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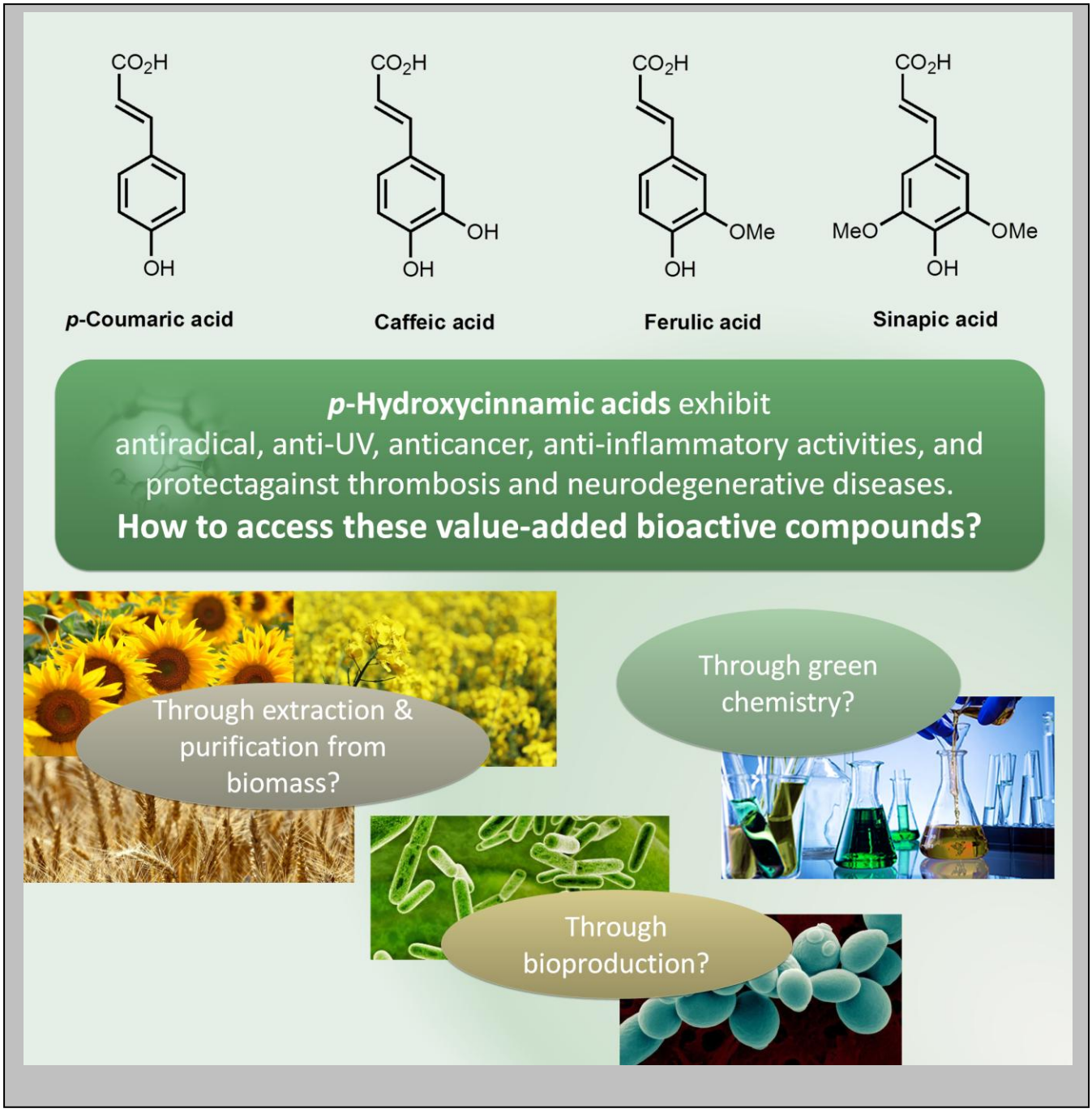
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Accessing *p*-Hydroxycinnamic acids: chemical synthesis, biomass recovery or engineered microbial production?

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Abstract: *p*-Hydroxycinnamic acids (*i.e.*, *p*-coumaric, ferulic, sinapic, and caffeic acids) are phenolic compounds involved *inter alia* in the biosynthesis pathway of lignin. These naturally occurring molecules not only exhibit numerous attractive properties, such as antioxidant, anti-UV, and anticancer activities, but they also have been used as building blocks for the synthesis of tailored monomers and functional additives for the food/feed, cosmetic and plastics sectors. Despite their numerous high value-added applications, the sourcing of *p*-hydroxycinnamic acids is not ensured at the industrial scale except for ferulic acid, and their production cost remains too high for commodity applications. These compounds can be either chemically synthesized, extracted from lignocellulosic biomass, and recently their production through bioconversion emerged. Herein we will discuss the different strategies described in the literature to produce these valuable molecules.

Keywords: *p*-hydroxycinnamic acid • ferulic acid • coumaric acid • caffeic acid • sinapic acid

1. Introduction

p-Hydroxycinnamic acids (*i.e. p*-coumaric acid (*p*-CA), caffeic acid (CA), ferulic acid (FA) and sinapic acid (SA)) have been known for centuries for their multiple biological properties (Figure 1). *p*-Hydroxycinnamic acids and corresponding specialized metabolites derivatives (mainly under ester forms) are produced by plants to provide them with resistance by connecting hemicelluloses and lignin in the plant cell wall (*e.g. p*-coumaric and ferulic acids),[1] or to protect them against oxidative stress, solar radiation[1,2] (*e.g.* sinapoyl malate) or insects[3] (*e.g.* chlorogenic acid) (Figure 3).

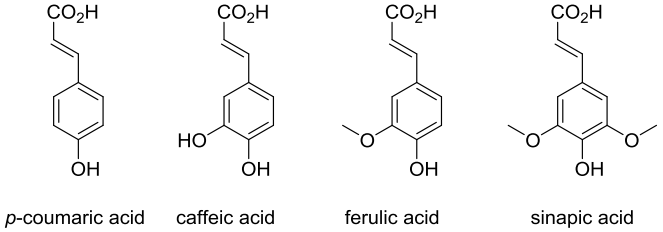


Figure 1. Structures of the main naturally occurring *p*-hydroxycinnamic acids.

