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Flavonoids from *Codonopsis* spp.: Pharmaceutical perspectives, extraction strategies, and prospects for pectinase-assisted green recovery

Duyen Thi My Nguyen [1], Anh Ngoc Nguyen [1], Phuc Nguyen Thien Le [1] and Phu Hong Le [2,*]

[1] *Department of Biotechnology, School of Biotechnology, International University, Vietnam National University of Ho Chi Minh City (VNU-HCM), Ho Chi Minh City, Vietnam.*
[2] *Department of Food Technology, School of Biotechnology, International University, Vietnam National University of Ho Chi Minh City (VNU-HCM), Ho Chi Minh City, Vietnam.*

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Abstract

Codonopsis spp. is a traditional medicinal herb that has attracted increasing attention due to its flavonoid content and its potential applications in food, nutraceutical, and pharmaceutical fields. However, the recovery of flavonoids from this plant remains challenging because these compounds are often associated with complex cell wall components, which limits extraction efficiency. This review aimed to summarize the bioactivities of flavonoids from *Codonopsis* spp., outlined the conventional and green extraction methods currently used for their recovery, and discussed the prospects of pectinase-assisted extraction as a promising strategy. The method included the overview and analysis of studies employing different extraction techniques, such as solvent extraction, Soxhlet extraction, heat reflux extraction, ultrasound-assisted extraction, microwave-assisted extraction, subcritical water extraction, natural deep eutectic solvents, and enzyme-assisted extraction. Findings revealed that flavonoids from *Codonopsis* spp. exhibit notable antioxidant, anti-inflammatory, and neuroprotective potential, while green extraction approaches, particularly pectinase-assisted extraction, offer advantages in improving flavonoid release under mild and more sustainable conditions. This review highlighted the potential of pectinase-assisted extraction as an eco-friendly approach for enhancing flavonoid recovery from *Codonopsis* spp. Future research should focus on process optimization, integration with other green technologies, and validation for larger-scale applications.

Keywords: Bioactivity; *Codonopsis* spp; Flavonoids; Green extraction; Pectinase-assisted extraction; Sustainable recovery

1 Introduction

Đảng Sâm (*Codonopsis* spp.) is a classical medicinal herb of the Campanulaceae family that is widely used across East Asia, particularly in traditional Chinese medicine. It has been historically valued for its role in boosting general vitality, strengthening the spleen and lungs, and regulating qi, the body's vital energy [1]. Over centuries of use, *Codonopsis* spp. has become a cornerstone of herbal prescriptions, often regarded as a gentler alternative to *Panax ginseng*. Modern phytochemical studies have revealed that the therapeutic benefits of this herb can be attributed to a diverse array of bioactive constituents, including polysaccharides, alkaloids, phenylpropanoids, and triterpenoid saponins. Among these, flavonoids have attracted particular attention due to their potent biological activities, namely antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective effects [2]. These secondary metabolites play a key role not only in the plant's defense mechanisms but also in contributing to the pharmacological potential of *Codonopsis* spp.

* Corresponding author: Phu Hong Le

Given their importance, the efficient recovery of flavonoids from this plant material has become a crucial focus for both scientific research and industrial application in food, nutraceutical, and pharmaceutical fields [3]. However, conventional methods often provide limited flavonoid extraction efficiency [4]. High flavonoid binding to the plant cell wall matrix identifies the sources of this inefficiency by affecting their solubility and extractability, specifically through interactions with pectin and cellulose. Success has come from recent studies on enzyme-assisted extraction (EAE), a green method with the efficiency to exceed such limitations. Pectinase has drawn particular interest since it breaks down pectin and hence facilitates the release of flavonoids bound to the cell wall. Pectinase-mediated extraction has improved flavonoid recovery and bioavailability in several medicinal plants [5]. Using this method on *Codonopsis* spp. might thus enhance not only the bioactive chemical concentration but also contribute to environmentally friendly manufacturing techniques. This review provides an overview of the bioactivities of flavonoids from *Codonopsis* spp., examines the conventional and green extraction approaches used for their recovery, and highlights the potential of pectinase-assisted extraction as a promising alternative.

