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Sustainable production of pharmaceutical, nutraceutical and bioactive compounds from biomass and waste

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Abstract

The aim of this tutorial review is to provide a general overview of processes, technologies and challenges in the production of pharmaceutical and bioactive compounds from food waste and lignocellulosic residues. Particular attention is given to benign-by-design processes instinctively devoted to environmental sustainability for the recovery of bioactive compounds from food waste as well as for the production of alcohols, acids, polyols, furans and aromatic compounds from lignocellulosic residues. At the same time, novel green synthetic routes for the production of active pharmaceutical ingredients and the development of novel bioactive compounds are discussed. Recent success industrial stories on the use of food waste and lignocellulosic residues for pharmaceutical and nutraceutical applications are also discussed.

Key learning points

1. Biomass-derived wastes and residues are sustainable starting materials for pharmaceutical and nutraceutical applications.
2. Several bioactive compounds (BC) can be efficiently recovered from fruit and vegetable loss (FL) by using innovative and environmental-friendly extraction methods.
3. Lignocellulosic residues (LR) can be depolymerized into polyols, acids, furans and phenolic compounds that can be used for the production of intermediates, active pharmaceutical ingredients (APIs) and excipients for the pharmaceutical industry.
4. Newly developed biobased BC could provide more sustainable and accessible new drugs.
5. In a circular economy perspective, bioactive compounds and pharmaceutical intermediates should be obtained from biomass waste and residues before their conversion into bulk chemicals, biofuels or energy in a high-to-low value cascade approach.

Introduction

"I only feel angry when I see waste. When I see people throwing away things we could use" is a famous statement by St. Teresa of Calcutta, 1979 Nobel Peace Prize laureate, aiming to draw the attention to an occidental society where everything appears to be disposable.

Food industries, agriculture and forest activities generate billions of tons of biowaste, residues and side-streams that need to be valorised in order to avoid their negative impact on human and animal health as well as on the environment (they cannot be burned due to the release of atmospheric pollutants, neither landfilled due to water/soil contamination and direct/indirect CH_4 and CO_2 emissions). In a circular economy perspective, biowaste can be efficiently processed for the production of value-added chemicals and products.[1] Modern biorefineries already ensure biomass/waste valorization into energy, fuels and building blocks; however, the chemical composition of food waste and lignocellulosic residues also facilitate their conversion into active pharmaceutical ingredients (API) and bioactive compounds (BC).

Pharmaceutical and nutraceutical industries have contributed to significant improvements in human well-being, while playing a fundamental role in our economy. The production of APIs is probably the core business of any pharmaceutical industry. The global API market size is projected to grow from EUR 158.9 billion (2020) to EUR 210.6 (2025), with an annual growth rate (CAGR) of 5.8% as a result of the rising geriatric population and the increasing burden of chronic diseases (diabetes and cancer in particular). Similarly, the worldwide market of nutraceutical products (dietary supplements, functional/pharmaceutical food & beverages and personal care products) is rapidly increasing (from EUR 324.2 billion of 2014 to EUR 613.7 billion by 2027 with a CARG of 8.3%).[2]
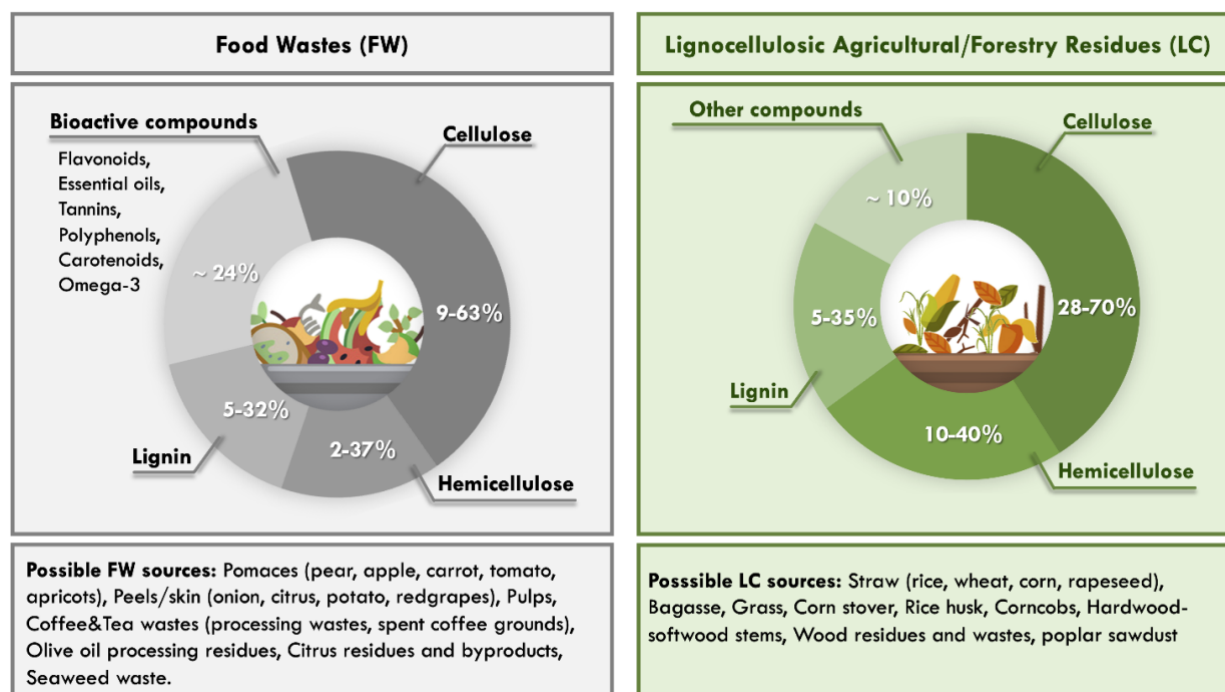
Fig. 1. Chemical composition of major biomass-derived waste and residues.

There are large margins to make pharmaceutical and nutraceutical industries more sustainable by using food loss (FL) and lignocellulosic agriculture/forestry residues (LR) as starting materials for the production of APIs and BCs (Fig. 1). LR have already been largely adopted for the production of energy (hydrogen, biogas), fuels (ethanol, biodiesel) and fine chemicals, but less explored in a pharmaceutical context.[3] At the same time, FL has the potential to be efficiently utilised for the extraction of biologically active ingredients (e.g., polyphenols, anthocyanins, flavonoids) for nutraceuticals.[4]

The development of new, sustainable methods for the production of pharmaceutical intermediates, APIs and BC from biomass resources will gain momentum for two main reasons. Firstly, such high value-added molecules would significantly increase the overall economic feasibility of a biorefinery; secondly, they can provide novel "greener" approaches for the pharmaceutical and nutraceutical industries.

The "12 Green Chemistry Principles" have been percolating the pharmaceutical industry over the last two decades, so that they are well established either by being integrated into individual company policies or advocated by leading organizations.[5] However, not all chemists operating in the pharma sector (i.e., process chemists and medicinal chemists) have equally implemented them into their daily practices. While rapid progress has been achieved in the implementation of Green Chemistry principles in the redesign of API manufacturing processes or in the development of synthetic sequences and pilot plant procedures, medicinal chemists have only recently started to consider their implementation for the discovery of novel BCs to feed the drug discovery and development pipeline.[6] In addition, most efforts have been concentrated on three of them (waste minimisation, avoiding the use of toxic and/or hazardous reagents/solvents, and biocatalysis) and only a growing emphasis on the use of renewable biomass as a feedstock emerged in the last decade.

In parallel, the nutraceutical industry sees the utilization of FL for BCs as a promising opportunity to reduce the cost of the formulated nutraceuticals and to decrease the use of synthetic chemicals in such formulations.

In this tutorial review a unified view is provided on the valorisation of (i) fruit and vegetable loss (FL) and (ii) lignocellulosic agricultural/forestry residues (LR) by highlighting their transformation into nutraceuticals and added value building block chemicals for the production of APIs and pharmaceuticals, in the framework of circular economy and green chemistry.

The chemical nature of food loss and lignocellulosic agricultural/forestry residues

Fruit and Vegetable loss (FL)

There is not a standardized definition of food waste. Taking into account all phases of the food supply chain, it is generally accepted to distinguish between:

- *food loss (FL)*, which refers to the decrease in mass or quality occurring upstream of the food supply chain (e.g., sowing, cultivation, harvesting, first transformation stages, industrial processing and manufacturing, distribution stages in the food supply chain);

- *food waste (FW)*, which relies to the waste generated downstream of the food supply chain (e.g retail and post-consumer stock, preparation and consumption activities).

In a perspective study, presented by the Food and Agriculture Organization of the United Nations (FAO), approximately 14% (1.3 billion tons) of the annual food produced globally is lost or wasted between harvest and retail. For example, the beverage industry (coffee, tea, fruit juices, beer, wine and distilled spirits) produces significative volumes of FL commonly under-utilized as animal feed. However, such type of waste holds important bioactive molecules that can be easily recovered and valorised for the preparation of new added value functional foods and drinks, as well as additive in many pharmaceutical, flavour, fragrance and cosmetic products.

