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Impact of extraction techniques on phytochemical composition and bioactivity of natural product mixtures

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Extraction methods critically influence the phytochemical profile and bioactivity of natural product mixtures, affecting their efficacy as therapeutic agents. This review assesses the impact of various extraction techniques—such as solvent-based extraction, ultrasound-assisted extraction, and enzymatic extraction—on the composition of bioactive compounds in plant extracts. We discuss how extraction parameters modify the bioactivity profiles, influencing their application in pharmaceuticals and nutrition. This review critically analyzes these techniques with a special focus on integrated (hybrid) strategies, revealing that while advanced methods like ultrasound-assisted extraction and microwave-assisted extraction offer improved efficiency, the greatest potential lies in the synergistic combination of methods to maximize yield and preserve bioactivity. The insights gathered here aim to guide researchers in developing optimal and sustainable extraction protocols for therapeutic applications.

KEYWORDS

extraction techniques, natural products, bioactive compounds, phytochemical composition, pharmaceutical and nutraceutical applications

1 Introduction

Natural products, particularly plant-derived extracts, have garnered immense interest due to their wide range of bioactivities and potential therapeutic applications (Tomlinson and Akerlele, 2015). They have been utilized in traditional medicine for centuries, and modern research continues to highlight their roles in treating various diseases, including inflammatory disorders, metabolic syndromes, and even cancer (Gurib-Fakim, 2006). The bioactive compounds within these extracts—such as polyphenols, flavonoids, alkaloids, terpenoids, and glycosides—exhibit diverse pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, and anticancer properties (Shanmugam et al., 2021). Consequently, these natural bioactives are increasingly incorporated into pharmaceuticals, nutraceuticals, functional foods, and even cosmetic formulations (da Silva et al., 2016a). However, to fully harness their therapeutic potential, an optimized extraction

process is essential to ensure the stability, yield, and bioactivity of these compounds (Bhadange et al., 2024).

The choice of extraction method plays a crucial role in determining the chemical composition and bioactivity of natural product mixtures (Doughari, 2012). Traditional extraction methods, such as maceration, Soxhlet extraction, and hydrodistillation, have long been used to isolate bioactive compounds from plant materials (Yolci Omeroglu et al., 2019). While these methods are relatively simple and cost-effective, they often suffer from major drawbacks, including low efficiency, long extraction times, high solvent consumption, and potential degradation of heat-sensitive compounds like flavonoids and polyphenols (Luksta and Spalvins, 2023). These limitations have driven the development of advanced extraction techniques, including ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), supercritical fluid extraction (SFE), and enzyme-assisted extraction (EAE) (Ahmad et al., 2025). These modern techniques offer significant advantages such as higher extraction yields, improved selectivity, reduced processing time, and better preservation of bioactive integrity (Usman et al., 2023).

Extraction efficiency is influenced by multiple parameters, including solvent type, pH, temperature, extraction duration, particle size, and mechanical forces applied (Spietelun et al., 2013). For example, polar solvents (e.g., methanol, ethanol, and water) are commonly used to extract hydrophilic compounds like phenolics and flavonoids, whereas non-polar solvents (e.g., hexane and chloroform) are more effective for lipophilic compounds such as terpenoids and carotenoids (Sicker et al., 2019). Additionally, innovative approaches like EAE allow for the selective breakdown of plant cell walls, facilitating the release of intracellular bioactive compounds while minimizing degradation (Sousa et al., 2023). Understanding how these parameters influence phytochemical composition is critical for optimizing extraction protocols (Doughari, 2012).

A major challenge in the field of natural product extraction is standardization (Kunle et al., 2012). The phytochemical composition of extracts can vary significantly depending on plant species, geographic origin, environmental conditions, and harvesting time, making it difficult to ensure batch-to-batch consistency (Atanasov et al., 2021). This variability poses a significant issue for pharmaceutical and nutraceutical applications, where bioactivity and safety must be precisely controlled (Butler, 2004). To address these challenges, advanced analytical techniques such as high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy have been employed to provide detailed chemical profiling and quality assessment of natural extracts (SL Mendez et al., 2015). These analytical tools not only improve reproducibility but also help in identifying the most effective extraction methods for preserving bioactive compounds (Altemimi et al., 2017).

Given the increasing demand for bioactive natural products in various industries, there is a critical need for systematic evaluations of extraction techniques (Patra et al., 2018). This review aims to comprehensively assess the impact of different extraction methods on the yield, phytochemical composition, and bioactivity of plant-based extracts. By comparing conventional and advanced extraction techniques, we highlight the advantages, limitations, and potential

applications of each method. Additionally, we explore the role of analytical technologies in ensuring standardized and high-quality natural product extracts. Through this discussion, we aim to contribute valuable insights toward the development of sustainable and efficient extraction strategies that enhance the therapeutic and commercial applications of bioactive natural compounds. While numerous reviews have summarized individual extraction techniques, this paper provides a unique contribution by critically analyzing the synergies and trade-offs of integrated (hybrid) extraction strategies.

1.1 Literature search strategy and scope of the review

This article provides a critical narrative review of the literature concerning extraction techniques for natural products. It is not intended to be a systematic review following PRISMA guidelines, but rather a comprehensive overview to identify current trends, challenges, and future perspectives. The literature was surveyed using major scientific databases, including Scopus, PubMed, and Google Scholar, with a primary focus on publications from the last 2 decades to cover recent advancements. However, seminal, highly-cited foundational papers from before this period were also included to provide essential historical context. Keywords used for the search included, but were not limited to: “natural product extraction,” “phytochemicals,” “bioactivity,” “ultrasound-assisted extraction,” “microwave-assisted extraction,” “supercritical fluid extraction,” “hybrid methods,” and “synergy.” The primary inclusion criterion was peer-reviewed research and review articles published in English that provided significant insights into extraction principles, applications, and challenges. Conference abstracts, patents, and non-English articles were excluded from this review.

