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Structure-Guided Selection of Natural Deep Eutectic Solvents for Phytochemical Extraction: A Critical Review

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Abstract
Natural deep eutectic solvents (NADES) have recently emerged as valuable alternative extraction media to recover plant-derived phytochemicals. Their interest derives from the propensity of combinations of naturally occurring hydrogen-bond acceptors and donors to form liquids with depressed melting points, tunable polarity, high solvation capacity and very low volatility. From their first systematic description as a potential green solvent system, research has progressed from proof-of-concept solubilization to extraction of phenolic acids, flavonoids, anthocyanins, alkaloids, saponins and other bioactive constituents. This critical review examines NADES from a phytochemical-selection perspective (rather than as replacements for conventional organic solvents). The review links molecular features of target compounds (hydrogen-bonding capacity, ionisation, polarity, aromaticity, lipophilicity and chemical stability) with solvent characteristics (hydrogen-bond basicity/acidity, water content, viscosity and component ratio). Representative studies illustrate that extraction performance is highly formulation-dependent (a solvent that favours one phytochemical class may not be optimal for another). NADES can also impact stability and, in some systems, apparent solubility or bioaccessibility of extracted compounds. However, the term "green" should not be assigned automatically: component toxicity, persistence, preparation energy, water demand, downstream recovery and life-cycle impacts must also be considered. The major unresolved issue is the lack of a predictive framework for selecting a NADES before experimental screening. A phytochemical-NADES selection framework is therefore proposed, together with reporting recommendations and a research agenda focused on standardisation, solvent recovery, comparative green metrics and structure-guided solvent design. The review provides a laboratory-independent conceptual basis for selecting NADES for phytochemical extraction and for designing future experimental studies.Keywords: natural deep eutectic solvents; NADES; green extraction; phytochemicals; flavonoids; polyphenols; anthocyanins; solvent design; sustainable extraction.

Introduction

The recovery of phytochemicals from plant biomass is of great interest in the research of natural products, food, nutraceutical, pharmaceutical chemistry and cosmetics. The conventional solid–liquid extraction typically uses solvents such as methanol, ethanol, acetone, ethyl acetate, hexane or their mixtures. These solvents are still useful because the polarity and volatility of them are well known, but many processes of extraction also have flammability, emission of volatile organic compounds, occupational exposure, energy intensive evaporation and considerable solvent

consumption. A green extraction aims to reduce these effects and maintain or improve the recovery and product quality.

Deep eutectic solvents (DES) have been presented as an alternative solvent family by a mixture of two or more components, which exhibit lower melting point than individually components. The natural DES (NADES) is a subset, in which the components are metabolites or other naturally occurring substances such as organic acids, sugars, amino acids, sugar alcohols and choline-derived compounds. The first NADES concept showed that mixtures of primary metabolites could form liquid phases and may have a physiological relevance in plants [1–3].

The attraction of the NADES for phytochemical extraction is not only due to their origin, their intermolecular interactions such as hydrogen bonding may produce strong and adjustable interactions with solutes. This could increase apparent solubility of selected compounds and affect the extraction selectivity. However, the high viscosity could limit the mass transfer, and the strong solvent–solute interactions could impede downstream isolation. Thus, the NADES should be seen as functional solvent system rather than universally better solvent than conventional solvents.

The literature has shown extensive reviews about NADES chemistry, phenolic extraction and application in phytonutrients [4–7]. The recent reviews have widened the discussion to the modern extraction technologies, medicinal plants, polyphenols, sustainability and deep-eutectic systems [8–11]. The present review brings a specific decision oriented perspective: how the molecular characteristics of a phytochemical can be used to rationalize the choice of a NADES family before extensive experimental optimization.

2. Literature-Search Methodology and Scope

This article was written as a critical, literature-based review, not an experimental research study. Literature sources were identified through searches of publisher and bibliographic repositories, including PubMed, ScienceDirect, ACS Publications and open-access journal archives. Search terms included “natural deep eutectic solvent”, “NADES”, “deep eutectic solvent”, “phytochemical extraction”, “polyphenol”, “flavonoid”, “anthocyanin”, “alkaloid”, “quercetin”, “green extraction”, “solubility”, “stability”, and “sustainability”. Foundational papers, representative examples of experimental studies, and relevant literature reviews published up to 30 June 2025 were prioritised.