FL arising from the fruit and vegetable processing industries are characterized by a chemical composition that differs one from another. The non-edible part, including products off-cuts (leaves, stems and other lignocellulose portions), is mainly composed by cellulose, hemicellulose and lignin while other parts such as pomace, peels/skins and seeds contain discrete level of sugars, (dietary) fibres, crude proteins, minerals, organic acids, vitamins and (poly)phenolic compounds that can be useful as nutrients and/or nutraceuticals for human health. In this regard, the term nutraceutical emerged as referring to "biologically active ingredients, present or obtainable from food and food-derived products, including food waste, and participate in metabolic processes, having a recognized health-promoting characteristic".[7] In particular, polyphenolic compounds - principally classified into flavonoids, tannins, phenolic acids, stilbenes and lignans - are largely present in fruit and vegetable waste (peels, rinds and seeds are particularly rich) and represent probably one of the most investigated classes of BC, due to their well-known antioxidant properties.

Lignocellulosic Agricultural and Forestry Residues and Wastes (LR)

Lignocellulosic biomass represents the most abundant renewable carbon source on the earth. Agricultural and forestry activities generate huge volumes of lignocellulosic residues that already represent a valid resource for the sustainable production of energy (e.g., H_2, CH_4) and fuels (e.g., biodiesel, wood pellets, bio-based technical fuels and additives).

Depending on the type of LR, holocellulose fraction (cellulose and hemicellulose) can account up to 70% of the dry lignocellulose and can be employed as renewable source of C6-C5 sugars and further converted into a wide range of molecules including acids, ethers, esters, alcohols/polyols and furan derivatives. All these compounds are widely recognized as renewable feedstocks for a bio-based chemical industry.

In particular, cellulose and hemicellulose derived polyols (e.g., sorbitol, mannitol, xylitol, glycerol) are widely adopted as excipients or as API for the treatment of constipation (vide infra) due to their sweet taste and tooth-friendliness.[8]

Furfural (FUR) and 5-hydroxymethylfurfural (5-HMF) are present as core molecule in a number of antihypertensive, antidepressant, anxiolytic and anti-inflammatory drugs, potentially considered as starting substrates for the production of biobased pharmaceutical ingredients and intermediates.[9]

The sub-phenolic structure of lignin (the third main component of lignocellulose) allows the production of lignophenols and lignans that can be directly employed as natural anti-inflammatory and antioxidant agents; furthermore via appropriate depolymerization processes, many aromatic precursors of biobased API/drugs can also be obtained.[10]

From lignocellulosic residues to compounds of nutraceutical and pharmaceutical interest

Availability and supply chains of FL and LR.

According to FAO statistics, the global production of fruits and vegetables reached a total of 1957 million tonnes in 2018 with Asia being, by far, the world's main producing region (Fig. 2). In industrialized areas, losses mainly occur at pre-processing stage (harvest, sorting and grading operations) while losses in post-harvest and processing activities also need to be taken also into account in developing countries (Fig. 2).

In terms of volumes, the main fruits are bananas/plantains (155 Mt/year), citrus (152 Mt/year), apples/pears/quinces/pomes (111 Mt/year), grapes (79 Mt/year), exotic fruits (28 Mt/year of pineapples, 13 Mt/year of papaya and 55 Mt/year of mangoes, mangosteens and guavas), tomatoes (182 Mt/year), carrots and turnips (40 Mt/year) that are largely used for the production of juices, jams, sauces and pulps.[11]

The processing operations of these fruits and vegetables generate large volumes of loss (e.g. citrus ~ 50%; banana ~ 35%; pineapple ~ 33%; apple ~ 25%; grape ~ 20%; tomato ~ 20%) in the form of leaves, skins, peels, seeds, pulps, shells and pomace that cannot be used for other purposes, posing serious management, economic and environmental problems while representing an promising renewable source of BC (Fig. 3).

Furthermore, the market size of processed fruits and vegetables is expected to exceeded EUR 300 Billion by 2026 with an estimated Compound Annual Growth Rate (CAGR) over 7%.[12]
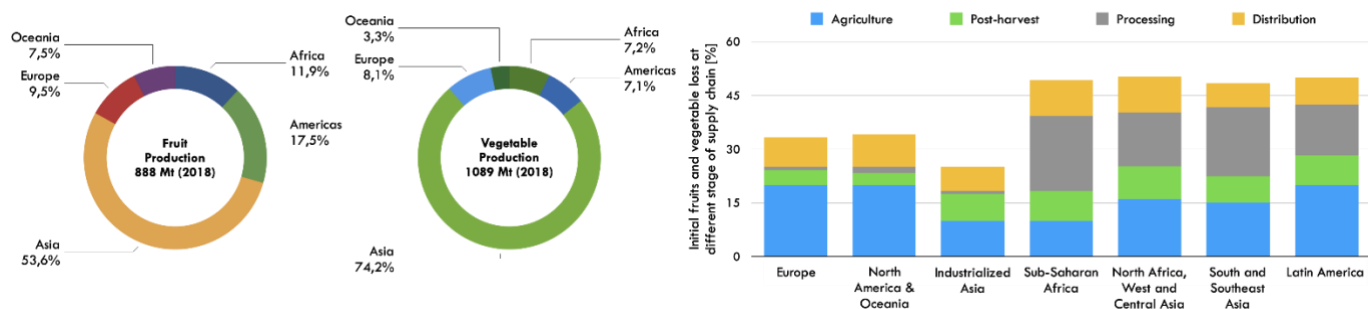
Fig. 2. Fruit and vegetable production in 2018 and their initial loss at different stages of supply-chain (adapted from Ref. 11).

An interesting case-study relates to waste generated in cashew nut processing factories, the so-called "cashew nut shell liquid" (CNSL) that – with a worldwide production of about 1 Mt/year in 2019 – represents a cheap source of natural unsaturated phenols (Fig.3).

At the same time, at least 20 billion tonnes/year of the primary lignocellulosic biomass (agricultural residues, stemwood and forest residues, perennial crops) has been estimated to remain potentially available worldwide (Fig. 4).

With respect to primary agricultural residues, maize (354.3 Mt/y), rice (731.3 Mt/y) and corn straw (128.0 Mt/y) as well as sugarcane bagasse (180.7 Mt/y) are the four majors lignocellulosic agrowaste feedstocks.[13] Wood residues production from forestry worldwide in 2019 was above 23 million m^3 (Fig. 3) according to information available from FAO statistics (http://www.fao.org/faostat/en/). In addition to forestry residues, readily available LR feedstocks are those arising from pruning of public parks, private gardens and yards that are generally disposed as municipal solid waste.

Even if the worldwide availability of FL and LR is extensive, a crucial point for their effective use as renewable feedstocks is an efficient supply chain of all upstream processes (e.g. harvesting, collection, treatment, transport, handling) necessary for biomass/food to reach the biorefinery facility avoiding, at the same time, their natural tendency to undergo microbial degradation. Literature on LR supply chains is widely available since such type of residues are largely employed for the production of 2nd generation biofuels.[14] Pre-processing (mechanical and/or chemical processes aimed to increase the volumetric density, preservation and handling of starting materials) and transportation steps constitute most significant impacts on the total environmental and economical sustainability of LR supply chain as a consequence of the high energy and fuel demand.[15]

The sustainability analysis of food supply chain is less investigated being, at the same time, regulated by legislative, social and cultural practices that greatly differ from regions to regions. In any case, the improvements of "on-farm" storage facilities, innovative low energy demanding pre-processing and preservation technologies as well as national/international policies aimed to strengthen links between all actors of the food chain may represent keystones for a future actual availability of FL and LR in large quantities.

For example, under the FAO's initiative, the German Corporation for International Cooperation (GIZ) partnered with a Nairobi company (Azuri Health) successfully developed a solar drying process for the preservation of mango (about half of the Kenyan mango is lost before reaching market).

Additionally, the Australian Government has recently launched the program "Stop Food Waste Australia" with 4 million AUD investment to reduce food waste by half by 2030. The program includes actions devoted to the valorisation of FL streams with direct involvement of all stakeholders across the supply chain for the generation of new products for the food industry and other economic sectors including added value chemicals, nutraceuticals and drugs.