2 Impact of extraction techniques on phytochemical composition and bioactivity

The efficacy of bioactive compounds derived from natural products is highly dependent on the extraction technique employed (Wijngaard et al., 2012). The choice of method influences the yield, stability, and pharmacological activity of phytochemicals, affecting their antioxidant, anti-inflammatory, antimicrobial, and therapeutic potential (Tauro et al., 2024). Various chemical, physical, and enzymatic factors contribute to extraction efficiency, including solvent type, temperature, pH, extraction duration, and mechanical forces (Wen et al., 2020). These factors not only dictate the quantity of bioactive compounds recovered but also their structural integrity and bioactivity (Ventura et al., 2017).

2.1 Influence of extraction techniques on phytochemical composition

Extraction methods significantly impact the solubility, stability, and concentration of bioactive compounds (Zhang et al., 2020).

Conventional approaches, which are discussed in detail in [Section 3](#), include traditional methods such as maceration, Soxhlet extraction, and hydrodistillation. While these techniques have been used for decades, they often suffer from low efficiency, high solvent consumption, and long extraction times ([Dhobi et al., 2009](#)). Moreover, heat-sensitive compounds such as polyphenols, flavonoids, and terpenoids are prone to degradation under prolonged exposure to high temperatures ([Valisakkagari et al., 2024](#)).

Modern advanced extraction techniques have been developed to overcome these limitations by enhancing extraction efficiency, reducing solvent use, and preserving bioactive integrity ([Khaw et al., 2017](#)). Depending on the method used, the composition of extracted phytochemicals can vary significantly ([Kumar et al., 2023](#)):

Solvent-based extractions are highly dependent on polarity, with polar solvents (e.g., ethanol, water) favoring hydrophilic compounds (e.g., flavonoids, tannins) and non-polar solvents (e.g., hexane, chloroform) extracting lipophilic bioactives (e.g., terpenoids, carotenoids) ([Da Silva et al., 2022](#)).

Mechanically-assisted extractions (e.g., ultrasound and microwave methods) enhance cell wall disruption, facilitating the release of intracellular compounds while minimizing structural degradation ([Rocchetti et al., 2022](#)).

Enzyme-assisted methods improve the selective extraction of glycosides, polysaccharides, and other cell wall-associated compounds, increasing bioavailability ([Wang et al., 2024](#)).

2.2 Effect of extraction techniques on bioactivity

The biological activity of plant extracts is influenced not only by the presence of bioactive compounds but also by their structural stability and bioavailability, which extraction methods affect ([Usman et al., 2022](#)). Studies comparing different extraction techniques have shown that optimized methods lead to higher antioxidant, anti-inflammatory, and antimicrobial effects due to the enhanced recovery of functional phytochemicals ([Kumar et al., 2023](#)).

The superiority of modern techniques is well-illustrated by flavonoid extraction from citrus peels. Conventional Soxhlet extraction requires prolonged heating at the solvent's boiling point (e.g., ~78°C for ethanol), which can cause thermal degradation of sensitive compounds ([Ćujić et al., 2016](#)). In contrast, UAE utilizes acoustic cavitation at lower temperatures, enabling a more efficient recovery of these phytochemicals ([Chemat et al., 2017](#)). Consequently, UAE extracts from citrus peels consistently show higher yields of flavonoids and superior antioxidant activity ([Khan et al., 2010](#)). This is therapeutically significant, as these flavonoids, such as hesperidin, are known to possess potent anti-inflammatory effects which are compromised by heat ([Parhiz et al., 2015](#); [Al-Khayri et al., 2022](#)).

Antioxidant Properties: Extraction techniques that efficiently retain polyphenols and flavonoids result in higher free radical scavenging potential, reducing oxidative stress ([Brglez Mojzer et al., 2016](#)).

Anti-Inflammatory Effects: Enhanced recovery of terpenoids and phenolic acids contributes to modulation of pro-inflammatory

pathways [e.g., inhibition of Nuclear Factor-kappa B (NF-κB), Cyclooxygenase-2 (COX-2) enzymes] ([da Cunha et al., 2022](#)).

Antimicrobial Properties: The preservation of alkaloids, tannins, and saponins through optimized extraction enhances their antibacterial and antifungal effects, preventing microbial contamination in food and pharmaceutical applications ([Oulahal and Degraeve, 2022](#)).

Additionally, extraction efficiency is linked to particle size, solvent polarity, and processing conditions. For example:

Reducing particle size increases the surface area for solvent penetration, improving yield ([Singh, 2017](#)).

Selecting the appropriate solvent ensures maximum solubility of the target compounds while minimizing unwanted co-extractions ([Reis et al., 2020](#)).

2.3 Challenges in standardizing extraction techniques

Although advanced extraction methods improve efficiency and bioactivity, achieving batch-to-batch consistency remains a challenge. Several factors contribute to variations in extract quality:

Raw Material Variability: Differences in geographical origin, cultivation practices, and harvesting conditions affect phytochemical composition ([Tiware and Cummins, 2013](#)).

Processing Inconsistencies: Variability in temperature, solvent selection, and extraction duration influences final extract quality ([Rajha et al., 2014](#)).

Regulatory Compliance: Standardization is crucial for pharmaceutical and nutraceutical applications, necessitating the use of analytical validation techniques (HPLC, GC-MS, NMR) ([Durazzo et al., 2022](#)).

2.4 Integrated (hybrid) extraction strategies: synergies and trade-offs

Emerging research suggests that combining multiple extraction techniques can maximize compound yield and functional properties. The rationale behind integrated or “hybrid” extraction strategies is to leverage the unique advantages of multiple techniques to create a synergistic effect that a single method cannot achieve ([Chemat et al., 2019a](#)). A prime example is the sequential combination of EAE and UAE. EAE can be initially employed to enzymatically degrade the rigid cellulose and pectin matrix of the plant cell wall, creating a more porous structure ([Muniglia et al., 2014](#)). Subsequently, the acoustic cavitation generated by UAE can penetrate this pre-weakened matrix more effectively, leading to a dramatic increase in the release of intracellular bioactive compounds ([Kumar et al., 2021](#)). This synergy allows for higher yields at lower temperatures and shorter times than either EAE or UAE could accomplish alone ([Puri et al., 2012](#); [Xiong et al., 2019](#)).