Studies have demonstrated that *p*-hydroxycinnamic acids also exhibit therapeutical properties such as anticancer,[4–6] antidiabetic,[4] anti-inflammatory activities,[4,5],[7] and prevent thrombosis and neurodegenerative diseases.[8,9] They can also serve as precursors for high value-added molecules such as vanillin,[10] monomers,[11–14] polymer additives,[15] anti-UV[16] and antioxidants,[17–19] making them very attractive in medicinal,[20] cosmetic[21] or food/feed markets which are constantly increasing (Table 1). *p*-Hydroxycinnamic acids have different assets: (1) they are renewable molecules that can be extracted from agricultural byproducts, (2) they can be obtained through local sourcing, entering in circular economy processes, and (3) they can allow obtaining *natural* labels. For example, vanillin is the most produced aroma in the world. Unfortunately, the extraction of vanillin from natural vanilla is not sufficient in terms of volume and covers only 1% of the world demand. Fortunately, vanillin can be

produced by a natural biotechnological process (fermentation) from ferulic acid which is currently extracted from rice bran oil for food application such as dairy products, confectionery, pastries.[22] The conversion of ferulic acid into vanillin allows to preserve the naturality, responding to growing demand with affordable price.[23] Increased demand for vanillin thus drives the demand for ferulic acid with an expected CGAR (Compound Annual Growth Rate) of 6.1% for the next five years and to reach 75 million USD in 2024 (53 million USD in 2019). In another hand, this demand limits availability of ferulic acid for other markets.[24]

The cosmetic industry is also interested in *p*-hydroxycinnamic acids. It is noteworthy to mention that coumaric, ferulic and caffeic acids derivatives are listed in the **Inventory of Existing Cosmetic Ingredients in China which gives access to this rapidly expanding market.[25] Indeed, cosmetic applications of** *p*-hydroxycinnamic acids already exist for some years for skin whitening agent,[26] as anti-age care[26] or as active compound for the treatment of skin disorders.[26]

Table 1. Price and market for *p*-HCA or precursors

Compounds	Range of price ($/kg)*[27]	Market (M$)	Estimated volume (t/year)
***p*-Coumaric acid**[28,29]	115 – 330	39.2 (2016)	118 – 340
Caffeic acid	450 – 900	N.A.	N.A.
Chlorogenic acid[30]	3 000 – 7 900	130 (2017)	16 – 43
Ferulic acid[31–33]	180 – 380	53 (2019)	139 – 294
Sinapic acid	370 – 1 200	N.A.	N.A.

* For purity > 95%, N.A. not available

This wide interest in *p*-HCAs is reflected by a growing number of publications on the subject (Figure 2). Over the past 10 years, this scientific output has doubled. Although, a very recent technoeconomic analysis reported a potential $5.05/kg for purified *p*-HCAs (*p*-CA and FA) from maize biorefinery,[34] they still exhibit high prices (Table 1) and their availability remains limited.

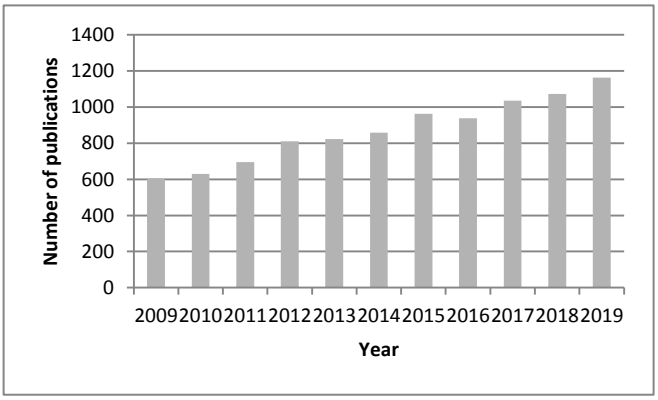


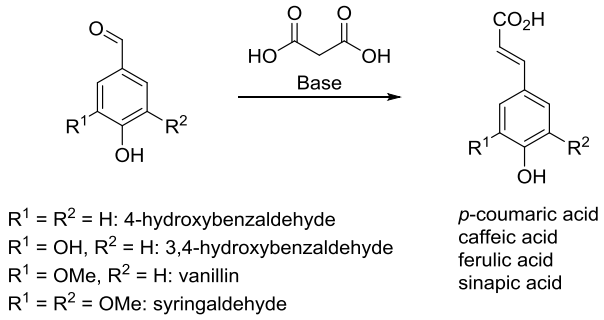
Figure 2. Number of publications dealing with *p*-HCAs in the past 10 years (from Science Direct 07/06/2020).

Herein, we will report and discuss (1) the recent advances in chemical synthesis of *p*-HCAs, (2) the various methodologies developed to recover *p*-HCAs from agricultural feedstock (at lab-scale), and (3) the emerging bioproduction of *p*-HCAs by engineered microorganisms.

2. Chemical synthesis

2.1. State of the art

The common chemical pathway to synthesize *p*-hydroxycinnamic acids (*p*-HCAs) is a base-catalyzed Knoevenagel-Doebner condensation between malonic acid and the corresponding aldehyde (Scheme 1). The usual procedure involves pyridine as solvent and catalyst. However, another amine (e.g. aniline, piperidine) is often added to enhance the reactivity.[35] Nevertheless, greener strategies emerged to perform this reaction (Table 2).



Scheme 1. Condensation of Knoevenagel-Doebner to produce *p*-HCAs.

