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ROYAL SOCIETY OF CHEMISTRY

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Silao de la Victoria, Gto, Mexico, August 21th 2025

SUSTAINABILITY SPOTLIGHT STATEMENT
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Agricultural and industrial biomass residues are generated in large quantities and, when underutilised, drive waste accumulation and environmental burdens. Simultaneously, conventional extraction processes still rely on fossil-derived solvents, perpetuating unsustainable production. Tackling both issues is crucial to reducing waste and promoting renewable alternatives. This review showcases sustainable advances in recovering high-value bioactive compounds through green solvents, solvent recyclability, and integrated biorefinery strategies, offering scalable and cleaner pathways than traditional methods. These innovations valorise waste, enhance resource efficiency, and minimise chemical hazards. The work aligns with UN SDG 12 (Responsible Consumption and Production) and SDG 9 (Industry, Innovation, and Infrastructure) by fostering circular economy models, while also contributing to SDG 3 (Good Health and Well-being) and SDG 13 (Climate Action).

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REVIEW

Recovery of Bioactive Plant Compounds from Biomass Waste Using Sustainable Methods: A Review

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The circular bioeconomy promotes the sustainable use of renewable biomass to enhance resource efficiency and reduce environmental impacts. In this context, residual plant biomass is an underutilised feedstock rich in high-value bioactive phytochemicals, including terpenes, phenolic compounds, and nitrogen-containing metabolites, with applications in the food, cosmetic, nutraceutical, and pharmaceutical sectors. However, their selective recovery remains challenging due to the complexity of plant matrices and the technical, economic, and environmental constraints of conventional extraction processes. This review critically examines recent advances in green extraction and purification technologies for the recovery of bioactive secondary metabolites from agricultural and medicinal plant residues. Environmentally benign and intensified methodologies—such as supercritical fluid extraction, deep eutectic solvents, microwave- and ultrasound-assisted extraction, and enzyme-assisted processes—are discussed with emphasis on matrix-dependent behaviour, scalability limitations, and integration potential within biorefinery frameworks. Techno-economic aspects, including capital and operational costs, industrial feasibility, and broader environmental, circularity, and societal considerations, are also addressed. Overall, this review provides a balanced perspective on the opportunities and limitations of sustainable bioactive recovery pathways.

Keywords: Green Extraction, Circular Bioeconomy, Biomass Valorisation, Sustainability, Biorefinery, Phytochemicals, Deep Eutectic Solvents, Supercritical Fluid Extraction.

1 Introduction.

Since the Second Industrial Revolution, human activity has exerted profound pressure on the environment, accelerating climate change and biodiversity loss. At the core of this environmental degradation lies a predominantly linear economic model that, although key to improving quality of life, has come at the cost of depleting finite natural resources.[1]

By contrast, the circular economy offers an alternative model that seeks to redefine growth by decoupling economic activity from the consumption of limited resources.[2,3] Within this framework, residual biomass has emerged as a renewable feedstock rich in phytochemicals with high functional and market value, offering bio-based substitutes for fossil-derived ingredients in the pharmaceutical, cosmetic, and food industries, and occupying a unique position among renewable sources for its capacity to supply energy while enabling the production of biobased products.[4] Globally, about 181.5 billion tonnes of waste biomass are produced annually, but only 8.2 billion tonnes of lignocellulosic biomass are currently used.[5] Among these resources, medicinal and aromatic plants (MAPs) stand out for their biochemical diversity and for producing approximately 330 million tonnes of residues annually from essential oil and herbal processing.[6] These residues represent a source of bioactive molecules that could support a transition toward sustainable value chains.

Phytochemicals are naturally occurring compounds commonly grouped into three major classes: terpenes, phenolic and nitrogen-containing compounds.[7] Recovering these molecules from biomass by-products both valorises waste and supports carbon neutrality,[8] advancing climate targets by supplying renewable carbon feedstocks.[9]

The sustainable development and utilisation of plant extracts and natural products offer a significant opportunity to strengthen the global bioeconomy, particularly in developing regions where biodiversity and agricultural residues are abundant. These natural compounds play crucial roles in four interrelated sectors of high socio-economic impact: food ingredients, flavouring agents and spices, perfumes and cosmetics, and pharmaceuticals.[10] Notably, between 1981 and 2019, approximately 60% of newly approved drugs were either natural products, derivatives, or synthetic mimetics inspired by natural structures, underscoring the continued relevance of nature-based solutions.[11]

Despite recent progress, the extraction, fractionation, and purification of phytochemicals from biomass remain technically challenging, often involving solvent-intensive, energy-demanding processes that are difficult to scale.[12] The development of green and selective extraction technologies is therefore essential to unlock the

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full potential of biomass within a circular bioeconomy. Recent studies have increasingly focused on such valorisation strategies, emphasising environmentally benign processes tailored to specific biomass matrices.[13]

Within this context, this review provides a focused overview of recent advances in green extraction and purification of secondary metabolites from plant-based residual biomass. It highlights environmentally sustainable, selective, and scalable methodologies. It deliberately excludes conversion routes that do not preserve molecular integrity (e.g., pyrolysis, gasification, fermentation, or other processes that transform native scaffolds). To promote clarity and comparability, the discussion is organised by product application into six categories: (1) Pigments and Natural Colourants; (2) Flavours & Fragrances; (3) Pharmacologically Relevant Metabolites; (4) Lipophilic Bioactive Compounds; (5) Natural Antioxidants and Phenolic Compounds; and (6) Agrochemicals. This structure elucidates the distinct challenges and opportunities within each category, guiding the design of biorefinery models that efficiently integrate green extraction strategies into high-value product chains.

2 Search strategy and data sources.

This review employed a structured, systematic literature search to identify, assess, and critically analyse studies on the recovery of bioactive phytochemicals from plant-based biomass waste.[14] A multi-database search was conducted using Scopus, Web of Science, PubMed, and SciELO.

Search queries combined keywords and Boolean operators. Core terms included biomass waste, agricultural by-products, green extraction, sustainable purification, phytochemicals, bioactive compound recovery, deep eutectic solvents, supercritical fluid extraction, enzyme-assisted extraction, and biorefinery valorisation. To ensure temporal relevance, priority was given to publications from 2015 to 2025, while seminal earlier works were retained when necessary to provide conceptual or methodological context.

Studies were selected based on their relevance to residual plant biomass, the level of methodological detail provided, and their potential to inform discussions on selectivity, scalability, process integration, and sustainability.

Eligible records included peer-reviewed journal articles and book chapters reporting the isolation or targeted recovery of bioactive secondary metabolites from plant-derived residues. Both conventional extraction techniques and green methodologies were considered. Conventional techniques were included when they served as relevant benchmarks for evaluating the advantages and limitations of greener alternatives. Studies focusing exclusively on thermochemical conversion routes, non-plant biomass, or crude extracts without purification were excluded.

All records were imported into a reference management software, and duplicates were removed prior to screening. Titles and abstracts were evaluated against predefined inclusion criteria, followed by full-text assessment of potentially relevant studies. The literature screening and selection process was conducted by the authors, with particular emphasis on methodological transparency, relevance to residual plant biomass, and applicability to sustainable extraction and purification schemes. Data were extracted using a standardised form that captured biomass source and yield, extraction method, and key parameters. To minimise omissions, backward citation tracking of all included studies was also conducted to identify additional relevant publications.

3 Selected Phytochemicals from Biomass Waste.

Biomass contains both primary and secondary metabolites; the latter, due to their bioactivity and broad industrial relevance, are key targets in modern biorefineries. Current efforts progress along two complementary avenues: (I) Developing profitable and sustainable methods for extracting and purifying high-value compounds; (II) Sourcing these bioactive compounds from non-edible feedstocks, particularly agro-industrial residues. Below, we describe selected examples of naturally occurring products whose isolation is of interest due to their biological and industrial properties.

3.1 Pigments and Natural Colourants.

Dyes are essential compounds widely used in industries such as textiles, printing, cosmetics, and food, to provide colour to different materials. Chemically, they are chromophoric substances that interact with substrates, absorbing characteristic wavelengths of light and resulting in visible colour. Most dyes contain conjugated π-electron systems that determine their light absorption properties and the hues they produce.

Natural dyes, obtained from renewable plant, animal, or marine sources, are gaining renewed importance as sustainable alternatives to synthetic dyes. They are biodegradable, non-toxic, and typically require minimal chemical processing, which reduces pollution and health risks. Compounds such as anthocyanins and flavonoids, together with carotenoids and chlorophylls, not only provide a wide range of natural colours but also exhibit antioxidant and antimicrobial activities, arising from their distinct chemical structures. Although their current applications are still limited, primarily in the food industry and, to a lesser extent, in textiles and coatings, ongoing research and innovation are expanding their potential, positioning natural dyes as key components in the transition toward a more sustainable and environmentally conscious industry.[15] Next, we present selected natural dyes and the extraction methods used to obtain them, highlighting their scalability and applications.

3.1.1 Lycopene. Lycopene **1** (Scheme 1), the red carotenoid responsible for the characteristic colour of tomatoes, is one of the most abundant dietary carotenoids and exhibits outstanding antioxidant activity, making it relevant to food preservation, functional foods, cosmetics, and pharmaceutical applications.[16]

Table 1 compares selected green extraction technologies relevant to lycopene **1** recovery from tomato-processing residues, highlighting key conditions, yields/purity, and the main advantages and limitations.

Traditionally, lycopene **1** has been extracted from tomato-processing waste using organic solvents such as *n*-hexane (*n*Hex), acetone, and ethyl acetate (AcOEt), achieving high purities (94–98%).[17] However, environmental and safety concerns associated with volatile organic solvents have driven a transition toward greener extraction strategies.

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Table 1. Comparison of selected green extraction technologies relevant to lycopene **1** recovery from tomato-processing residues.

Entry	Biomass	Scale	Methodology	Optimal conditions	Recovery (%)	Purity (%)	Key findings	Ref.
1	Tomato pulp waste without seeds	1 g	Maceration extraction optimised via FFD[a]	20 °C, 40 min; solvent: 25% acetone in *n*Hex (v/v); solvent volume: 40 mL.	94.7	98.3	Simple & scalable. High-purity all-trans lycopene. Minimises isomerisation and degradation	17a
2	Non-pretreated tomato peels	1-50 g	Maceration. Mixture design optimisation. Ternary solvents.	40 °C, 30 min, Optimised solvent %: 30.6 *n*Hex, 32.8 EtOH, 36.6 acetone	> 95		Tomato oleoresin with 13% (w/w) lycopene Strong antioxidant capacity (1582 µmol TE/g)	17c
3	Tomato skin	Lab	UAE, MAE,[b] PAE,[c] and combined MUAE[d]/UPAE[e] using green solvent (EtOH: AcOEt 2:3 v/v);		UPAE: 3.56% (highest); MUAE: 3.49%		UPAE showed the highest extraction efficiency and antioxidant activity.	18b
4	Tomato peel	Lab	Maceration in ROO[f] optimised by Box–Behnken Design	80 °C, 400 rpm, 45 min, 2.5% w/v peel: ROO ratio	99.3%		Enhances the oxidative stability and nutritional properties of ROO	19
5	Tomato peel	Lab	Enzymatic pretreatment + UAE, using *n*Hex	UAE: 15 min, 25–45 °C, after 180 min enzymatic treatment	1,018–1,120 mg/kg extract		Enzymatic hydrolysis enhanced lycopene release, UAE increased lycopene extraction	20
6	Tomato paste	60 g	$ScCO_2$,[g] factorial design; effect of T, P, flow rate, EtOH cosolvent	55 °C, 300 bar, 2 h, 4 kg/h CO_2 flow, 5% EtOH	53.9		Milling improves extraction; higher temperature and pressure raise yields but risk degradation.	22a
7	Tomato peel + seed (37:63 w/w)	4 g	$ScCO_2$, evaluation of temperature, pressure, flow rate, and seeds' role	90 °C, 40 MPa, 180 min, 2–4 mL/min CO_2	56% (vs 18% without seeds)		Seed oil enhanced lycopene extraction efficiency. Some losses occurred.	24a
8	Tomato skin	100 g	RSLDE[h] with Naviglio Extractor; pressure/depressurisation cycles; comparison with conventional solvent extraction	≈ 10 h, 60 pressure cycles; water as extraction fluid; SPE[i] purification with MeOH/acetone		>98%	Water enables fast, gentle extraction, yielding high-purity lycopene for nutraceutical use.	31b

[a]FFD: Full Factorial Design; [b]MAE: microwave-assisted extraction; [c]PAE: Pulsed electric field-assisted extraction; [d]MUAE: Low-temperature microwave-ultrasound-assisted extraction; [e]UPAE: electric field (PEF) and power ultrasound (US); [f]ROO: Refined Olive Oil; [g] Supercritical CO_2 ($ScCO_2$); [h] RSLDE**:** Rapid solid–liquid dynamic extraction; [i]SPE: Solid Phase Extraction.

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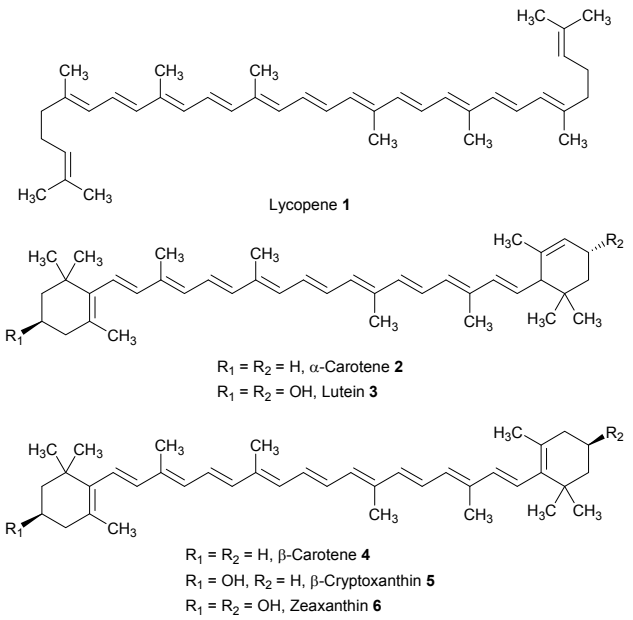


Scheme 1. Chemical structures of lycopene **1** and other carotenoids.