Beyond its phytochemical richness, *Codonopsis* spp. presents a compelling model for the advancement of sustainable extraction strategies. As the demand for plant-based therapeutics grows globally, there is increasing pressure to adopt methods that are not only efficient but also ecologically sound. Enzyme-assisted extraction, particularly using pectinase, offers dual benefits: it improves the release of cell wall-bound flavonoids while reducing reliance on harmful organic solvents. This aligns with the principles of green chemistry and supports a more responsible use of botanical resources. Furthermore, the optimization of EAE parameters -such as enzyme concentration, temperature, and incubation time, has been shown in other medicinal plants to significantly impact flavonoid yield and quality [6]. Applying this approach to Đảng Sâm not only has the potential to enhance therapeutic efficacy but may also open new avenues for its integration into functional food systems and biopharmaceutical applications. Thus, the investigation of pectinase-assisted flavonoid extraction holds both scientific value and practical relevance in the broader context of sustainable natural product development.

2 Health-promoting properties of flavonoids in Đảng Sâm (C*odonopsis* spp.)

Flavonoids are a large group of naturally occurring polyphenolic compounds widely distributed in the plant kingdom. As secondary metabolites, they play essential roles in plant development, stress tolerance, and defense mechanisms [4]. In recent years, flavonoids have attracted growing interest from the pharmaceutical, cosmetic, and functional food industries because of their wide range of biological activities, such as antioxidant, anti-inflammatory, neuroprotective, and anticancer activities [2]. Flavonoids are one of the most important bioactive constituents of Đảng Sâm and largely contribute to the traditional and modern medicinal values of the plant [3].

2.1 Antioxidant activity

One of the main beneficial roles of flavonoids involves their function as antioxidants. They have the potential to scavenge free radicals and thus prevent oxidative damage at the cellular level. The methanol extracts of *Codonopsis pilosula* were found to exhibit strong DPPH radical scavenging activity (87.3% at 1.0 $mg.mL^{-1}$) and a low IC_{50} value (0.41 $mg.mL^{-1}$). The extract also demonstrated strong radical scavenging capacity in the ABTS assay with an IC_{50} value of 0.35 $mg.mL^{-1}$ when compared with ascorbic acid [7]. *Codonopsis* spp. honey was additionally reported to possess antioxidant properties due to its phenolic acid and flavonoid content [8]. Although these findings support the antioxidant potential of *Codonopsis* spp., some evidence is based on flavonoid-rich extracts or related matrices rather than purified flavonoid fractions. Furthermore, many parts of *Codonopsis* spp. were found to have high polyphenolic content and strong antioxidant activity, suggesting the potential of different plant parts in functional food development [9]. These findings indicate that flavonoids from Đảng Sâm may exert preventive effects against oxidative stress-related conditions, including aging, cardiovascular diseases, neurodegenerative disorders, and metabolic syndromes. This underscores their significance in both clinical and preventive medicine.

2.2 Anti-inflammatory effects

Apart from their well-documented antioxidant activity, flavonoids isolated from *Codonopsis* spp. demonstrate pronounced anti-inflammatory effects through multiple molecular pathways. In in vitro studies, total flavonoid extracts significantly attenuated lipopolysaccharide (LPS)-induced inflammatory responses in RAW 264.7 macrophages by suppressing nitric oxide production and downregulating pro-inflammatory mediators, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) [10]. Furthermore, these flavonoids markedly reduced the expression levels of key inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), indicating their role in modulating cytokine-mediated signaling cascades [2]. Complementary in vivo experiments in murine models of acute inflammation confirmed that oral administration of *Codonopsis* spp. flavonoid fractions effectively suppressed edema formation and inflammatory cell infiltration, likely through inhibition of the NF-κB activation

pathway [10]. Collectively, these findings underscore the pharmacological potential of *Đảng Sâm* flavonoids as natural anti-inflammatory agents, offering mechanistic support for their traditional use in managing inflammatory disorders.

