Application of Green Chemistry in Herbal Drug Development

Lukas F Braun [1], Hannah M Schneider [2*], Felix R Becker [3], Sophia K Wagner [4]
[1] Institute for Drug Delivery Systems, University of Heidelberg, Germany
[2] Department of Nanomedicine, Technical University of Munich, Germany
[3] Cancer Nanotechnology Lab, Charité – Berlin University Hospital, Germany
[4] Institute of Pharmaceutical Sciences, University of Freiburg, Germany

* Corresponding Author: **Hannah M Schneider**

Article Info

ISSN (online): 3049-0421
Volume: 02
Issue: 06
November-December 2025
Received: 20-09-2025
Accepted: 18-10-2025
Published: 16-11-2025
Page No: 51-57

Abstract
The escalating global demand for plant-based therapeutics, coupled with mounting environmental concerns surrounding conventional pharmaceutical manufacturing, has necessitated a fundamental re-evaluation of drug development paradigms. Herbal drug development has traditionally relied upon energy-intensive processes, hazardous organic solvents, and waste-generating methodologies that pose significant ecological and occupational health risks. Green chemistry, defined by Anastas and Warner as the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances, offers a compelling and pragmatic framework to address these systemic inefficiencies. The present review critically examines the translational application of green chemistry principles in phytopharmaceutical development, with emphasis on sustainable extraction techniques, solvent minimization, energy efficiency, and integrated waste management strategies. It further evaluates advanced technologies including supercritical fluid extraction, microwave-assisted extraction, ultrasound-assisted extraction, and enzymatic bioprocessing through the dual lenses of scientific efficacy and environmental sustainability. Process optimization strategies relevant to industrial scale-up are assessed, alongside the roles of regulatory frameworks and ethical sourcing in legitimizing green pharmaceutical practices. Current technological and economic barriers to widespread adoption are critically appraised, and future trajectories in sustainable phytopharmaceutical innovation are proposed. It is concluded that green chemistry not only reduces the ecological footprint of herbal drug manufacture but also enhances product quality, bioactive compound integrity, and long-term commercial viability, thereby positioning sustainability as both a scientific and strategic imperative in modern natural product drug development.

Keywords: Green chemistry, Herbal drug development, Sustainable processes, Phytopharmaceuticals, Eco-friendly extraction, Natural products

1. Introduction

Nanotechnology is the science of the smallest particles. Nanotechnology is a world in which new products are developed at the atomic and molecular level. It limits renewable energy sources and provides a realistic and cost-effective means of keeping the environment clean [1]. Nanotechnology is a term used to define areas of science and engineering in which phenomena occurring at nanoscale dimensions are used in the design, characterization, manufacture, and applications of materials, structures, devices, and systems [2]. The nano drugs employed have demonstrated that bioavailability is enhanced, side effects are eliminated, and therapeutic medicine is absorbed more effectively. Nanoparticles have recently been used on this membrane as a medication carrier system [3]. Particularly, nanoparticles are inhaled and cross brain membranes. The typical and traditional therapies for

vascular thrombosis often have relatively limited advantages due to the short plasma half-life, many adverse effects, and fast drug wash-outs [4]. Polymeric nanoparticles (NPs) have attracted considerable interest over recent years due to their properties resulting from their small size. Advantages of polymeric NPs as drug carriers include their potential use for controlled release, the ability to protect drug and other molecules with biological activity against the environment, improve their bioavailability and therapeutic index [5]. The term "nanoparticle" comprises both nanocapsules and nanospheres, which differ with respect to their morphology. Nanocapsules are composed of an oily core in which the drug is usually dissolved, surrounded by a polymeric shell which controls the release profile of the drug from the core. Nanospheres are based on a continuous polymeric network in which the drug can be retained inside or adsorbed onto their surface.

