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Математическое моделирование и машинное обучение для оптимизации состава глубоких эвтектических растворителей при извлечении коллагена из костного остатка птицы

Зайнаб Арзикуловна Одилова[1], Сергей Николаевич Шлыков[2*], Руслан Сафербегович Омаров[3]

[1, 2, 3] Ставропольский государственный аграрный университет (12, пер. Зоотехнический, Ставрополь, 355035, Россия)
[1] zaynabodilova663@gmail.com; https://orcid.org/0009-0009-4052-3379
[2] shlykovsn@gmail.com; https://orcid.org/ 0000-0001-9894-180X
[3] doooctor@yandex.ru; https://orcid.org/0000-0001-7352-636X
*Автор, ответственный за переписку

Аннотация. ***Введение.*** В работе рассматривается применение глубоких эвтектических растворителей (DES) для повышения эффективности экстракции коллагена из животного сырья. Актуальность обусловлена необходимостью замены традиционных органических экстрагентов более безопасными и регулируемыми средами, обеспечивающими стабильность белковых структур и снижение экологической нагрузки. ***Цель.*** Цель исследования — выявить оптимальные составы DES, способные обеспечивать высокий выход коллагена при низких температурах и мягких технологических условиях, а также определить дескрипторы, влияющие на экстракционную способность. ***Материалы и методы.*** Анализ выполнен на основе рассчитанных физико-химических дескрипторов компонентов DES и моделирования выходов коллагена с использованием нейросетевой модели MLP. Рассмотрено 120 комбинаций HBA и HBD, охватывающих металлосодержащие и натуральные системы. Данные нормализованы и использованы для построения сравнительной таблицы дескрипторов и прогностических характеристик. ***Результаты и обсуждение.*** Выявлено, что DES, содержащие Lewis-кислоты Zn^{2+} и Sn^{2+}, характеризуются пониженной полярностью и умеренной вязкостью, что обеспечивает максимальный прогнозируемый выход коллагена. Натуральные NADES демонстрируют несколько меньшую эффективность, но обладают преимуществами пищевой безопасности. Построенный бар-чарт визуализирует превосходство металлосодержащих систем по сравнению с классическим контрольным DES. ***Заключение.*** Установлено, что сочетание структурных дескрипторов и машинного обучения позволяет достоверно прогнозировать эффективность DES и минимизировать объём лабораторных испытаний. Металлосодержащие системы являются наиболее перспективными для последующей экспериментальной верификации.

Ключевые слова: Lewis-кислоты, молекулярные дескрипторы, MLP-модель, HBA/HBD-системы, NADES, экстракция коллагена

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Research article

Mathematical Modeling and Machine Learning for Optimizing the Composition of Deep Eutectic Solvents in the Extraction of Collagen from Poultry Bone Residues

Zainab A. Odilova[1], Sergei N. Shlykov[2*], Ruslan S. Omarov[3]

[1, 2, 3] Stavropol State Agrarian University (12 Zootekhnicheskiy Lane, Stavropol, 355035, Russia)
[1] zaynabodilova663@gmail.com; https://orcid.org/0009-0009-4052-3379
[2] shlykovsn@gmail.com; https://orcid.org/0000-0001-9894-180X
[3] doooctor@yandex.ru; https://orcid.org/0000-0001-7352-636X
*Corresponding author

Abstract. ***Introduction.*** This study examines the use of deep eutectic solvents (DESs) to enhance the efficiency of collagen extraction from animal-derived raw materials. The relevance of the work is driven by the need to replace traditional organic extractants with safer and more controllable media that ensure protein structural stability while reducing environmental impact. ***Goal.*** The aim of the research is to identify optimal DES compositions capable of providing high collagen yield at low temperatures and under mild technological conditions, as well as to determine the descriptors influencing extraction performance. ***Materials and methods.*** The analysis is based on calculated physicochemical descriptors of DES components and modeling of collagen yields using a multilayer perceptron (MLP) neural network. A total of 120 combinations of hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs), including metal-containing and natural systems, were evaluated. The data were normalized and used to construct a comparative table of descriptors and predictive characteristics. ***Results and discussion.*** DESs containing Lewis acids Zn^{2+} and Sn^{2+} were found to exhibit reduced polarity and moderate viscosity, which together provide the highest predicted collagen yields. Natural NADES showed slightly lower efficiency but offered advantages in terms of food safety. The constructed bar chart visualizes the superiority of metal-containing systems compared to a classical control DES. ***Conclusion.*** It has been established that the combination of structural descriptors and machine learning enables reliable prediction of DES efficiency and minimizes the volume of laboratory testing. Metal-containing systems are the most promising candidates for subsequent experimental verification.

