AgriWasteValue

To transform agricultural by-products
and residues into bioactive compounds

PHLORIZIN APPLICATION POTENTIAL IN THE NUTRACEUTICAL SECTOR

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PHLORIZIN APPLICATION POTENTIAL IN THE NUTRACEUTICAL SECTOR

by Flora Mer, Biobased Products Project Manager, Valbiom

Introduction

Within the AgriWasteValue project, after collection of the pruning residues from apple, the residues were extracted using the hydro-alcoholic method. Different types of apple pruning extract were then produced.

The table 1 illustrates the content in polyphenols of apple pruning feedstocks, apple pruning extract and apple pruning extract enriched. The active ingredients contained in these extracts were identified using the UPLC-MS method.

Phlorizin is only one of a number of molecules found in high concentrations in apple pruning residues collected within the AgriWasteValue project.

This case study aims to analyse the potential of using phlorizin obtained from a by-product in the nutraceutical sector by having a clear view of actual phlorizin use and its specificities.

	APPLE PRUNING FEEDSTOCK	APPLE PRUNING EXTRACT ETOH70%	APPLE PRUNING EXTRACT ETOH70% ENRICHED
Polyphenols	5 %	30 %	70 %
Concentration due to the extraction process	-	6 times	14 times
Active ingredients	Phlorizin > Quercitrin > Avicularin > Epicatechin > Chlorogenic Acid		

Table 1: Composition of polyphenols in apple pruning feedstocks, apple pruning extract and apple pruning extract enriched (Celabor).

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Phlorizin and its sourcing

WHAT IS PHLORIZIN?

Phlorizin is a **phenolic compound** derived from phloretin via enzymatic modification. Compared to phlorizin, phloretin does not contain any glucose unit (Figure 1). Phloretin is mainly used in cosmetic applications. As we focused on the nutraceutical sector we will not detail the potential of application of phloretin.

Through oxidation, phlorizin is transformed into “POP” or “phlorizin oxidation product”. This derivative is interesting as it can be used as a colouring agent for the agri-food industry and, more specifically, in the nutraceutical sector.

The biochemical and organoleptic characteristics of phlorizin are the following:

- Molecular weight: 436.4 g/mol
- Molecular formula: $C_{21}H_{24}O_{10}$
- Weak basic compound, almost neutral
- Solid at room temperature, in ethanol and hot water. Poorly soluble in cold water.
- Melting point: 110°C
- Decomposition temperature: > 200°C
- Bitter taste

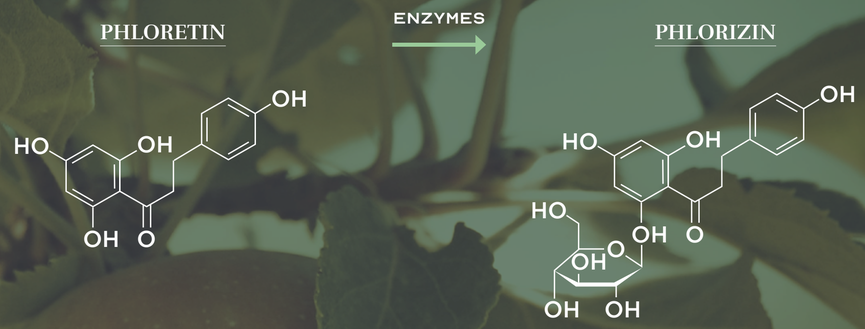

Figure 1: Molecular structure and transformation of phloretin into phlorizin - Adamcová et al., 2022

WHERE IS PHLORIZIN NATURALLY FOUND?

Phlorizin is a molecule that can be found in a number of different plants although apples are the principal source of phlorizin for human consumption.

The table 2 summarises potential plant sources of natural phlorizin.

Based on a review of the literature for each type of plant source, phlorizin has mainly been found in:

- Mexican oregano, mainly in the whole herb. The average concentration of phlorizin is 136 mg/100 g.
- Plum, mainly in the juice (flesh and skin). The average concentration of phlorizin is 5.85 mg/100 g.
- Apple, mainly in the whole apple. The average concentration of phlorizin is 2.69 mg/100 g.
- Pomegranate, mainly in the juice. The average concentration of phlorizin is 0.10 mg/100 g.

Phlorizin was detected but not quantified in the last plant, *Theobroma cacao*.