2.3 Neuroprotective properties

Flavonoids are increasingly recognized for their neuroprotective properties, primarily due to their ability to reduce oxidative stress and neuroinflammation, key factors in neurodegenerative disease progression. In Alzheimer's disease (AD) mouse models, flavonoid-rich extracts from *Codonopsis* spp. significantly reduced neuronal apoptosis and improved spatial learning and memory performance, as assessed by the Morris water maze test [11]. For *Codonopsis* spp., current evidence is still based largely on flavonoid-rich extracts and mixed fractions, suggesting neuroprotective potential while warranting further clarification of flavonoid-specific effects. Similarly, polysaccharide-flavonoid fractions from *Codonopsis* spp. improved memory and decreased hippocampal amyloid-beta ($A\beta_{1\text{-}42}$) deposition in senescence-accelerated mice. Furthermore, total flavonoids from Đảng Sâm were found to upregulate neurotrophic factors such as BDNF and NGF, promoting synaptic plasticity in oxidative stress-induced neuronal injury models [10]. These findings support the potential of Đảng Sâm flavonoids as natural neuroprotective agents, with implications for preventing and managing age-related cognitive decline and Alzheimer's disease.

2.4 Anticancer potential

Moreover, flavonoids from *Codonopsis* spp. display great potential for the therapy and prevention of cancer. These compounds have been shown to induce apoptosis in human colon cancer cells through mitochondrial pathways, thereby inhibiting tumor development [12]. Total flavonoids from Đảng Sâm were also found to suppress the migration and proliferation of hepatocellular carcinoma cells by modulating the PI3K/Akt signaling pathway. In addition, flavonoid fractions of *Codonopsis* spp. reduced toxicity to normal cells and enhanced the chemosensitivity of lung cancer cells to cisplatin, suggesting a dual role in increasing chemotherapeutic efficacy and minimizing adverse effects [10]. This supports their potential role as natural adjuvants in oncology consistent with the broader recognition of flavonoids as chemopreventive agents in various types of cancer, due to their ability to regulate oxidative stress, inflammation, and apoptotic signaling pathways [3]. Collectively, these results position Đảng Sâm flavonoids as valuable candidates for future development as natural adjuncts in cancer therapy.

2.5 Immunomodulation and liver protection

Apart from their well-documented antioxidant and anti-inflammatory properties, flavonoids also exert important health-promoting effects, particularly in immunomodulation and hepatoprotection [3]. Evidence from recent pharmacological reviews suggests that flavonoid-containing preparations of *Codonopsis* spp. may contribute to immunomodulatory effects, although direct evidence from isolated flavonoid fractions remains limited [10]. Furthermore, in CCl_4-induced liver injury models, administration of *Codonopsis* spp. flavonoids led to marked histological improvements and significantly decreased serum ALT and AST levels by 47.5% and 39.8%, respectively, reflecting potent hepatoprotective efficacy [13]. These quantitative findings have intensified scientific interest in investigating the pharmacological mechanisms and potential clinical applications of flavonoids from Đảng Sâm and other medicinal herbs.

3 Extraction methods for flavonoid recovery from Đảng Sâm (*Codonopsis* spp.)

Extraction methods for flavonoid recovery from *Codonopsis* spp. can be broadly grouped into conventional methods and green extraction methods. Conventional methods remain widely used because of their simplicity and established applicability, whereas green extraction methods have attracted increasing attention due to their potential to improve extraction efficiency while reducing solvent consumption, processing time, and environmental impact [14, 15].

3.1 Conventional extraction methods

Conventional extraction methods remain widely used for flavonoid recovery because of their operational simplicity, accessibility, and established use in phytochemical studies. However, these methods often require longer extraction times, larger solvent volumes, and, in some cases, elevated temperatures that may compromise thermolabile compounds. In medicinal root matrices such as *Codonopsis* spp., these limitations may reduce extraction efficiency and selectivity. Nevertheless, they continue to serve as practical baseline approaches for comparison with newer green extraction technologies [14].

3.1.1 Shaking-assisted extraction (SAE)

Shaking-assisted extraction (SAE) is a simple and cost-effective method that uses mechanical agitation to enhance the contact between plant material and solvent, thereby facilitating the diffusion of target compounds into the solvent phase [16]. Performed under mild temperature conditions, SAE is particularly suitable for extracting heat-sensitive flavonoids, as it helps preserve their structural integrity and bioactivity. Its low energy consumption and minimal equipment requirements make it especially suitable for small-scale laboratory applications and environmentally friendly extraction initiatives. However, SAE generally yields lower extraction efficiency and requires longer processing times compared to more advanced techniques such as ultrasound-assisted or microwave-assisted extraction [15]. Consequently, SAE can be considered as a simple and practical conventional extraction method, particularly when compound stability and ecological considerations are prioritized, although it may be less effective for plant materials and rigid cell wall structures.

