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Plantago lanceolata L. CROPS – SOURCE OF VALUABLE RAW MATERIAL FOR VARIOUS INDUSTRIAL APPLICATIONS

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Abstract

Plantago lanceolata L. (ribwort plantain) belonging to Plantaginaceae family is a perennial cosmopolitan species which shows high ecological plasticity, being found naturally in grassy areas on roadsides, in pastures and in crops as weeds. The species has a wide range of more or less developed industrial applications. In this review are presented data regarding ribwort plantain cultivation (cultivated area and input requirements), the main biologically active constituents, review of existing industrial applications, potential directions of use based on new achievements in biotechnology or on improvement of extraction and formulation technology (pharmaceutical products, supplements for veterinary use, cosmetics, insecticides, other intermediary products), restricting factors that could inhibit larger industrial use (issues related to the crop input, inconsistency in quality of the end-product, etc.), recommendations to use bio-products based on Plantago lanceolata raw material.
Although Plantago lanceolata L. is considered a weed, scientific data prove its importance in various domains and also open new directions for development of new and valuable natural products.

Key words*: Plantago lanceolata, plantain, crop, applications.*

REVIEW

AREAS OF ORIGIN AND CURRENT CULTIVATION

Plantago lanceolata L. (ribwort plantain) belonging to Plantaginaceae family is a cosmopolitan species - from Iceland south and east to Spain, northern and central Asia (www.pfaf.org).
In UK *Plantago lanceolata* is a relatively new crop while in Germany this species is one of the most cultivated (Europam). In Poland, ribwort plantain is a species recommended for enriching grassland biodiversity (Seidler-Lozykowska, 2009) and in Romania this species is mainly collected from the wild but there is a small cultivated area too (the main cultivar is "de Cluj", registered in 1975). In Slovenia, considering the principle of sustainable use, natural populations of *Plantago lanceolata* L. are successively introduced in the National Collection of Medicinal and Aromatic Plants (MAP's), where further activities (multiplication of plant materials, morphological and/or chemical characterization, selection and other pre-breeding studies) needed for future cultivation purposes are foreseen (Baričevič et al., 1994).
In Austria ribwort plantain is grown in the more humid areas; in the Mühlviertel county, province of Upper-Austria, ribwort plantain, marjoram, common balm, and peppermint are the most important crops, about 65% of the total herb acreage in this region being organic grown (Ruckenbauer, 2004).

GROWING CONDITIONS – INPUT REQUIREMENTS

Ribwort plantain is a perennial herb which shows high ecological plasticity, being found naturally in grassy areas on roadsides, in pastures and in crops as weeds. It shows moderate demands regarding soil and climatic factors. Resist well in drought and cold winters and it can tolerate maritime exposure (www.pfaf.org). This plant is not picky towards previous crop in the field, but is better to be sown after the land is cleaned of weeds and leaves, without plant debris. The plant could be maintained in culture 4-5 years (Roman et al., 2009). Physical purity of seed shall be a minimum of 85% and 75% germination (Roman et al., 2009). Plantain exploits nutrients from fertilizer, bringing special production increases.

Kolodziej (2006) showed that plantain cultivation without mineral fertilisation application produce significantly lower yields of leaves, characterised however by the highest active substances content and better sanitation.

Generally, in plantain crops have not noticed important diseases or pests. The annual production which can be obtained is about 10-12 tones of fresh leaves and 1.5 to 2 tones of dry leaves, respectively (Roman et al., 2009).

Significant differences were evident in plants grown under controlled conditions for all characters except seed number per capsule, indicating a genetic basis to population differences observed in the field. Inflorescence number per plant and capsule number per inflorescence showed significant variation within populations (Primack et al., 1981).

MAIN CONSTITUENTS

According to European Medicine Agency (EMEA) (EMEA, 2010) and other sources, the main constituents of *Plantago lanceolata* are:

Iridoidglycosides: Iridoidglycosides are chemotaxonomic markers of *Plantago* genus (Rymkiewicz, 1979). According to the iridoid fingerprint, *Plantago* species are classified as follows: species containing mainly aucubin and their derivatives (*P. major*, *P. cornuti*, *P. gentianoides*), species containing mainly aucubin and their derivatives like 10-O-acetyl-aucubin, monomelitoside and monomelitoside derivatives (*P. subulata*, *P. media*), species containing aucubin and catalpol (*P. lanceolata*, *P. altissima*, *P. argentea*, *P. lagopus*, *P. atrata*) and species containing aucubin and plantarenaloside (*P. afra*, *P. scraba*) (Taskova et al., 2002).