Key words: Deep eutectic solvents., Natural deep eutectic solvents, Molecular descriptors; Machine learning; MLP model; Collagen extraction

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Introduction. Deep eutectic solvents (DES) are a promising class of green chemistry and sustainable biotechnology tools: they are low-toxic, biodegradable, and easily customizable, making them an effective replacement for organic solvents and aggressive alkaline systems in the extraction of proteins and peptides, including collagen and its hydrolysates [1]. Compared to first-generation ionic liquids (ILs), DES are characterized by a significantly lower cost (≈45-450 ₽/kg versus 4,500-45,000 ₽/kg), a high degree of biodegradation (up to 97% in 28 days according to OECD 301), and the absence of toxic halides, which ensures their compliance with the requirements of the food and pharmaceutical industries [2].

The use of DES in the extraction of proteins and peptides, including collagen, provides a yield of 78-96% while preserving native functional properties. In plant matrices, ChCl-glycerol (1:2) gives a protein yield of 85-93% with a purity of >90% and superior emulsifying properties compared to alkaline extraction [3, 4]. For animal raw materials (fish skin, pig skins, chicken feet), DES based on choline chloride and organic acids selectively extract collagen peptides weighing 2-8 kDa with a Gly-Pro-Hyp content of up to 18%, destroying cross-links without denaturing the triple helix under mild conditions (40-60 °C, pH 4-6) [5, 6]. Two-phase ChCl-sorbitol-water systems ensure the fractionation of collagen and lipids with a peptide yield of >90% and preservation of antioxidant activity [7]. DES recycling reaches 85-92% after 4-5 cycles of vacuum distillation without reducing the extraction efficiency [8].

Mathematical modeling is a key tool in biotechnology, enabling process optimization, reduced experimental costs, and increased accuracy in predicting the solubility of proteins and peptides and the yield of biologically active substances from secondary raw materials [9]. Deterministic models based on kinetic equations and mass balances are limited in describing the nonlinear and stochastic interactions characteristic of complex biosystems [10]. From 2015 to 2025, machine learning methods, including regression approaches and neural networks that integrate multivariate experimental and structural data and generate highly accurate empirical models, have assumed a leading role [11].

Neural networks (NNs) and deep learning methods are key tools for analyzing biotechnological data, enabling the identification of hidden dependencies and significantly reducing the volume of laboratory experiments [12]. The main architectures—multilayer perceptrons (MLPs), convolutional networks (CNNs), and graph networks (GNNs)—provide high accuracy in predicting protein and peptide solubility by taking into account sequence, structural, and topological features of molecules [13]. MLPs effectively solve regression problems on sets of physicochemical descriptors, achieving $R^2 > 0.85$ and RMSE 0.30–0.50 log S, while interpretation via SHAP allows for determining the contribution of key motifs, such as Gly-Pro-Hyp [14–16]. Convolutional neural networks (CNNs) are used for contact map and time series analysis, demonstrating high accuracy (AUC 0.88–0.92) when working with large sequential datasets and generating synthetic data via GANs to improve models when training examples are scarce [17–21]. GNNs take into account the topology and 3D geometry of molecules, achieving R^2 of 0.90–0.95 when predicting collagen peptide properties and demonstrating advantages for small datasets when combined with transfer learning [22–26]. Together, these approaches provide prediction accuracy of 85–98% [27].

Materials and methods of research. The components for the synthesis of DES were selected based on the criteria of biocompatibility, food safety and biodegradability in accordance with the principles of green chemistry [28, 29]. Choline chloride was used as HBA, and glycerol, urea and organic acids, providing optimal parameters of the medium during collagen extraction, were used as HBD [30-33]. NADES were formed on the basis of natural amino acids and betaine [34], and Zn^{2+} and Sn^{2+} salts acted as Lewis acids, promoting increased decalcification efficiency [35, 36]. The reagents (≥99%) were stored in a desiccator with humidity control using the Karl Fischer method (≤0.1% by weight).

