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Novel Natural Deep Eutectic Solvent (NaDES) Yellow Choline Chloride and Molecular Docking Soybean Extract (*Glycine max*) as Diabetes Drugs Candidate

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***Abstract*—**Natural Deep Eutectic Solvent (NaDES) is an environmentally friendly extraction method to obtain soybean bioactive compounds, focusing on genistein compounds as drug candidates. The use of environmentally friendly extraction solvents could support green extraction to ensure the safety of natural medicinal candidates. HBA (Hydrogen Bonding Acceptor), yellow choline chloride (supplement in animal feed), and HBD (Hydrogen Bonding Donor) lactic acid. A UV-Vis spectrophotometer was used to detect genistein. MoE 2022.02 software was used in the molecular docking simulation, and the docking scoring methods affinity ΔG and GBVI/WSA (induced fit) were used. The PDB ID used was: 5nn8 (alpha glucosidase) and PDB ID: 7vsi (SGLT-2 Inhibitor). The results of genistein were obtained by 92,670 mg (0.9267%) in the 75 ^{0}C, 30 min ultrasonic NaDES extraction in HBD lactic acid. Genistein exhibited an affinity for the 5NN8 (alpha-glucosidase) and 7VSI (SGLT-2 Inhibitor) receptors of -6,230 and -8,768, respectively. These affinity values did not exceed the interaction values of the native ligands acarbose (alpha-glucosidase) and Empagliflozin (SGLT-2 Inhibitor), which were -8,988 and -12,302, respectively. Genistein compounds had the lowest RMSD value of 0.819 at 7vsi (SGLT-2 Inhibitor). These results suggested the possibility of a genistein pathway as a candicate diabetes drug. The NaDES extraction method demonstrated great potential for development into a green action that supported the green extraction process, and genistein was an isoflavone compound that could be a candidate for diabetes drugs.

Keywords*—Glycine max; Molecular docking; Natural Deep Eutectic Solvent (NaDES); UV-Vis spectrophotometer; Yellow Choline Chloride.*

1. INTRODUCTION

In the food, cosmetics, and pharmaceutical industries, Genistein is generally a natural ingredients-based preparation extracted using organic solvents, also known as conventional solvents (methanol, acetone, benzene, chloroform, petroleum ether, and hexane) [1,2]. Conventional are flammable, explosive, poorly biodegradable, and highly toxic [3]. Natural Deep Eutectic Solvent (NaDES) can be an alternative solution to replace conventional solvents with the development of extraction technology. Extraction technology with NADES is potentially environmentally friendly, non-flammable, non-volatile, effective, efficient, and non-toxic [4].

Eutectic solvents are homogeneous liquids whose melting points are lower than the individual melting points of each component in the mixture [5]. NaDES is the development of an analog ion solvent (Ionic Liquid Solvent / ILs), better known as DES (Deep Eutectic Solvent) [6]. This process is carried out by mixing hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD) until a hydrogen ratio is formed with a specific molar ratio [7-9]. The result of the process is then mixed with water in a specific ratio (v/v). NaDES is formed from natural eutectic compounds derived from plant metabolites. Choline chloride (ChCl), citric acid, malic acid, maleic acid, acetic acid, glucose, fructose, sucrose, trehalose, terpenoids, or water have been

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used as NaDES [10-12]. NaDES extraction will be more biodegradable in the environment. Thus, it will be biodegradable and have less toxicity [13]. NaDES can act as a natural solvent (as in natural matrices) [14-15].

NaDES which offers sustainability, biodegradability, flexibility of composition, and extraction of bioactive compounds, highlights its potential to be used as a green solvent for the extraction of phenolic compounds from olive pomace. These studies have shown improvements in the extraction of phenolic compounds compared to conventional solvents (aqueous ethanol and water) [16]. NaDES based on chlorine chloride is selected as the most promising [17]. NaDES is combined with ultrasound and shows that this approach using green NaDES solvent and ultrasound as alternative energy sources could be a good option for designing environmentally friendly extraction methods for the recovery of plant phenolic compounds [16].