Studies were considered relevant if they addressed (i) preparation or physicochemical properties of NADES/DES, (ii) extraction of plant-derived natural products, (iii) solvent-solute interactions, (iv) optimisation of extraction process, (v) implications for stability/solubility, or (vi) environmental/downstream-processing aspects. Papers focused exclusively on unrelated DES applications were employed only to inform on solvent principles. No numerical experimental result is presented as original data; quantitative values in the tables are reported solely if explicitly available in the cited literature.

3. From Deep Eutectic Solvents to NADES

A DES generally arises from a mixture of components that are able to interact strongly, typically a hydrogen-bond acceptor (HBA) and a hydrogen-bond donor (HBD). In a classical case, the interaction lowers the chemical potential of the system and depresses its melting point. NADES

extend the concept to naturally derived constituents. Choline chloride–based systems are well-established, but natural systems can also include organic acids, sugars, amino acids and polyols [1–3].

The concept was established through observations that many plant metabolites can be mixed to form liquids at suitable ratios and that such mixtures have distinctive solvent properties [1,2]. The key significance of this concept for extraction is that the solvent can be assembled from renewable molecules, while its polarity, acidity/basicity and hydrogen-bonding environment can be altered by varying components and ratios.

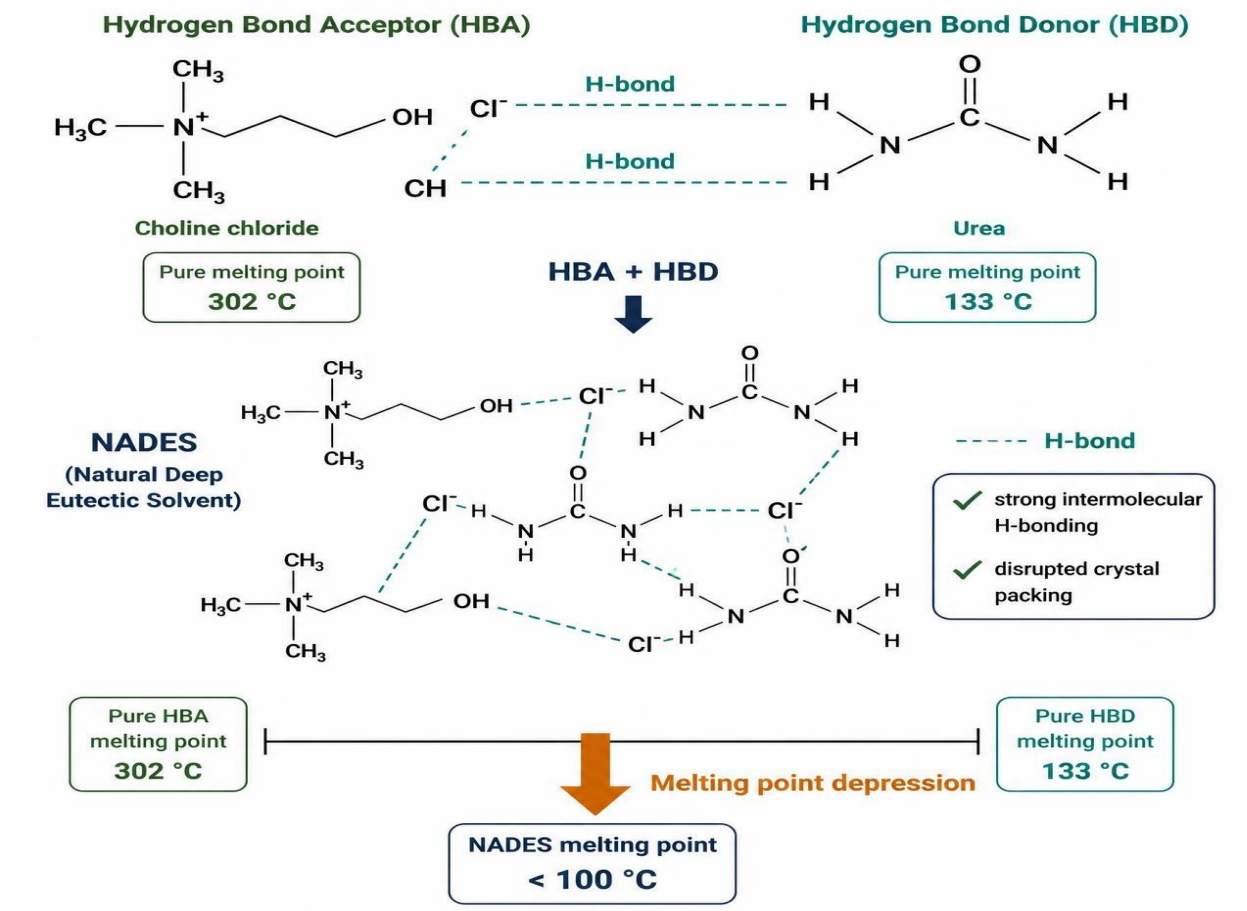
However, the NADES should not be regarded as a single solvent. “NADES” designates a design space. In particular, lactic-acid/glucose, malic-acid/sugar, choline chloride/polyol, betaine/organic-acid and sugar-based systems may behave quite differently. The extraction outcome therefore depends on the complete formulation and operating conditions rather than on the label of NADES.

