Advances in Extraction Techniques for Phytopharmaceuticals

Oliver J Collins [1*], Amelia R Thompson [2]
[1] Institute of Pharmaceutical Science, King's College London, United Kingdom
[2] Drug Delivery Research Group, University of Nottingham, United Kingdom

* Corresponding Author: **Oliver J Collins**

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Abstract
The extraction of bioactive compounds from plant-derived materials constitutes a foundational step in phytopharmaceutical development, directly influencing product yield, purity, and therapeutic efficacy. Conventional extraction techniques, including maceration, percolation, and Soxhlet extraction, although widely employed, are associated with significant limitations such as excessive solvent consumption, prolonged processing times, thermal degradation of labile constituents, and poor selectivity. These shortcomings have driven substantial research interest in advanced and green extraction technologies that offer superior performance across critical parameters. This review examines recent advancements in extraction methodologies for phytopharmaceuticals, with particular focus on supercritical fluid extraction, microwave-assisted extraction, ultrasound-assisted extraction, pressurized liquid extraction, and enzyme-assisted extraction. The principles, advantages, and limitations of each technique are discussed in the context of extraction efficiency, selectivity, environmental sustainability, and industrial scalability. Additionally, optimization strategies encompassing process parameter control, solvent selection, and analytical integration are evaluated. The review further addresses the regulatory and safety dimensions of modern extraction processes and explores translational challenges in scaling these technologies for commercial phytopharmaceutical manufacturing. Evidence from recent literature demonstrates that advanced extraction methods consistently outperform conventional approaches in yield, compound preservation, and environmental profile, positioning them as critical enablers of next-generation phytopharmaceutical products. Future perspectives highlight the convergence of green chemistry principles with digital process monitoring as a pathway to fully sustainable and efficient extraction platforms.

Keywords: Phytopharmaceuticals, Extraction techniques, Green extraction, Supercritical fluid extraction, Bioactive compounds Drug development

1. Introduction

Medicinal plants have served as the basis for human therapeutics throughout recorded history, and plant-derived compounds continue to constitute a substantial proportion of approved pharmaceutical agents worldwide [1, 2]. The global phytopharmaceutical market has expanded considerably in recent decades, driven by growing consumer interest in natural therapies, advances in analytical chemistry, and the identification of novel bioactive scaffolds from botanical sources [3]. Central to the development of any phytopharmaceutical product is the extraction process, which determines the qualitative and quantitative profile of bioactive constituents isolated from plant matrices. An inadequate extraction methodology may result in incomplete recovery of target compounds, co-extraction of undesirable impurities, or irreversible degradation of thermolabile or oxidation-sensitive molecules [4].

The pharmaceutical value of plant-derived extracts is contingent upon the chemical integrity and concentration of their

constituent bioactive compounds, including polyphenols, alkaloids, terpenoids, flavonoids, and glycosides [5, 6]. These molecules exhibit a broad spectrum of pharmacological activities and serve as lead structures in drug discovery programmes. However, the chemical diversity and structural complexity of plant matrices present significant challenges to efficient and selective extraction [7]. Matrix heterogeneity, variable compound polarity, and the presence of interfering macromolecules such as proteins, polysaccharides, and waxes complicate the isolation process and demand carefully optimised methodological approaches [8].

Conventional extraction methods, while accessible and well-characterised, are increasingly recognised as inadequate for high-efficiency, sustainability-oriented pharmaceutical manufacturing [9]. Their reliance on large volumes of organic solvents generates substantial waste streams, imposes environmental burden, and introduces regulatory compliance challenges under evolving pharmaceutical manufacturing guidelines [10]. Furthermore, extended processing times and elevated temperatures characteristic of several traditional methods are incompatible with the preservation of sensitive bioactive molecules [11]. The consequent impetus for methodological innovation has catalysed the development and refinement of a suite of advanced extraction technologies that collectively offer improved yield, selectivity, speed, and environmental performance [12].

This review critically examines the evolution of extraction techniques for phytopharmaceuticals, evaluating conventional approaches against modern alternatives with respect to efficiency, bioactive compound preservation, scalability, and regulatory compliance. The article aims to provide a rigorous analytical synthesis of current knowledge to guide researchers and industrial practitioners engaged in phytopharmaceutical development and manufacturing.