Pretreatment processes

The main inherent issue related to the conversion of agricultural and forestry residues/wastes is the recalcitrant nature of lignocellulose (difficult to deconstruct into its key components). Physical and/or chemical pretreatment processes are generally required with a general aim to (i) breakdown the carbohydrate-lignin matrix and (ii) to reduce the cellulose crystallinity.[16]

Physical pretreatments (e.g., milling, grinding, size reduction, chipping) generally ensure the increase of the available surface area reducing, at the same time, the degree of polymerization and crystallinity in cellulose.
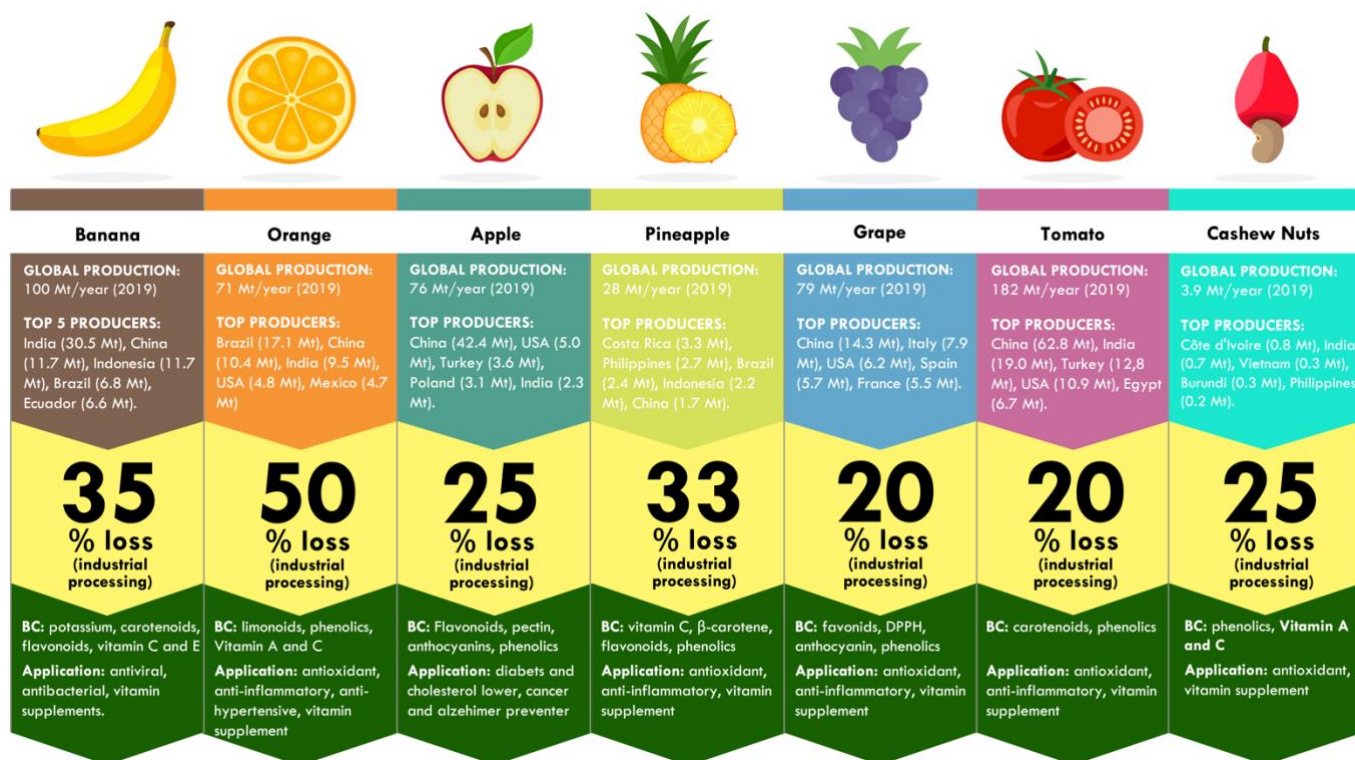
Banana

GLOBAL PRODUCTION: 100 Mt/year (2019)

TOP 5 PRODUCERS: India (30.5 Mt), China (11.7 Mt), Indonesia (11.7 Mt), Brazil (6.8 Mt), Ecuador (6.6 Mt).

35 % loss (industrial processing)

BC: potassium, carotenoids, flavonoids, vitamin C and E

Application: antiviral, antibacterial, vitamin supplements.

Orange

GLOBAL PRODUCTION: 71 Mt/year (2019)

TOP PRODUCERS: Brazil (17.1 Mt), China (10.4 Mt), India (9.5 Mt), USA (4.8 Mt), Mexico (4.7 Mt)

50 % loss (industrial processing)

BC: limonoids, phenolics, Vitamin A and C

Application: antioxidant, anti-inflammatory, anti-hypertensive, vitamin supplement

Apple

GLOBAL PRODUCTION: 76 Mt/year (2019)

TOP PRODUCERS: China (42.4 Mt), USA (5.0 Mt), Turkey (3.6 Mt), Poland (3.1 Mt), India (2.3 Mt).

25 % loss (industrial processing)

BC: Flavonoids, pectin, anthocyanins, phenolics

Application: diabets and cholesterol lower, cancer and alzehimer preventer

Pineapple

GLOBAL PRODUCTION: 28 Mt/year (2019)

TOP PRODUCERS: Costa Rica (3.3 Mt), Philippines (2.7 Mt), Brazil (2.4 Mt), Indonesia (2.2 Mt), China (1.7 Mt).

33 % loss (industrial processing)

BC: vitamin C, β-carotene, flavonoids, phenolics

Application: antioxidant, anti-inflammatory, vitamin supplement

Grape

GLOBAL PRODUCTION: 79 Mt/year (2019)

TOP PRODUCERS: China (14.3 Mt), Italy (7.9 Mt), USA (6.2 Mt), Spain (5.7 Mt), France (5.5 Mt).

20 % loss (industrial processing)

BC: favonids, DPPH, anthocyanin, phenolics

Application: antioxidant, anti-inflammatory, vitamin supplement

Tomato

GLOBAL PRODUCTION: 182 Mt/year (2019)

TOP PRODUCERS: China (62.8 Mt), India (19.0 Mt), Turkey (12,8 Mt), USA (10.9 Mt), Egypt (6.7 Mt).

20 % loss (industrial processing)

BC: carotenoids, phenolics

Application: antioxidant, anti-inflammatory, vitamin supplement

Cashew Nuts

GLOBAL PRODUCTION: 3.9 Mt/year (2019)

TOP PRODUCERS: Côte d'Ivoire (0.8 Mt), India (0.7 Mt), Vietnam (0.3 Mt), Burundi (0.3 Mt), Philippines (0.2 Mt).

25 % loss (industrial processing)

BC: phenolics, **Vitamin A and C**

Application: antioxidant, vitamin supplement

Fig. 3. Most processed fruits and vegetables worldwide: global production, top 5 producers, loss percentage after processing operations, recoverable BC and possible nutraceutical application.

Chemical pretreatments, implying the use of acids, alkali, salts and organic/ionic solvents, have been largely adopted for the efficient separation of lignin and hemicellulose. Even if these chemical pretreatments are carried out under mild conditions (room temperature and atmospheric pressure), environmental concerns related to solvent recovery/reuse arise, in particular, when strong acid/base are employed. Indeed, a combination of physico-chemical treatments (e.g., steam explosion, liquid/hot water, ammonia fibre/freeze explosion, CO_2 explosion, organosolv) are getting increasing attention even if they are generally expensive at industrial level.

Biological pretreatments have also been adopted, but their use for the large scale production of chemicals appears to be very limited due to their intrinsic slowness and poor selectivity.

Pretreatment processes ensure to obtain high-quality cellulose, hemicellulose and sugars often altering the native structure of lignin which strongly limits its further conversion. In this context, an efficient strategy to obtain aromatic compounds from LR is to primarily convert the lignin fraction into propylphenols and phenylpropanols using the so-called reductive catalytic fractionation (RCF) processes (also known as "lignin-first" biorefinery).[17]

Production of biobased polyols and furans

The first step for an efficient exploitation of the holocellulose fraction is the depolymerization of its macromolecular structure into hexoses (six-carbon sugars) and pentoses (five-carbon sugars) *via* chemical or enzymatic hydrolysis.

The use of a dilute acid solution is preferred as pretreatment for lignocellulosic biomass, giving a mixture of C6 and C5 sugars. Once glucose and xylose are respectively obtained from cellulose and hemicellulose, they can undergo various reactions (e.g. dehydration under acid conditions into furan derivatives; conversion to C6-C5 polyols using molecular hydrogen or an indirect H-source).
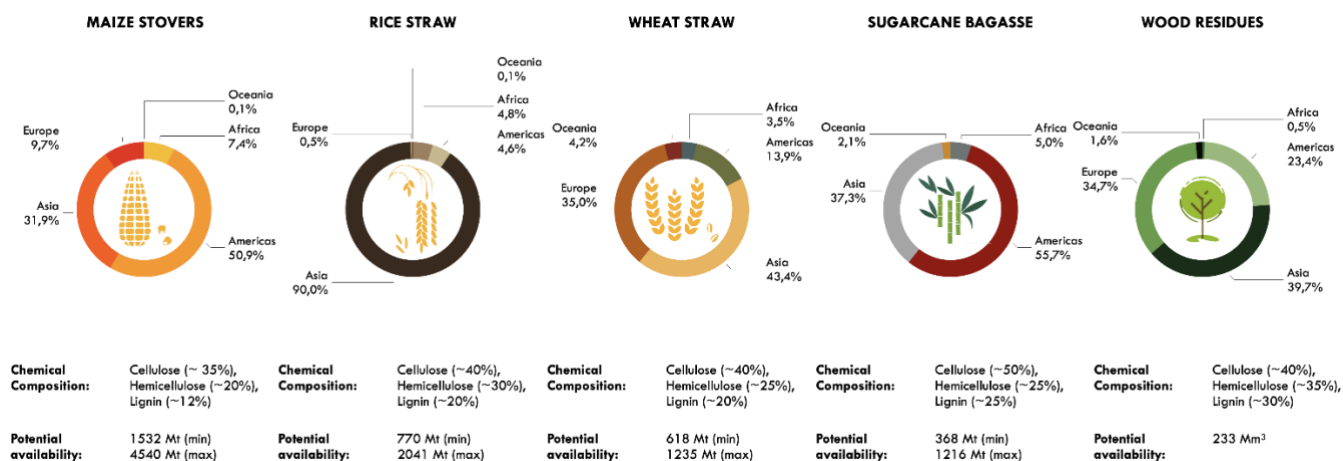
MAIZE STOVERS
Oceania 0,1%
Africa 7,4%
Europe 9,7%
Asia 31,9%
Americas 50,9%