As solvent-lean alternatives, recent studies have explored ultrasound-assisted extraction (UAE), either alone or combined with other emerging intensification tools such as microwave irradiation and pulsed electric fields, in conjunction with green media such as natural deep eutectic solvents (NADES).[18]

Edible oils, such as olive or sunflower oil, provide a food-grade medium that can both solubilise lycopene and enhance the oxidative stability of the extract. Olive oil maceration has achieved up to 99.3% recovery under optimised conditions (80 °C; 2.5% w/w biomass-to-oil), yielding 35 mg of lycopene **1** per kg of oil.[19] UAE enhances mass transfer, resulting in a recovery rate of approximately 87% using sunflower oil as solvent.[20] Nevertheless, oil type and processing intensity critically affect carotenoid stability. For example, high-intensity ultrasound can degrade labile constituents; hence, milder green conditions are recommended.[21]

Complementary to edible-oil maceration and UAE, $ScCO_2$ offers an environmentally friendly route to recover lycopene **1** from tomato by-products, typically affording high pigment purity. Extraction performance is governed by pressure–temperature coupling (higher values generally increase recovery), whereas temperatures >80 °C risk thermal degradation.[22] A major bottleneck is mass-transfer resistance across the chromoplast–cell-wall matrix; pretreatments such as milling or enzymatic hydrolysis mitigate this barrier and improve release.[23] Co-solvents (e.g., EtOHl, vegetable oils) broaden solvating power and can markedly increase recoveries.[24] Mechanistically, Squillace *et al*. quantified lycopene **1** solubility in tomato seed oil (ca. 460 µg g^{-1}) and showed preferential solubility for Z-isomers, thereby supporting the use of oil co-solvents to enhance mass transfer and overall yields.[25]

Addressing these matrix barriers directly, enzyme-assisted extraction depolymerises pectic and cellulosic structures, thereby enhancing lycopene **1** release. Since the mid-2000s, converging evidence has shown that pectinase-based preparations, particularly those containing polygalacturonase (PG) and pectin lyase (PL), are more effective than cellulase (CL) alone for extracting lycopene **1** from tomatoes; when pectinases and cellulase are applied together, their complementary action on the pectic matrix and the cellulose–hemicellulose network synergistically disrupts cell walls and facilitates chromoplast release.[26] Building on this principle, enzyme-assisted workflows that couple PG/PL/CL pretreatment followed by solvent extraction deliver lycopene-rich oleoresins, and optimisation further enhances phenolic content and antioxidant capacity.[27]

Moving toward greener alternatives, Cuccolini *et al*. developed a solvent-free process based on pH shifting and enzyme-assisted cell lysis. Using Prolyve 1000®, a protease derived from *Bacillus licheniformis*, they achieved up to 10% lycopene (w/w, dry basis), a 30-fold increase over untreated peels.[28] This approach was later optimised by Lombardelli *et al*., who tailored the enzymatic blend—PG and PL (26%), CL (57%), and xylanase (XL, 17%)—to the cell-wall composition of ripe tomatoes, further improving extraction efficiency.[26] In parallel, process intensification via ultrasound can act synergistically with enzymatic hydrolysis. Ladole *et al*. co-immobilised pectinase and cellulase on amino-functionalized magnetic nanoparticles and observed a ca 30% increase in lycopene yield from non-pretreated tomato peels when ultrasound and enzymes were applied simultaneously.[29] Consistent with this, a recent optimisation of cellulase, pectinase, ultrasound time, and pH achieved high recoveries under mild conditions. Scanning electron microscopy (SEM) images revealed increased porosity, and FTIR confirmed the absence of lycopene **1** degradation, supporting the combined approach's efficiency and sustainability.[30]

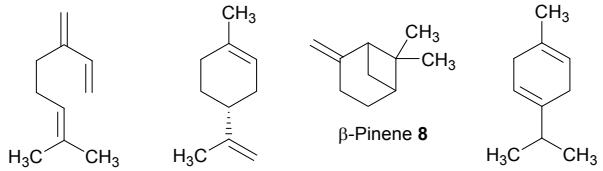
As a fully solvent-free alternative, RSLDE based on cyclic pressure gradients (e.g., Naviglio Extractor) avoids thermal stress. It eliminates the use of VOCs, affording high-purity lycopene **1** (>98% w/w) from tomato-processing waste while preserving biomass for downstream valorisation. Kinetic modelling supports the scalability of this technology, positioning RSLDE as a promising addition to the portfolio of green lycopene extraction methods.[31]

In conclusion, lycopene **1** extraction has shifted from solvent-heavy protocols to greener and potentially scalable routes, delivering high-purity products with a reduced environmental footprint.

3.2 Flavours and Fragrances.

Flavours and fragrances are essential to the sensory experience of food, beverages, and many consumer products, as they activate our chemical senses through direct interactions with specific molecules. Driven by increasing consumer demand for natural and sustainable ingredients, current research focuses on identifying and producing volatile compounds—such as esters, terpenoids, aldehydes, and alcohols—with desirable aroma and taste profiles from plant-based sources. In this context, representative compounds of high industrial interest illustrate the chemical diversity and commercial value of natural flavour and fragrance ingredients.[32]

3.2.1 (R)- (+)-Limonene. (R)-(+)-Limonene (**8**, Scheme 2), also known as d-limonene or 1-methyl-4-isopropenylcyclohex-1-ene, is a monocyclic terpene widely distributed in nature. It is particularly abundant in the essential oils (EOs) extracted from the peels of almost all *citrus* fruits, where it constitutes a significant component. Due to its pleasant citrus aroma and functional versatility, d-limonene **8** is among the most common and industrially significant terpenes. It is widely used in the food, cosmetics, and pharmaceutical industries. Beyond its flavour and fragrance, d-limonene **8** has been reported to have anti-inflammatory, antiviral, anticancer, and antidiabetic activities. It also serves practical roles, as it is a liquid, nonpolar solvent with a strong affinity for petroleum-based greases. This property has long made it a popular industrial cleaner and the active component in household pest-control formulations. Valued as a safer, biodegradable alternative to solvents like methyl ethyl ketone, xylene, and the now-banned chlorofluorocarbons, d-limonene **8** is also renewable.[33]



β-Myrcene **7** d-Limoneno, **8** β-Pinene **8** γ-terpinene **9**

Scheme 2. Examples of acyclic and cyclic structures of monoterpene hydrocarbons in essential oils.

Traditionally, d-limonene **8** has been recovered from *citrus* residues using conventional operations, including mechanical cold pressing, water/steam-based distillation**,** steam explosion, and SLE) with organic solvents. While simple and effective, these routes often require lengthy extraction times, high energy input, and substantial capital investment. Within this toolbox, *n*Hex SLE has been the workhorse; yet its health and environmental drawbacks have accelerated the shift toward bio-derived solvents.[34]

Against this backdrop, a comparative multi-solvent study benchmarked nine green candidates against *n*Hex, with cyclopentyl methyl ether (CPME) and 2-methyltetrahydrofuran (2-MeTHF) emerging as the top performers. Under optimised SLE conditions, CPME and 2-MeTHF afforded 1.78% and 1.37% d-limonene **8** from orange-peel waste, ~80% and 40% higher than *n*Hex (0.99%). Both solvents maintained performance across three reuse cycles, and their efficiencies were comparable to conventional hydrodistillation (HD) (~2% w/w d-limonene **8**), with microscopy indicating these gains were due to enhanced cell-wall disruption.[35]

Beyond liquid–solvent approaches, supercritical fluid extraction (SFE) has emerged as a green, high-efficiency alternative. $ScCO_2$ combines the gas-like diffusivity of a gas with the liquid-like solvating power of a liquid, while remaining non-toxic and easily removed via depressurisation.[36] Using a 65:35 d-limonene–canola oil model system under isobaric $ScCO_2$ (10 MPa), Yasumoto *et al*. demonstrated that temperature alone tunes purity versus yield: at 60 °C, d-limonene purity approached ~99%, whereas at 30 °C recovery peaked (~95% w/w); introducing a temperature gradient further sharpened separation.[37] In line with these results, SFE of *Citrus limon* peels produced essential oils containing 80–88% d-limonene **8**, optimised at 15 MPa and 40 °C.[38] Likewise, in *Citrus unshiu*, Safranko *et al.* reported d-limonene **8** as the dominant volatile, reaching 30.7 % at 300 bar.[39]

Complementary to the innovation in extraction media, process routes have also undergone significant advancements. By coupling microwaves directly to polar molecules within the plant matrix (chiefly intracellular water), MAE generates rapid, uniform volumetric heating that ruptures glandular structures and releases target compounds into an aqueous phase for streamlined distillation. Compared to conventional heating, MAE typically shortens extraction times from hours to minutes, reduces solvent use by ~50–80%, lowers energy demand, and often improves yield and selectivity while preserving bioactivity.[40]

As a representative case, a sequential microwave-assisted hydrodistillation (MAHD) was operated at a 750 g scale in two stages: (i) heating the charge to near its boiling point and (ii) distilling the oil. The resulting essential oil—dominated by d-limonene **8** (65.1 wt%), β-pinene **9** (14.5 wt%), and γ-terpinene **10** (9.7 wt%)—exhibited potent inhibition against *E. coli* and *S. aureus*. The spent matrix was then subjected to MAE, yielding a pigment fraction enriched in polyphenolics, which underscores how microwave-driven cascading not only accelerates extraction but also delivers bioactive-rich streams suitable for downstream purification and use.[41]

Consistent with these advantages, the work of Golmakani & Moayyedi comparing MAHD and solvent-less microwave extraction (SLME) with HD, demonstrated a reduction in extraction time from 120 min (HD) to just 15 min (MAHD, SLME) while maintaining comparable physical and chemical properties of the essential oils obtained from *Citrus limon* peel. Moreover, d-limonene **8** remained the major monoterpene across methods (HD: 65.1%, MAHD: 72.3%, SLME: 68.2%), confirming that green extraction-intensification strategies do not compromise the integrity of the target compound.[42] In line with these observations, Attard *et al*. further highlight MAE as a selective, rapid method for d-limonene **8** recovery from orange peels, reporting—under comparable setups—substantially higher yields (up to two-fold versus conventional heating), likely due to

favourable microwave–matrix interactions that promote concurrent cell rupture and diffusion.[43] Building on this comparative evidence, a solvent-free MAE process optimised via response surface methodology identified microwave power as the principal driver of performance and enabled rapid oil recovery without added water or organic solvents; under 1000 W for 10 min, fresh orange and lemon peels afforded 3.7% and 2.0% oil, respectively, with compositions dominated by β-myrcene **7** and d-limonene **8** (orange: 45% β-myrcene **7**, 29% d-limonene **8**; lemon: 19% β-myrcene **7**, 15% d-limonene **8**).[44]

This improved performance is not limited to *citrus* peel. A recent study on *Citrus limon* leaves demonstrated that SLME can also provide bioactive-rich essential oils, yielding 2.5% oil after 50 minutes at 110 °C and 300 W, with d-limonene **8** (34.1%) as the dominant component. [45] These extracts showed strong antioxidant activity and exhibited potent antimicrobial effects, supporting their application in food, cosmetic, and pharmaceutical formulations.

At the process scale, considerations such as feedstock viscosity and reactor configuration for a *citrus* biorefinery were addressed, identifying optimal MAHD conditions: 20 minutes at a solid-to-water ratio of 1:1.5 and constant pressure of 300 mbar. Under these conditions, orange peel afforded 1.8% (dry basis)—comparable to HD (1.7%; dry basis)—with no remarkable compositional differences; d-limonene **8** remained predominant (96.8% for HD; 97.4% for MAHD).[46]

Complementing these solvent-free, energy-efficient strategies, UAE offers a low-temperature acoustic route for recovering bioactive compounds. Ultrasound (>25 kHz) generates acoustic cavitation—microscopic bubbles that form and collapse—producing localised shear and microjets that rupture cell walls. This micro-disruption improves solvent penetration and mass transfer, accelerating the release of intracellular compounds while minimising reliance on organic solvents. The gains stem from the combined effects of cell fragmentation and enhanced diffusion, positioning UAE as a strong candidate for the sustainable extraction of citrus-derived d-limonene **8**.[47]

In a recent study on d-limonene **8** recovery from sweet lime (*Citrus limetta*) peel, UAE reduced the total extraction time to 15–20 min compared with ~185 min for the conventional process. Under optimised conditions, UAE yielded 3.29 g d-limonene **8** per 100 g peel (~97% of the essential oil), and SEM imaging confirmed ultrasound-induced disruption of cells and particles.[48]

Extending this concept, concomitant ultrasound–microwave irradiation (UMAE) couples cavitation-driven cell disruption with rapid volumetric heating, offering additive or synergistic benefits from the laboratory to industrial scales.[49] Although evidence remains limited, González-Rivera *et al*. showed that UMAE produced 1.53 % (w/w) essential oil from fresh orange peel in 60 min, matching HD (1.55) in less than half the time and saving >60% energy; d-limonene **8** dominated (~95%), underscoring UMAE's promise and the need to define optimal operating windows. [50]

In summary, citrus processing residues constitute a valuable renewable source of d-limonene **8** when combined with efficient extraction and process-intensification strategies. The adoption of green solvents and energy-efficient technologies enables high recovery while reducing processing time, solvent use, and environmental impact, reinforcing d-limonene **8** as a high-value terpene for sustainable industrial applications.