2. Conventional Extraction Methods

Maceration represents among the simplest and most historically entrenched extraction techniques, involving prolonged contact between comminuted plant material and a solvent at ambient or moderately elevated temperature [13]. The process relies principally on diffusion-driven mass transfer of soluble constituents from the plant matrix into the solvent phase. While maceration requires minimal equipment investment and is operationally straightforward, it is characterised by inherently low extraction efficiency attributable to the slow equilibration of solute concentrations across the plant cell membrane [14]. The extended contact times required, typically ranging from twenty-four to seventy-two hours, not only reduce throughput but also increase the risk of microbial contamination in aqueous or hydroalcoholic systems.

Percolation improves upon maceration by ensuring continuous contact between fresh solvent and plant material through a continuous downward flow regime [15]. The perpetual replenishment of depleted solvent maintains a favourable concentration gradient, thereby enhancing extraction completeness relative to static maceration. However, percolation remains relatively time-consuming and is limited in selectivity, recovering both target and non-target constituents with comparable efficiency. The technique is sensitive to particle size distribution and packing density, which, if poorly controlled, can produce channelling effects that reduce extraction uniformity [16].

Soxhlet extraction, developed in the nineteenth century, employs a cyclical solvent evaporation and condensation mechanism to maintain continuous contact between fresh solvent and the solid plant matrix contained within a porous thimble [17]. The method achieves comparatively high extraction efficiency and has been widely adopted as a reference standard in analytical and preparative applications. Nevertheless, the technique presents notable limitations that compromise its suitability for phytopharmaceutical manufacturing at scale. The prolonged exposure of plant material to elevated solvent temperatures during reflux cycles predisposes thermolabile compounds, including certain phenolic acids, glycosides, and volatile constituents, to thermal degradation [18]. Additionally, the large volumes of organic solvent required generate substantial waste and impose significant environmental and occupational safety considerations. The inherent batch-mode operation of the Soxhlet apparatus constrains throughput and impedes integration into continuous manufacturing workflows [19].

In aggregate, the limitations of conventional extraction methods — including high solvent consumption, long processing times, poor selectivity, and susceptibility to compound degradation — underscore the necessity for transition toward more advanced extraction technologies capable of meeting contemporary pharmaceutical manufacturing standards [20].

3. Advanced Extraction Techniques

3.1. Supercritical Fluid Extraction

Supercritical fluid extraction exploits the unique physicochemical properties of substances at conditions above their critical temperature and pressure, where they exhibit liquid-like density combined with gas-like diffusivity and viscosity [21]. Carbon dioxide is the most widely employed supercritical fluid in pharmaceutical applications, owing to its mild critical parameters (critical temperature of 31.1°C, critical pressure of 73.8 bar), chemical inertness, non-flammability, and low toxicity [22]. The tuneable solvating power of supercritical carbon dioxide, modulated through adjustments to temperature and pressure, confers exceptional selectivity for target compound classes. The addition of polar co-solvents such as ethanol further broadens the extractable polarity range, enabling recovery of a wider spectrum of bioactive constituents [23].

Supercritical fluid extraction offers several distinct advantages for phytopharmaceutical applications. The mild operating temperatures minimise thermal degradation of sensitive bioactives, and the rapid depressurisation-driven phase separation eliminates the need for post-extraction solvent removal steps, thereby reducing both processing time and residual solvent concerns [24]. The technique has been successfully applied to the extraction of essential oils, carotenoids, tocopherols, and lipophilic terpenoids from a variety of botanical matrices. Principal limitations include the high capital and operational cost of supercritical fluid extraction equipment, the complexity of system operation and maintenance, and reduced performance with highly polar analytes in the absence of appropriate co-solvents [25].