Mouterde and Allais used microwave-assisted activation to accelerate the formation of *p*-HCAs, while avoiding the formation of vinylphenols through decarboxylation, leading to *p*-HCAs in excellent yields (>85%) (Table 2, entry 1).[36] Zhu et al. performed the Knoevenagel-Doebner condensation in ethanol at room temperature using β-alanine and DBU (0.5 and 0.01 equiv. respectively) as catalysts to produce *p*-coumaric acid in 85% yield (Table 2, entry 2).[37] More recently, Peyrot et al. succeeded in eliminating the need of toxic amine catalyst by designing a proline-catalyzed Knoevenagel-Doebner condensation in ethanol to afford various *p*-HCAs in yields varying from 50 to 85% (Table 2, entry 3).[38] It is noteworthy to mention that this reaction was optimized to produce sinapic acid (85%) and that one may need to optimize it for the other *p*-HCAs to achieve better yields. Besides the aforementioned base-catalyzed methodologies, high-yielding acid-catalyzed approaches were investigated by Joshi Amol et al. and by Fiorito et al. The first ones used a mixture of sodium acetate and acetic acid (Table 2, entry 4),[39] whereas Fiorito et al. performed Knoevenagel-Doebner reaction in fruit juices, buttermilk or olive mill waste water under ultrasound irradiation using the intrinsic acidity of these products (Table 2, entry 5).[40] Heterogeneous catalysis was also explored by Elamathi et al., who synthesized *p*-HCAs in the presence of mesoporous carbon nitride (HMCN), a solid catalyst, in excellent yield in toluene (Table 2, entry 6).[41] Recently, Van Schijndel et al. proposed a solvent- and amine-free pathway involving

ammonium bicarbonate resulting in excellent yield (>90%) for coumaric, ferulic and sinapic acids (Table 2, entry 7).[42,43]

Table 2. Comparison of various methodologies to access *p*-coumaric acid through Knoevenagel-Doebner condensation.

Entry	Reference	Malonic acid (equiv.)	Catalyst (equiv)	Activation mode	Duration	Solvent & concentration	Yield
1	Mouterde and Allais 2018[36]	3	Piperidine (0.5)	MW 50 W till 90 °C	30 min	DMF 1.6 mol.L^{-1}	92% (*p*-CA)
2	Zhu et al. 2012[37]	1.1	β-alanine (0.5) & DBU (0.01)	none	8 h	EtOH 1.6 mol.L^{-1}	85% (*p*-CA)
3	Peyrot et al. 2019[38]	2	L-proline (0.5)	90 °C	16 h	EtOH 0.5 mol.L^{-1}	85% (SA)
4	Joshi Amol et al. 2017[39]	1	AcOH/AcONa	reflux	90 min	none	93% (FA)
5	Fiorito et al. 2016[40]	Meldrum's acid 1.01	none	US	15 min	olive mill waste water 0.5 mol.L^{-1}	98% (FA)
6	Elamathi et al. 2019[41]	2	HMCN (50 mg.mmol^{-1})	105 °C	1 h	Toluene 0.4 mol.L^{-1}	91% (CA)
7	Van Schijndel et al. 2017[42]	1	NH_4HCO_3 (0.1)	90 °C	2 h	none	95% (FA)

2.2. Discussion

The Knoevenagel-Doebner is an efficient procedure but it requires, as starting materials, benzaldehydes that are mainly produced from petroleum. Even if the production of vanillin and syringaldehyde from lignin oxidation is emerging, their cost remains quite high (Table 3). As naturalness, through labeling such as cosmos or USDA organic, is often required for high-value added markets (*e.g.* cosmetic), *p*-HCAs obtained through synthetic chemistry should be reserved for commodity applications only (*e.g*. polymers, additives).

As competitiveness in terms of cost is essentiall, we believe microwave-assisted synthetic procedure is not relevant as microwave pilots remain quite expensive. Procedures employing ethanol as solvent can be competitive since ethanol is cheap, easily distillable (recycling), and acceptable to be used at industrial scale. The main drawback of the aforementioned processes will be the use of amino-acids in large quantity (0.5 equiv). Recyclability of the catalyst is thus primordial for competitiveness. Heterogeneous catalysis allows the recovery of the catalyst by simple filtration. Knoevenagel reaction have been already catalyzed by immobilized amine or amino acid.[44,45] In another fashion, Fiorito et al. proposed to use waste water of olive oil or buttermilk to perform the Knoevenagel-Doebner condensation (here we will not consider the use of edible fruit juices). This procedure seems attractive as no organic solvent is used and the waste water can be reused for at least 6 cycles without adding any catalyst.[40] In addition, the reaction being activated by ultrasounds, no additional heating is required.

However, Meldrum's acid has to be used instead of malonic acid, which leads to the release of acetone in stoichiometric amount (1 mole of acetone for 1 mole of *p*-HCA). It is noteworthy to mention that the desired product precipitates in the media. Although this is an advantage, one must ensure that no other compound present in the waste water co-precipitates. Finally, solvent-free Knoevenagel-Doebner can be performed using acetic acid/sodium acetate or ammonium bicarbonate.[39,42,43] Viscosity can be an important drawback for the scale-up of these procedures. After completion, in the case of acetic acid/sodium acetate, one needs to be diluted in a mixture of ethanol and acetic acid, before washing with cold ethanol and recrystallization.[40] For the ammonium bicarbonate-based procedure, the dilution is performed with a saturated aqueous sodium bicarbonate solution which is then acidified with 6.0 M HCl, prior to recrystallization in ethanol.[42]In all cases, the recovery of the desired product is conducted through a precipitation/filtration sequence which can be followed by recrystallization to improve the purity further. All these techniques are commonly used in industry and are cost-efficient.

Table 3. Current average prices of phenolic aldehydes used to prepare *p*-HCAs.[27]

Compounds with purity > 95%	Average price/ kg (USD)
4-hydroxybenzaldehyde	80 - 200
3,4-dihydroxybenzaldehyde	240 - 400
Vanillin	90 - 130
Syringaldehyde	200 - 300

3. Recovery from agricultural by-products

3.1. State of the art

Since *p*-hydroxycinnamic acids are mainly esterified in biomass, their recovery as free acids requires a hydrolysis. For small secondary metabolites such as chlorogenic acid or sinapine (Figure 3), hydrolysis can be performed after a first step of extraction. On the contrary, to recover efficiently ferulic and *p*-coumaric acids covalently bounded to the cell-plant matrix (Figure 3), hydrolysis has to be concomitant with extraction.

