



Alcoholic Extracts of *Eleusine indica* as Alternative Diuretic Regimens: A Computational Based Investigation



Tapan Kumar Sahu^{1*}, Nityananda Sahoo¹, Gurudutta Pattnaik¹, Himansu Bhusan Samal¹,
Amulyaratna Behera¹ and Biswakanth Kar²

¹School of Pharmacy and Life Sciences, Centurion University of Technology and Management, Bhubaneswar-752050, India; ²School of Pharmaceutical Sciences, Siksha O Anusandhan Deemed to be University, Bhubaneswar-751003, India

E-mail/Orcid Id:

TKS, tapangouri1981@gmail.com, <https://orcid.org/0000-0003-0877-3190>; NS, nsahoo_scps05@yahoo.co.in, <https://orcid.org/0000-0001-8878-9621>;
GP, gurudutta.patnaik@gmail.com, <https://orcid.org/0000-0002-3532-721X>; HBS, hbsamal@gmail.com, <https://orcid.org/0000-0002-0803-6847>;
AB, amulya.smp@gmail.com, <https://orcid.org/0000-0003-1779-4364>; BK, biswakanth@gmail.com, <https://orcid.org/0000-0002-4530-1005>

Article History:

Received: 20th Dec., 2023

Accepted: 24th Febr., 2024

Published: 30th Mar., 2024

Keywords:

Diuretics, *Eleusine indica* (L) Gaertn, Natural diuretics, Gas Chromatography-Mass Spectrometry, Molecular docking, Toxicity prediction

How to cite this Article:

Tapan Kumar Sahu, Nityananda Sahoo, Gurudutta Pattnaik, Himansu Bhusan Samal, Amulyaratna Behera and Biswakanth Kar (2024). Alcoholic Extracts of *Eleusine indica* as Alternative Diuretic Regimens: A Computational Based Investigation. *International Journal of Experimental Research and Review*, 37(Spl.), 11-21.

DOI:

<https://doi.org/10.52756/ijerr.2024.v37spl.002>

Abstract: Diuretics are widely used in current clinical practice to increase urine production and excrete electrolytes, particularly sodium and chloride ions, without affecting the absorption of protein, vitamins, carbohydrates, or amino acids. From the time of mercury chloride and organomercurials in ancient times to now (with sulphonamides, thiazides, and furosemide), a lot has changed in the field of diuretics. However, long-term use of such synthetic diuretic agents in clinical practice produces several adverse effects, such as blurred vision, loss of appetite, stomach upset, carcinomas, headaches, phototoxic impact, weakness, etc., as has been observed from recent investigations. Natural regimens can serve as potential alternatives to using nontoxic diuretic agents. Based on long-term ethnomedicinal and biological activity records, we have explored the diuretic effects of the widely known perennial herb in Pacific Islands regions and a weed in agricultural fields, *Eleusine indica* (L) Gaertn phytoconstituents, on a computation platform. Therefore, we conducted a bio-assay-guided crude extraction using ethanol, followed by further gas chromatography-mass spectrometry (GC-MS) analyses of the extracted crude extracts. Further selected nine constituents (EI_1 to EI_9) carried out the diuretic potency against three putative target enzymes (ACE, KCNJ1, and SLC12A1) along with three standard drugs (VU590, TSM, and FSM) through molecular docking studies using AutoDock 4.2 software. We also predict physicochemical profiles, or Lipinski Rule of Five profiles, toxicity, and pharmacokinetics using various bioinformatics and cheminformatics tools. Based on the overall investigation, it was revealed that EI_6 [Z, Z-6,28-Heptatriacontadien-2-one] was the most potential, nontoxic, and drug-able candidate. In summary, advanced computational tools play a crucial role in selecting potential preclinical candidates within limited resources to accelerate the current drug discovery process.

Introduction

Since the 16th century, diuretics have been widely recommended for the treatment of hypertension, liver

cirrhosis, congestive heart failure, edema, water pinioning, etc. (Roush et al., 2014; Blowey, 2016; Scheen, 2018; Arumugham et al., 2023). In general terms, a diuretic, also



known as a water tablet, is any substance that promotes diuresis, which means increasing the excretion rate of water or urine from the body via the kidneys, to reduce several of the above disorders (Kehrenberg et al., 2022; Arumugham et al., 2023). During the ancient era, patients treated with syphilis medications used mercurous chloride and organomercurials, such as diuretics, to reduce overdose by increasing urine output (Cheng et al., 2017; Titko et al., 2020). In medical terms, diuretics are substances like acetazolamide that make the urine more alkaline and help increase excretion of overdoses or posing substances from the human body (Arumugham et al., 2023). Sulphanilamide, an antibacterial agent, gained widespread use as an alternative diuretic in the 20th century by inhibiting carbonic anhydrase and boosting urinary salt and potassium excretion rates. Subsequently, researchers used this carbonic anhydrase inhibitor to manage heart failure and hypertension, but they also noticed increased side effects from metabolic acidosis. Furthermore, a medical chemistry approach converted sulphanilamide to chlorothiazide (Diuril) by modifying the sulfamoyl and amino groups, resulting in improved saluretic effects with minimal or no increase in urinary bicarbonate excretion (Cheng et al., 2017; Zhao and Cao, 2022). In 1962, researchers transformed the sulphonamide moiety into furosemide, which emerged as the most potent diuretic in clinical practice to date (Sica et al., 2011; Escudero et al., 2022). However, several side effects such as blurred vision, loss of appetite, itching, stomach upset, headache, and weakness necessitate the need for natural-derived potential agents to replace these synthetic candidates.