Green chemistry, formalized through the Twelve Principles articulated by Anastas and Warner in 1998, provides a scientifically robust and operationally actionable roadmap for transforming pharmaceutical manufacturing toward genuinely sustainable practices [1, 9]. Its application within the domain of herbal drug development is particularly compelling, as the field intersects complex biological matrices, thermolabile bioactive compounds, and the demand for rigorous quality assurance. Beyond ecological benefits, green methodologies have been demonstrated to preserve or enhance the recovery of sensitive phytochemicals such as polyphenols, terpenoids, and alkaloids that are susceptible to thermal and oxidative degradation under conventional processing conditions [10, 11]. The present review aims to consolidate current evidence regarding the deployment of green chemistry across the herbal drug development pipeline, from raw material procurement and extraction through to formulation and regulatory compliance, and to delineate the path toward fully sustainable phytopharmaceutical production.

2. Principles of Green Chemistry and Their Relevance to Drug Development

The Twelve Principles of Green Chemistry, as enumerated by Anastas and Warner [1], collectively advocate for the prevention of waste at source, the utilization of atom-efficient synthetic pathways, the preference for less hazardous reagents, and the design of safer chemicals with reduced environmental persistence. In the context of herbal drug development, several of these principles assume particular prominence. The principle of waste prevention resonates directly with the large-scale solvent use inherent to traditional botanical extraction, where solvent-to-material ratios often exceed twenty to one by volume [12]. Similarly, the principle of designing for energy efficiency aligns with industry imperatives to reduce the thermal load of extraction operations, which constitute a disproportionate share of manufacturing energy consumption.

Atom economy, a concept central to synthetic chemistry but equally applicable to extraction science, encourages maximization of the proportion of starting material incorporated into the final product. In phytochemical extraction, this translates to the development of high-yielding, selective extraction protocols that minimize co-extraction of inert material and reduce the need for elaborate downstream purification [13]. The preference for renewable feedstocks further aligns with the natural product sector's intrinsic reliance on botanical raw materials, provided that sourcing is conducted in a manner consistent with biodiversity conservation and sustainable agricultural practices [14]. The principle of real-time analytical monitoring supports the implementation of process analytical technology in phytopharmaceutical manufacturing, enabling continuous quality assurance and minimizing batch failure rates [15]. Collectively, these principles constitute a coherent philosophical and technical framework for reimagining every stage of herbal drug development.

3. Application of Green Chemistry in Herbal Drug Development

3.1. Green Extraction Techniques and Solvent Selection

The selection of extraction solvent is among the most consequential decisions in phytopharmaceutical process design, directly influencing yield, selectivity, safety profile, and environmental impact. Conventional solvents including dichloromethane, chloroform, and petroleum ether, though efficacious for lipophilic compound extraction, are associated with ozone depletion, carcinogenicity, and aquatic toxicity [16]. Green solvent alternatives encompass ethanol, water, ethyl acetate, and bio-derived solvents such as ethyl lactate, d-limonene, and glycerol. These compounds offer favourable toxicological and environmental profiles, regulatory acceptability, and in many instances, comparable or superior extraction selectivity for targeted phytochemical classes [17]. The CHEM21 solvent selection guide and solvent sustainability tools developed by pharmaceutical consortia provide structured decision frameworks for solvent substitution that balance chemistry performance with environmental and safety metrics [18].

Water, the quintessential green solvent, merits particular discussion. Aqueous extraction systems, including pressurized hot water extraction (PHWE) and subcritical water extraction, exploit the dramatically altered physicochemical properties of water at elevated temperatures and pressures — reduced surface tension, increased diffusivity, and modified dielectric constant — to achieve solubilization of a broad spectrum of bioactive compounds without organic solvent use [19, 20]. These approaches have demonstrated particular efficacy for polyphenol extraction from plant matrices and represent a compelling convergence of green chemistry principles with practical pharmaceutical application.

3.2. Energy Efficiency and Waste Reduction

Energy consumption in pharmaceutical manufacturing is both a cost centre and an environmental liability. Conventional Soxhlet extraction, while exhaustive in analyte recovery, requires continuous heating for durations of six to forty-eight hours, conferring substantial thermal energy costs and risk of thermolabile compound degradation [21]. By contrast, advanced extraction technologies such as microwave-assisted extraction and ultrasound-assisted extraction achieve comparable or superior yields within dramatically compressed timeframes — typically two to thirty minutes — thereby reducing energy inputs by up to ninety percent in documented comparative studies [22, 23].