3.3 Pharmacologically Relevant Metabolites.

For millennia, medicinal and aromatic plants have underpinned healthcare, with ethnopharmacological knowledge first passed down orally and later codified in pharmacopoeias. As traditional remedies evolved into modern pharmacology, the isolation of active principles—such as morphine, digitoxin, and quinine—marked a turning point. Since then, many essential medicines have been derived from nature. Their enduring value reflects the exceptional structural diversity and evolutionary "fine-tuning" of natural products, which makes them potent modulators of complex biological pathways, especially in cancer and infectious diseases.[51]

Recent advances align closely with a circular-bioeconomy vision, in which agro-industrial residues are converted into standardised, renewable sources of bioactive compounds for therapeutic development. By applying green, intensified extraction routes (e.g., MAE, UAE, SFE), producers can secure a sustainable supply while preserving molecular integrity—positioning biowaste as a high-value pharmaceutical feedstock for the next generation of natural medicines.[52]

3.3.1 Artemisinic acid and Artemisinin. Amid rising resistance in *Plasmodium falciparum*, the WHO recommends artemisinin-based combination therapies as the standard of care for uncomplicated malaria. In 2021, WHO reported 241 million cases globally and at least 627,000 deaths. [53]

Artemisinin **10**, the key active pharmaceutical ingredient, is naturally produced in low yields (0.4%) from the plant *Artemisia annua*, making it insufficient to supply the over 300 million treatments required annually. To address this limitation, a scalable process has been developed in which dihydroartemisinic acid **12** —an inactive biological precursor—is photochemically oxidised with singlet oxygen (Scheme 3). This one-pot, continuous-flow process yields artemisinin **10** in 65% yield, producing batches of up to 365 kg from 600 kg of precursor, with an overall yield of 55%.[54]

To ensure a more sustainable supply chain, artemisinic acid **11** can be efficiently biosynthesised using metabolic engineering.[55] Additionally, dihydroartemisinic acid **12** of high purity (up to 98 wt%) can be recovered from Artemisinin Production Waste (APW)—an oily byproduct of *A. annua* extraction—through a purification strategy combining anion-exchange resin and silica gel column chromatography. Dihydroartemisinic acid **12** is first captured on an anion-exchange resin by exploiting its carboxylate. Of ten candidates, the styrene–divinylbenzene 717 resin showed the highest capacity and was selected for optimisation. Efficient desorption is achieved with 10% NH_4Cl in 80% EtOH. The enriched fraction is then polished by silica-gel chromatography (*n*Hex/AcOEt, 0–20%) followed by recrystallisation to remove oils and pigments. This sequence routinely affords ≥98%-pure dihydroartemisinic acid **12** with >80% overall recovery and has been validated at 10× scale, supporting industrial applicability [56]

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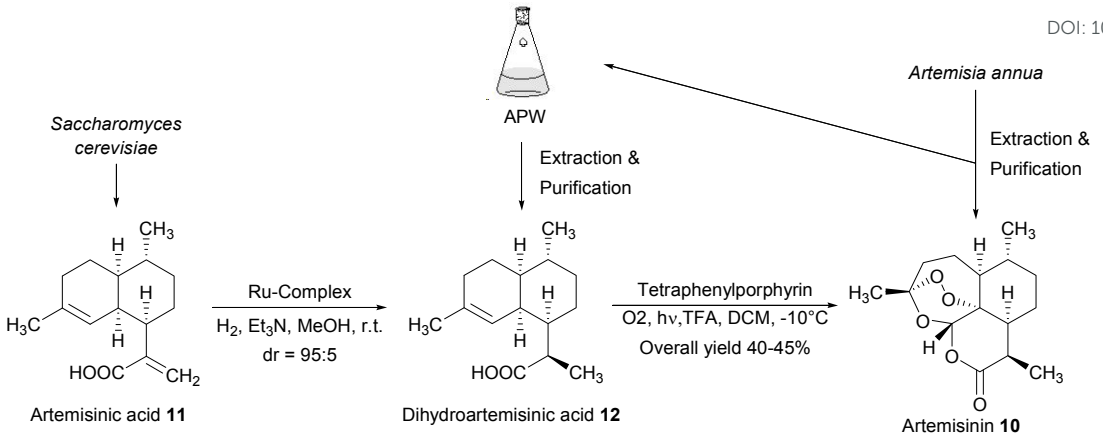


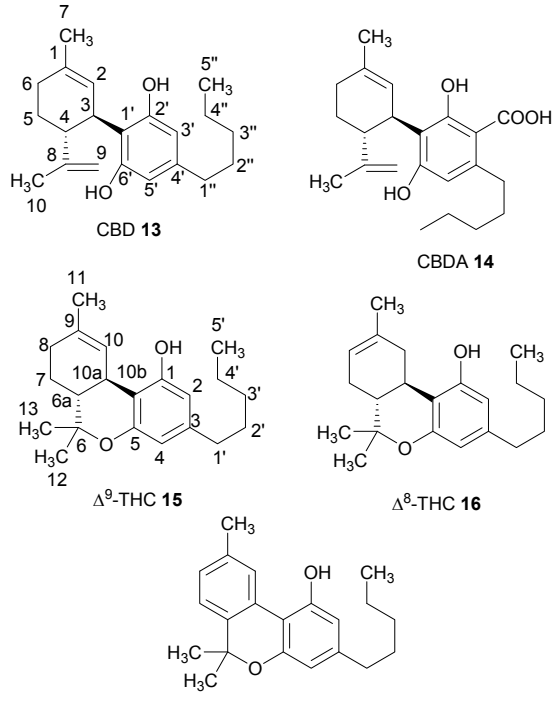
Scheme 3. Obtention of artemisinin **10** from natural sources and semi-synthetic processes.

Given the limitations of natural extraction, these innovations in synthetic biology and process engineering offer scalable, environmentally friendly alternatives for artemisinin **10** production. Together, these advances represent a promising approach for increasing the supply of antimalarial treatments.

3.3.2 Plant-derived Cannabinoids: cannabidiol 13 (CBD). Cannabinoids are a diverse group of bioactive compounds that interact with the human endocannabinoid system, producing distinct pharmacological effects. Their actions range from psychoactive and analgesic to anti-inflammatory and neuroprotective, making them an expanding focus of scientific and medical research and promising candidates for alleviating various human ailments. More than 100 phytocannabinoids have been identified, among which cannabidiol (CBD, **13**) and Δ^9-tetrahydrocannabinol (Δ9-THC, **15**) are the most extensively studied (Scheme 4). Of particular interest is CBD **13**, a non-psychoactive compound with therapeutic potential for numerous neurological and psychiatric disorders, including Parkinson's, Alzheimer's, anxiety, and depression.[57] Sativex®, an oromucosal spray containing an equimolar combination of CBD **13** and THC **15** (2.7 mg THC / 2.5 mg CBD per spray), is the first phytocannabinoid-based medicine and has been approved in several countries for the treatment of neuropathic pain associated with multiple sclerosis.[58]

Cannabinoids occur chiefly in *Cannabis*, a genus of the *Cannabaceae* family, where *Cannabis sativa* includes three morphological varieties: *sativa*, *indica*, and *ruderalis*. [59] Although hemp and marijuana belong to the same species (*C. sativa)*, they arise from distinct cultivars with different chemotypes, uses, and legal status. Drug-type *cannabis* has a high Δ^9-THC: CBD ratio (typically ~5–30% Δ^9-THC), producing psychoactive effects, whereas fiber-type *cannabis* (hemp) shows the opposite profile: very low Δ^9-THC **15** and relatively higher CBD **13**, lending itself to textiles, foods, cosmetics, and wellness products.[60] In many jurisdictions, "hemp" is now a legal term rather than a botanical one, referring to *cannabis* that contains no more than a defined THC **15** threshold (often ≤0.3%).[61]

This review centers on the by-products of hemp cultivation and processing. Hemp has been valued for millennia for its medicinal and industrial uses and is now legally cultivated worldwide as a highly versatile crop. It is grown for multiple components—fibers, seeds, leaves, and flowers—each with distinct applications: bast fibers prized for strength and durability in paper, textiles, automotive parts, and bio-based construction, and flowers rich in cannabinoids and terpenes with well-documented therapeutic potential.[62]



Scheme 4. Structures of the major cannabinoids.

As demand for hemp-based products rises, processing for fiber and seed production generates substantial residues, including hurds, leaves, and inflorescences, with up to 33% of the plant mass lost as dust during fiber separation. Often considered low-value waste due to their complex composition, rich in waxes and cannabinoids, these by-products remain underutilised despite their potential for the recovery of bio-based compounds of economic interest.[63]

Although CBD **13** is not present in its active form in raw industrial hemp, it can be obtained by decarboxylating its precursor, cannabidiolic acid (CBDA) **14**, a process typically induced by heat or light. Kinetic studies indicate pseudo–first-order behaviour

with optimal conversion at 140 °C for ~30 min, followed by product degradation, and a direct β-keto-acid mechanism whose rate depends on time, temperature, and matrix composition.[64] Fiorini *et al*. emphasise that proper pretreatment, particularly the decarboxylation of dry hemp inflorescences immediately before HD, is essential to obtaining CBD-rich essential oil. In contrast, steam distillation of fresh material yields low CBD **13** content.[65] These findings highlight the critical role of processing parameters in maximising the industrial value of hemp-derived products.

Among various extraction techniques, several patents describe the use of $ScCO_2$ to recover CBD **13** from industrial hemp waste, typically followed by purification steps including decarboxylation, distillation, flash chromatography, and crystallisation. For example, Eiroa Martínez *et al*. detail the extraction of CBD **13** from hemp waste pellets at 60°C and 300 bar, yielding a crude resin containing 20% of the phytocannabinoid **13**. Despite the relatively low concentration compared to solvent-based extractions, high-purity CBD **13** isolates (up to 99.8%) can be obtained following appropriate downstream processing.[66] Similarly, Pertile and Black describe extracting oil under milder conditions (35°C, 127 bar), followed by decarboxylation and purification using nonpolar solvents.[67]

Marzorati et al. investigated a downstream processing strategy to obtain CBD-enriched products from hemp inflorescences.[68] In their study, conventional MeOH-based recovery was compared with $ScCO_2$ processing. While MeOH consistently afforded higher overall mass yields, $ScCO_2$ produced fractions with markedly higher CBD **13** concentrations, as summarised in Table 2, reflecting its superior selectivity. A pre-treatment of dried biomass at 100 °C for 6 h prior to processing enhanced CBD **13** yields by promoting CBDA **14** decarboxylation (entries 3–4). This approach generated a crude oil containing approximately 50 wt% CBD **13**. Subsequent purification via winterisation and flash chromatography on Celite® effectively removed waxes and Δ^9-THC **15**, affording a final product with nearly 80 wt% CBD **13** purity (entry 5).

In contrast, Calmanti *et al*. adopted a more refined and environmentally conscious strategy from industrial hemp, incorporating mild decarboxylation (80 °C, 24 h), $ScCO_2$ extraction under gentler conditions (40 °C, 250 bar), selective winterisation with acetonitrile, followed by C18 reversed-phase filtration, silica gel chromatography, and final crystallisation to obtain CBD **13** with a purity exceeding 99% and an overall yield of 52%.[69] This multistep approach not only enabled the isolation of crystalline CBD **13** with pharmaceutical-grade purity but also prioritised solvent recovery and minimised product losses throughout the process. Overall, the Calmanti *et al*. protocol demonstrates superior selectivity, scalability, and sustainability, making it a more suitable option for industrial-scale production of high-purity CBD **13**.

Although $ScCO_2$ extraction is a promising and environmentally friendly route for valorising industrial hemp waste, complementary approaches have been explored to further enhance process efficiency and applicability. Among these, pressurised liquid extraction (PLE) combined with thermochemical decarboxylation has proven highly effective for isolating CBD **13** from leaves, seeds, stalks, and small inflorescences. In this approach, acidic cannabinoids are thermally converted to their neutral forms using water as the PLE medium (140 °C, 11.0 MPa, two 3-min static cycles). Despite the poor aqueous solubility of cannabinoids, water is intentionally used as the reaction medium, yielding a 99.2% conversion of CBDA **15** to CBD **13**. The thermally treated biomass is then extracted with EtOH to give a CBD-rich extract (75.8 % purity), and subsequent C18 reversed-phase chromatography followed by crystallisation affords CBD **13** at 91.8 % purity.[70]

Table 2. Extraction performance (MeOH vs $ScCO_2$) and cannabinoid contents (CBD **13**, Δ^9-THC **15**) across purification stages, as reported by Marzorati et al.[68]

	Methodology	Extraction (%)	CBD (wt. %)	Δ^9-THC (wt. %)
1	Sample: MeOH (ratio 1:10, w/w), 2h, r.t.	22	3.0 ± 0.5	-
2	$ScCO_2$ (380 bar, 60-80°C)	14	15.8 ± 0.3	-
3	1) 100°C for 6h 2) MeOH extraction	17	45.2 ± 0.2	-
4	1) 100°C for 6h 2) $ScCO_2$ extraction	13	50.2 ± 0.2	3.01 ± 0.01
5	1) 100°C for 6h 2) $ScCO_2$ extraction, 60°C and 380bar 3) Winterisation with EtOH 4) Flash chromatography, adsorption on Celite		79.0 ± 0.4	n.d.*

* n.d.: not detected.

In summary, these studies demonstrate that the recovery of CBD **13** from industrial hemp by-products is strongly influenced by the interplay among biomass pretreatment, extraction strategy, and downstream purification. While $ScCO_2$ enables high selectivity and access to pharmaceutical-grade CBD **13** through carefully designed multistep protocols, alternative approaches such as PLE combined with controlled decarboxylation offer efficient and versatile routes for converting diverse hemp residues into CBD-rich products. Collectively, these findings highlight the substantial potential of hemp processing residues as renewable feedstocks for the sustainable production of high-value cannabinoids and underscore the importance of process optimisation in maximising their industrial valorisation.