3.1.2 Solvent extraction

Solvent extraction is among the most widely used techniques, involving solvents such as ethanol, methanol, acetone, or water to isolate flavonoids from plant matrices. It is characterized by its simplicity and efficiency; however, it faces several limitations, including solvent toxicity, the risk of degradation of thermally labile compounds, and the high energy demand associated with solvent recovery [17]. Within the *Codonopsis* genus, including *Codonopsis pilosula* and *Codonopsis javanica*, solvent extraction has demonstrated notable effectiveness. For instance, in *C. javanica*, where it was found that 60% ethanol yielded the highest flavonoid content at 1.6 mg quercetin equivalents per gram dry weight (mg QE/g DW), emphasizing the importance of optimizing solvent concentration for maximal yield [18].

3.1.3 Soxhlet extraction

Soxhlet extraction is a classical yet effective technique that continuously recycles solvent to achieve exhaustive recovery of target compounds. It offers advantages in terms of high yield and reproducibility, as well as compatibility with automated setups, but the prolonged heating inherent to the process can lead to degradation of thermolabile constituents such as certain flavonoids [18]. In *C. javanica*, Soxhlet extraction has been systematically optimized for total phenolic content, total flavonoid content, and antioxidant activity. Under the optimal conditions: 70% ethanol, particle size of 0.5 mm, extraction temperature of 80°C, material-to-solvent ratio of 1:20 (w/v), and three extraction cycles, the total flavonoid content reached 19.47 ± 0.41 mg rutin equivalents per gram dry weight (mg RE/g DW), accompanied by a DPPH radical scavenging activity of 81.26 ± 1.25% [19]. These results highlight the capacity of Soxhlet extraction, when properly optimized, to achieve high recovery of bioactive flavonoids from complex root matrices. Such findings not only confirm its relevance for *Codonopsis spp.* but also provide a valuable benchmark for adapting this method to Đảng Sâm in both research and industrial applications.

3.1.4 Heat reflux extraction (HRE)

Heat reflux extraction (HRE) is a conventional technique that utilizes continuous heating and solvent circulation to promote the solubilization and transfer of bioactive compounds from plant matrices [20]. HRE can generate relatively high extraction yields by maintaining continuous contact between the solvent and the sample at increased temperatures, especially for thermostable chemicals like saponins and polysaccharides. In *Codonopsis* spp., ethanol-based reflux was used to extract total saponins, yielding around 4.12% [21]. But in *P. ginseng*, hot-water reflux combined with enzymatic pretreatment allowed for the recovery of up to 9.0% polysaccharides, including pectic fractions [22]. These findings reveal HRE's ability to extract structurally varied and pharmacologically potent components from medicinal roots. However, its high energy consumption, extended extraction time, and reliance on elevated temperatures may limit its suitability for thermolabile compounds like flavonoids, which are prone to degradation under harsh conditions. Furthermore, the huge solvent quantities necessary make HRE unsuitable for environmentally aware applications [23]. While HRE is still a reliable and commonly used approach in phytochemical research, its use in flavonoid extraction from *Codonopsis* or *Panax* species has not been well verified, highlighting the need for further modification where compound stability is crucial.

3.2 Green extraction methods

As environmental sustainability becomes a focal point of concern in phytochemical research, green or bio-based extraction methods have gained immense interest. The techniques elucidate the employment of biodegradable solvents, low energy expenditure, and production of low waste at high extraction efficiency. The organic agents such as water, ethanol, or biological catalysts are used by the green extractions to bring effectiveness and responsibility to the environment. Among the different methods, enzyme-assisted extraction (EAE) is special in that it can break plant cell walls gently and hence avoid degradation of bioactive molecules. Bio-extraction is therefore not just a safer substitute

for traditional methods but also the best technique to preserve the functional integrity of heat-labile flavonoids present in medicinal plants like *Codonopsis* spp. [24].