In addition to this EAE-UAE combination, other hybrid approaches have also demonstrated significant potential. These include:

Microwave-assisted hydrodistillation (MAHD): This method integrates microwave heating into the hydrodistillation process. The rapid, internal heating generated by microwaves shortens the

distillation time significantly and can improve the yield and quality of essential oils compared to traditional hydrodistillation alone (Lucchesi et al., 2004; Golmakani and Rezaei, 2008).

Supercritical fluid extraction with a co-solvent (SFE-CO₂ w/co-solvent): While not a sequential hybrid method, this approach “integrates” a polar co-solvent (like ethanol) into the non-polar SC-CO₂ fluid. This dramatically enhances the extraction efficiency for moderately polar compounds, such as certain flavonoids and phenolic acids, which are poorly soluble in pure SC-CO₂ (Gallego et al., 2019; Paucar et al., 2023).

However, these integrated approaches are not without significant trade-offs that require critical consideration. Combining multiple techniques inevitably increases process complexity, the number of parameters to optimize, and overall operational costs, which can be a barrier for industrial scale-up (Nde and Foncha, 2020; Ahangari et al., 2021). For instance, a hybrid SFE-ultrasound system requires high-pressure equipment coupled with a high-power ultrasonic transducer, representing a substantial capital investment (De Melo et al., 2014). Furthermore, a multi-step process introduces additional potential points of failure and may increase total processing time, even if individual steps are rapid. Therefore, the decision to implement a hybrid system must be justified by a significant and measurable improvement in yield, purity, or bioactivity that outweighs these practical and economic challenges (Chemat et al., 2019a).

3 Conventional extraction methods and their limitations

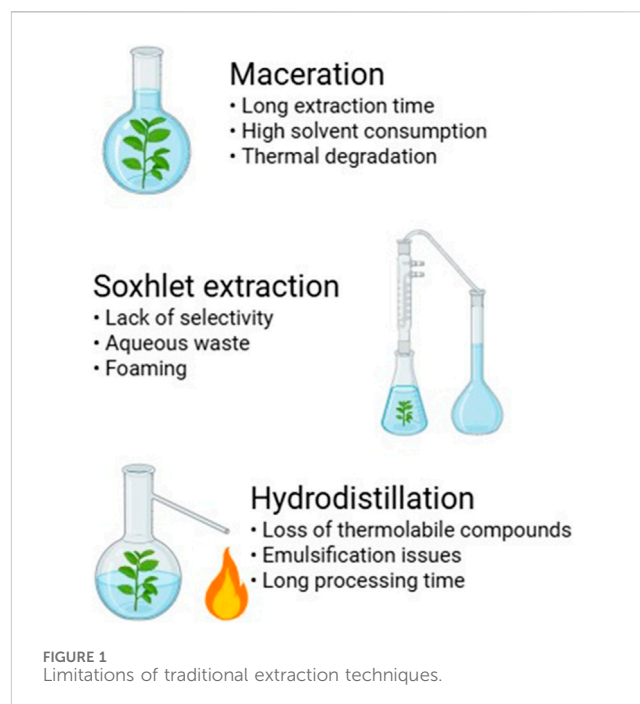
Traditional extraction techniques, such as maceration, Soxhlet extraction, and hydrodistillation, have long been used to obtain bioactive compounds from plant materials (Yolci Omeroglu et al., 2019). These methods rely on physical and chemical interactions between the solvent and plant matrix to extract target compounds (Ingle et al., 2017). While conventional techniques are widely utilized due to their simplicity and cost-effectiveness, they also present significant limitations, including long extraction times, high solvent consumption, thermal degradation, and lack of selectivity (Manousi et al., 2019).

3.1 Maceration

Maceration is one of the simplest and most commonly used extraction methods, involving soaking plant material in a suitable solvent at room temperature for an extended period (Hidayat and Wulandari, 2021). This technique allows for the passive diffusion of bioactive compounds into the solvent (Chongo, 2025). However, it is highly time-consuming and often leads to incomplete extraction (Shikov et al., 2022). Additionally, maceration may result in the co-extraction of undesirable compounds, affecting the purity and bioactivity of the final extract (Chuo et al., 2022).

3.2 Soxhlet extraction

Soxhlet extraction is a continuous solvent extraction technique that involves repeated percolation of hot solvent over the plant



material (López-Bascón and De Castro, 2020). This method increases extraction efficiency compared to maceration by continuously replenishing the solvent, allowing for better solubility and diffusion of target compounds (Şahin et al., 2011). However, its major drawback is the prolonged exposure to high temperatures, which can degrade heat-sensitive bioactive compounds such as polyphenols and flavonoids (Antony and Farid, 2022). Additionally, Soxhlet extraction requires a large volume of solvent, making it less environmentally friendly and cost-effective (Trolles-Cavalcante et al., 2021).

3.3 Hydrodistillation

Hydrodistillation is primarily used for extracting essential oils and volatile compounds from plant materials (Abbas et al., 2017). This method involves boiling plant material in water or steam to release volatile compounds, which are then condensed and collected (Perović et al., 2024). While effective for obtaining essential oils, hydrodistillation poses challenges such as the loss of thermolabile compounds, emulsification issues, and long processing times (Pheko-Ofithile and Makhzoum, 2024). Furthermore, the high temperatures used in hydrodistillation can alter the chemical composition of extracted oils, affecting their bioactivity and fragrance profile (Lainez-Cerón et al., 2021) (Figure 1).

4 Factors influencing extraction efficiency and bioactivity

The efficiency of bioactive compound extraction and the biological activity of the final extract depend on multiple physicochemical and process-related factors (Da Silva R. P. et al., 2016). These factors influence the yield, stability, solubility, and

pharmacological effectiveness of extracted phytochemicals. Optimizing these parameters is essential to ensure that bioactive compounds are recovered efficiently while maintaining their structural integrity.

