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Review Article

Application of Natural Deep Eutectic Solvents (NADES) in the Natural Product of Antioxidant Activity

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ABSTRACT

The extraction of bioactive compounds from plant-based materials poses significant challenges due to the limitations of traditional organic solvents, including toxicity and environmental impact. Natural Deep Eutectic Solvents (NADES), formed from natural components at defined molar ratios, have emerged as green, sustainable alternatives for efficient extraction. This literature review aims to investigate the applications, compositions, and effectiveness of NADES in extracting antioxidant-rich compounds from natural sources. Relevant peer-reviewed articles published within the last ten years were retrieved from Google Scholar and PubMed using keywords such as "NADES," "natural product," and "antioxidant activity." Studies included using NADES to extract phytochemicals, pharmaceuticals, or food compounds and address their toxicity, safety, and physicochemical properties. Non-peer-reviewed articles, unrelated solvent systems, and duplicate studies were excluded. The review identified compelling NADES compositions, including choline chloride: lactic acid (1:2), choline chloride: oxalic acid (1:1), and citric acid: glycerol (1:1), which demonstrated high extraction efficiency and antioxidant activity. The tunability of hydrogen bond donor and acceptor ratios allows NADES to be optimized for specific bioactive compounds. In conclusion, NADES offers a promising and eco-friendly approach for future applications in natural product extraction.

Keywords: NADES; natural product; antioxidant activity

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INTRODUCTION

The growing interest of the food, pharmaceutical, and cosmetic industries in natural bioactive compounds or plant secondary metabolites has driven the need for more advanced and efficient analytical and extraction methods. Extracting these bioactive compounds from plant sources remains a significant challenge, especially with the growing emphasis on stringent quality control of final products and increased awareness of environmental sustainability.

To obtain extracts with high potential bioactive compounds, several factors must be considered, one of which is the extraction process. The use of appropriate methods will yield better results, such as green extraction methods that can be sourced from a wide variety of plant materials and include primary and secondary metabolites such as proteins, fats and oils, dietary fiber, sugars, antioxidants, essential oils and fragrances, and pigments.

A study by González et al. showed that sugar-based NADES have low toxicity and are biodegradable. This makes them a safer option compared to more hazardous conventional solvents or ionic liquids. However, it should be noted that some NADES can promote algae growth at certain concentrations, potentially leading to eutrophication if released into the environment (González-Laredo et al. 2023). NADES are composed of naturally occurring substances, which generally ensures a high degree of biodegradability. According to recent studies, most NADES degrade completely in less than 30 days under standard testing conditions (Smith, Abbott, and Ryder 2014).

Recent in vitro and in vivo studies have provided insight into the safety of various NADES compositions. Kristina et al. conducted a detailed toxicity assessment of NADES formed from choline chloride with different hydrogen bond donors—acids, amides, and alcohols. Toxicity was tested on both bacterial strains (*Escherichia coli* and *Staphylococcus aureus*) and human cell lines, including MCF-1, HEK293T, and HeLa. The study revealed that NADES containing acidic components showed significantly higher toxicity compared to those containing amides or alcohols, particularly in human cell lines (Radošević et al. 2018).

Currently, a widely developed method for obtaining safe solvents involves using eutectic solvents or natural deep eutectic solvents (NADES), derived from natural materials. Research conducted by Yang et al. (2022), shows that NADES can enhance the antioxidant activity of ellagic acid, as tested using the DPPH method. Additionally. Another study by Yulianita et al. (2022), reported that the best flavonoid content was achieved using NADES solvent 2, a combination of choline chloride and oxalic acid, with optimal extraction conditions at 48°C, 60 minutes, and a NADES:water ratio of 90%, resulting in a flavonoid content of 1.4161%.

In a study by Gu et al. (2014), the extraction of phenolic compounds using NADES based on choline chloride:lactic acid (1:2) produced higher antioxidant

activity compared to conventional solvents, as tested using the DPPH method. This antioxidant activity demonstrated a significant increase in the free radical scavenging ability of the extracted phenolic compounds.

Therefore, this journal aims to critically analyze NADES solvents as green solvents in their application to enhance the extraction performance of plant metabolites in terms of extractability, as well as stability, bioactivity, solubility, and bioavailability, particularly the antioxidant activity obtained.

METHODS

The research method employed in this study is a review article using a scientific literature review. The data sources used are scientific articles indexed nationally and internationally within the last 10 years, obtained through Google Scholar and PubMed. The articles used discuss the application of NADES solvents and antioxidant activity, with keywords such as "NADES," "natural product," and "antioxidant activity". Subject Focus: Studies discussing NADES as extraction solvents for natural products, phytochemicals, pharmaceuticals, or food components. Studies evaluating toxicity, safety, biocompatibility, and physicochemical properties of NADES. Experimental Design: In vitro, in vivo, or computational studies related to the use or effect of NADES. Non-peer-reviewed sources such as conference abstracts without full text. Articles not related to NADES (e.g., those about synthetic Deep Eutectic Solvents or unrelated solvent systems). Studies focusing only on ionic liquids or other synthetic solvents without mention of NADES. Duplicate publications or preprints of studies that have already been published in peer-reviewed journals.