3.4 Lipophilic Bioactive Compounds.

Lipophilic bioactive compounds constitute a particularly valuable fraction of plant-derived phytochemicals recovered from biomass waste. Beyond the well-known polar constituents, many agro-industrial residues are enriched in a diverse unsaponifiable fraction that includes pentacyclic triterpenes, phytosterols, and tocopherols. These molecules share key features, including

hydrophobic character, low volatility, and high chemical stability. At the same time, they display a range of biological and functional properties—including antioxidant and anti-inflammatory activities as well as cholesterol-lowering and membrane-stabilising effects—that make them relevant to food, cosmetic, nutraceutical, and pharmaceutical formulations. Consequently, the selective recovery of these lipophilic compounds from residual biomass aligns well with circular bioeconomy strategies, adding value to waste streams while reducing dependence on conventional raw materials.[71]

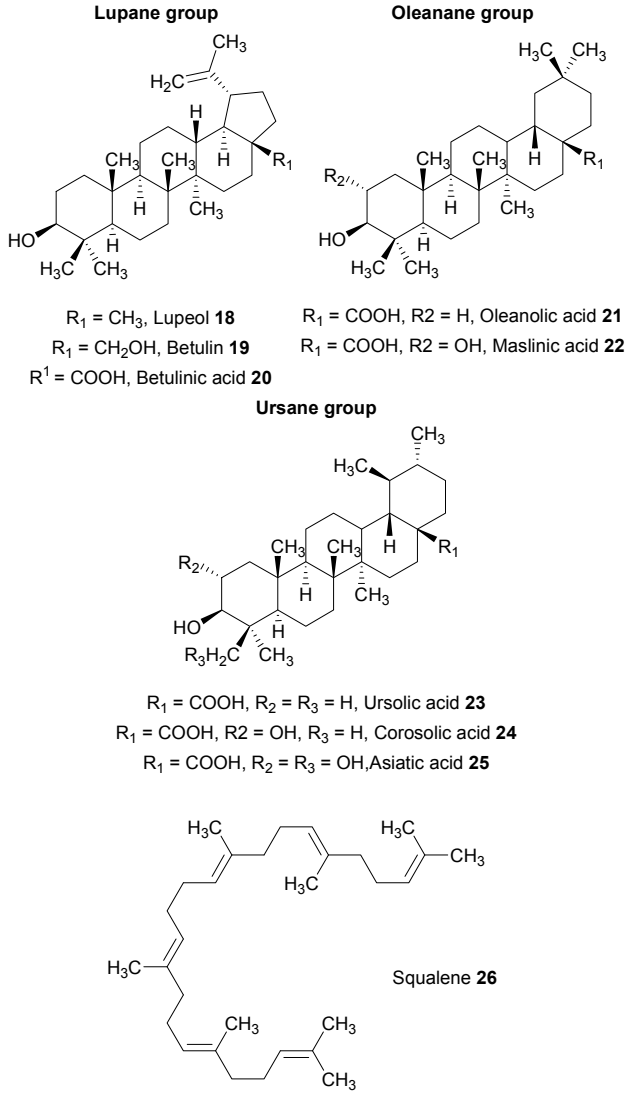
Within this group, pentacyclic triterpene acids such as oleanolic **21** (OA), maslinic **22** (MA) and ursolic **23** (UA) acids typically coexist with phytosterols and tocopherols in the same matrices, making them attractive targets for integrated recovery schemes. In the following sections, we discuss representative examples of these compounds and highlight their occurrence in biomass.

3.4.1 Pentacyclic triterpene acids (OA, MA, UA). Triterpenes constitute a broad and structurally diverse class of natural metabolites biosynthesised via cyclisation of the C_{30} precursor squalene **26**. Central to this pathway are 2,3-oxidosqualene cyclases, key enzymes that convert 2,3-oxidosqualene into a wide array of cyclic triterpenes and sterols. These metabolites are widely distributed in nature and display a broad spectrum of pharmacological activities. Structurally, triterpenoids are generally divided into tetracyclic and pentacyclic families, the latter of which—particularly pentacyclic triterpene acids (PTAs)—has attracted increasing scientific and industrial interest. While the lupane, oleanane, and ursane scaffolds are the most extensively investigated, other frameworks, such as hopane, taraxastane, and friedelane, have also emerged as promising bioactive architectures (Scheme 5). Their therapeutic potential is supported by experimental and clinical evidence demonstrating anti-inflammatory, anticancer, antimicrobial, neuroprotective, and metabolism-modulating effects. Several PTAs have already progressed into clinical use, especially in the management of liver disorders and type 2 diabetes.[72]

Among natural sources, *Olea europaea* (olive tree) stands out not only for its cultural and nutritional significance within the Mediterranean diet, but also for its remarkable abundance of PTAs. However, olive processing generates vast quantities of by-products—estimated at 30 million cubic meters annually—representing an environmental burden and an economic challenge for producers.[73]

OA **21** and MA **22** exemplify the intrinsic difficulties in isolating structurally similar PTAs, as their close resemblance necessitates highly selective purification methods. For instance, flash chromatography on silica gel using *n*Hex/AcOEt (79:21) affords up to 10.9 mg/g of OA **21**, whereas an AcOEt/AcOH (92:8) system yields 6.25 mg/g of MA **22**.[74] Although these values surpass earlier reports, they still rely on solvent-intensive, non-sustainable chromatographic conditions.

Recent studies focused on valorising olive-derived residues reveal strong matrix-dependent behaviour. Velasco *et al*. demonstrated that PTAs preferentially partition into lipophilic fractions of crude olive pomace oil, which contained markedly higher concentrations (2.5–48.4 g·kg^{-1}) than corresponding semisolid matrices (1.2–3.0 g·kg^{-1}). Moreover, the dominant triterpene shifted with matrix composition— OA **21** dominated semisolid forms, while MA **22** was more abundant in oil fractions—highlighting the need for matrix-tailored extraction strategies.[75]



Scheme 5. Scheme 5. Classification of pentacyclic triterpenes into the Lupane, Oleanane, and Ursane groups, shown together with squalene as their common structural precursor.

In parallel, greener separation platforms have gained traction as alternatives to traditional solvent-intensive workflows. A notable example of SFE with pH-zone refining centrifugal partition chromatography (CPC) is the use of $ScCO_2$ with EtOH as a cosolvent, which enables efficient recovery of triterpenoids. Subsequent CPC using MtBE/acetonitrile/water (4:1:5) affords baseline separation of OA **21** and MA **22** with purities of 94–97% and recoveries above 95%.[76]

Beyond these compositional effects, recent biorefinery-oriented workflows have demonstrated that pretreatment steps can significantly impact subsequent PTAs recovery. A representative case is the MAE using water as the solvent for olive pomace, initially optimised using response surface methodology to maximise the solubilisation of polar constituents.[77] Under the selected conditions (100 °C, 16 min, 12% w/v), this process yields

two complementary streams: (i) an aqueous extract enriched in hydrophilic compounds and (ii) a structurally modified solid residue enriched in PTAs. The treated solid then constitutes an advantageous substrate for a second extraction stage. EtOH maceration of this residue affords substantially higher levels of OA **21** and MA **22** —3.60 and 9.54 $mg \cdot g^{-1}$ extracted solid, respectively—than those obtained from the untreated biomass. This enhancement is attributed to MAE-induced tissue disruption and to the increased proportion of lipophilic extractives in the residual solid, which together facilitate the release of triterpenoids.

Complementary insights arise from a comparative evaluation of UAE, MAE, and conventional solvent extraction for the recovery of OA **21** and MA **22** from olive pomace. Xie *et al*. demonstrated that UAE yields the highest extraction efficiencies, driven by intense acoustic cavitation, faster mass transfer, and more favourable kinetic and thermodynamic parameters.[78] Under optimal UAE conditions, OA **21** and MA **22** concentrations reached 29.8 and 381.2 $mg \cdot g^{-1}$, outperforming both MAE and solvent extraction. Notably, SEM analyses revealed extensive cell-wall rupture under UAE, far exceeding the structural damage caused by MAE or solvent extraction, thereby explaining the superior release of intracellular triterpenes. In addition to offering higher yields and significantly shorter extraction times, UAE also showed the lowest E-factor, energy consumption, and carbon emissions, establishing it as the greenest and most effective technique for PTAs and phenolic recovery from olive pomace.

Extending beyond olive-derived matrices, *Eucalyptus* species offer another underutilised source of PTAs, particularly within the pulp and paper industry, which generates substantial lignocellulosic waste (approx. 0.27 tons per ton of cellulose).[79] Oliveira *et al*. proposed an integrated biorefinery strategy for *Eucalyptus globulus* leaves, wherein essential oils (EOs) are first obtained via HD. The residual biomass is then subjected to PTAs extraction using the same EOs, rich in 1,8-cineole, as a bio-based solvent. The comparable extraction efficiencies of whole EOs (2.8% dw) and pure 1,8-cineole (2.7% dw) validate the effectiveness of this solvent recycling strategy. Both solvents achieved high recoveries of OA **21** (6.0 and 5.7 $g \cdot kg^{-1}$ dry weight) and UA **23** (18.3 and 17.9 $g \cdot kg^{-1}$ dry weight), demonstrating the viability of solvent-saving, circular-integrated protocols (Figure 1).[80]

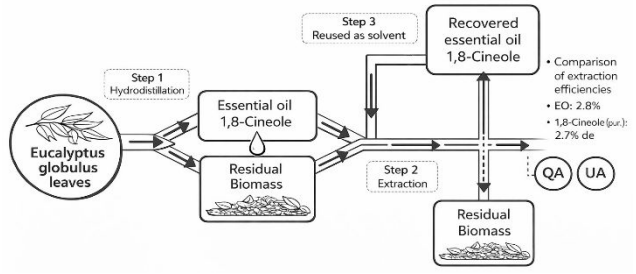


Figure 1. Integrated biorefinery for the recovery of EOs and PTAs from *Eucalyptus globulus* Leaves.

Complementary to EO-based systems, another promising alternative is the use of Deep Eutectic Solvents (DESs)—particularly Natural Deep Eutectic Solvents (NADESs) composed of primary metabolites such as organic acids, amino acids, or sugars—which offer low volatility, tuneable polarity, and high solubilization capacity, while remaining biodegradable and non-toxic.[81]

Silva *et al*. evaluated green extraction strategies using NADESs and showed that a menthol: thymol (1:2) eutectic mixture at room temperature outperformed conventional methods, including $ScCO_2$ and Soxhlet extraction. Yields of 0.84 wt.% OA **21** and 1.8 wt% UA **23** from *Eucalyptus globulus* bark illustrate both the efficiency and the environmental benefits of DES-based extraction.[82] The synergistic use of DESs with ultrasound has also emerged as a powerful strategy. In *Eriobotrya japonica* leaves, a thymol: benzyl alcohol DESs (2:1 molar ratio) under mild conditions (60 °C, 60 min, 1:10 solid-to-solvent ratio) produced a crude extract containing 81.2% PTAs—mainly OA **21**, MA **22**, UA **23** and corosolic acid (CA) **24**. Subsequent purification yielded UA **23** and CA **24** at purities of 93.9% and 69.3%, respectively. Meanwhile, solvent recovery via low-pressure C18 reversed-phase chromatography ensured consistent extraction efficiency across multiple reuse cycles.[83]

Hydrophobic DESs derived from menthol have also shown a remarkable capacity to enhance the solubility of UA **23**. A 1:1 menthol: thymol eutectic system increased its solubility by almost an order of magnitude relative to EtOH (36.2 vs. 4.16 $\mu g \cdot mL^{-1}$) in apple-peel extraction.[84]

Other green solvents have been proposed for PTAs recovery from non-olive residues. Dimethyl carbonate (DMC)—a biodegradable, low-toxicity solvent—has been used for the selective extraction of OA **21** from grape pomace, delivering the highest molar selectivity (61%) among the solvents tested (n-BuOH, acetone, AcOEt and 2-MeTHF) and maintaining its efficiency over three reuse cycles.[85] In addition, ionic liquids (ILs) have been explored as alternative media for PTA extraction. Although pure PTAs were not isolated, de Faria *et al.* assessed aqueous ILs solutions as hydrotropes or surfactants to enhance PTAs solubility. Hydrotropic systems afforded only modest gains, whereas surfactant-type ILs, particularly 1-tetradecyl-3-methylimidazolium chloride at 500 mM and 80 °C, delivered markedly improved recoveries. From green apple peels, this approach afforded 2.62 wt% PTAs, outperforming chloroform (2.48 wt%) and acetone (1.37 wt%) under comparable extraction conditions.[86]

Overall, recent advances show that matrix-tailored pretreatments and green, intensified extraction strategies enable the efficient and sustainable recovery of high-PTAs from agro-industrial residues, reinforcing their potential within integrated biorefinery frameworks.

3.4.2 Phytosterols and Tocopherols. Tocopherols, the vitamin E homologues (α-, β-, γ- and δ-tocopherols), and phytosterols — particularly β-sitosterol — (Scheme 6) represent two major families of lipophilic phytochemicals that have attracted considerable attention due to their well-documented health benefits.

Biosynthetically and structurally related to triterpenes, phytosterols are plant-derived sterols that are structurally analogous to cholesterol but differ in side-chain substitutions and

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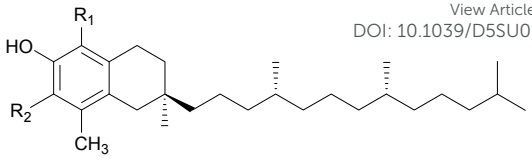
ring saturation patterns. Because of this structural similarity, they competitively inhibit intestinal cholesterol absorption, thereby reducing plasma low-density lipoprotein (LDL) cholesterol levels. In addition to their cholesterol-lowering properties, phytosterols exhibit anti-inflammatory and anticancer activities. Long-term consumption of phytosterol-rich foods has been associated with a reduced risk of cancer, as well as the prevention of cardiovascular and cerebrovascular diseases. As humans cannot synthesise phytosterols endogenously, dietary sources such as vegetable oils, nuts, and mushrooms are essential, providing mainly β-sitosterol **31**, campesterol **32**, and soya sterols. [87]

Tocopherols **27**-**30** act as potent lipid-soluble antioxidants and are involved in key physiological processes, including membrane stabilisation, immune modulation, and the prevention of oxidative damage.[88]

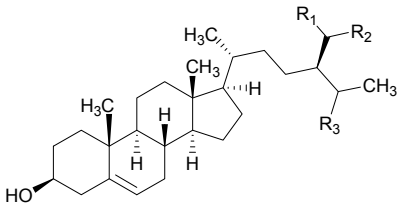
Together, phytosterols and tocopherols are widely recognised as bioactive components of high nutritional and functional value. Their co-occurrence in the unsaponifiable fraction of many plant oils and agro-industrial residues, combined with their similar hydrophobic character, makes them attractive targets for integrated and sustainable recovery strategies within circular biorefinery frameworks.