RICE STRAW
Oceania 0,1%
Africa 4,8%
Americas 4,6%
Europe 0,5%
Asia 90,0%

WHEAT STRAW
Oceania 4,2%
Africa 3,5%
Americas 13,9%
Europe 35,0%
Asia 43,4%

SUGARCANE BAGASSE
Oceania 2,1%
Africa 5,0%
Asia 37,3%
Americas 55,7%

WOOD RESIDUES
Oceania 1,6%
Africa 0,5%
Americas 23,4%
Europe 34,7%
Asia 39,7%

Chemical Composition:	Cellulose (~ 35%), Hemicellulose (~20%), Lignin (~12%)	Chemical Composition:	Cellulose (~40%), Hemicellulose (~30%), Lignin (~20%)	Chemical Composition:	Cellulose (~40%), Hemicellulose (~25%), Lignin (~20%)	Chemical Composition:	Cellulose (~50%), Hemicellulose (~25%), Lignin (~25%)	Chemical Composition:	Cellulose (~40%), Hemicellulose (~35%), Lignin (~30%)
Potential availability:	1532 Mt (min) 4540 Mt (max)	Potential availability:	770 Mt (min) 2041 Mt (max)	Potential availability:	618 Mt (min) 1235 Mt (max)	Potential availability:	368 Mt (min) 1216 Mt (max)	Potential availability:	233 Mm³

Fig. 4. Potential availability of main of agricultural and forestry lignocellulosic residues per region (source: Ref. 13 and FAOSTAT - http://www.fao.org/faostat/en/)

Sugar polyols can be directly obtained in a one-pot heterogeneous catalytic process from cellulose and hemicellulose fractions and, in less extent, directly from agricultural and forestry raw materials

Sorbitol (C6 polyols) and xylitol (C5 polyols) have been included in the list of the 12 high value-added biomass-derived platform molecules that can be obtainable from renewable resources and agricultural/forestry biowaste.[18]

Sorbitol is largely used as sweetener, humectant and emulsifier ingredient for several applications including food, pharmaceuticals and cosmetics. Nutraceutical and pharmaceutical industries rely on sorbitol for the preparation of diabetic and dietetic foods&beverages. It is also used as excipient in the formulation of capsules and tablets allowing the stabilisation of APIs while ensuring, at the same time, a sweet taste and a cooling sensation. D-sorbitol is also the starting substrate for the two-step microbial production of L-Ascorbic Acid (Vitamin C).

Biomass-derived sugars including (i) corn starch glucose, (ii) corn steep liquor (a by-product of corn wet-milling) and (iii) maltose represent valid resources for the production of sorbitol. In a typical batch process (Fig. 5), a hydrogenation heterogeneous metal catalyst is suspended in an aqueous solution of glucose (30-60 wt%) and the reactor pressurized at the desired H_2 pressure (> 100 bar) at temperatures between 100 to 200 °C.[19]

In order to avoid D-glucose isomerization into mannose (with the concurrent formation of mannitol as hydrogenation by-product), the pH is generally maintained in the range 8.0–9.0. Nickel- and ruthenium-based catalysts are generally adopted, with the latter being preferred for its limited metal leaching and improved performance both in terms of glucose conversion (~100%) as well as sorbitol production (> 95%). The ensuing ready-commercial sorbitol solution is then decolorated and concentrated under vacuum to achieve a sorbitol syrup (70 wt%) that can be further concentrated/crystallized.

Continuous processes, using sublimed or fixed-bed catalysts, have been successfully employed under analogous process conditions. Other methods for the preparation of sorbitol include the electrolytic reduction of glucose and biological fermentation of corn syrup. Nevertheless, such processes have not achieved a technological development suitable for industrial implementation.

Xylitol, a C5 polyol, can be only obtained from biomass (an analogous petrochemical source is not possible) and traces its origin back to 1940 as a consequence of the sugar-shortage occurred during the Second World War. The estimated global market of xylitol actually exceeds 260 kton (value ca. one billion euros). Xylitol is largely employed in the preparation of sugar-free chewing gums being the sweetest polyols producing, at the same time, a very low calories and glycaemic index product. At an industrial scale, xylitol is produced in high yields (up to 98%) from the catalytic hydrogenation of xylose with a very similar process to those used for sorbitol. Corn husks, birch and beech woods, nuts, corncobs and sugarcane bagasse, rice and wheat straw, containing a high amount of hemicellulose fraction, can be effective renewable sources of xylitol.[20]
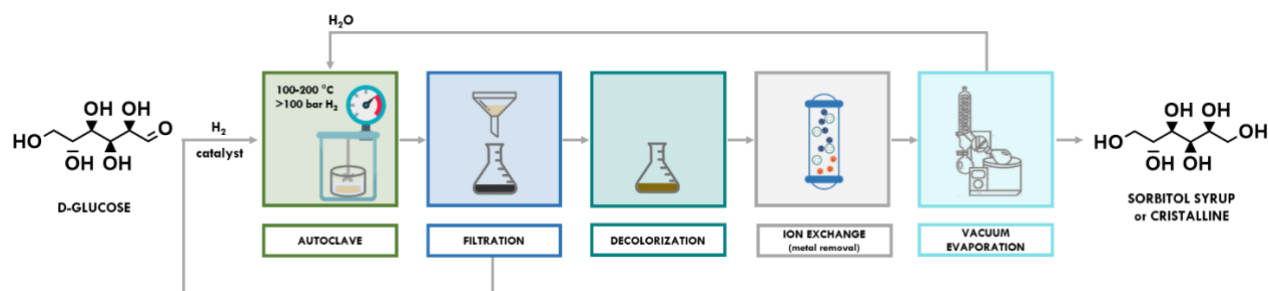
Fig. 5. Simplified flow diagram for the industrial production of sorbitol from glucose.

In 2020, Fazer Finland Ltd started to build a xylitol manufacturing facility using oat hulls, a side stream of the oat milling process, as raw material employing a state-of-the-art technology similar to that described above.

5-hydroxymethylFUR (5-HMF) and furfural (FUR) can also be efficiently prepared either form biomass derived sugars as well as from LR.[9] 5-HMF, also known as the "sleeping giant" due to its significant unexpressed potential as platform chemical in chemical manufacturing, can be produced in a 3-step reaction that involves (i) hydrolysis of cellulose into glucose followed by its (ii) isomerization into fructose that is finally (iii) dehydrated into 5-HMF. Despite the apparent simplicity of these chemical processes, various side chain reactions may occur (e.g., rehydration into levulinic and formic acids via cross-repolymerization as well as polymerisation/polycondensation with concurrent formation of humins) thus limiting overall 5-HMF yields.

5-HMF is currently produced at commercial-scale (20 ton/year) from renewable feedstocks by AVA Biochem in Muttenz, Switzerland.

One of the key challenges for the industrial production of 5-HMF is the separation and purification process. A detailed overview on industrial 5-HMF processes patented by several chemical companies (e.g., BASF SE, Novamont s.p.a., Sartec corp., Avalon, etc. etc.) highlighting also the aspects related to the catalyst recycling and regeneration was recently reviewed.[21]

Furfural (FUR) is produced is produced at industrial scale either in batch or in continuous reactors exclusively from lignocellulosic biomass using homogeneous or heterogeneous catalysts (FUR can often be also produced from C5-sugars and polysaccharides using critical solvents or hot water pretreatments). In the case of one-pot processes, the choice of an appropriate catalyst is critical in order (i) to promote the selective dissolution of hemicellulose from biomass and (ii) to enhance the hemicellulose depolymerization into of C5 sugars at their relative FUR conversion in good/high yields.

Fractionations processes devoted to delignification are often accompanied by concurred solubilization and (partial) depolymerization of hemicellulose that is therefore readily available to be further converted into value-added chemicals. The hydrolysis and dehydration of the hemicellulosic fraction can be successfully accomplished by using of mineral (H_2SO_4, HCl, H_3PO_4) and organic ($HCOOH$, $C_4H_4O_4$, $C_4H_6O_4$, CH_3SO_3H) acids in water or in aqueous-based biphasic systems. The addition of organic solvents allows to extract FUR from the aqueous phase thus limiting side reactions and, importantly, improving overall FUR yield.