4. Chemistry of NADES Formation

The most essential characteristic of the deep eutectic mixture is the strongest possible non-covalent interaction between the components. In particular, hydrogen bonding results in the charge transfer between components and reduced ability to crystallize for each of the involved compounds. The interactions can also be ionic, van der Waals, and others, depending on the system, and they are responsible for the ability of the mixture to act as a liquid solvent [2,3].

A simple way to represent the interactions is to write the following equation:

HBA ••• HBD ⇌ HBA/HBD-associated liquid



The eutectic depression of the melting point cannot be explained by the simple mixing of the two solutions due to the strong interactions between components. This fact has been demonstrated by spectroscopic and physicochemical analyses of the mixtures [1,2]. For example, similar interactions can be found in the case of a phytochemical extraction – the same hydrogen bonds can be formed between the solvent molecules and the target compound.

Therefore, the molar ratio of the components is a very important factor in the preparation of a deep eutectic solvent. For example, the increase of the amount of the acidic HBD leads to more acidic solutions, which can influence the speciation of phenolics or alkaloids in the extract. On the other hand, raising the content of the polyol or water will respectively change the viscosity and weaken the deep-eutectic interactions. However, there is no optimal ratio that would be the best for all cases.

5. Classification of NADES Relevant to Phytochemical Extraction

NADES family	Representative components	chemical feature	Potential targets
Organic-acid based	Lactic acid, malic acid, citric acid + sugar/polyol	Acidic, strongly H-bonding	Anthocyanins, phenolic acids, flavonoids

Sugar based	Glucose, fructose, sucrose + organic acid/polyol	Highly hydrophilic, H-bond rich	Phenolics, anthocyanins, polar glycosides
Polyol based	Glycerol, propylene glycol + choline/betaine or acids	Hydrophilic, tunable viscosity	Flavonoids, phenolic acids, alkaloids
Amino-acid based	Amino acids + organic acids/sugars	Polar; acid/base functionality	Ionisable phenolics and nitrogen compounds
Choline/betaine based	Choline chloride or betaine + HBD	Ionic/H-bonding character	Broad range of polar phytochemicals
Hydrophobic NADES	Terpenoid/fatty-acid or hydrophobic natural components	Low water affinity; lipophilic	Terpenoids, pigments and less-polar constituents

6. Physicochemical Properties of Extraction

6.1 Polarity and solvation

The nature of interactions between the target phytochemical and the plant matrix, as well as the solvent, determines the efficiency of phytochemical extraction. The polarity of NADES can be adjusted so that the mixture is more compatible with polar glycosides or, in hydrophobic systems, with less-polar molecules. Thus, the initial assumption about the high polarity of all NADES is fundamentally wrong.

6.2 Hydrogen-bonding ability

Hydrogen bonding plays an important role in the formation of NADES and in the solubilisation of phytochemicals. Phenolic compounds contain hydroxyl groups which can act as proton donors and acceptors, and carbonyl groups which are additional sites for hydrogen bonding. The presence in a solvent of a complementary capacity for hydrogen bonding may improve the extent of solubilisation. Too strong an interaction can make efficient subsequent separation challenging.