The herbal substance contains about 2-3% iridoidglycosides with aucubin and catalpol as the main compounds, as well as asperuloside, globularin and desacetylasperuloside-acid methylester (Handzhieva et al., 1991).

The iridoid content depends on the maturity of the leaves. Young leaves contain up to 9%, while in the older ones iridoids are present only in traces (Klockars et al., 1993). Chemical variation within and between individuals was studied and it was found that young and intermediate age leaves have the highest content of catalpol while aucubin (biosynthetic precursor of catalpol) is predominant in the leaves of intermediate age and less in the mature ones (Bowers et al., 1992).

Significant variation in iridoid glycosides (IGs) content between shoot and root tissues across development was also observed: allocation of IGs into root tissues linearly increased from younger to older plants, while non-linear shifts in allocation of IGs during ontogeny were observed for shoot tissues. Finally, root:shoot ratios only weakly explained overall allocation of resources into defenses, with young stages showing a positive relationship, while older stages showed a negative relationship between root:shoot ratios and IG concentrations. Ontogenetic trajectories in plant quality and defenses within and among plant tissues can strongly influence insect herbivores' performance and/or predation risk; thus, they are likely to play a significant role in mediating species interactions (Quintero et al., 2012).

Mucilage: ~6.5%. *P. lanceolata* leaves contain polysaccharides with L-arabinose (~20%), D-galactose (~28%), D-glucose (~6%), D-manose (~2%), L-manose (~4%), D-galacturonic acid (~31%), D-glucuronic acid (~7%), and minor proportions of L-fructose and D-xilose. Chromatographic separation of the crude polysaccharide resulted in the obtainment of three distinct fractions, out of which 2 are neutral and a molecular weight between 8000-45000 Da, and one is acidic and it has a molecular weight of 70000Da (Braeutigam et al., 1985).

Polyphenols: Acteoside (verbascoside) is the main phenyletaonidic compound in *P. lanceolata*; other compounds are cistanoside F, lavandulyfolioside, plantamajoside and isoacetoside (Murai et al., 1995).

Based on the differences in polyphenolic compounds structure (iridoids, flavonoids, phenyletanoids) of different *Plantago* species, a classification in two groups was proposed: one group with *P. asiatica* and *P. major* as main representatives and the other one with *P. depressa* and *P. lanceolata* (Nishibe et al., 1995).

Chemotaxonomic analysis of *Plantago* genus showed that caffeic, vanilic, ferulic , syringic and p-cumaric acids occur most frequently but there is no chemotaxonomic semnification for this aspect (Andrzejewska-Golec et al., 1986). The herbal substance also contains 6.5% tannins, phenolic carboxylic acids including p-hydroxybenzoic-, protocatechuic, gentisinic-, chlorogenic- and neochlorogenic acid (Maksyutina, 1971), among others.

It was showed that cultivated ribwort plantain has a higher polyphenol composition, both in terms of quality (various phenolic compounds with antioxidant character) and quantitative (1000 mg/100 g) than of wild specimens (Varban and Varban, 2012).

Flavonoids class includes apigenin and luteolin as well as their derivatives with the main compounds apigenin-6,8-di-C-glucoside and luteolin-7-O-glucuronide, luteolin-7-O-glucoside and 7-O-glucuronide-3'-glucoside, in addition to the 7-O-glucuronyl-glycosides of apigenin and luteolin as well as apigenin-7-O-glucoside and 7-O-glucuronide (EMEA, 2011; Wichtl, 2004).

Volatile oil: The volatile compound proportion corresponds to 0.05%, 0.03% and 0.001% of fresh weight for fruits, leaves and scapes, respectively. Thirty-five and twenty-six components were identified from fruits and leaves, respectively, while scapes contained only seven volatile components as it was showed by GC/MS. The major constituents of fruits were oct-1-en-3-ol (24.9%), hexahydrofarnesylacetone (15.7%), vanillic acid (9.8%) and neophytadienes (>10%); leaves contained mainly oct-1-en-3-ol (41.1%), (E),4(3-oxo-2,6,6-trimethylcyclo-hex-2-en-1-yl)-3-buten-2-ol (15.6%), 6-(3-hydroxy-1-butenyl)-1,5,5-trimethyl-7-oxabicyclo[4,1,0]heptan-3-ol (6.9%) and benzoic acid (6.3%). Neophytadienes were mainly found in both scapes of wild ribworts and leaves of seedling cultures (Fons et al., 1998).