PLANT SPECIES FAMILY	EXAMPLES OF PLANTS CONTAINING PHLORIZIN	PHLORIZIN LOCATION IN THE PLANT
Poaceae	Wheat, rice, barley, maize, sorghum, rye, sugar cane, herbs	• Roots, bark • Seeds, mainly skin and juice • Stems, roots and leaves
Rosaceae	Apple, pear, plum, cherry	
Fabaceae	Soya (glycine max)	
Cucurbitaceae	Squash, courgette, pumpkin, melon, gherkin, watermelon	
Theobroma cacao	Cocoa	

Table 2: Potential plant sources of natural phlorizin

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FOCUS ON PHLORIZIN CONCENTRATION IN APPLE PRUNING RESIDUES

A review of the literature reveals that the majority of studies have focused on phlorizin concentration in apples (seed, skin, flesh, pulp, juice) but not on other parts of the apple tree. Other papers that have also been published have additionally studied the root bark of the tree.

However, two very recently published papers have also analysed other parts of the apple tree including the bark, buds, leaves and twigs. These are presented in the following section.

A paper published by **Adamcová et al., 2022** filled the data gap in the literature and presented some very interesting results for the detection of phenolic compounds (including phlorizin and phloretin) in the leaves, bark and buds of 13 different cultivars. Five main phenolic compounds were quantified.

The table 3 presents concentration levels of the individual phenolic compounds analysed in the bark of 13 apple cultivars that were collected and dried in September 2018.

An analysis of the different parts of the plants was completed and the results were compared. The key takeaways were the following:

CULTIVAR	PHLORIZIN (MG/G ± SD)
'Melrose'	76.59 ± 0.53
'Melodie'	67.73 ± 0.09
'James Grieve'	82.55 ± 0.59
'Rubinola'	70.31 ± 0.70
'Goldstar'	54.52 ± 0.40
'Meteor'	56.59 ± 1.70
'Prüsvitné letní'	57.48 ± 0.15
'Topaz'	86.03 ± 0.41
'Red Bilt'	85.62 ± 0.11
'Spartan'	102.69 ± 0.55
'Fragrance'	82.50 ± 0.12
'Gloster'	76.85 ± 0.17
'Bohemia Gold'	65.08 ± 0.29

Concentrations ± standard deviation (RSD, %) calculated from the mean of three measurements.

Table 3: Content of phenolic compounds in the bark of 13 cultivars (all values in mg/g of dried weight (DW)) - Adamcová et al., 2022

- Although phlorizin was the major component found in leaves, bark and buds, phlorizin was also present in varying proportions.
- The average concentration was as follows:
  - >71.8 mg/g of DW of phlorizin in the leaves
  - >74.2 mg/g of DW of phlorizin in the bark
  - >100.8 mg/g of DW of phlorizin in the buds
- In comparison, the concentration of phlorizin in apple fruit ranges from 75.4 to 151.7 µg/g DW.
  - >The concentration of phlorizin in bark, leaves and buds is 1000 times more concentrated than in the fruit.
  - >The fact that the values of phenolic compounds are several times greater in these materials (bark, leaves, buds) than in the fruit (mg vs. µg) could make it attractive for new nutraceutical product development.

In a study conducted by **Táborský et al., 2021**, the content of phlorizin was analysed in four different cultivars. Bark stood out as the most important source of phlorizin (up to 917 mg/g DW) (Figure 2).

Another interesting fact resulting from this study was that both the type of matrix and the period of vegetation have a significant impact on phlorizin content.

Why the phenolic compounds is richer in leaves, bark and buds?

The phenolic compounds in plants have a physiological defensive role. This may explain why the leaves, bark and buds are richer in phenolic compounds than the fruits.

They are exposed to a long-term stress (e.g., intensive sun exposure, pests), which can lead to increased large accumulation of phenolic compounds to protect the plant.

In addition, the fruit is necessary for the reproduction of the tree. the plant therfore has no interest in including pnenolic compounds in this part.