4.1 Solvent selection

Solvent choice is one of the most critical factors in determining extraction efficiency. The polarity of the solvent plays a key role in selecting specific classes of bioactive compounds:

Polar solvents (e.g., water, ethanol, methanol) efficiently extract hydrophilic compounds such as flavonoids, polyphenols, and anthocyanins (Tzanova et al., 2020).

Non-polar solvents (e.g., hexane, chloroform, ethyl acetate) are better suited for lipophilic bioactives such as terpenoids, carotenoids, and essential oils (Siddiqui et al., 2024).

Binary or ternary solvent systems (e.g., ethanol-water mixtures) enhance the extraction of a broad range of phytochemicals, improving both yield and bioactivity (Natolino et al., 2024).

The critical role of solvent polarity and the benefits of mixed-solvent systems are well-illustrated by the extraction of polyphenols from green tea (*Camellia sinensis*). For instance, a study demonstrated that using a 70% ethanol-water mixture yielded significantly higher total phenolic content and antioxidant activity compared to using either pure water or absolute ethanol (Calderón-Oliver and Ponce-Alquicira, 2021; Maslov et al., 2022). Pure water primarily extracts highly polar compounds, while absolute ethanol is less effective for these (Cheng et al., 2021). The ethanol-water mixture, however, creates a solvent environment with intermediate polarity, capable of efficiently extracting a wider spectrum of polyphenols, which in turn leads to enhanced synergistic bioactivity (Plaskova and Mlcek, 2023). This highlights the necessity of optimizing solvent systems to match the polarity of the target bioactive compounds.

In recent years, green solvents (defined as environmentally benign solvents, typically derived from renewable resources, that are characterized by low toxicity, biodegradability, and high efficiency) have gained attention for their eco-friendly and efficient extraction capabilities. Among these, Deep Eutectic Solvents (DES), typically formed from natural compounds like choline chloride and organic acids, are emerging as promising alternatives to volatile organic solvents (Dai et al., 2013; Prabhune and Dey, 2023; Stanisz et al., 2024; Suthar, 2025). For example, a study on the extraction of anthocyanins from grape skin showed that a specific DES formulation achieved a higher extraction yield and resulted in an extract with greater antioxidant stability compared to conventional acidified ethanol, all while being biodegradable and non-toxic (Jeong et al., 2015; Bosiljkov et al., 2017; Foroutani et al., 2024). This demonstrates the potential of green solvents to not only reduce environmental impact but also, in some cases, enhance the quality and stability of the extracted bioactive compounds (Chemat et al., 2019b; Aduloju et al., 2023; Ferreira and Sarraçuca, 2024).

4.2 Temperature and extraction time

Both temperature and extraction time significantly affect the yield and stability of bioactive compounds:

Higher temperatures can increase solubility, diffusion rates, and mass transfer, leading to improved extraction efficiency (Kuosmanen et al., 2003).

However, prolonged exposure to high temperatures may cause oxidative degradation of thermolabile compounds such as vitamin C, polyphenols, and essential oils (Awad et al., 2021).

For instance:

Flavonoids and phenolic acids exhibit enhanced extraction at moderate temperatures (40°C–60°C), but temperatures above 80°C may lead to degradation (Antony and Farid, 2022).

Terpenoids and alkaloids, which are more stable, can be extracted efficiently at higher temperatures (70°C–100°C) (Rasul, 2018).

Supercritical CO₂ extraction operates at relatively low temperatures, making it ideal for preserving heat-sensitive compounds while maintaining high efficiency (Wang et al., 2021).

The extraction duration also plays a crucial role in maximizing bioactive compound recovery (Belščak-Cvitanović and Komes, 2017). Extended extraction times can increase yield but may lead to oxidation, hydrolysis, or polymerization, altering the bioactivity of sensitive phytochemicals (Brglez Mojzer et al., 2016).

4.3 pH and enzyme-assisted extraction

The pH of the extraction medium can influence solubility, ionization, and stability of bioactive compounds:

Acidic conditions (pH < 5) favor the extraction of anthocyanins and organic acids but may cause degradation of certain polyphenols (Friedman and Jürgens, 2000; Enaru et al., 2021).

Alkaline conditions (pH > 7) enhance the solubility of alkaloids but may degrade phenolic compounds (Yubin et al., 2014; Oreopoulou et al., 2019).

EAE enhances extraction efficiency by breaking down plant cell walls and releasing intracellular bioactives (Wijesinghe and Jeon, 2012):

Cellulases and pectinases degrade plant fiber matrices, facilitating the release of flavonoids and glycosides (Costa et al., 2020).

Proteases can help recover bioactive peptides from protein-rich plant materials (David Troncoso et al., 2022).

Hemicellulases improve the extraction of arabinoxylans and other polysaccharides (de Souza and Kawaguti, 2021).

EAE is particularly useful in the food and pharmaceutical industries, as it reduces the need for harsh solvents and improves bioavailability.