3.2. Microwave-Assisted Extraction

Microwave-assisted extraction harnesses the dielectric heating properties of polar solvents and moisture-containing plant matrices to achieve rapid, uniform thermal energy transfer within the extraction system [26]. Microwave

irradiation induces dipolar rotation and ionic conduction, generating localised thermal effects that disrupt plant cell walls and accelerate solute diffusion into the surrounding solvent. The technique substantially reduces extraction times compared with conventional methods, with most procedures completed within minutes rather than hours [27]. Solvent consumption is correspondingly reduced, contributing to an improved environmental profile relative to Soxhlet and maceration techniques.

Microwave-assisted extraction has demonstrated efficacy in recovering phenolic compounds, flavonoids, antioxidants, and essential oils from a diverse range of botanical substrates [28]. The method is adaptable to both focused and multimode microwave configurations, with focused systems offering superior temperature and power control for analytical-scale applications. Limitations of microwave-assisted extraction include the risk of thermal degradation of heat-sensitive analytes, restricted applicability to non-polar solvents with low microwave absorptivity, and technical challenges associated with moisture-free matrix extraction [29].

3.3. Ultrasound-Assisted Extraction

Ultrasound-assisted extraction employs acoustic cavitation to enhance mass transfer between plant matrix and solvent [30]. The collapse of cavitation bubbles generated by high-frequency ultrasonic irradiation produces localised microjets and shock waves of considerable energy, resulting in disruption of plant cell walls, enhanced solute diffusion, and increased contact area between solvent and plant material. The technique operates at ambient or mildly elevated temperatures, making it particularly advantageous for the extraction of thermolabile bioactive compounds, including certain polyphenols and glucosinolates [31].

Ultrasound-assisted extraction is operationally straightforward, amenable to a wide range of solvents, and compatible with both batch and continuous processing configurations. Published evidence consistently demonstrates significantly improved extraction yields and reduced processing times relative to maceration and percolation under comparable conditions [32]. Scale-up of ultrasound-assisted extraction at the industrial level presents engineering challenges related to uniform energy distribution, transducer degradation over time, and power efficiency, representing the primary barriers to widespread commercial adoption [33].

3.4. Pressurised Liquid Extraction

Pressurised liquid extraction, also referred to as accelerated solvent extraction, operates at elevated temperatures and pressures that maintain solvents in the liquid phase beyond their atmospheric boiling points [34]. The elevated temperature conditions enhance both solubility of target analytes and diffusion coefficients, while increased pressure suppresses solvent evaporation and allows penetration into the plant matrix under conditions of enhanced solvating power. The technique is characterised by rapid extraction cycles, high reproducibility, and compatibility with automated sample processing workflows.

Pressurised liquid extraction is particularly well-suited to analytical and quality control applications in pharmaceutical settings, offering extraction times of fifteen to forty-five minutes with minimal solvent consumption relative to Soxhlet methods [35]. The technique exhibits broad applicability across compound classes of varying polarity, and its automated nature reduces inter-operator variability. The primary limitations are the high capital cost of commercial instrumentation and the technical demands of pressure system management [36].

3.5. Enzyme-Assisted Extraction

Enzyme-assisted extraction employs hydrolytic enzymes, including cellulases, hemicellulases, pectinases, and proteases, to degrade structural components of the plant cell wall, thereby facilitating the release of intracellular bioactive compounds into the extraction medium [37]. The technique exploits the highly specific catalytic activity of enzymes to disrupt cell wall polysaccharide networks under mild aqueous conditions, obviating the requirement for organic solvents and high-energy processing. This renders enzyme-assisted extraction particularly compatible with green chemistry principles and sustainable manufacturing frameworks [38].

Enzyme-assisted extraction has demonstrated favourable performance in the recovery of polyphenols, essential oils, and polysaccharides from a variety of plant sources. The high specificity of enzymatic hydrolysis can contribute to enhanced selectivity, reducing the co-extraction of undesired matrix components [39]. Operational limitations include the susceptibility of enzyme activity to pH and temperature fluctuations, the cost of commercial enzyme preparations, and the extended processing times associated with some enzymatic hydrolysis protocols. The technique remains at an early stage of industrial implementation but shows considerable promise as a component of integrated green extraction platforms [40].