The interaction of drugs with receptors via molecular docking studies has emerged as an exemplary method for elucidating biochemical processes. This study can be utilized to assess the potency of the target compound in terms of potential disease pathology conditions [18]. Furthermore, this methodology is more cost-effective than in vitro or in vivo studies and can be incorporated into research designs.

Genistein is a naturally occurring compound and structurally belongs to a class of compounds known as isoflavones. Genistein is found in various soybeans and soy products, including tofu and its products [19]. Genistein, an isoflavone derived from soybeans, has shown significant bioactive effects in drug candidates [20]. This study aims to successfully extract genistein compounds from soybean (*Glycine max*) samples using the NaDES method. The novelty of this study is the use of hydrogen bonding acceptor (HBA) choline chloride yellow, commonly used as a feed supplement, such as animal feed supplements.

2. EXPERIMENTAL SECTION

2.1. Materials

Genistein (98% purity Merck, Germany), yellow choline chloride (supplement in animal feed) and HBD (Hydrogen Bonding Donor) lactic acid, aquadest, Windows 11 and MoE (Molecular Operating Environment) docking software version 2022.02.

2.2. Instrumentation

UV-Vis spectrophotometer (Shimadzu® UV-1800), Kuvet, ultrasonic (BAKU® BK-1200), hotplate stirrer (IKA® C-MAG HS7), glass bottles, beakers (IWAKI® Pyrex), centrifuge (Hettich® EBA 20), Whatman filter paper No.1, stirring rods (5 cm) and laptop Lenovo® IdeaPad 1 14AMN7 (Processor: AMD Ryzen 3 7320U with Radeon Graphics).

2.3. Sampling

Sampling was carried out in Jambi City, Jambi Province. Samples of soybean (*Glycine max*) were obtained from farmers / local farmers in the city of Jambi.

2.4. Preparation of NaDES (Natural Deep Eutectic Solvent)

NaDES used include mixing HBA (Hydrogen Bonding Acceptor) Choline chloride (ChCl) [12,21] and HBD (Hydrogen Bonding Donor) organic acids (lactic acid) [22]. The NaDES components were weighed according to a predetermined ratio (1:1) molar and added aqua demineralization equivalent to the weight of HBA+HBD (100%), then the mixture was heated on a hotplate stirrer at a temperature of 80 ^{0}C, stirrer speed no.3 up to 3 h. The results were filtered to obtain a homogeneous solution [12,17,23-24].

2.5. NaDES Extraction Method Ultrasonic (UAE)

A natural deep eutectic solvent-based ultrasonicated extraction method (NaDES-UAE) was applied for the development of the extraction method. Briefly, a certain amount of natural products was mixed with NaDES solution. The pre-made NaDES solvent (50 mL) was mixed with a sample of crushed soybeans (10 g). The mixed solution was extracted with the help of ultrasonic (UAE) at a temperature of 75 ^{0}C for 30 min. Then, the solution was separated with the help of a centrifuge for 20 min at a speed of 5000 rpm. Then, the sample was ready to be calculated to acquire of genistein that had been successfully extracted. The extract solution was stored at room temperature [10,22,25-26].

2.6. Detection using UV-Vis Spectrophotometers

Detection of genistein compounds from ultrasonic extraction method treatment (UAE) was carried out using a UV-Vis spectrophotometer at the wavelength (259 nm-266 nm) [27-29]. The creation of calibration curves by making 5 concentration variations using the standard compound of genistein. Furthermore, the identification of genistein compounds that were successfully extracted from the treatment designed in the development of the NaDES-based ultrasound extraction method (UAE) was carried out.

