AgriWasteValue

To transform agricultural by-products
and residues into bioactive compounds

APPLICATION OF ARBUTIN IN THE COSMETIC SECTOR

With the financial support
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APPLICATION OF ARBUTIN IN THE COSMETIC SECTOR

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Analysis of the skin lightning agents market

GLOBAL MARKET FOR SKIN LIGHTENING AGENTS

The term "skin lightening agents" refers to a set of cosmetic products used for whitening the skin.

According to a report from ReportLinker, the global market for skin lighteners will reach 11.8 billion USD by 2026, growing at a CAGR (compound annual growth rate) of 6.6% over the period 2020-2026 (Figure 1).

In the USA, the market for skin lighteners is estimated at 327.6 million USD for the year 2021, while the forecast for China is that sales will reach 5.5 billion USD by 2026 with a CAGR of 8.4% for the period 2020-2026.

Within Europe, it is thought that the German market will increase by approximately 3.6% CAGR while the rest of the European market will reach 127.4 million USD by the end of the period in question.

Skin whitening products are available in numerous forms including creams, cleansers, masks, soaps, lotions and pills. Sales of skin lightener products such as creams, bleaches and deodorants, among others, have been growing at a brisk pace, in part driven by increasing the accessibility and affordability of these products.

THE DEMAND FOR PLANT EXTRACT INGREDIENTS FOR SKINCARE PRODUCTS

Nowadays, synthetic products represent the largest market share of skin lightening products. Indeed, in 2018, 88.1% of products in the overall market were synthetic (Figure 2).

In the dermatology and cosmetic sector, chemical ingredients are used for treating skin conditions such as problems with pigmentation.

The segment representing natural ingredients is projected to grow at a CAGR of 8.1% from 2019 to 2025. A growing consumer shift towards natural products, owing to their health benefits, is contributing to the segmental growth. These products are produced using plant extracts as well as ingredients from fruit for skin treatment. Natural products that have no side effects on the skin are a key factor driving increasing numbers of consumers to opt for skin-lightening products that are made of natural and organic ingredients, resulting in the high growth rate of the sector.

GLOBAL SKIN LIGHTENERS MARKET

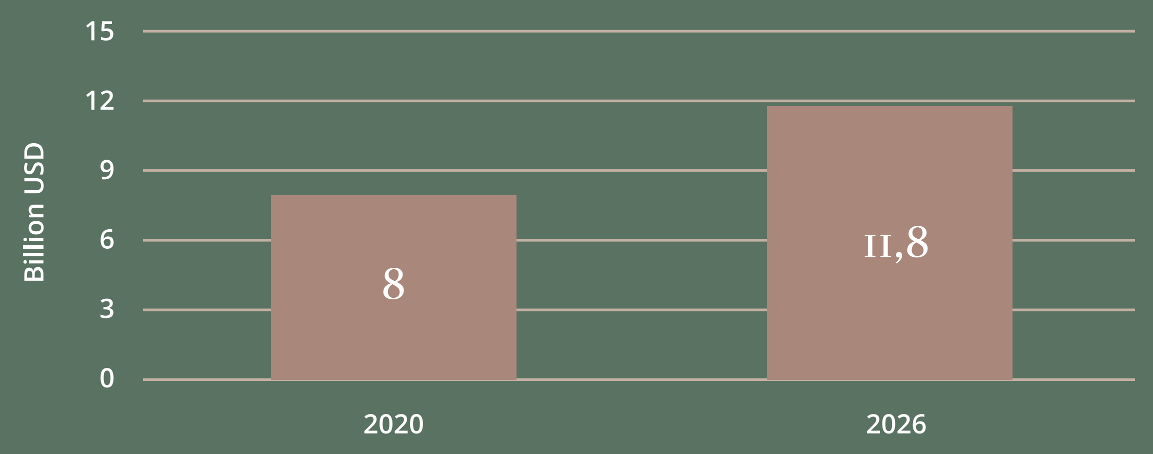

Figure 1: Global skin lighteners Market (Report Linker, 2022)

GLOBAL SKIN LIGHTENING PRODUCTS MARKET SHARE, BY NATURE, 2018 (%)

