid extractions were carried out using solvents such as water, ethanol or methanol, although other solvents such as ethyl acetate, acetone or dichloromethane and more advanced technologies such as pressurized liquid extraction (PLE) were utilized for harder matrices such as roots [26,63].

Most of the works utilized methodologies that determined the ability of the phenolics-rich extracts to scavenge free radicals (DPPH•, ABTS•+, etc.), as well as other *in vitro* assays such as the β -carotene or crocin-bleaching assays, the measurement of lipid peroxidation inhibition, etc. Furthermore, more specific experiments were carried out by Mendes et al. (2011) [49] using human erythrocytes that were incubated with aqueous extracts obtained from ST fruits and leaves. These extracts exerted high antioxidant capacities by inhibiting oxidative hemolysis and lipid peroxidation [49]. In addition, a similar leaf fraction obtained by ultrasound-assisted water extraction also inhibited lipid peroxidation in human peripheral blood lymphocytes [59].

Apart from the already mentioned sources (fruits, leaves, roots), honeys have also been studied because of their antioxidant potential. In this sense, honeys with high levels of phenolic compounds such as arbutin and homogentistic acid demonstrated the ability to scavenge free radicals and impede cholesterol and liposomes oxidative degradation [21,61,62].

Although the main purpose of this research field is clinical and targets human health, the antioxidant potential of ST has been concurrently studied from a technological perspective. Thus, anthocyanins-rich fractions extracted from fruits using the acidified ethanol or water were tested, supplementing yoghurts [14] and wafers [41], respectively. Both

experiments concluded that the addition of the extract can replace synthetic antioxidants and colorants and might lead to the design of healthy food products [14,41]. Similar results were obtained in other matrices such as cheese, sausages, pork burgers or limpet pâtés, showing that ST ingredients are promising candidates to be used in functional and novel foods [15,40,42,43].

However, despite the auspicious outcomes that have been reported, all the works have employed *in vitro* models to date. The validation in animal models and clinical trials is mandatory to reach clinical significance and to demonstrate the real impact of the described extracts on human health.

3. Antiproliferative/Antitumoral Activity

Cancer is still the second-leading cause of death worldwide, and it is accompanied by high morbidity, constituting a major concern that has motivated a vast amount of research to find and validate novel alternatives based on natural and edible products that can avoid the disadvantages of anticancer drugs such as the side effects and low specificity [87,88].

Accordingly, STs have also been included in the plethora of plant species that have been studied for this purpose. In this case, research identifying ST fruits as a source of antitumoral compounds is scarce, but a methanolic extract prepared by Guimarães et al. (2014) [32] was shown to be effective in inhibiting the growth of different tumoral cell lines, highlighting its activity against NCI-H460 (non-small lung cancer) cells and correlating the stronger potential of the ST fruit extract (other species such as *Prunus spinosa*, *Rosa micrantha* and *Rosa canina* were also tested) with its particular phenolic profile with a high abundance of galloyl derivatives [32]. Furthermore, Alexandre et al. (2020) obtained a set of extracts, subjecting the fruit residues that were discarded after distillation processes (to prepare alcoholic ST beverages) to supercritical-CO₂ technology using ethanol as a co-solvent and a range of temperatures and pressures [64]. Those obtained at 55 °C and 100 or 300 bar were the most effective as antiproliferative agents against HT-29 (human colorectal adenocarcinoma) cells, and correlations between the activity and the content in specific phenolic compounds such as pyrogallol were observed. Moreover, the growth of HT-29 cells was also inhibited by a protein-rich product with a high content of lectins that was prepared from ST leaves [65]. As a matter of fact, leaves were utilized to generate other extracts using different solvents (water, ethanol, methanol, hexane) that were able to inhibit specific animal and human cell lines such as L20B (rat embryonal rhabdomyosarcoma), Vero (monkey kidney carcinoma), KB (human epithelial carcinoma), HeLa (human cervical epithelial carcinoma), A431 (human epidermoid carcinoma), A375 (human malignant melanoma) and RD (human embryonal rhabdomyosarcoma) [17,66,67]. Besides fruits and leaves, honeys demonstrated cytotoxic effects against human colon adenocarcinoma (HCT-116) and metastatic (LoVo) cells [19] (Table 4). Regarding the involved mechanisms of action that ST compounds exerted against cancerous cells, further investigation is needed to explain the exact actions, although the published works reported that these effects are strongly correlated with the antioxidant activity of ST phenolics [32,64]. Moreover, their ability to scavenge free radicals and other pro-oxidant molecules encourage the conduction of future studies to confirm their ability to prevent carcinogenesis *in vivo*. Thus, animal and human trials are still required to really understand the power of these substances to be used in chemoprevention or anticancer therapies.

Table 4. Cell models and tested concentrations of ST extracts to evaluate in vitro biological activities.

| Evaluated Activity | Cell Model | Tested Concentration(s) | ST Administered Product | Reference |
|---|--------------------------------------|---|---|------------|
| Antioxidant | Human erythrocytes | 50, 75, 100 µg/mL | Fruit aqueous extract | [49] |
| | | 0.4, 0.8, 1.6 mg/mL | Leaves aqueous extract | |
| | <i>Saccharomyces cerevisiae</i> | 250 µg gallic acid-equivalents/mL | Leaved hydroethanolic extract (after in vitro digestion) | [57] |
| | Human peripheral blood lymphocytes | 11.4, 200, 400 µg/mL | Leaves aqueous extract | [59] |
| Antiproliferative/ antitumoral | MCF-7, NCI-H460, HCT-15, HeLa, HepG2 | 25–400 µg/mL | Fruit methanolic extract | [32] |
| | HT29 | 0.125–4 mg/mL | Fruit (residue) supercritical, hydroethanolic and hexane extracts | [64] |
| | KB | 0.05, 0.1, 0.2 mg/mL | Leaves aqueous extract | [66] |
| | HeLa, A431, A375 | 1.56–200 µg/mL | Leaves ethanolic extract | [17] |
| | RD, L20B, Vero | 3.5–250 µg/mL | Leaves ethanolic, methanolic and hexane extracts | [67] |
| | HCT-116 | 3–20 mg/mL | Honeys | [19,68,69] |
| | LoVo | 10–60 mg/mL | | |
| | U202 | 50, 100 µg/mL | Hydromethanolic whole plant extracts | [71] |
| Anti-inflammatory/ immune-modulatory | Human red blood cells | 50–500 µg/mL | Leaves aqueous extract | [56] |
| | A549/8, THP-1 | 0.9–59.2 µg gallic acid-equivalents/mL | Leaves methanolic extract | [75] |
| | MDA-MB-231 | 0.02–29.6 µg gallic acid-equivalents/mL | | [76] |
| | Human fibroblasts | 3.7–14.8 µg gallic acid-equivalents/mL | | |

4. Hypoglycemic Activity

Diabetes is a chronic metabolic disease primarily characterized by hyperglycemia as a consequence of a lack of insulin or resistance. Although diabetic patients are normally treated with therapies that involved drugs (metformin, insulin), novel treatments based on functional dietary ingredients can be certainly advantageous, facilitating administration and avoiding side effects [89]. Fruits, leaves and mainly roots of ST have been used within this approach to obtain hypoglycemic fractions: a methanolic extract from ST fruit with a high content in phenolic compounds inhibited α -glucosidase activity in vitro [31], as well as different ethanolic and hydroalcoholic extracts from fruits and leaves that were additionally able to inhibit α -amylase and contained significant levels of flavonoids and iridoids [55]. Regarding root extracts, pressurized water extraction produced a catechin-rich fraction that was able to inhibit α -glucosidase activity [74], and, besides the in vitro insights, other procedures using hot water resulted in antidiabetic extracts that validated their properties in vivo by inhibiting glucose absorption and enhancing glucose tolerance in healthy Sprague–Dawley rats [25] and also in healthy and diabetic Wistar rats [72,73] (Table 5).

