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Screening of Hydrophilic Deep Eutectic Solvents for Ultrasound Probe-assisted Extraction of Rosmarinic Acid from *Salvia officinalis* with High Performance Liquid Chromatography Analysis

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Abstract: This study investigates the potential of hydrophilic deep eutectic solvents (DESs) for the extraction of rosmarinic acid (RA) and antioxidant compounds from Salvia officinalis (sage) using ultrasound probe-assisted extraction. Six DESs were formulated using choline chloride (ChCl) as the hydrogen bond acceptor and either ethylene glycol or glycerol as the hydrogen bond donor, in molar ratios of 1:1, 1:2, and 2:1. All DESs were prepared without added water. Under fixed extraction conditions (10 min, 30% amplitude, 1:10 solid–liquid ratio), the RA content was quantified by high-performance liquid chromatography (HPLC). Among the DESs, ChCl:glycerol, 1:2 (DES-5) showed the highest extraction potential exhibited by the highest peak intensity in the chromatogram and was selected for further investigation. Antioxidant activity of DES-5 was assessed via the ORAC assay. Methanol was used as a reference solvent for comparison. The ORAC value of methanol extract was 9,270 ± 2.82 µmol TE/ 100 ml, while that of DES-5 was 33,690 ± 4.98 µmol TE/100 ml, indicating a stronger radical scavenging capacity in DES-5 extract. Based on the promising ORAC value observed, DES-5 extract was further explored by modifying its composition through the addition of water; 10%, 20% and 30%, to evaluate it effect on RA yield. Results revealed that moderate water addition of 10% enhanced RA recovery, resulting in the highest yield of 73.38 mg/g DW RA compared to 66.59 mg/g DW at 20% water and 72.39 mg/g DW at 30% water. The study demonstrates the viability of DESs, particularly DES-5, as sustainable alternatives to conventional solvents for the recovery of bioactives from medicinal plants.

Keywords: Ultrasound probe-assisted extraction, HPLC, Sage, Hydrophilic deep eutectic solvents, Rosmarinic acid

Introduction

Salvia officinalis L., commonly known as sage, is a medicinal herb from the mint family, Lamiaceae. Native to the Mediterranean, sage is now grown in Europe, North America, and Asia (Jakovljević et al., 2019). It is valued for its aromatic properties and widespread use in folk medicine for treating digestion issues, inflammation, sore

throat, abdominal pain, and cough (Güler et al., 2015). Phenolic compounds in sage, particularly rosmarinic acid (RA), carnosic acid, and carnosol, are extensively studied for their therapeutic potential in sage (Pavić et al., 2019; Sik et al., 2020; Jakovljević et al., 2021; Christaki et al., 2022).

The extraction methods and solvents applied have a significant impact on how well plants can be extracted. Several extraction techniques including maceration (Sik et al., 2020), hydro-distillation (Christaki et al., 2022), supercritical fluid extraction (Pavlić et al., 2018; Jokić et al., 2018; Pavić et al., 2019; Chadni et al., 2023) and ultrasound-assisted extraction (Dent et al. 2015; Jakovljević et al. 2021; Brindisi et al. 2021), have been employed to produce sage extracts rich in bioactive compounds. In order to effectively isolate this polar compound of RA, the best extraction technique must be chosen. In order to avoid degradation during processing, the selected extraction technique needs to consider RA sensitivity to heat and chemicals (Bitwell et al., 2023). Selecting the appropriate solvent helps to maximize extraction yield and selectivity while minimising impurities because polar compounds usually dissolve well in polar solvents (Abubakar & Haque, 2020). Organic solvents commonly utilised for the extraction of sage due to different polarities of the active compounds (Dent et al., 2015; Pavlić et al., 2018; Brindisi et al., 2021), however toxicity of solvent residue represent the main drawbacks (Ruesgas-Ramón et al. 2017). There is a growing need for greener alternatives, such as ionic liquids, DESs, and natural eutectic solvents, which are gaining attention for their lower toxicity, adjustable viscosity, and higher biodegradability (El Achkar et al., 2021). Unlike traditional solvents, DESs are easy to prepare from naturally occurring, low-cost components, making them a greener and more sustainable option (Abubakar & Haque, 2020; Grozdanova et al., 2020). They also offer superior extraction performance, such as higher yields of bioactive compounds contributing to more efficient and economical processes (Kanyairita et al., 2024; Ruesgas-Ramón et al., 2017). Furthermore, DESs are particularly suitable for applications involving medicinal plants, as they can improve the solubility and stability of sensitive phytochemicals while eliminating the risk of residual toxic solvents in the final product (Socas-Rodríguez et al., 2021; Gómez-Urios et al., 2023; Kalyniukova et al., 2024). These advantages positioned DESs as a promising alternative for safe, efficient, and sustainable herbal extraction. Hydrophilic DESs is used in this study to extract polar compound of RA. Choline chloride DES is typically considered hydrophilic (Wojeicchowski et al., 2021). It is a quarternary ammonium salt and is often used as an hydrogen bond acceptor (HBA) in hydrophilic DES. Hydrophilic DES is ideal for extracting hydrophilic compounds like RA that is more soluble in polar solvents. Hydrogen bond donor (HBD) like glycerol or ethylene glycol, is rich in hydroxyl groups, which efficiently participate in hydrogen bonding interactions. However, high viscosity is the fundamental limitation with DESs, but this can be improved by adding water to the solvent and enhance its ability to interact with solutes (Zhang et al., 2022).