Waste minimization strategies include solvent recycling through distillation loops integrated into closed-loop extraction systems, valorization of extraction residues as agricultural amendments or secondary biorefinery feedstocks, and the adoption of continuous flow extraction

platforms that reduce total solvent inventory requirements [24]. Life cycle assessment tools provide a standardized methodology for quantifying the cumulative environmental impact of these interventions across the full manufacturing value chain [25].

4. Advanced Green Technologies in Phytopharmaceutical Production

4.1. Supercritical Fluid Extraction

Supercritical fluid extraction (SFE), most commonly employing carbon dioxide as the extraction medium, represents a landmark advance in sustainable phytochemical isolation. Supercritical CO2 (critical temperature 31.1°C, critical pressure 73.8 bar) offers a non-toxic, non-flammable, and readily recoverable medium with tunable solvating power modulated through pressure and temperature adjustment [26]. SFE delivers extracts of exceptional purity, minimal solvent residue, and preserved thermolabile bioactivity, attributes that are particularly advantageous for volatile terpenoid and lipophilic cannabinoid extraction. Industrial SFE installations are commercially established in the nutraceutical and flavour industries, confirming scale-up feasibility, though capital equipment costs remain a significant barrier to entry for smaller phytopharmaceutical manufacturers [27].

4.2. Microwave-Assisted and Ultrasound-Assisted Extraction

Microwave-assisted extraction (MAE) utilises dielectric heating to rapidly elevate the temperature of polar solvents and plant cell moisture, causing cell disruption and accelerated analyte release into the extraction medium. Comparative studies have demonstrated MAE to achieve extraction yields equivalent to conventional Soxhlet methodology for flavonoids, saponins, and alkaloids at fifteen to thirty minute extraction durations, compared with six to twenty-four hours for reflux-based approaches [22, 28]. Ultrasound-assisted extraction (UAE) operates via acoustic cavitation, whereby the growth and violent collapse of microbubbles generated by high-frequency ultrasound creates intense local microjets that disrupt cell wall architecture, enhance mass transfer, and increase solvent penetration into the plant matrix [23]. Both technologies are compatible with aqueous and mixed aqueous-organic solvent systems, support reduced solvent volumes, and operate at ambient or mildly elevated temperatures conducive to bioactive compound preservation. Their suitability for scale-up in pharmaceutical manufacturing contexts has been established through pilot-scale and industrial validation studies [29].

4.3. Biotechnological Approaches

Enzyme-assisted extraction (EAE) represents an elegant biotechnological application of green chemistry principles, employing carbohydrases, proteases, and cell-wall-degrading enzymes to facilitate analyte release under mild aqueous conditions in the absence of organic solvents [30]. Cellulases, pectinases, and hemicellulases act synergistically to degrade the polysaccharide architecture of plant cell walls, rendering intracellular metabolites accessible to aqueous extraction media. EAE has been documented to significantly enhance the recovery of polyphenols and essential oil components from diverse botanical substrates while conferring improvements in extract clarity and downstream filterability [31]. Microbial fermentation-based biotransformation represents an additional avenue through which the structural diversity and bioactivity of phytochemical extracts may be modulated, enabling the generation of novel pharmacophores from renewable natural substrates with minimal chemical reagent input [14].

5. Process Optimization and Industrial Scale-Up

The translation of green extraction methodologies from laboratory discovery to commercial-scale phytopharmaceutical manufacture constitutes a central challenge in the field. Process optimization tools including response surface methodology (RSM) and Design of Experiments (DoE) frameworks enable systematic exploration of the multidimensional parameter spaces governing extraction yield, selectivity, and energy consumption, thereby identifying operating conditions that simultaneously maximize product quality and minimize resource inputs [32]. These chemometric approaches have been extensively validated for MAE, UAE, and SFE processes applied to phytochemical systems, generating predictive models that support rational scale-up from bench to pilot to industrial scale.

Industrial adoption of green extraction technologies requires careful techno-economic analysis to quantify the return on investment associated with capital equipment replacement and operational re-engineering. Continuous flow extraction systems integrated with in-line membrane filtration and solvent recovery loops offer compelling economic and environmental advantages for large-scale production, reducing solvent inventory, labour input, and batch cycle times [33]. The implementation of Process Analytical Technology (PAT) tools, including near-infrared spectroscopy, Raman spectroscopy, and ultraviolet-visible inline monitoring, enables real-time quality verification and adaptive process control, supporting both green chemistry objectives and pharmacopoeial compliance requirements [15].