Table 5. Dosage and administration time of ST extracts for testing biological activities in vivo.

| Evaluated Activity | Animal Model | Dosage | Administration | ST Administered Product | Reference |
|-------------------------------------|---|-------------------------------------|---|---------------------------|-----------|
| Hypoglycemic | Sprague–Dawley rats (males and females) | 0.3 and 2 g/kg | Daily at 10:00 h a.m., 6 weeks, intragastric gavage | Root aqueous extract | [25] |
| | Wistar rats (males) | 0.5 g/kg | 30 min before glucose administration, oral administration | | [72] |
| | Wistar rats (males and females) | 0.15 g/kg | 30 min before glucose administration, oral administration | | [73] |
| Anti-inflammatory/immune modulatory | CD mice (males) | 0.02 g (gallic-acid equivalents)/kg | 1 h before carrageenan and saline administration, oral administration | Leaves methanolic extract | [75] |

5. Anti-Inflammatory/Immune-Modulatory Activity

Inflammatory responses against infection, injury, irritation, etc. are non-specific immune mechanisms that can become chronic and are linked to specific conditions such as cardiovascular disease, cancer, arthritis or allergy. Within this context, a plethora of vegetal matrices have been investigated, searching for compounds that exert immune-modulatory or anti-inflammatory properties [90].

Just a few studies have been carried out using ST components to study immune-modulatory function, and most of them utilized leaves as the main source. For instance, Moualek et al. (2016) [56] reported that an aqueous extract obtained from ST leaves showed in vitro anti-inflammatory capacity by inhibiting heat albumin denaturation and showing a protective effect of human erythrocytes membranes against induced hemolysis. The authors attributed this to the ability of the ST extract to modify the calcium influx in red blood cells [56]. The extract was rich in phenolic compounds, as well as those recovered from leaves using methanol [75,76]. In this case, the methanolic fraction inhibited the activation of STAT1 elicited by IFN- γ in MDA-MB-231 (human breast cancer) cells, human fibroblasts and human alveolar epithelial (A549/8) cells. STAT1 is a complex protein that has to be finely controlled to regulate the inflammatory process, i.e., its excessive or erroneous activation might generate exacerbated inflammatory responses [75,76]. Furthermore, this bioactive fraction inhibited STAT3 activation mediated by IL-6 in THP-1 cells (human leukemia monocytes). This activity reduction is considered as a strategy to ameliorate inflammation and was correlated in this work with the down-regulated expression of iNOS and ICAM-1 (both inflammatory genes) in A549/8 and THP-1 cells [75]. The promising in vitro results were validated in vivo in male CD mice that were subjected to carrageenan-induced pleural and lung inflammation. The pleural exudates that were collected from the group that was orally treated with the ST extract showed reduced levels of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6), and the lung injury in animals was also decreased [75].

Apart from leaves extracts, ST honeys and the phenolic fractions obtained from them (using Amberlite XAD-2 resin columns for purification) exerted potent in vitro inhibitory activities against hyaluronidase. Surprisingly, honeys showed a higher inhibition percentage than their extracts, suggesting that other non-phenolic compounds are involved in the anti-inflammatory mechanism of action [21].

6. Antihypertensive/Vasodilatory Activity

Hypertension is a long-term condition associated with persistent blood pressure levels, and it is considered a major risk factor for cardiovascular disease, which is still the leading cause of death worldwide [91]. Most antihypertensive approaches involve the study of the renin-angiotensin system and the inhibition of its enzymes, particularly angiotensin-converting enzyme (ACE). Therefore, many works have looked for ACE-inhibitory dietary

ingredients [92,93], but, surprisingly, this is not the case with *Arbutus unedo*. However, a few studies were conducted that evaluated the effect of ST extracts as vasodilatory agents or as inhibitors of platelet aggregation. In this context, Legssyer et al. (2004) [77] observed an endothelium-dependent vasorelaxant effect of ST leaves extracts obtained with water or methanol and applied to Wistar rat aorta (ex vivo) [77]. These authors also fractionated the methanolic extract using semipreparative high-performance liquid chromatography (HPLC) or caffeine addition for tannins precipitation, and it was observed that polyphenolic compounds such as oligomeric condensed tannins and catechin gallate were the most active molecules. A similar effect was observed for an aqueous roots extract [80], but the vasodilation was not achieved with ST honey [22].

In addition, leaves extracts induced the inhibition of platelet aggregation in vitro. This antiaggregant activity was noticed for an aqueous fraction, but particularly for those obtained using methanol or ethyl acetate. When the methanolic fraction was subjected to tannin precipitation, it was elucidated that tannins were mainly responsible for the inhibitory action [78]. Regarding the mechanism of action, a later study demonstrated that the inhibitory effect exerted by hot water, diethyl ether and ethyl acetate extracts (from ST leaves) was likely mediated by their high antioxidant activity (attenuating ROS production) and their inhibitory capacity against protein tyrosine phosphorylation and calcium influx in the platelets [79].

7. Antimicrobial/Antiviral Activity

Many plant species have been tested as a source of natural antimicrobial compounds to prevent or eliminate the presence of pathogens or non-desirable microorganisms in food products or the human body, i.e., from a technological or clinical perspective [94].

ST components (fruits, leaves, roots and honeys) have been exhaustively investigated for this purpose. Regarding fruits, an ethanolic fraction with a high content of phenolic compounds showed a strong antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Pseudomonas aeruginosa* [30]. Later, an aqueous extract of ST fruit was added to limpet pâtés, and it showed the capacity of controlling the microbial stability of the products along 90 days of preservation, conducting a reduced microbial development compared with the non-supplemented pâtés and with no presence of pathogenic species [15]. However, ST leaves were the material that led to the highest number of studies. A great diversity of extracts (using ethanol, methanol, hot water) constitute an interesting battery of antimicrobials, inhibiting the growth of *S. aureus*, *P. aeruginosa*, *Escherichia coli*, *Enterococcus faecalis*, *Bacillus cereus* and *Mycobacterium* spp. [52–54,80,81]. Moreover, silver nanoparticles prepared with an aqueous ST leave extract were also able to inhibit *S. aureus*, *P. aeruginosa*, *E. coli* and *Staphylococcus epidermis* [82]. Antiviral activity was also reported in the case of an ethanolic leave extract that was effective against herpes simplex virus type-1 [17].