2.7. Molecular Docking Genistein (*Glycine max*) as a Candidate for Diabetes-Structure Based Drug Design (SBDD)

The 2022.02 MoE (Molecular Operating Environment) software was used in the molecular docking study [30-32]. The PDB code ID used: 5nn8 (alpha-glucosidase) [33] and 7vsi (SGLT-2 Inhibitor) [34] were obtained from https://www.rcsb.org/. Soybean (*Glycine max*)

contains anthocyanin (cyanidin-3-O-glucoside), phenolicacids (p-hydroxybenzoic, gallic, vanillin, syringic acid), isoflavones (daidzein, glycitein and genistein) [35], All compounds were downloaded from the website https://pubchem.ncbi.nlm.nih.gov/.

All ligands were optimized with forcefield mmff94x gradient 0.00001 kcal/mol/a^2. Receptors were optimized forcefield charmm27, and the coordinates were determined origin × dan radius x. Then, structure preparation > protonate 3D > quick preparation was performed with a gradient of 0.001 kcal/mol/a^2. Native ligand redocking was carried out on each receptor to obtain the docking score method. Docking of the target compound was carried out with placement "triangle matcher" and refinement "induced fit" with 50 poses. The 10 best poses were then analyzed [30-32,36-37].

3. RESULT AND DISCUSSION

NaDES solvent was obtained by mixing HBA (Hydrogen Bonding Acceptor), yellow choline chloride (supplement in animal feed), and HBD (Hydrogen Bonding Donor), lactic acid in a ratio of (1:1) molar and adding aqua distillate 100% of the weight of the solvent mixture. In this study, yellow choline chloride (supplement in animal feed) was used as HBA in NaDES solvent. Other studies used standard research choline chloride that was white or clear [10-12]. Furthermore, the development of the extraction method was carried out with ultrasonic treatment at a temperature of 75 ^{0}C for 30 min, then the results were separated by centrifuges and ready to calculate genistein compounds contained in the NaDES extraction results from soybeans (*Glycine max*) (**Fig. 1**). The principles of NaDES extraction include the use of a simple and rapid breakthrough extraction method, the application of temperatures below 100 ^{0}C, and the completion of the extraction process in less than 1 h. This method is more efficient than conventional extraction techniques [2,5,10,17,38-43].

The linear regression equation "y=0.074x+0.158" was obtained with the order of concentrations of 5; 10; 15; 20; and 25 ppm, respectively. An absorbance of 2.585 was obtained at the genistein compound from the NaDES extraction of soybeans (*Glycine max*) by dilution. The genistein compound successfully obtained was 92.670 mg from 10 g of soybeans. The compound yield value was 0.9267%.

(a) (b)

Fig. 1. (a) NaDES solvent manufacturing process (b) Ultrasonic extraction of soybean

Genistein compounds (**Fig. 2**) are the targeted compounds in this series of studies. Furthermore, this compound was studied for its interaction with receptors that have an impact on the potential for reducing blood sugar levels with a working pathway as alpha-glucosidase PBD ID: 5nn8 [33] and SGLT-2 Inhibitor PDB ID: 7vsi [34]. The docking score methods used were affinity and GBVA/WSA. The method obtained scores of 100% and 67% on GDP ID: 5NN8 and GDP ID: 7VSI, respectively. The sequences of target amino acids at the PBD alpha glucosidase receptor ID: 5nn8 were ASP 282, ASP 404, ASP 518, ASP 616, MET 519, ARG 600, and HIS 674. The sequences of target amino acids on the SGLT-2 inhibitor PBD ID: 7vsi receptor were ASN 75, GLU 99, GLN 457, HIS 80, LYS 321, and THR 87.

A total of 8 compounds [35] were docked on each PDB code. The best value is not found in the genistein compounds, which are in the group of isoflavones, but in the group of anthocyanins. However, the genistein compounds can still show interactions with target receptors. A good value from the results of docking genistein compounds with PBD ID: 7vsi as an SGLT-2 inhibitor, genistein showed the best RMSD value (**Table 1**) of all existing compounds.