Ultrasound-assisted extraction (UAE) is recognised as an "eco-friendly" or "green" method and is a key enabling technology in biorefineries. It has been acknowledged for its industrial applications in enhancing efficiency, shortening extraction time (Vilkhu et al., 2008) and reduced solvent consumption (Nour et al., 2016). In liquids, ultrasound works by causing cavitational bubbles to burst, which produces strong shear forces, high pressures, and temperatures that rapidly disrupt plant tissues, allowing the release of cellular material and improving mass transfer (Dent et al., 2015). Few studies have examined the impact of various DESs on the extraction of beneficial chemical compounds from sage using this method (Georgantzi et al., 2017; Jakovljević et al., 2021; Albalushi et al., 2023). In paper by Georgantzi et al. (2017), they investigated combination of lactic acid-based DES with cyclodextrin for the extraction of total polyphenols and flavonoids from selected native Greek medicinal plants including sage, while Jakovljević et al. (2021) studied choline chloride-based DES for the extraction of carnosic acid and carnosol from sage. Results from Albalushi et al. (2023) revealed that choline chloride-based DES with ethylene glycol as HBA and 30% water led to a better extraction of RA than with other HBA such as acetic acid, propanoic acid, and malonic acid. There was similarity between all the studies, where they used ultrasonic bath for the extraction, whereas in the present study, ultrasound probe-assisted was utilised for the extraction. As studies utilising ultrasound probe-assisted extraction remain relatively scarce, the ultrasound probe was chosen in this study due to its ability to deliver more precise treatment, resulting in higher yields compared to other apparatus like ultrasonic reactor and ultrasound bath, as previously reported by Jacotet-Navarro et al. (2015).

In this work, tailored hydrophilic DESs were prepared for the extraction of RA from sage leaves. The suitable DESs based on its stability were used in the extraction process and their performance were assessed based on the yield of RA using HPLC and antioxidant potential. The findings provide a greener alternative to traditional extraction methods. The approach aligned with the goals of biorefinery, green chemistry and sustainable development, that aimed to reduce environmental impact while enhance process efficiency and product quality.

Method

Materials and Chemicals

Choline chloride (99% purity), ethylene glycol (99.9% purity), glycerol (99.9% purity), and RA (99.7% purity) were purchased from local supplier. Ultrapure water was obtained using Milli-Q water purification system. All solvents used were of analytical or HPLC grade. All components, HBA and HBD (with 99% purity, analytical grade), as listed in Table 1 for preparing eutectic solvents were commercially available from local suppliers.

