Review

Plantago media L.—Explored and Potential Applications of an Underutilized Plant

Radu Claudiu Fierascu 1,2, Irina Fierascu 1,3,* Alina Ortan 3 and Alina Paunescu 4

Abstract: The search of valuable natural compounds should be directed towards alternative vegetal resources, and to the re-discovery of underutilized plants. Belonging to the Plantaginaceae family, the hoary plantain (Plantago media L.) represents one of the lesser studied species from the Plantago genus. The literature study revealed the under-utilization of the hoary plantain, a surprising aspect, considering its widespread. If the composition of Plantago media L. is rather well established, its applications are not nearly studied as for other Plantago species. The goal of the present paper is to summarize the findings regarding the applications of P. media, and, having as starting point the applications of related species, to propose new emerging areas of research, such as the biomedical applications validation through in vivo assays, and the evaluation of its potential towards industrial applications (i.e., development of food or personal care products), pisciculture or zootechny, phytoremediation and other environmental protection applications, or in the nanotechnology area (materials phytosynthesis). The present work constitutes not only a brief presentation of this plant’s present and potential applications, but also an invitation to research groups world-wide to explore the available vegetal resources.

Keywords: Plantago media L; composition; biomedical applications; potential uses

1. Introduction

Accompanying the development of human civilization, plants were commonly used as food, feed or for empirical medicinal purposes [1]. The development of the modern medicine led to the loss of important ethnomedicinal data, accompanied by the disappearance or the reduction of the growing area of medicinally important plants [2]. However, the last decades led to the resurrection of alternative, plant-based medicine [3], together with a search of alternative, “bio” products [4], as well as the discovery of new potential applications of the vegetal materials [5]. Several plant-originating biomolecules have even pursued the long road from “plant to pharmacy shelf”, resulting in economically important commercial products [6]. With the identification of commercially valuable phytochemicals, the vegetal resources could become the subject of over-harvesting, producing environmental or ecological imbalances [6]. This could be avoided by continuously searching for alternative vegetal resources, and by the re-discovery of underutilized plants.

The Plantaginaceae family contains herbs or small shrubs, their habitat ranging from terrestrial to aquatic. The family contains only one genus and approximatively 270 species [7]. Plantago genus is characterized by a wide variety of component phytochemicals, but the most encountered are the iridoid glucosides, flavonoids, hydroxycinnamic acids,
terpenoids, polysaccharides, unsaturated fatty acids, vitamins, alkaloids, terpenes and saponins (leaves), respectively xylose and galacturonic acid (mucilaginous seeds) [8,9]. The genus is world-wide represented, several species having a weedy character [7].

Belonging to the Plantaginaceae family, the hoary plantain (Plantago media L.) represents one of the lesser studied species from the Plantago genus. Native to Eurasia and introduced in most parts of the world [10], the plant is a perennial herb, characteristically growing on chalk or limestone soils, but often also encountered on heavy clay soils. Its habitat is mainly related to the presence of a calcium source, being encountered mainly on downland grassland, calcareous pasture or even in water-meadows beneficiary of calcareous water [11]. The species is morphologically characterized by the slender stalk (5 to 50 cm), basal, finely-haired elliptic to ovate leaves, developing in rosette pattern, over 3 cm wide, presenting 7–9 veins and equipped with midribs that can be easily separated from the mesophyll tissue, curly, abundant, or sparsely scattered lamina trichomes on both epidermis, a petiole shorter than the leaf lamina, delicate pink-white flowers (appearing May–September) that are pollinated by wind and insects, and contains 4 seeds per capsule [12–19]. A tetraploid species, P. media shows treading resistance, a feature related to the resistance being represented by the strong root contraction [10]. The hoary plantain is edible (fresh young leaves being used in fresh salads or cooked as other leafy green vegetables) [20] and its uses were apparently common in the past, its seeds being encountered in the archaeological excavations from Roman period Britain [21,22] and even earlier [23]. Its use in folk medicine included several applications, such as antimicrobial, anti-inflammatory, anti-histaminic, hemostatic, cicatrizing, expectorant and diuretic [20,24]. The commonly used part for medical purposes is the leaves, used for the preparation of infusions [22].

The present work aims to summarize the scientific findings regarding P. media composition and potential uses, based on published research data, highlighting the importance of this natural resource. The methodology for the article collection contained the survey of the main scientific data-bases (Scopus, Web of Science, ScienceDirect, and PubMed), using as specific keyword “Plantago media”. The validation of the articles was performed manually (by reading the entire article). Another important aspect covered by the present work is represented by the proposal of new emerging areas of research for P. media (by comparison with related species), such as the development of food or personal care products, the use in pisciculture or zootechny, phytoremediation and other environmental protection applications, or in the nanotechnology area (materials phytosynthesis).

2. Main Constituents and Applications

2.1. General Composition

As previously mentioned, the composition of other Plantago species (P. lanceolata, P. major, P. ovata) is well-established and known, subject of several review papers [25–28]. P. media, in turn, did not receive such attention from the scientific community, no review paper presenting the species composition being identified. As a genus characteristic, the most important components of the hoary plantain are the polysaccharides [29]. Ollenikov et al. identified in the P. media extracts several important polysaccharides (galactose, arabinose, xylose, mannose, glucose, as well as trace amounts of rhamnose and fucose) [30] (Table 1). It is worth to be noted that, according to some authors, the total polysaccharide content was found to be the highest in P. media, compared with other species [31].

Some studies also evaluated the composition of P. media in terms of total sterol esters, total lipids and total fatty acids, also identifying several individual components [32]. Total fiber and lipid content were also evaluated by other groups [33], revealing a relatively low amount of lipids and a total fiber higher than the level recorded for vegetables like beets or spinach (2.25 g/100 g fresh weight). The study also quantified the presence of other compounds (vitamin C, oxalic acid) and minerals (Na, K, Ca, Mg, P, Fe, Cu, Zn, Mn), P. media revealing higher levels in K, Ca, P, Fe, Cu, and Zn, compared with other Plantago species (P. major and P. lanceolata) [33], suggesting that P. media could represent a valuable
source of minerals. Total available carbohydrates were also evaluated, suggesting a low content for *P. media* (1.99 g/100 g fresh leaves) [33].

Although several alkaloids were identified in other *Plantago* species (indicain and plantagonin in *P. major* [34], dictyoquinazol C and sampanagine in *P. ovata* [35]), no alkaloids were identified in the published studies regarding *P. media*.

The general composition of *P. media* can be completed with the presence of other documented compounds, such as iridoids (aucubin, melittoside, monomelittoside, 10-acetylmomelittoside, 10-acetylaucubin, catalpol), hydroxycinnamic acids (caffeic, chlorogenic, ferulic, gallic, neochlorogenic acid isochlorogenic acids), flavonoids (luteolin, apigenin, kaempferol), glycosides (verbascoside, plantamajoside, homoplantaginin), phytosterols (campesterol, stigmasterol, sitosterol), saturated and unsaturated fatty acids (linoleic acid, hexadecatrienoic acid, palmitic acid, myristic acid, palmitoleic acid, behenic acid, erucic acid) and carotenoids (β-carotene, violaxanthin, lutein, neoxanthin, zeaxanthin), the latter having an important photoprotection role for the photosynthetic apparatus, leading to an increase resistance to excess solar radiation [36]. Some authors [8] designate the aucubin-related iridoids levels (aucubin, catalpol, 10-O-acetylaucubin, monomelittoside, 10-acetylmonomelittoside, melittoside) as species-specific, differentiating the hoary plantain among others *Plantago* species.