One of the most promising sources of these high-value molecules is deodoriser distillate (DD), a secondary byproduct generated during the steam deodorisation step of edible oil refining, primarily used to reduce free fatty acids (FFAs). DD is a complex mixture composed of FFAs, mono-, di-, and triglycerides, sterol esters, phytosterols, tocopherols **27**-**30**, and squalene **26**. These complex compositions pose a challenge for the efficient extraction of tocopherols **27**-**30** for industrial applications. Given that millions of tons of DD are discarded each year globally, valorising it through the recovery of nutraceutical and cosmeceutical ingredients offers a valuable opportunity to reduce environmental burdens.[89]

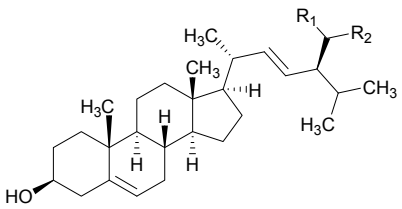
Several extraction and purification methodologies have been developed for DD, particularly from soybean (SODD) and rapeseed oils (RODD). Among these, $ScCO_2$ extraction has emerged as a commercially viable technique. Recent studies based on detailed process simulations have confirmed the technical and economic viability of recovering squalene **26** from DD via an integrated strategy combining supercritical EtOH esterification, $ScCO_2$ extraction, and purification. Olive DD showed the highest performance, yielding up to 95 g/kg of squalene **26** with 99% purity and surpassing other feedstocks. Additionally, valuable co-products, such as high-purity ethyl esters and tocopherol–sterol mixtures, enhance the overall process value.[90] Notably, Asl *et al*. reported that $ScCO_2$ extraction of saponified RODD using 5% EtOH as a cosolvent achieved three times higher efficiency than a modified Soxhlet method, yielding extracts rich in phytosterols—primarily β-sitosterol **31** (50 wt.%) and campesterol **32** (36.3 wt%).[91]



$R_1 = R_2 = CH_3$, α-Tocopherol **27**
$R_1 = CH_3$, $R_2 = H$, β-Tocopherol **28**
$R_1 = H$, $R_2 = CH_3$, γ-Tocopherol **29**
$R_1 = H$, $R_2 = H$, δ-Tocopherol **30**



$R_1 = R_2 = CH_3$, $R_3 = H$, β-Sitosterol **31**
$R_1 = R_2 = H$, $R_3 = CH_3$, Campesterol **32**



$R_1 = H$, $R_2 = CH_3$, Stigmasterol **33**
$R_1 = R_2 = H$, Brassicasterol **34**

Scheme 6. Chemical structures of selected phytosterols and tocopherols.

In addition to supercritical extraction, crystallisation has proven effective for the recovery of phytosterols. Yang *et al*. reported a two-step protocol involving the alkaline hydrolysis of SODD, followed by crystallisation in an acetone–EtOH mixture (4:1 v/v) at a 1:2.5 (mass/mass) sample-to-solvent ratio. This process yielded a white solid containing 23.0 wt.% phytosterols, initially 91.8 wt.% and increasing to 97.2 wt.% after three crystallisation cycles, highlighting its potential scalability and efficiency. [92]

Beyond being a valuable source of bioactive compounds, DD has also been explored as a versatile feedstock for the integrated production of biodiesel and the recovery of functional ingredients such as fatty acid sterol esters (FASEs). Biodiesel can be produced from DD via chemical transesterification, supercritical fluid processing, or enzymatic catalysis. Among these, enzymatic methods have gained increasing interest due to their milder reaction conditions, higher selectivity, fewer side products, and overall environmental compatibility.[93]

Early advances in the enzymatic valorisation of SODD were made by Shimada *et al*., who showed that *Candida rugosa* lipase selectively esterified sterols without affecting tocopherols, even in the presence of water. Their method combined distillation to concentrate tocopherols, enzymatic esterification of sterols with FFAs, and molecular distillation, allowing the recovery of a distillate with 65 wt% tocopherols and a residue enriched in FASEs, with over 95% of sterols esterified after two treatments.[94]

Building on this, Watanabe *et al*. developed a two-step enzymatic process that also included the hydrolysis of acylglycerols and methyl esterification of FFAs to FAMEs. After 40 h, 80% of sterols were converted to FASEs, acylglycerols were fully hydrolysed, and FFA content dropped by 78%. A second enzymatic treatment, after short-path distillation, further purified the products: tocopherols reached 76.4% purity (89.6% recovery) and sterols 97.2% (86.3% recovery).[95] Torres *et al*. further refined this concept with a dual-lipase system combining C. rugosa and Novozym 435, thereby enhancing selectivity, process simplicity, and scalability without requiring water or vacuum, paving the way for efficient downstream purification via supercritical fluid extraction.[96]

Recently, Lv *et al*. developed a green method using an immobilised lipase, MAS1-H108A, coupled with molecular distillation. This system achieved a 97.8% FAME yield, enabling the recovery of a high-value heavy phase enriched in tocopherols, squalene **26**, and β-sitosterol **31**, with excellent enzyme reusability (Figure 2). The integration of enzymatic catalysis and distillation, therefore, presents a compelling model for sustainable industrial-scale valorisation.[97] In parallel, a complementary process-simulation strategy has been proposed to optimise tocopherol recovery from SODD by molecular distillation: a scalable computer-simulated model based on a simplified pseudo-binary mixture of α-tocopherol and glycerol trioleate predicted a tocopherol purity of 44.87% for the simplified distillate, in excellent agreement with the experimental value of 43.75% under typical molecular distillation conditions (180 °C, 2.5 Pa).[98]

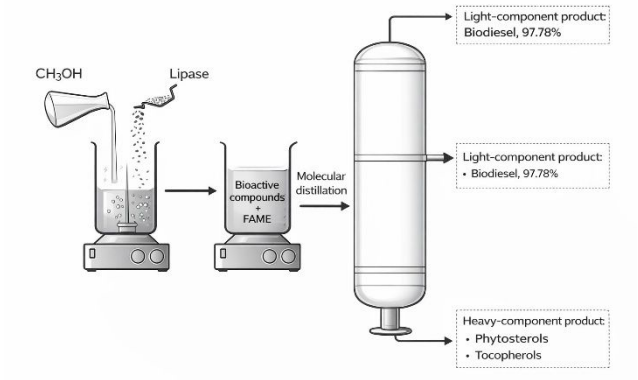


Figure 2. Synergically synthesising biodiesel and recovering bioactive compounds by combining an enzymatic process and molecular distillation.

Another promising methodology is SPE, which has shown great potential for the selective recovery of tocopherols and sterols. For industrial applicability, the porous materials used in SPE must be cost-effective and offer high selectivity and capacity. Zeolites, especially those modified to alter their aluminium or silicon content, have shown exceptional performance in this context.[99] For instance, the KOH-modified ZSM-5 zeolite significantly outperformed both unmodified and HCl-treated versions in extracting α-tocopherol **27** and β-sitosterol **31** from sunflower oil DOD. Under optimised conditions, the recovery rates reached 99.20% for α-tocopherol **21** and 97.32% for β-sitosterol **25**.[100]

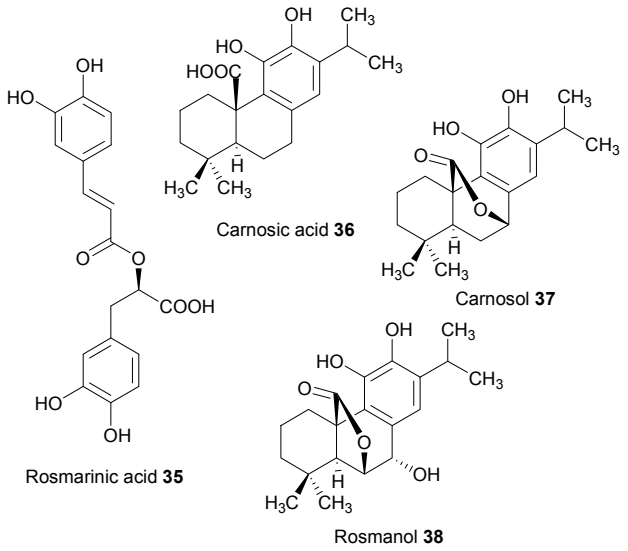
Overall, recent advances demonstrate that DD and related agro-industrial residues are highly promising feedstocks for the integrated and sustainable recovery of phytosterols and tocopherols, with supercritical fluids, enzymatic processes, and selective separation techniques enabling high yields, purity, and scalability within biorefinery-oriented frameworks.

3.5 Natural Antioxidants and Phenolic Compounds.

Natural antioxidants constitute a broad group of non-enzymatic molecules capable of preventing or delaying the oxidation of key biomolecules—lipids, proteins, and DNA—even at very low concentrations. Their relevance spans from food preservation to human health, as they act by scavenging free radicals, chelating transition metals, and interrupting oxidative chain reactions. While endogenous antioxidants offer a first line of defense, dietary antioxidants such as polyphenols, vitamins, flavonoids, and thiol-containing compounds play a vital complementary role, mitigating oxidative stress associated with chronic diseases and protecting against nutrient degradation. Plant-derived antioxidants have gained increasing prominence due to their biocompatibility, consumer preference for natural additives, and multifunctional properties in both food and nutraceutical applications.[101] Within this context, *Citrus* flavanones, such as hesperidin, and *Oleaceae* secoiridoids, including oleuropein, as well as *Lamiaceae* polyphenols, including rosmarinic acid, and pungent alkamides and capsaicinoids, represent key antioxidant families of high industrial and biological value. Their structural diversity, abundance in agro-industrial residues, and strong radical-scavenging capacity make them essential targets for sustainable extraction, valorisation, and application across modern biorefinery and clean-label preservation strategies.

3.5.1 Abietane diterpenes and Rosmarinic Acid from *Lamiaceae*.

The Lamiaceae family is a prolific source of bioactive metabolites, notably the phenolic compound rosmarinic acid **35** and the abietane-type diterpenes carnosic acid **36** and carnosol **37** (Scheme 7), which are widely recognised for their strong antioxidant capacity and multifunctional bioactivity. Abietane diterpenoids, particularly abundant in genera such as Salvia and Rosmarinus, comprise a structurally diverse class associated with a broad range of pharmacological effects, including anti-inflammatory, antimicrobial, antitumour, and neuroprotective activities.[102] Complementing these diterpenes, rosmarinic acid **35** acts as a signature antioxidant of rosemary and related species, with reported roles in antiviral and antibacterial defence, neuroprotection, and food preservation.[103] Together, these compounds constitute key antioxidant systems within the *Lamiaceae* family, underscoring both the biological significance of this botanical group and its growing relevance for food, cosmetic, and health-related applications.[104]

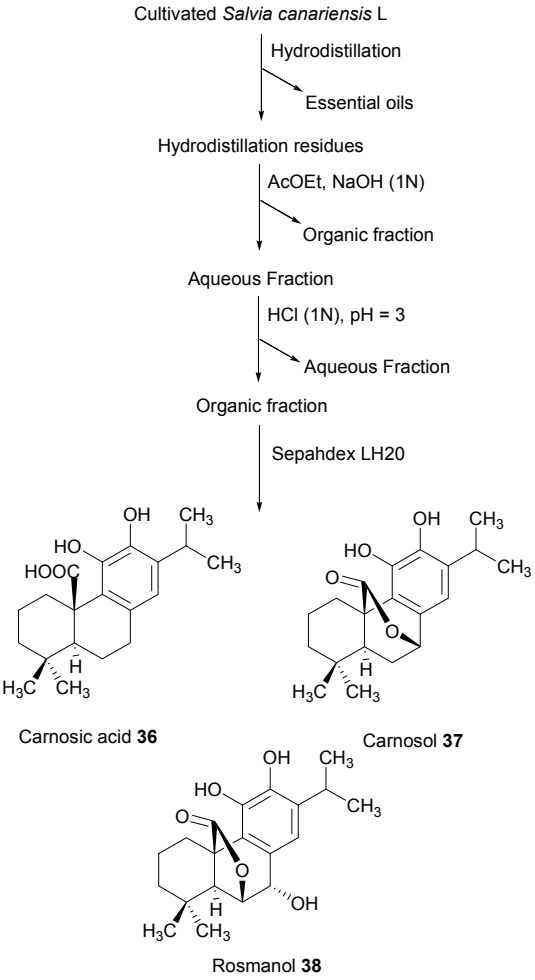


Scheme 7. Structural representation of potent antioxidant metabolites from the *Lamiaceae* family.

Driven by increasing industrial demand, the selective isolation of rosmarinic acid **35**, carnosic acid **36**, and carnosol **37** has become a significant research focus, particularly for the development of sustainable and resource-efficient supply chains. In this context, rosemary-derived matrices, especially leaves and post-distillation residues, have emerged as renewable, underutilised feedstocks. These byproducts, rich in phenolic compounds, exemplify a waste-to-value strategy by enabling the recovery of high-value antioxidants while simultaneously reducing agro-industrial waste streams.[105] Supporting this perspective, Chen *et al*. reported the isolation of novel labdane- and isopimarane-type diterpenoids with pronounced neuroprotective activity from solid residues remaining after essential oil extraction, highlighting the untapped chemical potential of rosemary byproducts. [106]

Despite this chemical richness, the efficient exploitation of these metabolites is constrained by their variable natural abundance. In rosemary, carnosic acid **36** content fluctuates seasonally and decreases under abiotic stress, consistent with its role as a stress-responsive antioxidant.[107] To overcome supply limitations, *in vitro* cultures of *R. officinalis* have been explored as alternative production platforms, enabling controlled biosynthesis under optimised conditions.[108] However, these systems often suffer from low yields and high operational costs, limiting their industrial scalability.