Table 1. Chemical composition of prepared DESs

HBA	HBD	Molar ratio	Abbreviation
Choline chloride	Ethylene glycol	1:1	DES-1
Choline chloride	Ethylene glycol	1:2	DES-2
Choline chloride	Ethylene glycol	2:1	DES-3
Choline chloride	Glycerol	1:1	DES-4
Choline chloride	Glycerol	1:2	DES-5
Choline chloride	Glycerol	2:1	DES-6

Preparation of *Salvia officinalis* Leaves

Salvia officinalis plants were purchased from Glorious Nursery, Petaling Jaya, Selangor. Harvesting was done a day after receiving the plants. Pre-processing activities like cutting, sorting, and cleaning were done after harvesting. Sample identification was done by botanist at Forest Research Institute Malaysia to ensure correct species, Salvia officinalis L., is used in the entire study. Voucher specimen of the plant (PID 010124-01) was stored in Herbarium Specimens Room at FRIM. The fresh processed leaves were dried using freeze dryer (Albalushi et al., 2023; Ghanem et al., 2023). Low-temperature drying was selected during the drying of fresh leaves to preserve RA, which is sensitive to heat (Bitwell et al., 2023). Dried leaves were ground and sieved using sieve shaker and properly kept for further use (Jakovljević et al., 2021). The final particle size of the ground leaves was 300 microns.

Preparation of Hydrophilic DESs

Hydrophilic DESs were prepared by mixing HBA and HBD components with different molar ratios of 1:1, 1:2, 2:1 in beakers with magnetic stirrers. Different molar ratios were applied to determine which combinations could form stable eutectic mixtures under various conditions for use in the extraction process, while excessively high ratios were excluded to avoid unnecessary volume increase and material wastage. Then, the mixture was heated at 80°C for 20 min with constant stirring at 350 rpm until a clear liquid form with no turbidity (Gajardo-Parra et al., 2019). After 24 hours of cooling at room temperature, the DES were assessed for crystallisation, and those exhibited instability at room temperature were excluded. They were used in the extraction process immediately after successfully prepared.

Ultrasound Probe-assisted Extraction of Rosmarinic Acid

After characterisation, the selected DESs were used in the extraction process. Ultrasound-assisted extraction was done in an ultrasonic probe system. Samples of 1 g powdered sage leaves were extracted with 20 mL of different solvents (ethanol and selected DESs). The mixture went through extraction at 30% power amplitude, for 10 min with 50% duty cycle. Each extraction was performed in triplicate. The selected UAE parameters were based on conditions commonly reported in the literature for extracting phenolic compounds from plant materials using ultrasound probe systems (Fu et al., 2021; Patil et al., 2021; Kobus et al., 2023). After the extraction process, extracts were centrifuged at 10,000 rpm for 5 min, and the supernatant was withdrawn and diluted. The supernatants were prepared to be used in the HPLC analysis. The promising UAE-DES extract based on HPLC results was further evaluated by varying water content (0%, 10%, 20%, 30%).

HPLC Analysis

All extracts were subjected to dilution with HPLC grade methanol to achieve the desired concentration in order to be analysed using HPLC (Insumrong et al., 2022). After dilution, extracts were filtered using 0.45 µm syringe filter. A 10 µl aliquot was prepared and then injected for the analysis. The samples were analysed using an

HPLC system equipped with a quaternary gradient pump, an autosampler (Waters 717), and a PDA detector (Waters 2996 PDA) scanning from 190 nm to 400 nm, along with a Waters XBridgeTM Kinetex 5 µm Biphenyl 170541 column. The gradient system used two solvents: solvent A (0.1% analytical grade formic acid in water) and solvent B (acetonitrile). The gradient program was as follows: 85% A at 0 min, 75% A at 3 min, 75% A at 7 min, 85% A at 10 min, 85% A at 15 min, 45% A at 21 min and 45% A at 40 min. The flow rate was set at 1 ml/min with a sample volume of 10 µl. Retention time data, HPLC profiles and UV spectra for clear and distinct peaks were analysed and recorded. Separated RA compounds were monitored at 254 nm.

Determination of Antioxidant Capacity by ORAC Method

The ORAC assay was performed to evaluate the total antioxidant capacity of the potential DES and methanol extract. The analysis was conducted in a 96-well microplate using a fluorescence plate reader (BMG Labtech, Offenburg, Germany), following a modified protocol by Takatsuka et al. (2025) and Choudhari et al. (2011). In each well, 150 µL of 75 nM fluorescein solution was mixed with 25 µL of appropriately diluted extract and incubated at 37°C for 30 minutes. The reaction was initiated by the manual addition of 25 µL of 240 mM AAPH (2,2'-azobis-2-methyl-propanimidamide). Fluorescence was measured at excitation/emission wavelengths of 485/538 nm every 90 seconds for 120 minutes at 37°C. Sodium phosphate buffer (75 mM, pH 7.4) was used as the blank, and 25 µL of Trolox was included as the standard. Results were expressed as µmol of Trolox equivalents per ml sample (µmol TE/100 ml). To support the compound quantification from HPLC results, this assay provides complementary evidence of the antioxidant activity of the extracts.