Table 1. General composition of *Plantago media* L., according to cited literature data.

| Identified Compounds | Reference | Identified Compounds | Reference |
|----------------------|-----------|----------------------|-----------|
| **Polysaccharides**  |           | **Flavonoids**       |           |
| Galactose            | [30]      | Luteolin             | [37]      |
| Arabinose            | [30]      | Apigenin             | [37]      |
| Xylose               | [30]      | Kaempferol           | [37]      |
| Mannose              | [30]      |                      |           |
| Glucose              | [30]      | Phytosterols         |           |
| Rhamnose             | [30]      | Campesterol          | [32]      |
| Fucose               | [30]      | Stigmasterol         | [32]      |
| Aucubin              | [38]      | Linoeleic acid       | [32]      |
| Melittoside          | [38]      | Linoeleic acid       | [32]      |
| Monomelittoside      | [38]      | Hexadecatrienoic acid| [33]      |
| **Hydroxycinnamic acids** |   | **Fatty acids**      |           |
| Caffeic acid         | [30]      | Palmitic acid        | [33]      |
| Chlorogenic acid     | [30]      | Myristic acid        | [33]      |
| Ferulic acid         | [37]      |                      |           |
| Gallic acid          | [37]      | Violaxanthin         | [36]      |
| Neochlorogenic acid  | [37]      | Lutein               | [40]      |
| Isocholorgenic acid  | [37]      | Neoxanthin           | [40]      |
| **Glycosides**       |           | Zeaxanthin           | [36]      |
| Verbascoside         | [30]      |                      |           |
| Plantamajoside       | [30]      | Other compounds      |           |
| Homoplantaginin      | [41]      | Oxalic acid          | [33]      |
| Martynoside          | [42]      | Vitamin C            | [33]      |

The above-presented compounds only show a general composition of the species, the actual levels and, in some cases, the presence/absence of some of the minor compounds varying in the literature data. As for any plant material, the phytoconstituents levels in the plant extracts are dependent on several factors (including, but not limited to ecological factors, zoning, culture technology, or processing methods) [6]. For example, as a response to environmental conditions, several morpho-physiological parameters (such as specific leaf area density and organ mass) were found to be modified in a comparative study on
two hoary plantain populations by Rozentsvet et al. [44]. The changes were also reflected in different lipids and fatty acids content, that also varied with the ontogenetic stage.

*P. media* was defined as “salt-sensitive”, its exposure to up to 200 mM NaCl leading to a reduction of shoot length and stomatal conductance, as well as in a decrease of superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR) activities with increasing salinity, suggesting a sensitive structural arrangement in leaves of the hoary plantain against stress [45]. On the other hand, the plant is resistant to excess solar radiation, a character associated with the presence of the carotenoids, their resistance being attributed to the activation of non-photochemical quenching mechanisms associated with the xanthophyll cycle de-epoxidation [36]. As such, the levels of photosynthetic pigments are higher in the plants grown in the shade, compared with those grown in high light conditions (up to two times higher) [18,40].

The different types of other compounds identified in the composition of *P. media* also have important roles in its development. Phenolic compounds represent the most important class of natural antioxidants, multiple studies presenting the direct correlation between the phenolic content and the antioxidant activity of different plant tissues [46].

The iridoid glycosides present in the leaves of *Plantago* (their level being correlated with the plant’s ontogenetic stage) are also part of the plants’ defense mechanisms against external factors (pathogens or non-adapted herbivores), as demonstrated for other *Plantago* species [47,48]. The phytosterols are related to the humidity adaptation of the plants, pathogens defense or regulation of the membrane fluidity and permeability [49,50].

The polysaccharides present in the seed coats of *Plantago* species swell in contact with water, forming a high-viscosity mucilage; the mucilage facilitates the attachment of seeds to humans and animals, and thus contributing to the spread of the plant [51]; it also protects myxospermatic diaspores in the passage through the digestive system of birds [52].

Flavonoids and phenolic acids, accumulating in the plant tissues in response to various biotic and abiotic stress, ensure the adaptation of the plant, through multiple physiological functions, while also having other roles, such as growth regulation, pigmentation, respectively precursor molecules for other physiological important compounds [53].

Fatty acids are commonly used throughout the plant kingdom as a source of carbon and energy [54], while vitamin C, besides its well-known antioxidant effect, also has multiple roles in the plant physiology, as recently presented by Paciolla et al. [55].

All the above-mentioned compounds were found to possess important biological properties, which is expected to reflect in the future studies regarding the properties of *P. media* extracts.

### 2.2. Documented Applications

Generally speaking, plants contain several types of compounds which provides good antioxidant activity [56], such as phenolic acids, flavonoids or terpenes. In recent years, the focus of both scientific community and of the desire for healthier foods led to the exploitation of natural resources for the separation of natural antioxidants as viable alternatives for the synthetic additives [56]. The antioxidant character of individual compounds or mixtures (such as natural extracts) allows their application in food industry (to delay the autooxidation, neutralize free radicals) [57] or in cosmetic industry (i.e., by harvesting their protecting effect for the skin from photoaging) [58]. Indirectly, as the oxidative stress represents a major factor related to the apparition of several diseases (cardiovascular, neurodegenerative, oncological, etc.), the antioxidants could contribute to the development of scientifically solid nutraceuticals [57].

The antioxidant capacity of natural extracts can be evaluated by a series of in vitro or in vivo assays, each one having their advantages and shortcomings. As a general remark, the in vitro assays should be considered as a “preliminary test”, with little biological relevance, whose conclusions should be verified by in vivo assays [56]. However, as those preliminary assays are easily accessible, inexpensive and require minimal instrumentation, most pioneering works for vegetal species are performed in vitro. This is also the case of
Plants media, whose antioxidant activity was firstly reported by Beara et al. [59] in a comparative study, involving several antioxidant assays, registering an average, assay-dependent antioxidant capacity, by comparison with other Plantago species and with the standard 3,5-di-tert-butyl-4-hydroxytoluene (BHT). For example, the extract had a good antioxidant activity in the DPPH assay (2,2′-diphenyl-1-picrylhydrazyl radical reduction assay) and, especially, FRAP (ferric reducing antioxidant power) assay, while poorly performing in the others assays [59]. The correlations identified by the authors between the total phenolics, respectively, total flavonoid contents and the results of the antioxidant assays were satisfactory only for the DPPH and FRAP assays (R² > 0.94), suggesting the involvement of other compounds in the scavenging of the radical species used for the assays [59]. The quantification of the two types of phytoconstituents revealed that the evaluated P. media extract had the highest phenolics content (compared with extracts obtained by the same procedure from P. argentea, P. holosteum, P. major, and P. maritima), and an average flavonoids content (higher than P. argentea and P. major, lower than P. holosteum and P. maritima). Similar results were obtained by Gonda et al. [60] in the CUPRAC (cupric reducing antioxidant capacity) assay (see Table 2), classifying P. media as an average antioxidant source, under the values obtained for P. lanceolata and P. maritima, although superior to the more studied P. major, or P. altissima. The authors identified a direct correlation between the total phenylethanoid content (higher than P. altissima, P. major, and equal to P. lanceolata) and the antioxidant potential. The aucubin content was found to be lowest among the studied extracts, equal to the one in P. major [60].

The results obtained by Grigore et al. [61] in the antioxidant enzyme activity assays suggest a higher antioxidant potential of P. media (compared with other Plantago species), and a superior activity in the flowering phenophase. Lukova et al. also obtained superior results in the in vitro antioxidant assays for the hoary plantain, compared with P. major and P. lanceolata, although significantly lower compared with the values obtained for the BTH standard, for ethanol extracts, hemicellulose, respectively xylanase hydrolysates) [31,62].

The hydroalcoholic extract of P. media also proved to have high antioxidant capacity, even when compared with known medicinal plants (such as woundwort—Anthyllis vulneraria L. or wild thyme—Thymus serpyllum L.) [63]. The hydroalcoholic extract also exhibited superior antioxidant properties (DPPH and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid—ABTS assays) compared with P. cornuti, P. lanceolata and P. major, at the same time showing no pro-oxidant properties (in the hemoglobin-oxidation in the presence of laccase) The total phenolics content of the extract was also found to be correlated with the results of the antioxidant assays (the highest among the four Plantago species studied), underlying the importance of this class of phytoconstituents for developing antioxidant recipes [64].

The first identified report regarding the potential biomedical applications of hoary plantain is represented by the study of Kunvári et al. [41] regarding the antitumoral potential of two glycosides isolated from the plant. The study revealed an important antitumoral potential of the compounds, exhibited through the significant inhibition of isolated EGF-R tyrosine kinases.