Other compounds. The coumarin aesculetin, the xanthophyll decomposition product loliolide and small amounts of a hemolytic and antimicrobial saponin are also present. Inorganic constituents include 1% silicilic acid and mineral salts with a high proportion of zinc and potassium (EMEA, 2011).

REVIEW OF *PLANTAGO LANCEOLATA* USES

Plantago lanceolata raw material is suitable for various applications. There are about 45 registered international patents concerning *Plantago lanceolata* leaves and only few are applied in industry.

Pharmaceutical products:

Generally, plantain leaves are applied externally to heal sores and wounds; against furuncles, against insect and snake bites (Pieroni et al., 2004; De Natale et al., 2007; Tita et al., 2009) and internally as expectorant, antitussive, emollient, anti-inflammatory, astringent, antimicrobial, bronchitis, laryngo-tracheal catarrh, diarrhoea (Tita et al., 2009; Neves et al., 2009).

Plantaginis lanceolatae folium has monograph in European and British Pharmacopoeia, ESCOP, German Commission E and French Avis aux fabr. monographs and also a monograph published on EMEA (Herbal Medicinal Products committee assessment). Plant material of interest for pharmaceutical purposes is represented by whole or fragmented, dried leaf and scape of *Plantago lanceolata* L.

According to EMEA, traditional uses for *Plantago lanceolata* leaves are: “Indications for the internal administration are catarrhs of the respiratory tract and inflammation of oral and pharyngeal mucosa. Externally applied it is used for inflammation of the skin”.

According to the overviews of the market in the Member States of the European Union, there were herbal preparations with a well-established use status (herbal substance (cut); dry extract, liquid extract, soft extract, expressed juice from the fresh herb) and also herbal preparations under traditional use (herbal substance (cut), powdered herbal substance, liquid extract, syrup) (EMEA, 2011).

European manufacturers use Plantaginis folium (alone or in combination with other plants) for various medicinal purposes: digestion (Finland, Romania), expectorant (Slovenia, Italy, Romania), antimicrobial, astringent, soothing irritations (Poland, Belgium) or in various forms: herbal tea, tablets, syrup, etc.

In homeopathy - drugs with medical prescription - *Plantago lanceolata* is commercialized as drops, granules.

Cosmetics

Plantago lanceolata leaves are used in cosmetic industry by many European manufacturers for a large variety of products: creams, lotions, solution for spa use, etc.

An *in vivo* study conducted in Germany by Rahn Cosmetics AG (http://www.rahn-group.com/en/cosmetics/product/20/) showed that a product containing *Plantago lanceolata* water extract, *Mahonia aquifolium* and salicylic acid effectively reduces existent skin impurities and optimises the skin appearance due to its antibacterial, keratolytic and antiinflammatory action.

In Switzerland, another company utilizes *Plantago lanceolata* leaf extract for enhancing collagen production and wound healing and for exerting an antioxidant effect (http://www.anshulindia.com/pdfs/DSM%20Pentapharm%20Products.pdf).

Products for veterinary use

Leaves are edible and sometimes eaten as vegetable. *Plantago lanceolata* is occasionally grown as a fodder crop and considered to be of better quality than *Plantago major* (Gurib-Fakim, 2006). It may also be recommended as an alternative to hay in sheep (Al-Mamun et al., 2007).

Ribwort forage is new as feedstuffs to piglets, but have previously been fed to deer, calves, lambs and young rabbits with good growth performance results. One of the first studies on the impact on growth performance, digestibility and coliform counts of feeding ribwort forage to piglets showed that the higher digestibility of non-starch polysaccharides observed with inclusion of ribwort is a result of increased hindgut fermentation due to more easily degradable polysaccharides in the herbs than the cereals. The use of fibre-rich feedstuffs to weaned piglets was promising, but the low palatability of ribwort could limit the inclusion level in the diet (Ivarsson et al., 2011).

Moreover, it was showed that in the case of European wild boar (*Sus scrofa* L.), *P. lanceolata* has a high digestibility coefficient and digestible energy content (Quijada et al., 2012).