Results and Discussion

Selection of the Best Hydrophilic DESs for Extraction

Six DESs were synthesised using ChCl as the HBA and various HBDs of ethylene glycol (EG) and glycerol (Gly), at different molar ratios (1:1, 1:2, and 2:1) as tabulated in Table 2. The selection of appropriate DESs is crucial for the efficient extraction of bioactive compounds. In this study, the stability of DESs at room temperature was a key criterion for selection, as it ensures the practicality and reproducibility of the extraction process. The formation of stable DESs depends on the nature of the HBA and HBD, as well as their molar ratio. Choline chloride was chosen as the HBA due to its ability to form strong hydrogen bonds with various HBDs (Gajardo-Parra et al., 2019). The choice of HBD in this study was based on their availability, low toxicity, and potential for forming stable DES with ChCl. The results showed that not all combinations of ChCl and HBDs resulted in stable DES at room temperature. Some combinations crystallised or solidified upon cooling, indicating weaker interactions between the components. The inability of some combinations to form clear solutions even at elevated temperatures suggests incompatibility or insufficient interaction between the components.

Table 2. DES formation and crystallisation

			Molar ratios		Formation of DES			
Abbreviation	HBAs	HBDs	HBA	HBD	Clear homogeneous solution	Crystallised	Solidified	Unable to remain clear homogeneous solution
DES-1			1	1				
DES-2		Ethylene	1	2	√			
DES-3	Choline	glycol	2	1			√	√
DES-4	chloride		1	1		√		
DES-5		Glycerol	1	2	√			
DES-6			2	1		√		√

Notes: The DESs were classified into four main groups based on their stability at room temperature (25°C); i) Stable DES: Maintained a clear, homogeneous solution at room temperature, ii) Unstable DES (Crystallised): Formed a clear solution at 80°C but crystallised upon cooling to 25°C, iii) Unstable DES (Solidified): Formed a clear solution at 80°C but solidified upon cooling to 25°C, iv) Unable to form DES: Failed to form a clear, homogeneous solution even at 80°C.

The stable DES identified in this study were DES-2 and DES-5, offer promising alternatives to conventional organic solvents for the extraction of RA from sage leaves. These DESs were selected for further utilisation in the extraction process due to their ability to form a homogeneous extraction medium, which is essential for efficient mass transfer and interaction with the target compound.

HPLC Profiles of Different Ultrasound Probe-assisted Extracts

The chromatograms in Figure 1 provide a detailed analysis of rosmarinic acid (RA) in both the standard solution and sage extracts, with a distinct peak observed at a UV wavelength of 254 nm. Identification of RA in the sage extracts was confirmed by comparing the retention times with that of the standard compound. RA was consistently detected at 13.701 minutes in the standard solution and between 13.573 and 13.870 minutes in the sage extracts, indicating successful extraction and detection.

