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REVIEW: MODERN EXTRACTION METHODS FOR EXTRACTION OF PROANTHOCYANIDINS FROM NATURAL PRODUCTS

Tinjauan Literatur: Metode Ekstraksi Modern untuk Mengekstraksi Senyawa Proantosianidin dari Bahan Alam

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ABSTRAK

Proantosianidin banyak ditemukan pada berbagai tanaman dan memiliki efek menguntungkan bagi kesehatan karena memiliki aktivitas antioksidan dan antiinflamasi. Studi literatur ini bertujuan mengkaji metode ekstraksi modern untuk mengekstraksi senyawa proantosianidin dari bahan alam. Metode ekstraksi konvensional, seperti maserasi dan soxhlet, sering kali menurunkan perolehan senyawa proantosianidin karena senyawa tersebut sensitif terhadap panas dan mudah teroksidasi. Oleh karena itu, diperlukan kajian literatur yang mengulas lebih lanjut mengenai sejumlah metode ekstraksi modern untuk mengekstraksi senyawa proantosianidin dari bahan alam. Kajian ini disusun berdasarkan pencarian literatur secara sistematis pada lima basis data akademik utama, yaitu ScienceDirect, PubMed, Google Scholar, NCBI, dan BMC, dengan mempertimbangkan artikel-artikel peer-reviewed yang relevan. Metode ekstraksi modern yang diulas dalam artikel ini meliputi Ultrasound-Assisted Extraction (UAE), Microwave-Assisted Extraction (MAE), Enzyme-Assisted Extraction (EAE), dan Pressurized Liquid Extraction (PLE). Tinjauan literatur komprehensif dari 23 artikel menunjukkan bahwa UAE dan MAE adalah metode ekstraksi modern paling efektif dan efisien untuk mengekstraksi senyawa proantosianidin dari bahan alam. Analisis ini mendukung pemanfaatan metode ekstraksi modern untuk memaksimalkan hasil dan kualitas proantosianidin dari bahan alam untuk sejumlah keperluan farmasetik dan nutraseutikal.

Kata kunci: *proantosianidin, ultrasound-assisted extraction, microwave-assisted extraction, natural products, senyawa bioaktif.*

ABSTRACT

Proanthocyanidins are widely distributed in many plant species and are recognized for their beneficial health effects, particularly their antioxidant and anti-inflammatory activities. This literature review aims to evaluate modern extraction techniques used to isolate proanthocyanidins from natural sources. Conventional methods, such as maceration and Soxhlet extraction, often result in reduced yields because proanthocyanidins are heat-sensitive and susceptible to oxidation. To address these limitations, this review explores alternative modern extraction approaches. Relevant peer-reviewed articles were identified through a comprehensive

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search of five academic databases: ScienceDirect, PubMed, Google Scholar, NCBI, and BMC. The modern extraction techniques examined include Ultrasound-Assisted Extraction (UAE), Microwave-Assisted Extraction (MAE), Enzyme-Assisted Extraction (EAE), and Pressurized Liquid Extraction (PLE). Evidence from 23 selected studies shows that UAE and MAE are among the most effective and efficient methods for extracting proanthocyanidins from natural matrices. These findings underscore the potential of modern extraction technologies to improve both the yield and quality of proanthocyanidins, supporting their broader application in pharmaceutical and nutraceutical fields.

Keywords: *proanthocyanidins, ultrasound-assisted extraction, microwave-assisted extraction, natural products, bioactive compounds.*

INTRODUCTION

Tannins are a diverse group of plant secondary metabolites that are broadly classified into two categories: condensed tannins and hydrolyzable tannins (Das *et al.*, 2020). Condensed tannins, more commonly referred to as proanthocyanidins, are oligomeric or polymeric flavonoids composed primarily of flavan-3-ol or flavan-3,4-diol units (Cosme *et al.*, 2025). In contrast, hydrolyzable tannins consist of ellagic acid and gallic acid (Brus *et al.*, 2021). Proanthocyanidins are particularly abundant across a wide range of botanical sources including fruits, flowers, bark, stems, and seeds, and serve as protective agents against fungi, pathogens, and herbivorous insects (Rauf *et al.*, 2019). As highlighted by (Kurniawan and Zahra, 2021), these compounds are generally colorless and ubiquitous in higher plants, with especially high concentrations in woody species and ferns. Growing scientific interest in proanthocyanidins stems from their pronounced bioactivities, notably their potent antioxidant and anti-inflammatory properties (Unusan, 2020), superior radical-scavenging capacity (Zhang *et al.*, 2019; Li *et al.*, 2024), and broad pharmacological implications in mitigating oxidative stress–related disorders (Yang *et al.*, 2018). Consequently, focusing on proanthocyanidins provides a strong rationale for exploring their therapeutic potential in comparison with other classes of tannins (Smeriglio *et al.*, 2017).