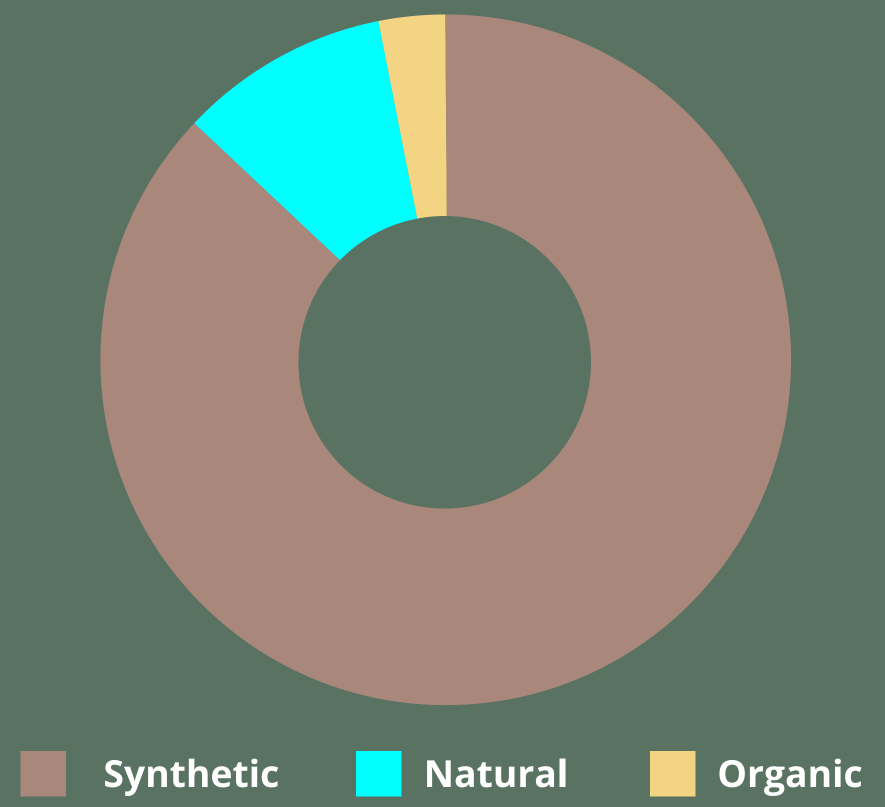

Figure 2: Global skin lightening products market share, by nature, 2018 (Million Insights, 2020)

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Ingredients from botanical extracts for skin-lightening products and their sources

Based on the publication of Zhu et al. 2008[1], in the search of new depigmenting agents, the investigation of natural plant extracts has led to the identification of many potentially active compounds (Table 1). It is only now that people are beginning to realise the potential of natural extracts for skin-lightening applications.

Active compounds isolated from plants, such as arbutin, aloesin, gentisic acid, flavonoids, hesperidin, liquorice, niacinamide, yeast derivatives, and polyphenols, inhibit melanogenesis without melanocytotoxicity by different mechanisms as shown in Table 1.

In the following sub-section, arbutin and alpha-arbutin as botanical extracts with depigmenting activity will be focused on.

[1]Zhu W. and Gao J., 2008. The use of botanical extracts as topical skin-lightening agents for the improvement of skin pigmentation disorders.

COMPONENT	PLANT SOURCE	DEPIGMENTING MECHANISM
Arbutins		
Arbutin	Pear, cranberry, blueberry, bearberry shrub	Inhibit tyrosinase Inhibit DHICA polymerase
α-Arbutin	Pear, cranberry, blueberry, bearberry shrub	Inhibit tyrosinase Inhibit DHICA polymerase
Deoxyarbutin	Pear, cranberry, blueberry, bearberry shrub	Inhibit tyrosinase Inhibit 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerase
Aloesin	Aloe	Inhibit tyrosinase, competitively inhibit 3,4-dihydroxyphenylalanine (DOPA) oxidase
Flavonoids		
Flavones	Most plants	Inhibit tyrosinase - uncompetitively
Flavonols	Most plants	Copper chelation
Hesperidin	Citrus fruits	Inhibit tyrosinase - antioxidant of collagen
p-Coumaric acid	Panax ginseng	Inhibit L-tyrosine oxidation
Niacinamide	Root vegetables, yeast	Inhibit Melanin transfer, antioxidant of collagen
Licorice extracts		
Glabridin	Liquorice	Inhibit tyrosinase ROS scavenger
Liquiritin	Liquorice	Melanin dispersibility - epidermal removal
Mulberry	Morus alba	Inhibit tyrosinase ROS scavenger
Polyphenols		
Procyanidins	Grape seeds, cranberry	Inhibit tyrosinase ROS scavenger
Ellagic acid	Strawberry, geranium	Copper chelation Inhibit melanocyte proliferation
Traditional Chinese medicine		
18α-GL	Liquorice	Inhibit tyrosinase
Sophorcarpidine	Kuhseng	Inhibit tyrosinase

Table 1: Overview of botanical extracts with depigmenting activity (Zhu et al. 2008)

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Arbutin and its main derivative

This section will describe arbutin and its main derivative: alpha-arbutin.