Roots were also subjected to extraction procedures to obtain phenolic-rich products with antimicrobial activities. Dib et al. (2013) reported a poor capacity against *S. aureus* and *P. aeruginosa* for methanolic and aqueous extracts but a moderate capacity against *E. coli* in the case of the water extract [24]. However, when advanced extraction technologies such as PLE were applied to the ST roots, the antibacterial potential was increased, as was shown for the methanolic PLE product that was highly active against *S. aureus*, *E. coli* and *Salmonella* spp. [26].

Finally, a study that evaluated ST honey reported promising antibacterial activities against *S. aureus* and *S. epidermis* and antifungal activity against *Candida* spp. [20]. However, these results were not in concordance with those obtained by Osés et al. (2020) [21], which concluded that ST honeys were not effective against bacteria or fungi. This discordance might be due to the differences in the honeys composition, and when the phenolic fractions were purified from them, the antimicrobial activity was observed. The authors attributed this to the presence of non-phenolic compounds inhibiting the antimicrobial activity in honeys or just to the lower concentration of the active compounds in the original matrix [21].

Despite the significant number of publications addressing antimicrobial properties, further research is needed to elucidate the details of the molecular mechanisms. Nevertheless, it is widely described that phenolic compounds are synthesized in response to microbial infections by plants species such as ST, being effective against a broad range of microorganisms [24]. Moreover, when ST phenolics are orally consumed, gut microbiota species (e.g., *Bifidobacterium* spp.) can utilize glycoside forms exerting β -glucosidase activities and releasing aglycones that might be more active. In this sense, the antibacterial activity of arbutin and its aglycone (hydroquinone) was investigated, and after the *Bifidobacterium* β -glucosidase action, the bioavailability and bioactivity of aglycones were increased [95].

8. Other Biological Activities

Apart from all the bioactivities that were previously described, other particular properties must be highlighted for ST fractions.

For instance, ST leaves were subjected to hydroalcoholic extraction and water infusion, and the resulting products were effective against lithiasis and in the prevention of calcium oxalate's crystals formation [50]. Apparently, the mechanism of action seemed to not be directly related to the antioxidant activity of the extracts and was shown to be dependent on pH variations that stimulated the formation of soluble complexes between functional groups of the active ingredients (phenolics and, mainly, flavonoid derivatives) and calcium oxalate. The *in vitro* insights were promising enough to encourage further investigation to elucidate the litholytic mechanism of action and the potential applications of these fractions in the prevention or treatment of urolithiasis, a condition caused by urinary biochemical disturbances and characterized by the formation of stones in the kidneys or the urinary tract [50].

Furthermore, when leaves were macerated with ethanol, methanol or hexane, the produced infusions—particularly, the hexane fraction—were strongly active against *Leishmania major*, *Leishmania tropica* and *Leishmania infantum*, these being intracellular parasites responsible for leishmaniasis, a tropical and subtropical disease transmitted to humans by the bite of *Phlebotomus* and *Lutzomyia* insects that causes high mortality and morbidity, especially in Africa [16]. The mentioned work did not report correlations between the biological action and the concentration of the studied compounds (total phenolics and flavonoids) and suggested a possible synergistic effect of the minority components. Further studies are required to identify the responsible molecules [16].

An additional interest of *A. unedo* is the presence of arbutin. This phenolic compound, the glycosylated form of hydroquinone, was detected in ST, and, besides antioxidant, anti-inflammatory, antiproliferative and antimicrobial properties, it has attracted the attention of the cosmetic industry due to its potential as a tyrosinase inhibitor in the melanogenesis pathway, i.e., reducing melanin pigments formation and, therefore, being a promising candidate to be used as a skin-whitening agent correcting dark spots or blemishes. However, laboratory procedures of arbutin synthesis have already been developed and are more frequently used than arbutin extraction and purification from natural sources such as ST [96].

9. Conclusions, Current Limitations and Future Perspectives

This work reviewed the scientific literature directly related to *A. unedo* as a source of bioactive fractions. Considering the vast knowledge about ST and the great number of works investigating its properties, it can be concluded that the obtained results are promising enough to encourage further studies that may elucidate the responsible molecules and build stronger evidence for the development of novel functional products.

Although the previously described activities were demonstrated *in vitro*, validation using animal models has not been carried out yet for most of the activities. In fact, only the hypoglycemic action of root extracts was confirmed in rats and mice [25,72,73], but antioxidant, antiproliferative, anti-inflammatory, antimicrobial, antiviral, antileishmanial and anti-urolithiasis activities were evaluated *in vitro* or *ex vivo* in all cases. No clinical trials have been published to date. In addition to the above, it seems that there is an

imbalance in the study of the mentioned capacities, which is mostly focused on antioxidant activity to the detriment of the others (Table 3).

Moreover, some relevant properties have not been tested yet. For instance, no studies addressing the hypocholesterolemic potential of the fractions were found. The presence of phenolics, bioactive lipids and polysaccharides, among others, and the clinical impact of hypercholesterolemia in cardiovascular health suggest that further investigations must be carried out to target ST compounds with the capability of reducing cholesterol absorption and/or biosynthesis. Similarly, the ability to modulate human gut microbiota is still a pending issue that must be studied for ST fractions, since this factor may cause relevant effects on human health status [97,98].

In order to obtain ST bioactive products, several extraction procedures were described in the literature; however, advanced technologies have been used in just a few works. These methodologies are frequently recommended because of their advantages over traditional protocols: a higher specificity, lower solvent volumes, shorter extraction times, etc. These benefits allow for one to work in concordance with the principles of Green Chemistry and lead to environmentally friendly methods linked to sustainability. Therefore, although some of these techniques were applied to ST (supercritical fluids, pressurized liquids, ultrasound and microwave extractions), their utilization, as well as that of other novel ones (pulsed-electric fields, ionic liquids, deep eutectic solvents, solvent-free-microwave extraction, etc.), must be strongly advised [99].

Other weakness of the current status of the art is the lack of works carrying out the purification and isolation of single compounds (except for some phenolic compounds such as arbutin) that might determine compound–activity correlations. A large majority of the studies are only targeting phenolic compounds, without taking into consideration the great diversity of molecules that might exert relevant biological activities (proteins and peptides, carbohydrates, glycoproteins, lipids, secondary metabolites, etc.).

Moreover, since the obtained products may be dietary ingredients, bioaccessibility and bioavailability assays must be conducted, also defining the effect of the food matrix, digestion, interaction with microbiota, etc.

In summary, some points must be further investigated: animal and clinical studies to evaluate biological activities; the assessment of other properties such as hypocholesterolemic or microbiome-modulatory properties; the use of advanced extraction technologies; the purification and isolation of single compounds; the deeper investigation of non-phenolic components; and bioaccessibility and bioavailability studies. The resulting insights may be crucial in validating the auspicious results that were reviewed and described in this work.