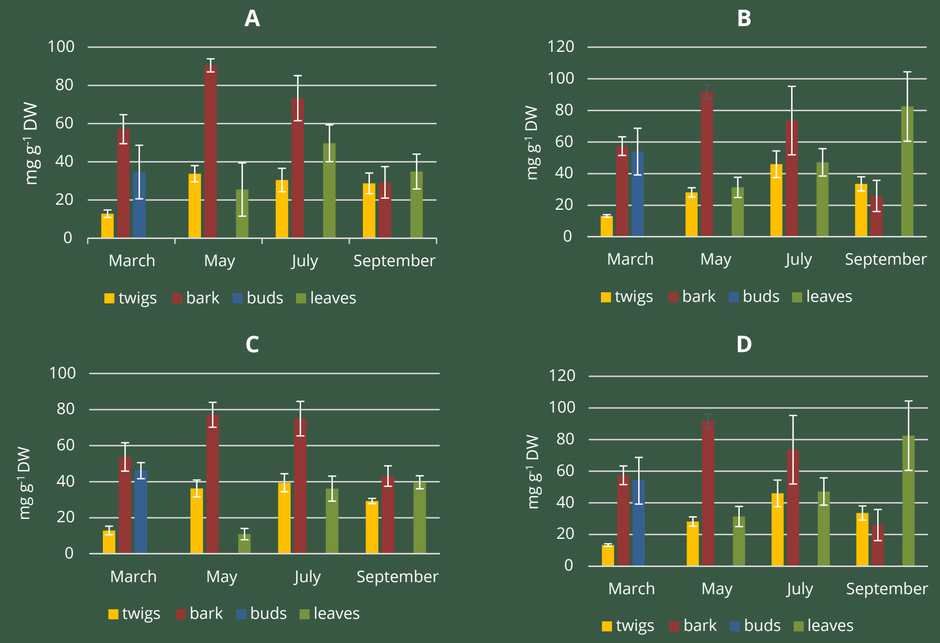

Figure 2: Content of phlorizin in different apple cultivars (A) 'Jonagold', (B) ´Opal´, (C) ´Redlane´, and (D) ´Rozela´ during the vegetation period. (Táborský et al., 2021)

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The health benefits of phlorizin

The figure 3 below summarises the different activities of phlorizin and the health benefits.

The use of phlorizin is widespread and reasonably interesting in respect of the current challenges being faced by society. For example, the number of new cases of diabetes and pre-diabetes being diagnosed is increasing significantly.

The following claims are pending approbation for apple extract containing polyphenols:

- "Can help moderate postprandial blood glucose levels"
- "Can help decrease blood glucose levels"

PHYSIOLOGICAL ACTIVITIES
Antioxidant **Anti-inflammatory**
Anti-obesity
Anti-aging
Protection against UV radiation
Cardioprotective
Neuroprotective
Hepatoprotective
Hypolipidemic effect
Immunomodulatory

Functional food

PHARMACOLOGICAL EFFECTS
Anti-diabetic *A competitive inhibitor of D glucose on the SGLTs and GLUTs transporters*
Anti-hyperglycemia
Anti-inflammatory
Anti-hypertension
Anti-microbial
Anti-tumor

Nutraceuticals & Drugs

Figure 3: Potential applications and further use of phlorizin – Tian et al., 2021

Benchmark

In order to evaluate the potential of how phlorizin obtained from apple pruning residues could be interesting for today's market, it is imperative to map current suppliers and retailers offering these ingredients and actual food supplement.

THE INGREDIENT APPROACH

Twenty-three suppliers of phlorizin were identified, the majority of whom were located in China (75% of the suppliers focused on the industrial sector) (Table 4). The suppliers identified in Germany, France and the United States supplied phlorizin predominantly for research applications.

The table 4 summarises phlorizin suppliers, focusing on industrial applications.
A dichotomy exists between *"generic ingredients"* and *"branded ingredients"* regarding prices and active ingredient concentration.

The "branded ingredients" are scientifically proven blends backed by in vitro tests and clinical studies which have confirmed the effectiveness of formulas which include phlorizin. Branded ingredients are less concentrated in phlorizin and more expensive.

SUPPLIER		Skyherb	Symrise	NutriHerb	Salus Nutra	JF Natural	Roelmi HPC	Natural Field	Aktin Chemicals	Bioriginal
COUNTRY		China	Germany	China	China	China	Italy	China	China	Canada
FORMULA		Apple Phlorizin Polyphenols	Apple Phlorizin Polyphenols	Phlorizin	Phlorizin	Phlorizin	Apple Phlorizin Polyphenols	Phlorizin	Phlorizin	Apple Phlorizin Polyphenols
CONCENTRATION OF ACTIVE INGREDIENT		>40,1%	>5%	>98%	>98%	>98%	5%< x <10%	>80%	98%	5%
SOURCE		Apple (whole fruit)	Apple	Roots and branches of apple tree	Bark of roots of apple tree	Branches of apple trees	Apple (whole fruit)	Bark of roots of apple tree	Bark of roots of apple tree	Skin of unripe apples
PRIX/KG USD	*10 kg*	150	495	138,5	117,2	160	375	110	121	NC
	100 kg	125	468	123,1	114	145	310	102	110	NC
	1000 kg	122	451	109,2	110	128	240	99	106	NC