Natural sources rich in proanthocyanidins include grapes, blackberries, strawberries, walnuts, cashews, hazelnuts, mangoes, and tea (Das *et al.*, 2020). To access these compounds, efficient extraction strategies are essential. Broadly defined, extraction is the transfer of a target compound from its original matrix either solid or liquid into a suitable solvent (Aji, Bahri and Tantalia, 2018). The aim is to isolate bioactive constituents from natural products using solvent systems optimized for their physicochemical properties (Candra, Andayani and Wirasisya, 2021). Several factors influence the efficiency of extraction, including the chosen method, duration of extraction, solvent-to-material ratio, and the solvent type itself (Zulfina, Safriani and Husna, 2018).

Traditionally, proanthocyanidins have been obtained through conventional extraction techniques such as maceration, percolation, reflux, Soxhlet extraction, and decoction (Bitwell *et al.*, 2023; Arrofiqi,

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Sakti and Mayangsari, 2024; Firdiyansyah *et al.*, 2024). These approaches are simple and widely applied, particularly for thermolabile plant constituents. However, they also present significant drawbacks, including susceptibility to hydrolysis, oxidation, and ionization, which may degrade proanthocyanidins during processing (Hilbig *et al.*, 2018) To address these limitations, modern extraction technologies have been developed that employ physical or enzymatic enhancement to improve yield and efficiency (Mungwari *et al.*, 2025). Among them are Ultrasound-Assisted Extraction (UAE), Microwave-Assisted Extraction (MAE), Enzyme-Assisted Extraction (EAE), High Hydrostatic Pressure Extraction (HHPE), and Pressurized Liquid Extraction (PLE). Compared with conventional methods, these modern techniques generally achieve faster extraction, higher selectivity, and lower solvent consumption, thereby reducing both processing time and environmental burden (Khaw *et al.,* 2017).

Despite the increasing application of advanced extraction technologies in natural product research, there remains a scarcity of comprehensive studies that specifically address their use in isolating proanthocyanidins. To bridge this gap, the present review critically examines current modern extraction strategies and evaluates their suitability for obtaining proanthocyanidins from diverse natural sources.

METHODS

This study employed a narrative literature review approach to examine recent advancements in modern extraction techniques for isolating proanthocyanidins from natural sources. The methodological framework was informed by established guidelines for narrative reviews (Sakti *et al.*, 2025), and adapted to align with the specific objectives and scope of this paper.

A systematic search of relevant literature was conducted across five major academic databases: ScienceDirect, PubMed, Google Scholar, NCBI, and BMC. The search strategy combined Boolean operators with the following keywords: “Proanthocyanidin,” “Total Proanthocyanidin Content,” “Ultrasound-Assisted Extraction (UAE),” “Microwave-Assisted Extraction (MAE),” “Pressurized Liquid Extraction (PLE),” and “Enzyme-Assisted Extraction (EAE).”

Inclusion criteria required that studies be peer-reviewed journal articles published between 2014 and 2023, with a primary focus on modern extraction methodologies applied to the isolation of proanthocyanidins from natural matrices. Exclusion criteria encompassed articles that relied solely on conventional extraction methods, non–peer-reviewed publications, and studies unrelated to proanthocyanidin extraction.

The initial search identified 167 articles. A two-stage screening process comprising title and abstract review followed by full-text eligibility assessment narrowed this number to 23 studies that met the inclusion criteria and were subjected to detailed analysis and synthesis. The selection pathway is presented in a PRISMA-style flow diagram (Figure 1), included to enhance transparency and

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methodological clarity. Although the PRISMA framework is not mandatory for narrative reviews, its application here strengthens the reproducibility and rigor of the review process.