Biobased aromatic compounds and intermediates from lignin fractions

For decades, lignin was relegated to the role of "ugly-ducking" since its native structure was altered during physico-chemical pretreatments of LR. The most striking example is the case of kraft lignin that is readily available from pulp and paper industries but, at the same time, very difficult to be used for the production of chemicals since the pulping conditions adopted lead to the cleavage of β-O-4 linkages (the abundant etheric substructure of lignin with a bond dissociation energy of about 290 kJ/mol) with the concurrent formation of more stable carbon-carbon bonds. Only two products have been produced to date at an industrial scale from lignin: ferulic acid and vanillin.[22] The first can be obtained from alkaline or enzymatic hydrolysis while the latter is largely produced (3000 tons/year) *via* catalytic oxidative processes of lignin.

Both compounds have many direct nutraceutical and pharmaceutical applications: ferulic acid is characterized by antioxidant, anti-inflammatory, antimicrobial activities, being main ingredient to several nutraceuticals and cosmetics. Vanillin, included in the main Western pharmacopoeias, and well-known as a flavouring agent in food and fragrance industry, has been reported to have potential beneficial effects in experimental models of Parkinson's, Alzheimer's and Huntington's diseases together with its well-known anti-inflammatory and antioxidant properties.

The Norwegian company Borregaard® produces vanillin from an aqueous alkaline oxidation of lignosulfonates (obtained from the sulfite pulping of wood) at high temperatures and pressures. Vanillin production can be maximized (i) in the presence of high O_2 pressure, with an (ii) operative temperature range of 120-200°C for (iii) short reaction times (30 min - 2 h) at (iv) high alkali concentrations (pH > 12). Vanillin and other value-added phenolic compounds (e.g., syringaldehyde) are generally extracted from reaction media using organic solvents while unreacted lignin is recovered by precipitation in acidic conditions.[23] Accordingly, the hydrolysis reaction of lignin allows the isolation of p-coumaric acid that is a compound of interest for nutraceutical and pharmaceutical industry for its antioxidant, anti-inflammatory, antineoplastic properties.

Relevant examples are available in literature for the preparation of APIs from lignin-derived chemicals. For example, vanillin could be used as starting material for the synthesis of valuable compounds including dihydrocapsaicin and dihydrocapsiate, with pharmacological properties for anti-inflammatory and anticancer applications.[24] In addition, ferulic acid, also a lignin derived chemical, could be upgraded for the preparation of indanones (via hydrogenation and subsequent cyclization) and beta-tetralones (through its conversion into acid chlorides, reaction with (trimethylsilyl)diazomethane) and further cyclization).[25]

Significant advances have also been made in the reductive upgrading of lignin into high value-added pharmaceutical ingredients and intermediates.[26] The reductive catalytic depolymerization of lignin is carried in the presence of a heterogeneous metal/bimetallic catalyst in the presence of a direct (H_2) or from an indirect (e.g., formic acid, tetralin, silanes, simple primary and secondary alcohols) hydrogen source and involves several reactions such as hydrogenolysis, hydrogenation and hydrocracking. These reductive processes are generally promoted by redox catalysts (Pd/C and Ru/C being the most adopted) in the presence of organic solvents (generally methanol, ethanol, 2-propanol, dioxane) used as such or of their mixture with water under relative mild conditions (150–250 °C for 2–8 h) both in batch and in a continuous apparatus. The main depolymerization products include syringyl, guaiacyl and tricin derivatives that can be used for the preparation of biobased drugs and chemical compounds with relevant pharmacological effects.

Furthermore, *m*-cresol, a lignin-derived compound, can be used as starting material for the preparation of (-)-menthol, one of the largest produced (with 30.000 metric tons per year) and demanded chemicals. Besides its well-known flavouring characteristics, being present in a wide range of products from food to oral hygiene and cosmetics, (-)-menthol also possesses analgesic properties. The synthesis of the aforementioned chemical, from *meta*-cresol, has been proposed through a two step approach based on the preparation of thymol via isopropylation, and its subsequent hydrogenation.[27] (-)-Menthol could be also produced from terpenoids, in particular, (+)-citronellal (obtained from the upgrading of citral oils) via isopulegol cyclisation.[28]

A new frontier in the synthesis of biobased drugs has been opened by Barta´s research group with the so called "cleave and couple" synthetic protocol in which the concurrent depolymerization of lignin and the formation of C−C and C−N bonds in monolignols facilitates the preparation of a series of 2-benzazepine derivatives (commonly used as antidepressants).[25]

Production of active pharmaceutical ingredients, nutraceuticals and bioactive compounds from food waste and lignocellulosic residues

The use of FL and LR to produce pharmaceuticals presents advantages with respect to fossil-based resources. Locally sourced feedstocks seem more favourable in terms of environmental, health, price, and security uncertainties over the short and long run. Bristol Myers Squib, for example, took advantage of bio-based materials already in 2004: the company replaced an 11-step route for paclitaxel (the API in Taxol) by harvesting it directly from plant cell cultures.[7] Furthermore, bio-based ethanol and 2-methyl tetrahydrofuran from biomass waste have entered the repertoire of solvents conventionally used in the pharma industry.[29]

In the following sections, selected examples of (1) pharmaceutical substances, reported with specific monographs in Western Pharmacopoeias (European Pharmacopoeia Ph. Eur. and United States Pharmacopoeia-National Formulary USP-NF) (2) nutraceuticals and (3) BCs (drug candidates) obtained from biomass resources from different origins will be discussed. For the sake of clarity about actual applicability, examples that have been already translated into practical applications will be disclosed.

Biomass-derived pharmaceutical substances in Pharmacopoeias

In a pharmaceutical context, biomass-derived platform molecules may find direct application as starting materials, reagents, and solvents, intended for production of intermediates, APIs or excipients. Successful cases of biomass-derived pharmaceutical substances include organic acids (succinic acid, lactic acid), amino acids (aspartic acid, glutamic acid), glycerol, sorbitol, xylitol.[30] It should be noted that any chemical to be employed as pharmaceutical should satisfy stringent pharmacopoeia purity requirements. A desirable outcome would be that the major role played by pharmacopoeias in ensuring the quality of APIs, excipients and drug products while protecting public health, would not conflict with the flexibility needed to encourage the advancement of new bio-based manufacturing technologies. Technical grade compounds derived from biomass can contain related substances (by-products/impurities) which represent an issue in pharmaceutical manufacturing. A notorious example is the use of diethylene glycol-contaminated glycerol for the preparation of acetaminophene syrup, which caused at least 80 children fatalities in the 90s in Haiti as a consequence of sudden kidney failure. Consequently, the USP monograph of glycerol and successively of other compounds (*e.g.,* sorbitol solution) were revised as requested by the Food and Drug Administration (FDA), including tests demonstrating the absence of diethylene and ethylene glycol.

According to the report of the European Commission, Directorate-General Energy, commercially available succinic acid is currently mainly obtained from biorefinery sugar fermentation.[31] Pharmaceutical grade bio-succinic acid has been recently produced under the FDA good manufacturing practices (GMP). Biosuccinium®, the trade name of succinic acid produced from renewable plant-based resources by Roquette S.p.A., complies with the high standard purity (99.5% min.) established by USP-NF; thus, it can be used as a pharmaceutical ingredient, as a buffer for the preparation of various formulations and for the synthesis of drug esters

(*e.g.,* antibody-drug conjugates). In general, succinylation of bioactive compounds results in related prodrugs whose by-product after cleavage (succinic acid) is safe. Succinylation is currently applied for the preparation of several drugs.

Bio-based L-(+)-lactic acid is produced as an enantiopure compound via sugar (glucose, sucrose, or lactose) fermentation. Biological routes are preferred to chemical syntheses mainly because the latter generates a racemic mixture, whereas the major demand is for L-(+)-lactic acid. L-(+)-lactic acid at the highest purity level finds application in the pharmaceutical industry as a chiral synthon. Additionally, it has been recently approved by the European Biocidal Products Regulation to be employed in human hygiene, as disinfectant (not for human applications), veterinary hygiene, food, and feed area, with the use as a preservative for products during storage also undergoing initial application for approval. Based on L-(+)-lactic acid produced by fermenting carbohydrates, followed by stringent purification techniques, Corbion N.V. produces a line of pharmaceuticals for many applications, e.g., Purasal/PF® contains sodium lactate used as API in i.v. solutions and different types of dialysis for Chronic Kidney Disease patients (CKD), like CAPD (Continuous Ambulatory Peritoneal Dialysis). Similar products commercialized with different names by Corbion are widely utilised in personal care products (oral care, skin care) and metal sequestration.

As APIs, both sorbitol and xylitol are currently employed not only for the treatment of occasional constipation, but also as osmotic diuretics removing the excess water out of the body (e.g., in brain swelling and acute kidney failure), by infusion of their solution (10-20% in sterilized water). Xivia®, xylitol by Dupont, produced by catalytic reduction of D-xylose form woody hemicellulose upon crystallization, is obtained with a purity over 99%, thus in compliance with Ph. Eur. and USP-NF.

Recovery of BCs by alternative extraction techniques

Valorization of residues from the food and agricultural industries can be analyzed from different perspectives, including the catalytic upgrading and, as a rising trend, the extraction of BCs. This leads to the environmentally friendly production of active ingredients having applications in different sectors, particularly the nutraceutical industry.