6.3 Viscosity and mass transfer

High viscosity is one of the main properties of NADESs that significantly limit their application. One such property is the reduced ability to penetrate plant tissues and the sluggish diffusion of dissolved substances from broken cells. The reduction in solution viscosity is associated with the addition of water; however, an excess of it leads to the destruction of the eutectic structure. Therefore, for the extraction process, it is necessary to optimise the amount of water in the solution rather than use the maximum possible amount.

6.4 Acidity and ionization

Organic–acid–based NADs can render an acidic environment, which can be beneficial to stabilize certain anthocyanins and influence the ionization forms of acidic or basic phytochemicals. Since ionization can affect both solubility and interactions with the matrix, reporting the pH or the acidity is relevant.

6.5 Thermal stability

Temperature influences viscosity, diffusion and solute stability. Moderate heating can accelerate extraction, but thermolabile compounds may degrade. Optimisation should therefore balance mass transfer against chemical stability.

6.6 Water content

Water is a co-solvent and structural modifier. At low to moderate levels, it can decrease viscosity and facilitate diffusion. At high levels, the system may behave increasingly like an aqueous solution, potentially losing some characteristic deep-eutectic interactions. Water content must therefore be treated as a formulation variable.

7. Mechanistic View of NADES-Based Extraction

Extraction can be viewed as a sequence of coupled events: wetting of the plant surface, penetration into the matrix, disruption or swelling of cellular structures, desorption of the target molecule, diffusion into the solvent, and stabilisation or transformation after release. NADES can influence several steps simultaneously.

At the molecular level, the target phytochemical competes between interactions with the plant matrix and interactions with the solvent. Phenolic compounds can form hydrogen bonds with cell-wall polysaccharides and proteins. A suitably designed NADES can compete for these interactions and increase transfer into the liquid phase. For anthocyanins, solvent acidity and composition may additionally influence colour stability and degradation. For alkaloids, acid–base interactions can be particularly important because protonation changes aqueous and organic-phase behaviour.

This mechanistic picture explains why “highest total extract yield” is not equivalent to “best phytochemical extraction”. A solvent may dissolve many matrix constituents and produce a high crude yield while providing poor selectivity for the desired marker. Target-specific recovery, purity, stability and downstream processing should therefore be evaluated together.

8. Phytochemical Structure as a Basis for NADES Selection

Phytochemical class	Structural characteristics	NADES features to consider	limitations
Phenolic acids	Aromatic ring, phenolic OH, carboxyl group	H-bonding; moderate polarity; acidity	Co-extraction; ionisation
Flavonols e.g. quercetin	Multiple OH groups, aromatic rings, carbonyl	H-bond-rich, moderately polar NADES; water-assisted viscosity control	Strong solvent binding; difficult recovery
Flavonoid glycosides	Flavonoid core + sugar	More hydrophilic; sugar/organic-acid NADES	Hydrolysis or degradation under harsh acidity
Anthocyanins	Cationic/flavylium system; glycosylation	Acidic NADES; stabilising HBDs; moderate water	pH-sensitive degradation

Alkaloids	Basic nitrogen, variable aromaticity	Acid–base-tunable systems; polarity matched to alkaloid	Speciation and matrix binding
Saponins	Large glycosidic + hydrophobic domains	Amphiphilic/hydrophilic NADES; viscosity control	Foaming; broad co-extraction
Carotenoids	Highly conjugated, lipophilic	Hydrophobic NADES or low-polarity systems	Oxidation; light/heat sensitivity
Terpenoids	Variable polarity; often lipophilic	Hydrophobic NADES where appropriate	Low water compatibility; recovery

9. Evidence from Representative Phytochemical Extractions

The experimental literature contains a number of studies showcasing the interplay between extraction processes and the physicochemical properties of the solvent. Dai et al. showed the ability of NADES to extract anthocyans from Catharanthus roseus and proposed the application of selected NADES as an alternative to conventional organic solvents, including acidic ethanol, with some NADES showing increased stability of the extracted compounds [12]. The study highlights the potential contribution of the extraction medium beyond its role as a diluent and/or transport agent.