In this review, the selected studies were compared according to the modern extraction techniques employed, including ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), pressurized liquid extraction (PLE), high hydrostatic pressure extraction (HHPE), and enzyme-assisted extraction (EAE). Key extraction parameters such as temperature, extraction time, power, and pH, were analyzed alongside the reported yields of proanthocyanidins. This comparative evaluation provides insight into both the efficiency and the limitations of each method under varying operational conditions.

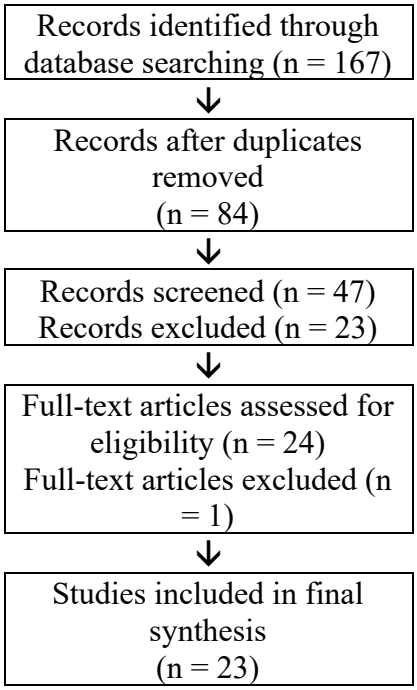

Figure 1. PRISMA-style flow diagram outlining the article selection process.

RESULTS AND DISCUSSION

Fundamentals of Modern Extraction Methods

Extraction represents a core process in natural product research, enabling the separation of bioactive compounds from plant matrices through the use of suitable solvents (Firdiyansyah *et al.*, 2024). Over time, a wide spectrum of extraction approaches has been developed, ranging from conventional to semi-modern and fully modern techniques (Zhang, Lin and Ye, 2018).

Modern extraction strategies fundamentally differ from traditional ones in that they integrate physical energy sources such as ultrasound, microwaves, or high pressure with carefully optimized solvent systems. This integration enhances mass transfer, minimizes degradation of thermolabile compounds, and improves selectivity. More importantly, these methods accelerate solute–solvent interactions under controlled conditions, which not only improves efficiency but also strengthens reproducibility and aligns with principles of sustainability. However, the broader adoption of modern extraction techniques is shaped by practical constraints. The requirement for specialized equipment, relatively high initial investment, and trained personnel often restricts their application, particularly in resource-limited laboratories or industrial settings (Khaw *et al.*, 2017; Chaves *et al.*, 2020).

The performance of modern extraction methods is influenced by several key parameters, including extraction time, temperature, pressure, solvent choice, and the amount of applied energy (Sakti,

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Rahmawati and Fazadini, 2024). Selecting an appropriate method also requires careful consideration of the physicochemical characteristics of the plant material, as these properties can substantially determine both the yield and quality of the extracted compounds (Zhang *et al.*, 2023).

Advantages and Disadvantages of Modern Extraction Methods

Ultrasound Assisted Extraction (UAE)

Ultrasound-assisted extraction (UAE) offers several notable advantages, one of which is the relatively low solvent requirement compared with conventional approaches (Kunarto *et al.*, 2019). Importantly, the chemical composition of the plant material remains largely intact during extraction, preserving the integrity of its particles and compounds (Adhiksana, 2017). UAE also improves solvent penetration across cell walls, accelerates mass transfer, enhances extraction yield, and allows the process to be conducted at low temperatures while significantly shortening extraction time (Kristina, Yusasrini and Yusa, 2022).

The underlying principle of UAE lies in the application of ultrasonic waves to the plant matrix, which induce the formation of cavitation bubbles in the solvent. Upon collapse, these bubbles generate localized high pressure and intense shear forces that mechanically disrupt cell wall structures. This disruption facilitates the release of intracellular phytochemicals into the solvent, thereby increasing extraction efficiency and reproducibility (Lavilla and Bendicho, 2017; Tang *et al.*, 2024; Siddique, Rashid and Ali, 2025).