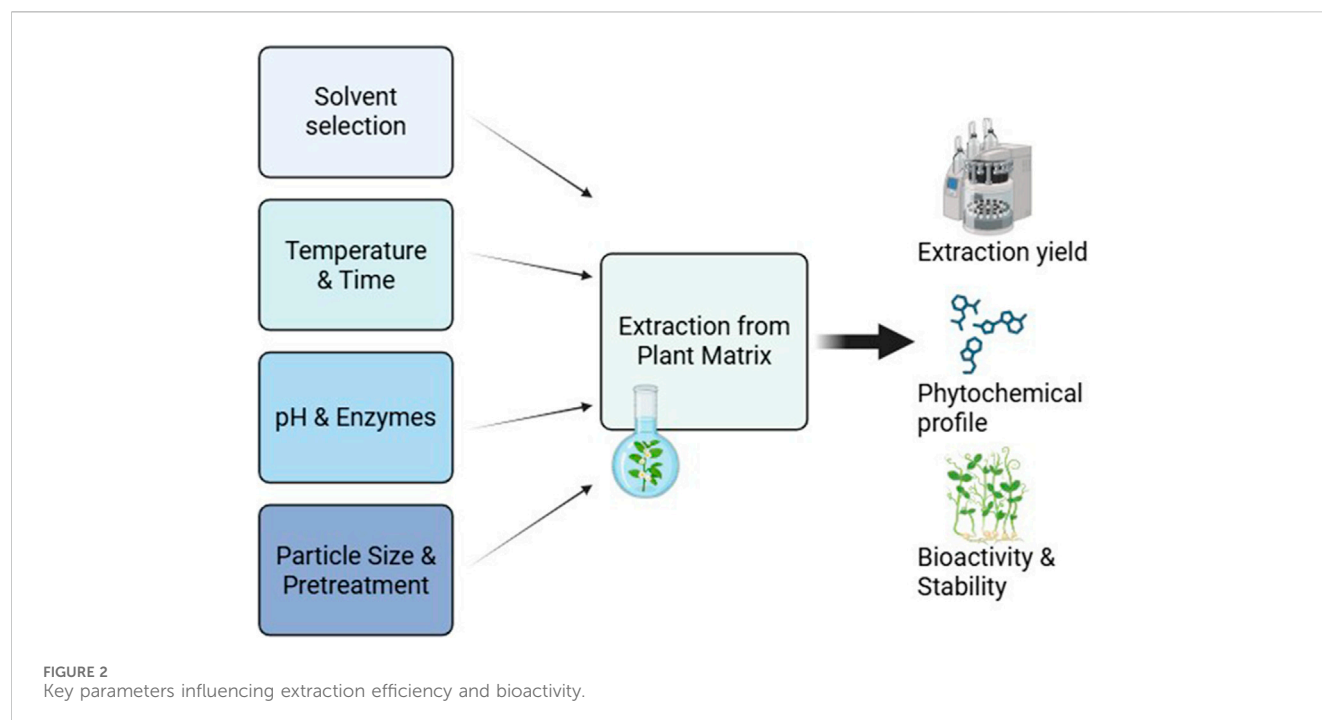
4.4 Particle size and pretreatment methods

Reducing the particle size of plant material can enhance solvent penetration and increase surface area, improving extraction efficiency (Ameer et al., 2017). Various pretreatment techniques have been employed to optimize extraction:

Grinding and milling: Reduces particle size, enhancing mass transfer (Kratky and Jirout, 2011).

Freeze-drying: Preserves bioactive integrity while facilitating better solvent diffusion (Rezvanhah et al., 2020).

Microwave and ultrasound pretreatment: Improves cell wall disruption, leading to higher yields (Passos et al., 2015).



4.5 Advanced extraction optimization strategies

To maximize extraction efficiency, various optimization approaches have been explored:

Multistage extraction: Sequentially using different solvents to target multiple bioactive groups (Wen et al., 2020).

Solvent recycling and green extraction: Employing eco-friendly solvents and low-energy extraction methods to reduce environmental impact (Hessel et al., 2022).

Automated process control: Using real-time monitoring and AI-driven optimization to improve reproducibility and efficiency (Yingngam et al., 2024).

By understanding and optimizing these factors, researchers can significantly improve the yield, stability, and bioactivity of natural product extractions, leading to more effective pharmaceutical, nutraceutical, and functional food applications (Figure 2).

5 Advanced extraction techniques for enhanced bioactivity

Advanced extraction techniques have been developed to address the limitations of conventional methods, offering improved efficiency, selectivity, and preservation of bioactive compounds (Zia et al., 2022). These techniques leverage modern technologies to enhance the recovery of bioactive molecules while minimizing degradation and solvent usage (Rifna et al., 2023).

5.1 Ultrasound-assisted extraction

UAE employs high-frequency sound waves to create cavitation, which disrupts plant cell walls and facilitates the

release of intracellular compounds (Islam et al., 2023). This method enhances the extraction efficiency of phenolics, flavonoids, and other bioactive molecules while reducing extraction time and solvent consumption (Lovrić et al., 2017; Anaya-Esparza et al., 2023; Demesa et al., 2024).

5.2 Microwave-assisted extraction

MAE uses microwave radiation to rapidly heat the solvent and plant matrix, increasing the diffusion of target compounds. This technique has been shown to improve the recovery of thermolabile bioactives and enhance antioxidant potential compared to conventional extraction methods (Kanitkar et al., 2011).

5.3 Supercritical fluid extraction

SFE, particularly with supercritical carbon dioxide (SC-CO₂), is effective for extracting non-polar compounds such as terpenoids and lipophilic antioxidants (Dashtian et al., 2024). The adjustable pressure and temperature conditions allow for selective extraction while reducing solvent residues in the final product (Herrero et al., 2010). These advanced techniques provide promising alternatives to conventional extraction methods, ensuring higher efficiency and improved bioactivity of natural product extracts (Khaw et al., 2017).

5.4 Critical considerations and parameter sensitivity

While advanced techniques like UAE and MAE are widely praised for their high efficiency and reduced processing times, it