The polysaccharidic fraction of the P. media was proven as an efficient anti-atherogenic agent, recording a 42.77% alkaline phosphatase binding (compared with the heparin control) [30], while the alcohol and lyophilic extracts presented mycostatic activity to several yeast and fungi strains (superior for the alcohol extract) best results being obtained against Aspergillus oryzae (clinical strain). The effect can be correlated with the levels of quantified polyphenolics (flavonoids, hydroxycinnamic acids) in the lyophilic extract, the highest content being recorded for verbascoside (2.013%), plantamajoside (1.723%), respectively ferulic acid (1.526%). [37].
## Table 2. Biomedical properties of Plantago media.

| Plant Parts Used | Plant Treatment/Applied as | Application | Results | Reference |
|------------------|----------------------------|-------------|---------|-----------|
| Aerial parts     | Maceration (80% methanol, 72 h, room temperature), filtration, evaporation; extract redissolved in water (1 g/mL) | Antioxidant | DPPH assay: IC₅₀ = 5.77 mg/L; BHA assay: IC₅₀ = 271.08 mg/L; NOSC assay: IC₅₀ = 54.20 mg/L; FRAP assay: IC₅₀ = 1.48 mg/L | [98] |
|                  | Nonpolar compounds removed with and concentrated—17.6% yield. Redissolved in 80% aqueous methanol for application (20% (w/v)) | Antioxidant | CUPRAC assay: 5.296 µmol AAE/g d.w. | [60] |
| Leaves           | 50% EtOH extract (100 °C, 60 min) | Antioxidant | CUPRAC assay: 0.2368 µmol AAE/g d.w. | [60] |
| Leaves           | Methanol extract (no details provided) | Antioxidant | POD assay: 1.9/2.5/0.8 activity units/mg protein (vegetative/flowering/fruiting phase) | [61] |
| Leaves           | Ethanol extract (no details provided) | Antioxidant | CUPRAC assay: 69.10 µM TE/g d.w. | [31] |
| Leaves           | Hydrolyzed in the presence of hemicellulase enzymes (hemicellulose-H/xylanase-X, 4 h, 45 °C), filtered, coagulated (95% ethanol) | Antioxidant | DPPH assay: 75.48% | [62] |
| Leaves           | Ethanol (50%) extract (solid: liquid ratio 1:20), 30 min., room temperature | Antioxidant | DPPH assay: ~2.2 mg QE/g plant | [63] |
| Leaves           | Percolation (70% ethanol, 72 h.) | Antioxidant | ABTS assay: ~275 µg TE/g plant | [64] |
| Isolated compounds | Individual compounds (verbascoside, homoplantaginin) evaluation | Antitumoral, tyrosine kinase inhibitor | Significant inhibition of isolated EGF-R tyrosine kinases, variable in vitro antiproliferative activity | [40] |
| Leaves           | From the biomass without alcohol-soluble components: extraction with water (1:25, followed by extraction with acidic acid/ammonium-oxide solutions (0.5%, 1:20); extract was concentrated and dialyzed; undialyzed residue precipitation by HCl (1%) in EtOH (95%) (1:5). Precipitates were centrifuged, washed (EtOH), and dried to result pectinic substances (PS) phase. Purified PS phase—raw material without alcohol-soluble components was concentrated, dialyzed, precipitated, washed, dried followed by low-molecular-weight glucose removal and precipitation with acetone | Anti-atherogenic activity | Precent binding of ALP relative to the control = 42.77/35.2% (at 20 mg/mL) | [30] |
| Leaves           | Repeated alcohol extraction (1:5) from dried material (80% ethanol, 60 °C) followed by lyophilization (alcoholic/lyophilic extract) | Myostatic activity | Disc-diffusion assay against Candida albicans, C. utilis, Mucor rouxii, Aspergillus niger, Microsporum canis, Trichophyton rubrum, Epidermophyton floccosum Wolf | [57] |
| Leaves           | Methanol extraction (80%, solid: liquid ratio 1:10, 72 h, room temperature) | Anti-inflammatory activity | Evaluation of PGE₂, TXA₂ = 70/70% (compared with control); qPCR examination of PLA₂, COX-1, COX-2, mPGES-1, mPGES-2, cPGES, TXAS upregulation of COX-1, mPGES-1, TXAS downregulation COX-2, mPGES-2, cPGES, did not influenced PLA₂; Trypan blue exclusion test on monocytes: no impact on cell viability at up to 0.5 mg/mL | [43] |

where: AAE—ascorbic acid equivalents; ABTS—2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; ALP—alkaline phosphatase; COX—cyclooxygenase 1; COX—cyclooxygenase 2; cPGES—cytosolic prostaglandin E synthase-1; CUPRAC—cupric-reducing antioxidant capacity; CH—cholinuminescence; DPPH—2,2-diphenyl-1-picrylhydrazyl; d.w.—dry weight; EtOH—ethanol; FRAP—ferric ion reducing antioxidant power; HRS—hydroxyl radical scavenger; IC₅₀—concentration of extract leading to a 50% inhibition; IZ—inhibition zone; LP—lipid peroxidation; LPS—lipopolysaccharide; mPGES-1—microsomal prostaglandin E synthase-1; mPGES-2—microsomal prostaglandin E synthase-2; NOSC—NO scavenger capacity; ORAC—oxygen radical absorbance capacity; PGE₂—prostaglandin E₂; PLA₂—phospholipase A₂; POD—Peroxidase activity; QE—quercetin equivalents; qPCR—quantitative polymerase chain reaction; SASC—superoxide anion scavenger capacity; SOD—superoxide dismutase activity; TE—Trolox equivalents; TXA₂—thromboxane A₂; TXAS—thromboxane A synthase; U937—human myeloid leukaemia cell line.
Hydroalcoholic (80% methanol) extract of *P. media* showed inhibition activity of prostaglandin E2 (PGE\(_2\)) and thromboxane (TXA\(_2\)) eicosanoids production (similar to aspirin) at low-dose concentration (especially for PGE\(_2\)), supporting future investigation of the species as a potential anti-inflammatory agent. In the same time, the extract did not present any significant cytotoxic potential. The studied extract revealed high levels of caffeic acid phenolic acids, flavonoids and triterpenic acids; also, the *P. media* showed the highest level of aucubin (44.272 mg/g) from the studies species (*P. altissima*, *P. argentea*, *P. holosteum*, *P. lanceolata*, *P. major*) [43].

Table 2 summarizes the biomedical properties of *P. media*, as presented in the cited literature data.

3. *Plantago media* L. Future Perspectives

The potential applications of *P. media* will be detailed in regard to other potential applications of *Plantago* species, in respect to recent literature data published.

3.1. Health Applications

Supplemental applications of the *P. media* products in the health area could be suggested by other *Plantago* species properties. Several review papers present the potential uses of, in example, *P. lanceolata*, *P. ovata* or polysaccharide from *Plantago* sp. in this area [27,29,65,66]. These works could constitute a good starting point for the development of new nutraceuticals based on *P. media*. As previously presented (as the main application already studied, although trough in vitro assays—Table 2), the hoary plantain represents a potential source of antioxidative compounds; this is also confirmed by the study of other *Plantago* species, several of them possessing antioxidative potential (Table 3). Either if there are discussed aqueous, alcoholic, or organic extracts, polysaccharide fraction or mucilage, *Plantago* sp. (*P. albicans*, *P. coronopus*, *P. lanceolata*, *P. major*, *P. ovata*, *P. squarrosa*) exhibited good antioxidative potential in in vitro assays.

*P. squarrosa* and *P. major* L. exhibited anti-microbial potential [67,68] against several gram-positive and gram-negative bacteria or fungi, a good support of the mycostatic potential observed for *P. media* [37]. Another very important potential activity is represented by the antiviral potential. Chathuranga et al. [69] evaluated the antiviral potential of *P. asiatica* and its component verbascoside (acteoside), a compound that, as previously presented, can be found in relatively high quantities in *P. media* [37], against the respiratory syncytial virus, the in vivo assays suggesting a possible anti-viral path to be followed.

The anti-inflammatory potential of *P. media* [43] was supported by the application of *P. major* and *P. lanceolata* extracts as anti-inflammatory agents (either in vitro, in carrageenan-induced paw edema model, by determining the expression of the proinflammatory enzyme, cyclooxygenase, or on oral epithelial cells), an effect attributed to the presence of phenylethanoid compounds (in particular, verbascoside) [70–73].

An anti-tumoral potential was observed for *P. major* and *P. lanceolata* extracts [74–76], as well as for the polysaccharide fraction of *P. ovata* [77]. All the previously presented activities for different *Plantago* sp. represent a good indicator, supporting the reported applications of *P. media*.