Although UAE is widely recognized as a green and efficient technique, it also presents notable limitations. The cavitation phenomenon generated during sonication can create extreme localized conditions reaching up to 5000 K and 1000 atm that risk degrading thermolabile or oxidation-sensitive compounds and altering their chemical profiles. Extraction efficiency is highly dependent on multiple parameters, including frequency, intensity, solvent type, solid–liquid ratio, and extraction time, where suboptimal conditions may compromise yields or compound stability. Equipment-related issues further constrain its application: ultrasonic baths, though inexpensive, often provide non-uniform energy distribution, limited control of power and temperature, and low reproducibility, while ultrasonic probes, despite greater efficiency, require precise optimization for each matrix and may damage sample vessels. Moreover, UAE performance is matrix- and compound-specific, with some reports indicating that conventional methods can outperform UAE for certain biomolecules, necessitating case-by-case optimization. Finally, large-scale application remains challenging due to difficulties in maintaining homogeneous energy distribution, increased energy consumption, and the high cost of industrial ultrasound systems. (Lavilla and Bendicho, 2017; Carreira-Casais *et al.*, 2021).

Microwave Assisted Extraction (MAE)

Microwave-assisted extraction (MAE) provides several clear advantages over conventional techniques, including rapid extraction, higher yields, and reduced

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solvent consumption, which together enhance cost-effectiveness (Zahar et al., 2021). Despite these benefits, MAE also presents limitations. Post-extraction steps such as centrifugation or filtration are often required to remove impurities, adding complexity to the overall workflow (Biswas *et al.*, 2023). Moreover, the efficiency of MAE decreases substantially when non-polar or volatile solvents are employed, as these solvents are poorly compatible with microwave energy and the targeted bioactive compounds (Llompart, Celeiro and Dagnac, 2019).

It is also important to acknowledge that MAE is not universally applicable to all plant-derived materials. As a heat-intensive process, the actual temperature achieved within the extraction vessel is difficult to measure directly; only the applied microwave power (in watts) can be monitored in practice (Yeasmen and Orsat, 2023). This limitation raises concerns when working with matrices rich in thermolabile phytochemicals or volatile aromatic constituents, as uncontrolled or excessive heating can result in degradation or significant losses of these sensitive compounds (Nithya *et al.*, 2023).

Enzyme Assisted Extraction (EAE)

The core principle of enzyme-assisted extraction (EAE) involves the selective hydrolysis of structural polysaccharides in plant cell walls, including cellulose, hemicellulose, and pectin (Streimikyte, Viskelis and Viskelis, 2022; Kleekayai *et al.*, 2023). Enzymatic degradation of these rigid components weakens the cell wall matrix, thereby facilitating the release of intracellular bioactive compounds into the solvent (Shivakumar *et al.*, 2024). This high degree of specificity distinguishes EAE from conventional physical or chemical extraction techniques, as it allows for the targeted recovery of compounds under relatively mild conditions. Consequently, EAE is particularly advantageous for preserving the activity and structural integrity of thermolabile phytochemicals (Sánchez-Camargo *et al.*, 2020; Abedelmaksoud *et al.*, 2025).

Several advantages have been attributed to EAE, including its capacity to selectively produce desired components, high extraction yields with good purity, non-toxicity, environmental sustainability, and scalability for industrial applications (Shawky, Zhu and Tian, 2025). Despite these strengths, the method is not without limitations. The most critical drawback lies in the high cost of enzymes, which can restrict its broader adoption, particularly in large-scale or resource-limited settings (Krakowska-Sieprawska *et al.*, 2021).

Pressurized Liquid Extraction (PLE)

PLE offers benefits such as low solvent consumption, rapid processing times, and high yields (Machado *et al.*, 2024). However, a significant disadvantage of this method is the use of very high temperatures during extraction, which can result in the co-extraction of undesirable compounds (Maleta *et al.*, 2018).

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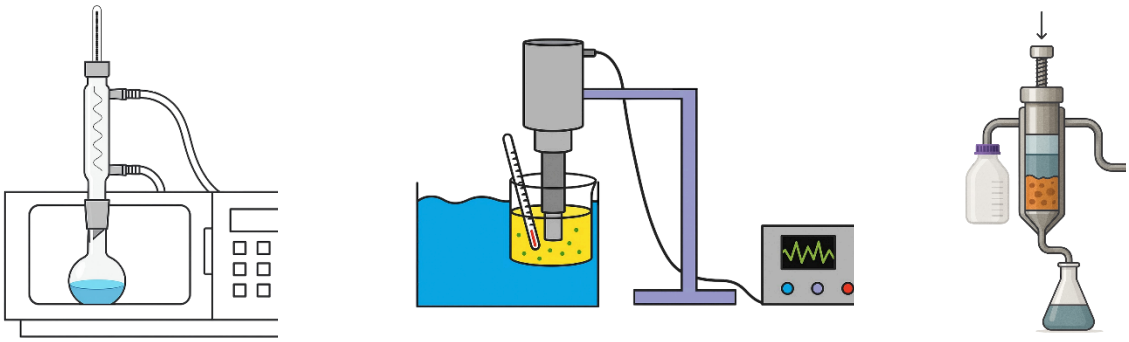

