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Natural deep eutectic solvents (NaDES) improves extraction and antioxidant activity of stem bark of *Garcinia cowa* Roxb.

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ABSTRACT: *Garcinia cowa Roxb*. ex DC. is a plant belonging to the Clusiaceae family, and commonly dicovered in Southeast and South Asia. This study aimed to assess the efficiency of eight natural deep eutectic solvents (NaDES) in extracting total xanthones and phenolic compounds from the stem bark using ultrasound-assisted extraction as there is limited research on the use of NaDES in this plant extraction process. The study also examined their antioxidant properties. The NaDES were synthesized with choline chloride and betaine as hydrogen-bond acceptors, accompanied by various acids, alcohols, and glucose as hydrogen-bond donors. In comparison, ethanol was used as standard solvent. The NaDES exhibited higher densities than water, ranging from 1.059 to 1.244 g/cm^3, with density increasing according to the number of hydroxyl groups present in the constituents. The total phenolic content (TPC) varied from 22.82 to 28.73 mg GAE/g extract, with NaDES1 (a combination of choline chloride, 1,2-propanediol, and water in a ratio of 1:3:1) showing the highest TPC at 28.73±0.18 mg GAE/g extract. It also exhibited significant antioxidant activities, as demonstrated by DPPH (28.98±0.03 µg/mL) and FRAP assays (43.66±1.51 mmol trolox/g dw). A significant negative correlation was observed between total xanthone, total phenolic content, and IC_{50} values. These findings suggest that NaDES, particularly NaDES1, have considerable advantages in extracting phenolic compounds and xanthones from *G. cowa* stem bark, resulting in enhanced antioxidant properties.This highlights the potential of NaDES as eco-friendly and effective solvents for the extraction of bioactive compounds from plant materials.

Keywords : Antioxidant activity; DPPH; *Garcinia cowa* Roxb; NaDES.

INTRODUCTION

Garcinia cowa Roxb. ex DC. is an evergreen species of the Clusiaceae family that is widespread across Southeast and South Asia. Fruits are edible and used in the production of preserves and flavorings, whereas oil extracted from the seeds is used in soap and lubricant manufacturing. In traditional medicine, it is recognized for its therapeutic effects, which include enhancing circulation, alleviating coughing, reducing fever, and providing anti-inflammatory and antioxidant benefits owing to its diverse plant compounds. Research has been conducted on various plant parts, such as the leaves, fruit rind, stem bark, and latex, that can scavenge free radicals. G. *cowa* contains a wide range of phytochemicals, including xanthones, phloroglucinols, and polyprenylated benzophenones, which exhibit numerous pharmacological properties such as antioxidant, antimicrobial, antidiabetic, anti-inflammatory, gastroprotective, antiparkinsonian, and anticancer effects [1]. The plant's antioxidant properties are largely due to its substantial phenolic content and the presence of bioactive substances such as flavonoids and xanthones. Xanthones act as chemotaxonomic indicators of this plant, with 78 distinct compounds isolated and identified from *G. cowa*, of which forty-six were xanthones. The bark extract of *G. cowa* is particularly rich in unique xanthones and phenolic compounds. It exhibits strong antioxidant properties, which are distinct from the chemical compositions and activities of the leaves, fruit rind, and roots [2].

Numerous studies have highlighted the use of solvents such as methanol, dichloromethane, ethyl acetate, acetone, and ethanol for extracting bioactive compounds from *Garcinia cowa*. The antioxidant

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effect of *G. cowa* depends on the extraction solvent used. Ethyl acetate extracts, particularly those from stem bark, exhibit higher antioxidant activities than other solvents such as hexane and methanol [2]. Despite the effectiveness of these conventional solvents in extracting phenolic compounds, they pose challenges such as being volatile, explosive, toxic, and harmful to the environment. Consequently, numerous eco-friendly alternative solvents with reduced toxicity, lower cost, and improved extractability have emerged [3].