Extraction of small *p*-hydroxycinnamate esters is generally performed with water/alcohol solution. Indeed, efficient eco-extraction can be achieved with an aqueous ethanolic mixture from traditional medicinal plants[46] or agricultural by-product such as mustard seeds meal.[47,48] Whereas caffeoylquinic acids seem the major source of caffeic acid, sinapine, the choline ester of sinapic acid, is the main source of sinapic acid in plants. It is worth mentioning that activations using microwaves,[49,50] ultrasounds[51,52] or enzymes[53],[54] can be used to assist extractions of these compounds. In addition, pressurized liquid extraction (PLE)[53],[55,56] emerged also to recover such compounds. Recently, Duan et al. reported the use of deep eutectic solvent for caffeoyl quinic acids extraction.[57] Derivatives of caffeic acid were extracted from numerous plants leading to various pharmaceutical and cosmetic applications.[58–60]

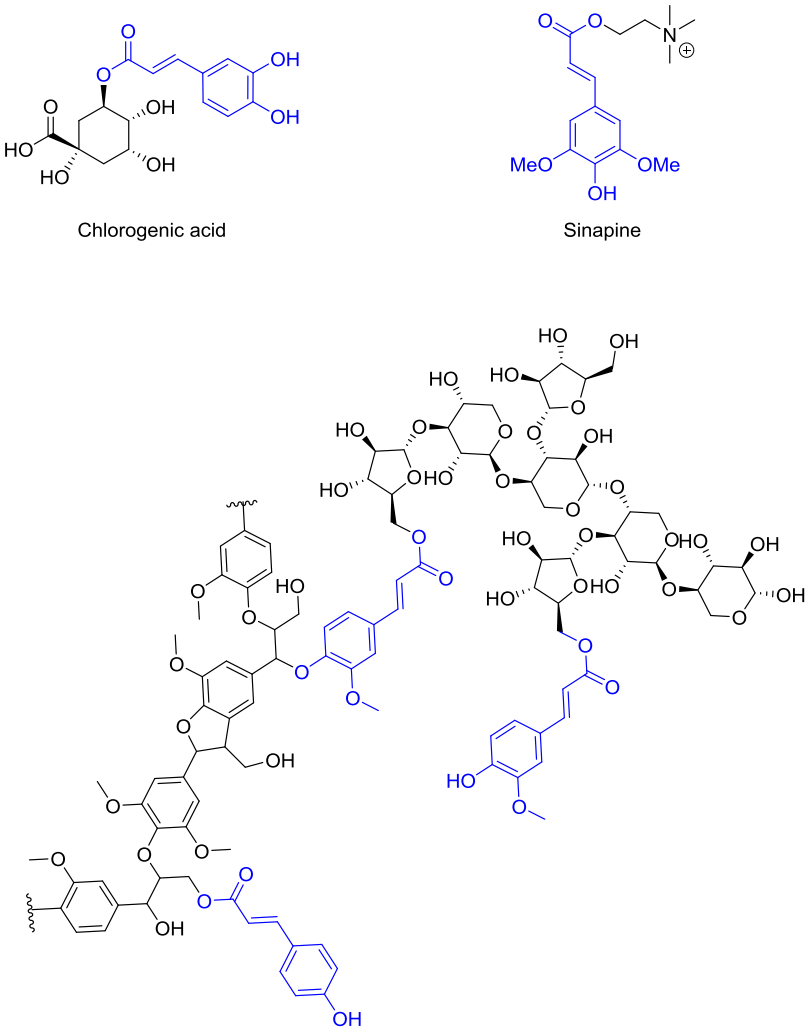


Figure 3. Examples of *p*-HCAs derivatives (left) and ferulate and *p*-coumarate moities in plant cell wall (right).

As these extracts already exhibit interesting properties, few works were dedicated to specific recovery of pure caffeic acid.

De Leonardis et al. have reported a process to obtain a caffeic acid enriched extract (58% purity) from sunflower seed shell through filtration, acidification and extraction.[61] Apart from analytical techniques such as HPLC, the only industrially relevant process reported for caffeic acid purification is high-speed counter-current chromatography (HSCCC).[62,63] Final purities were reported as high as 95%. In the case of sinapic acid, literature reported different methodologies such as zeolite absorption (96.3% recovery with 80% purity),[64] ion exchange chromatography (60% recovery, 20 cycles),[65] membrane filtration[66] or precipitation.[67]

p-Coumaric and ferulic acids, that are quite abundant in crops such as maize, wheat and rice, are bounded in the plant cell wall. For extracting them, alkaline hydrolysis using NaOH was the most popular technique.[68–73] However enzymatic hydrolyses were also actively investigated (e.g. Table 4, entries 1 and 2).[74–80] Extractions by PLE,[81,82] microwaves[83,84] or extrusion[83] were explored but their efficiency appears limited, probably due to the encasement of ferulic and *p*-coumaric acids in the matrix of plant cells (Table 4, entries 3 and 4). To overcome this limitation, reductive catalytic fractionation (RCF) on

herbaceous feedstock can be an alternative to cleave both ether and ester linkages. However, this procedure often led to the formation of saturated compounds.[85,86] In 2018, Wang et al. proposed a supported $ZnMoO_4$ catalyst able to release *p*-hydroxycinnamic methyl esters from corncob sawdust without affecting the double bond.[87] Nevertheless, RCF is always performed under harsh conditions (140-240 °C, 20-60 bars). In another strategy, Zhao et al. tested mild alkaline conditions leading to quantitative recovery of *p*-CA and FA after 5 washings procedure (Table 4, entry 5).[88] Finally, sequential alkaline/acidic hydrolysis was performed on sugarcane bagasse to enhance recovery of *p*-coumaric acid from 0.7 to 4.4% weight of dry biomass and ferulic acid from 0.4 to 0.79% by cleaving both ester and ether linkages.[89]

Most of the time, hydrolysis leads to complex liquors due to co-extraction of sugars, proteins and other polyphenols. Processes including concentration/purification step(s) thus need to be designed to further increase the extract purity. Purification of the desired product can be performed through organic extraction,[81] ethanol washing,[90] absorption on activated charcoal,[91,92] zeolites,[83] resins,[72,75,80,92–96] magnetic nanoparticles[97] or cyclodextrin,[98] membrane filtration,[71,99] preparative HPTLC[100] and HSCCC.[101] An overview of these methodologies is illustrated in Table 5. In 2012, Salgado et al. have followed three of these processes (Table 5, entries 1, 4 and 6) to recover ferulic acid from grass hydrolysate ranging from 6.0 to 58.8% of recovery (Scheme 2).[102] For the purification of *p*-coumaric acid, Zhao et al. proposed a six-step procedure from sugarcane bagasse including alkaline hydrolysis, ultrafiltration, discoloration under activated charcoal (between 5 and 16% loss of *p*-CA), absorption on D201 resin (76.5%), desorption (91.2%) and crystallization that allow to achieve high purity (95.2%).