6. Green Chemistry and Bioactive Compound Preservation

The quality, safety, and therapeutic efficacy of herbal drug formulations are fundamentally dependent upon the chemical integrity of bioactive constituents through the entire manufacturing process. Conventional extraction methodologies expose thermolabile compounds — including phenolic glycosides, essential oil monoterpenes, and anthocyanins — to prolonged thermal stress that promotes oxidative degradation, epimerization, and hydrolysis [10]. Green extraction approaches operating at reduced temperatures and durations measurably attenuate these degradation pathways. Supercritical CO2 extraction and UAE in particular have been documented to yield extracts with superior antioxidant activity, higher total polyphenol content, and greater microbiological cleanliness relative to conventional ethanol reflux procedures [26, 29].

From a formulation perspective, the reduced solvent residue profiles of green extracts confer direct safety and quality

benefits, facilitating compliance with International Council for Harmonisation (ICH) Q3C residual solvent guidelines without the need for extensive post-extraction solvent removal operations [34]. Furthermore, the consistency and reproducibility of green extraction processes, supported by PAT integration and mathematical process models, yield standardized extracts of defined biomarker content, a prerequisite for the clinical translation of herbal medicines and their regulatory acceptance as pharmaceutical-grade products [15, 35].

7. Regulatory, Environmental, and Ethical Considerations

The regulatory landscape governing herbal drug development is evolving in parallel with growing awareness of environmental sustainability imperatives. The European Medicines Agency (EMA), the United States Food and Drug Administration (FDA), and the World Health Organization (WHO) have progressively incorporated sustainability criteria into guidance frameworks for herbal medicinal product manufacturing [36]. EMA guidance on herbal medicinal products explicitly addresses solvent selection and residue limits, while WHO guidelines on good agricultural and collection practices (GACP) encompass ethical sourcing, biodiversity conservation, and ecologically sustainable harvesting regimes — all directly resonant with green chemistry objectives [37].

Environmental impact assessment through life cycle analysis (LCA) is increasingly mandated or recommended for pharmaceutical manufacturing processes as part of corporate sustainability reporting obligations under frameworks including the Global Reporting Initiative (GRI) and the UN Sustainable Development Goals (SDGs) [25]. Ethical considerations surrounding equitable benefit-sharing with plant-source communities under the Nagoya Protocol, intellectual property protections for indigenous botanical knowledge, and the prevention of biopiracy constitute important non-technical dimensions of sustainable herbal drug development that the green chemistry framework does not fully address but that responsible pharmaceutical actors must integrate into their operational philosophy [38].

8. Challenges and Barriers to Adoption

Despite compelling scientific evidence supporting the efficacy and sustainability of green chemistry approaches in phytopharmaceutical production, significant barriers to widespread industrial adoption persist. Capital expenditure associated with SFE and industrial MAE or UAE installations represents a primary deterrent, particularly for small and medium-sized manufacturers operating in price-sensitive generic herbal medicine markets [27]. The technical complexity of operating and maintaining supercritical fluid systems, and the requirement for specialized engineering expertise, further constrains accessibility. Regulatory validation of novel extraction processes within existing quality-by-design (QbD) frameworks demands substantial analytical resource investment and may extend product development timelines, creating disincentives for innovation adoption [35].

The complexity and variability of botanical raw material composition, driven by genotypic diversity, geographic origin, seasonal variation, and post-harvest handling differences, presents persistent challenges for the development of robust, standardized green extraction processes [39]. The absence of universally adopted green metrics for phytopharmaceutical manufacturing — analogous to the E-factor and atom economy measures employed in synthetic chemistry — impedes objective benchmarking of process sustainability improvements and complicates regulatory submissions. Addressing these challenges will necessitate coordinated investment in technology infrastructure, harmonized regulatory science, industry-academic collaboration, and the development of standardized reporting frameworks for pharmaceutical green chemistry metrics [40].