Other studies, in turn, would suggest potential applications of the hoary plantain that are waiting to be explored. For example, a hepatoprotective action was observed for the defatted aqueous methanolic extract obtained from the leaves of *P. major* (effect attributed to verbascoside) [70], *P. ovata* husk mucilage [78] and seed aqueous extract [79], *P. asiatica* seeds polysaccharide fraction [80], *P. psyllium* seeds ethanolic extract (for which the total phenolics and total flavonoids contents were determined as 16.17 mg gallic acid equivalents/g dried weight, respectively 1.9 mg rutin equivalents/g dried weight) [81] and *P. albicans* leaves aqueous extract (total phenolics content 592.75 mg gallic acid equivalents/g, total flavonoids content 116.7 mg catechin equivalents/g [82], in several hepatic damage models, Table 3). Considering the variety of extracts and fractions used, the results would suggest a hepatoprotective potential for the *P. media*, also.
The renoprotective effect of the *P. major* Soxhlet extracts (ethanol, 70%) was evaluated in Cisplatin and Adriamycin induced renal dysfunction in animal models [83–85], while the *P. albicans* leaves extract and *P. asiatica* and *P. depressa* (a species to which, according to recent phylogenetic analyses, *P. media* is closely related [19]) seeds extracts proved to have an anti-obesity potential, by effectively improving lipid and glucose metabolism in high-fat diet-induced obese mice [86–88].

The flavonoid fraction isolated and the leaves extract obtained from *P. major* (a species that, as previously stated [59], presents a lower total flavonoids content, compared with *P. media*), were evaluated as antiarrhythmic agents (by functional modulation of Na\(^+\) and Ca\(^{2+}\)-channels in cardiomyocytes) [89], respectively as anxiolytic agents [90]. Arabinoxylan (a polysaccharide isolated from different *Plantago* sp.) proved to have anti-diabetic (by improvement of carbohydrate, lipid and amino acid metabolism) [91] and prebiotic (by enhancing the growth and antimicrobial activity of *Lactobacillus casei*) properties [92].

The *Plantago asiatica* L. extract and polysaccharide fraction were proved to have antihypertensive effect (trough angiotensin-converting-enzyme 46 inhibition, while simultaneously protecting organ damage against hypertension) [93], respectively to alleviates nonylphenol induced reproductive system injury (via PI3K/Akt/mTOR pathway) [94].

The whole plant extract of *Plantago rugelii* Decne was evaluated by Ogbiko et al. [95] in an anti-ulcer study, the results suggesting that the infusion (200 and 400 mg/kg) had a protective effect against gastric ulceration (induced by aspirin and HCl). Similar results were obtained by Bagheri et al. [79], using the aqueous *P. ovata* seeds extract, in an indomethacin-induced rat model, observing a reduction in microscopic and macroscopic ulcer index. Seed mucilage of *P. ovata* was used by Basiri et al. [96] as a potent lead biosorbent (increasing fecal excretion and decreasing lead tissue absorption) in mice models.

All these potential applications of *Plantago* sp. remains to be studied for *P. media*, as no studies in those area were performed to this date, up to our knowledge.

### 3.2. Other Applications

Besides the health-related applications, *Plantago* sp. were evaluated for a series of industrial applications. The methanol extract of *P. lanceolata* could find application in fish farming, as its application was proven to promote growth, as well as to enhance immune responses and antioxidant enzyme activities in rainbow trout [97], while verbascoside and aucubin was proved to reduce NH\(_3\) production on rumen fermentation, reducing the N losses in the urine [98].

*P. lanceolata* extracts were proposed for the development of natural cosmetics (due to their UV protecting activity, as well as skin regeneration stimulation) [99], while the gum isolated from *P. major* seeds proved to have emulsifying and foaming properties, which supports the use of the fraction as an alternative hydrocolloid for emulsion and foam-based foods [100]. Related to the food industry, *P. major* mucilage (extracted either by hot-water extraction or ultrasound assisted extraction) was used for the development edible and biodegradable films [101,102]. This could lead to the development of bioproducts for increasing the shelf-life of meat products. For example, the application of the edible film (with a 1.5% dill essential oil content) increased the shelf life of beef by 9 days [101].

The mucilage separated from *Plantago* sp. could also find application in other important areas, such as scaffolds for cell culture, drug delivery systems or food additives. This would involve the development of biocompatible materials, such as those proposed by Allafchian et al. [103], based on *P. ovata* mucilage and polyvinyl alcohol.

Correlated with their metal-uptake capacity, *Plantago* sp. could be used for phytoremediation potential. This application was studied, for example, for *P. lanceolata* and *P. major* for the removal of toxic heavy metals (Pb, As, Cd) [104,105]. The studies revealed a higher concentration of heavy metals in the roots, compared with the leaves, thus suggesting a limited mobility of the heavy metals, as a part of the resistance mechanism to heavy metals (involving an avoidance strategy, such as the immobilization of the metal at root level and
Plants 2021, 10, 265

9 of 15

in cell walls) [105]. The same plant was proved efficient in the phytoremediation of organic pollutants contaminated sites [106].

Another potential application of *P. media*, correlated with their metal up-take capacity could be in the improvement of mineral concentrations in the diet of livestock, to prevent the apparition of mineral deficiency, trough increasing species diversity in swards [107]. However, the hoary plantain affinity towards different metals could represent a drawback, as some studies [108] suggest a potential for *P. media* to up-take hazardous heavy metals. Although this aspect could be beneficial for phytoremediation strategies, it needs to be considered for other application, the control of heavy metals content in extracts should be performed before their application. The use of *P. lanceolata* in cattle diet was proven to reduce N₂O emissions [109] and to increase the growth performance and carcass characteristics of lambs [110], areas in which *P. media* could find applications.

Another environmental application of *Plantago* sp. is represented by its mucilage ability to remove organic pollutants. The biocomposite membrane (*P. psyllium* mucilage, eggshell membrane and alginate) proposed by Mirzaei and Javanbakht [111] proved to have the ability to remove cationic and anionic dyes (methylene blue and methyl orange) from aqueous solutions, reaching an adsorption capacity of 5.45 and, respectively, 3.25 mg/g. Another potential application of the *Plantago* sp. is represented by their chemical inhibitor potential. For example, the polysaccharide fraction of *P. ovata* was proposed as a green corrosion inhibitor by Mobin and Rizvi [112], their study suggesting a protective effect of the developed material for the carbon steel in hydrochloric medium, presenting a good inhibition efficiency (92.53%) accompanied by a low risk of environmental pollution. The authors assign the main corrosion inhibitor role to the highly branched polysaccharide arabinosyl (galaturonic acid) rhamnosylxylan [112].

Finally, a new and promising application of *Plantago* sp. is related to the nanotechnology area, in particular for the nanoparticles phytosynthesis (synthesis of materials using plant extracts). Briefly, the phytosynthesis mechanisms involve the reduction of metals from metallic salts precursors to zero-valent nanoparticles or metallic oxides, using the different plant phytoconstituents [113]. The mechanism, presented in multiple studies [114] uses the phytoconstituents both as reduction and capping agents. This alternative method of nanoparticles synthesis leads to materials with enhanced properties, valuable for a series of medical and industrial applications [113,115], enhancing the intrinsic properties of the nanoparticles [116], as well as a potential reduction of their toxicity [114]. The application was explored for *P. major* aqueous leaves extracts, leading to the synthesis of silver nanoparticles (AgNPs) and iron oxide nanoparticles (IONPs—spherical, 4.6–30.6 nm) and the exploration of their environmental applications, for the enhanced phytoremediation of soil and water contaminated with the insecticide fipronil [117] and for the removal of methyl orange dye, respectively [118].
Table 3. Examples of Plantago sp. Applications—starting point for future P. media studies.