Table 4. Examples of *p*-HCA release from recent works.

Entry	References	Biomass	Extraction	*p*-HCA release (%)[a]
1	Dupoiron et al. 2017	Wheat bran	Enzymatic	48.5% FA
2	Gopalan et al. 2018	Wheat bran	Enzymatic	34.6% FA
3	Pazo-Cepeda et al. 2019	Wheat bran	Pressurized Liquid	14.8% FA
4	Bichot et al. 2020	Corn stalk	Microwave	4.2% FA and 13.1% *p*-CA
5	Zhao et al. 2013	Rice straw	CACCO[b] process	56% *p*-CA and 78% FA[c]

[a]These percentages were calculated on the basis of an alkali extraction which is considered to release 100% of *p*-HCA. [b]Calcium capturing by carbonation, [c]Without washing step.

Unfortunately, global yield was not reported (Table 5, entry 7).[94] Jiang et al. achieved high recovery from sorghum pith, however no information on its purity was provided (Table 5, entry 11).[72] Purity higher than 90% can be achieved for ferulic acid (Table 5, entries 9, 14 and 16), however only Dupoiron et al. reported the efficiency of their process with 52% of the initially present FA recovered.

A very elegant antibodies-based approach discriminating *p*-HCAs was developed by Salmela et al. to bind specifically *p*-hydroxycinnamic acids.[103] Molecular imprinted polymers (MIPs) were also developed to specifically target *p*-HCAs,[104–108] but not yet applied on biomass hydrolyzates.

Karlen et al. designed a process from corn stover (alkaline treatment, ethanol washing, acidic precipitation) and performed a technoeconomic analysis leading to a price of $\$5.05.kg^{-1}$ of *p*-HCA. They concluded that concentration of the extract is crucial and they proposed to use genetically modified corn to enhance *p*-HCA content in plant. In addition, their analysis shows the need for more efficient recovery/purification process.[34]

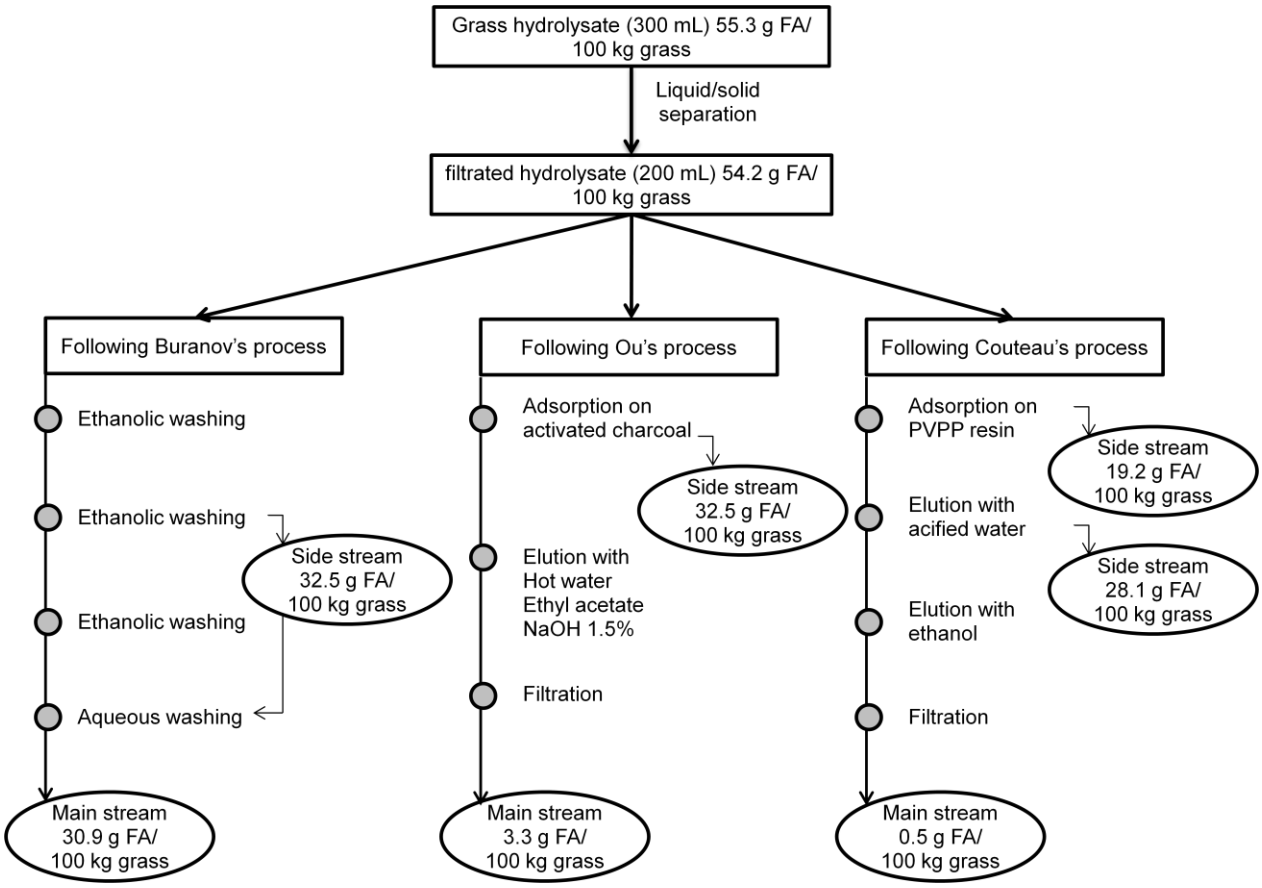
Table 5. Reported procedures for recovery of *p*-coumaric acid and ferulic acid.