Traditionally, carnosic acid **36** and carnosol **37** have been extracted using organic solvents due to their poor water solubility. A representative example is the maceration of HD residues of *Salvia canariensis* L. in acetone, followed by alkaline treatment and purification using Sephadex® LH-20 column chromatography, affording carnosol **37** with 99% purity (by NMR) and a yield of 1.8 g per 100 g of dried extract (Scheme 8).[109] Sephadex LH-20, an epichlorohydrin-crosslinked dextran gel, is widely employed for the purification of phenolics and diterpenes due to its size-exclusion and adsorption properties, and can be reused after appropriate washing. However, despite its effectiveness, chromatographic methods based on Sephadex LH-20 or other resins often deliver only moderate selectivity and rely on volatile organic solvents such as acetone or MeOH, raising environmental and safety concerns.



Scheme 8. Extraction process of carnosic acid **36** and carnosol **37** from cultivated *S. canariensis*.

These limitations have motivated the exploration of adsorption-based alternatives, particularly SPE approaches employing non-ionic macroporous resins, which enable phenolic recovery from aqueous matrices with reduced solvent consumption and simplified downstream processing.

Indeed, similar limitations have been reported in related systems. For instance, Kim *et al*. employed Sephadex LH-20 with 100% MeOH to purify rosmarinic acid **35** from *Melissa officinalis* extracts, obtaining the compound with a purity of only 38.8%.[110] Likewise, Zhang *et al*. used NK-109 macroporous resin to purify rosmarinic acid **29** from Perilla seed extracts, achieving 42.1% purity, with adsorption behaviour fitting pseudo-second-order kinetics and the Langmuir model. [111] These studies highlight the robustness of classical column chromatography but also its limited selectivity and efficiency when applied to complex plant matrices.

Distillation effluents from rosemary, sage, thyme, and oregano have been identified as rich sources of rosmarinic acid **35** and related phenolics, which can be efficiently concentrated and partially fractionated via dynamic or static adsorption–desorption with macroporous resins, particularly XAD-7.[112] Optimized SPE-

based methodologies yield fractions with increased total phenolic content and enhanced antioxidant and hypoglycaemic activities, while offering practical advantages over conventional extraction approaches, including lower reagent consumption, reduced operational costs, simplified handling, and scalability.

In parallel, alternative green extraction methods, such as hydrotropic extraction, have emerged as promising approaches for the recovery of poorly water-soluble phytochemicals. Hydrotropes are small amphiphilic molecules capable of markedly enhancing aqueous solubility through noncovalent interactions—such as π–π stacking and dipole–dipole interactions—without micelle formation. This mechanism can increase solubility by up to 200-fold while simultaneously promoting cell wall disruption.[113] Hydrotropic extractions typically involve maceration in a hydrotropic solution, followed by dilution below the minimal hydrotropic concentration to induce target compound precipitation and subsequent filtration.[114]

The Nardello-Rataj group demonstrated the effectiveness of this approach using alkyl polyglycosides and polyethylene glycol derivatives, with isoamyl xyloside showing superior selectivity for carnosic acid **36** over UA **23** under mild conditions (30% hydrotrope, 25 °C), achieving 23.3% carnosic acid **36** content.[115] Further studies reported yields of carnosic acid **36**, ranging from 1.02–1.21 g L^{-1}, highlighting the potential of hydrotropic systems for low-energy, solvent-free recovery.[116]

Another promising approach is the use of choline chloride: lactic acid (1:2) NADES, which enabled the extraction of 1.44 g of carnosic acid **36** and 0.48 g of carnosol **37** per 100 g of *Salvia officinalis* L., outperforming $ScCO_2$ extraction from both *Salvia* and *Rosmarinus officinalis*.[117,118] Further innovation was achieved by combining NADESs with thermoswitchable ionic liquid systems. A choline chloride–lactic acid/[BMIM]PF_6/H_2O system enabled homogeneous extraction at 60 °C and spontaneous phase separation upon cooling, allowing *in situ* fractionation: rosmarinic acid **35** was recovered in the aqueous phase with 89.0% efficiency, while carnosic acid **36** concentrated in the ionic liquid phase with 97.5% recovery.[119] This integrated extraction–separation strategy significantly reduces process complexity and eliminates hazardous solvents.

Selectivity can be further tuned by adjusting NADES polarity. For example, menthol: lactic acid systems preferentially extract nonpolar compounds, whereas lactic acid: glucose mixtures target polar phenolics. When used as biphasic systems, both compound classes can be recovered simultaneously under identical conditions. Significantly, NADESs also enhance compound stability: carnosol **36** retained 75% of its antioxidant activity after three months in NADESs, whereas it fully degraded in MeOH within 15 days.[120]

Complementary separation strategies have further advanced the selective recovery of these key phenolic and diterpenoid constituents. In a comparative study, SPE and liquid–liquid extraction (LLE) were evaluated as practical alternatives to conventional purification methods.

SPE using the macroporous weakly polar resin CAD-40 proved particularly effective for diterpenoid enrichment, affording carnosic acid **36** with 76.8% purity, whereas LLE with AcOEt was better suited for isolating the more polar phenolic fraction from diluted extracts, reaching rosmarinic acid **35 with** purities of up to 56.3%. Notably, the combined SPE–LLE approach outperformed traditional column chromatography and previously reported LLE protocols, providing both higher extraction efficiency and improved product quality. Adsorption studies indicated that the separation mechanism is predominantly governed by physical interactions, as evidenced by the good agreement between the experimental data and the Freundlich isotherm.[121]

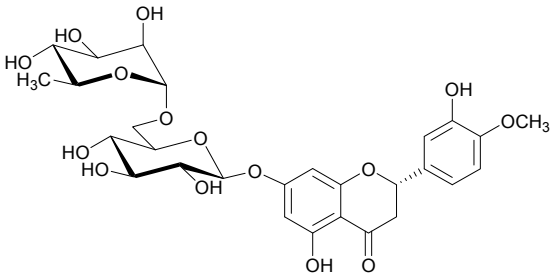
In parallel, MAE using PEG-400 further enhanced overall yields under optimised conditions, particularly when phosphoric acid was employed to promote cell wall disruption, while preserving antioxidant activity.[122] Complementing these approaches, Mo *et al*. reported a simple yet highly efficient protocol based on acidic aqueous ethanol extraction followed by multistep purification, achieving carnosic acid 36 purities of 98% or higher and extraction efficiencies above 94%.[123]

Overall, these studies demonstrate that while classical chromatographic approaches such as Sephadex LH-20 remain valuable benchmarks, emerging green extraction and hybrid SPE–LLE strategies offer superior selectivity, efficiency, and sustainability. The integration of biodegradable solvents reduced solvent consumption, and in situ fractionation represents a decisive step toward cost-effective industrial recovery of rosmarinic acid **35** and abietane diterpenes from *Lamiaceae* matrices.

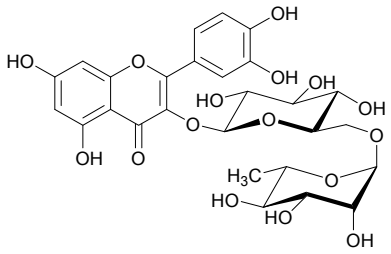
3.5.2 Phenolic Compounds from *Citrus*: Hesperidin and related flavanones. Hesperidin **39** is a flavonoid known to promote wound healing by enhancing collagen synthesis, vasculogenesis, and angiogenesis. Additionally, it has shown potential in preventing the progression of neurodegenerative disorders such as Parkinson's and Alzheimer's disease.[124] Rutin **40**, another flavonoid with strong antioxidant properties, also contributes to vascular health and has been reported to support and accelerate wound healing (Scheme 9).[125]

A recent study developed a green extraction method for isolating hesperidin **39** from fresh orange bagasse using aqueous $CaCl_2$ and pH modulation, thereby avoiding the use of organic solvents and reducing energy input. This eco-friendly process yielded hesperidin **39** at 1.2% concentration and 97.2% purity.[126]

In contrast, a conventional method using a methanolic extract followed by crystallisation in a water/dichloromethane mixture yielded a higher percentage (2.8%), but with lower purity (89.4%). Notably, the hesperidin **39** obtained via this second method served as the precursor for the synthesis of diosmetin **41**, a flavone with documented bioactivity (Scheme 10).[127]

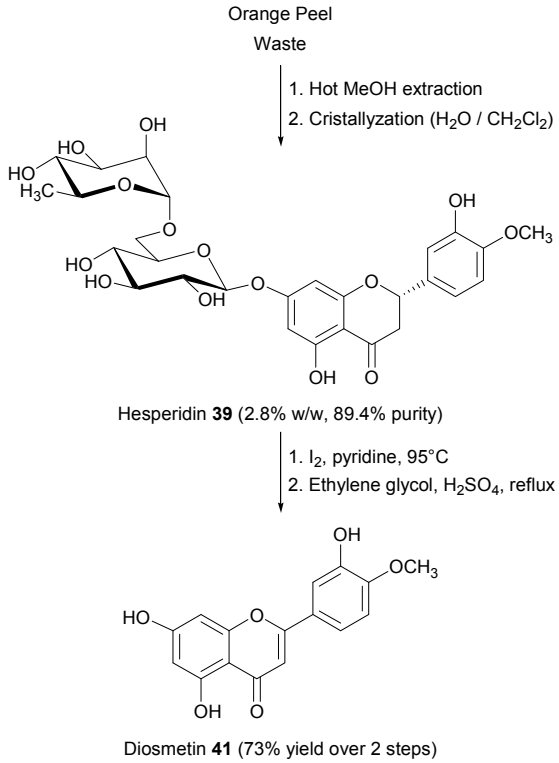


Hesperidin **39**



Rutin **40**

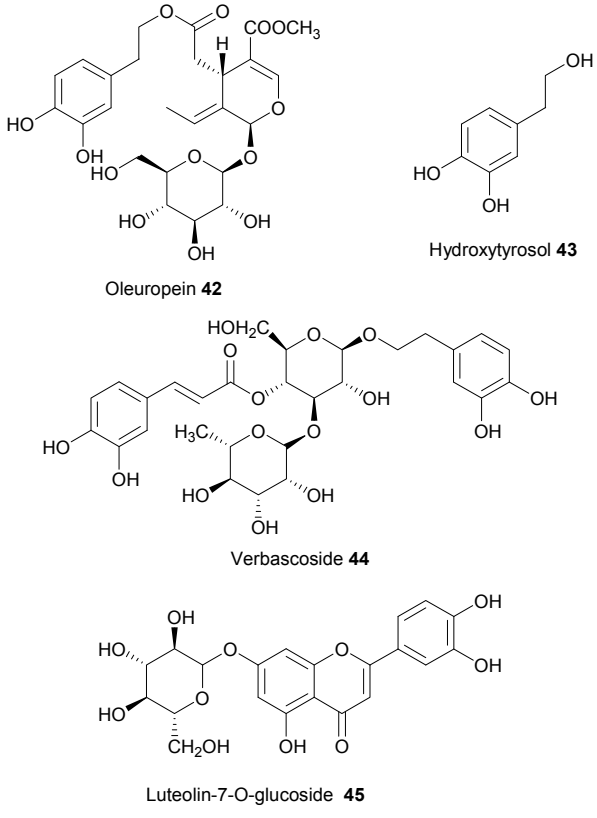
Scheme 9. Structure of hesperidin **39** and rutin **40**.



Scheme 10. Isolation of hesperidin **39** from orange peel waste and its transformation into diosmetin **41**.

3.5.3 Secoiridoids from Oleaceae: Oleuropein and derivatives. Harvesting olive trees (*Olea europaea* L.) yields an estimated 25 kg of branches and leaves per tree annually, a biomass stream traditionally regarded as agricultural waste.[128] Nevertheless, olive leaves have gained increasing interest in biorefinery and valorisation strategies due to their abundance, renewability, low cost, and, most importantly, their rich and diverse phytochemical composition. This biomass represents a promising raw material for the recovery of bioactive compounds, particularly phenolics and flavonoids, with well-documented antioxidant, antimicrobial, and anti-inflammatory activities. Among these, oleuropein **42** and hydroxytyrosol **43** stand out as the most abundant and biologically active constituents of the olive tree, alongside other valuable compounds such as rutin **40**, verbascoside **44**, luteolin-7-O-glucoside **45**, and catechins (Scheme 11).[129]

Several extraction strategies have been explored to effectively recover these compounds, ranging from conventional methods to novel green technologies. Boli *et al.*[130] systematically compared EtOH, water, and choline chloride–based DESs, as well as their mixtures with EtOH or water, demonstrating that solvent polarity and viscosity play a decisive role in extraction performance. While EtOH showed high selectivity toward oleuropein **42**, DESs systems exhibited enhanced total phenolic recovery when combined with EtOH, owing to reduced viscosity and improved mass transfer. Moreover, MAE produced phenolic profiles comparable to or superior to those of conventional maceration, while significantly reducing processing time and solvent consumption.



Oleuropein **42**

Hydroxytyrosol **43**

Verbascoside **44**

Luteolin-7-O-glucoside **45**

Scheme 11. Chemical structures of some of the compounds isolated from *Olea europaea* L.