| Species                  | Product                                                                 | Application                                      | Reference |
|--------------------------|-------------------------------------------------------------------------|--------------------------------------------------|-----------|
| Plantago albidens L.     | Leaves extract, (dichloromethane)                                       | Antioxidant, anti-obesity                        | [85]      |
| Plantago coronopus L.    | Leaves and flowers, organic and water extracts                           | Antioxidant                                      | [119]     |
| Plantago lanceolata L.   | Leaves, aqueous, ethanolic, aqueous-glycerine, and aqueous-glycol extracts | Antioxidant                                      | [99]      |
| Plantago major L.        | Aerial parts, defatted aqueous methanolic extract                        | Antioxidant, anti-inflammatory, and hepatoprotective | [70]      |
| Plantago ovata Forsk     | Husk and seeds polysaccharide fraction                                   | Antioxidant and anti-carcinogenic                | [77]      |
| Plantago ovata Forsk     | Husk mucilage                                                            | Antioxidant and hepatoprotective (CCL-induced)   | [78]      |
| Plantago squarrosa Murray| Whole plant, macerated in methanol (70%)                                | Antioxidant, antimicrobial                        | [67]      |
| Plantago depressa Willd. | Whole plant aqueous extract                                              | Anti-viral (respiratory syncytial virus)         | [69]      |
| Plantago lagopus L.      | Leaves, n hexane insoluble fraction of dichloromethane extract            | Anti-inflammatory                                | [71]      |
| Plantago major L.        | Aerial parts, Soxhlet extraction                                         | Anti-inflammatory                                | [72]      |
| Plantago major L.        | Leaves, aqueous and ethanol extract                                      | Anti-inflammatory                                | [73]      |
| Plantago depressa Willd. | Whole plant, aqueous and alcoholic extract                               | Cytotoxic (tumoral cell lines)                   | [74]      |
| Plantago major L.        | Whole plant, 80% methanol extract                                        | Cytotoxic and genotoxic activity (tumoral cell lines) | [75]      |
| Plantago ovata Forsk     | Seeds, aqueous extract                                                   | Anti-ulcer and hepatoprotective                  | [79]      |
| Plantago lataca L.       | Seeds, polysaccharide fraction                                            | Hepatoprotective                                 | [80]      |
| Plantago major L.        | Seeds, ethanolic extract                                                 | Hepatoprotective                                 | [81]      |
| Plantago major L.        | Leaves, aqueous extract                                                  | Hepatoprotective                                 | [82]      |
| Plantago major L.        | Whole plant, Soxhlet ethanol (70%) extraction                             | Renoprotective (Cisplatin induced)               | [83]      |
| Plantago major L.        | Soxhlet ethanol (70%) extraction                                          | Renoprotective (Adriamycin induced)              | [85]      |
| Plantago major L.        | Seeds, reflux extractions                                                | Anti-obesity                                     | [87]      |
| Plantago major L.        | Seeds, reflux extractions                                                | Anti-obesity                                     | [88]      |
| Plantago depressa Willd. | Leaves extract, 70% ethanol, percolation Arabinoxylan (polysaccharide)    | Anti-diabetic                                    | [91]      |
| Plantago asiatica L.     | Arabinoxylan (polysaccharide) extracted from seed husk                   | Prebiotic                                         | [92]      |
| Plantago asiatica L.     | Seeds, reflux extraction                                                 | Anti-hypertensive                                | [93]      |
| Plantago asiatica L.     | Seeds, polysaccharide fraction                                            | Reproductive system injury alleviation           | [94]      |
| Plantago major L.        | Whole plant, methanol maceration (72 h.)                                 | Anti-ulcer                                       | [95]      |
| Plantago major L.        | Seeds mucilage                                                           | Lead biosorbent                                  | [96]      |
| Plantago major L.        | Seeds mucilage, hot water extraction                                     | Phenolic applications                            | [97]      |
| Plantago major L.        | Seeds mucilage, ultrasound assisted extraction                           | Livestock feed                                   | [98]      |
| Plantago major L.        | Seeds mucilage, organic water extraction                                 | Development of natural cosmetics                 | [99]      |
| Plantago major L.        | Seeds, gum fraction                                                      | Emulsifying and foaming properties               | [100]     |
| Plantago major L.        | Seeds, polysaccharide fraction                                            | Edible coating                                   | [101]     |
| Plantago major L.        | Whole plant, methanol maceration (72 h.)                                 | Biodegradable films                              | [102]     |
| Plantago major L.        | Whole plant                                                              | Biocompatible nanotubers                         | [103]     |
| Plantago major L.        | Whole plant                                                              | Phytochemical applications                       | [104]     |
| Plantago major L.        | Whole plant                                                              | Phytoremediation (Pb, As, Cd)                    | [105]     |
| Plantago major L.        | Whole plant                                                              | Phytoremediation (Cypermethrin)                  | [106]     |
| Plantago major L.        | Whole plant                                                              | Livestock diet (improvement of mineral concentrations levels) | [107] |
| Plantago major L.        | Whole plant                                                              | Livestock diet (reduction of NOx emissions)      | [109]     |
| Plantago major L.        | Whole plant                                                              | Performance and carcass characteristics           | [110]     |
| Plantago major L.        | Seeds mucilage                                                           | Dye removal                                      | [111]     |
| Plantago major L.        | Polysaccharide fraction                                                  | Corrosion inhibitor                              | [112]     |
| Plantago major L.        | Leaves aqueous extract (100 °C, 60 min)                                  | Phytosynthesis of AgNPs                          | [117]     |
| Plantago major L.        | Leaves aqueous extract (100 °C, 15 min)                                  | Phytosynthesis of iron oxide NPs                 | [118]     |

4. Conclusions

The literature study revealed the under-utilization of the hoary plantain, a surprising aspect, considering its widespread. If the composition of Plantago media L. is rather well established, its applications are not nearly studied as for other Plantago species. By comparing the results obtained using the hoary plantain with other species belonging to the
Plantago genus, it can be observed that the applications evaluated are only related to the biomedical field, and only through in vitro assays. They should be further developed using in vivo assays, as should other biomedical potential applications be explored. Also, the use of *P. media* and its natural products should be explored for further important applications, such as industrial applications (for development of food or personal care products), for pisciculture or zootechny, for phytoremediation and other environmental protection applications, or even for nanotechnological uses (a field with tremendous potential, as the phytosynthesis of different materials could find application in several areas).

**Author Contributions:** All authors contributed to the present work. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded through the project SusMAPWaste, SMIS 104323, Contract No. 89/09.09.2016, from the Operational Program Competitiveness 2014–2020, project co-financed from the European Regional Development Fund.

**Institutional Review Board Statement:** Not applicable.

**Data Availability Statement:** No new data were created or analyzed in this study. Data sharing is not applicable to this article.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

**References**

1. Cheminal, A.; Kokkoris, I.P.; Strid, A.; Dimopoulos, P. Medicinal and aromatic *Lamiaceae* plants in Greece: Linking diversity and distribution patterns with ecosystem services. *Fores*ts 2020, 11, 661. [CrossRef]
2. Singh, B.; Singh, B.; Kishor, A.; Singh, S.; Bhat, M.N.; Surmal, O.; Musarella, C.M. Exploring plant-based ethnomedicine and quantitative ethnopharmacology: Medicinal plants utilized by the population of Jasrota Hill in Western Himalaya. *Sustainability* 2020, 12, 7526. [CrossRef]
3. Atanasov, A.G.; Waltenberger, B.; Pferschy-Wenzig, E.M.; Linder, T.; Wawrosch, C.; Uhrin, P.; Temml, V.; Wang, L.; Schweiger, S.; Heiss, E.H.; et al. Discovery and resupply of pharmacologically active plant-derived natural products: A review. *Biotechnol. Adv.* 2015, 33, 1582–1614. [CrossRef] [PubMed]
4. Süntar, I. Importance of ethnopharmacological studies in drug discovery: Role of medicinal plants. *Phytochem. Rev.* 2020, 19, 1199–1209. [CrossRef]
5. Schillberg, S.; Raven, N.; Spiegel, H.; Rasche, S.; Buntru, M. Critical analysis of the commercial potential of plants for the production of recombinant proteins. *Front. Plant Sci.* 2019, 10, 720. [CrossRef] [PubMed]
6. Fierascu, R.C.; Fierascu, I.; Ortan, A.; Georgiev, M.I.; Sieniawska, E. Innovative approaches for recovery of phytoconstituents from medicinal/aromatic plants and biotechnological production. *Molecules* 2020, 25, 309. [CrossRef]
7. Schwarzbach, A.E. Plantaginaceae. In *Flowering Plants Dicotyledons. The Families and Genera of Vascular Plants*; Kadereit, J.W., Ed.; Springer: Berlin/Heidelberg, Germany, 2004; Volume 7, pp. 327–329.
8. Taskova, R.; Evstatieva, L.; Handjieva, N.; Popov, S. Iridoid patterns of Genus *Plantago* L. and their systematic significance. *Z Naturforsch.* C 2002, 57, 42–50. [CrossRef]
9. Hegnauer, R. *Chemotaxonomie der Pflanzen*; Birkhäuser: Basel, Switzerland, 1969; Volume 5, pp. 330–337.
10. Van der Aart, P.J.M.; Vulto, J.C.; Soekarjo, R.; van Damme, J.M.M. General Biology of *Plantago*. In *Plantago: A Multidisciplinary Study. Ecological Studies (Analysis and Synthesis)*; Kuiper, P.C., Bos, M., Eds.; Springer: Berlin/Heidelberg, Germany, 1992; Volume 89, pp. 4–19.
11. Grose, D. *The Flora of Wiltshire*; Wiltshire Archaeological and Natural History Society: Devizes, UK, 1957.
12. Bley, L.F. Einige Versuche über die Bestandtheile der Blüthen des Wegerichs (*Plantago lanceolata*). *Archív Pharm.* 1846, 96, 169–173. [CrossRef]
13. Schier, W. Morphological and anatomical differentiation between *Plantago lanceolata*, *P. major* and *P. media*. *Dtsch. Apoth. Ztg.* 1990, 130, 1457–1458.
14. Ivanovici, N.; Ţărau, G.; Liviatodosi, A.; Iriza, E.; Danciu, A.; Țolea, L.; Tudosie, D.; Munteanu, F.; Bogdan, D.; Ciobâncă, V. Contributions to the characterization of Plantago species from Romania. *Ann. West Univ. Timişoara Biol.* 2010, 13, 37–76.
15. Lukova, P.; Dimitrova-Dyulgerova, I.; Karcheva-Bahchevanska, D.; Mladenov, R.; Iliév, I.; Nikolova, M. Comparative morphological and qualitative phytochemical analysis of *Plantago media* L. leaves with *P. major* L. and *P. lanceolata* L. leaves. *Int. J. Med. Res. Pharm. Sci.* 2017, 4, 20–26.
16. Cavers, P.B.; Bassett, L.J.; Crompton, C.W. The biology of Canadian weeds: 47. Plantago lanceolata L. Can. J. Plant Sci. 1980, 60, 1269–1282. [CrossRef]