Dai and Row employed choline chloride and betaine-based NADES in the ultrasound-assisted accelerated extraction of quercetin from onion and broccoli alongside HPLC analysis, demonstrating the ability to tune the physicochemical properties of the solvent to achieve optimal recovery, with particularly promising results for isorhamnetin and kaempferol [13]. Guo et al. combined the use of NADES with high-speed homogenisation and cavitation-burst technology in the extraction of mulberry anthocyanins, demonstrating the potential of the synergistic relationships between NADES and intensified extraction technologies [14].

The one-pot extraction and hydrolysis of rutin into quercetin in Sophora japonica using NADES as the extraction medium highlights another potential advantage of NADES in phytochemical extraction – the opportunity to combine the extraction value of the NADES with additional unit operations, such as enzymatic hydrolysis, potentially streamlining downstream processing [15]. Duan et al. highlighted the importance of the choice of hydrogen bond donor and acceptor and their impact on the performance of DES in the extraction of a range of target compounds from diverse botanical sources through an extensive survey of the literature, which identified temperature, water content and physicochemical properties of the target compounds as key parameters influencing the observed interactions [16]. Redha et al. and Li et al. (and later researchers) noted the variability of the behaviour of phytochemicals from different classes in different solvents or solvent blends, highlighting the need to consider both phytochemical class and the characteristics of the solvent blends when designing phytochemical extractions [5,6,8].

Source	**NADES or DES approach**	**Main finding**	**Reference**

Catharanthus roseus anthocyanins	Lactic-acid/glucose and 1,2-propanediol/choline chloride systems	Selected NADES showed extraction performance comparable with conventional solvents; improved stability was observed for cyanidins in a tested lactic-acid/glucose system.	Dai et al. 2016 [12]
Onion and broccoli quercetin	Choline chloride- and betaine-based NADES + ultrasound	Optimised systems produced high recoveries for quercetin, isorhamnetin and kaempferol.	Dai & Row 2019 [13]
Mulberry anthocyanins	Choline chloride–citric acid–glucose NADES + HSH-CBE	Integrated extraction improved anthocyanin recovery and stability; process variables were optimised statistically.	Guo et al. 2019 [14]
Sophora japonica rutin → quercetin	NADES extraction + enzymatic hydrolysis	One-pot extraction/conversion approach reduced separation between extraction and hydrolysis.	Zang et al. 2020 [15]
Broad natural products	DES screening and comparative evaluation	Extraction performance depended on solvent composition and target compound properties.	Duan et al. 2016 [16]
Phenolic compounds from natural sources	Green DES review	Component structure, molar ratio, temperature, solid/liquid ratio and water content were identified as key factors.	Redha 2021 [5]
Phytonutrients	NADES review	Applications extend beyond extraction to solubility, stability and bioavailability.	Li 2022 [6]
Medicinal plants	NADES review	HBD selection and solvent formulation remain central optimisation variables.	Huang et al. 2025 [8]

10. NADES and Major Phytochemical Classes

10.1 Phenolic acids

Phenolic acids such as gallic, caffeic, ferulic and chlorogenic acids contain combinations of phenolic hydroxyl and carboxyl groups, which are both polar and ionisable. Hydrogen-bonding and acidic/basic solvent environments therefore respond to their presence, which allows NADES containing organic acids, sugars or polyols to provide strong interactions, but the selectivity can be compromised by co-extraction of other polar constituents.

10.2 Flavonoids

Flavonoids contain aromatic rings and oxygenated functional groups. Aglycones such as quercetin are less water-soluble than many of their glycosides due to their planar aromatic structure and intermolecular crystal packing. NADES can provide an increase in apparent solubility by providing a suitable hydrogen-bonding environment, and the quercetin extraction literature demonstrates that NADES formulation and the application of ultrasonic energy can lead to high analytical recovery [13].

10.3 Anthocyanins

Anthocyanins are particularly susceptible to pH, temperature, oxygen and light, so acidic NADES can be used to provide conditions under which the coloured anthocyanin forms are more stable. Dai et al. reported enhanced stability for cyanidins in a selected NADES relative to that provided by acidified ethanol [12]. This supports the consideration of both recovery and stability rather than simply extraction yield.

10.4 Alkaloids

Alkaloids vary widely in their structures, but generally contain basic nitrogen functionality, and therefore their extraction can be affected by protonation phenomena and acid–base equilibria. Acidic NADES may enhance the transfer of some alkaloids into the solvent phase, but neutral or less-polar systems may be preferable for selected free-base compounds - the appropriate choice must always be based upon the target alkaloid rather than the use of a NADES formulation universally.