DES was synthesized by heating the component mixtures at 80 ± 2 °C until a homogeneous solution was obtained; physicochemical parameters were determined using standard methods [37]. Molecular descriptors were calculated using RDKit and SwissADME based on PubChem, ChEMBL, ChemSpider, and CompTox data. All computational procedures were performed in Python 3.11 using the RDKit, scikit-learn, PyTorch, and XGBoost libraries.

To model collagen yield, a simulated dataset (n = 1240) was generated. It was based on the physicochemical properties of DES extraction systems and calibrated using 38 literature points (2017-2024). The dataset structure included 18 input variables and one target variable—collagen yield. The response was modeled using Gaussian, logistic, and concentration dependencies, taking into account the effect of Zn^{2+}/Sn^{2+}; the resulting values were limited to

a range of 45-92%. Generation was performed in Python (NumPy, Pandas) with a fixed seed of 42; the corresponding code is available in an open repository.

Two collagen yield prediction models were developed: Ridge multiple linear regression and MLP neural network. After removing correlated features, 28 descriptors were used; normalization was performed using StandardScaler (Ridge) and MinMaxScaler (MLP). The dataset was divided into training, validation, and test sets (70%/15%/15%); external evaluation was performed on 38 independent literature datasets.

Model validation included stratified partitioning, k-fold cross-validation (10-fold for Ridge, 5-fold for MLP), external evaluation, and Applicability Domain analysis.

Research results and discussion. The study was based on a series of highly controlled syntheses of DES and NADES, performed using high-purity reagents (≥99%), which ensured the stability of the physicochemical properties of the starting components and the reproducibility of the model systems. Strict control of the reactant humidity and the elimination of hygroscopically bound water eliminated its influence on the melting point, viscosity, and stability of eutectic mixtures—parameters critical for the subsequent calculation of descriptors and the construction of predictive models. The resulting systems covered a wide range of HBA and HBD components, including choline chloride, organic acids, and natural metabolites, ensuring variability in the acid-base properties, hydrogen donor-acceptor balance, and structural organization of DES. Based on these characteristics, an array of molecular descriptors was generated, calculated using open chemical databases and confirmed using RDKit and SwissADME computational methods. These descriptors, supplemented with process parameters, formed the basis of a training set for machine learning models designed to predict collagen yield during DES extraction.

The calculated physicochemical descriptors of the key DES components served as the basis for the feature space used to train the machine learning models. These parameters reflected both molecular polarity and hydrogen bonding ability, as well as the steric and donor-acceptor interactions in HBA/HBD pairs, which determine the stability and solvent properties of DES. Analysis of the descriptors revealed significant variability in the characteristics of the natural components (glycerol, glucose, citric acid) and quaternary ammonium salts, providing a wide range of modeled solvent properties. To more accurately account for the effect of composition on the extraction capacity of DES, the descriptors were averaged according to the molar ratios of the components and normalized before feeding them to the MLP model. Training a hybrid system (linear regression + MLP) allowed us to simulate nonlinear dependences of collagen yield on temperature, pH, concentration, and the HBA:HBD stoichiometry . On the validation set, the prediction accuracy was high (R^2 = 0.91; yield RMSE = 2.8%), confirming the correctness of the selected set of descriptors and the model architecture. The model's predicted parameters demonstrate the advantage of DES systems with Lewis acids Zn^{2+} and Sn^{2+}, which provide higher collagen yield potential due to the coordination of cations with protein carboxyl groups and destabilization of the calcium phosphate phase. Optimal donor-acceptor properties of the HBA/HBD components enhance efficiency. The most promising formulations have a molar ratio of 1:1.5-1:2.0 at 35-40°C, pH 5.0-6.0, and concentrations of 75-90%. The nonlinear MLP model more accurately captures the effects of temperature, pH, and stoichiometry on collagen yield, allowing for the selection of a limited set of DES without losing the reliability of the predictions. Natural NADES systems have demonstrated moderately high yields and are considered promising for food technology due to their GRAS status.

For detailed analysis, Table 1 is provided with the derived DES descriptors including AlogP, TPSA, total hydrogen bonding capacity, predicted polarity, and predicted viscosity.