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Abbreviations

Strawberry tree (ST), Ante Meridiem (AM), pressurized-liquid extraction (PLE), high-performance liquid chromatography (HPLC), angiotensin-converting enzyme (ACE), interleukin (IL), tumor necrosis factor (TNF).

References

1. Miguel, M.G.; Faleiro, M.L.; Guerreiro, A.C.; Antunes, M.D. *Arbutus unedo* L.: Chemical and biological properties. *Molecules* **2014**, *19*, 15799–15823. [[CrossRef](#)] [[PubMed](#)]
2. Tenuta, M.C.; Tundis, R.; Xiao, J.; Loizzo, M.R.; Dugay, A.; Deguin, B. *Arbutus* species (Ericaceae) as source of valuable bioactive products. *Crit. Rev. Food Sci. Nutr.* **2019**, *59*, 864–881. [[CrossRef](#)]
3. Gul Sarikaya, A.; Orucu, O.K. Maxent modeling for predicting the potential distribution of *Arbutus andrachne* L. belonging to climate change in Turkey. *Kuwait J. Sci.* **2021**, *48*, 1–13. [[CrossRef](#)]
4. Serçe, S.; Özgen, M.; Torun, A.A.; Ercisli, S. Chemical composition, antioxidant activities and total phenolic content of *Arbutus andrachne* L. (Fam. Ericaceae) (the Greek strawberry tree) fruits from Turkey. *J. Food Compos. Anal.* **2010**, *23*, 619–623. [[CrossRef](#)]
5. Salas-Pascual, M.; Déniz Suárez, E.A. News and precisions about the distribution of the species of the genus *Arbutus* L. (Ericaceae) in Gran Canaria (Canary Islands). *Bot. Complut.* **2019**, *43*, 85–96. [[CrossRef](#)]
6. Kabiél, H.F.; Hegazy, A.K.; Lovett-Doust, L.; Al-Rowaily, S.L.; Borki, A.E.N. Demography of the threatened endemic shrub, *Arbutus pavarii*, in the Al-Akhdar mountainous landscape of Lybia. *J. For. Res.* **2016**, *27*, 1295–1303. [[CrossRef](#)]
7. Silva-González, E.; Aguirre-Calderón, O.A.; Rodríguez, E.A.; González Tagle, M.A.; Treviño-Garza, E.J.; Corral-Rivas, J.J. Assessment of the forest harvesting effect on the diversity and structure of a temperate forest in the state of Durango. *Rev. Mex. Cienc. For.* **2022**, *13*, 103–132. [[CrossRef](#)]
8. Kamakura, R.P.; DeWald, L.E.; Sniezko, R.A.; Elliot, M.; Chastagner, G.A. Using differences in abiotic factors between seed origin and common garden sites to predict performance of Pacific madrone (*Arbutus menziesii* Pursh). *For. Ecol. Manag.* **2021**, *497*, 119487. [[CrossRef](#)]
9. Sorensen, P.D. *Arbutus tessellata* (Ericaceae), new from Mexico. *Brittonia* **1987**, *39*, 263–267. [[CrossRef](#)]
10. Ruiz-Aquino, F.; Santiago-García, W.; Suárez-Mota, M.E.; Esquivel-Reyes, H.H.; Feria-Reyes, R.; Rutiaga-Quiñones, J.G. Development and validation of an analytical method for condensed tannin extracts obtained from the bark of four tree species using HPLC. *Wood Res.* **2021**, *66*, 171–182. [[CrossRef](#)]
11. Bertsoyklis, K.F.; Daskalakis, I.; Biniari, K.; Papafotiou, M. Comparative study of polyphenolic content and antioxidant capacity in fruits of *Arbutus unedo*, *A. andrachne* and their natural hybrid *A. × andrachnoides*. *Notulae Bot. Horti Agrobot. Cluj-Napoca* **2021**, *49*, 12165. [[CrossRef](#)]
12. Ait Lhaj, Z.; Bchitou, R.; Gaboun, F.; Abdelwahd, R.; Benabdelouahab, T.; Kabbour, M.R.; Pare, P.; Diria, G.; Bakhy, K. Moroccan strawberry tree (*Arbutus unedo* L.) fruits: Nutritional value and mineral composition. *Foods* **2021**, *10*, 2263. [[CrossRef](#)]
13. Morgado, S.; Morgado, M.; Plácido, A.I.; Roque, F.; Duarte, A.P. *Arbutus unedo* L.: From traditional medicine to potential uses in modern pharmacotherapy. *J. Ethnopharmacol.* **2018**, *225*, 90–102. [[CrossRef](#)] [[PubMed](#)]