17. Farcaș, A.D.; Moș, A.C.; Pârvu, A.E.; Toma, V.A.; Popa, M.A.; Mihai, M.C.; Sevestre, B.; Roman, I.; Vlase, L.; Pârvu, M. In Vivo pharmacological and anti-inflammatory evaluation of xerophyte Plantago sempervirens Crantz. Oxid. Med. Cell Longev. 2019, 2019, 5049643. [CrossRef] [PubMed]

18. Miszalski, Z.; Skoczowski, A.; Silina, E.; Dymova, O.; Golovko, T.; Kornas, A.; Strzalka, K. Photosynthetic activity of vascular bundles in Plantago media leaves. J. Plant Physiol. 2016, 204, 36–43. [CrossRef]

19. Abrahamczyk, S.; Dannenberg, L.S.; Weigend, M. Pollination modes and divergent flower traits in three species of Plantago subgenus Plantago (Plantaginaceae). Flora 2020, 267, 151601. [CrossRef]

20. Min, J.; Tao, T. Characterization of the complete chloroplast genome of Plantago media, a Chinese herb from three China. Mitochondrial DNA B 2020, 5, 1861–1862. [CrossRef]

21. Blamey, M.; Fitter, R.; Fitter, A. Wild Flowers of Britain and Ireland: The Complete Guide to the British and Irish Flora; A & C Black: London, UK, 2003.

22. Parnell, J.; Curtis, T. Webb’s an Irish Flora; Cork University Press: Cork, Ireland, 2012.

23. Mohsenzadeh, S.; Sheidai, M.; Ghahremaninejad, F.; Koohdar, F. A palynological study of the genus Plantago (Plantaginaceae). Grana 2020, 2020, 1–12. [CrossRef]

24. Bojor, O. Guide of Medicinal and Aromatic Plants from A to Z. Ghidul Plantelor Medicinale și Aromatice de la A la Z; Fiat Lux: Bucharest, Romania, 2003; pp. 94–95. (In Romanian)

25. Mayer, J.G. Plantain (Plantago lanceolata)—Medicinal plant of the year 2014. Z. Phytother. 2013, 34, 242–243. [CrossRef]

26. Adom, M.B.; Taher, M.; Mutalabisin, M.F.; Amri, M.S.; Abdul Kudos, M.B.; Wan Sulaiman, M.W.A.; Sengupta, P.; Susanti, D. Functional plasticity of photosynthetic apparatus in natural conditions. Trends Food Sci. Technol. 2020, 96, 166–175. [CrossRef]

27. Franco, E.A.N.; Sanches-Silva, A.; Ribeiro-Santos, R.; de Melo, N.R. Psyllium (Plantago ovata Forsk): From evidence of health benefits to its food application. Acta Pharm. Belg. 2020, 2019, 75–86. [CrossRef]

28. Belorio, M.; Gómez, M. Psyllium: A useful functional ingredient in food systems. Crit. Rev. Food Sci. Nutr. 2020. [CrossRef] [PubMed]

29. Ji, X.; Hou, C.; Guo, X. Physicochemical properties, structures, bioactivities and future prospective for polysaccharides from Plantago L. (Plantaginaceae): A review. Int. J. Biol. Macromol. 2019, 135, 637–646. [CrossRef] [PubMed]

30. Olennikov, D.N.; Tankhaeva, L.M.; Stolbikova, A.V.; Petrov, E.V. Phenylpropanoids and polysaccharides from Plantago major. Biomed. Pharmacother. 2017, 96, 348–360. [CrossRef]

31. Lukova, P.; Karcheva-Bahchevanska, D.; Dimitrova-Dyulgerova, I.; Katsarov, P.; Mladenov, R.; Iliev, I.; Nikolova, M. A comparative pharmacognostic study and assessment of antioxidant capacity of three species from Plantago genus. Farmacia 2018, 66, 609–614. [CrossRef] [PubMed]

32. Kuiper, D.; Kuiper, P.J.C. Lipid Composition of the roots of Plantago species: Response to alteration of the level of mineral nutrition and ecological significance. Physiol. Plant. 1978, 44, 81–86. [CrossRef]

33. Guıl-Guerrero, J.L. Nutritional composition of Plantago species (P. major L., P. lanceolata L., and P. media L.). Ecol. Food Nutrit. 2001, 40, 481–495. [CrossRef]

34. Samuelson, A.B. The traditional uses, chemical constituents and biological activities of Plantago major L. A review. J Ethnopharmacol 2000, 71, 1–21. [CrossRef]

35. Patel, M.K.; Mishra, A.; Jaiswar, S.; Jha, B. Metabolic profiling and scavenging activities of developing circumsiccisile fruit of psyllium (Plantago ovata Forsk.) reveal variation in primary and secondary metabolites. BMC Plant Biol. 2020, 20, 116. [CrossRef] [PubMed]

36. Golovko, T.; Dymova, O.; Zakhozhiy, I.; Dalke, I.; Tabalenkova, G. Photoprotection by carotenoids of Plantago media photosynthetic apparatus in natural conditions. Acta Biochim. Pol. 2012, 59, 145–147. [CrossRef]

37. Volodymirvna, K.T.; Pavlyyna, S.H.; Kostyantynivna, Y.O.; Vladylenovych, M.O.; Oleksandrivna, M.O. Mycostatic activity of extracts from leaves of Plantago media L. and Plantago altissima L. Ann. Trop Med. Public Health 2020, 3, 299–303.

38. Saadi, H.; Handjieva, N.; Popov, S.; Evtatievat, L. Iridoids from Plantago media. Phytochemistry 1990, 29, 3938–3939. [CrossRef]

39. Long, C.; Moulis, C.; Stanislas, E.; Fouraste, I. L’aucuboside et le catalpol dans les feuilles de Plantago lanceolata L., Plantago major L. et Plantago media L. J. Pharm. Belg. 1995, 50, 484–488. [CrossRef]

40. Golovko, T.K.; Dalke, I.V.; Zakhozhiy, I.G.; Dymova, O.V.; Tabalenkova, G.N. Functional plasticity of photosynthetic apparatus and its resistance to photoinhibition in Plantago media. Russ. J. Plant Physiol. 2011, 58, 549–559. [CrossRef]

41. Kunvári, M.; Páska, C.; László, M.; Orfi, L.; Kővesdi, I.; Eros, D.; Bókönyi, G.; Kéri, G.; Gyurján, I. Biological activity and structure of antitumor compounds from Plantago media L. Acta Pharm. Hung. 1999, 69, 232–239. [PubMed]

42. Budzianowska, A.; Kikowska, M.; Małkiewicz, M.; Karolak, I.; Budzianowski, J. Phenylethanol glycosides in Plantago media L. organs obtained in In Vitro cultures. Acta Biol. Cracov. Bot. 2019, 61, 75–86.