Studies on calves showed good results too. *Plantago lanceolata* L. dried leaves are used as tea as an appetizer and digestive and the fresh leaves are topically applied with cream from cows' milk and bread or clay as a suppurative (also for cows, especially for treating inflamed hooves) (Pieroni et al., 2009). Also, the inclusion of *P. lanceolata* as a supplemental forage significantly reduces the egg output of gastrointestinal nematodes in calves (Sievers et al., 2006).

Another study showed the healing potential of water-soluble extract of *Plantago lanceolata* as a topical ointment on experimental tendinitis in burros induced by bacterial collagenase. The positive effects of the *Plantago* in the healing of tendinitis can be attributed to its anti-inflammatory properties owing to acteoside, a phenylethanoid, which inhibits arachidonic acid in the cyclooxygenase pathway (Oloumi et al., 2011).

Insecticide

A recent study showed that *P. lanceolata* extracts have potential for use in the development of new products to control the coffee leaf miner (*Leucoptera coffeella* Guérin-Mèneville & Perrottet) by reducing its oviposition and egg hatching, apparently as a result of action of plant metabolites on the embryo. Adults originating from eggs treated with the extract exhibited similar survival rates, but a higher female/ male ratio (Alves et al., 2011).

The compounds found in *Plantago lanceolata* have potential for use in selectively targeting plant-parasitic nematodes in pest management systems. Further research is needed to isolate and identify *Plantago*-specific compounds, to determine their toxicity to additional plant-parasitic nematodes, and to understand the fate of these compounds in soil (Meyer et al., 2006).

Metal removal

P. lanceolata can be used as a good bioindicator for heavy metal accumulation in industrial and urban areas. Data on accumulative capacity allow us to recommend this species not only for Zn and Pb, but for indication of Cd, too (Dimitrova and Yurukova, 2005).

In a study carried out to evaluate copper resistance by rhizosphere microorganisms from *Plantago lanceolata* L., the results indicated that some isolates are potential agents for copper bioremoval and bacterial stimulation of copper biosorption by this herbal species. Speciation of copper revealed high copper biotransformation, reducing Cu(II) to Cu(I), capacity (Andreazza et al., 2012).

Other intermediary products

A large variety of intermediary products for various further uses are produced in Europe: hydroalcoholic extract - Romania, France, liquid extract -Bulgaria, Poland, dry extract - Bulgaria, Poland, Slovakia, mother tincture - France, glycerine extract – France.

These extracts are standardized and they can be applied in many different final products, from cosmetics to nutritional supplements.

APPLICATIONS UNDER STUDY

In vitro cultures are already used for plant regeneration and micropropagation. As regards callus culture, it was proved that the leaf and root mucilage content in the intact plant of *P. lanceolata* is 10% g/g dw and in seeds is 5% g/g dw while in the callus is about 14.75%g/g dw. Callus could have up to 3 times more mucilage than seeds, leaf and root parts (Mirmasumi et al., 2001).

Also, hairy root cultures are able to biotransform an outer precursor such as cinnamic acid into a phenolic derivative. Further investigation should be carried out in order to optimize the culture conditions and increase the bioproduction of biologically active metabolites. -*P. lanceolata* may be transformed by *Agrobacterium rhizogenes* and two phenylethanoid heterosides, i.e. p-cumaroyl-glucose and feruloyl-glucose are neo-synthesized and accumulated in the roots of seedlings fed with cinnamic acid (Fons et al., 2008). A recent study showed that a phenolic acid mixture produced during the fungal proliferation protected acteoside from breakdown, possibly via its antioxidant activity and metal complexing ability. It was shown that plant-associated microorganisms can increase or decrease the stability of chief metabolites in herbal matrices, and can significantly alter the chemical pattern of the plant matrix (Kiss et al., 2013).

Products based on improvement of extraction and formulation technology are also developing. New type of nanomaterials has been already synthesized using iridoidic extract separated from *Plantago lanceolata* by successive extraction in aqueous media. The obtained nanodrops were then encapsulated in silica resulting porous core - shell particles which were characterized by Dynamic Light Scattering and electronic microscopy confirming the nanostructure of the new biomaterials. Preclinical tests performed on mice revealed a positive action on the healing process, and the crude extract processed as nanopowder showed a protective action against diarrhoea disorder (Radu et al., 2009).