An alternative and selective approach is supercritical antisolvent fractionation (SAF), which utilises $ScCO_2$ as a nonpolar antisolvent. This technique enables the selective precipitation of target compounds while leaving other compounds dissolved. Baldino *et al.*[131] applied SAF to EtOH extracts of olive leaves, increasing the oleuropein **42** concentration from 20% to 36%

(w/w) at 150 bar and 35 °C. Chinnarasu *et al*. demonstrated a similar enhancement using PLE followed by $ScCO_2$ treatment, which tripled the antioxidant activity of the extract.[132]

Recent studies further support the potential of olive leaf extracts in food preservation and health-related applications. For instance, oleuropein-rich extracts obtained from different olive cultivars have been reported to exhibit high antioxidant and antimicrobial activity against *S. aureus* and other foodborne pathogens, highlighting their functional role in extending shelf life.[133]

Comparative evaluations of conventional and intensified extraction techniques—including heat reflux, MAE, UAE, and high-pressure-assisted extraction—have consistently identified oleuropein **42** as the predominant polyphenol in olive leaf extracts, with comparable overall yields across methods.[134] Further process optimisation, such as the application of microwave pretreatment prior to UAE, has been shown to substantially enhance total phenolic recovery relative to conventional maceration. [135]

The effectiveness of UAE is primarily attributed to acoustic cavitation, which facilitates cell wall disruption and the release of intracellular phenolics. In addition to temperature, key operational parameters such as ultrasound frequency and amplitude critically influence extraction efficiency, enabling selective enrichment of oleuropein **42** and luteolin-7-glucoside **45** under mild conditions. [136]

Pre-extraction processing also plays a decisive role, as drying conditions have been shown to markedly affect phenolic recovery. Room-temperature drying followed by alcoholic extraction has been associated with higher oleuropein **42** yields and enhanced antioxidant activity, reflecting synergistic interactions among phenolic constituents. [137]

In another study focused on process optimisation, Lama-Muñoz et al. investigated dynamic maceration and PLE using response surface methodologies to evaluate the influence of temperature, EtOH concentration, and leaf moisture. Under optimised PLE conditions (190 °C, 5% moisture and 80% aqueous EtOH), yields of 63.35 g kg^{-1} of oleuropein **42** and 2.71 g kg^{-1} of luteolin-7-O-glucoside **45** were achieved, with an associated antioxidant activity of 146.5 mmol Trolox kg^{-1}. Notably, reducing the EtOH concentration to 60% resulted in a markedly higher antioxidant capacity (362.55 mmol Trolox kg^{-1}), despite a lower total phenolic yield. These findings highlight the complex relationship between phenolic composition and antioxidant efficacy, underscoring the importance of qualitative phenolic profiles over absolute concentrations.[138]

In conclusion, olive leaves are a sustainable source of bioactive phenolics, with cultivar selection and processing conditions strongly influencing both yield and bioactivity. Among emerging techniques, PLE and SAF stand out for their efficiency, selectivity and scalability, supporting the valorisation of olive leaf biomass within integrated biorefinery and circular bioeconomy frameworks for functional food and nutraceutical applications.

3.5.4 Alkamides and Capsaicinoids (Capsaicin-like molecules). Capsaicinoids constitute a family of bioactive alkamides responsible for the characteristic pungency and diverse pharmacological properties of *Capsicum* species. Among them, capsaicin **46** (Scheme 12) is the most abundant and extensively studied compound. Capsaicin **46** exhibits well-documented analgesic activity, particularly in the management of chronic pain, and has also been reported to exert anticancer effects through multiple molecular mechanisms. Furthermore, several studies have demonstrated that capsaicin **46** consumption can suppress appetite, enhance energy expenditure, and support weight management, suggesting its potential role in obesity management.[139] In addition to these effects, capsaicinoids display strong antioxidant activity, efficiently scavenging reactive oxygen species (ROS) implicated in oxidative stress and the progression of chronic diseases.[140]

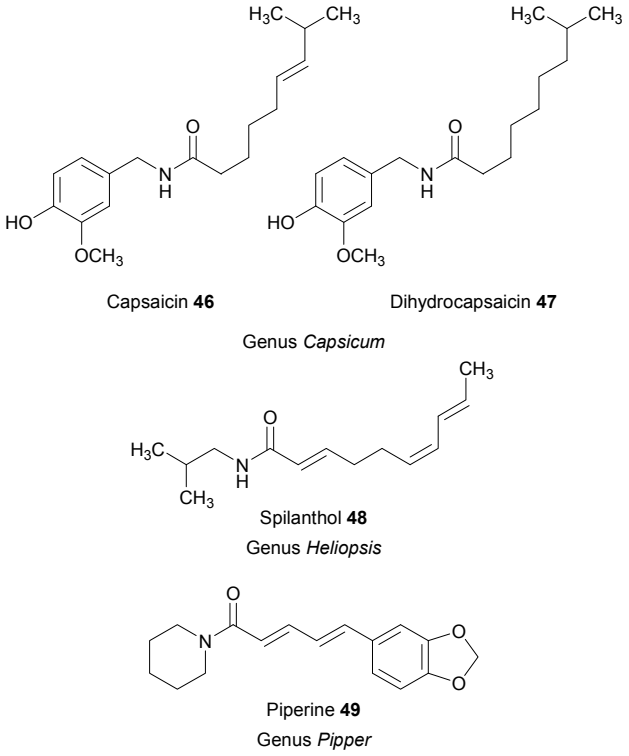


Figure 12. Chemical structure of some alkamides of biological interest.

Beyond capsaicinoids, other structurally related bioactive alkamides—such as spilanthol (also known as affinin) **48**, the major *N*-alkylamide of *Acmella oleracea*—share comparable physicochemical properties, biological activities, and technological challenges during extraction and purification. These capsaicin-like molecules are typically amphiphilic, thermolabile, and present at relatively low concentrations in complex plant matrices, making their selective and sustainable recovery particularly demanding.[141]

To overcome the limitations of conventional capsaicinoids extraction methods, such as Soxhlet, maceration, and HD, considerable effort has been devoted to developing alternative extraction techniques. Traditional approaches are often characterised by long extraction times, high solvent consumption, limited selectivity and the risk of thermal degradation of sensitive phytochemicals. One of the recently reported approaches for obtaining high-purity capsaicinoids from ground habanero

pepper (*Capsicum chinense*) involves a two-step MAE process. In this strategy, the milled chilli matrix is first irradiated under solvent-free conditions, followed by microwave irradiation in EtOH. This intensified MAE protocol achieved a total capsaicinoid recovery of 91.84%, with capsaicin **46** as the major component (56.22%), followed by dihydrocapsaicin **47** (35.62%). Compared with conventional Soxhlet extraction, the MAE process provided higher extraction efficiency, significantly reduced processing times and lower energy consumption, demonstrating its potential as a more sustainable alternative for the selective recovery of capsaicinoids from habanero peppers.[142]

Aqueous two-phase systems (ATPS) are formed by two hydrophilic components—such as alcohols, polymers, ionic liquids, or inorganic salts—that spontaneously separate into two immiscible aqueous phases. Target compounds distribute between these phases according to their physicochemical properties and the system's specific composition. Using this approach, Zhao *et al*. developed a three-step separation and purification strategy for capsaicin **40** from *Capsicum* oleoresin. In the initial extraction step, crude capsaicin **40** was recovered using an EtOH–K_2CO_3-based ATPS, yielding an 85.4% recovery. Subsequent purification was performed in two chromatographic steps using D101 macroporous resin, followed by SKP-10-4300 reversed-phase resin, resulting in an overall increase in capsaicin 40 purity from 7% to 85%. [143] Similarly, Fan et al. reported a maximum capsaicin recovery of 95.5% using an ethylene oxide–propylene oxide copolymer–K_2HPO_4–EtOH ATPS, followed by adsorption on macroporous resin to reach purities above 85%.[144] Comparable sustainable strategies have recently been extended to spilanthol **41**, which has been successfully extracted using NADES combined with simplified SPE protocols based exclusively on ethanol–water systems. These approaches achieved spilanthol **41** purities exceeding 90% while avoiding halogenated solvents and reducing chromatographic complexity, thereby closely paralleling ATPS-based capsaicin purification in terms of green chemistry principles and process efficiency. [145]

Beyond improvements in extraction efficiency, increasing attention has been directed towards the development of sustainable separation and purification strategies for capsaicinoids. Despite their effectiveness, ATPS- and resin-based purification strategies often rely on multiple chromatographic steps, which can increase operational costs and limit large-scale applicability. Similar limitations have been highlighted in the purification of spilanthol, where conventional column chromatography or solvent-intensive clean-up procedures, although effective, pose challenges related to solvent use, scalability, and compound stability.[146] To address these issues, hybrid approaches combining MAE with ATPS have been proposed. For instance, the elimination of chromatographic steps through MAE of Capsicum chinense var. cumari-do-Pará, followed by an EtOH–NaH_2PO_4 ATPS, enabled the isolation of capsaicin **40** with an extraction efficiency of 85.6%.[147]

Collectively, these studies demonstrate that capsaicinoids, exemplified by capsaicin **40**, and structurally related alkamides such as spilanthol **41** can be addressed within a unified conceptual framework for sustainable extraction and purification. The convergence of MAE, ATPS, NADES, and low-solvent SPE approaches underscores the potential for transferable green methodologies applicable to a broader class of bioactive *N*-alkylamides derived from biomass waste.

3.6 Agrochemicals

The intensive use of synthetic agrochemicals has ensured high agricultural productivity but has also raised concerns regarding environmental persistence, non-target toxicity, and the rapid development of pest resistance, thereby accelerating the search for bio-based alternatives derived from natural sources.[148,149] In this context, plant secondary metabolites recovered from agro-industrial waste have emerged as promising candidates for sustainable pest management due to their insecticidal, antifeedant, antiviral, and growth-regulating activities. Among these, limonoids from citrus residues stand out as key bioactive constituents, whose occurrence in both aglycone and glycosylated forms enables selective recovery and functional diversification. Moreover, the variability of limonoid profiles across citrus species, cultivars, and developmental stages highlights the importance of rational biomass selection when designing efficient and sustainable valorisation strategies.[150]

3.6.1 Limonoids: Limonin as a Lead Agrochemical. Limonoids constitute a distinctive class of highly oxygenated tetranortriterpenoids predominantly found in the *Rutaceae* and *Meliaceae* families. Among them, limonin **50** (Figure 13) is consistently reported as the most abundant limonoid in *citrus* fruits and their industrial by-products, including seeds, peels, and pomace. Its widespread distribution, chemical stability, and well-defined molecular scaffold have positioned limonin **50** as a primary target for recovery from *citrus* waste streams. [151]

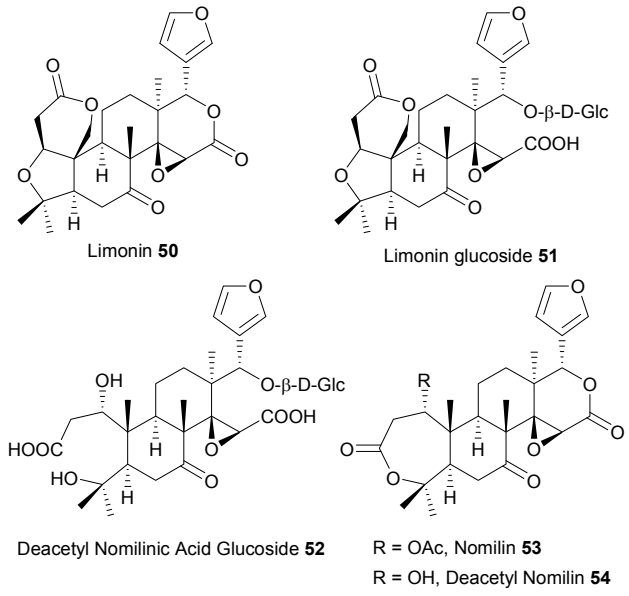


Figure 13. Representative structures of major citrus limonoids.

Beyond its abundance, limonin **50** displays a broad spectrum of biological activities relevant to crop protection, including insecticidal, antifeedant, insect growth–regulatory, and antiviral effects.[152] This multifunctionality is particularly advantageous for integrated pest management strategies, where compounds that act through multiple biological pathways can help mitigate the

development of pest resistance. Nevertheless, the moderate intrinsic potency of limonin **50** has driven sustained efforts to enhance its performance through optimised extraction strategies and targeted structural modification.[153]

From a processing perspective, significant advances have been made in the sustainable recovery of limonin **50** from *citrus* biomass. $ScCO_2$ extraction has emerged as an effective green technology for selectively isolating limonoid aglycones, offering high extraction efficiency while minimising thermal degradation. Several studies have demonstrated that careful optimisation of pressure, temperature, and co-solvent composition enables efficient recovery of limonin **50** from citrus seeds and peels, supporting the scalability of this approach.[154]

Complementary to $scCO_2$-based approaches, hydrotropic extraction has been proposed as an innovative aqueous strategy that simultaneously recovers water-insoluble limonoid aglycones and water-soluble limonoid glucosides in a single step. Using *Citrus aurantium* seeds as a model matrix, Dandekar *et al*. demonstrated a hydrotropy-assisted extraction–purification process based on sodium cumene sulphonate, followed by adsorption onto a polystyrenic SP700 resin and gradient elution with water/MeOH mixtures. This methodology enabled the isolation of three structurally distinct limonoids—limonin **50** (410 mg), deacetyl nomilinic acid glucoside **52** (310 mg), and deacetyl nomilin **54** (155 mg)—from 250 g of seed material. Notably, coupling hydrotropy with resin-based fractionation enabled efficient separation across a broad polarity range while substantially reducing organic solvent consumption, positioning this approach as a viable alternative to supercritical and solvent-intensive processes.[155]

In contrast to physicochemical extraction methods, enzymatic strategies offer a biologically inspired route for limonoid recovery under particularly mild conditions. An early contribution was reported by Lim *et al*., who investigated the enzymatic hydrolysis of citron (*Citrus junos*) processing waste using pectinase and cellulase. Through response surface optimisation, limonin **50** concentrations of up to 3.5 mg per 100 g of processed waste were achieved at approximately 50 °C and pH ≈5, together with the co-recovery of structurally related limonoids such as nomilin **53**.[156]

Building on this work, Ramos-Ibarra *et al*. demonstrated that enzyme-assisted treatment of *Citrus sinensis* and *Citrus aurantiifolia* seeds using a commercial pectinase–cellulase complex significantly enhanced limonin **50** releases. Under optimised conditions, limonin **43** recoveries reached 3.7 mg g^{-1} dry seed, corresponding to approximately a two-fold increase relative to non-enzymatic or conventional solvent-based extractions.[157]

Overall, limonin **50** exemplifies how a naturally abundant metabolite derived from citrus industrial residues can be valorised as a lead compound for sustainable agrochemical development. The convergence of green extraction technologies highlights the strong potential of limonoids as renewable, multifunctional building blocks for environmentally responsible crop protection strategies.