(a) (b) (c)

Figure 2. Schematic representation of modern extraction methods: (a) Microwave-Assisted Extraction (MAE), (b) Ultrasound-Assisted Extraction (UAE), and (c) Pressurized Liquid Extraction (PLE).

Table 1. Summary of the advantages and disadvantages of modern extraction methods

Extraction Method	**Advantages**	**Disadvantages**
Ultrasound-Assisted Extraction (UAE)	– Requires relatively low solvent volumes. – Preserves chemical integrity of compounds. – Enhances solvent penetration and mass transfer. – Short extraction times at low temperatures. – High reproducibility and yield under optimal conditions.	– Cavitation may degrade thermolabile/oxidation-sensitive compounds. – Strongly dependent on parameters (frequency, intensity, solvent, ratio, time) – Ultrasonic baths: uneven energy distribution, poor reproducibility. – Ultrasonic probes: require precise optimization, risk vessel damage. – Matrix- and compound-specific efficiency. – Challenging scale-up: energy distribution, cost, and energy demand.
Microwave-Assisted Extraction (MAE)	– Rapid extraction. – Higher yields than conventional methods. – Lower solvent consumption → cost-effective. – Efficient for polar solvents and heat-stable compounds.	– Requires additional post-extraction steps (filtration/centrifugation). – Less effective with non-polar or volatile solvents. – Actual vessel temperature difficult to control (monitored only by power in watts). – Risk of degradation for thermolabile or volatile compounds.
Enzyme-Assisted Extraction (EAE)	– Highly selective release of target compounds.	– High cost of enzymes limits industrial adoption.

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	− Gentle conditions preserve thermolabile compounds. − Produces extracts with high purity and yield. − Environmentally friendly and scalable − Non-toxic, sustainable process.	− Requires optimization of enzyme type and dosage. − Process time may be longer than physical methods.
Pressurized Liquid Extraction (PLE)	− Low solvent consumption. − Rapid processing times. − High yields achievable.	− High temperatures may degrade or co-extract unwanted compounds. − Requires specialized high-pressure equipment. − Limited applicability to heat-sensitive compounds.

Application of Modern Extraction Methods for Extracting Proanthocyanidins from Natural Products

Ultrasound Assisted Extraction (UAE)

Ultrasound-assisted extraction (UAE) is a modern technique that employs ultrasonic waves to recover substantial amounts of bioactive compounds in a relatively short period (Zahari *et al.*, 2020). The principle of UAE relies on the propagation of ultrasound waves through a solvent–solid system, generating cavitation bubbles around the plant matrix. The implosion of these bubbles produces localized heating and shear forces that simultaneously disrupt cell walls and facilitate the release of intracellular constituents (Shen *et al.*, 2023). This dual effect mechanical disruption coupled with enhanced diffusion underpins the efficiency of UAE and often results in higher extraction yields compared with conventional methods (Adhiksana, 2017).

In practice, UAE commonly operates at frequencies around 40 kHz, a range considered optimal because it provides a balance between cavitation intensity and bubble stability (Dzah *et al.*, 2020). At this frequency, the collapse of cavitation bubbles is sufficiently powerful to rupture cell walls and release phytochemicals, yet gentle enough to limit degradation of thermolabile compounds (Panda and Manickam, 2019). Frequencies below 20 kHz may produce excessively violent cavitation that damages target molecules, whereas frequencies above 80 kHz generate weaker cavitation, thereby reducing extraction efficiency (Cravotto and Binello, 2016).