Appl'In®, branded ingredient
- Inhibition of glucose absorption
- In vitro + clinical studies

SelectSIEVE® Apple, a branded ingredient
- weight management
- women's health
- sports nutrition
- In vitro + clinical studies

AppleZin®, branded ingredient
- Glycation inhibition
- Inflammatory response

Table 4: Phlorizin and/or phloretin suppliers and its characteristics (Data from Nutrikeo, 2022)

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The key takeaways regarding ingredient suppliers are the following:

- 40% of phlorizin ingredients available are obtained from the whole fruit. All branded ingredients are coming from the fruit.
- 20% of phlorizin ingredients available originate in pruning residues (branches and bark) and are exclusively provided by Chinese suppliers.
- 40% of phlorizin ingredients available are from root bark and are, once again, exclusively provided by Chinese suppliers.

It can be very challenging to be certain of the precise source of plants and from exactly where in the plant phlorizin is obtained. Full transparency of the extract production can therefore never be guaranteed. For example, when questioning a Chinese supplier, it is impossible to know how phlorizin extraction from the branches and the bark of plants is performed.

THE FOOD SUPPLEMENT APPROACH

After an analysis of ingredients' suppliers had been performed, market research was carried out to list the main phlorizin containing food supplements (Table 5). The results were relatively limited and concentration of the active ingredient was found to be low (see the table below). For all nutraceuticals currently available on the market, the source of active ingredient is the apple/fruit.

With the exception of Life Extension in the USA, the majority of players are small pharmaceutical laboratories.

The "daily treatment costs" (DTC) are much the same with the exception of the only food supplement based on a branded ingredient which is the "Api nature".

LABORATORY	COUNTRY	PRODUCT	FORMULA	CONCENTRATION OF ACTIVE INGREDIENT	SOURCE OF ACTIVE INGREDIENT	PRICE (EUR)	DTC (EUR)	DAILY DOSE OF PHLORIZIN (MG)	DTC / DOSE OF ACTIVE INGREDIENT
super smart	Luxemburg		Apple extract standardised with 80% polyphenols and 5% phlorizin	5%	Apple	25	0,83	30	0,028
Api-Nature	France		Ceylon cinnamon, Nutritional peptin, (peptides, hydrolysed seawater, dry extract of mulberry leaf, dry extract of Banaba, Select-Sieve (R) Apple, Chrome picolinate	0,34%	Apple	14,5	0,73	4,5	0,161
LIFE EXTENSION	USA		Apple extract (Malus domestic) (fruit and skin) (standardised with 50% polyphenols and 5% phlorizin, from green organic apples	5%	Apple	21,9	0,73	30	0,024

Table 5: Benchmark of phlorizin containing food supplements on the market and/or phloretin (Data from Nutrikeo, 2022)

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Regulatory framework

This section outlines the regulations for launching extracts obtained from apple pruning residues as food supplements.

IN EUROPE

If phlorizin is to be commercialised as a food supplement, it will most probably be considered “Novel food”.

According to Regulation (EU) 2015/2283, a food is a "Novel Food" if it fulfils two conditions:

- It was not used to any significant degree for human consumption within the European Union before 15 May 1997, and
- It falls under at least one of the following categories listed in the regulations:
  - >New/modified molecular structure
  - >Micro-organisms, fungi, algae
  - >Mineral origin
  - >Plants
  - >Animals
  - >Cell/tissue cultures
  - >Process not used before 1997 in the EU
  - >Manufactured nano-materials
  - >Nutrients/substances from a process not used before 1997 in the EU or containing nano-materials
  - >Exclusively used in food supplements in the EU before 1997

This means that any food belonging to one of the categories of the regulation that was used significantly in human food before 15 May 1997 cannot be said to fall within the scope of the Novel Food Regulation.

The EU Novel food catalogue is available at the following link: Novel food catalogue (europa.eu). The novel food catalog is a non-exhaustive list drawn up by the European Commission which gives guidance on whether a food is a novel food or not.

Once a novel food has been authorised, it will be added to the *“Union list of authorized novel foods”*.