Entry	Ref	Raw material	Pre-treatment	Purification step	Purity	Efficiency
1	Couteau et al. 1997[75]	Sugar beet pulp	Twin-screw extraction and enzymatic hydrolysis	Activated charcoal (GAC) (Absorption 47%, desorption 97%), polystyrenic resin (XAD-16) (Absorption 72%, desorption 97%) or polyvinylpolypyrrolidone resin (PVPP) (Absorption 42%, desorption 98%)	38% GAC, 22% XAD-16, 62% PVPP (FA)	46% GAC, 70% XAD-16, 41% or 51%[a] PVPP
2	Couteau et al. 1998[91]	Sugar beet pulp	Twin-screw extraction and enzymatic hydrolysis	Microfiltration (3 µm). Absorption on activated charcoal (GAC) / desorption, by EtOH 96%. Crystallization	50% (FA)	6 cycles to achieve 97%
3	Scordino et al. 2005[93]	Pigmented orange pulp wash water	Centrifugation	Polystyrenic (Exa 90, Exa 118) and methacrylic resins (Exa 31). Best result Exa 118	65% (*p*-HCAs)	58%
4	Ou et al. 2007[92]	Sugarcane bagasse	Alkaline hydrolysis	Ultrafiltration 20 kDa (n.r.) Activated charcoal absorption (98.6%) and desorption (85.3%) + Anionic exchange chromatography on D201 (n.r.) and crystallization	Clean TLC (FA)	n.r. 6%[a,b]
5	Tilay et al. 2008[100]	Maize bran	Alkaline hydrolysis	Adsorption on Amberlit XAD-16 and desorption with ethanolic NH_4OH solution (0.1%), and preparative HPTLC	51% before HPTLC, 95% after	58% before HPTLC, n.r. after
6	Buranov and Mazza 2009[90]	Flax shives, wheat and corn bran	Alkaline hydrolysis	Ultrafiltration and Ethanol solubilisation / centrifugation cycles (2 times)	Clean TLC and FTIR (FA)	n.r. 56%[a]
7	Zhao et al. 2011[94]	Sugarcane bagasse	Alkaline hydrolysis	Ultrafiltration 200 kDa. Activated charcoal discoloration (5 to 16% loss). Anionic exchange chromatography on D201 (absorption 73.5% and desorption 81.8% over 6 cycles) concentration and crystallization	95.2% *p*-CA	8.56 g/kg of sugarcane bagasse
8	Liu et al. 2012[109]	Wheat bran	US assisted ethanolic alkaline extraction	Ultrafiltration 10 kDa	17.3% FA	n.r.
9	Xiong et al. 2014[110]	Volatile oil of *Rhizoma chuanxiong*	none	HSCCC *n*-butanol/acetic acid/water (4:1:5 v/v)	93% FA	n.r.
10	Zhao et al. 2014[71]	Corn bran	Alkaline hydrolysis and EtOH addition	Ultrafiltration (concentration) + nanofiltration + precipitation	84.4% FA	8.47 g/kg 50%
11	Jiang et al. 2016[72]	Sorghum pith	Alkaline hydrolysis	Acidification. Absorption on HP20 resin. Desorption aqueous EtOH 60%	n.r. *p*-CA	87.4%
12	Qu et al. 2017[97]	Wheat bran	US assisted ethanolic extraction	Absorption on magnetic nanoparticles modified by deep-eutectic solvent absorption. Desorption (77.9 to 97.5%)	n.r.	88.7%
13	Chu et al.	Wild rice	US assisted	Absorption on resin D101	n.r.	n.r.

	2018[95]		ethanolic extraction			
14	Dupoiron et al. 2018[96]	Wheat bran	Enzymatic hydrolysis	Acidification + Electrodialysis + weak anionic exchange chromatography on A21 + crystallization	90-95% FA	52%
15	Gopalan et al. 2018[80]	Wheat bran	Enzymatic hydrolysis	Absorption on XAD 4 and desorption	n.r.	99%
16	Abu-Omar et al. 2018[81]	Corn and Miscanthus	PSE, alkaline hydrolysis	Precipitation of lignin and polysaccharides. Organic extraction (EtOAc). Crystallization	> 98%	n.r.
17	Domingos et al. 2020[99]	Wheat bran	Enzymatic hydrolysis[79]	Diananofiltration (NTR7450) at pH = 9	n.r.	95%
18	Tamao and Malapert 2020[98]	Olive mill waste water	Acid aqueous phase	Aggregates formation with cyclodextrin. Microfiltration. Drying. Dissociation using EtOH	n.r.	n.r.

n.r. : not reported

[a] From Salgado *et al.* [b] Recovered from grass after desorption of activated charcoal, anionic exchange chromatography was not performed.



Scheme 2. Simplified flow chart of processes followed by Salgado *et al.* [102]

3.2. Discussion

Despite the large number of publications dealing with the extraction of phenolic compounds, a few focus specifically on *p*-HCAs, and even fewer reports on performing purification steps in order to recover *p*-HCAs with high purity. Comparison between these research works is thus very complex due to the diversity in raw materials, pretreatments and extraction techniques prior downstream processing.

Concerning the extraction, we have distinguished two different cases. Firstly, the free esterified *p*-HCAs (*e.g.* chlorogenic acid, sinapine), *i.e.* those that are not bounded to the cell wall matrix and therefore directly extractible. For these compounds, efficient eco-compatible extractions were reported using aqueous ethanol solution,[46,48] with or without physical activation, especially through ultra-sound.[51] Secondly, the encased *p*-HCAs, mainly *p*-coumaric and ferulic acids, are often extracted through alkaline hydrolysis of the vegetal matrix. Unfortunately, this procedure is considered as non-natural in cosmetic and food market, thus drastically reducing their value. On the contrary, as enzymatic hydrolysis is considered natural, pure feruloyl esterases can be used to achieve efficient hydrolysis for small molecules,[111,112] however they show low efficiency on cell wall matrix.[80] To achieve high release of *p*-CA or FA, complementing feruloyl esterases with hemicellulases and cellulases is required.[79] Note that those enzymes are not only produced at the industrial scale, but they also are often supplied in the form of a cocktail, lowering the price and possibly containing secondary activities such as feruloyl

esterases.[113] Other advantages of enzymes are their substrate specificity (discrimination between the *p*-HCAs),[114] recyclability[115] and no deleterious effect on the substrate that can be reused for further applications (*e.g.* feed, methanisation, ethanol production). Moreover, the use of enzymes can simplify the downstream processing as few degradation products are recovered compared to alkaline hydrolysis (*e.g.* discoloration step).