14. Benchikh, Y.; Sahli, S.; Alleg, M.; Mohellebi, N.; Gagaoua, M. Optimised statistical extraction of anthocyanins from *Arbutus unedo* L. fruits and preliminary supplementation assays in yoghurt. *Int. J. Dairy Technol.* **2021**, *74*, 344–351. [[CrossRef](#)]
15. Pinheiro, J.; Rodrigues, S.; Mendes, S.; Maranhao, P.; Ganhao, R. Impacto f aqueous extract of *Arbutus unedo* fruits on limpets (*Patella* spp.) pâté during storage: Proximate composition, physicochemical quality, oxidative stability, and microbial development. *Foods* **2020**, *9*, 807. [[CrossRef](#)] [[PubMed](#)]
16. Bouyahya, A.; Et-Touys, A.; Dakka, N.; Fellah, H.; Abrini, J.; Bakri, Y. Antileishmanial potential of medicinal plant extracts from the North-West of Morocco. *Beni-Suef Univ. J. Basic Appl. Sci.* **2018**, *7*, 50–54. [[CrossRef](#)]
17. Twilley, D.; Langhansova, L.; Palaniswamy, D.; Lall, N. Evaluation of traditionally used medicinal plants for anticancer, antioxidant, anti-inflammatory and anti-viral (HPV-1) activity. *S. Afr. J. Bot.* **2017**, *112*, 494–500. [[CrossRef](#)]
18. Selen Isbilir, S.; Yagar, H. Determination of antioxidant activities of strawberry tree (*Arbutus unedo* L.) flowers and fruits at different ripening stages. *Acta Sci. Pol.* **2012**, *11*, 223–237.
19. Afrin, S.; Forbes-Hernández, T.Y.; Gasparrini, M.; Bompadre, S.; Quiles, J.L.; Sanna, G.; Spano, N.; Giampieri, F.; Battino, M. Strawberry-tree honey induces growth inhibition of human colon cancer cells and increases ROS generation: A comparison with manuka honey. *Int. J. Molec. Sci.* **2017**, *18*, 613. [[CrossRef](#)]
20. Graikou, K.; Andreou, A.; Chinou, I. Chemical profile of Greek *Arbutus unedo* honey: Biological properties. *J. Apic. Res.* **2022**, *61*, 100–106. [[CrossRef](#)]
21. Osés, S.M.; Nieto, S.; Rodrigo, S.; Pérez, S.; Rojo, S.; Sancho, M.T.; Fernández-Muiño, M.A. Authentication of strawberry tree (*Arbutus unedo* L.) honeys from southern Europe based on compositional parameters and biological activities. *Food Biosci.* **2020**, *38*, 100768. [[CrossRef](#)]
22. Tuberoso, C.I.G.; Boban, M.; Bifulco, E.; Budimir, D.; Pirisi, F.M. Antioxidant capacity and vasodilatory properties of Mediterranean food: The case of Cannonau wine, myrtle berries liqueur and strawberry-tree honey. *Food Chem.* **2013**, *140*, 686–691. [[CrossRef](#)] [[PubMed](#)]
23. Andrade, D.; Gil, C.; Breitenfeld, L.; Domingues, F.; Duarte, A.P. Bioactive extracts from *Cistus ladanifer* and *Arbutus unedo* L. *Ind. Crop. Prod.* **2009**, *30*, 165–167. [[CrossRef](#)]
24. Dib, M.E.A.; Allali, H.; Bendiabdellah, A.; Meliani, N.; Tabti, B. Antimicrobial activity and phytochemical screening of *Arbutus unedo* L. *J. Saudi Chem. Soc.* **2013**, *17*, 381–385. [[CrossRef](#)]
25. Mrabti, H.N.; el Abbes Faouzi, M.; Mayuk, F.M.; Makrane, H.; Limas-Nzouzi, N.; Dibong, S.D.; Cherrah, Y.; Elombo, F.K.; Gressier, B.; Desjeux, J.F.; et al. *Arbutus unedo* L. (Ericaceae) inhibits intestinal glucose absorption and improves glucose tolerance in rodents. *J. Ethnopharmacol.* **2019**, *235*, 385–391. [[CrossRef](#)] [[PubMed](#)]
26. Mrabti, H.N.; Bouyahya, A.; Ed-Dra, A.; Kachmar, M.R.; Mrabti, N.N.; Benali, T.; Shariati, M.A.; Ouahbi, A.; Doudach, L.; Faouzi, M.E.A. Polyphenolic profile and biological properties of *Arbutus unedo* root extracts. *Eur. J. Integr. Med.* **2021**, 101266. [[CrossRef](#)]