9. Conclusion and Future Directions

Green chemistry has emerged as a scientifically mature, industrially feasible, and environmentally imperative paradigm for herbal drug development. The progressive substitution of hazardous solvents with bio-derived or water-based alternatives, the deployment of energy-efficient extraction technologies, the integration of real-time process monitoring, and the adoption of waste valorization strategies collectively demonstrate that sustainable phytopharmaceutical production is not merely aspirational but operationally achievable at commercial scale. The documented benefits extend beyond environmental metrics to encompass measurable improvements in bioactive compound quality, extract standardization, and regulatory compliance.

Future research priorities in this domain include the development of integrated bio-refinery platforms that simultaneously optimize primary phytochemical extraction and valorize co-extraction residues as value-added co-products, the application of artificial intelligence and machine learning for predictive process optimization in complex botanical systems, and the advancement of solvent-free extraction modalities including mechanochemical and cold plasma technologies. The full realization of green chemistry's potential in herbal drug development will require sustained commitment from manufacturers, regulators, funding bodies, and academic researchers to build the interdisciplinary knowledge base and policy environment necessary for transformative, sector-wide sustainability transition.

Figures

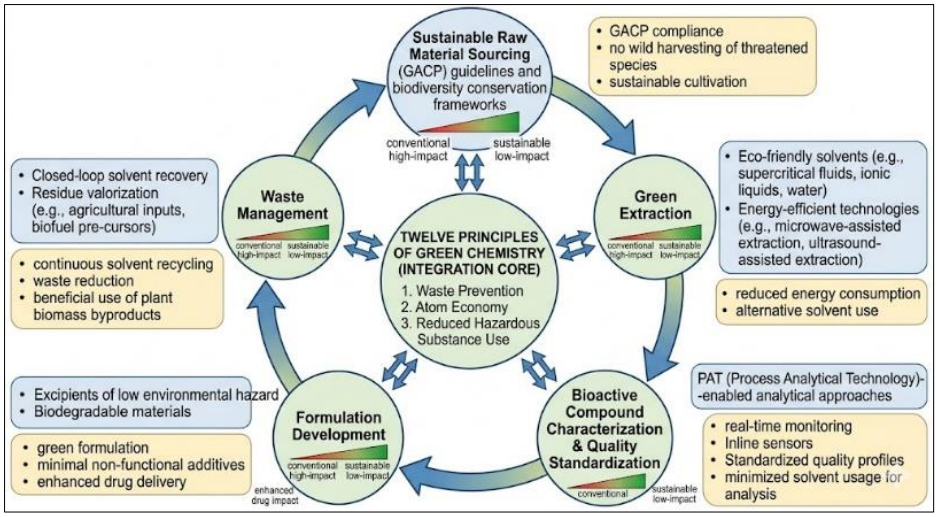

Fig 1: Schematic representation of the integration of the Twelve Principles of Green Chemistry into the herbal drug development process

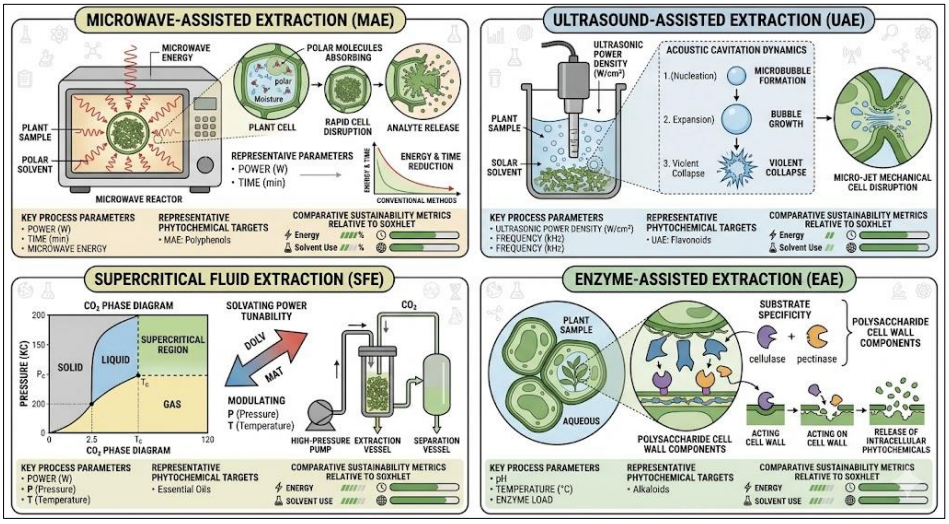

Fig 2: Comparative illustration of green extraction techniques and their operational principles, presented as a quadrant diagram