Natural deep eutectic solvents are the primary metabolites usually found in plant cell vesicles. It consists of sugars (sucrose, glucose, and fructose), organic acids (malic acid, citric acid, and lactic acid), amino acids (such as proline and glycine) serving as hydrogen-bond donors, and hydrogen bond acceptor (HBA) molecules (such as choline chloride or betaine) [4]. The interactions between HBDs and HBAs not only lower the melting point of the resulting solvent but also enhance its biodegradability and non-toxicity, making NaDES an attractive alternative to traditional organic solvents. The design of these solvents can be tailored by adjusting the molar ratios of HBDs and HBAs, thus allowing for the optimization of their physicochemical properties for specific applications. The intermolecular hydrogen bonding among these groups produces highly structured, viscous liquids with distinctive physical properties and solubility behaviors compared to traditional solvents. These liquids can form hydrogen bonds with phenolic chemicals, enhancing their solubility within the NaDES network. NaDES has many advantages over traditional extraction solvents, including near-zero vapor pressure, adjustable viscosity, and excellent solubility, which can exceed 12,000 times that of compounds in water. NaDES also offer significant advantages in terms of biodegradability, sustainability, cost-effectiveness, and ease of solvent manufacture. These characteristics indicate their potential as extraction media for natural products and their possible use in food, medicine, and cosmetics [5].

The current literature lacks research on the extraction of *G. cowa* stem bark and its antioxidant properties using NaDES. Eight natural deep eutectic solvents were syntesized to assess their effectiveness in extracting total xanthones and total phenolic content, as well as to evaluate the antioxidant properties of *G. cowa* Roxb stem bark. NaDES were created using HBAs (choline chloride and betaine) and HBDs (1,2 propanediol, glycerol, glucose, lactic acid, citric acid, and malic acid) with water added. For comparison, ethanol was used as the conventional solvent. In addition, ultrasound-assisted extraction (UAE) was employed to improve the extraction efficiency.

▪ MATERIALS AND METHODS

Materials

The material used in this study was the stem bark of *Garcinia cowa* Roxb. , distilled water, ethanol p.a (Merck®,USA), methanol p.a (Merck®, USA), hydrochloric acid, iron (III) chloride (FeCl3), DPPH (Sygma®), vitamin C (Merck®, USA), Choline Chloride (Xi'an Rongsheng®, China), betaine, glycerol, glucose, maltose, fructose, propylene glycol (Merck®, USA), sucrose, lactic acid, malic acid, TPTZ (2,4,6-tripyridil-s-triazine) (Sygma), gallic acid, Folin-Ciocalteu (Sygma®) 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox).

Preparation of a natural deep eutectic solvent (NaDES)

Eight natural deep eutectic solvents (NaDESs) were prepared by heating and stirring, as described in the literature with slight modifications [6]. Choline chloride and betaine were measured for the hydrogen bond acceptor (HBA) and then mixed with 1,2-propanediol, glycerol, glucose, lactic acid, citric acid anhydrous, and malic acid in the appropriate amounts to achieve the desired molar ratio (HBA: HBD). The mixture was stirred continuously at 50 °C for 2 to 4 hours until it became clear and transparent. The composition and molecular ratios of NaDES are listed in Table 1.

Characterization of natural deep eutectic solvent

The analysis of natural deep eutectic solvents includes evaluating their viscosity and density. The viscosity was evaluated using a Brookfield viscometer. The viscosity was ascertained by employing spindle number 1 with a speed of 30 rpm until a stable viscosity value was achieved. The density of the substance was quantified through the utilization of a pycnometer.

Extract preparation

The ground stem bark of *G. cowa* was mixed with a eutectic solvent at a ratio of 15 mL per gram. The mixture was subjected to ultrasonic-assisted extraction for 30 min to extract compounds from the plant material. The extracts were centrifuged at 3000 rpm for 20 minutes to effectively separate solid particles from the liquid extract. The supernatant was subsequently filtered to remove any remaining solid particles before phytochemical analysis and antioxidant activity tests.

Table 1. Compositions of the natural deep eutectic solvents utilized in the study.