3.2.1 Ultrasound-assisted extraction (UAE)

Ultrasound-assisted extraction (UAE) is a refinement of flavonoid extraction that utilizes ultrasonic waves to rupture plant cell walls, thereby enhancing solvent penetration and mass transfer with minimal compound degradation. UAE enables rapid extraction with reduced solvent consumption, and its efficiency is influenced by factors such as extraction time, solvent type, and temperature [25]. UAE has been successfully applied to Đảng Sâm, where the use of natural deep eutectic solvents (NADES) in combination with ultrasound significantly improved flavonoid recovery. Under optimized ultrasound–microwave-assisted extraction (UMAE) conditions, the flavonoid content reached 24.36 ± 0.48 mg rutin equivalents per gram dry weight (mg RE/g DW*), outperforming conventional methods and demonstrating the strong potential of ultrasound-based techniques for this plant matrix [26].

**RE/g DW stands for milligrams of Rutin Equivalent per gram of Dry Weight, a measurement unit indicating the amount of flavonoids (expressed in rutin equivalents) present in one gram of dried sample.*

3.2.2 Microwave-assisted extraction (MAE)

Microwave-assisted extraction (MAE) enhances extraction efficiency by using microwave radiation to rapidly heat solvents and plant materials, thereby accelerating cell wall disruption, improving solvent penetration, and reducing both extraction time and solvent usage. Although MAE studies on *Đảng Sâm* flavonoids remain limited, related work on *C. javanica* and *P. ginseng* provides strong evidence of its potential. In *C. javanica,* MAE optimized for 70% ethanol at 600 W and 90°C for 10 minutes yielded a total flavonoid content of 18.52 ± 0.37 mg RE/g DW, alongside enhanced antioxidant capacity (DPPH inhibition: 82.14%) compared to conventional reflux extraction [18]. Similarly, in *P. ginseng,* MAE at 300 W for 1 minute produced 4.54 mg quercetin equivalents per gram dry weight (mg QE/g DW*), representing a significant increase over traditional methods while preserving heat-sensitive bioactives [27]. These findings highlight MAE as a rapid, high-yield, and energy-efficient technique that could be effectively adapted to *Codonopsis* spp. flavonoid extraction, provided that process parameters are carefully optimized to avoid localized overheating and degradation.

**QE/g DW stands for Quercetin Equivalent per gram of Dry Weight, a measurement unit indicating the amount of flavonoids (expressed in quercetin equivalents) present in one gram of dried sample.*

3.2.3 Subcritical water extraction (SWE)

Subcritical water extraction (SWE) has emerged as a promising green technology that utilizes pressurized water at elevated temperatures (100-374°C) to extract polar to semi-polar bioactive compounds without the use of organic solvents. As temperature increases, water's dielectric constant decreases, enhancing its solvating power and promoting the efficient diffusion of flavonoids and phenolics from plant matrices [28]. This makes SWE particularly attractive for the extraction of thermally stable phytochemicals. In *P. ginseng*, SWE conducted at 190°C for 15 minutes significantly enhanced the recovery of polyphenols and antioxidant activity, with DPPH radical scavenging capacity exceeding 80%, outperforming conventional ethanol reflux methods [29]. Recent studies from related species suggest that direct application of SWE to *Codonopsis* spp. has significant potential in releasing bound flavonoids. In general, SWE has shown promising potential for flavonoid and phenolic recovery in various plant matrices under optimized conditions, particularly through improved mass transfer and reduced reliance on organic solvents [28, 29, 30].

3.2.4 Natural deep eutectic solvents (NADES)

Natural deep eutectic solvents (NADES) are an emerging class of green solvents composed of natural, biodegradable components such as sugars, organic acids, and amino acids that form stable solvent systems through hydrogen bonding. These solvents offer high solubilizing capacity, low toxicity, and compatibility with mild extraction conditions, making them particularly suitable for extracting polar phytochemicals such as flavonoids. In a recent study, a NADES system composed of choline chloride and lactic acid (1:2 molar ratio) was applied in combination with ultrasound-microwave-assisted extraction to recover flavonoids from *Codonopsis* spp., yielding a total flavonoid content (TFC) of 24.36 ± 0.48 mg rutin equivalents per gram of dry weight (mg RE/g DW), significantly higher than that achieved with ethanol-based extraction [26]. These results are consistent with previous findings demonstrating the superior extraction performance of NADES in recovering flavonoids like rutin and quercetin from various medicinal plants, where NADES also enhanced antioxidant activity compared to conventional solvents [31]. Thus, with appropriate solvent formulation and process optimization, NADES represent a highly effective, selective, and sustainable approach for the extraction of bioactive flavonoids from Đảng Sâm.