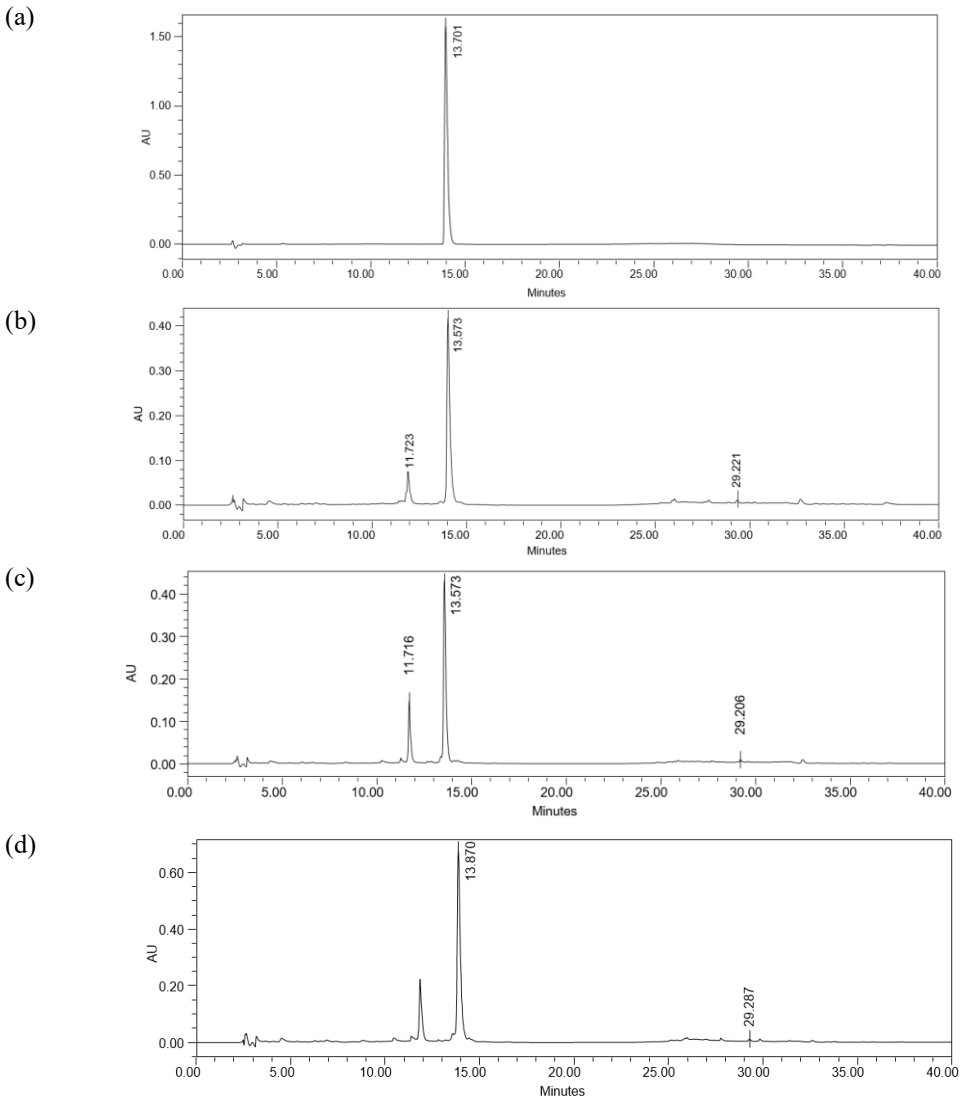
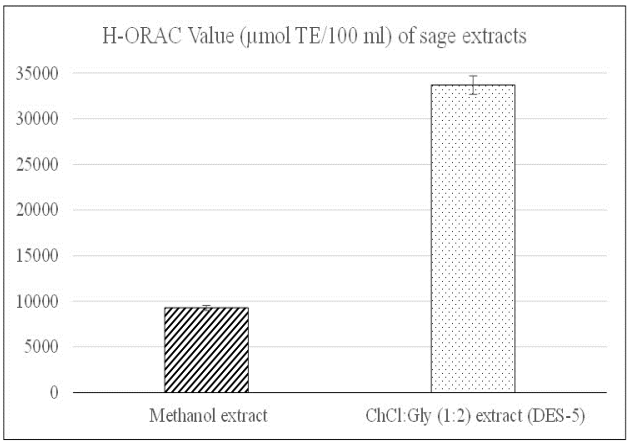


Figure 1. HPLC Chromatograms of RA and sage extracts, (a) RA; (b) Methanol extract; (c) DES-2; (d) DES-5

In order to study the influence of hydrophilic DES solvents on the composition of RA, sage leaves were extracted under standardised conditions using ultrasound probe-assisted extraction (10 min, 30% amplitude, 1:10 solid-liquid ratio). Quantitative HPLC analysis was performed to analyse the samples. As shown by chromatographic analysis in Figure 1, among the extraction solvents used, sage extracted with DES-5 exhibited the highest peak intensity in the chromatogram, suggesting greater content, followed by methanol extract and DES-2 extract. This trend was further supported by the Oxygen Radical Absorbance Capacity (ORAC) values presented in Figure 2, which measure the antioxidant capacity of the extracts.