Table 1. S value (ΔG) and RMSD

No	Group	Compound Name	5nn8 (alfa glucosidase)		7vsi (SGLT-2 Inhibitor)	
			S (ΔG)	RMSD	S (ΔG)	RMSD
1	Anthocyanin	cyanidin-3-O-glucoside	-8.909	1.703	-11.992	1.231
2	Isoflavones	daidzein	-5.872	1.846	-7.968	0.824
3		genistein	-6.230	1.214	-8.768	0.819
4		glycitein	-6.804	0.997	-8.598	1.519
5	Phenolic acids	p-hydroxybenzoic	-4.865	1.347	-5.718	1.261
6		gallic acid	-5.162	0.920	-6.175	0.870
7		vanillin	-5.951	1.224	-6.303	1.379
8		syringic acid	-6.688	1.155	-7.755	1.649
9	Native Ligand	acarbose (alfa glucosidase)	-8.988	1.043	-	-
10		empagliflozin (SGLT-2 Inhibitor)	-	-	-12.302	1.556

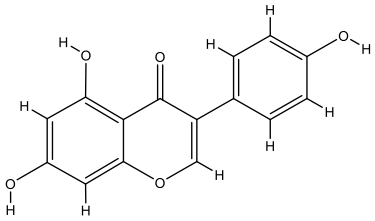

Fig. 2. Chemical structure of genistein

The RMSD value definitively explains the possibility of occurrences in the computational state of docking ligand and receptor interactions. When the RMSD value is below 2, the state can occur in reality. However, an RMSD value above 2 results is an invalid result [44-45]. This shows the reliability of genistein compounds against SGLT-2 inhibitor receptors [37,46-51].

This result is a molecular docking simulation study that can be used as supporting data for other supporting tests, such as in vitro studies and in vivo studies. The stability of the target compound to bind to amino acid receptors (**Fig. 3**) is also a further concern known as molecular dynamic studies.

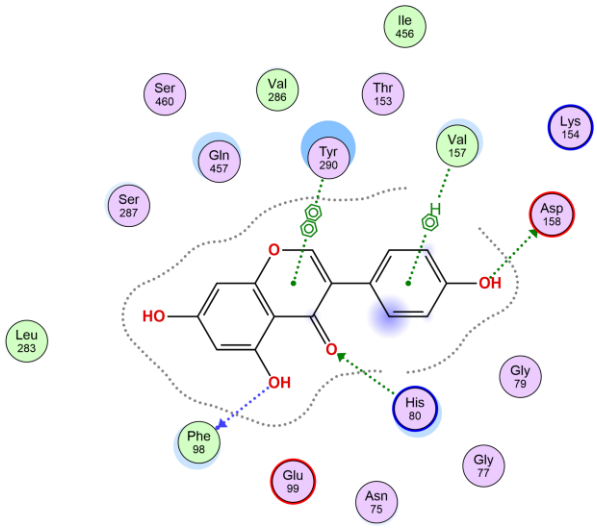

Fig. 4. Ligand interaction of genistein compound on SGLT-2 Inhibitor (PDB ID: 7vsi)

CONCLUSION

This study successfully demonstrated the extraction of soybean with genistein compound detection using yellow choline chloride as a hydrogen bonding acceptor (HBA) in an ultrasonic NaDES treatment method. The in silico analysis results demonstrated the potential of soybean extraction as a candidate for diabetes treatment, specifically as an alpha-glucosidase and SGLT-2 inhibitor.

SUPPORTING INFORMATION

There is no supporting information in this paper. The data supporting this research's findings are available on request from the corresponding author (RY).

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CONFLICT OF INTEREST

There was no conflict of interest in this study

AUTHOR CONTRIBUTIONS

The study was designed by RY, SP, and SHA. The NaDES preparation was conducted by PE, BA, and ASA. RY and LA performed the molecular docking analysis. RY, SP, and SHA wrote and revised the manuscript. All authors agreed to the final version of this manuscript.

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