4 Techno-Economic Assessment of Bioactive Recovery Pathways.

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4.1 Key Economic Indicators and Assumptions

Techno-economic assessment (TEA) is a key tool for determining the industrial viability of bioactive compound recovery from biomass waste streams, particularly when embedded within integrated biorefinery schemes aligned with circular bioeconomy principles. Rather than focusing solely on individual cost items, recent studies emphasise that economic performance is primarily governed by process integration, co-product valorisation, and long-term operational stability, as neglecting these factors frequently leads to unrealistic profitability projections.[158]

Across reported TEA case studies, a limited number of parameters consistently dominate overall process economics. These include process throughput, equipment lifetime, and the efficiency of solvent, water, or sorbent regeneration, which often exert a stronger influence on operating costs than energy consumption itself.[159] This is especially evident in adsorption- and membrane-based recovery systems, where material durability and fouling behaviour directly determine replacement frequency and long-term cost structures.[160]

Feedstock availability and logistics represent another critical, yet frequently underestimated, economic constraint. Although biomass residues are commonly assumed to be low-cost or cost-free, expenses associated with collection, stabilisation, drying, storage, and transport can account for a substantial fraction of Operational Expenditure (OPEX), particularly for wet, bulky, or seasonally available matrices such as fruit pomace, winery residues, or algal biomass. These constraints become increasingly relevant at an industrial scale, where continuous operation requires reliable, year-round supply chains. [159, 161]

The economic performance of green extraction technologies is also highly sensitive to assumptions regarding solvent recovery, energy integration, and scale-dependent efficiencies. Hydrothermal, membrane-based, and adsorption-driven processes show markedly improved competitiveness upon scale-up when heat recovery, process intensification, and renewable energy integration are implemented, whereas laboratory-scale assumptions often underestimate the impact of solvent recycling efficiency and sorbent lifespan on unit production costs.[161]

Finally, TEA outcomes are strongly market dependent. High-value pharmaceutical and nutraceutical applications can sustain higher production costs due to elevated market prices and strict purity requirements, while food, cosmetic, and agrochemical uses demand high-throughput, cost-efficient processes operating at moderate purity levels. This market-driven cost tolerance and the associated trade-offs between economic performance and sustainability objectives are a recurring conclusion across TEA and combined TEA– life cycle assessment (LCA) studies on phenolics, polysaccharides, and antioxidant extracts. [162]

4.2 Process–Compound Coupling, Case Studies, and Scaling-Up Considerations

Case studies reported in the literature clearly demonstrate that the techno-economic viability of bioactive compound recovery pathways depends strongly on the coupling of specific phytochemicals with appropriate extraction and purification

technologies, as well as on their integration within multiproduct and cascade-based processing schemes. In general, approaches enabling the sequential recovery of several compound classes from a single biomass consistently outperform isolated, single-product processes by distributing capital and operating costs across multiple revenue streams and improving overall biomass utilisation.[163]

A representative example is the techno-economic evaluation of sequential hydrothermal extraction for potato peel valorisation, where multi-stage processes allowing the recovery of polyphenols, glycoalkaloids, and polysaccharides achieved superior economic performance compared with single-stage routes, despite higher capital expenditure associated with increased process complexity.[158] Similar advantages have been reported for citrus peel and olive-derived by-products, where integrated biorefinery configurations combine early recovery of volatile fractions, such as essential oils or limonene, with subsequent solvent-based, membrane-assisted, or adsorption-driven extraction of phenolic compounds.[161a, 164]

For phenolic-rich liquid and semi-solid residues, including olive mill wastewater and processing streams from *Lamiaceae* and *Oleaceae* species, adsorption–desorption approaches based on polymeric resins or membrane concentration have emerged as economically competitive alternatives to solvent-intensive extraction. TEA consistently identify resin lifespan, regeneration efficiency, and fouling behaviour as dominant contributors to operating costs, frequently exceeding the impact of energy consumption.[161a]

Beyond terrestrial biomass, cascade extraction strategies have also been validated for marine resources such as brown macroalgae. Combined TEA–LCA studies demonstrate that integrated biorefinery concepts can achieve favourable economic and environmental performance when feedstock costs, extraction efficiency, and membrane performance are carefully optimised, with co-product valorisation playing a decisive role in achieving positive net present values at an industrial scale.[161]

Recent work on walnut by-products (*Juglans regia* L.) provides a particularly illustrative example of successful process scalability under realistic conditions. In this study, polyphenols were extracted from walnut shell and pruning residues using an ethanol–water system under mild operating conditions. While laboratory-scale optimisation identified optimal extraction parameters (60% ethanol, solid-to-solvent ratio 1:4, particle size 6 mm, 25 °C, 1.5 h), subsequent validation at semi-industrial scale yielded higher extraction yields than those at laboratory scale, reaching 35.4% for walnut shells and 23.3% for pruning residues. [165]

Selected case studies on lycopene extraction from tomato processing residues further reinforce the importance of integrated economic and environmental evaluation. Although multiple extraction technologies have been demonstrated at laboratory scale, their industrial feasibility remains strongly dependent on capital investment, operating costs, energy demand, and solvent recovery efficiency, and comprehensive comparative LCA–TEA studies across alternative technologies remain limited. [166] Membrane-based pervaporation has emerged as a promising option, combining moderate capital requirements with comparatively low environmental impacts, although membrane replacement frequency and solvent selection remain critical economic drivers. [167] In contrast, supercritical CO_2 extraction can deliver higher profitability under optimised conditions, but this advantage is often offset by increased capital investment and energy consumption. [166]

Comparable conclusions have been reported for limonene recovery from citrus processing residues, where process simulation and TEA indicate that high-purity d-limonene can be obtained via conventional separation routes such as vacuum fractional distillation, with economic performance strongly dependent on production scale and feedstock sourcing strategies. [168] Although $ScCO_2$-based routes can achieve near-complete recovery, their higher energy demand and solvent circulation requirements significantly influence manufacturing costs.[169] Sustainability-oriented assessments consistently show that limonene production is most competitive when embedded in fully integrated orange peel biorefineries, coupling essential oil and polyphenol recovery with downstream processes such as enzymatic saccharification and anaerobic digestion.[170]

Finally, case studies on rosemary biomass demonstrate that integrated and intensified extraction schemes can significantly improve the economic performance of abietane-type diterpene recovery. Process intensification strategies combining $ScCO_2$ extraction and pressurised water extraction within a single multipurpose unit reduce annual production costs by approximately 25–30% compared with single-step supercritical extraction, reinforcing the industrial potential of integrated, multiproduct biorefinery schemes. [171]

From a scaling-up perspective, laboratory-optimised processes face additional challenges, including limitations in mass and heat transfer, large-volume solvent handling, membrane fouling, and sorbent degradation when processing complex biomass matrices. Studies on NADES-, hydrothermal-, and membrane-based systems indicate that viscosity, fouling propensity, and cleaning frequency can significantly affect both capital and operating costs at an industrial scale. [160b, 161] Regulatory constraints related to solvent residues and product specifications further increase economic uncertainty, particularly for food and pharmaceutical applications.

Despite these challenges, pilot- and demonstration-scale studies increasingly confirm that well-designed, modular processes incorporating heat integration, solvent reuse, and co-product valorisation can achieve competitive economic performance. Early integration of TEA, combined with sensitivity and scenario analysis, is therefore essential to guide technology selection, prioritise research efforts, and minimise scale-up risks in the sustainable recovery of bioactive compounds from biomass waste streams.

5. Environmental, Circularity, and Societal Dimensions of Bioactive Recovery

Environmental assessment, particularly through LCA, plays a central role in determining whether bioactive compound recovery pathways genuinely deliver sustainability benefits. Although green extraction technologies are frequently promoted

as environmentally friendly, their overall environmental performance depends strongly on system-level factors, including energy sources, solvent production routes, process efficiency, and scale of operation. For example, $ScCO_2$ extraction may exhibit higher energy demands than conventional solvent-based methods; however, these impacts can be substantially mitigated through renewable energy integration, efficient heat recovery, and CO_2 recycling strategies.

LCA studies consistently demonstrate that the valorisation of biomass waste into high-value phytochemicals can significantly reduce environmental burdens when compared with conventional disposal scenarios such as landfilling or incineration. Avoiding impacts associated with waste management and the displacement of fossil-based or synthetically produced additives contributes positively to overall environmental performance. Nevertheless, comprehensive and harmonised LCA data remain limited for many emerging extraction and purification technologies, highlighting the need for consistent methodological frameworks to enable meaningful cross-comparisons and informed decision-making.

Beyond environmental performance, bioactive recovery from agro-industrial residues aligns directly with the principles of the circular bioeconomy by promoting resource efficiency, waste minimisation, and value retention. Transforming low-value or problematic waste streams into functional ingredients closes material loops and creates additional revenue streams for agricultural and food-processing sectors. Integrated biorefinery approaches, in which multiple products are sequentially recovered from the same biomass, exemplify circular design by maximising resource utilisation while simultaneously enhancing economic resilience and reducing environmental footprints. Moreover, decentralised valorisation of locally generated residues can strengthen regional bioeconomies, particularly in agricultural areas where waste accumulation poses both environmental and logistical challenges.

Social acceptance and regulatory compliance are equally decisive for the successful implementation of bioactive recovery pathways. Regulatory frameworks governing food, pharmaceutical, cosmetic, and agrochemical applications impose strict requirements on raw material traceability, solvent selection, residual contaminants, and product safety. While compliance with these regulations can increase development costs and complexity, it also provides market confidence and facilitates consumer trust. From a social perspective, biomass valorisation can support rural development, job creation, and income diversification for agro-industrial stakeholders. Transparent communication about the safety, quality, and sustainability of products derived from biomass residues is essential to address potential consumer concerns about the use of “waste-derived” materials. When robust regulatory compliance is combined with credible environmental assessment and circular design principles, bioactive recovery from biomass waste can achieve broad societal acceptance across multiple industrial sectors.

6. Conclusions and Future Perspectives

The valorisation of plant-based biomass waste as a renewable source of high-value phytochemicals represents a strategically important pathway at the convergence of Green Chemistry, Circular Bioeconomy, and sustainable industrial development. As illustrated throughout this review, a wide diversity of bioactive compounds, including pigments, flavours and fragrances, pharmacologically relevant metabolites, lipophilic constituents, phenolics, and agrochemical precursors, can be selectively recovered from agro-industrial residues using both established and emerging green extraction and purification technologies, supporting the development of more sustainable and circular bio-based value chains.

Beyond extraction efficiency alone, techno-economic and environmental analyses demonstrate that industrial viability critically depends on intelligent process integration, solvent recovery and reuse, energy optimisation, and alignment with end-use market requirements. Integrated biorefinery concepts, particularly those enabling multiproduct recovery and cascade valorisation, consistently outperform single-product approaches by enhancing resource efficiency, economic resilience, and environmental performance. Nevertheless, translating these strategies into industrial practice will require further efforts in process integration, scale-up validation, and the adoption of standardised sustainability metrics to enable fair comparisons between competing technologies.

From a sustainability perspective, combined TEA–LCA studies highlight that the environmental benefits of bioactive recovery are strongly context-dependent, being maximised when waste-derived feedstocks displace fossil-based or synthetically produced ingredients and when avoided waste management impacts are properly accounted for. However, the limited availability of comprehensive, comparable life-cycle assessment data for emerging extraction technologies underscores the need for harmonised assessment frameworks and early-stage sustainability screening.

Future research should therefore prioritise the systematic integration of techno-economic assessment, life cycle analysis, and regulatory considerations from the earliest stages of process development. Greater emphasis on scalable multiproduct recovery schemes, digital process optimisation, and decentralised, region-specific valorisation strategies will be essential to strengthen local bioeconomies and reduce logistical and environmental burdens. In parallel, regulatory-aware process design and transparent communication of safety and sustainability attributes will be critical to foster market acceptance, particularly in food, pharmaceutical, cosmetic, and agrochemical applications.

Ultimately, the successful implementation of green and integrated recovery strategies has the potential to transform agro-industrial residues from an environmental liability into a cornerstone of resilient, sustainable, and competitive bio-based industries. By coupling chemical innovation with system-level thinking, biomass waste valorisation can play a decisive role in advancing circular production models and supporting the transition toward a more sustainable industrial future.

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Author contributions

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Abbreviations

AcOH	Acetic acid
AcOEt	Ethyl acetate
APW	Artemisinin Production Waste
ATPS	Aqueous two-phase systems
CA	Corosolic acid
CAPEX	Capital Expenditure
CBD	Cannabidiol
CBDA	Cannabidiolic acid
CL	Cellulase
CPC	Centrifugal partition chromatography
CPME	Cyclopentyl methyl ether
DESs	Deep Eutectic Solvents
DMC	Dimethyl carbonate
DD	Deodorizer distillate
DW	Dry weight
EOs	Essential oils
EtOH	Ethanol
FAMEs	Fatty acid methyl esters
FASEs	Fatty acid sterol esters
FFA	Free fatty acids
HD	Conventional hydrodistillation
nHex	n-Hexane
ILs	Ionic liquids
LLE	Liquid–liquid extraction
LCA	Life cycle assessment
MA	Maslinic acid
MAPs	Medicinal and aromatic plants
MAE	Microwave-assisted extraction
MAHD	Microwave-assisted hydrodistillation
MeOH	Methanol
2-MeTHF	2-Methyltetrahydrofuran
MtBE	Methyl tert-butyl ether
NADES	Natural Deep Eutectic Solvents
OA	Oleanolic acid
OLE	Oleuropein
OPEX	Operational Expenditure
PG	Polygalacturonase
PL	Pectin lyase
PLE	Pressurised liquid extraction
PTAs	Pentacyclic triterpenes acids
ROS	Reactive oxygen species
RODD	Rapeseed oil deodoriser distillate
SAF	Supercritical antisolvent fractionation
$ScCO_2$	Supercritical carbon dioxide
SFE	Supercritical fluid extraction
SLE	Solid–liquid extraction
SLME	Solvent-less microwave extraction
SODD	Soybeanoil deodoriser distillate
SPE	Solid phase extraction
TEA	Techno-Economic Assessment
Δ^9-THC	Delta-9-tetrahydrocannabinol
UA	Ursolic Acid
UAE	Ultrasound-assisted extraction
WHO	World Health Organisation
XL	Xylanase

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Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.