4. Optimisation Strategies and Analytical Integration

The performance of any extraction technique is fundamentally governed by a set of interrelated process parameters that must be systematically optimised to achieve maximum efficiency and selectivity [41]. For solvent-based methods, solvent polarity, pH, and concentration exert primary influence on the solubility and partitioning of target analytes. Temperature and contact time modulate diffusion kinetics and compound stability, necessitating careful calibration to balance extraction completeness against the risk of degradation [42]. Particle size of the plant matrix is a further critical variable, as fine grinding increases surface area and facilitates solute diffusion, though excessive reduction may cause filtration difficulties or promote extraction of undesirable macromolecular components.

Response surface methodology and design of experiments approaches have been widely employed to optimise multivariate extraction parameters simultaneously, offering efficiency advantages over traditional one-factor-at-a-time approaches [43]. Central composite designs, Box-Behnken designs, and Doehlert matrices have all been applied successfully to the optimisation of supercritical fluid, microwave-assisted, and ultrasound-assisted extraction conditions, yielding mathematical models that predict optimal parameter combinations with high reliability.

The integration of extraction processes with downstream analytical techniques represents a further dimension of optimisation that has gained considerable traction in pharmaceutical research and quality control settings [44]. On-line coupling of supercritical fluid extraction with supercritical fluid chromatography or high-performance liquid chromatography eliminates intermediate sample handling steps, reduces analyte loss, and enables rapid

profiling of complex botanical extracts. Similarly, hyphenation of pressurised liquid extraction with mass spectrometry facilitates comprehensive metabolite characterisation and supports both identity confirmation and quantitative analysis within streamlined workflows [45].

5. Preservation of Bioactive Compounds and Extract Quality

The maintenance of chemical integrity and biological activity of extracted compounds throughout the isolation process is a paramount consideration in phytopharmaceutical development [46]. Many pharmacologically relevant plant constituents, including flavonoids, anthocyanins, terpene lactones, and certain alkaloids, are susceptible to oxidative, hydrolytic, or thermal degradation under the processing conditions encountered in conventional extraction methods. The adoption of advanced extraction techniques that operate under milder conditions, with reduced solvent exposure and abbreviated processing times, directly addresses this challenge.

Antioxidant supplementation of extraction solvents, nitrogen purging to minimise dissolved oxygen, and refrigerated post-extraction handling collectively contribute to the stabilisation of labile bioactives during processing [47]. In the context of supercritical fluid extraction, the inherent oxygen exclusion afforded by the carbon dioxide extraction medium provides an additional protective mechanism against oxidative degradation. Ultrasound-assisted extraction at low temperatures has been shown to preserve the phenolic composition and radical scavenging activity of botanical extracts to a significantly greater degree than Soxhlet extraction, as documented in comparative studies on berry, citrus, and medicinal herb substrates [48].

The quality and reproducibility of phytopharmaceutical extracts are further dependent upon the standardisation of raw material quality, including species authentication, geographic provenance, harvest timing, and post-harvest processing conditions [49]. Chemometric analysis of extract fingerprints obtained by high-performance liquid chromatography with diode array or mass spectrometric detection facilitates batch-to-batch quality assurance and supports the identification of marker compounds for standardisation purposes. The integration of advanced extraction with rigorous analytical characterisation thus constitutes a prerequisite for the consistent manufacture of high-quality phytopharmaceutical products [50].

6. Industrial Applications and Translational Aspects

The translation of advanced extraction technologies from laboratory to industrial scale presents multifaceted engineering, regulatory, and economic challenges that must be systematically addressed to realise their commercial potential [51]. Scale-up of supercritical fluid extraction requires substantial investment in high-pressure vessel infrastructure, ancillary equipment, and safety systems, with capital expenditure representing the primary barrier to adoption for small and medium-sized enterprises in the phytopharmaceutical sector. In contrast, the scale-up of ultrasound-assisted and microwave-assisted extraction is technically more tractable, with commercial systems of pilot and industrial scale already available and deployed in cosmetic, food, and nutraceutical manufacturing contexts [52].