MOLECULAR STRUCTURE

Before moving onto the arbutin molecule, it is important to take a step back and speak about hydroquinone. Hydroquinone is an aromatic organic compound that is a type of phenol and a derivative of benzene. Hydroquinone has been prescribed as the primary therapy for a number of hyperpigmentation disorders including melasma. However, since 2001, the use of hydroquinone as an ingredient in cosmetics has been banned because of the high risk of carcinogenesis that has been found to result from prolonged exposure. As a result, researchers have spent the last few years trying to find an alternative for hydroquinone for skin lightening products. It is also for this reason that arbutin is increasingly being studied.

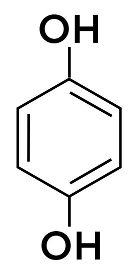
Arbutin is a compound with a structure in which one molecule of D-glucose is bound to hydroquinone. Arbutin is identified as a hydroquinone derivative. It is a 4-hydroxyphenol-β-glucopyranoside also known as β-arbutin.

The D-glucose bound to hydroquinone exists in different anomeric forms in aqueous solutions, with β-arbutin being the dominant form.

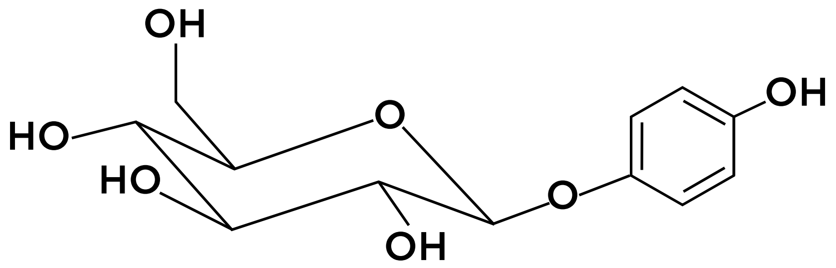
A derivative of arbutin where the anomeric form of D-glucose is found is α-arbutin which is also a hydroquinone.

Both arbutin and α-arbutin have been studied for several years to determine whether either could be considered a suitable alternative to hydroquinone for skin lightening purposes.

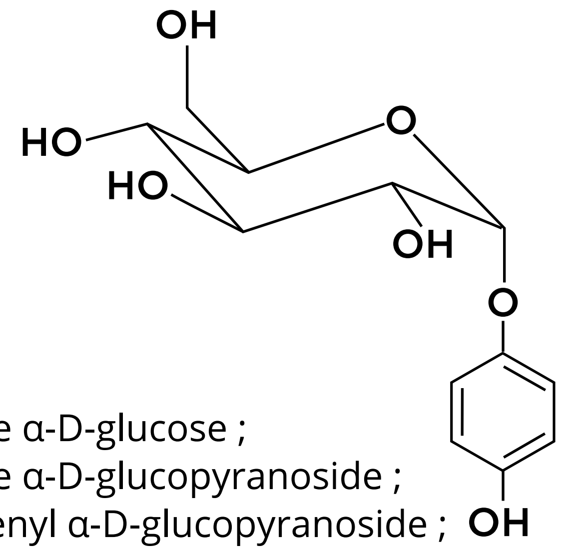
The chemical structures of these molecules are presented in Figure 1.



1
Hydroquinone ;
1,4-Dihydroxybenzene ;



2
β-Arbutin ;
Hydroquinone β-D-glucose ;
Hydroquinone β-D-glucopyranoside ;
4-Hydroxyphenyl β-D-glucopyranoside ;



3
α-Arbutin ;
Hydroquinone α-D-glucose ;
Hydroquinone α-D-glucopyranoside ;
4-Hydroxyphenyl α-D-glucopyranoside ;

Figure 3: Chemical structures of hydroquinone, arbutin (beta-arbutin) and alpha-arbutin (Boo, 2021)

SOURCING ARBUTIN

Natural sourcing

As shown in Table 1, arbutin is present in a number of different plant sources. It is the main active molecule present in the leaves of the *Arctostaphyllos uva ursi* (Ericaceae), commonly named bearberry (Migas et al. 2015). In fact, arbutin-containing extracts from the leaves of *Arctostaphylos uva ursi* have been used in phytotherapy for centuries, and nowadays it is recognized as a medicinal herbal plant. Arbutin is also found in other plants such as pears, cranberries and blueberries and can be extracted from these vegetal sources.