RESULTS AND DISCUSSION

Green extraction represents an alternative solvent that meets the criteria of being "green," making it environmentally friendly and relatively safe. Some advantages of green solvents include easy preparation (synthesized with eco-friendly materials and procedures), reduced hazards, energy efficiency, recyclability, and biodegradability. Therefore, the development of NADES as a future solvent is gaining momentum.

NADES is defined as a mixture of two or more natural components that, at a specific molar ratio, experience a melting point depression and become liquid at room temperature. NADES has significant potential for industrial-scale applications, particularly in the food, pharmaceutical, and cosmetic sectors. Research by Satija et al. (2024), shows that NADES can be utilized for large-scale industrial applications with minimal environmental impact. Furthermore, studies by Villa et al. (2024), indicate that due to their unique properties, NADES can be recommended for various cosmetic and pharmaceutical applications, from

sustainable extraction and obtaining ready-to-use materials to the development of biocompatible responsive drug delivery systems.

Although NADES offers many advantages, several challenges still need to be addressed. One major issue is the optimization of NADES production costs for large-scale applications, which is essential for their commercial viability. Additionally, there is a need for the standardization of extraction methods to ensure reproducibility and consistency of results across different studies and industries. Furthermore, more comprehensive studies are required to evaluate the toxicity and safety of NADES, particularly when used in food and pharmaceutical products, to ensure their safe application in these sensitive fields.

Additionally, research by Dewi, Zahrina, and Yelmida (2021), indicates that some NADES may have limitations in thermal stability, affecting their application in high-temperature processes. These challenges need to be addressed through further research and innovation in NADES formulation. NADES is created with a composition of compounds acting as hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD). NADES offers advantages such as being naturally biodegradable, non-toxic, and easy to produce. NADES can also dissolve macromolecular compounds and be used to determine the physicochemical properties and stability of a solvent. Overall, NADES is a promising innovation across various industries due to its flexibility as a safe, stable, and environmentally friendly green solvent. The ideal materials for NADES synthesis typically come from safe and readily available natural compounds.

The most common and effective materials used in the formulation of NADES include a variety of compounds with specific functional roles. Organic acids such as citric acid, lactic acid, oxalic acid, and malic acid are frequently utilized due to their strong ability to form hydrogen bonds. Amines and nitrogen-containing compounds like urea, betaine, and choline chloride are also commonly incorporated, serving as hydrogen bond donors and offering excellent solubility and compatibility for specific applications. Sugars such as glucose and fructose enhance the solubility and stability of NADES, acting as effective hydrogen bond donors while also helping to reduce viscosity. Similarly, alcohols and sugar alcohols, including glycerol and sorbitol, are added to decrease viscosity and increase stability, particularly in the extraction of bioactive compounds. Amino acids like proline are selected for their ability to create NADES with high solubility and stability, and when combined with sugars or organic acids, they form highly versatile mixtures. Lastly, vitamins such as ascorbic acid (vitamin C) are used in NADES intended for food or cosmetic applications, offering antioxidant benefits and improved stability.

In research conducted by Yang et al. (2023), choline chloride and betaine were selected as HBA, while oxalic acid, DL-malic acid, citric acid, and malonic acid were used as HBD. HBA and HBD were accurately weighed using an electronic balance and mixed in specific proportions, then heated in a water bath

at 55°C for 4–6 hours and stirred until a clear and uniform liquid formed. However, the betaine-oxalic acid and betaine-citric acid groups could not remain colorless and clear at room temperature, so they were excluded. In total, seven types of NADES solvents were synthesized based on different molar ratios of HBA and HBD, as shown in the table 1.

Table 1. NADES Composition

HBA	HBD	Mole Ratio
Choline chloride	DL-malic acid	1:1
Choline chloride	Citric acid	1:1
Choline chloride	Malonic acid	1:1
Choline chloride	Oxalic acid	1:1
Betaine	DL-malic acid	1:1
Betaine	Malonic acid	1:2
Betaine	Citric acid	1:1

Combinations such as choline chloride:oxalic acid and choline chloride:citric acid have been proven to provide optimal results for the extraction of certain bioactive compounds (Yang et al. 2023; Radošević et al. 2018). Adjusting the composition of NADES based on the chemical properties of the sample allows for high flexibility in its application.