43. Majkić, T.; Bekvalac, K.; Beara, I. Plantain (Plantago L.) species as modulators of prostaglandin E2 and thromboxane A2 production in inflammation. J. Ethnopharmacol. 2020, 262, 113140. [CrossRef]

44. Rozenstvet, O.; Grebkenka, T.; Nesterov, V.; Bogdanova, E. Seasonal dynamic of morpho-physiological properties and the lipid composition of Plantago media (Plantaginaceae) in the Middle Volga region. Plant Physiol. Biochem. 2016, 104, 92–98. [CrossRef]

45. Hedive Sekmen, A.; Türkan, I.; Takio, S. Differential responses of antioxidative enzymes and lipid peroxidation to salt stress in salt-tolerant Plantago maritima and salt-sensitive Plantago media. Physiol. Plant. 2007, 131, 399–411. [CrossRef]
72. Vandana, J.; Gupta, A.K.; Mukerjee, A. Phytochemical screening and evaluation of anti-inflammatory activity of aerial part extracts of Plantago major L. Asian J. Pharm. Clin. Res. 2017, 10, 307–311. [CrossRef]

73. Zubair, M.; Widén, C.; Renvert, S.; Rumpunen, K. Water and ethanol extracts of Plantago major leaves show anti-inflammatory activity on oral epithelial cells. J. Tradit. Complement. Med. 2019, 9, 169–171. [CrossRef]

74. Alsaraf, K.M.; Mohammad, M.H.; Al-Shammari, A.M.; Abbas, I.S. Selective cytotoxic effect of Plantago lanceolata L. against breast cancer cells. J. Egypt Nat. Cancer Inst. 2019, 31, 10. [CrossRef]

75. Kartini Piyaviriyakul, S.; Thongpraditchote, S.; Siripong, P.; Vallisuta, O. Effects of Plantago major extracts and its chemical compounds on proliferation of cancer cells and cytokine production of lipopolysaccharide-activated THP-1 macrophages. Pharmacog. Mag. 2017, 13, 393–399. [CrossRef]

76. Ždralović, A.; Mesic, A.; Eminić, I.; Parić, A. Cytotoxic and genotoxic activity of Plantago major L. extracts. Cytogenet. Cell Genet. 2019, 72, 35–40.

77. Patel, M.K.; Tanna, B.; Gupta, H.; Mishra, A.; Jha, B. Physicochemical, scavenging and anti-proliferative analyses of polysaccharides extracted from psyllium (Plantago ovata Forssk) husk and seeds. Int. J. Biol. Macromol. 2019, 133, 190–201. [CrossRef]

78. Wahid, A.; Mahmoud, S.M.N.; Attia, E.Z.; Yousef, A.E.S.A.; Okasha, A.M.M.; Soliman, H.A. Dietary fiber of psyllium husk (Plantago ovata) as a potential antioxidant and hepatoprotective agent against CCl₄-induced hepatic damage in rats. S. Afr. J. Bot. 2020, 130, 208–214. [CrossRef]

79. Bagheri, S.M.; Zare-Mohazabieh, F.; Momeni-Asl, H.; Yadegari, M.; Mirjalili, A.; Anvari, M. Antiulcer and hepatoprotective effects of aqueous extract of Plantago major against methotrexate-ulcerated rats. Biomed. J. 2018, 41, 41–45. [CrossRef]

80. Li, F.; Huang, D.; Nie, S.; Xie, M. Polysaccharide from the seeds of Plantago asiatica L. protect against lipopolysaccharide-induced liver injury. J. Med. Food. 2019, 22, 1058–1066. [CrossRef] [PubMed]

81. Abouzied, M.M.; Mahmoud, S.M.; Wahid, A.; Ahmed, A.E.; Okasha, A.M.; Soliman, H.A.; Thagfan, S.S.A.; Attia, E.Z. A study of the hepatoprotective effect of Plantago psyllium L. seed extract against Carbon tetrachloride induced hepatic injury in rats. J. Appl. Biomed. 2020, 18, 80–86. [CrossRef]

82. Barkaoui, T.; Hamimed, S.; Bellamine, H.; Bankaji, I.; Sleimi, N.; Landoulsi, A. Alleviated actions of Plantago albican extract on lead acetate-produced hepatic damage in rats through antioxidant and free radical scavenging capacities. J. Med. Food. 2020, 23, 1201–1215. [CrossRef] [PubMed]

83. Parhizgar, S.; Hosseinian, S.; Hadjzadeh, M.A.R.; Soukhtanloo, M.; Ebrahimzadeh, A.; Mohebbati, R.; Yazd, Z.N.E.; Khajavi Rad, A. Renoprotective effect of Plantago major against nephrotoxicity and oxidative stress induced by cisplatin. Iran J. Kidney Dis. 2016, 10, 182–188. [CrossRef]

84. Parhizgar, S.; Hosseinian, S.; Soukhtanloo, M.; Bideskan, A.E.; Haghshenas, M.; Rad, A.K. Plantago major protects against cisplatin-induced renal dysfunction and tissue damage in rats. Saudi J. Kidney Dis. Transpl. 2018, 29, 1057–1064. [CrossRef]

85. Yazd, Z.N.E.; Noshahr, Z.S.; Hosseinian, S.; Shaﬁei, M.N.; Bideskan, A.E.; Mohebbati, R.; Heravi, N.E.; Shahram, S.; Mahzari, S.; Rad, A.K. Renoprotective effect of Plantago major against proteinuria and apoptosis induced by adriamycin in rat. J. Pharmacopunct. 2019, 22, 35–40.

86. Samout, N.; Ettaya, A.; Bouzenna, H.; Ncib, S.; Elfeki, A.; Hfaiedh, N. Beneficial effects of Plantago albican on high-fat diet-induced obesity in rats. Biomed. Pharmacother. 2016, 84, 1768–1775. [CrossRef]

87. Yang, Q.; Qi, M.; Tong, R.; Wang, D.; Ding, L.; Li, Z.; Huang, C.; Wang, Z.; Yang, L. Plantago asiatica L. seed extract improves lipid accumulation and hyperglycemia in high-fat diet-induced obese mice. Int. J. Molec. Sci. 2017, 18, 1393. [CrossRef]

88. Ji-Ping, L.; Ren-Chao, T.; Xiao-Meng, S.; Hao-Yue, Z.; Shuai, S.; Ai-Zhen, X.; Zheng-Tao, W.; Li, Y. Comparison of main chemical composition of Plantago asiatica L. and P. depressa Willd. seed extracts and their anti-obesity effects in high-fat diet-induced obese mice. Phytother. Res. 2021, 81, 153362. [CrossRef]

89. Khushmatov, S.S.; Makhmu dov, R.R. Antiarrhythmic activity of the flavonoid fraction of Plantago major L. extract. Pharm. Chem. J. 2019, 52, 992–995. [CrossRef]

90. Mojthahedin, A. Study of anxiolytic effect of hydro-alcoholic leaf extract of Plantago major L. in rats and interaction with epinephrine: Role of Adrenergic system. Der Pharm. Lett. 2016, 8, 202–206.