Among the critical parameters governing UAE performance, frequency and power are particularly decisive. Cavitation intensity is directly influenced by the applied power, with greater energy input generally enhancing yield, though excessive levels risk degradation of phenolic structures (Gil-Martín *et al.*, 2022). Typically, UAE is conducted within a frequency range of 20–100 kHz, but higher frequencies result in fewer cavitation events and can compromise proanthocyanidin recovery (Rutkowska,

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Namieśnik and Konieczka, 2017). In addition to frequency and power, solvent type, extraction time, and temperature are equally important. The choice of solvent determines solubilization efficiency; moderately polar solvents such as ethyl acetate often outperform highly polar or non-polar alternatives. Extraction time must be optimized, as prolonged durations can trigger oxidation and structural alterations of proanthocyanidins, while insufficient time leads to incomplete release (Bhadange, Carpenter and Saharan, 2024). Similarly, temperature accelerates diffusion and mass transfer but, if excessive, causes thermal degradation of polyphenolic compounds (Lee *et al.*, 2024). As summarized in Table 1, optimal recovery of proanthocyanidins was achieved at 40 kHz, 35 °C, and an extraction duration of 50 minutes using ethyl acetate, yielding 291.85 ± 14.29 mg PC/g DW. These findings highlight that each UAE parameter exerts a distinct but interdependent effect on extraction performance. An intermediate frequency ensures efficient cavitation, moderate power levels enhance yield without promoting degradation, and appropriate solvent polarity maximizes solubilization. Together with carefully controlled temperature and time, these factors collectively determine the efficiency, selectivity, and overall quality of proanthocyanidin recovery.

Table 2. Summary of modern extraction method applications for extracting proanthocyanidins from natural products

Natural Products	Extraction Methods	Extraction Conditions	Total Proanthocyanidins (mgPC/gDW)	References
Kiwi (*Actinidia chinensis*)	UAE	40 kHz at 70°C for 15 minutes using acetone as solvent	122.19	(Lv *et al.*, 2021)
Grape (*Vitis vinifera*)	UAE	26 kHz at 80°C for 20 minutes using ethanol as solvent	95.46	(Da Porto, Natolino and Scalet, 2018)
Perilla (*Perilla frutescens*)	UAE	40 kHz at 53°C for 29 minutes using 62% ethanol as solvent	2.19	(Li *et al.*, 2019)
Camphor Tree (*Cinnamomum longepaniculatum*)	UAE	40 kHz at 100°C for 44 minutes using 70% ethanol as solvent	7.88	(Liu *et al.*, 2017)
Mung Bean (*Glycine max* L.)	UAE	20 kHz at 40°C for 13 minutes	21.40	(Khonchaisri *et al.*, 2022)

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Bayberry (*Myrica rubra*)	UAE	48°C for 39 minutes using methanol as solvent	17.26	(Dong *et al.*, 2021)
Dandelion (*Taraxacum officinale*)	UAE	60°C for 30 minutes using acetone as solvent	7.00	(Stanković *et al.*, 2022)
Blueberry (*Vaccinium* sect. *Cyanococcus*)	UAE	50°C for 15 minutes using 68% ethanol as solvent	212.72	(Wang *et al.*, 2018)
Almond (*Prunus dulcis*)	UAE	75°C for 20 minutes using 50% PEG as solvent	32.68	(Ma *et al.*, 2014)
Roselle (*Hibiscus sabdariffa* L.)	UAE	40 kHz at 32°C for 45 minutes using ethanol as solvent	0.75	(Pozos *et al.*, 2020)
Purple Bush (*Clemo heratensis*)	UAE	40 kHz at 30°C for 45 minutes using ethanol as solvent	4.09	(Nasseri *et al.*, 2019)
Phlomis crinita Cav.	UAE	40 kHz at 35°C for 50 minutes using ethyl acetate as solvent	291.85	(Nabti, Bourkaib and Boukhalfa, 2023)
Camphor (*Cinnamomum camphora*)	MAE	530 W for 18 minutes using 77% ethanol as solvent	81.56	(Liu *et al.*, 2021)
Acacia (*Acacia mangium*)	MAE	100 W for 3 minutes using ethanol as solvent	26.61	(Iriany, Pandiangan and Eka, 2017)
Indian Gooseberry (*Phyllanthus emblica* L.)	MAE	100 W for 1 minute using ethyl acetate as solvent	36.86	(Iriany, Angkasa and Namira, 2021)
Grape Pomace (*Vitis vinifera* L.)	MAE	99°C for 4 minutes using a solvent combination of choline chloride and lactic acid	135.00	(Neto *et al.*, 2021)
Grape Seeds (*Vitis vinifera* L.)	MAE	800 W at 170°C for 55 minutes using 94% ethanol as solvent	56.37	(Chen *et al.*, 2020)
Cinnamon Leaves (*Cinnamomum pedunculatum*)	MAE	540 W for 40 minutes using 71% ethanol as solvent	71.97	(Zhao *et al.*, 2020)
Carob (*Ceratonia siliqua*)	MAE	340 W for 4.5 minutes using ethanol as solvent	4.11	(Huma *et al.*, 2018)