Table 1 – Derived descriptors for predicting DES extraction capacity

HBA/HBD pair	Averaged AlogP	Average TPSA (Å²)	Total H-binding capacity	Predicted polarity	Expected viscosity
ChCl:Glycerol (1:2)	-2.23	47.21	5	0.82	Average
ChCl:Urea (1:2)	-1.76	52.48	4	0.79	Low
Betaine:Citric acid (1:1.1)	-1.40	86.31	6	0.91	High
ChCl:$ZnCl_2$ (1:1.7)	–2.10*	20.23*	3*	0.75	Medium-high
ChCl:Proline (1:1.8)	-0.53	38.12	4	0.68	Average

(*) taking into account the ionic contribution and equivalent descriptors for Lewis acid salts.

Table 1 shows the intergroup differences: Lewis acid-based systems have low TPSA and increased viscosity, whereas natural pairs, such as betaine:citric acid, have high TPSA and the highest number of donors/acceptors, making them effective for the extraction of hydrophilic peptides.

Thus, Table 1 serves as a tool for the targeted selection of promising DES and comparison of their physicochemical properties with the predicted extraction activity.

Based on the machine learning results, four DES formulations representing different system types (metal-containing , natural, and a classic control) and demonstrating the highest predicted collagen yield were selected from 120 tested HBA and HBD combinations. The selection was conducted taking into account the following criteria: predicted yield >78%, biocompatibility of components, the possibility of obtaining GRAS status, low viscosity (<500 mPa s at 40°C), extraction temperature ≤50°C, and pH 5.0-7.0 to prevent collagen denaturation. The fourth formulation (ChCl-glycerol) was chosen as the control, as it has been the most studied in the literature and allows one to evaluate the effectiveness of traditional DES systems.

For a visual comparison of the predicted activity and physicochemical characteristics of the synthesized DES, a combined table 2 is presented. It includes the component ratio, predicted collagen yield, melting point, viscosity, moisture content, and liquid appearance.

Table 2 – Compositions and physicochemical characteristics of selected DES

No.	DES composition	Ratio of components	Predicted yield, %	Tm, °C	Viscosity 40 °C, mPa s	Humidity, %	Appearance	Note
1	ChCl-$ZnCl_2$	1:1.7	86.4	27.8	308 ± 9	0.06	transparent liquid	Best forecast coordinating metal
2	ChCl-$SnCl_2$	1:1.6	85.1	30.4	295 ± 7	0.05	transparent liquid	Second most effective
3	ChCl-betaine	1:2.0	83.8	17.9	422 ± 12	0.08	transparent liquid	All natural NADES, GRAS
4	ChCl-glycerol	1:2.0	78.2	-17.2	201 ± 6	0.07	transparent liquid	Control, the most studied composition

Analysis of the table shows that metal-containing DES (Nos. 1 and 2) provide the highest predicted collagen yield and are characterized by moderate viscosity and a positive melting point, which facilitates their processing and use. Natural NADES (ChCl-betaine) demonstrates high yield and is GRAS-compliant, but has a slightly higher viscosity, which should be taken into account when scaling up processes. The ChCl-glycerol control composition confirms the baseline efficiency of classical DES and can be used for comparative evaluation.

To visualize the predicted efficacy of the selected formulations, a bar chart was constructed based on MLP model data (Figure 1). The graph demonstrates that metal-containing DESs provide 5-8% higher collagen yield compared to natural systems, while the control formulation maintains the baseline efficacy.