10.5 Carotenoids and less-polar compounds

Highly lipophilic compounds such as carotenoids do not match well with the strongly hydrophilic NADES. Hydrophobic DES/NADES systems are therefore of interest, but this field is far less developed than that of hydrophilic polyphenol extraction. Oxidation, light sensitivity and downstream recovery are major factors.

10.6 Saponins and complex glycosides

Saponins are composed of hydrophilic sugar chains and hydrophobic aglycones. Thus, they are amphiphilic molecules that are sensitive to the polarity of the solvent as well as the capability to form Hydrogen bonds. Although NADES may enhance the extraction, crude extracts obtained by such a process may contain numerous other matrix compounds extracted along with the target compound and thus, attention should be paid to the selectivity of the extraction and the need for downstream purification.

11. Role of Water in NADES

Water plays a dual role in NADES extractions. On the one hand, the addition of water decreases the solution viscosity and, in general, facilitates mass transfer, but, on the other hand, water affects the hydrogen-bond network that determines the deep-eutectic nature of the system. As a result, a small/moderate amount of water may accelerate the kinetics of extraction, whereas an excessive amount may render the solvent as an ordinary aqueous solution. Thus, the optimization of the water amount is target- and formulation-dependent [5,8,11].

The amount of water should be reported unequivocally for reproducibility reasons, specifying if it was expressed as mass fraction, volume fraction or percentage of the solvent. This is important, as different authors can report "30% water NADES" referring to different quantities (e.g. mass or volume basis). At the moment, such a lack of information limits the possibility of comparing different reports directly.

12. Extraction Technology Coupled with NADES

Technology	**Potential advantage with NADES**
Conventional stirring/maceration	Simple and low equipment requirement
Ultrasound-assisted extraction	Improves cell disruption and mass transfer
Microwave-assisted extraction	Rapid heating and shorter extraction
Pressurised liquid extraction	Fast penetration and controlled temperature/pressure
High-speed homogenisation/cavitation	Strong physical disruption; useful for fresh tissues
Enzyme-assisted extraction	Can weaken cell walls and improve release

Recent reviews emphasise that combining DES/NADES with modern extraction technologies can reduce extraction time and improve recovery, but the solvent and process variables interact. Optimising ultrasound power without controlling viscosity, for example, may produce misleading conclusions [9,10].

1. NADES V/S Conventional Organic Solvents

Criterion	**NADES**	**Conventional organic solvents**
Volatility	Generally very low	Often moderate to high
Flammability	Depends on components; often lower than volatile solvents	Many common solvents are flammable

Formulation flexibility	High; component identity and ratio can be changed	Usually a single defined solvent or blend
Biodegradability	Often favourable for genuinely natural components, but formulation-dependent	Highly variable
Viscosity	Often high	Usually lower
Downstream evaporation	Difficult because of low vapour pressure	Often straightforward
Target selectivity	Potentially tunable	Well-established and predictable for many solvents
Analytical compatibility	Requires method-specific consideration	Extensive established methods
Green credentials	Potentially strong, not automatic	Variable and solvent-specific

The comparison demonstrates why NADES are best viewed as an additional solvent-design platform, rather than unconditional replacement. Low volatility and renewable components can be advantages, but difficult solvent removal and high viscosity can increase downstream or energy costs. Sustainability should therefore be evaluated across the entire process [7,17].

15. Safety, Toxicity and Regulatory Considerations

The term "natural" does not equate to non-toxic, safe for ingestion or environmentally benign. NADES components can have significantly different toxicological profiles, and toxicity can vary with concentration, composition and exposure route. For pharmaceutical, nutraceutical or food applications, the safety of each component and the intended residual-solvent exposure must be evaluated.

Another consideration is biological activity of the solvent itself. A NADES could influence membrane permeability, enzyme activity or assay responses. As a result, apparent enhancement of the bioactivity of an extract should not be automatically attributed to the extracted phytochemicals, unless appropriate controls separate solvent effects from phytochemical effects. Recent reviews increasingly highlight safety and regulatory assessment as a barrier to translation [8,10].