Eutectic solvents	Components	Molar ratio
NaDES1	Choline chloride-1,2 propanediol-water	1:3:1
NaDES2	Choline chloride-glycerin-water	1:2:1
NaDES3	Choline chloride-glucose-water	1:1:1
NaDES4	Choline chloride-lactic acid-water	1:1:1
NaDES5	Betain-1,2 propanediol-water	1:3:1
NaDES6	Betain -lactic acid-water	1:1:1
NaDES7	Betain, citric acid, water	1:1:2
NaDES8	Betain-malic acid-water	1:1:1

The polarity of NaDES components plays a crucial role in their effectiveness. Polarity is closely related to the ability of a solvent to form hydrogen bonds with solutes. Phenolic compounds often contain hydroxyl groups that can engage in hydrogen bonding. NaDES, in which the organic acid-based NaDES were found to be the most polar, while the sugar and alcohol-based NaDES were the least polar [7].

Total phenolic content

The total phenolic content was measured using a colorimetric method employing the Folin–Ciocalteu reagent, following a previously established procedure with slight modifications [8]. The absorbance was measured at a wavelength of 750 nm, and the results were presented as gallic acid equivalents (mg GAE/g extract), calculated based on the linear relationship established by the standard curve (1–5 µg/mL).

Total xanthone content

The total xanthone content in the extract was measured using a spectrophotometer at a wavelength of 243 nm using a calibration curve with a comparison standard of α-mangostin 3– 8µg/mL [9].

DPPH radical scavenging activity assay

In this study, the DPPH radical scavenging activity of the extract was determined by the colorimetric method, as described previously with several modifications [8]. 1.0 mL of a 0.4 mM DPPH solution in ethanol was prepared and mixed with 1.0 mL of extract at concentrations ranging from 5 to 100 µg/mL. The mixture was incubated at room temperature for 30 min. The DPPH radical scavenging activity was determined at a wavelength of 518 nm. The DPPH radical-scavenging activity of the extract was computed using the following formula:

$$\%\ inhibition\ = 1 - \frac{Ac - As}{Ac}\ x\ 100\%$$

Where: Ac is the absorbance of the control, and As is the absorbance of the extract.

Ferric-reducing antioxidant power (FRAP)

The power capacity was assessed using the Ferric Reducing Antioxidant Power (FRAP) method [10]. The FRAP reagent mixture was composed of an acetate buffer (300 mmol, pH 3.6), TPTZ (40 mmol dissolved in 40 mmol HCl), and ferric chloride (20 mmol dissolved in water), combined in a 10:1:1 ratio. Absorbance was measured at 600 nm using a microplate reader. Trolox, ranging from 6 to 18 µmol/L, served as the standard for calibration curve calculation. The FRAP reducing power capacity was reported in mmol Trolox/g dw.

Analysis data

The experimental data underwent triplicate analysis. Statistical evaluation was conducted using one-way ANOVA following confirmation of the dependent variable's normal distribution. Results were considered statistically significant when the p-values were less than 0.05.

▪ RESULTS

Characterization of natural deep eutectic solvent

The density and viscosity of solvents significantly influence the transport phenomena involved in the extraction process. Table 2 lists the viscosities and densities of the NaDES. The viscosity of NaDES with polyalcohol (1,2-propanediol) as an HBD is lower than that of other HBDs. Moreover, NaDES 8, which contains betaine-malic acid-water was the most viscous NaDES. These data are in accordance with a study that found that NaDES prepared with malic acid were characterized by high viscosity [11].

Table 2. Viscosity and density of natural deep eutectic solvents (NaDES).

NaDES	Viscosity (cP)	Density (g/cm³)
NaDES 1	37	1.059
NaDES 2	100	1.228
NaDES 3	134	1.207
NaDES 4	53	1.105
NaDES 5	62	1.073
NaDES 6	255	1.191
NaDES 7	160	1.188
NaDES 8	342.5	1.244

The density of NaDES is a crucial physical property. Generally, all studied NaDES exhibit higher densities than water. The density of a NaDES is dependent on the water content, temperature, composition, type, and size of HBA and HBD. The density of NaDES may be influenced by the number of hydroxyl groups and the length of their chains. The density of NaDES increases with an increase in the number of hydroxyl groups and the expansion of the carbon chain on the donor of hydrogen bonds (HBDs) [10]. The range of the obtained densities was 1.059–1.244 g/mL. Lower-density NaDES are more effective for extracting specific phytochemicals because of their improved mass transfer properties [12].