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Sweet Cherry (*Prunus avium* L.)	EAE	70°C for 18.4 minutes at pH 10 using pectinase enzyme	29.20	(Domínguez-rodríguez, Luisa and Plaza, 2021)
País grape skins (*Vitis vinifera* L. cv. País)	EAE	0.01 g/mL S/L ratio, 1% E/S, pH 5.0, 37 °C for 3 h	~22.80	(Fernández, Vega and Aspé, 2015)
Lingonberry (*Vaccinium vitis-idaea* L.)	PLE	10.3 MPa at 50°C for 15 minutes using ethanol as solvent	289.59	(Kitryt *et al.*, 2020)
Cranberry (*Vaccinium* subg. *Oxycoccus*)	PLE	10.3 MPa at 83°C for 15 minutes using ethanol as solvent	198.50	(Tamkut *et al.*, 2020)

Microwave Assisted Extraction (MAE)

Microwave-assisted extraction (MAE) is a modern technique that uses microwave radiation to extract compounds from natural matrices. It is particularly effective for thermolabile substances, as it reduces processing time and minimizes prolonged exposure to high temperatures (Sasongko *et al.*, 2018). The principle of MAE is based on the ability of microwaves to heat intracellular water, causing it to evaporate and generate pressure on the cell walls. This pressure leads to cell rupture, thereby facilitating the release of target compounds (Wadli and Hasdar, 2021).

Several factors influence the efficiency of MAE, including the material-to-solvent ratio, microwave power, extraction time, extraction temperature, and solvent type (Hidayat, Puspawati and Yusasrini, 2022). As shown in Table 2, the most significant parameters affecting proanthocyanidin yield are extraction time, microwave power, and solvent selection. Under optimized conditions 10 minutes of extraction at 230 watts the yield reached 144.86 ± 3.93 mg PC/g DW, whereas the lowest yield (26.61 mg PC/g DW) was obtained at 3 minutes and 100 watts. These results suggest that longer extraction times and higher microwave power enhance proanthocyanidin recovery, likely due to greater heat generation that accelerates cell wall rupture and solute diffusion (Hidayat, Puspawati and Yusasrini, 2022).

Further evidence of optimization was provided by (Chen *et al.*, 2020), who employed response surface methodology (RSM) and central composite design (CCD) to define ideal conditions for both proanthocyanidins (PACs) and monomeric catechins. For catechins, the optimal setting was 170 °C, 94% ethanol, and 55 minutes, yielding up to 18.3 mg/g DW. For total PACs, the optimum was 120 °C, 68% ethanol, and 41 minutes, producing 113.6 mg CE/g DW. An overlaid contour plot identified a “sweet spot” at 140–150 °C, 60–70% ethanol, and 50 minutes, where both compounds were jointly optimized, yielding 100–110 mg CE/g DW PACs and 12–14 mg/g DW catechins. These findings

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confirm that MAE conditions can be tailored depending on whether the extraction goal is to prioritize depolymerized catechins, intact PACs, or a balanced recovery of both.

The study clearly demonstrated that there are indeed optimal conditions for maximizing both proanthocyanidin (PAC) and monomeric catechin recovery through microwave-assisted extraction (MAE). Using response surface methodology and central composite design, the authors determined that the optimum setting for monomeric catechins was 170 °C, 94% ethanol, and 55 min, yielding up to 18.3 mg/g DW of catechins, whereas the optimum for total PACs was 120 °C, 68% ethanol, and 41 min, yielding 113.6 mg CE/g DW. These results indicate that the most suitable conditions depend on whether the objective is to maximize depolymerized catechins or intact PACs. An overlaid contour plot further revealed a "sweet spot" at approximately 140–150 °C, 60–70% ethanol, and 50 min, where both responses were jointly optimized (PACs at 100–110 mg CE/g DW and catechins at 12–14 mg/g DW). Thus, the study confirms that well-defined optimal conditions exist, and these can be tailored depending on whether the extraction aims to prioritize catechins, PACs, or a balance of both

Finally, extraction duration remains a critical parameter. Extended extraction times increase the contact between plant material and solvent, thereby improving yield, although excessive heating may compromise compound stability (Winata and Yunianta, 2015).