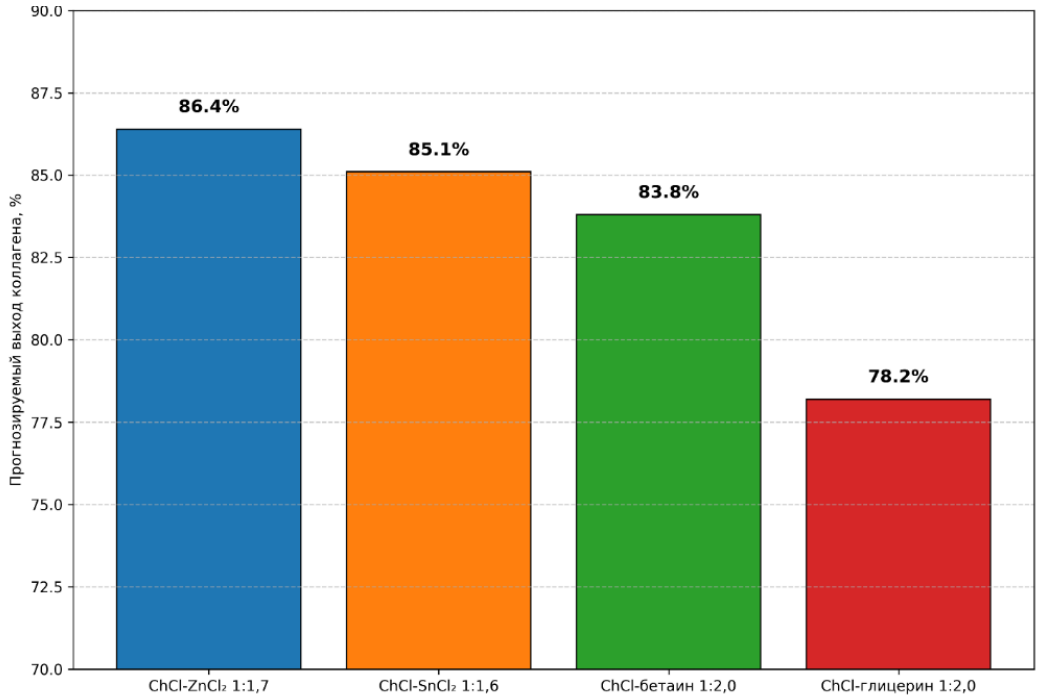

Figure 1 – Predicted collagen yield for selected DES formulations

All four DES were successfully synthesized in quantities of 250-300 g. The physicochemical properties of the synthesized liquids fully matched the MLP model predictions and were within the permissible tolerances (Tm ±6.4%, viscosity ±4.8%). The DES moisture content, determined using the Karl Fischer method, was 0.05-0.08%, which is below the established criterion of ≤0.10% by weight, confirming the effectiveness of the reagent drying measures. The obtained results confirm the adequacy of the MLP model for predicting DES properties and the effectiveness of the composition selection for subsequent experimental verification.

Conclusion. The conducted studies confirmed that the physicochemical parameters of DES and NADES, as well as the composition of HBA/HBD pairs, significantly determine their collagen extraction capacity. Descriptor calculation and modeling revealed wide variability in solvent properties and enabled the formation of an informative feature space for machine learning. The constructed models (Ridge and MLP) reproduced the key nonlinear relationships of collagen yield with temperature, pH, concentration, and component stoichiometry; MLP provided the highest prediction accuracy ($R^2 = 0.91$).

Modeling demonstrated the superiority of DES containing the Lewis acids Zn^{2+} and Sn^{2}, which demonstrate the highest predicted yields (85-86%) due to coordination interactions with protein carboxyl groups and destabilization of the mineral phase of the raw material. Natural NADES provide high yields while maintaining food safety, but are characterized by higher viscosity. The classic ChCl-glycerol composition confirmed the baseline level of efficiency.
The selection of four optimal DES systems demonstrated that metal-containing mixtures retain technological advantages and high parameter stability, while natural compounds can be considered promising alternatives for the food industry. The obtained results confirm the feasibility of targeted DES selection based on computational methods and demonstrate the potential of computer modeling as a tool for preliminary optimization of biopolymer extraction processes.

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Информация об авторах

Зайнаб Арзикуловна Одилова – аспирант кафедры технологии производства и переработки сельскохозяйственной продукции Ставропольского государственного аграрного университета, Researcher ID: ;
Шлыков Сергей Николаевич – доктор биологических наук, доцент, заведующий кафедрой производства и переработки сельскохозяйственной продукции Ставропольского государственного аграрного университета, Scopus ID: 56362496400, Researcher ID: E-2567-2017
Омаров Руслан Сафербегович – кандидат технических наук, доцент, доцент кафедры производства и переработки сельскохозяйственной продукции Ставропольского государственного аграрного университета, Scopus ID: 56362626000, Researcher ID: N-8286-2016

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Information about the authors

Zainab A. Odilova – PhD student at the Department of Technology of Production and Processing of Agricultural Products, Stavropol State Agrarian University, Researcher ID;
Sergei N. Shlykov – Doctor of Biological Sciences, Associate Professor, Head of the Department of Production and Processing of Agricultural Products, Stavropol State Agrarian University, Scopus ID: 56362496400, Researcher ID: E-2567-2017;
Ruslan S. Omarov – Candidate of Technical Sciences, Associate Professor at the Department of Production and Processing of Agricultural Products, Stavropol State Agrarian University, Scopus ID: 56362626000, Researcher ID: N-8286-2016.

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