As pear is one of the fruits studied in the AgriWasteValue project, we will focus more on this source of arbutin.

Sasaki et al., 2014, published a paper where they compared arbutin content in branches, leaves, stems and fruits of Japanese pear *Pyrus pyrifolia*. The focus of this study was also to find uses for by-products such as pruning residues from pear trees that are currently not used and go to waste on fruit farms.

The proportion of arbutin extracted from different parts of the plant (per g dry of matter) in descending order were as follows:

> branches (12.8 mg)
> leaves (12.1 mg)
> peel (5.70 mg)
> flesh (0.26 mg)
> stems (0.13 mg)

These results indicated that the highest levels of arbutin were obtained from the branches, leaves, and fruit peel. The results from the study also confirmed the discarded branches of pear trees as a potentially valuable source of arbutin.

A Chinese university has created an innovative method for extracting arbutin from pear leaves and has introduced an application to register it for a patent. According to the inventors, the raw material used in the method is a waste material generated from the harvesting of fruit trees. There are a number of different sources of the raw material, it is easy to collect, and the cost is low; the extraction method is simple in terms of the technology required, simple to operate, and obtains arbutin with a high level of purity. More information: CN103408610A - Method for extracting arbutin from pear leaves - Google Patents.

A review of the literature shows that a lot of the publications on the subject originate in Asia.

Synthetical production

Arbutin can be prepared by the bioconversion or chemical synthesis of hydroquinone.

Arbutin is relatively easy to synthesise chemically from hydroquinone or to enzymatically obtain its glucoside using enzymes such as amylosaccarases.

Biotechnology can also be used to produce arbutin by fermenting soybeans with bacteria trained for the purpose (e.g. Bacillus subtilis).

Figure 4: Bearberry leaves

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ARBUTIN AND ALPHA-ARBUTIN ACTIVITY

Principal activity

The principal use of arbutin and α-arbutin is in the cosmetics sector, as presented in Table 1, where it is used to “lighten” skin tone. In fact, both inhibit the biosynthesis of melanin responsible for skin pigmentation. The principal use of arbutin and α-arbutin is therefore depigmentation.

There are also a number of published studies that have demonstrated that arbutin and α-arbutin also have antioxidant properties (Boo, 2021).

Comparison of efficacy of arbutin and α-arbutin

Several scientific studies have compared the efficacy of arbutin and α-arbutin. Results have not been consistent and some studies found no difference between them while others found a real difference. For example, some studies have found that α-arbutin is 10 times more effective than arbutin.

However, and as suggested by Boo, 2021, there is still no real consensus as to whether arbutin or α-arbutin is better in terms of efficacy for:

- Tyrosine inhibition,
- Cell melanin synthesis

That said, there are results from animal tests and clinical trials that have proven arbutin and α-arbutin can alleviate skin pigmentation (Boo, 2021).

SAFETY AND REGULATORY ASPECTS

Arbutin and α-arbutin have not yet been regulated under Cosmetic Regulation No 1223/2009.

The reported functions for both arbutin and α-arbutin in cosmetic products are antioxidant, skin bleaching and skin conditioning.

There is a disagreement over how arbutin works and whether or not it is broken down into hydroquinone and glucose.

A look at the existing literature led to the following conclusions:

- There remains a possibility that a small amount of hydroquinone (which may be produced as a product of arbutin decomposition) contributes to the inhibition of melanin synthesis or the inactivation of tyrosinase in cells.
- However, the majority of evidence supports the theory that arbutin has intrinsic properties that inhibit cellular melanogenesis and reduces cellular tyrosinase activity regardless of the release of hydroquinone.

In 2015, the Scientific Committee on Consumer Safety (SCCS) of the European Union published the following statement:

- For **arbutin**: the SCCS considers the use of arbutin to be safe for consumers in cosmetic products in a concentration up to 7% in face creams provided that the contamination of hydroquinone in the cosmetic formulations remain below 1 ppm.
- For **α-arbutin**: the SCCS considers the use of α-arbutin to be safe for consumers in cosmetic products in a concentration up to 2% in face creams and up to 0.5% in body lotions.