Total phenolic content

Many intrinsic characteristics, notably diffusion, surface tension, viscosity, density, polarity, physicochemical interactions, and solubility, influence the extraction efficiency of NaDES. The results show the extraction performances of NaDES and ethanol as conventional solvents (Table 3 and Fig. 1). In this research, the phenolic content of the extracts ranged from 22.82 to 28.73 mgGAE/g extract, with the highest concentration obtained when extracting with NaDES 1 and 5. The total phenol content of the extract produced using NADES 1 and NADES 5 solvents was significantly different results from extraction using ethanol ($p<0.05$).

Table 3. Total phenolic content, total xanthone content, and antioxidant activities of stembark of *G. cowa* Roxb. extracted with natural deep eutectic solvents and ethanol.

Extracts	Total phenolic content mgGAE/g extract	Total xanthone (mg/g dw)	Antioxidant activity	
			DPPH Assay (µg/mL)	FRAP Assay (mmol trolox/g dw)
NaDES 1	28.73±0.18^{a}	199.95±2.18^{b}	28.98±0.03^{a}	43.66±1.51^{a}
NaDES 2	24.59±0.04^{c}	94.51±0.13^{f}	30.28±0.09^{b}	31.75±0.32^{c}
NaDES 3	24.21±0.16^{c}	105.39±0.37^{e}	30.88±0.07^{d}	27.48±0.51^{e}
NaDES 4	25.35±0.19^{b}	122.95±0.47^{d}	29.02±0.09^{a}	31.52±0.17^{cd}
NaDES 5	28.64±0.19^{a}	143.45±0.26^{c}	30.64±0.04^{c}	22.30±0.87^{f}
NaDES 6	25.61±0.11^{b}	39.51±1.26^{i}	36.57±0.06^{f}	30.58±0.67^{cd}
NaDES 7	23.39±0.21^{d}	55.80±1.04^{h}	57.86±0.15^{g}	38.39±1.38^{b}
NaDES 8	24.32±0.15^{c}	52.39±0.71^{g}	35.75±0.02^{e}	28.85±0.96^{de}
Ethanol	22.82±0.02^{e}	246.43±1.72^{a}	30.88±0.07^{d}	26.59±1.41^{e}

Note: [a,b,c,d,e,f] Superscript letters that differ indicate significant differences ($p \leq 0.05$)

Total xanthone determination

As shown in Table 3, the less-polar polyalcohol-based natural deep eutectic solvents (NaDES) extracted higher amounts of total xanthones compared to NaDES made from organic acids such as malic and citric acid. Specifically, NaDES 1 and NaDES 5 yielded total xanthone values of 199.95±2.18 and 143.45±0.26 mg/g dw, respectively. However, the ethanolic extract exhibited the highest total xanthone content, with a value of 246.43±1.72, which is significantly greater than that of the polyalcohol-based components.

DPPH radical scavenging activity assay

DPPH radical scavenging assays were conducted to assess the antioxidant capacity of the extracts. The method used is based on the transfer of hydrogen atoms. Table 3 presents the results for extracts obtained from stem bark using Ultrasonic Assisted Extraction (UAE) with various Natural Deep Eutectic Solvents (NaDES). According to the DPPH assay, almost all extracts derived from UAE with the different NaDES showed significant differences in their antioxidant capacities ($p \leq 0.05$). The extracts using NaDES 1 exhibited the highest IC_{50} values, followed by those from NaDES 4, with no significant differences observed between these two extracts ($p > 0.05$). In contrast, preparations with NaDES 7 demonstrated the lowest capacity to scavenge DPPH radicals.