Purification of *p*-HCAs from agricultural by-products requires multi-steps, firstly a solid/liquid extraction followed by a solid/liquid separation that can be performed by filtration[71,79,90,97] or centrifugation.[88,92,94] Then various strategies were investigated to recover *p*-HCAs from the liquid part. Even if absorption on various supports is highly popular,[72,75,80,91,93–97] absorption/desorption process suffers from important drawbacks such as low selectivity of absorption,[64,75,91,93,96] high consumption of chemicals (salt and/or solvent) for desorption and generation of solid waste due to resin aging. Moreover, the use of solvents has to be reflected taking into account the energy consumption necessary to their recycling (evaporation/condensation) that can highly impact the total process cost.[34] Same issues will be encountered using solvent extraction or ethanol washing. In the same fashion, acid/base procedures generate lot of waste water which needs to be treated. In this context, membrane filtration seems a more eco-friendly technology, as it is performed in water and integrated multi-step is possible.[99] Micro- and/or ultra-filtration can be performed to retain high molecular mass (proteins, oligosaccharides) from the filtrate. Then nano-filtration was conducted to achieve separation between small molecules and *p*-HCAs. Finally a concentration step can be performed to enrich retentate in the desired molecule and recycle aqueous media.[71,99] To achieve high purity, crystallization could be performed when only one *p*-HCA is present in the media.[81,94,96] For example, in maize where both *p*-CA and FA are extracted, crystallization will lead to co-precipitation. Genetic modifications proposed by Karlen et al. to overcome this problem, will face another issue, at least in Europe, with GMO restriction.[34] Finally, HSCCC can be used to recover several compounds of interest.[62,63]

4. Production by engineered microorganisms

4.1. State of the art

p-Hydroxycinnamic acids are plant secondary metabolites derived from aromatic amino acids, L-phenylalanine and L-tyrosine in the phenylpropanoid pathway.[116] Although this pathway does not exist naturally in microbial strains used in industries (*e.g. Escherichia coli* and *Saccharomyces cerevisiae*), it can be implemented by heterologously expressing genes coding for pathway of interest enzymes.

Through the shikimate pathway, microorganisms are able to produce L-phenylalanine and L-tyrosine, precursors of *p*-HCA from sugars (*i.e.* D-glucose). There has been a lot of work on rewiring carbon flux toward the production of those precursors in order to produce various secondary metabolites in attractive yields. The work concerns mostly overexpression of key genes in the metabolism, knocking-down competitive pathway (*i.e.* Ehrlich pathway), elimination of enzyme and transcriptional regulations. Several recent reviews[117–121] as well as a Frontiers Research Topic published in 2020,[122] focus on this subject and clearly show the breadth and current significance of microbial production of aromatic amino acids derivatives.

Besides engineering the carbon flux, great effort has been made to produce heterologously *p*-CA with various microorganisms, as it is the first *p*-HCA within the biosynthetic pathway. Work focus on new genes discoveries and knocking-down *p*-HCA consuming pathway.

In 2015, Vargas-Tah and Gosset published a review on the production of *p*-HCAs in engineered microbes.[123] At that time, the maximum of production reported was achieved by Nijkamp et al. into an engineered *Pseudomonas putida (P. putida)*, a solvent tolerant bacterium, with 1.74 g/L of *p*-CA in a fed-batch cultivation with controlled L-phenylalanine feeding (Table 6, entry 1).[124] After that, with an engineered *S. cerevisiae*, Rodriguez et al. in 2015 produced a final titter of 1.93 $g.L^{-1}$ of *p*-CA in fed-batch deep-well plate fermentation with D-glucose as substrate (Table 6, entry 2). This improvement was due to their engineering work on *S. cerevisiae* shikimate pathway.[125] The most recent and advanced work on the subject is the one of Liu et al. in 2019, who worked among others on the pentose phosphate pathway in order to enhance the pool of erythrose-4-phosphate. By means of their strategy and a fed-batch fermentation they produced 12.5 $g.L^{-1}$ of *p*-CA using an engineered *S. cerevisiae* strain (Table 6, entry 3).[126] Other recent works on the matter, although they did not achieve the highest productivity, seem interesting. First, Borja et al. in 2019 choose for the bioproduction of *p*-CA a *S. cerevisiae* strain able to consume D-xylose as sole carbon source, a non-fermentable sugar (Table 6, entry 4).[127] By using a non-fermentable sugar, they avoided the Crabtree effect and succeeded to further direct carbon flow towards *p*-CA production, they obtained a 45-fold-increase in *p*-CA production over their control with D-glucose as substrate. Finally, Gu et al. in 2020 engineered a *Yarrowia lipolytica* (*Y. lipolytica*) strain to produce aromatic-derived natural products, among other *p*-CA (Table 6, entry 5).[128] They chose this yeast as host, as it can use renewable low-cost carbon feedstock as substrate. They obtained a final production of 593.53 $mg.L^{-1}$ *p*-CA in shake flask with D-glucose as substrate. It is noteworthy to mention that DuPont de Nemours and Co. has filed patents on the production of *p*-coumaric acid through a multistep procedure (*i.e.* production of L-tyrosine then *p*-coumaric acid production).[129–131] This process is described in a mini review from Sariaslani in 2007.[132] For the microbial production of caffeic acid (CA), the approach essentially consisted in the expression of a gene coding for a *p*-CA 3-hydroxylase (C3H) in an engineered microorganism. Gosset's team investigated progresses on CA production in engineered *Escherichia coli* (*E. coli*) in a review in 2019 (Table 6, entries 6 and 7).[133] For now, the C3H catalytic activity seems to be insufficient to cope with carbon flow upstream when expressed in a *p*-CA producer microorganism (trace of *p*-CA and other precursor were found in culture medium).

Finally, microbial production of ferulic acid has been mainly performed through the expression of a gene coding for a CA 3-*O*-methyltransferase, catalyzing the 3-*O*-methylation of CA into FA. The highest microbial production of ferulic acid was recently achieved by Rodrigues et al. in an Engineered *E. Coli* using L-tyrosine as precursor with 0.257 $mg.L^{-1}$ (Table 6, entry 8).[134] Previously, Kang *et al.* in 2012, obtained 0.196 $mg.L^{-1}$ of ferulic acid with a L-tyrosine overproducing *E. coli* strain (Table 6, entry 9). [135].