Even if the valorization of food and agricultural residues for the preparation of BCs can be considered as "intrinsically" sustainable, other factors including the extraction method and the employed reagents and solvents, also need to be taken into account. Extraction is the key step in the recovery of BCs from food loss and lignocellulosic agricultural/forestry residues. Classical techniques (e.g. Soxhlet extraction, hydro-distillation and maceration) are generally based on the use of solvents in possible combination with applied heat. These extractive processes are very simple to manage and can be easily scaled up at industrial level; however, they present several limitations such as (i) long time/energy-demanding procedures, (ii) poor selectivity, (iii) the necessity of purification steps and (iv) the large volumes of solvents. In this section, considering their environmental-friendly character, several extraction methods will be discussed, including microwave-assisted, ultrasound-assisted, mechanochemical-assisted and enzymatic-assisted extractions (Fig. 6).

Towards the development of more cost-efficient procedures for the extraction of BCs from FL, the incorporation of alternative technologies is highly needed. In this regard, microwave-assisted strategies are a noteworthy opportunity due to their multiple advantages including the possibility to decrease process time and to increase product yields as well as the rapid and localised heating (often leading to unique chemical behaviour).

Microwave-assisted extraction (MAE) has demonstrated its suitability, for instance, in treating walnut-shell residues.[32]
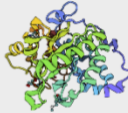
TYPE OF EXTRACTION	CONVENTIONAL (soxhlet, distillation, maceration)	MICROWAVE	ULTRASOUND	MECHANOCHEMICAL	ENZYMATIC
Advantages	High simplicity Easy scalable	Improved selectivity High yields Short extraction times	High energy-efficiency High yield Short extraction times Cost-effectiveness	Reduced use of solvents and reagents Short extraction times Simplicity	Use of water as main solvent High extraction selectivity and yield
Limitations	Long time/energy demanding procedures Poor selectivity Large volumes of solvents	Low yields towards the extraction of nonpolar compounds Unfit for heat-labile biomolecules	Need of optimization of the system (geometry, frequency, power and cycle propagation)	Lower recovery yields of phenolics	High cost of enzymes Low operational and storage stability of enzymes, hindering scalability
Extracted compounds	Phenolics, lipids/fat, oils	Phenolics	Phenolics, chlorophyll, carotenoids and lipids	Phenolics	Phytochemicals

Fig. 6. Comparative analysis of several approaches for the extraction of nutraceuticals from biomass-derived residues.

Additionally, microwave-assisted extraction allowed pilot scale production for the treatment of citrus peel towards pectin production. An LCA study of this pilot plant, fundamental to estimate the environmental impacts and resources used all over a product's life cycle, has been also reported.[33] Such analysis revealed that, even if avoiding the use of hydrochloric acid could have an inherent advantage associated to the elimination of acid derived residues, its overall environmental impact is negligible, considering the energy savings achieved by using HCl. At pilot scale premises, the microwave-assisted extraction was compared with conventional thermal techniques, pointing to improved green credentials (more environmentally friendly) and a feasible alternative to conventional extraction.[33]

The use of ultrasound irradiation could also offer a broad range of possibilities, going from laboratory to industrial applications, since it constitutes one of the less energy consuming strategies, as well resulting in a minimum formation of side-products. As compared to conventional protocols, ultrasound-assisted approaches could result in unexpected mechanisms and enhanced reaction kinetics. The extraction of BCs during ultrasound-treatment occurs due to the localized stirring, as consequence of the cavitation phenomenon.[34]

Mechanochemistry could be defined as a chemical reaction that is induced by the direct absorption of the mechanical influence. Mechanochemical methods could result in highly efficient and sustainable processes, reducing the use of solvents and required times, being reproducible, versatile and simple. Unlike thermal-assisted protocols, mechanochemical processes occur under the effect of unbalanced mechanical forces; hence a different chemical and physical behaviour of the reactants is expected. Mechanochemical methods for the extraction of BCs have been explored with various food and agricultural residues. Mechanochemistry exhibited, so far, optimum results in terms of recovery yields and processes time with respect to conventional techniques e.g. Soxhlet extraction.[35]

Enzymes could also be employed as systems with high selectivity and specificity for the extraction of valuable bioactive compounds under moderated conditions, avoiding the use of harmful reactants. Indeed, the enzyme-assisted extraction is a highly sustainable approach to obtain high-added value chemicals for nutraceutical applications including polyphenols and polysaccharides. In this case, it is relevant to have a better understanding of both, the extraction and the hydrolytic characteristics of the enzyme, as well as its interaction with plant cells. Enzyme-assisted extraction is based on the arrangement of the enzyme structure to achieve a better interaction between the desired substrate and the active centres of the enzyme.[36]

Hydrolases are among most common enzymes able to catalyse the hydrolysis of chemical bonds within the cell wall of polysaccharides. The use of enzymes implies also to consider different parameters including temperature and pH, in order to avoid proteins denaturalization. In any case, the use of mild extraction temperatures leads to improved energy-consuming and cost-efficient processes.[36] Cellulases, pectinases and glucanases constitute most employed extraction enzymes.

Nutraceuticals extracted from food loss and lignocellulosic residues

Herbal & Antioxidant Derivatives (H&AD) is an Italian company that is marketing worldwide food supplements and nutraceuticals from the waste of bergamot's industry processing. The peel of the bergamot fruit (*Citrus bergamia*) is widely employed by the perfume industry for its essential oil, while the fruit itself (pulp and juice) is considered waste. H&AD re-evaluated the use of bergamot waste by exploiting its high polyphenol content (which can lead to soil contamination if not properly discarded/valorised). H&AD patented an innovative process involving ultrafiltration and absorptive extraction to provides a nutraceutical composition marketed as Bergacyn®. The benefits of Bergacyn® are supported by clinical research in patients. Notably, in 2019, H&AD established a partnership with US natural product company DolCas biotech LLC, to further implement the sourcing of nutraceuticals from upcycled raw materials.[37]

Another collaborative project among Swisse Wellness, the Fight Food Waste Cooperative Research Centre, Viridi Innovation Pty Ltd, Austeng and Swinburne University of Technology aims to convert grape residues (skins and seeds) from Australian wine industry into nutraceutical ingredients. Due to the high polyphenol content, the majority of winery waste ends up as toxic soil. This project will utilize 250 tonnes of predominantly Pinot marc to produce grape seed extract from the 2020 vintage to go into the Asian market.[38] A novel procedure, based on microwave-/ultrasound-assisted extraction, followed by incubation with enzymes from *Basidiomycete* and *Ascomycete fungi*, to extract polyphenols from grape waste has been patented. As for 2021, the laboratory stage validation has been successfully accomplished and an industrial scale pilot plant is being built.[39]

Another example of FL exploitation to nutraceuticals is that pursued by the Danish biotech startup Kaffe Bueno. Kaffe Bueno upcycles spent coffee grounds (SCG) to active and functional ingredients for nutraceuticals, functional foods and cosmetics. SCG are a valuable source of antioxidants and fatty acids with multiple health benefits.[40] Kaffe Bueno has developed a biopreservation system and optimized a supercritical CO_2 extraction to produce a lipid fraction. The resulting defatted coffee grounds shows still high content of protein (4/9 essential amino acids) and insoluble dietary fibres. Currently, three products are on the market (Kaffe Bueno Oil®, Kafflour® and Kaffibre®), employed as ingredients in nutraceuticals and cosmetics, as well as food additive. In June 2020, Kaffe Bueno partnered with Givaudan – the Swiss-based global leader of beauty ingredients – to market its coffee oil under the trade name Koffee' Up®. Importantly, Kaffe Bueno aims to reach a capacity of 1,200 tonnes of SCG processed per year by 2026. Another success story is that of Repolar Pharmaceuticals in the 2000s. Based on a Norwegian traditional medication used for treating wounds, a multidisciplinary team developed a resin-based product starting from resin collected from Norwegian Spruce Tree (*Picea abies*) damaged by events, such as lightning strikes.[41] The resin is a complex mixture of acids (e.g., abietic, neoabietic,

dehydroabietic, pimaric, and palustric acids) and lignans (e.g., pino-, larici-, matairesinol, and p-hydroxycinnamic acid), which has been shown to possess antimicrobial and anti-inflammatory properties and to promote re-epithelialisation. In 2008, Repolar launched a resin-based ointment named Abilar®. The commercial production of Abilar® has reached a stable level of sales over the years.[42]

Synthesis of APIs from LR

According to the World Health Organization (WHO), the definition of an API is any substance used in a finished pharmaceutical product, whose ultimate goal is to furnish a pharmacological activity or some direct effect in the diagnosis, treatment or prevention of a disease. Bio-based chemicals have a significant potential to replace fossil-based counterparts as starting reagents for API synthesis. However, to the best of our knowledge, there is no API that currently produced starting from bio-based sources.
Furan moieties are present in a wide range of pharmacophores. For instance, furosemide is a widely prescribed drug for the treatment of fluid retention related to heart problems, liver and kidney diseases and has been recognized as one of the most effective and safe products, according to the list of Essential Medicines from the WHO.[43] Such pharmaceutical product (4-chloro-N-furfuryl-5-sulfamoylanthranylic acid) could be synthesized by reaction between 5-aminosulfonyl-4,6-dichlorobenzoic acid and furfuryl amine. In particular, furfuryl amine could be directly obtained from furfural through reductive amination processes.