Ferric-reducing antioxidant power (FRAP)

The antioxidant capacity of the extracts was evaluated based on their ability to reduce the ferric tripyridyltriazine complex (Fe^{3+}-TPTZ) to ferrous tripyridyltriazine (Fe^{2+}-TPTZ) in an acidic environment. This reduction results in a bright blue color, which can be measured at an absorption peak of 600 nm. The NaDES 1 extract exhibited the greatest value compared with the other NaDES, measuring 43.66±1.51 mmol trolox/gdw. This value is also markedly greater than that of the ethanolic extract.

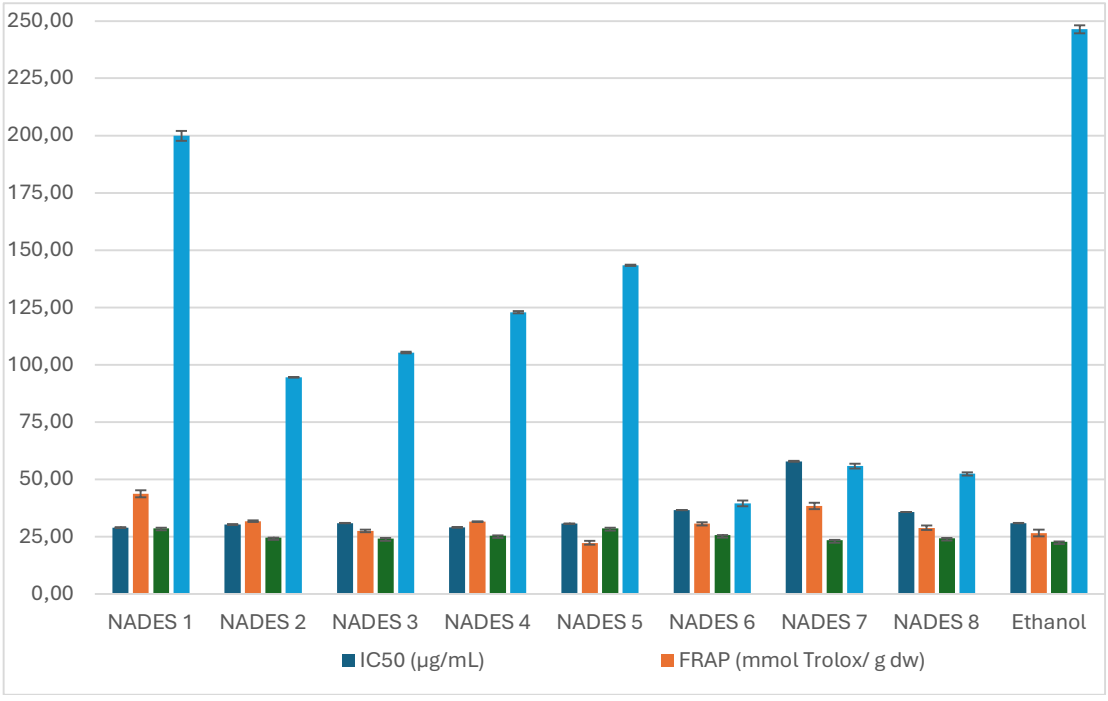

Figure 1. Total phenolic content, total xanthone content, and antioxidant activity of *G. cowa* Roxb. stem bark extracted using NaDES and ethanol were expressed as mean ± standard deviation.

DISCUSSION

The synthesis of natural deep eutectic solvents (NaDES) has a significant impact on their fundamental physicochemical properties, such as density, viscosity, polarity, and solubility, all of which influence their extraction efficiency. In this study, we used choline chloride and betaine as hydrogen bond acceptors (HBA), along with various acids (malic, lactic, and citric acids), alcohols (1,2-propanediol and glycerol), and glucose as hydrogen bond donors (HBD). All the examined NaDES demonstrated higher densities than water (see Table 2). At room temperature, the densities ranged from 1.059 for the composition that included choline chloride, 1,2-propanediol, and water, to 1.244 for the NaDES made up of betaine and malic acid as hydrogen bond donors. Although the analysis revealed slight discrepancies among the densities of the solvents examined, it can be concluded that the densities seemed to increase in accordance with the number of hydroxyl groups available in the constituents [2].