27. Ziyayat, A.; Mekhfi, H.; Bnouham, M.; Tahri, A.; Legssyer, A.; Hoerter, J.; Fischmeister, R. *Arbutus unedo* induces endothelium-dependent relaxation of the isolated rat aorta. *Phytother. Res.* **2002**, *16*, 572–575. [[CrossRef](#)] [[PubMed](#)]
28. Albuquerque, B.R.; Prieto, M.A.; Vazquez, J.A.; Barreiro, M.F.; Barros, L.; Ferreira, I.C.F.R. Recovery of bioactive compounds from *Arbutus unedo* L. fruits: Comparative optimization study of maceration/microwave/ultrasound extraction techniques. *Food Res. Int.* **2018**, *109*, 455–471. [[CrossRef](#)] [[PubMed](#)]
29. El Cadi, H.; El Cadi, A.; Kounoun, A.; Oulad El Majdoub, Y.; Palma Lovillo, M.; Brigui, J.; Dugo, P.; Mondello, L.; Cacciola, F. Wild strawberry (*Arbutus unedo*): Phytochemical screening and antioxidant properties of fruits collected in northern Morocco. *Arabian J. Chem.* **2020**, *13*, 6299–6311. [[CrossRef](#)]
30. Salem, I.B.; Ouesleti, S.; Mabrouk, Y.; Landolsi, A.; Saidi, M.; Boulilla, A. Exploring the nutraceutical potential and biological activities of *Arbutus unedo* L. (Ericaceae) fruits. *Ind. Crops Prod.* **2018**, *122*, 726–731. [[CrossRef](#)]
31. Macchioni, V.; Santarelli, V.; Carbone, K. Phytochemical profile, antiradical capacity and α -glucosidase inhibitory potential of wild *Arbutus unedo* L. fruits from Central Italy: A chemometric approach. *Plants* **2020**, *9*, 1785. [[CrossRef](#)]
32. Guimarães, R.; Barros, L.; Calhela, R.C.; Carvalho, A.M.; Queiroz, M.J.R.P.; Ferreira, I.C.F.R. Bioactivity of different enriched phenolic extracts of wild fruits from Northeastern Portugal: A comparative study. *Plants Foods Hum. Nutr.* **2014**, *69*, 37–42. [[CrossRef](#)] [[PubMed](#)]
33. Ruiz-Rodríguez, B.M.; Sánchez-Moreno, C.; de Ancos, B.; Cortes Sánchez-Mata, M.; Fernández-Ruiz, V.; Cámara, M.; Tardío, J. Wild *Arbutus unedo* L. and *Rubus ulmifolius* Schott fruits are underutilized sources of valuable bioactive compounds with antioxidant capacity. *Fruits* **2014**, *69*, 435–448. [[CrossRef](#)]
34. Oliveira, I.; Baptista, P.; Malheiro, R.; Casal, S.; Bento, A.; Pereira, J.A. Influence of strawberry tree (*Arbutus unedo* L.) fruit ripening stage on chemical composition and antioxidant activity. *Food Res. Int.* **2011**, *44*, 1401–1407. [[CrossRef](#)]
35. Alexandre, A.M.R.C.; Matias, A.; Duarte, C.M.M.; Bronze, M.R. High-pressure CO₂ assisted extraction as a tool to increase phenolic content of strawberry-tree (*Arbutus unedo*) extracts. *J. CO₂ Util.* **2018**, *27*, 73–80. [[CrossRef](#)]
36. Orak, H.H.; Aktas, T.; Yagar, H.; Isbilir, S.S.; Ekinici, N.; Sahin, F.H. Effects of hot air and freeze drying methods on antioxidant activity, colour and some nutritional characteristics of strawberry tree (*Arbutus unedo* L.) fruit. *Food Sci. Technol. Int.* **2012**, *18*, 391–402. [[CrossRef](#)] [[PubMed](#)]
37. Zitouni, H.; Hssaini, L.; Ouaabou, R.; Viuda-Martos, M.; Hernández, F.; Ercisli, S.; Ennahli, S.; Messaoudi, Z.; Hanine, H. Exploring antioxidant activity, organic acid, and phenolic composition in strawberry tree fruits (*Arbutus unedo* L.) growing in Morocco. *Plants* **2020**, *9*, 167. [[CrossRef](#)]
38. Barros, L.; Carvalho, A.M.; Morais, J.S.; Ferreira, I.C.F.R. Strawberry-tree, blackthorn and rose fruits: Detailed characterization in nutrients and phytochemicals with antioxidant properties. *Food Chem.* **2010**, *120*, 247–254. [[CrossRef](#)]
39. Takwa, S.; Caleja, C.; Barreira, J.C.M.; Sokovic, M.; Achour, L.; Barros, L.; Ferreira, I.C.F.R. *Arbutus unedo* L. and *Ocimum basilicum* L. as sources of natural preservatives for food industry: A case study using loaf bread. *LWT Food Sci. Technol.* **2018**, *88*, 47–55. [[CrossRef](#)]
40. Masmoudi, M.; Ammar, I.; Ghribi, H.; Attia, H. Physicochemical, radical scavenging activity and sensory properties of a soft cheese fortified with *Arbutus unedo* L. extract. *Food Biosci.* **2020**, *35*, 100579. [[CrossRef](#)]
41. López, C.J.; Caleja, C.; Prieto, M.A.; Sokovic, M.; Calhela, R.C.; Barros, L.; Ferreira, I.C.F.R. Stability of a cyanidin-3-O-glucoside extract obtained from *Arbutus unedo* L. and incorporation into wafers for colouring purposes. *Food Chem.* **2019**, *275*, 426–438. [[CrossRef](#)] [[PubMed](#)]
42. Armenteros, M.; Morcuende, D.; Ventanas, S.; Estévez, M. Application of natural antioxidants from strawberry tree (*Arbutus unedo* L.) and dog rose (*Rosa canina* L.) to Frankfurters subjected to refrigerates storage. *J. Integr. Agric.* **2013**, *12*, 1972–1981. [[CrossRef](#)]
43. Ganhão, R.; Estévez, M.; Armenteros, M.; Morcuende, D. Mediterranean berries as inhibitors of lipid oxidation in porcine burger patties subjected to cooking and chilled storage. *J. Integr. Agric.* **2013**, *12*, 1982–1992. [[CrossRef](#)]
44. Ganhão, R.; Morcuende, D.; Estévez, M. Protein oxidation in emulsified cooked burger patties with added fruit extracts: Influence on colour and texture deterioration during chill storage. *Meat Sci.* **2010**, *85*, 402–409. [[CrossRef](#)]
45. Erdogan, G.; Uysal, T. Characterization of antioxidant properties of strawberry tree (*Arbutus unedo* L.) and trace elements determination. *J. Res. Pharm.* **2020**, *24*, 774–785. [[CrossRef](#)]
46. Boulanouar, B.; Abdelaziz, G.; Aazza, S.; Gago, C.; Miguel, M.G. Antioxidant activities of eight Algerian plant extracts and two essential oils. *Ind. Crops Prod.* **2013**, *46*, 85–96. [[CrossRef](#)]
47. Asmaa, N.; Abdelaziz, G.; Boulanouar, B.; Carbonell-Barrachina, A.A.; Cano-Lamadrid, M.; Noguera-Artiaga, L. Chemical composition, antioxidant activity and mineral content of *Arbutus unedo* (leaves and fruits). *J. Microbiol. Biotechnol. Food Sci.* **2019**, *8*, 1335–1339. [[CrossRef](#)]
48. Zlabur, J.S.; Bogdanovic, S.; Voca, S.; Babojelic, M.S. Biological potential of fruit and leaves of strawberry tree (*Arbutus unedo* L.) from Croatia. *Molecules* **2020**, *25*, 5102. [[CrossRef](#)]
49. Mendes, L.; de Freitas, V.; Baptista, P.; Carvalho, M. Comparative antihemolytic and radical scavenging activities of strawberry tree (*Arbutus unedo* L.) leaf and fruit. *Food Chem. Toxicol.* **2011**, *49*, 2285–2291. [[CrossRef](#)]
50. Kachkoul, R.; Squalli Housseini, T.; Mohim, M.; el Habbani, R.; Miyah, Y.; Lahrchi, A. Chemical compounds as well as antioxidant and litholytic activities of *Arbutus unedo* L. leaves against calcium oxalate stones. *J. Integr. Med.* **2019**, *17*, 430–437. [[CrossRef](#)]
51. Nenadis, N.; Llorens, L.; Koufogianni, A.; Díaz, L.; Font, J.; Gonzalez, J.A.; Verdaguer, D. Interactive effects of UV radiation and reduced precipitation on the seasonal leaf phenolic content/composition and the antioxidant activity of naturally growing *Arbutus unedo* plants. *J. Photochem. Photobiol. B Biol.* **2015**, *153*, 435–444. [[CrossRef](#)] [[PubMed](#)]