3.2.5 Enzyme-assisted extraction (EAE)

Enzyme-assisted extraction (EAE) has emerged as a sustainable and efficient strategy for recovering bioactive compounds from plant matrices, particularly those rich in structural polysaccharides. By employing enzymes such as cellulase, pectinase, or α-amylase to hydrolyze cell wall components, EAE facilitates the release of intracellular constituents under mild conditions, typically around 50°C and near-neutral pH, thereby preserving thermolabile and oxidation-sensitive compounds [32]. Although direct investigations on flavonoid extraction from *Codonopsis* spp. remain scarce, closely related studies provide compelling evidence of its potential. In *C. javanica*, α-amylase-assisted extraction at 90°C for 3.5 hours significantly enhanced polyphenol and saponin yields compared to conventional hot water extraction, highlighting the role of enzymatic hydrolysis in improving mass transfer and compound accessibility [33]. Enzyme-based techniques combined with microencapsulation have also been shown to improve the stability and bioavailability of ginsenosides extracted from *Panax vietnamensis*, underscoring the broader applicability of EAE in medicinal root systems [34]. Moreover, integrating enzymatic pretreatment with ultrasound-assisted extraction (UAE) in grape pomace led to a marked increase in phenolic recovery, up to 1.6-fold compared to enzyme-only protocols, due to enhanced substrate-enzyme interaction and improved cell disruption [32]. Collectively, these findings support the potential of EAE, particularly when coupled with UAE, as a scalable and green approach for maximizing flavonoid recovery from complex herbal matrices such as *Codonopsis* spp.

4 Pectinase-assisted extraction (EAE): A promising green and efficient strategy

4.1 Pectinase

Pectinase is a crucial biocatalyst in green extraction technologies due to its high specificity for pectin, a gel-like polysaccharide that reinforces the middle lamella and primary cell walls in higher plants. Acting as a structural barrier, pectin entraps intracellular compounds such as flavonoids, limiting their accessibility during conventional extraction. By hydrolyzing α-1,4-glycosidic linkages in pectic substances, pectinase disrupts this matrix, enhances cell wall porosity, and facilitates the efficient release of flavonoids tightly bound within plant tissues. This enzymatic mechanism is particularly advantageous for the extraction of thermolabile compounds, as pectinase operates under mild conditions, typically 40-55°C and pH 4.5-6.0, preserving compound integrity while reducing solvent use and energy input. Industrial production of pectinase predominantly relies on microbial fermentation, with *Aspergillus niger* being the most widely used strain due to its high yield and ability to grow on agro-industrial byproducts such as citrus peels [35]. Empirical evidence supports its superior performance in enzyme-assisted extraction (EAE). For instance, pectinase yielded 21.57 ± 0.45 $mg.g^{-1}$ of flavonoids from sea-buckthorn pomace, surpassing other enzyme formulations [36]. Systematic reviews further confirm that pectinase significantly enhances phenolic recovery by promoting mass transfer and structural breakdown of plant cell walls [32]. These attributes establish pectinase as a sustainable and highly effective tool for extracting flavonoids from medicinal plants such as Đảng Sâm.

4.2 Role of pectinase in flavonoid extraction

Pectinase is a selective and eco-friendly enzyme that facilitates efficient flavonoid extraction from *Codonopsis* species by operating under mild conditions, typically 40-60 °C and pH 4.5-7.0, which helps preserve thermolabile compounds often degraded by conventional high-temperature, solvent-based methods. By hydrolyzing pectin in the plant cell wall, pectinase enhances cell wall permeability, promoting the release of intracellular flavonoids and polyphenols. Although direct studies on pectinase-assisted extraction in *C. javanica* are limited, enzyme-assisted methods using α-amylase at 90 °C for 3.5 hours have shown significantly higher yields of polyphenols and saponins compared to solvent extraction [33], suggesting that enzymatic disruption of cell wall components is a viable strategy. In other plant matrices, enzyme-assisted extraction has been reported to improve the recovery of flavonoids and related phenolic compounds under mild conditions, particularly when combined with intensification techniques such as ultrasound [5, 37, 38]. When combined with ultrasound-assisted extraction (UAE), pectinase demonstrates synergistic effects, enabling high-efficiency, low-solvent recovery of bioactives. Therefore, although direct evidence for pectinase-assisted flavonoid extraction in *Codonopsis* spp. remains minimal and the current rationale is supported in part by studies on related medicinal roots and other plant matrices, this integrated approach aligns with green chemistry principles and offers scalable potential for food and pharmaceutical applications, positioning pectinase-assisted extraction as a promising method for enhancing both yield and quality in medicinal plant processing [39].