16. Downstream Opoerations

NADES have low vapour pressure, which can be an advantage during extraction but a problem when the desired phytochemical must be isolated from the solvent. Conventional rotary evaporation cannot simply remove a NADES as it would ethanol or ethyl acetate. Researchers therefore need alternative strategies such as liquid–liquid partitioning, adsorption/resin chromatography, precipitation, antisolvent addition, membrane processes or using the NADES-containing extract in a final formulation.

The appropriate downstream method will depend on whether the goal is an isolated pure compound or a standardised botanical extract. For a standardised extract, retention of the NADES may be acceptable or even desirable if safety and regulatory requirements are met. For pharmaceutical-grade isolation, however, solvent removal and recovery may dominate process economics.

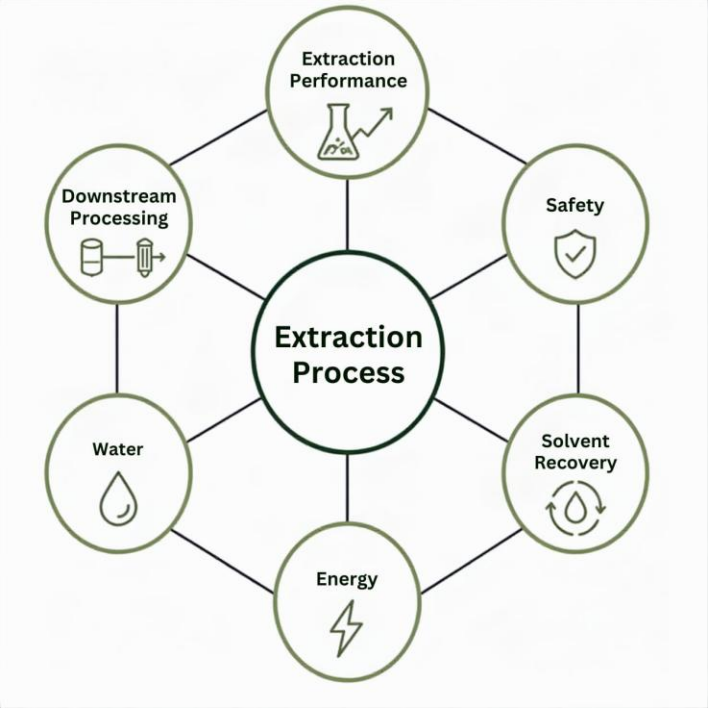
This distinction should be factored into the initial solvent-selection decision. A NADES that provides the highest extraction yield may not be the most practical choice if its strong interaction with the target makes purification disproportionately challenging.

17. Green chemistry assessment of NADES

A proper sustainability assessment would look beyond simply the number of volatile organic solvents used. Some relevant performance indicators would include solvent mass, solvent renewability, toxicity, biodegradability, water use, energy demand, extraction time, solvent recovery, product recovery, waste production and the fate of the co-extracted material. Life-cycle assessment can be extremely helpful when contrasting a NADES process against an ethanol–water or another conventional alternative.

NADES preparation may require heating, mixing and sometimes purification of components. If a solvent is prepared using highly purified ingredients, large amounts of water and energy, its overall environmental benefit would be less than could be expected. On the other hand, using low-cost natural feedstocks and recovering the solvent can bolster the sustainability claim. These trade-offs should be reported explicitly.

Literature increasingly recognises this issue. Recent reviews have called for more complete economic and environmental evaluation, especially for scale-up and industrial implementation [8-11].



18. Proposed phytochemical-NADES selection framework

A rational selection process based on the literature can be structured into six stages.

Stage 1 – Define the target: identify the exact phytochemical or phytochemical class, desired purity and intended application.

Stage 2 – Characterise the molecule conceptually: record hydrogen-bond donors/acceptors, ionisable groups, aromaticity, approximate polarity/lipophilicity, molecular size and chemical stability.

Stage 3 – Select a NADES family: match the target with hydrophilic, acidic, neutral, basic or hydrophobic solvent characteristics.

Stage 4 – Control solvent structure: shortlist component identity, molar ratio and water content rather than screening dozens of arbitrary formulations.

Stage 5 – Match the extraction technology: select maceration, ultrasound, microwave, pressure or enzyme assistance according to matrix and viscosity.