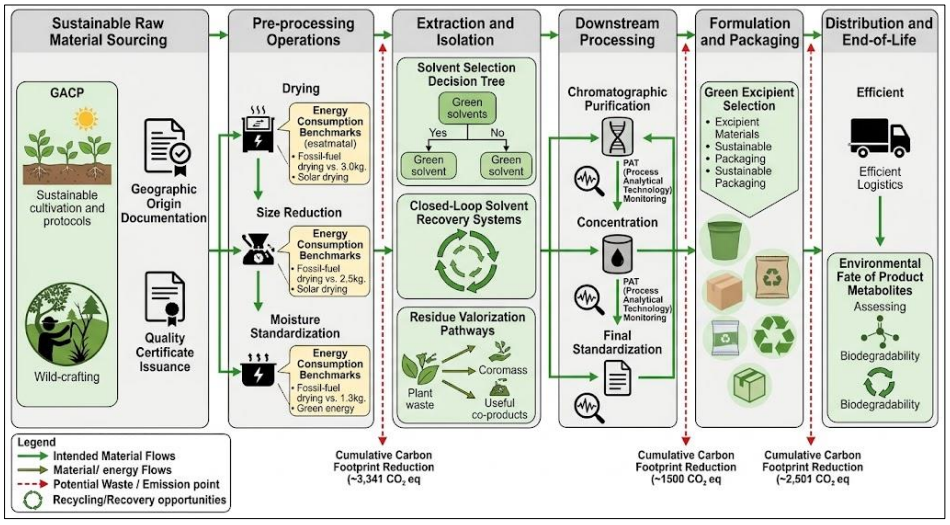

Fig 3: Life cycle flow diagram of a sustainable herbal drug development system, presented as a linear multi-stage process map with environmental impact overlays.

Tables

Table 1: Comparison of Conventional and Green Chemistry-Based Approaches in Herbal Drug Development

Parameter	Conventional Approach	Green Chemistry Approach	Key Improvement
Solvent use	Chlorinated solvents (DCM, CHCl3), hexane, methanol in large volumes	Ethanol, water, bio-derived solvents (ethyl lactate, d-limonene) in reduced volumes	Reduced toxicity, improved regulatory compliance, lower environmental load
Energy consumption	High; Soxhlet 6–48 h continuous heating; maceration 24–72 h	Low; MAE 2–30 min; UAE 10–60 min; SFE 30–90 min	Up to 90% energy reduction; decreased GHG emissions
Extraction time	Hours to days	Minutes to hours	Enhanced throughput; reduced thermal degradation risk
Waste generation	High solvent effluent; residue landfill disposal	Closed-loop solvent recovery; residue valorization as biomass	Significant reduction in hazardous waste streams
Bioactive yield & quality	Variable; thermolabile compound degradation common	Higher or equivalent yield; preservation of thermolabile constituents	Improved extract standardization and clinical translatability
Worker safety	Significant occupational exposure to volatile organic compounds	Reduced or eliminated VOC exposure; lower carcinogenic risk	Enhanced occupational health outcomes
Regulatory status	ICH Class 2/Class 1 solvents often employed	ICH Class 3 solvents or solvent-free; improved compliance pathway	Simplified residual solvent validation
Scalability	Well-established; low capital equipment cost	Established for MAE/UAE; SFE requires higher capital investment	Emerging industrial-scale installations reduce cost barriers

DCM = dichloromethane; MAE = microwave-assisted extraction; UAE = ultrasound-assisted extraction; SFE = supercritical fluid extraction; GHG = greenhouse gas; ICH = International Council for Harmonisation; VOC = volatile organic compound.