The nutraceutical and cosmeceutical industries have led the industrial adoption of advanced extraction technologies, leveraging their advantages in yield, compound quality, and environmental performance to differentiate product offerings. Supercritical carbon dioxide extraction has achieved commercial maturity in the production of standardised phytochemical concentrates, including lycopene from tomato, astaxanthin from microalgae, and ginkgolide-enriched extracts from Ginkgo biloba [53]. The pharmaceutical industry, while more conservative in adopting novel manufacturing technologies owing to regulatory requirements and process validation obligations, is increasingly recognising the quality and efficiency advantages of advanced extraction methods.

Continuous manufacturing paradigms, which are progressively displacing batch production in pharmaceutical manufacturing, offer natural compatibility with several advanced extraction modalities, particularly pressurised liquid extraction and flow-through supercritical fluid extraction configurations [54]. The integration of extraction into end-to-end continuous manufacturing platforms, encompassing upstream cultivation or procurement, extraction, purification, formulation, and quality testing, represents a strategic objective for next-generation phytopharmaceutical manufacturing. Process analytical technology tools, including near-infrared spectroscopy, Raman spectroscopy, and inline chromatographic monitoring, are being deployed to enable real-time process control and quality assurance throughout integrated continuous extraction systems [55].

7. Regulatory, Safety, and Sustainability Considerations

The regulatory framework governing phytopharmaceutical extraction processes reflects the dual character of these products at the interface of natural product chemistry and pharmaceutical manufacturing [56]. Regulatory authorities including the European Medicines Agency, the United States Food and Drug Administration, and the World Health Organization have issued guidelines addressing the quality, safety, and manufacturing standards applicable to herbal medicines and botanical drug products. These guidelines mandate the characterisation and control of extraction solvents as critical process materials, the validation of extraction methods with respect to efficiency and reproducibility, and the establishment of specification limits for residual solvents in final products in accordance with International Council for Harmonisation guidelines [57].

The green extraction concept, articulated through Chemat and colleagues' foundational principles, provides a philosophical and operational framework for the design of sustainable phytopharmaceutical extraction processes that minimise energy consumption, solvent use, waste generation, and environmental impact [58]. The twelve principles of green chemistry, adapted to extraction science, advocate for the use of renewable and non-toxic solvents, energy-efficient processing technologies, waste prevention, and integration of extraction with renewable energy sources. The adoption of these principles not only advances environmental sustainability but also confers regulatory compliance advantages in jurisdictions where solvent residue limits and waste disposal obligations impose operational constraints.

Safety considerations specific to advanced extraction technologies include the management of high-pressure systems in supercritical fluid extraction, the electromagnetic radiation exposure associated with microwave-assisted extraction, and the acoustic energy hazards intrinsic to

ultrasound-assisted extraction [59]. Comprehensive risk assessment, engineering controls, and personnel training are essential components of safe advanced extraction operations. The use of generally recognised as safe solvents, including water, ethanol, and carbon dioxide, in advanced green extraction methods also reduces occupational chemical exposure risks relative to conventional methods employing chlorinated solvents, hexane, or other volatile organic compounds [60].

8. Future Directions and Conclusions

The continued advancement of extraction technologies for phytopharmaceuticals is anticipated to proceed along several convergent trajectories that collectively address the twin imperatives of efficiency and sustainability. The integration of machine learning and artificial intelligence with extraction process design and optimisation offers transformative potential, enabling the rapid identification of optimal parameter combinations for novel botanical matrices without the extensive empirical experimentation currently required [61]. Digital twin modelling of extraction processes, informed by real-time sensor data, promises to reduce scale-up uncertainty and facilitate regulatory approval of innovative extraction configurations [62].

Emerging techniques including pulsed electric field extraction, subcritical water extraction, and high hydrostatic pressure extraction are attracting growing research attention as complementary or alternative modalities to established advanced methods [63]. Pulsed electric field extraction exploits electroporation of plant cell membranes to enhance intracellular solute release under non-thermal conditions, offering particular promise for the recovery of heat-sensitive bioactives. Subcritical water extraction employs pressurised hot water as a tunable, environmentally benign solvent that exhibits polarity characteristics intermediate between ambient liquid water and steam, enabling selective extraction of target compound classes across a range of temperatures [64].