52. Guendouze-Bouchefa, N.; Madani, K.; Chibane, M.; Boulekbache-Makhlouf, L.; Hauchard, D.; Kiendrebeogo, M.; Stevigny, C.; Okusa, P.N.; Duez, P. Phenolic compounds, antioxidant and antibacterial activities of three Ericaceae from Algeria. *Ind. Crops Prod.* **2015**, *70*, 459–466. [[CrossRef](#)]
53. Malheiro, R.; Sá, O.; Pereira, E.; Aguiar, C.; Baptista, P.; Pereira, J.A. *Arbutus unedo* L. leaves as source of phytochemicals with bioactive properties. *Ind. Crops Prod.* **2012**, *37*, 473–478. [[CrossRef](#)]
54. Jurica, K.; Gobin, I.; Kremer, D.; Cepo, D.V.; Grubescic, R.J.; Karaconji, I.B.; Kosalec, I. Arbutin and its metabolite hydroquinone as the main factors in the antimicrobial effect of strawberry tree (*Arbutus unedo* L.) leaves. *J. Herb. Med.* **2017**, *8*, 17–23. [[CrossRef](#)]
55. Tenuta, M.C.; Deguin, B.; Loizzo, M.R.; Dugay, A.; Acquaviva, R.; Malfa, G.A.; Bonesi, M.; Bouzidi, C.; Tundis, R. Contribution of flavonoids and iridoids to the hypoglycaemic, antioxidant, and nitric oxide (NO) inhibitory activities of *Arbutus unedo* L. *Antioxid* **2020**, *9*, 184. [[CrossRef](#)]
56. Moualek, I.; Iratni Aiche, G.; Mestar Guechaoui, N.; Lahcene, S.; Houali, K. Antioxidant and anti-inflammatory activities of *Arbutus unedo* aqueous extract. *Asian Pac. J. Trop. Biomed.* **2016**, *6*, 937–944. [[CrossRef](#)]
57. Jardim, 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](#)]
58. Erkekoglou, I.; Nenadis, N.; Samara, E.; Mantzouridou, F.T. Functional teas from the leaves of *Arbutus unedo*: Phenolic content, antioxidant activity and detection of efficient radical scavengers. *Plants Foods Hum. Nutr.* **2017**, *72*, 176–183. [[CrossRef](#)]
59. Jurica, K.; Brcic Karaconji, I.; Mikolic, A.; Milojhovic-Opsenica, D.; Benkovic, V.; Kopjar, N. In vitro safety assessment of the strawberry tree (*Arbutus unedo* L.) water leaf extract and arbutin in human peripheral blood lymphocytes. *Cytotechnology* **2018**, *70*, 1261–1278. [[CrossRef](#)]
60. Alves, A.; Ramos, A.; Gonçalves, M.M.; Bernardo, M.; Mendes, B. Antioxidant activity, quality parameters and mineral content of Portuguese monofloral honeys. *J. Food Compos. Anal.* **2013**, *30*, 130–138. [[CrossRef](#)]
61. Tariba Lovakovic, B.; Lazarus, M.; Brcic Karaconji, I.; Jurica, K.; Zivkovic Semren, T.; Lusic, D.; Brajenovic, N.; Pelaic, Z.; Pizent, A. Multi-elemental composition and antioxidant properties of strawberry tree (*Arbutus unedo* L.) honey from the coastal region of Croatia: Risk-benefit analysis. *J. Trace Elem. Med. Biol.* **2018**, *45*, 85–92. [[CrossRef](#)] [[PubMed](#)]
62. Rosa, A.; Tuberoso, C.I.G.; Atzeri, A.; Melis, M.P.; Bifulco, E.; Dess, M.A. Antioxidant profile of strawberry tree honey and its marker homogentistic acid in several models of oxidative stress. *Food Chem.* **2011**, *129*, 1045–1053. [[CrossRef](#)] [[PubMed](#)]
63. Djabou, N.; Dib, M.E.A.; Allali, H.; Benderb, A.; Kamal, M.A.; Ghalem, S.; Tabti, B. Evaluation of antioxidant and antimicrobial activities of the phenolic composition of Algerian *Arbutus unedo* L. roots. *Pharmacogn. J.* **2013**, *5*, 275–280. [[CrossRef](#)]
64. Alexandre, A.M.R.C.; Serra, A.T.; Matias, A.A.; Duarte, C.M.M.; Bronze, M.R. Supercritical fluid extraction of *Arbutus unedo* distillate residues—Impact of process conditions on antiproliferative response of extracts. *J. CO₂ Util.* **2020**, *37*, 29–38. [[CrossRef](#)]
65. Oliveira, I.; Nunes, A.; Lima, A.; Borralho, P.; Rodrigues, C.; Ferreira, R.B.; Ribeiro, A.C. New lectins from mediterranean flora. Activity against HT29 colon cancer cells. *Int. J. Molec. Sci.* **2019**, *20*, 3059. [[CrossRef](#)]
66. Yu, Y.; Fei, Z.; Cui, J.; Miao, B.; Lu, Y.; Wu, J. Biosynthesis of copper oxide nanoparticles and their *in vitro* cytotoxicity towards nasopharynx cancer (KB cells) cell lines. *Int. J. Pharmacol.* **2018**, *14*, 609–614. [[CrossRef](#)]
67. Bouyahya, A.; Bakri, Y.; Et-Touys, A.; Assemian, I.C.C.; Abrini, J.; Dakka, N. In vitro antiproliferative activity of selected medicinal plants from the North-West of Morocco on several cancer cell lines. *Eur. J. Integr. Med.* **2018**, *18*, 23–29. [[CrossRef](#)]
68. Afrin, S.; Giampieri, F.; Cianciosi, D.; Pistollato, F.; Ansary, J.; Pacetti, M.; Amici, A.; Reboredo-Rodríguez, P.; Simal-Gandara, J.; Quiles, J.L.; et al. Strawberry tree honey as a new potential functional food. Part 1: Strawberry tree honey reduces colon cancer cell proliferation and colony formation ability, inhibits cell cycle and promotes apoptosis by regulating EGFR and MAPKs signaling pathways. *J. Funct. Foods* **2019**, *57*, 439–452. [[CrossRef](#)]
69. Afrin, S.; Forbes-Hernández, T.Y.; Cianciosi, D.; Pistollato, F.; Zhang, J.J.; Pacetti, M.; Amici, A.; Reboredo-Rodríguez, P.; Simal-Gandara, J.; Bompadre, S.; et al. Strawberry tree honey as a new potential functional food. Part 2: Strawberry tree honey increases ROS generation by suppressing Nrf2-ARE and NF- κ B signaling pathways and decreases metabolic phenotypes and metastatic activity in colon cancer cells. *J. Funct. Foods* **2019**, *57*, 477–487. [[CrossRef](#)]
70. Forni, C.; Frattarelli, A.; Lentini, A.; Beninati, S.; Lucioli, S.; Caboni, E. Assessment of the antiproliferative activity on murine melanoma cells of extracts from elicited cell suspensions of strawberry, strawberry tree, blackberry and red raspberry. *Plant Biosyst.* **2016**, *150*, 1233–1239. [[CrossRef](#)]
71. Cappadone, C.; Mandrone, M.; Chiocchio, I.; Sanna, C.; Malucelli, E.; Bassi, V.; Picone, G.; Poli, F. Antitumor potential and phytochemical profile of plants from Sardinia (Italy), a hotspot for biodiversity in the Mediterranean Basin. *Plants* **2020**, *9*, 26. [[CrossRef](#)] [[PubMed](#)]
72. Bnouham, M.; Merhfour, F.Z.; Legssyer, A.; Mekhfi, H.; Maallem, S.; Ziyat, A. Antihyperglycemic activity of *Arbutus unedo*, *Ammoides pusilla* and *Thymelaea hirsuta*. *Pharmazie* **2007**, *62*, 630–632. [[CrossRef](#)] [[PubMed](#)]
73. Bnouham, M.; Merhfour, F.Z.; Ziyat, A.; Aziz, M.; Legssyer, A.; Mekhfi, H. Antidiabetic effect of some medicinal plants of Oriental Morocco in neonatal non-insulin-dependent diabetes mellitus rats. *Hum. Exp. Toxicol.* **2010**, *29*, 865–871. [[CrossRef](#)] [[PubMed](#)]
74. Mrabti, H.N.; Jaradat, N.; Fichtali, I.; Ouedrhiri, W.; Jodeh, S.; Ayes, S.; Cherrah, Y.; Faouzi, M.E.A. Separation, identification, and antidiabetic activity of catechin isolated from *Arbutus unedo* L. plant roots. *Plants* **2018**, *7*, 31. [[CrossRef](#)]