An assessment of the status of the apple wood extract produced within the AgriWasteValue project under the Novel Food regulation was carried out by a regulatory expert. The extract assessed was taken from *Malus Domestica* and concentrated with 70% polyphenols. Their conclusions were as follows:

Malus domestica is not listed in the Novel Food Catalogue of the European Union. However, the fruit of Malus sylvestris (European wild apple) is considered a non-Novel Food. In addition, the bud, flower, leaf and root of Malus sylvestris are mentioned as a non-Novel Food in food supplements.

Based on current Novel Food regulations (Regulation (EU) 2015/2283) and the elements relating to Malus domestica (history of use, presence in legislative lists, etc.) and the ingredient (manufacturing process, composition, etc.), apple wood extract could most probably be classified as a Novel Food.

Several elements support this potential Novel Food status:

- *There is an absence of evidence of significant human consumption of apple wood in foodstuffs in the European Union before 1997.*
- *The trunk and branch bark is not listed in the European Union Catalogue or in any legally accepted list.*
- *The extract is enriched with polyphenols, meaning that its composition is significantly different from the raw material.*

Please note the new Regulation 2015/2283 on Novel Food no longer allows similarity to an equivalent ingredient (here: root bark, since this part is considered as non-Novel Food in Belgium and listed in legal lists of several member states) to be recognized.

Therefore, if a particular company wishes to use this ingredient in for human consumption within the EU, a Novel Food application file will have to be submitted and approved by the European Commission. Prior to this, and according to Article 4 of the Regulation (EU) 2015/2283, a consultation request of the Novel Food status of this apple wood extract could be initiated. However, the lack of proof of consumption of the ingredient in the European Union before 1997 seems to be a blocking element in this evaluation.

It is highly likely that the submission of a novel food application to the European Union would be needed. This process is cost-intensive (approx. 400 000 euros in particular for toxicological studies) and relatively long (at least 17 months). It is possible to follow novel food applications submitted with the following link: Summary of applications and notifications (europa.eu).

IN THE UNITED STATES

It appears challenging to commercialise phlorizin (or raw polyphenol extract) from apple pruning residues in Europe at the present time, and therefore the feasibility of selling this ingredient in the United States was considered.

According to the “Food and Drug Administration” (FDA), a dietary supplement is an orally administered product that contains “food ingredients” intended to supplement the diet.

There is no available list of food ingredients that are permitted in American food supplements. However, there are several lists of prohibited / toxic ingredients and plants.

Phlorizin does not appear on any list of prohibited or negative substances.

Phlorizin is also listed as a “substance added to food” under the name TRILOBATIN and can be used as a flavouring substance or adjuvant.

In the case of AgriwasteValue, the origin of the phlorizin is from pruning residues. As a flavouring substance, the origin is not specified, only the substance is important.

However, in the USA, an ingredient is considered as NDI (new dietary ingredient) if it was not used in food supplements before 15 October 1994. It must also be verified that it has not been chemically modified. There is no authoritative list of food ingredients that were marketed in food supplements before 15 October 1994. Therefore, manufacturers and distributors (you) are responsible for determining whether an ingredient is a "novel dietary ingredient" and, if not, for documenting either that a dietary supplement containing the dietary ingredient was marketed prior to 15 October 1994 or that the dietary ingredient was marketed for use in dietary supplements prior to that date. “Chemically modified" includes changes in the manufacturing process, the part of the plant used, etc.

To date, one NDI has been submitted on an apple extract (in 2010): a powder which is a mixture of polyphenolics extracted directly from immature apples (i.e., family Rosaceae , genus Malus) of the species Malus pumila Mill, Malus pumila var. domestica (Borkh.) C.K. Schneid, or Malus asiatica Nakai (Missouri Botanical Garden 2010) (Applephenon).

Due to their status as flavouring substances, the NDI risk could be ruled out, but using plant parts that are not generally food grade could turn your ingredients into NDI.

If in doubt, it is advisable to submit a Marketing Notification (75 days procedure).

In conclusion, for the United States:

- As phlorizin is not prohibited, it can theoretically be used in dietary supplements.
- However, the fact that they come from apple tree prunings implies a NDI risk. It is advised to submit a marketing notification.