Stage 6 – Evaluate the whole process: compare target recovery, selectivity, stability, solvent consumption, energy, safety and downstream recovery.

This framework is not a replacement for experimentation. Its role is to reduce blind trial-and-error and make solvent selection chemically interpretable. It also creates a reproducible logic for a literature review because published studies can be compared according to the same variables.

19. Experimental Path Selection Matrix

Characteristics	**Preferred NADES tendency**	**Reasoning**
Many OH groups; polar flavonoid	H-bond-rich hydrophilic NADES	Complementary solvation
Strongly acidic phenolic compound	Moderately polar; controlled acidity	Ionisation and H-bonding can be tuned
Anthocyanin	Mildly acidic NADES with stabilising HBD	Supports favourable chemical form and stability
Basic alkaloid	Acid/base-tunable NADES	Controls protonation and solubility
Highly lipophilic carotenoid	Hydrophobic NADES	Improves compatibility with non-polar target
Thermolabile compound	Low/moderate-temperature process	Reduces degradation
High-viscosity matrix	Water-modified NADES + physical intensification	Improves mass transfer
Pure-compound isolation required	Moderate solvent–solute affinity and recoverable system	Simplifies downstream purification

20. Research Gaps Identified from the Literature

1. Standardisation of NADES composition and water-content reporting remains incomplete.
2. Many studies screen several solvents empirically without a predictive molecular rationale.
3. Comparisons with conventional solvents are not always performed at equivalent solid-to-liquid ratios, extraction times or analytical endpoints.
4. Total phenolic/antioxidant assays are sometimes used without compound-specific identification.
5. Downstream recovery of target compounds from NADES is less developed than extraction itself.

6. Solvent recycling and full life-cycle assessment are underreported relative to extraction yield.
7. Negative results and unsuccessful solvent formulations are rarely reported, creating publication bias toward high-performing systems.
8. Safety data are insufficient for many multi-component NADES formulations intended for food or pharmaceutical applications.
9. Scale-up studies must account for viscosity, mixing, heat transfer, solvent recovery and raw-material variability.
10. Computational and data-driven prediction of target–NADES compatibility remains an important opportunity.

21. Future Perspectives

The next stage of NADES research is likely to move from solvent discovery toward solvent design. Instead of asking "which NADES gives the highest yield?", researchers can ask "which molecular interactions should a solvent provide for this target under the required process conditions?" This shift would integrate physical chemistry, natural-product chemistry, computational modelling and green-engineering metrics.

Machine learning may assist this process if sufficiently standardised datasets become available. Useful descriptors could include H-bond donor/acceptor counts, molecular volume, polarity indices, viscosity, water content, acidity, extraction temperature and target molecular descriptors. The response variable should preferably be target-specific recovery or partition behaviour rather than total extract yield.

A second major direction is multifunctional NADES. Recent literature suggests that NADES may simultaneously extract and stabilise sensitive phytochemicals [12,18]. If validated, this could reduce processing steps and protect unstable compounds. However, such claims should be supported by appropriate stability studies and controls.

Finally, industrial translation will depend on process economics. A solvent that is excellent in a small-scale vial may not remain optimal at kilogram scale. Mixing power, heat transfer, solvent preparation, recovery and product purification must be integrated into future studies.

24. Conclusions

Natural deep eutectic solvents offer great versatility for the extraction of phytochemicals by tailoring hydrogen-bonding, polarity, acidity, viscosity, and water compatibility. Published studies report successful applications to flavonoids, anthocyanins, phenolics, alkaloids, and other natural products. However, the evidence highlights the system-specific nature of NADES performance, which cannot be captured by general claims about higher yields or environmental benefits.

The key message of this work is that future NADES research needs to transition into structure-based solvent selection, taking into consideration the molecular properties of the target phytochemicals, their interactions with the matrix and extraction technology, and down-stream requirements. Water contents, viscosities, and acidity of the NADES are critical factors for recovery and stability, next to total extract yields and antioxidant assays. This work suggests that NADES research on phytochemical extrac-tion has the potential to develop into a truly sustainable

field, if attention is given to standardized reporting, solvent recovery, safety assess-ment, scale-up, and sustainability assessments.

The framework presented here provides a starting point for such an approach based on published studies by reducing the number of empirical screening experiments needed and focusing future research on a more chemically informative set of variables.

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