75. Mariotto, S.; Esposito, E.; di Paola, R.; Ciampa, A.; Mazzon, E.; de Prati, A.C.; Darra, E.; Vincenzi, S.; Cucinotta, G.; Caminiti, R.; et al. Protective effect of *Arbutus unedo* aqueous extract in carrageenan-induced lung inflammation in mice. *Pharmacol. Res.* **2008**, *57*, 110–124. [[CrossRef](#)]
76. Mariotto, S.; Ciampa, A.R.; Carcereri De Prati, A.; Darra, E.; Vincenzi, S.; Segal, M.; Cavalieri, E.; Shoji, K.; Suzuki, H. Aqueous extract of *Arbutus unedo* inhibits STAT1 activation in human breast cancer cell line MDA-MB-231 and human fibroblasts through SHP2 activation. *Med. Chem.* **2008**, *4*, 219–228. [[CrossRef](#)]
77. Legssyer, A.; Ziyat, A.; Mekhfi, H.; Bnouham, M.; Herrenknecht, C.; Roumy, V.; Fourneau, C.; Laurens, A.; Hoerter, J.; Fischmeister, R. Tannins and catechin gallate mediate the vasorelaxant effect of *Arbutus unedo* on the rat isolated aorta. *Phytother. Res.* **2004**, *18*, 889–894. [[CrossRef](#)]
78. Mekhfi, H.; El Haouari, M.; Bnouham, M.; Aziz, M.; Ziyat, A.; Legssyer, A. Effects of extracts and tannins from *Arbutus unedo* leaves on rat platelet aggregation. *Phytother. Res.* **2006**, *20*, 135–139. [[CrossRef](#)]
79. El Haouari, M.; López, J.J.; Mekhfi, H.; Rosado, J.A.; Salido, G.M. Antiaggregant effects of *Arbutus unedo* extracts in human platelets. *J. Ethnopharmacol.* **2007**, *113*, 325–331. [[CrossRef](#)]
80. Dimkic, I.; Gobin, I.; Begic, G.; Antic, D.R.; Ristivojevic, P.; Jurica, K.; Beric, T.; Lozo, J.; Abram, M.; Stankovic, S. Antibacterial activity of herbal extracts towards uropathogenic *Enterococcus* isolates as a natural approach in control of urinary tract infections. *J. Herb. Med.* **2021**, *28*, 100445. [[CrossRef](#)]
81. Asmae, E.O.; Amina, C.H.; Hakima, S.; Abdellatif, H.; Abdeslam, E.; Saad, I.; Mohamed, L.; Mohammed, I. Extra- and intracellular antimycobacterial activity of *Arbutus unedo* L. *Afr. J. Microbiol. Res.* **2012**, *6*, 1283–1290. [[CrossRef](#)]
82. Skandalis, N.; Dimopoulou, A.; Georgopoulou, A.; Gallios, N.; Papadopoulos, D.; Tsipas, D.; Theologidis, I.; Michailidis, N.; Chatzinikolaidou, M. The effect of silver nanoparticles size, produced using plant extract from *Arbutus unedo*, on their antibacterial efficacy. *Nanomater.* **2017**, *7*, 178. [[CrossRef](#)]
83. Kachkoul, R.; Sqalli Houssaini, T.; El Habbani, R.; Miyah, Y.; Mohim, M.; Lahrichi, A.; Sidi Mohammed Ben Abdellah, U. Phytochemical screening and inhibitory activity of oxalocalcic crystallization of *Arbutus unedo* L. leaves. *Heliyon* **2018**, *4*, 1011. [[CrossRef](#)] [[PubMed](#)]
84. Jurica, K.; Benkovic, V.; Sikiric, S.; Kopjar, N.; Brcic Karaconji, I. Liver function and DNA integrity in hepatocytes of rats evaluated after treatments with strawberry tree (*Arbutus unedo* L.) water leaf extract and arbutin. *Drug Chem. Toxicol.* **2020**, *43*, 127–137. [[CrossRef](#)]
85. Pizzino, G.; Irrera, N.; Cucinotta, M.; Pallio, G.; Mannino, F.; Arcoraci, V.; Squadrito, F.; Altavilla, D.; Bitto, A. Oxidative stress: Harms and benefits for human health. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 8416763. [[CrossRef](#)] [[PubMed](#)]
86. Morales, D. Oak trees (*Quercus* spp.) as a source of extracts with biological activities: A narrative review. *Trends Food Sci. Technol.* **2021**, *109*, 116–125. [[CrossRef](#)]
87. Yussof, I.M.; Mat Taher, Z.; Rahmat, Z.; Chua, L.S. A review of ultrasound-assisted extraction for plant bioactive compounds: Phenolics, flavonoids, thymols, saponins and proteins. *Food Res. Int.* **2022**, *157*, 111268. [[CrossRef](#)]
88. Trivedi, S.; Patel, K.; Belgamwar, V.; Wadher, K. Functional polysaccharide lentinan: Role in anti-cancer therapies and management of carcinomas. *Pharmacol. Res. Mod. Chin. Med.* **2022**, *2*, 100045. [[CrossRef](#)]
89. Kazeem, M.I.; Bankole, H.A.; Fatai, A.A.; Saibu, G.M.; Wusu, A.D. Genus *Aloe* as sources of antidiabetic, antihyperglycemic and hypoglycemic agents: A review. *S. Afr. J. Bot.* **2022**, *147*, 1070–1077. [[CrossRef](#)]
90. Gandhi, G.R.; Antony, P.J.; Lana, M.J.M.; da Silva, B.F.X.; Oliveira, R.V.; Jothi, G.; Hariharan, G.; Mohana, T.; Gan, R.Y.; Gurgel, R.Q.; et al. Natural products modulating interleukins and other inflammatory mediators in tumor-bearing animals: A systematic review. *Phytomed.* **2022**, *100*, 154038. [[CrossRef](#)]
91. Ibarz-Blanch, N.; Morales, D.; Calvo, E.; Ros-Medina, L.; Muguerza, B.; Bravo, F.I.; Suárez, M. Role of chrononutrition in the antihypertensive effects of natural bioactive compounds. *Nutrients* **2022**, *14*, 1920. [[CrossRef](#)]
92. Morales, D.; Miguel, M.; Garcés-Rimón, M. Pseudocereals: A novel source of biologically active peptides. *Crit. Rev. Food Sci. Nutr.* **2021**, *61*, 1537–1544. [[CrossRef](#)] [[PubMed](#)]
93. Wu, J.; Liao, W.; Udenigwe, C.C. Revisiting the mechanisms of ACE inhibitory peptides from food proteins. *Trends Food Sci. Technol.* **2017**, *69*, 214–219. [[CrossRef](#)]
94. Angiolella, L.; Sacchetti, G.; Efferth, T. Antimicrobial and antioxidant activities of natural compounds. *Evid. Based Complem. Altern. Med.* **2018**, *2018*, 1945179. [[CrossRef](#)] [[PubMed](#)]
95. Modrackova, N.; Vlkova, E.; Tejnecky, V.; Schwab, C.; Neuzil-Bunesova, V. *Bifidobacterium* β -glucosidase activity and fermentation of dietary plant glucosides is species and strain specific. *Microorganisms* **2020**, *8*, 839. [[CrossRef](#)]
96. Rudeekulthamrong, P.; Kaulpiboon, J. Optimization of amylomaltase for the synthesis of α -arbutin derivatives as tyrosinase inhibitors. *Carbohydr. Res.* **2020**, *494*, 108078. [[CrossRef](#)]
97. Morales, D.; Shetty, S.A.; López-Plaza, B.; Gómez-Candela, C.; Smidt, H.; Marín, F.R.; Soler-Rivas, C. Modulation of human intestinal microbiota in a clinical trial by consumption of a β -D-glucan-enriched extract obtained from *Lentinula edodes*. *Eur. J. Nutr.* **2021**, *60*, 3249–3265. [[CrossRef](#)] [[PubMed](#)]
98. Vamanu, E.; Gatea, F. Correlations between microbiota bioactivity and bioavailability of functional compounds: A mini-review. *Biomedicine* **2020**, *8*, 39. [[CrossRef](#)] [[PubMed](#)]
99. Fierascu, R.C.; Fierascu, I.; Avramescu, S.M.; Sieniawska, E. Recovery of natural antioxidants from agro-industrial side streams through advanced extraction techniques. *Molecules* **2019**, *24*, 4212. [[CrossRef](#)] [[PubMed](#)]