The convergence of advanced extraction technologies with synthetic biology, metabolic engineering, and *in vitro* plant cell culture production systems represents a longer-term perspective with profound implications for phytopharmaceutical supply chain security and batch consistency [65]. Engineered biosynthetic pathways in microbial or plant cell culture hosts, combined with optimised extraction methodologies tailored to defined production matrices, may ultimately supplant field-grown botanical material as the preferred substrate for phytopharmaceutical ingredient manufacturing [66].

In conclusion, this review has documented substantial and continuing progress in extraction technologies for phytopharmaceuticals, characterised by the displacement of energy- and solvent-intensive conventional methods by advanced techniques that offer superior efficiency, selectivity, bioactive compound preservation, and environmental performance. Supercritical fluid extraction, microwave-assisted extraction, ultrasound-assisted extraction, pressurised liquid extraction, and enzyme-assisted extraction each present distinct performance profiles that render them suitable for specific compound classes, botanical matrices, and manufacturing contexts. The optimisation of these techniques through design of experiments and integration with advanced analytical platforms further enhances their applicability and reliability. While industrial translation remains constrained by capital cost, engineering complexity, and regulatory requirements, the trajectory of technological development and the growing imperative for sustainable pharmaceutical manufacturing strongly support the continued adoption and refinement of advanced extraction methodologies in phytopharmaceutical development.

Figures

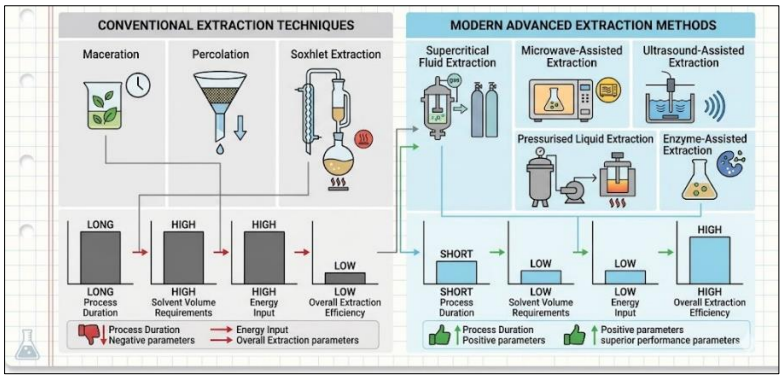

Fig 1: Comparative process flow diagram illustrating the principal operational differences between conventional extraction techniques (maceration, percolation, and Soxhlet extraction) and modern advanced extraction methods (supercritical fluid extraction, microwave-assisted extraction, ultrasound-assisted extraction, pressurised liquid extraction, and enzyme-assisted extraction).

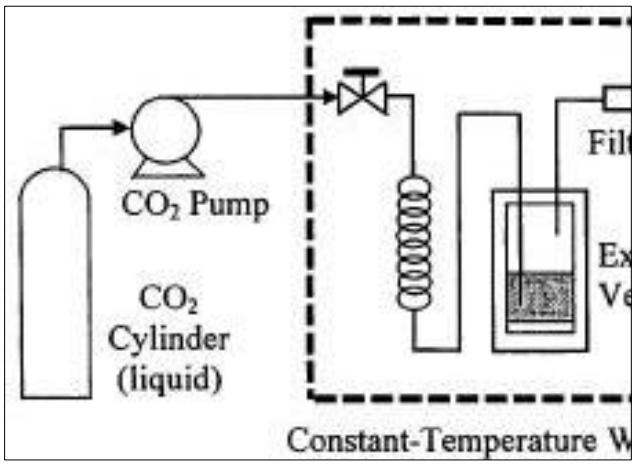

Fig 2: Schematic representation of the working principles of supercritical fluid extraction and microwave-assisted extraction.