However, the Scientific Committee on Consumer Safety (SCCS) of the European Union delivered a new and preliminary statement, on 25 March 2022, regarding the safety of the use of arbutin and α-arbutin. The preliminary version from 15-16 March 2022 is available here: Safety of alpha-arbutin and beta-arbutin in cosmetic products (europa.eu).

The table below presents the preliminary findings published in a safety statement in 2022.

In conclusion, and due to the new preliminary statement released by the SCCS, there remains a lack of data to attest to the safety of the previous concentration of arbutin and α-arbutin in cosmetic products. The final opinion will be given once all comments received during the commenting period as well as any additional information received have been assessed.

	QUESTIONS	SCCS OPINION
1	In light of the data provided, does the SCCS consider α-arbutin safe when used in face creams up to a maximum concentration of 2% and in body lotions up to a maximum concentration of 0.5 %?	Having considered the data provided, and other relevant information available in scientific literature, **the SCCS cannot conclude on the safety of α-arbutin when used in face creams up to a maximum concentration of 2% and in body lotions up to a maximum concentration of 0.5%. Relevant data on the degradation/metabolism of α-arbutin, exposed to the skin microbiome/enzymes, are not available and the release of hydroquinone and its final fate are not documented.** These data are essentially required for safety assessment.
2	In the event that the estimated exposure to α-arbutin from cosmetic products is found to be of concern, SCCS is asked to recommend safe concentration limits.	For the reasons given under question 1, the SCCS cannot recommend a safe concentration of α-arbutin.
3	In light of the data provided, does the SCCS consider β-arbutin safe when used in face creams up to a maximum concentration of 7% ?	No information was provided during the call for data. The SCCS has, therefore, considered the information available in scientific literature but regarded **it insufficient to conclude on the safety of beta-arbutin when used in face cream up to a maximum concentration of 7%. Also, relevant data on the fate of beta-arbutin, when applied to human skin and its microbiome/enzymes, are not available and the release of hydroquinone and its final fate have not been documented.**
4	In the event that the estimated exposure to β-arbutin from cosmetic products is found to be of concern, SCCS is asked to recommend safe concentration limits.	For the reasons given under question 3, the SCCS cannot recommend a safe concentration of beta-arbutin.
5	In light of the data provided, does the SCCS consider that the presence of hydroquinone in the cosmetic formulations must remain below 1 ppm for both α- and β- arbutin containing products?	Hydroquinone should remain as low as possible in formulations containing α- or β- arbutin and should not be higher than the unavoidable traces in both arbutins. In the new studies, submitted by the applicant, 3ppm was the LOQ/LOD of the methodology used.
6	Does the SCCS have any further scientific concerns regarding the use of a- and β- arbutin in cosmetic products in relation to aggregate exposure from such substances in cosmetics?	Safe concentrations for either of the arbutins in cosmetic products cannot be established without the data on the release of hydroquinone and their final fate.

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BENCHMARK

Now that why arbutin could be of interest has been described, together with its potential as a depigmenting product, it is time to have a look at what is already on the market in terms of cosmetic products.

This section presents some companies that currently supply products containing arbutin and α-arbutin along with retailers offering these ingredients in their cosmetic products.

The ingredient approach

Some suppliers of arbutin and α-arbutin were contacted for a clearer understanding of what is already available on the market and to determine the main origin of these ingredients.

The table summarises the main suppliers that are all located in China.

All the suppliers offering arbutin or α-arbutin are from China. They are, in the majority of cases, offering α-arbutin rather than arbutin. The ingredients offered by the suppliers are have a synthetical origin.

Prices differ greatly, regarding, among other things, price term.

COMPANY	MOLECULE	COUNTRY OF SOURCING	ORIGIN OF THE MOLECULE	PRICE (EUROS/KG) FOR 1 KG ORDER	PRICE CONDITION
Gfn Selco (ingredient distributed by Kreglinger in Belgium)	Alpha-Arbutin	China	The origin of the alpha-arbutin is synthetic. It is from sugar cane enzymatical conversion.	700	CIP Brussels
	Arbutin	China	The origin of the arbutin is synthetic.	150	CIP Brussels
Top science	Alpha-Arbutin	China	The alpha-arbutin is chemically synthesised. The starting materials are sucrose and hydroquinone. The sucrose is vegetal in origin and the hydroquinone is chemical in origin.	304	CIP Brussels by air/ddu by courier
Lenutra	Alpha-Arbutin	China	The alpha-arbutin is made from glucose, quinol and culture solution. The glucose comes from sugarcane.	145,35	FOB China
Lzchems	Alpha-Arbutin	China	Alpha-Arbutin is fermented from glucose and hydroquinone. Bulk production is not from a vegetal source.	83,13	FOB Shangaï

THE COSMETIC PRODUCT APPROACH

The following table describes some products already on the market that contain arbutin or α-arbutin.