Enzyme Assisted Extraction (EAE)

Enzyme-assisted extraction (EAE) is a modern technique that employs specific enzymes to promote the release of bioactive compounds from plant matrices (Wirajana *et al.*, 2019). The enzymes most commonly applied include pectinase, cellulase, and hemicellulase, which hydrolyze structural polysaccharides such as pectin, cellulose, and hemicellulose. By degrading these components of the cell wall, EAE facilitates the liberation of phytochemicals that are otherwise bound to lipid or carbohydrate chains (Shinwari, 2021).

As shown in Table 2, the application of pectinase under optimized conditions 18.4 minutes at 70 °C and pH 10 produced 29.2 ± 0.9 mg PC/g DW of proanthocyanidins (Domínguez-Rodríguez, Marina and Plaza, 2021). Likewise, cellulase-assisted extraction of País grape skins (*Vitis vinifera* L. cv. País) at a solid-to-liquid ratio of 0.01 g/mL, enzyme-to-substrate ratio of 1%, pH 5.0, and 37 °C for 3 hours yielded approximately 22.8 ± 0.9 mg PC/g DW (Fernández, Vega and Aspé, 2015). These findings demonstrate that the efficiency of EAE is strongly influenced by enzyme type, concentration, and operational parameters such as pH, temperature, and incubation time. In general, cellulase and pectinase enhance the recovery of proanthocyanidins by disrupting plant cell wall matrices, although the optimal yield can vary considerably depending on both the raw material and the extraction conditions.

Pressurized Liquid Extraction (PLE)

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Pressurized liquid extraction (PLE) is a modern approach that utilizes solvents under elevated temperature and pressure to accelerate mass transfer and enhance extraction efficiency (Raut *et al.*, 2015). Pressure is a key parameter, as increasing pressure improves solvent penetration and matrix wetting, thereby facilitating the release of bound compounds (Alvarez-Rivera *et al.*, 2020). In practice, operating pressures typically range between 10 and 15 MPa (de Menezes Rodrigues, Cardozo-Filho and da Silva, 2017).

Temperature also plays a pivotal role in PLE performance. Higher temperatures reduce solvent viscosity and surface tension, which improves solubility and accelerates diffusion of proanthocyanidins (Plaza and Turner, 2015). However, excessive heat may trigger degradation or oxidation of thermolabile compounds, ultimately reducing yields. Thus, achieving a balance between sufficient thermal energy for efficient mass transfer and the stability of sensitive phytochemicals is essential.

The effects of temperature and pressure in PLE are synergistic. Elevated temperatures enhance diffusion, while sufficient pressure is required to maintain the solvent in a liquid state above its boiling point, ensuring consistent contact with the plant matrix (Hoff and Pizzolato, 2018). This interplay prevents premature solvent evaporation and sustains high extraction efficiency. For example, as shown in Table 2, the highest yield of proanthocyanidins (289.59 ± 11.91 mg PC/g DW) was obtained at 10.3 MPa and 50°C for 15 minutes conditions that maximize solute diffusion without compromising compound stability (Kitryt *et al.*, 2020).

CONCLUSION

This review underscores the effectiveness of modern extraction techniques namely ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), enzyme-assisted extraction (EAE), and pressurized liquid extraction (PLE) in isolating proanthocyanidins from natural products. Among these, UAE demonstrates the highest yields when parameters such as frequency, temperature, and extraction time are carefully optimized, highlighting its potential for pharmaceutical applications. Both MAE and PLE also exhibit considerable promise, particularly in handling thermolabile compounds, though their performance depends heavily on solvent selection and process conditions to minimize compound degradation. EAE offers additional advantages in terms of environmental sustainability and the production of high-purity extracts, but its broader application remains constrained by the high cost of enzymes.

Collectively, these modern methods provide clear advantages over conventional techniques, including greater efficiency, enhanced yields, and improved preservation of bioactive compounds. Their continued refinement and wider adoption could strengthen the utilization of proanthocyanidins in pharmaceutical, nutraceutical, and other value-added applications.

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