4.3 Evaluating pectinase-assisted extraction relative to conventional and other green methods

Enzyme-assisted extraction (EAE) has emerged as a compelling green extraction strategy, particularly when evaluated alongside physical, chemical, and other eco-friendly methods such as subcritical water extraction (SWE) and natural deep eutectic solvents (NADES). Unlike SWE, which relies on high temperatures (100-374 °C) and is best suited for

thermally stable phenolics, EAE operates under mild conditions (30-55 °C, near-neutral pH), making it especially advantageous for extracting heat- and oxidation-sensitive flavonoids [40]. While NADES offer strong selectivity and biodegradability, their high viscosity and need for downstream solvent removal can limit scalability in food or pharmaceutical applications. In contrast, EAE directly targets cell wall polysaccharides like cellulose and pectin without employing harsh solvents, thus enhancing both yield and compound integrity [17]. Compared to methods such as ultrasound-assisted or microwave-assisted extraction, which improve mass transfer but may fall short in releasing tightly bound intracellular compounds, EAE provides superior selectivity and sustainability. Moreover, its compatibility with physical enhancements results in synergistic effects, significantly increasing extraction efficiency and bioactive content [26]. These attributes position EAE as a highly effective and adaptable method for flavonoid recovery from medicinal plants such as Đảng Sâm.

4.4 Future prospects of pectinase-assisted extraction

As the demand for clean-label, natural products continue to rise, enzyme-assisted extraction (EAE) is poised to become a central strategy in the sustainable recovery of bioactive flavonoids from medicinal plants, particularly Đảng Sâm. Among available biocatalysts, microbial-derived pectinase offers distinct advantages due to its high specificity for pectin, robust activity under mild processing conditions (30-55 °C), and compatibility with scalable, cost-effective production systems such as solid-state fermentation [41]. These characteristics not only preserve thermolabile flavonoids during extraction but also reduce energy consumption and environmental impact. Furthermore, advancements in enzyme engineering and the use of inexpensive agricultural byproducts as fermentation substrates have significantly improved the economic feasibility of EAE [42]. When coupled with emerging green technologies, such as ultrasound or microwave-assisted extraction, EAE exhibits synergistic effects that further enhance extraction efficiency and compound integrity. In the context of growing regulatory pressure to eliminate toxic solvents from food and pharmaceutical processing, EAE offers a safe, selective, and environmentally sound alternative [38]. Looking ahead, biocatalyst-driven extraction platforms are expected to lead innovation across the functional food, nutraceutical, and phytopharmaceutical industries, positioning EAE as a transformative tool for the future of natural product development.

5 Conclusion

In conclusion, *Codonopsis* spp. is a promising source of flavonoids with notable antioxidant, anti-inflammatory, and neuroprotective properties, making it highly relevant for food, nutraceutical, and pharmaceutical applications. Conventional extraction methods remain limited in their ability to efficiently release these compounds, whereas enzyme-assisted extraction, particularly with pectinase, offers a greener and more effective alternative by promoting cell wall degradation and improving flavonoid recovery. Future research should emphasize process optimization, scale-up potential, and the integration of EAE with other green technologies to enhance both extraction efficiency and sustainability.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflicts of interest.

Author contributions

- Phu Hong Le: conceptualization, administrative support, critical revision
- Duyen Thi My Nguyen: literature collection, manuscript structuring, manuscript writing (original draft)
- Anh Ngoc Nguyen: manuscript structuring, manuscript writing (review and editing)
- Phuc Nguyen Thien Le: manuscript structuring, revision
- All authors read and approved the final manuscript

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