In another example, furfural could be employed for the preparation of ancarolol. Such compound could have potential applications as beta-blocker, representing an alternative for other commercial antihypertensives (e.g. atenolol), and its structure is based on a furan ring, an *ortho*-aminophenol unit and glycerol-derived moiety.[44]

5-(chloromethyl)furfural (CMF), has been proposed as a building block for synthesizing ranitidine (**1**), a drug currently used to treat peptic ulcer and gastroesophageal reflux disease.[45] **1** is a member of the class of furans, acting as a histamine H_2-receptor antagonist, thus inhibiting gastric acid secretion. In a retrosynthetic analysis, a structural similarity was observed with CMF, where the introduction of the (dimethylamino)methyl group could be achieved by reductive amination of the aldehyde carbonyl group, and the sulfide bond generated by the nucleophilic substitution on the chloromethyl functionality (Scheme 1).
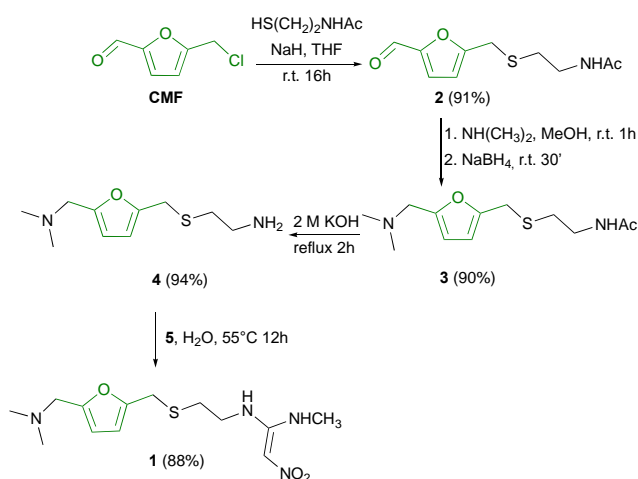
Scheme 1. Biomass-derived CMF as starting material for the synthesis of **1**.

Compared to the original patent synthetic route, both are four-steps processes. However, the patented synthetic protocol starts from the reduction of furfural, followed by aminomethylation and two consecutive nucleophilic substitutions involving cysteamine and 1-methylthio-1-methylamino-2-nitroethylene (**5**) (yields of first three steps are <50%). In contrast, the synthesis developed by Mascal *et al* is simpler, accessible and more efficient, involving the substitution of the chloride of CMF with commercial N-acetyl-cysteamine (91% yield).[45] The simple reductive amination of **2** with dimethylamine gives **3** in 90% yield, which is then deprotected, via KOH hydrolysis, to **4** (94%). Substitution at the primary amine with **5** is also a simple step and affords **1**, culminating in an overall 68% yield.
Given the high yields and by-products generation that can be easily removed by non-chromatographic methods, this synthetic protocol provides a sustainable and efficient alternative to the previously reported route and a potentially more economic access to this API.

Paracetamol **6** (acetaminophen) is another notable example of an API that can be potentially derived from biomass **6**,[46] included in the WHO List of Essential Medicines as one of the most consumed analgesics and fever-reducing APIs worldwide. Despite the relative simplicity of its structure, many routes have been explored for its production over the last century. However, the majority

of them are based on the acetylation of *p*-aminophenol **7** as the final step. This is the reason why the sustainable access to this key intermediate is of particular interest. An inexpensive method for producing **6** from biomass-derived *p*-hydroxybenzamide has been recently patented.[46] A remarkable feature of the process is that *p*-hydroxybenzamide can be produced from *p*-hydroxybenzoate, derived from the lignin fraction of biomass residues. In detail, *p*-hydroxybenzamide is formed when *p*-hydroxybenzoate is pretreated with ammonia in an extractive process. Compared to the current industrial protocol (involving nitration and further reduction of the petrochemically-derived phenol to afford **7**), this synthetic route utilizes a low-cost Hofmann-type reaction to achieve the desired conversion. The Paracetamol could be also potentially derived from terpenoids feedstocks. Terpenes could constitute a sustainable alternative for the preparation of this important pharmaceutical product. In particular, β-pinene, which could be readily obtained from residues generated in the pulp and paper industries, constitute a possible starting synthon for the synthesis of paracetamol.[47]

As illustrated in Scheme 2, the Hofmann-type rearrangement proceeds by dissolving *p*-hydroxybenzamide in alkaline water, followed by addition of sodium hypochlorite. Acetylation of **7** with acetic anhydride affords **6** in 82% yield. Such sustainable synthetic procedure for the preparation of a blockbuster drug such as paracetamol (**6**) might be useful for the pharma industry.
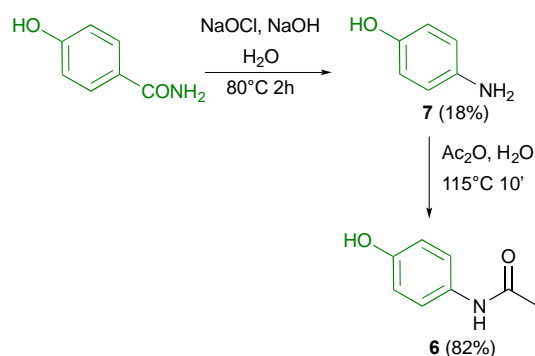
Scheme 2. Biomass-derived *p*-hydroxybenzamide as starting material for the synthesis of **6**.
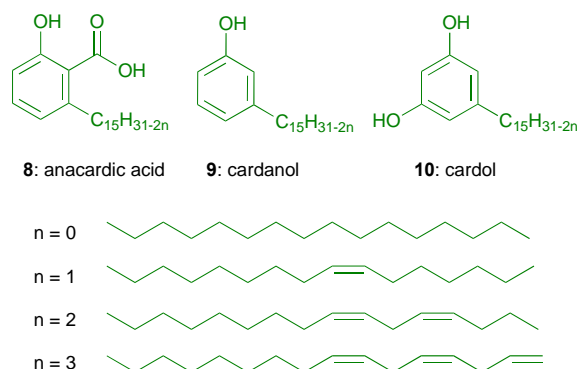

Fig. 7. Chemical structures of CNSL components **8**-**10**.

A sustainable conversion of cashew nut shell liquid (CNSL)-biomass into a building block that can be easily transformed into an API has been recently reported by Shi *et al.*[48] CNSL is a FL generated from cashew nut processing, with no sustainable disposal. Chemically, CNSL mainly consists of phenolic lipids, i.e., anacardic acid **8**, cardanol **9**, and cardol **10**, whose pentadecyl alkyl side chains show a variable degree of unsaturation, depending on the production method (Fig. 8).

Starting from the intriguing structural features of CNSL components (aromatic and olefin functional groups), Shi *et al.* successfully developed a synthetic protocol to phenylephrine (**11**) (Scheme 3).[48] Phenylephrine belongs to the class of phenylethanolamines, mediating on vasoconstriction, mydriasis and nasal decongestion by acting as an α-sympathomimetic agent. The original manufacturing method involves an eight-step process requiring multiple protection and deprotection reaction steps, which are not necessary in the proposed novel synthetic protocol (Scheme 3).
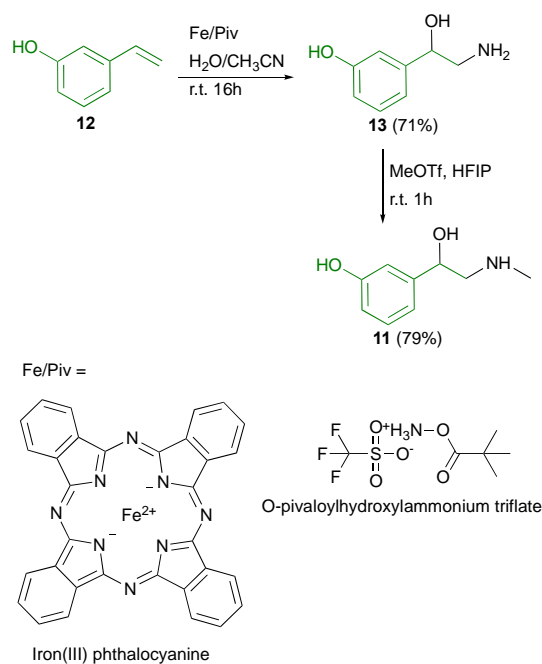
Scheme 3. Biomass-derived 3-vinylphenol (**12**) as starting material for the synthesis of **11**.

In fact, the developed synthesis of **11** involves 3-vinylphenol (**12**) as starting compound, directly produced from cardanol by ethenolysis, followed by isomerising metathesis. The ensuing hydroxyamination reaction on the double bond of **12** in the presence of an iron catalyst and O-pivaloylhydroxylammonium triflate furnishes **13** in 71% yield. To avoid protecting/deprotecting hydroxyl groups, a selective methylation of the primary amine of **13** has been achieved by employing 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent and methyl triflate (MeOTf) as methylating agent, providing **11** in high yields (79%). The proposed synthetic protocol, starting from inexpensive cardanol, an inedible CNSL component, may allow the sustainable conversion of CNSL-derived 3-vinylphenol to phenylephrine (**11**).