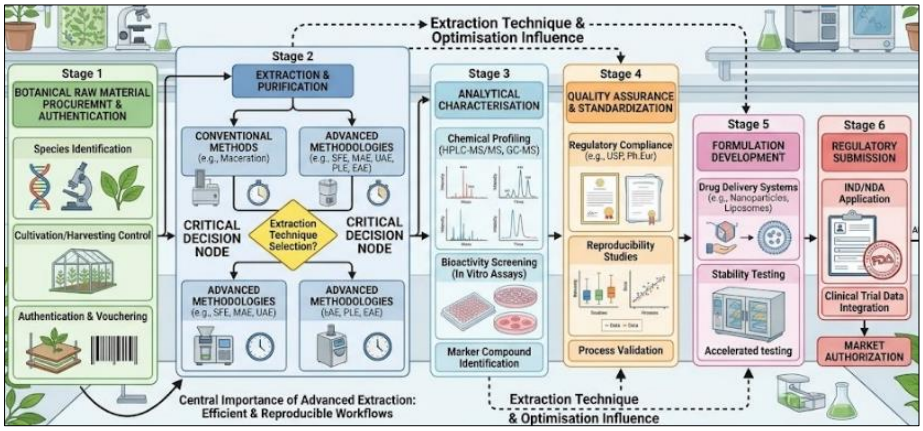

Fig 3: Integrated phytopharmaceutical development pipeline depicting the sequential stages from botanical raw material procurement and authentication through extraction, analytical characterisation, quality assurance, formulation development, and regulatory submission.

Tables

Table 1: Comparative Analysis of Conventional and Advanced Extraction Techniques

Parameter	Maceration	Soxhlet	Percolation	SFE	MAE	UAE	PLE	EAE
Extraction Efficiency	Low–Moderate	Moderate–High	Moderate	High	High	Moderate–High	High	Moderate–High
Time Required	24–72 hours	4–48 hours	1–8 hours	0.5–2 hours	0.1–0.5 hours	0.5–1 hour	0.5–2 hours	2–6 hours
Solvent Consumption	High	High	Moderate–High	Low (CO_2)	Low–Moderate	Low–Moderate	Low	Moderate
Temperature Sensitivity	Low	High	Moderate	Adjustable	Moderate	Low–Moderate	High	Low
Selectivity	Low	Low	Moderate	High	Moderate–High	Moderate	High	High
Scalability	Easy	Moderate	Moderate	Difficult	Moderate	Moderate	Difficult	Moderate
Environmental Impact	High	High	High	Low	Low–Moderate	Low–Moderate	Low	Low
Equipment Cost	Low	Low	Low	Very High	Moderate	Moderate	High	Moderate
Bioactive Preservation	Moderate	Low	Moderate	High	Moderate–High	High	High	High

Table 2: Summary of Advantages, Limitations, and Industrial Applicability of Extraction Techniques

Technique	Key Advantages	Major Limitations	Industrial Applicability
Maceration	Simple, low-cost, no specialized equipment	Long duration, high solvent use, low selectivity	Widely used; suitable for heat-labile compounds at small scale
Soxhlet Extraction	Exhaustive extraction; well-established	Thermal degradation risk; high solvent use; time-consuming	Moderate; used as analytical reference method
Percolation	Continuous fresh solvent contact; moderate speed	Moderate solvent use; limited control over contact time	Common in herbal preparation; scalable at moderate cost
Supercritical Fluid Extraction (SFE)	High selectivity; low residual solvent; tunable parameters	Very high capital cost; complex operation; poor for polar analytes	Pharmaceutical and nutraceutical industries; coffee decaffeination
Microwave-Assisted Extraction (MAE)	Rapid; reduced solvent use; uniform heating	Limited to microwave-absorbing matrices; thermal degradation risk	Moderate; cosmetics, food, and pharmaceutical sectors
Ultrasound-Assisted Extraction (UAE)	Mild conditions; cell disruption; enhanced diffusion	Scale-up challenges; transducer fouling; energy cost	Moderate; particularly suitable for heat-sensitive bioactives
Pressurized Liquid Extraction (PLE)	Fast; automated; reduced solvent; high reproducibility	High equipment cost; pressure management complexity	Pharmaceutical QC and nutraceutical processing
Enzyme-Assisted Extraction (EAE)	High specificity; aqueous solvent; mild conditions	Enzyme cost; pH and temperature sensitivity; long processing	Emerging; suitable for polysaccharides and phenolics

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