The ORAC values of DES-5 and methanol extract showed a clear difference, as illustrated in the figure. DES-5 exhibited a higher ORAC value compared to methanol extract, indicating stronger antioxidant capacity. This enhanced activity in the DES extract may be attributed to the ability of DESs to better solubilise and stabilise phenolic compounds like RA, due to their strong hydrogen bonding interactions and polarity. Together, these results highlight the effectiveness of DES-5 not only in extracting RA but also in preserving the extract's bioactivity. In contrast, methanol, while commonly used as an organic solvent, may not provide the same level of extraction efficiency for RA as compared to DES-5. The ORAC assay was conducted only for the baseline DES-5 extract to provide a general indication of antioxidant activity under the initial extraction conditions. The ORAC value of methanol extract was 9,270 ± 2.82 µmol TE/ 100 ml, while that of ChCl:Gly (1:2) was 33,690 ± 4.98 µmol TE/100 ml, indicating a stronger radical scavenging capacity in ChCl:Gly (1:2) extract. The promising antioxidant result from the baseline DES-5 supports its potential and justifies further exploration of ORAC values across other optimised DES conditions in future work.



Values are presented as mean ± standard error (n = 3)

Figure 2. ORAC values of methanol extract and DES-5

The findings highlight the potential of DES-5 as a green and effective solvent for extracting antioxidant compounds. Given the promising ORAC value observed, we further explored the performance of the DES by modifying its composition through the addition of water; 10%, 20% and 30%. This step was taken to address one of the known limitations of DES, its inherently high viscosity which can hinder mass transfer and extraction efficiency. By adjusting the water content, we investigated its effect on the extraction of RA, aiming to optimise its extraction performance.

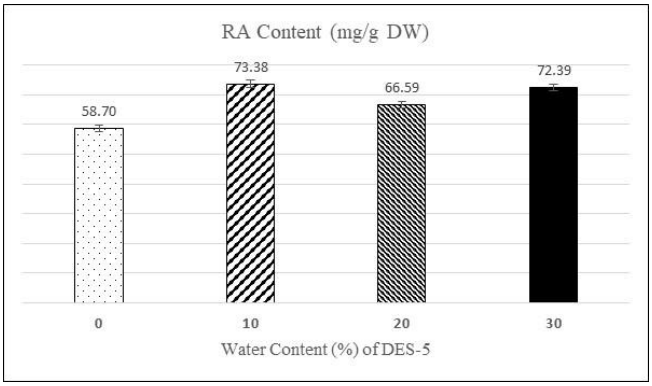


Figure 3. RA at different water content percentages in DES-5

The impact of different water contents in DES-5 on the yield of RA was clearly observed in Figure 3, with 10% water content resulting in the highest yield of 73.38 ± 1.56 mg/g DW, compared to 66.59 ± 1.09 mg/g DW at 20% water and 72.39 ± 1.05 mg/g DW at 30%. Pure DES-5 (0% water) with yield of 58.70 ± 1.09 mg/g DW was used as a reference. The improved yield at 10% water as compared to pure DES-5 can be attributed to reduced viscosity, which enhances mass transfer and facilitates better diffusion of the solvent into the plant matrix. However, further increases in water content to 20% likely disrupted the hydrogen bonding network within the DES, weakening its solvating capacity and reducing extraction efficiency. Interestingly, the yield at 30% was not significantly different from that at 10%, suggesting that further addition of water does not

necessarily enhance extraction. In fact, excessive water may disrupt the DES-5 hydrogen bonding structure, weakening its solvating power and leading to inconsistent extraction behavior. Maintaining a lower water content helps preserve the key interactions responsible for effective and selective RA extraction. These results suggest that adding a small amount of water can significantly improve DES-5 performance, but excessive dilution may compromise its extraction ability.

Conclusion

This study successfully synthesised six hydrophilic DES for the extraction of RA from sage leaves. Among these, DES-2 and DES-5 were found to be stable at room temperature and suitable for application in the extraction process. DES-5 showed promising extraction performance and antioxidant activity. Water content influenced RA recovery where 10% water content appears to offer a balanced condition for efficient RA extraction, making it a promising formulation for further optimisation and application.

Recommendations

* Based on the results, it is recommended to optimise extraction parameters to maximise RA content while minimising the co-extraction of unwanted compounds.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM journal belongs to the authors.

Conflict of Interest

* The authors declare that they have no conflicts of interest

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