Table 6. Advance on *p*-HCAs bioproduction in engineered strains.

Entry	Reference	Organism	Carbon source	Precursor added	*p*-HCA ($g.L^{-1}$)
1	Nijkamp et al. 2007[124]	*P. putida* S12 C3	D-glucose	none	1.74 (*p*-CA)
2	Rodriguez et al. 2015[125]	*S. cerevisiae*	D-glucose	none	1.93 (*p*-CA)
3	Liu et al. 2019[126]	*S. cerevisiae*	D-glucose	none	12.5 (*p*-CA)
4	Borja et al. 2019[127]	*S. cerevisiae*	D-xylose	none	0.242 (*p*-CA)

5	Gu et al. 2020[128]	*Y. lipolytica*	D-glucose	none	0.594 (*p*-CA)
6	Huang et al. 2013[136]	*E. coli*	D-glucose & glycerol	*none*	0.766 (CA)
7	Furuya et al. 2014[137]	*E. coli*	glycerol	*p*-coumaric acid	10.2 (CA)
8	Rodrigues et al. 2020[134]	*E. coli*	LB medium	L-tyrosine	0.257 (FA)
9	Kang *et al.* 2012[135]	*E. coli*	D-glucose	none	0.196 (FA)

4. 2. Discussion

Biotechnological production of *p*-CA offers two main advantages as it can potentially provide both high productivity and naturalness. Nevertheless, more research and development are necessary in order to achieve the production of all the different compounds of the metabolic pathway. Indeed, to date,only *p*-coumaric acid has been produced in industrially attractive amounts with D-glucose as substrate (107.9 $mg.L^{-1}.h^{-1}$).

Work is currently underway to enhance and reach industrially-relevant productivity of other *p*-HCA and derived molecules. As previously mentioned, although preliminary results were reported for caffeic and ferulic acids with modest productivities, no data are available for sinapic acid yet. Very recently, Valanciene et al. have reviewed the biosynthesis of phenolic acids and their bioproduction pointing some limitations such as intrinsic toxicity and formation of by-products in the case of heterologous production.[138] In addition, some drawbacks must be overcome such as poor solubility of *p*-HCAs in water, or high cost of growth media. With regards to the toxicity of the *p*-HCAs, the use of a solvent tolerant strain (such as *P. putida* or an engineered strain) can be a solution to face the toxicity and it has been already applied.[124] The host is a complicated choice, bacteria being prokaryotic organisms, the heterologous expression of cytochrome p450 enzymes (*i.e. p*-coumarate 3-hydroxylase), can be difficult, therefore, implementing *p*-HCAs pathway into yeasts (*i.e. S. cerevisiae*) could be simpler. Moreover, a yeast-based bioprocess can reduce operating cost for bioproduction as most of the time no pH regulation is required.[139]

Recent works demonstrated the importance of fermentation feeding in microbial *p*-HCA production and especially with *S. cerevisiae*, where the Crabtree effect impacted the production.[127] Nevertheless, there is a lack of work on optimization of fermentation process on this subject while this could unlock some issue.

Another way to decrease the cost of bioprocesses is to work on the medium. First, using co-products as nutrient source for strains instead of well-defined growth media and purified D-glucose could be an option.[140] The recent work of Gu et al. may be one of the solution.[128] Using *Y. lipolytica* for *p*-HCA production will allow the use of renewable low-cost carbon feedstock as substrate, but a lot of engineering work needs to be done. Optimizing and defining a medium for *p*-HCA production could also be a solution.[141] This last optimization step can be completed only when an efficient strain is available and must be carried out and designed by taking into account the downstream process as the complexity of the medium could have an impact on the good recovery of *p*-HCA.

Another important issue will be the development of efficient and cheap downstream processing to recover pure *p*-HCA from the growth medium. This aspect can be nourished by the studies performed on the recovery of *p*-HCAs from biomass by-product. *In situ* product recovery approaches (*i.e.* ISPR) could

address those drawbacks by managing, at the same time, toxicity, solubility and purification.[132,139] However, solvents used in the extracting phase have to be judiciously chosen in order to not replace one toxicity by another.[142] In the purification process, it can be difficult to discriminate *p*-HCAs and selectively recover one due to very close molecular proximity. For *p*-CA, as it is the first in the biosynthetic pathway, no other *p*-HCAs will be produced, thus greatly simplifying its purification. Nevertheless, for the following compounds in the biosynthetic pathway, *i.e.* caffeic, ferulic and sinapic acids, the total consumption of their precursors will be crucial to ensure high yield and purity. As of now, precursors are still accumulated and present in broth cultures.[134] It is well known that the global cost of bioprocesses is often largely impacted by the cost of downstream processing. Even if a recent economical and environmental predictive study by Krömer et al. is encouraging on the viability of such bioprocess,[139] there is still a long way to achieve efficient and competitive biotechnological production of *p*-HCAs. However, the high number of recent publications on this topic demonstrates an impressive dynamism which is promising.

5. Conclusion

Recovery of *p*-HCAs from biomass has been extensively studied. Efficient protocols of eco-extraction were developed and the release of *p*-HCAs from esterified compounds can be achieved by enzymatic hydrolysis even if alkali treatment remains dominant. Ferulic acid extraction has already reached industrialization thanks to the push market represented by vanillin. In the short term, extraction and purification of all *p*-HCAs from biomass seems possible. For purification, support-free liquid-liquid chromatographic technics (such as HSCCC, or centrifugal partition chromatography) and membrane purification are promising industrial techniques. However, the cost of such processes to recover one minor compound from a complex mixture can limit usages to high-value added and niche markets. Currently, as prices of the *p*-hydroxybenzaldehyde precursors are high, the chemical pathway is limited. A decrease of those prices through lignin biorefinery development could unlock this pathway and commodity market could be addressed in mid- to long-term. Finally, *p*-HCAs production through biotechnology seems to be the most promising approach to conciliate high quantity, reasonable cost and naturalness.

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