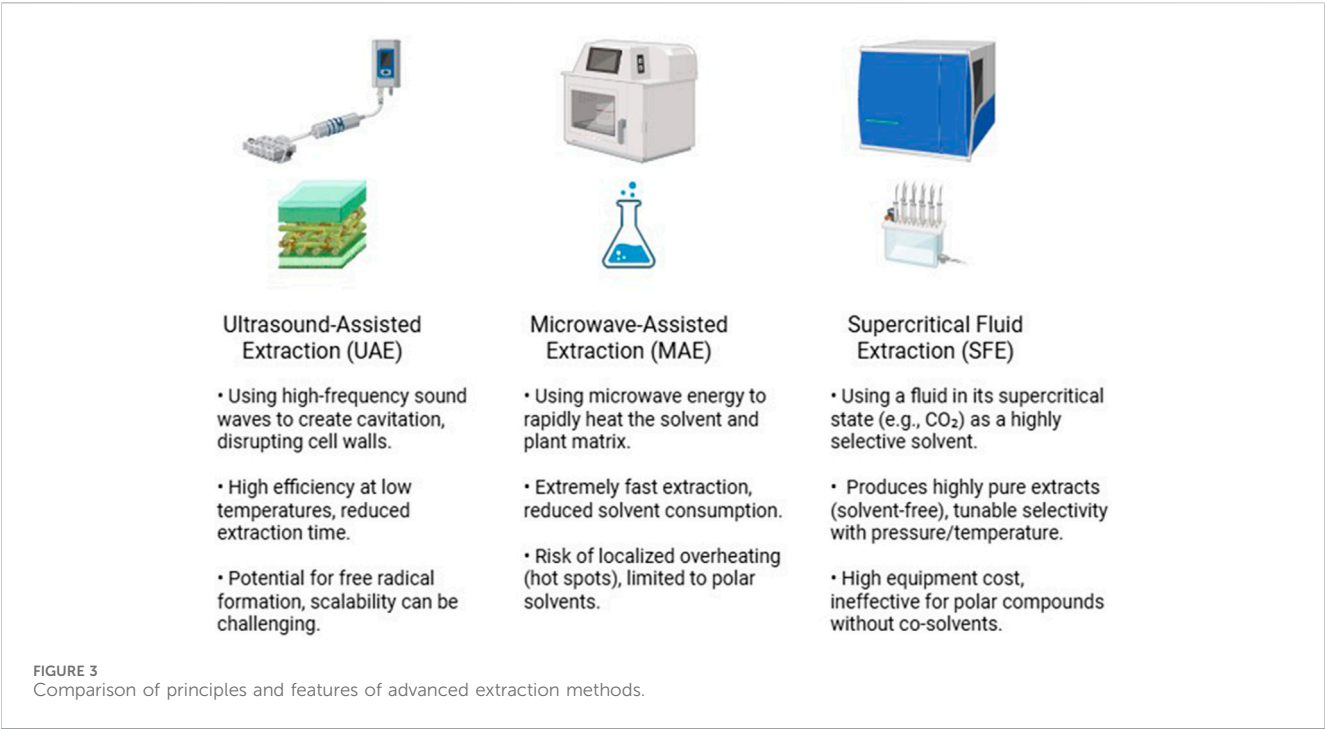


TABLE 1 Comparison of conventional extraction methods.

Method	Principle	Processing time	Relative yield	Energy use	Thermal stability	Selectivity	Initial cost
Maceration	Soaking material in solvent at room temperature (Othman et al., 2024)	Very Long	Low	Very Low	Good	Low	Low
Soxhlet Extraction	Continuous washing with fresh, hot, refluxing solvent (Malabadi et al., 2024)	Long	Moderate-High	High	Poor	Low-Moderate	Low
Hydrodistillation	Co-distillation of volatile compounds with boiling water or steam (Paini et al., 2025)	Long	Variable (High for volatiles)	High	Poor	High (for volatiles)	Low
UAE	Disrupts cell walls using high-frequency acoustic cavitation (Sethi and Rathod, 2024)	Short	High	Low-Medium	Good	Moderate	Medium
MAE	Uses microwave energy for rapid, direct heating of the matrix (Dhotre, 2025)	Very Short	High	Medium	Fair	Moderate-High	Medium
SFE	Uses a fluid (mainly CO ₂) in its supercritical state as a solvent (Herzyk et al., 2024)	Medium	High	High	Excellent	High	High

is crucial to recognize that their effectiveness is not universal and is highly parameter-dependent. A critical review of the literature reveals that direct comparisons can yield variable outcomes, highlighting that there is no single “best” method for all applications (Azwanida, 2015). This variability often stems from the sensitivity of these methods to processing parameters. For example, while moderate sonication power in UAE can enhance cell disruption, excessive power or prolonged exposure can generate free radicals, leading to the degradation of thermolabile compounds like certain flavonoids (Shirsath et al., 2012; Chemat et al., 2017). In such cases, the final extract may exhibit lower bioactivity than one obtained from a carefully optimized conventional method (Kumar

et al., 2021). Similarly, the effectiveness of MAE is highly dependent on the dielectric properties of the solvent and the matrix (Camel, 2000; Vinatoru et al., 2017). Improper settings can cause uneven heating and “hot spots,” which can compromise compound integrity (Mandal et al., 2007; Chemat et al., 2020; Bhadange et al., 2024). Therefore, a more nuanced perspective is required. The selection of an advanced technique must be accompanied by rigorous optimization of its key parameters (e.g., power, temperature, time, solvent choice) tailored to the specific phytochemicals and plant matrix (Bezerra et al., 2008). Simply adopting an advanced method without this critical optimization does not guarantee a superior result (Figure 3; Table 1).

6 Analytical techniques for phytochemical profiling

The accurate identification and quantification of phytochemicals in plant extracts are essential for evaluating their bioactivity and therapeutic potential (Doughari, 2012). Various analytical techniques have been developed to profile the complex composition of natural product mixtures, allowing researchers to assess extraction efficiency, standardize bioactive compounds, and ensure batch-to-batch consistency (Nikam et al., 2012).

6.1 High-performance liquid chromatography

HPLC is a widely used analytical method for separating, identifying, and quantifying phytochemicals in plant extracts (Boligon and Athayde, 2014). It operates by passing a liquid mobile phase through a column packed with a stationary phase, where compounds interact based on their polarity and affinity (Žuvela et al., 2019). This technique is effective for detecting flavonoids, polyphenols, alkaloids, and glycosides (Wolfender, 2009; Yuan et al., 2019).

Application: Used extensively in pharmaceutical and nutraceutical industries for quality control and standardization of plant extracts (Choudhary and Sekhon, 2011).

Advantages: High resolution, sensitivity, and reproducibility.