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Outlook: the potential for phlorizin in nutraceuticals

The key takeaways of the following case study looking at the potential of phlorizin in nutraceuticals were the following:

- **SCIENTIFIC LEGITIMACY:** Phlorizin appears to be physiologically interesting for nutraceutical applications and this has been supported by scientific studies.
- **SUSTAINABLE ORIGIN:** The pruning residues of apple trees contain 1000 times more phlorizin than the fruit. However, this only accounts for 20% of the product from nutraceutical suppliers to date. Furthermore, it is not always easy to have full traceability of the sourcing.
- **DICHOTOMY OF INGREDIENTS ON THE MARKET:** There are two types available:
  - > Branded ingredients with high added value.
  - > Generic ingredients with the supply dominated by China.
- **LOW VISIBILITY:** The availability of food supplements based on phlorizin remains poor and it is still easier to find products based on "polyphenols of apples" rather than titrated in phlorizin.

Phlorizin is a legitimate and sustainable ingredient but inadequately represented on the market and bounded by strict regulations in Europe (Novel Food).

The conclusion that was arrived at is there are great opportunities for phlorizin despite a market that is insufficiently aware of it:

- **PLANT SOURCING and SUSTAINABILITY:** A review of the literature confirms the AgriWasteValue project results and relevance, the bark of the apple tree contains a high concentration of phlorizin. Moreover, the use of bark for phlorizin production is a fitting way **to increase the value of residues**. A local origin (from Europe vs from China) can also facilitate **full traceability** from field to product.
- **HEALTH BENEFITS WITH HIGH DEMAND:** Among other health application properties, phlorizin is a glycaemia regulator / anti-diabetic, with two health claims pending approbation and additionally has anti-oxidant, anti-inflammatory and slimming properties. In a real context, the number of people with diabetes is increasing which means that the demand for these molecules will be higher.
- **MARKET:** At the present time it is recommended to submit a market notification in the United States to validate if the ingredient coming from the pruning residues would be NDI. If they considered that phlorizin coming from pruning residues is not considered as NDI, it appears easier to commercialise it in the United States than in Europe. It would be important to focus on a region in the United States where consumers are concerned about sustainability like the West Coast, where people tend to be more interested in sustainability and health.

A few limitations were also identified that need to be considered with some interesting perspectives.

Many people are ill-informed about phlorizin as available products are based on “polyphenols of apple”. The term “polyphenols of apple” is, however, more familiar to consumers.

It is potentially interesting to focus on a raw apple extract as produced in the AgriWasteValue project compared to isolated molecules.

“Branded ingredients” based on raw apple extract could have an equally high potential.

There needs to be a sharp focus on “sustainability” and “traceability” in any communication about phlorizin if it is to be a serious competitor to other ingredients.

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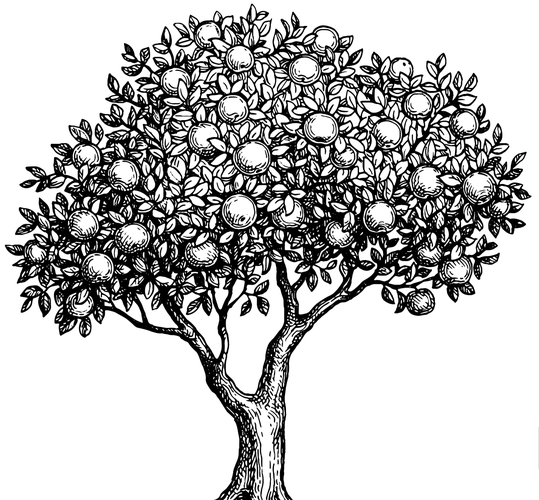

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AgriWasteValue project

The majority of natural actives used in cosmetic or nutraceutical formulations are currently imported to Europe, although a huge diversity of resources is present in North-West Europe. This means that a large amount of residues in covered areas, known for their arboriculture and viticulture sectors, are not being fully exploited for the sourcing of natural actives and are therefore going to waste.

The AgriWasteValue project aims to take agricultural residues from the European North-West regions and to transform them into bioactive compounds. These will be used, initially in key industrial sectors such as cosmetic and nutraceutical fields and then, in a second phase, in the energy, chemical and agricultural fields.

The agricultural residues and biomass that will be used for this project come principally from pruning vines and apple and pear trees.

The project is possible thanks to the financial support of the European Regional Development Fund (ERDF) and Wallonia.

Budget of the project :

- Global budget : 3.193.157,19€

- Fund ERDF : 1.744.580,84€

The AgriWasteValue project is a transnational cooperation that will open up new ways of recycling residues from the agricultural, viticulture and arboriculture sectors.

Contact

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