The three products presented below are all made with α-arbutin rather than arbutin. This confirms that ingredient suppliers are correct in their decision to offer α-arbutin more frequently than arbutin.

Unfortunately, there is no transparency regarding the source of α-arbutin. It can either be natural or synthetic. By cross-referencing the information received from the ingredient suppliers, there is high probability that the origin of the α-arbutin in these products is synthetic.

LABORATORY	COUNTRY	PRODUCT	FORMULATION	CONCENTRATION OF ACTIVE INGREDIENT	ACTIVE INGREDIENT SOURCE	VOLUME (ML)	PRICE (EURO)
Typology	France		Anti-hyperpigmentation Serum alpha-arbutin 2% + Lemon extract	2% alpha-arbutin	Unknown	30	29.7
Dermaceutic	France		Depigmenting cream and anti-brown spots cream. Composition: Kojic acid, alpha-arbutin, Licorice, White mulberry, Glycolic acid, Salicylic acid	Unknown concentration of alpha-arbutin	Unknown	15	37
The Ordinary	Canada		Anti-hyperpigmentation concentrated serum with purified alpha-arbutin combined with hyaluronic acid.	2% alpha-arbutin	Unknown	30	8.9

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Potential for arbutin and alpha-arbutin from pruning residues

This section will describe the potential of arbutin and alpha-arbutin coming from pruning residues.

CONCENTRATION OF ARBUTIN IN PEAR PRUNING RESIDUES

As described in the above section, Sasaki et al. 2014 demonstrated that it would be interesting if it were possible to extract arbutin from pruning residues as it is one of the parts of the fruit tree where arbutin is found in the most highly concentrated levels.

The AgriWasteValue project extracted molecules from pear pruning residues and discovered that there is a relatively interesting concentration of arbutin, in both alpha and beta forms.

The first analysis results (Celabor) revealed that the quantity of arbutin found is between those ranges:

- 3-6 mg of alpha-arbutin/100 mg of dry matter extract
- 3-6 mg of beta-arbutin/100 mg of dry matter extract

Those results are actually interesting as it seems the pear extract contains alpha-arbutin as much as beta-arbutin.

More investigation needs to be done to confirm those values. It could be worthwhile to look at a wider range of pear varieties and to carry out a differentiation test in the analysis between alpha-arbutin and beta-arbutin.

DIFFERENTIATION ON THE MARKET

Both the existing literature and Agriwastevalue project have demonstrated that extracting arbutin from pruning residues appears promising.

However, cosmetic products containing arbutin from natural sources would need to differentiate themselves on the market:

- Highlight the natural sourcing of the arbutin. Indeed, arbutin is mainly chemically synthetised as it is quite simple to do it and seems to be much cheaper.
- Highlight the sourcing coming from a by-product not used for the moment. It answers to one of the actual challenge of making a society based on circular economy.
- Highlight the “local” aspect
- Highlight natural sourcing traceability

Outlook

The global market of skin lightening product is increasing sharply. Arbutin is considered as one of the most interesting molecules that could be used as a skin lightening agent. However, for the moment, arbutin is mainly sourced from synthetic products which is not aligned with the increasing demand and trend for natural ingredients in cosmetics.

Looking at the literature and the AgriWasteValue project, pear pruning residues appear to be a relatively interesting source for extracting arbutin. However, to compete with chemically synthetic arbutin it would be necessary to highlight the benefits of arbutin originating in pruning residues:

- Using a by-product
- Being more local
- Being natural
- Making 100% traceability

From a safety point of view and efficacy between the alpha- and beta-arbutin, further research is needed. Indeed, the SCCS has not finalized their opinion regarding safety aspects since additional data will be submitted for further assessment.

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Interreg North-West Europe AgriWasteValue

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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

Do not hesitate to contact **Flora Mer (f.mer@valbiom.be)** if you are interested to know more about the case study or AgriWasteValue project.

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