91. Nie, Q.; Chen, H.; Hu, J.; Gao, H.; Fan, L.; Long, Z.; Nie, S. Arabinoxylan attenuates type 2 diabetes by improvement of carbohydrate, lipid, and amino acid metabolism. Molec. Nutr. Food Res. 2018, 62, 1800222. [CrossRef] [PubMed]

92. Pandey, A.; Koruri, S.S.; Chowdhury, R.; Bhattacharya, P. Prebiotic influence of Plantago ovata on free and microencapsulated L. casei—Growth kinetics, antimicrobial activity and microcapsules stability. Int. J. Pharm. Pharm. Sci. 2016, 8, 89–97

93. Tong, R.C.; Qi, M.; Yang, Q.M.; Li, P.F.; Wang, D.D.; Lan, J.P.; Wang, Z.T.; Yang, L. Extract of Plantago asiatica L. seeds ameliorates hypertension in spontaneously hypertensive rats by inhibition of angiotensin converting enzyme. Front. Pharmacol. 2019, 10, 403. [CrossRef] [PubMed]

94. Li, F.; Huang, D.; Yang, W.; Liu, X.; Nie, S.; Xie, M. Polysaccharide from the seeds of Plantago asiatica L. alleviates nonyphenol induced reproductive system injury of male rats via PI3K/Akt/mTOR pathway. J. Funct. Foods. 2020, 66, 103828. [CrossRef]

95. Ogbioko, C.; Eboka, U.C.; Igbe, I.; Usman, D.M. Anti-ulcer activity of methanol extract of Plantago rugelii Decne. (Plantaginaceae). Trop. J. Nat. Prod. Res. 2017, 1, 84–88. [CrossRef]

96. Basiri, S.; Shekarforoush, S.S.; Mazkour, S.; Modabber, P.; Kordshouli, F.Z. Evaluating the potential of mucilaginous seed of psyllium (Plantago ovata) as a new lead biosorbent. Bioact. Carbohydr. Diet Fibre 2020, 24, 100242. [CrossRef]
97. Elbesthi, R.T.A.; Özdemir, K.Y.; Taştan, Y.; Bilen, S.; Sönmez, A.Y. Effects of ribwort plantain (Plantago lanceolata) extract on blood parameters, immune response, antioxidant enzyme activities, and growth performance in rainbow trout (Oncorhynchus mykiss). *Fish Physiol. Biochem.* 2020, 46, 1295–1307. [CrossRef]

98. Navarrete, S.; Kemp, P.D.; Pain, S.J.; Back, P.J. Bioactive compounds, aucubin and acteoside, in plantain (Plantago lanceolata L.) and their effect on In Vitro rumen fermentation. *Anim. Feed Sci. Technol.* 2016, 222, 158–167. [CrossRef]

99. Niziol-Lukszewska, Z.; Gaweł-Beben, K.; Rybczyńska-Tkacz, K.; Jakubczyk, A.; Karaś, M.; Bujak, T. Biochemical properties, UV-protecting and fibroblast growth-stimulating activity of Plantago lanceolata L. extracts. *Ind. Crops Prod.* 2019, 138, 111453. [CrossRef]

100. Niknam, R.; Ghanbarzadeh, B.; Ayaseh, A.; Rezagholi, F. The hydrocolloid extracted from Plantago major seed: Effects on emulsifying and foaming properties. *J. Disp. Sci. Technol.* 2020, 41, 667–673. [CrossRef]

101. Behbahani, B.A.; Shahidi, F.; Yazdi, F.T.; Mortazavi, S.A.; Mohebbi, M. Use of Plantago major seed mucilage as a novel edible coating incorporated with *Anethum graveolens* essential oil on shelf life extension of beef in refrigerated storage. *Int. J. Biol. Macromol.* 2017, 94, 515–526. [CrossRef] [PubMed]

102. Niknam, R.; Ghanbarzadeh, B.; Ayaseh, A.; Hamishehkar, H. Plantago major seed gum based biodegradable films: Effects of various plant oils on microstructure and physicochemical properties of emulsified films. *Polym. Test.* 2019, 77, 105868. [CrossRef]

103. Allafchian, A.R.; Kalani, S.; Golkar, P.; Mohammadi, H.; Jalali, S.A.H. A comprehensive study on *Plantago ovata* PVA biocompatible nanofibers: Fabrication, characterization, and biological assessment. *J. Appl. Polym. Sci.* 2020, 137, 49560. [CrossRef]

104. Salas-Luévano, M.A.; Mauricio-Castillo, J.A.; Gonzalez-Rivera, M.L.; Vega-Carrillo, H.R.; Salas-Muñoz, S. Accumulation andphytostabilization of As, Pb and Cd in plants growing inside mine tailings reforested in Zacatecas, Mexico. *Environ. Earth Sci.* 2017, 76, 806. [CrossRef]

105. Romeh, A.A.; Khamis, M.A.; Metwally, S.M. Potential of *Plantago major* L. for phytoremediation of lead-contaminated soil and water. *Water Air Soil Pollut.* 2016, 227, 9. [CrossRef]

106. Aioub, A.A.A.; Zuo, Y.; Li, Y.; Qie, X.; Zhang, X.; Essmat, N.; Wu, W.; Hu, Z. Transcriptome analysis of *Plantago major* as a phytoremediator to identify some genes related to cypermethrin detoxification. *Environ. Sci. Pollut. Res.* 2020, [CrossRef]

107. Darch, T.; McGrath, S.P.; Lee, M.R.F.; Beaumont, D.A.; Blackwell, M.S.A.; Horrocks, C.A.; Evans, J.; Storkey, J. The mineral composition of wild-type and cultivated varieties of pasture species. *Agronomy* 2020, 10, 1463. [CrossRef]

108. Vaculík, M.; Jurkovič, L.; Matejkovič, P.; Molnárlová, M.; Lux, A. Potential risk of Arsenic and Antimony accumulation by medicinal plants naturally growing on old mining sites. *Water Air Soil Pollut.* 2013, 224, 1546. [CrossRef]

109. Simon, P.L.; de Klein, C.A.M.; Worth, W.; Rutherford, A.J.; Dieckow, J. The efficacy of *Plantago lanceolata* for mitigating nitrous oxide emissions from cattle urine patches. *Sci. Total Environ.* 2019, 691, 430–441. [CrossRef]

110. Somasiri, S.C.; Kenyon, P.R.; Kemp, P.D.; Morel, P.C.H.; Morris, S. Growth performance and carcass characteristics of lambs grazing forage mixes inclusive of plantain (*Plantago lanceolata* L.) and chicory (*Cichorium intybus* L.). *Small Rumin. Res.* 2015, 127, 20–27. [CrossRef]

111. Mirzaei, S.; Javanbakht, V. Dye removal from aqueous solution by a novel dual cross-linked biocomposite obtained from mucilage of *Plantago Psyllium* and eggshell membrane. *Int. J. Biol. Macromol.* 2019, 134, 1204. [CrossRef] [PubMed]

112. Mobin, M.; Rizvi, M. Polysaccharide from *Plantago* as a green corrosion inhibitor for carbon steel in 1 M HCl solution. *Carbohydr. Polym.* 2017, 160, 172–183. [CrossRef] [PubMed]

113. Fierascu, I.; Fierascu, I.C.; Dinu-Pirvă, C.E.; Fierascu, R.C.; Anuta, V.; Velescu, B.S.; Jingga, M.; Jingga, V. A short overview of recent developments on antimicrobial coatings based on phytosynthesized metal nanoparticles. *Coatings* 2019, 9, 787. [CrossRef]

114. Fierascu, I.; Fierascu, I.C.; Brazdies, R.I.; Baroi, A.M.; Fios, T.; Fierascu, R.C. Phytosynthesized metallic nanoparticles-between nanomedicine and toxicology. A brief review of 2019’s findings. *Mater. Sci. Pol.* 2020, 13, 574. [CrossRef]

115. Fierascu, R.C.; Ortan, A.; Avramescu, S.M.; Fierascu, I. Phytocatalysts: Green synthesis, characterization, and applications. *Molecules* 2019, 24, 3418. [CrossRef]

116. Fierascu, R.C.; Fierascu, I.; Lungulescu, E.M.; Nicula, N.; Somoghi, A.; Ditu, L.M.; Ungureanu, C.; Sutan, A.N.; Drăghicăceanu, O.A.; Paunescu, A.; et al. Phytosynthesis and radiation-assisted methods for obtaining metal nanoparticles. *J. Mat. Sci.* 2020, 55, 1915–1932. [CrossRef]

117. Romeh, A.A.A. Green silver nanoparticles for enhancing the phytoremediation of soil and water contaminated by fipronil and degradation products. *Water Air Soil Pollut.* 2018, 229, 147. [CrossRef]

118. Lohrasbi, S.; Khoubanian, M.A.J.; Beheeshtkhoon, N.; Ghasemi, Y.; Amani, A.M.; Taghizadeh, S. Green synthesis of iron nanoparticles using *Plantago major* leaf extract and their application as a catalyst for the decolorization of azo dye. *BioNanoScience* 2019, 9, 317–322. [CrossRef]

119. Pereira, C.G.; Custódio, L.; Rodrigues, M.J.; Neng, N.R.; Nogueira, J.M.F.; Carlier, J.; Costa, M.C.; Varela, J.; Barreira, L. Profiling of antioxidant potential and phytoconstituents of *Plantago coronopus*. *Brasil. J. Biol.* 2017, 77, 632–641. [CrossRef]