Table 2: Advantages, Limitations, and Sustainability Aspects of Green Technologies in Phytopharmaceutical Production

Technology	Key Advantages	Principal Limitations	Sustainability Benefits	Maturity Level
Supercritical Fluid Extraction (SFE)	Solvent-free; high purity; tunable selectivity; thermolabile compound preservation	High capital cost; limited polarity range without modifiers; complex equipment	No organic solvent residue; CO2 recycled; low environmental impact	Commercially established
Microwave-Assisted Extraction (MAE)	Rapid (2–30 min); high yield; reduced solvent volume; automated systems available	Unsuitable for non-polar solvents; potential hotspot degradation; moderate capital cost	90% energy reduction vs. Soxhlet; significantly reduced solvent use	Pilot and industrial scale validated
Ultrasound-Assisted Extraction (UAE)	Ambient temperature operation; compatible with diverse solvents; simple equipment	Probe erosion in industrial scale; parameter standardization challenges	Lower temperature reduces degradation; energy-efficient at laboratory scale	Established to pilot scale
Enzyme-Assisted Extraction (EAE)	Aqueous medium; mild conditions; improved yield of glycosylated compounds	Enzyme cost; substrate specificity constraints; longer processing time	No organic solvent; biodegradable reagents; minimal waste	Laboratory to pilot scale
Pressurized Hot Water Extraction (PHWE)	Water as sole solvent; high extraction efficiency; no solvent residues	High-pressure equipment required; selectivity limited to polar compounds	Complete solvent elimination; lower carbon footprint	Pilot scale; limited commercial adoption
High-Pressure Processing (HPP)	Non-thermal; preserves bioactivity; simultaneous extraction and sterilization	Batch process limitations; high capital cost; low industrial throughput	Low energy relative to thermal sterilization; no chemical additives	Commercial food sector; pharmaceutical adoption emerging

Maturity levels: 'Commercially established' denotes full industrial implementation; 'pilot and industrial scale validated' denotes demonstrated feasibility at manufacturing scale; 'established to pilot scale' denotes proven feasibility with continued scale-up required.

References

1. Anastas PT, Warner JC. Green chemistry: theory and practice. Oxford: Oxford University Press; 1998.
2. Azmir J, Zaidul ISM, Rahman MM, *et al*. Techniques for extraction of bioactive compounds from plant materials: a review. J Food Eng. 2013;117(4):426–436.
3. Chemat F, Vian MA, Cravotto G. Green extraction of natural products: concept and principles. Int J Mol Sci. 2012;13(7):8615–8627.
4. Grand View Research. Herbal medicine market size, share & trends analysis report. San Francisco: Grand View Research; 2022.
5. Pan SY, Zhou SF, Gao SH, *et al*. New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. Evid Based Complement Alternat Med. 2013;2013:627375.
6. Prat D, Wells A, Hayler J, *et al*. CHEM21 selection guide of classical- and less classical-solvents. Green Chem. 2016;18(1):288–296.
7. Sheldon RA. Metrics of green chemistry and sustainability: past, present, and future. ACS Sustain Chem Eng. 2018;6(1):32–48.
8. Henderson RK, Jiménez-González C, Constable DJ, *et al*. Expanding GSK's solvent selection guide – embedding sustainability into solvent selection starting at medicinal chemistry. Green Chem. 2011;13(4):854–862.
9. Anastas PT, Kirchhoff MM. Origins, current status, and future challenges of green chemistry. Acc Chem Res. 2002;35(9):686–694.
10. Ignat I, Volf I, Popa VI. A critical review of methods for characterisation of polyphenolic compounds in fruits and vegetables. Food Chem. 2011;126(4):1821–1835.