The composition of NADES based on choline chloride:lactic acid with a ratio of 1:2 demonstrates excellent extraction capabilities, especially for phenolic compounds from plant materials. Lactic acid in this NADES functions as a solvent capable of effectively breaking down the plant cell matrix, enabling the extraction of bioactive compounds such as phenolic acids and flavonoids. Studies have shown that this combination not only increases extraction efficiency but also improves the purity of the extracted compounds and enhances the antioxidant activity of the obtained compounds.

Furthermore, a study by López-Salazar et al. (2023), indicated that using NADES based on choline chloride:lactic acid not only improves extraction efficiency but also minimizes damage to bioactive compounds during the extraction process, making it a more environmentally friendly and efficient choice compared to conventional organic solvents.

Research by Chaves et al. (2020), showed that NADES based on citric acid:glycerol (1:1) is effective in extracting flavonoids from medicinal plants, yielding high antioxidant activity tested using the FRAP method. The extraction results also revealed that the obtained flavonoid compounds have better metal ion-binding capabilities, which are crucial in pharmaceutical applications.

In a study by Ahmad et al. (2024), it was found that a mixture of citric acid and glycerol as a composition for NADES as an alternative green solvent can extract polyphenols from *E. bulbosa* tubers, achieving equal or better results compared to the NADES compositions in previous studies.

The use of Natural Deep Eutectic Solvents (NADES) has gained increasing attention for the extraction of bioactive compounds, particularly to enhance antioxidant activity from various natural sources. Various combinations of NADES have proven effective in extracting phenolic compounds, flavonoids, and anthocyanins, often yielding better results than conventional solvents.

Sebbah et al. (2025), demonstrated that a menthol:lactic acid (1:1) NADES combination significantly enhanced the antioxidant activity of Portulaca oleracea leaf extracts, achieving an IC_{50} value of 28.10 µg/µL, along with high total phenolic content (TPC) and total flavonoid content (TFC). Similarly, Latifah and Nuh (2024) reported that using sodium acetate:lactic acid (1:3) NADES with Microwave-Assisted Extraction (MAE) on Gedong mango leaves produced strong antioxidant activity (IC_{50} = 21.666 ppm) and a high flavonoid content.

In contrast, Nurbaeti (2023), found that the extraction of red ginger (*Zingiber officinale*) using a betaine:HCl:citric acid NADES yielded a relatively low antioxidant activity (IC_{50} = 255.998 ppm), indicating that further optimization is necessary. Meanwhile, Panjaitan (2024), successfully extracted propolis (*Geniotrigona thoracica*) using a choline chloride:glucose (2:1) NADES, achieving a remarkably low IC_{50} value (2.08 bpj) and high levels of TPC and TFC.

Research conducted by Bubalo et al. (2015), on wild thyme (*Thymus serpyllum*) and by Mansinhos et al. (2021), on *Lavandula pedunculata* highlighted that specific NADES formulations, particularly when coupled with Ultrasound-Assisted Extraction (UAE), significantly improved the phenolic and flavonoid content of the extracts. Additionally, Popovic et al. (2022), demonstrated that the use of a choline chloride:sorbitol NADES with MAE increased the polyphenol extraction efficiency from sour cherry pomace by three to four times compared to conventional methods.

Further studies by da Silva et al. (2021), on blueberries and Faggian et al. (2016), on rutin indicated that NADES can enhance the stability, solubility, and bioavailability of phenolic compounds. Similarly, Guo et al. (2019), found that NADES based on choline chloride:glucose were more effective than conventional solvents for extracting anthocyanins from mulberries.

In the case of turmeric (*Curcuma longa*), Doldolova et al. (2021), reported that NADES-based MAE resulted in a lower IC_{50} value compared to water or ethanol extractions, suggesting faster and more efficient curcumin extraction. Huang et al. (2021), also optimized the extraction of puerarin from Radix Pueraria using a choline chloride:urea NADES.

Studies by Shikov et al. (2020), on *Rhodiola rosea* and Ivanović et al. (2021), Helichrysum arenarium confirmed that UAE combined with NADES can enhance phenolic extraction yields. Moreover, Bosiljkov et al. (2017), demonstrated that the application of NADES on wine lees could double the polyphenol content extracted. Lastly, Alañón et al. (2020), showed that a lactic acid:glucose NADES combination enabled a sustainable extraction of active compounds from *Hibiscus sabdariffa*.

CONCLUSIONS

Natural Deep Eutectic Solvents (NADES) are green solvents consisting of a mixture of hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD) in specific molar ratios, designed as environmentally friendly solvent alternatives. Some of the most effective NADES formulations proven in research include choline chloride:lactic acid (1:2), choline chloride:oxalic acid (1:1), and citric acid:glycerol (1:1). By adjusting the HBA and HBD ratios, NADES formulations can be optimized for various bioactive compounds, making them flexible and highly beneficial for diverse industrial needs. This advantage positions NADES as a future solution for more efficient, eco-friendly, and sustainable extraction processes.

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