Limitations: Requires extensive sample preparation and solvent use (Dong, 2013).

6.2 Gas chromatography-mass spectrometry

Gas Chromatography-Mass Spectrometry (GC-MS) is ideal for analyzing volatile and semi-volatile phytochemicals, such as essential oils, terpenoids, and fatty acids (Ye, 2009). It works by vaporizing a sample and passing it through a column where compounds are separated based on their volatility (Hubschmann, 2025). The separated compounds are then identified based on their mass-to-charge ratio (Xie et al., 2019).

Application: Used in essential oil profiling, fragrance analysis, and food quality testing (Song and Liu, 2018).

Advantages: High specificity, rapid analysis, and excellent compound identification (Hao et al., 2007).

Limitations: Not suitable for non-volatile or thermally unstable compounds (Kornilova et al., 2013; Beale et al., 2018).

6.3 Nuclear magnetic resonance spectroscopy

NMR spectroscopy provides structural and compositional insights into phytochemicals by detecting the interactions of atomic nuclei with an external magnetic field (Gautam et al., 2025). Unlike chromatographic methods, NMR is non-destructive and provides a comprehensive overview of molecular structures (Cade-Menun, 2005).

Application: Used for metabolomics studies, structural elucidation, and complex mixture analysis (Letertre et al., 2020).

Advantages: No extensive sample preparation, provides detailed molecular information.

Limitations: High cost of equipment and expertise required for data interpretation (Marcone et al., 2013).

6.4 Fourier Transform Infrared spectroscopy

Fourier Transform Infrared (FTIR) spectroscopy identifies functional groups in phytochemicals based on their absorption of infrared light (Vijayalakshmi and Ravindhran, 2012). It provides molecular fingerprints that are useful in distinguishing different plant metabolites (Rebiai et al., 2022).

Application: Used for rapid quality control, authentication of herbal medicines, and detecting adulteration (Huck, 2015).

Advantages: Fast, cost-effective, and non-destructive (Kumari et al., 2018).

Limitations: Limited ability to distinguish structurally similar compounds (Baker et al., 2014).

6.5 Ultra-high-performance liquid chromatography

Ultra-High-Performance Liquid Chromatography (UHPLC) is an advanced form of HPLC that operates under higher pressure, allowing for faster separation and improved resolution (Dong and Zhang, 2014). This technique is particularly beneficial for analyzing complex phytochemical mixtures and detecting minor bioactive constituents (Wu et al., 2013).

Application: Used in pharmaceutical analysis, high-throughput screening, and quality control of functional foods (Ahmed et al., 2023).

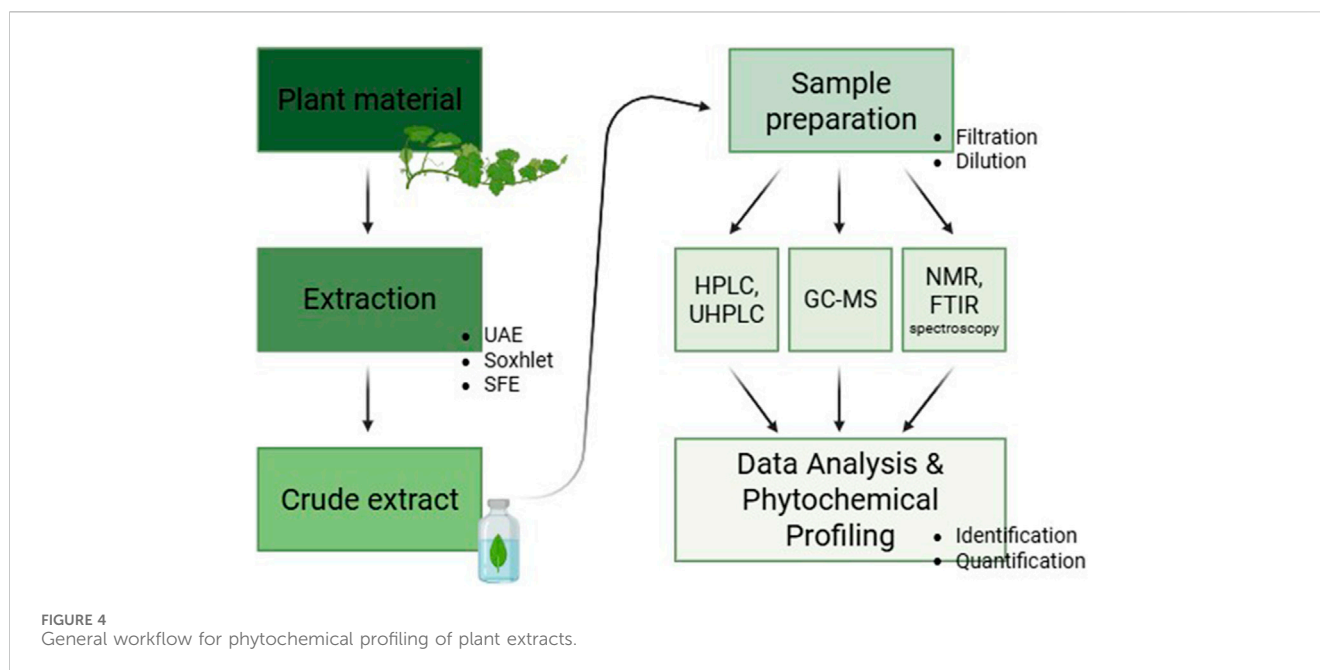
Advantages: Increased resolution, faster analysis time, and lower solvent consumption (Dong and Zhang, 2014).

Limitations: Higher instrument cost and maintenance requirements (Dong and Zhang, 2014).

These analytical techniques are essential for accurately profiling phytochemicals and ensuring the quality and efficacy of natural product extracts. The choice of method depends on the nature of the compounds being analyzed, as well as the intended application. By integrating multiple techniques, researchers can achieve a comprehensive understanding of phytochemical composition and bioactivity, leading to improved standardization in pharmaceuticals, nutraceuticals, and functional foods (Figure 4).