**Novel bioactive molecules synthesized starting from FL and LR**

In addition to pharmaceutical and nutraceutical substances, the use of biomass (both FL and LR) holds promise to the generation of new BCs to be then optimized/converted into new drugs. BCs can be defined as novel compounds that exert biological/pharmacological effects but, being at an early stage of the pharmaceutical investigation, still do not meet few drug-likeness criteria including high activity for the target protein, the absence of effect on other targets and optimum pharmacokinetic properties. Clearly, they are not present in pharmacopoeias as they have not received regulatory approval.

As a starting material for the synthesis of new BCs, FL and LR offer economical and ethical advantages with respect to both fossil-based and natural chemicals currently used for medicinal chemistry activities being: (i) an inedible raw material not depleting natural resources; (ii) able to promote waste valorisation. In addition, BCs are drug precursors, more market-competitive than other chemicals (e.g., adhesives or additives), thus better and ensuring the economic sustainability of the whole process.

Food waste CNSL has been recently exploited for the synthesis of biologically active phenolic derivatives, which could potentially lead to new drugs. Despite the wide range of biological activities, CNSL phenolic lipids (**8-10**) themselves are not active enough for a realistic therapeutic application. Approaches aimed to the synthetic elaboration and diversification towards more complex biologically-active molecules, to be further optimized into drug candidates, consequently deserve to be pursued.

In this context, the use of CNSL represents a key opportunity especially for neglected tropical diseases (NTD) drug discovery, since tropical/subtropical countries (South Asia, Africa, South America) are among the largest CNSL-producers (also most affected by such diseases). Bolognesi and colleagues argued to obtain semi-synthetic derivatives of CNSL by applying a medicinal chemistry strategy aimed to provide synergy and increased potency for hybrid drugs.[49] In particular, the chemical structures of CNSL derivatives (**14**-**16**) and that of 2-phenoxy-1,4-naphthoquinone (**17**), endowed with a trypanocidal profile, were combined. A simple, accessible and scalable protocol based on a nucleophilic substitution to combine CNSL phenols **14-16** and 2-bromo-1,4-naphtoquinones **33-37** was developed. This, coupled with the cheapness and easily availability of the starting material, should make the entire production process, potentially affordable on a local basis. The synthesized derivatives inhibited parasite growth, displaying rapid trypanocidal activity in the low micromolar range and no discernible toxicity on human cell lines. Their mode of action appeared to be linked to mitochondrial damage.[49] Accordingly, a small library of hybrid drugs **18-32** was designed and synthesized, with general structures reported in Scheme 4.

While further rounds of optimization are required before these BCs can be turned into valuable drugs for NTD, such CNSL-based hybrids appear promising. Importantly, the utilization of CNSL and its components for combating NTD could be of high importance and economic feasibility in developing countries that cultivate and process cashew (e.g., Africa, India, Brazil) and, at the same time, represent endemic areas.
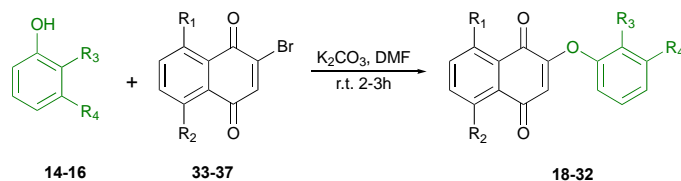
Scheme 4. CNSL as starting material for the synthesis of hybrid drugs **18-32.**

Conclusive remarks

A unified view on the upgrading of food loss and lignocellulosic residues into value-added chemicals for pharmaceutical and nutraceutical applications has been provided.

Presently, biowaste feedstocks are employed biorefineries for the production of biofuels and chemicals. This type of upgrading is short-sighted since a complete valorisation of food waste and lignocellulosic residues should be replaced with a cascade high-to-low value approach where bioactive compounds and pharmaceutical intermediates can be obtained before biowaste conversion into bulk chemicals and especially biofuels or renewable energy (low value) (Fig. 7).

The remarkable potential of food and agricultural residues, as unexpensive and renewable feedstocks, for the preparation of pharmaceutical and bioactive compounds should be exploited but importantly considering the environmental impact of the overall production process. These include catalysed approaches, the use of green solvents, short reaction times, moderated conditions and simple separation and purification steps as well as overall positive LCA and techno-economic assessments.

Pharmaceutical and nutraceutical industries need to be reoriented to the use of biomass-based feedstocks. In this regard, various scientific and technological challenges need to be addressed including (i) the direct use of agro-industrial and domestic wastes as feedstocks; (ii) the development of more efficient catalysts for the desired chemical transformations that can be easily recoverable from reaction media; (iii) the adoption of efficient and low energy-demanding separation and purification methods; and (iv) the implementation of continuous processes that can operate at industrial scale.

After analysing the ongoing progress and the illustrative examples described in this review, the use of biomass in the production of nutraceuticals and pharmaceuticals will soon take off, although at different extents. Being not distinct from other food-derived categories, nutraceuticals are not regulated in the same way that drugs are. Due to the lack of stringent regulatory constraints with respect to safety, efficacy, quality testing and marketing authorisation procedures, FL could easily replace nature as a source of bioactive compounds in nutraceutical formulations. Unfortunately, the same does not apply to pharmaceutical products. First, the replacement of a fossil fuel-based raw material with a bio-based counterpart for the manufacturing of an API is not so straightforward. Critical requirements are the quality and purity characteristics of the starting material, to ensure the safety of the patient population, and good manufacturing practice (GMP) standards. Secondly, the road from biomass components to new drugs is even more complex. These molecules must undergo several rounds of "tailor-made" manipulation of the structure so as to comply with stringent drug-likeness criteria.

A highly effective conversion of inexpensive, abundant, renewable biomass to valuable products will encompass a number of disciplines and wide expertise; not something one sector/company can do on their own. Additionally, effective solutions to valorise food loss and lignocellulosic residues as well as efficient supply chains are foremost necessary. The implementation of novel technologies, not just at lab scale but importantly at industrial premises is, at the same time, a significant challenge that needs to be further addressed.

These all sound a highly challenging dream which in any case should encourage scientists to redouble efforts on the waste-to-pharma concept for the potential benefits on human and animal health as well as for a more sustainable future.
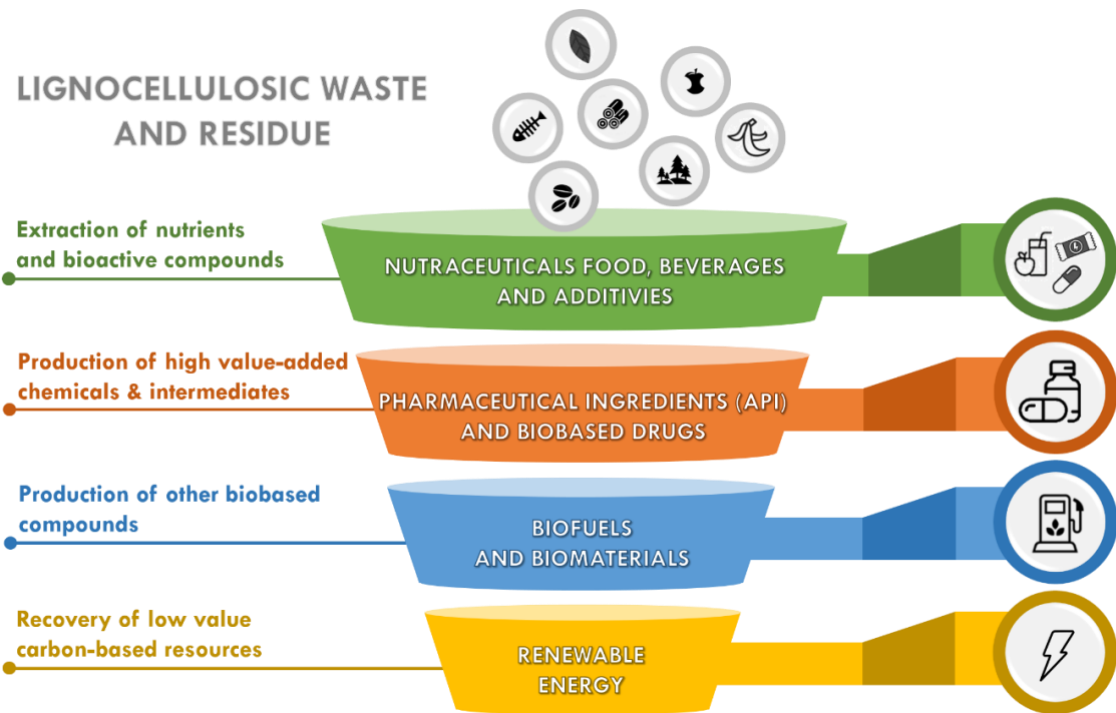
Fig. 7. High-to-low value cascade approach for the valorization of biomass-derived wastes and residues.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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