Moreover, these days modified polysaccharides have been the major area of scientific research. Polysaccharides such as starch, cellulose, chitosan, dextrin, guar-gum, psyllium are cost effective, biodegradable and quite efficient towards various technological processes - drug-delivery, agriculture (insecticide and pesticide delivery), water treatment (removal of toxic metal ions from waste water and flocculation) and membrane technology (Kaith and Kumar, 2007).

RESTRICTING FACTORS THAT COULD INHIBIT LARGER INDUSTRIAL USE

As regards the agricultural raw material, there are some issues related to the crop input. *Plantago lanceolata* is a common weed and some of the manufacturers use wild crafted raw material which leads to inconsistency in quality of the end-product. Much attention should be paid to conditions for cultivation which are essentials to valuable end-products. The contents of aucubin and acteoside are extremely lower in plants grown in the shade. Moreover, the contents of aucubin and acteoside are apparently lower in the plants treated with nitrogen than in those that did not receive it, although nitrogen application enhances the growth of the cultivars, especially the top fresh weight (Yoshifumi et al., 2001).

The content of aucubin and catalpol varies also depending on the time of harvesting. Before the flowering period the content of aucubin is very low in every organ and reaches its maximum in autumn with aucubin at levels of 1-3% and catalpol up to 1% (EMEA, 2011).

Mucilage content is lower than in *Plantago ovata* which gives about 25% of good quality mucilage. This mucilage has various industrial applications (thickener, hydrocolloidal agent) as well as medicinal properties (source of dietary fibres, hypocholesterolemic and antidiabetic activities). Because of the poor yield, *P. lanceolata* mucilage is not suitable enough for industrial production.

Ribwort plantain grows well under cool temperatures, improving its productivity in dry. In a study developed in US it was showed that plantain growth rates were greater in September than they were in July, increasing by 62% in the normal and 29% in the wet treatment. Imposition of summer drought on plantain increased winter survival from <10% in the normal and wet treatments to 41% in the dry treatment (Howard Skinner et al., 2002).

After harvesting the herb has to be dried directly to avoid fermentative processes. After hydrolysis aucubin is converted to dark brown polymers, which are responsible for the dark coloration of improperly dried drug material. The herbal substance is commonly dried at temperatures of 40-50°C. During this process the content of aucubin decreases. Drying at room temperature results in aucubin contents twice as high (EMEA, 2011).

As regards industrial raw material, especially for pharmaceutical applications, there are some research gaps that need to be filled. There are no consistent human data available regarding pharmacodynamic and pharmacokinetic properties of *Plantago lanceolata* leaves. Although various pharmacological effects have been described for the total extract of *Plantago lanceolata* and constituents thereof, these effects or dose response studies have never been verified in controlled clinical studies. Also, for children and adolescents no data are available, thus, the oromucosal administration should be limited to adults.

Plantain is generally considered as one of the most important dicotyledons that cause allergic diseases in Europe. Further studies on polyamine and allergy relation with other genus are carried out; the results of this research are in progress.

Regarding the above mentioned aspects, high and sometimes restrictive *costs* are involved for clinical trials, classic or organic cultivation (comparing to wild crafting), additional operations for primary processing.

RECOMMENDATIONS TO USE BIO-PRODUCTS BASED ON *PLANTAGO LANCEOLATA* RAW MATERIAL

Some measures concern the improvement of quality and yield of raw material and biologically active constituents. In this respect, studies for selecting mutants with high stress or salt resistance, freezing tolerance or with high bioactive compound contents should be carried out. Also, optimization of post-harvest processes to maintain a good yield of active principles, initiation of large scale organic cultivation and also improvement of technology for primary and secondary processing are important steps for high valorification of *Plantago lanceolata*. Product quality is ensured also by standardization, especially for pharmaceutically products; in this case, the quality and thus the concentration of active compounds is much more relevant than the total yield.

As regards pharmaceutical products, there is a strong need for appropriate pharmacological testing and controlled clinical studies. New pharmaceutical applications of ribwort plantain were already verified on animal models: immunostimulant effect, antitoxic effect, procoagulant effect, antihelminthic effect, antiulcerous activity.

Further studies on polyamine and allergy relation with other genus having different species, which have different allergy degrees, should be continued.

Veterinary medicine is also a niche that is worth to exploit both for food and non-food use of ribwort plantain. No less important is the financial help for cultivation; it is important to understand the influence of controlled conditions for natural, inovative and high quality end-products.

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