7 Challenges and future perspectives in standardizing and scaling up extraction methods

Despite significant advancements in extraction technologies, challenges remain in standardizing and scaling up these processes for industrial applications (More et al., 2022). The reproducibility, efficiency, and sustainability of extraction methods must be



addressed to ensure consistency in phytochemical composition and bioactivity across different production batches (Da Silva et al., 2022). Additionally, regulatory frameworks, cost-effectiveness, and environmental considerations play crucial roles in determining the feasibility of large-scale extraction operations (Bouizgma et al., 2025).

7.1 Standardization of extraction methods

Achieving standardization in natural product extraction is challenging due to the inherent variability in plant materials, including differences in species, growing conditions, and harvesting times (Bandaranayake, 2006; Afshar et al., 2022). The same extraction method may yield different phytochemical profiles depending on these variables (Wong et al., 2022). Therefore, standardized protocols must be established to ensure batch-to-batch consistency.

Reproducibility Issues: Variability in raw materials affects extraction efficiency, necessitating strict control of processing parameters such as solvent type, temperature, and extraction time (Sridhar et al., 2022).

Optimization of Key Parameters: Developing standardized protocols for solvent concentration, pH, pressure, and extraction duration is critical to achieving reliable results (Risticvic et al., 2010).

Regulatory Compliance: The standardization of extraction methods is essential for meeting pharmaceutical and nutraceutical regulatory guidelines (e.g., FDA, EMA, WHO) (Hossain et al., 2022).

7.2 Challenges in scaling up extraction processes

While many extraction techniques are effective in laboratory-scale studies, their industrial-scale implementation presents technical and economic challenges.

Equipment and Infrastructure Limitations: Large-scale extraction requires specialized equipment such as high-pressure supercritical CO₂ systems or industrial-scale ultrasonic reactors, which involve high capital investment (Duba and Fiori, 2019).

Energy and Solvent Consumption: Scaling up extraction processes can significantly increase energy consumption and solvent use, leading to higher production costs and potential environmental impact (Pai et al., 2022).

Process Efficiency and Yield Optimization: Industrial-scale extractions must be optimized to maximize yield while maintaining bioactivity, ensuring cost-effectiveness without compromising product quality (Yadav et al., 2024).

7.3 Environmental and sustainability considerations

The environmental impact of large-scale extraction processes is a growing concern, particularly with the use of organic solvents and excessive energy consumption.

Green Extraction Technologies: Sustainable alternatives such as supercritical CO₂ extraction, pressurized liquid extraction, and enzymatic-assisted extraction are being explored to minimize solvent waste and energy use (Alexandre et al., 2018).

Solvent-Free and Low-Energy Approaches: Techniques like subcritical water extraction and membrane-based separation systems offer eco-friendly solutions for extracting bioactive compounds with minimal environmental impact (Mondal et al., 2025).

Waste Management and Byproduct Utilization: Developing methods to recycle solvents and utilize extraction byproducts in secondary applications (e.g., animal feed, fertilizers) can enhance the sustainability of extraction operations (Soh and Eckelman, 2016).

7.4 Future perspectives and innovations

While significant progress has been made, several key gaps in the literature need to be addressed to advance the field. Future research should be prioritized in the following areas.

- **Techno-Economic Analyses (TEA):** Direct and rigorous cost-benefit analyses comparing advanced extraction techniques (e.g., SFE vs MAE for a specific high-value compound) are urgently needed (Feng et al., 2022). Such studies are critical for guiding industrial adoption and determining economic viability (Apostolakou et al., 2009).
- **Optimization of Hybrid Systems:** As integrated extraction strategies show great promise, systematic research is required to optimize the parameters of these multi-step processes (Rodríguez-Pérez et al., 2016). Understanding the synergistic and antagonistic interactions between different techniques is key to maximizing their potential (Macedo et al., 2023).
- **Automation and Process Control:** While artificial intelligence (AI)-driven optimization shows promise, developing and validating cost-effective, real-time monitoring sensors for industrial-scale extractions remains a key challenge that requires further research (van den Berg et al., 2013; Grassi and Alamprese, 2018).
- **Bioavailability Enhancement:** Although nanoencapsulation can improve stability, more clinical research is needed to develop scalable, food-grade nano-delivery systems and to confirm their long-term *in vivo* efficacy and safety (McClements, 2014).
- **Scalability of Green Solvents:** While green solvents like DES are effective at the lab scale, research into their large-scale production, stability, and efficient recycling is still in its early stages and presents a major hurdle for industrial implementation (Socas-Rodríguez et al., 2021).

8 Conclusion

The choice of an extraction technique is a critical determinant in harnessing the therapeutic potential of natural products. It governs not only the yield and phytochemical composition of an extract but, more importantly, the preservation of the inherent bioactivity of its constituent compounds. This review has illustrated that while conventional methods are simple, they often compromise compound integrity due to harsh conditions. In contrast, advanced techniques such as UAE, MAE, and SFE offer superior efficiency and preservation, though their effectiveness is highly dependent on rigorous parameter optimization, as underscored by the literature's variable findings.

Ultimately, this review highlights that the future of natural product valorization lies in the intelligent integration of hybrid strategies to maximize recovery while ensuring sustainability and economic viability.

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A well-chosen and meticulously optimized extraction strategy is the essential first step in translating the rich chemical diversity of natural products into safe and effective therapeutic agents for pharmaceutical and nutraceutical applications.

Author contributions

SS: Conceptualization, Writing – original draft. YY: Data curation, Writing – original draft. YJ: Investigation, Writing – original draft. JH: Data curation, Writing – original draft, Writing – review and editing. YX: Investigation, Writing – original draft. MC: Visualization, Writing – review and editing. S-JB: Resources, Writing – review and editing. DR: Writing – review and editing. WP: Funding acquisition, Writing – review and editing. K-TH: Supervision, Project administration, Writing – review and editing. SZ: Conceptualization, Supervision, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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