11. Dai J, Mumper RJ. Plant phenolics: extraction, analysis and their antioxidant and anticancer properties. Molecules. 2010;15(10):7313–7352.
12. Luque de Castro MD, Priego-Capote F. Soxhlet extraction: past and present panacea. J Chromatogr A. 2010;1217(16):2383–2389.
13. Constable DJ, Curzons AD, Cunningham VL. Metrics to 'green' chemistry – which are the best? Green Chem. 2002;4(6):521–527.
14. Verpoorte R, Contin A, Memelink J. Biotechnology for the production of plant secondary metabolites. Phytochem Rev. 2002;1(1):13–25.
15. Lee SL, O'Connor TF, Yang X, *et al*. Modernizing pharmaceutical manufacturing: from batch to continuous production. J Pharm Innov. 2015;10(3):191–199.
16. Grodowska K, Parczewski A. Organic solvents in the pharmaceutical industry. Acta Pol Pharm. 2010;67(1):3–12.
17. Capello C, Fischer U, Hungerbühler K. What is a green solvent? A comprehensive framework for the environmental assessment of solvents. Green Chem. 2007;9(9):927–934.
18. Alfonsi K, Colberg J, Dunn PJ, *et al*. Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation. Green Chem. 2008;10(1):31–36.
19. Teo CC, Tan SN, Yong JW, *et al*. Pressurized hot water extraction (PHWE). J Chromatogr A. 2010;1217(16):2484–2494.
20. Herrero M, Cifuentes A, Ibáñez E. Sub- and supercritical fluid extraction of functional ingredients from different natural sources. Food Chem. 2006;98(1):136–148.
21. Luque-García JL, Luque de Castro MD. Ultrasound: a powerful tool for leaching. TrAC Trends Anal Chem. 2003;22(1):41–47.
22. Kaufmann B, Christen P. Recent extraction techniques for natural products: microwave-assisted extraction and pressurised solvent extraction. Phytochem Anal. 2002;13(2):105–113.
23. Vilkhu K, Mawson R, Simons L, Bates D. Applications and opportunities for ultrasound-assisted extraction in the food industry – a review. Innov Food Sci Emerg Technol. 2008;9(2):161–169.
24. Moulton G, Sherwood S, Sherwood D. Towards closed-loop pharmaceutical manufacturing systems. Org Process Res Dev. 2019;23(6):1207–1221.
25. Jiménez-González C, Overcash MR. The evolution of life cycle assessment in pharmaceutical and chemical applications – a perspective. Green Chem. 2014;16(7):3392–3400.
26. Reverchon E, De Marco I. Supercritical fluid extraction and fractionation of natural matter. J Supercrit Fluids. 2006;38(2):146–166.
27. Brunner G. Supercritical fluids: technology and application to food processing. J Food Eng. 2005;67(1–2):21–33.
28. Chemat F, Rombaut N, Meullemiestre A, *et al*. Review of green food processing techniques: preservation, transformation, and extraction. Innov Food Sci Emerg Technol. 2017;41:357–377.
29. Tiwari BK. Ultrasound: a clean, green extraction technology. TrAC Trends Anal Chem. 2015;71:100–109.
30. Puri M, Sharma D, Barrow CJ. Enzyme-assisted extraction of bioactives from plants. Trends Biotechnol. 2012;30(1):37–44.
31. Benucci I, Liburdi K, Cacciotti I, *et al*. Enzyme-assisted extraction of plant polyphenols: recent advances and future perspectives. J Food Biochem. 2022;46(3):e14038.
32. Bezerra MA, Santelli RE, Oliveira EP, *et al*. Response surface methodology (RSM) as a tool for optimization in analytical chemistry. Talanta. 2008;76(5):965–977.
33. Plumb K. Continuous processing in the pharmaceutical industry: changing the mind set. Chem Eng Res Des. 2005;83(6):730–738.
34. International Council for Harmonisation (ICH). Guideline Q3C(R8): Impurities – guideline for residual solvents. Geneva: ICH; 2021.
35. Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. Pharm Res. 2008;25(4):781–791.
36. European Medicines Agency (EMA). Guideline on quality of herbal medicinal products/traditional herbal medicinal products. Amsterdam: EMA; 2016.
37. World Health Organization (WHO). WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants. Geneva: WHO; 2003.
38. Convention on Biological Diversity (CBD). Nagoya Protocol on access to genetic resources and the fair and equitable sharing of benefits arising from their utilization. Montreal: CBD Secretariat; 2011.
39. Weckerle CS, de Boer HJ, Puri RK, *et al*. Addressing the 'research gap' in the documentation of medicinal plant diversity. J Ethnopharmacol. 2011;137(1):975–978.
40. Constable DJ, Jiménez-González C, Henderson RK. Perspective on solvent waste issues and opportunities for more sustainable approaches to pharmaceutical manufacturing. Org Process Res Dev. 2007;11(1):133–137.