The total phenolic content (TPC) values ranged from 22.82 to 28.73 mg/g of extract. Additionally, the total xanthone content, DPPH radical scavenging activity, and FRAP values varied from 39.51 to 246.43 mg/g dw, 28.98 to 57.86 µg/mL, and 22.30 to 43.66 mmol trolox/g dw, respectively. As illustrated in Figure 1, the TPC, DPPH radical scavenging activity, and FRAP values were higher in the NaDES 1 samples. Our results concur with an earlier study, which showed that NaDES composed of choline chloride-1,2 propanediol-water (1:3) obtained the highest α-mangostin extraction yield from the pericarp of *Garcinia mangostana* at 2.6% [13]. The interaction between choline chloride and polyols, such as glycerol and 1,2-propanediol, is primarily driven by hydrogen bonding. In this interaction, the chloride ion in choline chloride acts as a hydrogen bond acceptor, while the hydroxyl groups in polyols serve as hydrogen bond donors. This interaction is crucial for the stability and solubility of natural deep eutectic solvents (NaDES).

Table 4 presents the Pearson correlation coefficients between total phenolic content (TPC), total xanthone, and antioxidant activities of stem bark extracts in various solvents. The study reveals a significant negative correlation between the IC_{50} values and the total xanthone content. A moderate Pearson's correlation was observed between total xanthone and DPPH data ($r=-0.508$; $p<0.01$), indicating that xanthones were the primary compounds responsible for the antioxidant activities in these extracts. Xanthones, which are the major components of *G. cowa* extract, are polyphenolic compounds that contain multiple phenol units in their structure [2]. Specifically, they have a tricyclic aromatic ring system that includes phenolic hydroxyl groups, which are characteristic of phenolic compounds [14].

A considerable correlation was found between TPC and scavenge of DPPH radicals, yielding a value of 0.398 with $p<0.05$. These findings align with previous reports indicating a correlation between TPC values and the antioxidant activity of plant extracts [15]. The stem bark of *G. cowa* is a rich source of a variety of bioactive compounds, including xanthones, flavonoids, and benzophenones, which belong to the phenolic compound family and contribute to the antioxidant properties [16]. Phenolic compounds are widely recognized for their antioxidant properties, especially their capacity to neutralize free radicals such as DPPH (1,1-diphenyl-2-picrylhydrazyl). The process through which phenolic compounds neutralize DPPH free radicals is primarily facilitated by two key mechanisms: Hydrogen Atom Transfer (HAT) and Single Electron Transfer (SET). Compounds with multiple hydroxyl groups in phenolic structures demonstrate greater scavenging activity because they can donate hydrogen atoms with greater ease. Despite the significant potential of NaDES, their high viscosity is a notable drawback. A small amount of water can tailor the viscosity of NaDES, and it also influences the conductivity [17]. According to the results shown in Figure 1, NaDES 1 with the lowest viscosity yielded significantly highest total phenolics, antioxidant capacity (FRAP), and DPPH scavenging activity. Considering these factors, NaDES 1 was chosen for further research.

Tabel 4. Correlation coefficients of total phenolic content (TPC), total xanthone content, and antioxidant activities of *G. cowa* Roxb. stem bark extract.

Assays	TPC	Xanthone total	DPPH	FRAP
TPC	1			
Xanthone total	0.201	1		
DPPH	-0.398*	-0.508**	1	
FRAP	0.151	-0.002	0.329	1

*The correlation is significant at the 0.05 level.
**The correlation is significant at the 0.01 level

CONCLUSION

According to the solvent extraction screening results, most NaDES demonstrated extraction yields comparable to, or even greater than, ethanol. NaDES 1, which consists of choline chloride, 1,2-propanediol, and water in a ratio of 1:3:1, exhibited significant advantages in extracting total phenolic content, total xanthone, and antioxidant activity.

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