Simultaneously, natural regimens are always considered alternative or complementary agents as food and nutraceutical supplements, along with multi-potential therapeutic agents (Li and Vederas, 2009; Swain and Padhy, 2015; Chopra and Dhingra, 2021; Sahoo et al., 2022a; Anbalagan et al., 2023; Bhosale et al., 2023). From ancient times to date, nearly 80–85% of people have been interested in natural remedies or natural-derived products to avoid the side effects of synthetic drugs, and we all know the cost (Swain and Padhy, 2015; Dias et al., 2012; Atanasov et al., 2021). For example, dandelion, coffee, tea, horsetail, ginger, asparagus, cucumber, celery, parsley, etc. are considered natural diuretics with a lot of additional benefits like immune-stimulant, anti-inflammatory, and antioxidant potency for the removal of poisonous substances from the body (Maughan and Griffin, 2003; Wright et al., 2007; Liu et al., 2015). Nonetheless, more scientific research is also going on to prove the ancient ethnopharmacology for use in mainstream applications. In

addition, in Asian and African regions, massive amounts of aromatic medical plants have been identified, but most medical applications are still unknown or limited, with some regional ethnomedicinal use without proper scientific investigations. Currently, the drug screening procedure has been revolutionized through high-through instrumental and artificial intelligence-based screening, which is more beneficial to explore the potential therapeutic potency of each plant species along with derived secondary metabolites (Swain and Padhy, 2016; Sahoo et al., 2021; Sahoo et al., 2022a and 2022b; Swain et al., 2022a).

In this perspective, *Eleusine indica* (L) Gaertn (vernacular/local name: Bena ghasa), belonging to the Poaceae family, is a perennial herb in Pacific Islands regions and a weed in agricultural fields (Ceasar and Ignacimuthu, 2015; Ong et al., 2027). Indeed, this weed cum herb is widely cultivated and used as a vegetable and fruit in Malaysia (locally known as rumput sambau) and other tropical and subtropical regions of the globe. The positive part of the weed has lots of traditional medicinal uses, including leaves used for microbial infection, muscle pain, cough, scorpion poisoning, hastening the delivery of placentas for women after the birth of a baby, and relieving pain during vaginal bleeding (Dorce et al., 2017; Sukor et al., 2023). The root extracts are widely used for the treatment of asthma; whole plant extracts for urinary infection; areal plant extracts with rice are also used for flu viral infection; and root extracts with *Capsicum* sp. (Solanaceae) for piles. From several recent scientific investigations, exhibited antioxidant, antidiabetic, antibacterial, anticonvulsant, anti-inflammatory, hepatoprotective, antipyretic, analgesic, etc., activities (Dorce et al., 2017; Ogbole et al., 2027; Puah et al., 2022). In addition, a few active phytochemicals, like hexanoic acid, sioschaftoside, sitosterol, stigasterol, isovitexin, vitexin, coumatin, etc., have been identified through column-chromatography, gas chromatography-mass spectrometry (GCMS), and liquid chromatography-mass spectrometry (LCMS) approaches (Ong et al., 2016; Sukor et al., 2023). From an extensive literature search with recorded potential biological activity, we have collected these *E. indica* from local areas and prepared ethanoic extracts, followed by a bioassay-guided extraction method for further GCMS study. Using computer programs, we also did molecular docking with three possible target enzymes and some known phytoconstituents to test how well they work as diuretics. In addition, it analyzes the toxicity, drug-ability, and pharmacokinetic profiles of selected compounds using various bioinformatics and cheminformatics tools systematically.

Materials and Methods

For crude extraction, we obtained synthetic-grade reagents, solvents, plasticware, and glassware from SRL, Tarsons Pvt. Ltd., Mumbai, India, through local vendors. The entire computational work was analysed on a Linux-Ubuntu 16.04 LTS workstation with several cheminformatics software packages (Swain et al., 2022a; Sahoo et al., 2022b).

Bio-assay guided extraction and GC-MS analysis

We collected the *E. indica* herbs from the peripheral agricultural field in Ganjam district, Odisha. The plant was identified and authenticated by taxonomist Dr. A. Leelaveni, Asst. Professor, PG Department of Botany, Berhampur University. After washing the whole plant with fresh water, we rinsed it in distilled water and shade-dried it at room temperature for 20–30 days. After being crushed using a laboratory blender and preserved at airtight concentrations to avoid contact with moisture and any outside exposures, the dry powder samples (200g) were individually extracted first with n-hexane to remove fatty materials and later with ethanol solvent (300 mL) in the Soxhlet apparatus for 2 days. Next, we filtered the ethanol extracts using Whatman No. 1 filter paper, resulting in the collection of approximately 2 grams of powder. We will conduct further GC-MS studies and analyse the compounds using the NIST library for additional computational study (Konappa et al., 2020; Ralte et al., 2022). We performed the analysis on a Perkin Elmer Turbo Mass Spectrophotometer (USA) model Claurus 590 Gas Chromatography/Claurus SQ 8S Mass Spectrometer (equipped with a liquid auto sampler). The total run time was 35 minutes. We analysed GC-MS using electron impact ionization at 70 eV and analysed the data using a total ion chromatogram.

Target protein and ligand structure preparation for molecular docking study

Based on high-intensity GC-MS spectra, we have selected nine constituents (EI_1 to EI_9) as ligands for the docking study, and those ligand structures were retrieved from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) by recording their unique ids. Further, based on thiazides, furosemide mode of action, including a literature search, selected three putative enzymes, namely angiotensin-converting enzyme (ACE), potassium inwardly rectifying channel subfamily J member 1 (KCNJ1), and sodium channel epithelial 1 subunit alpha (SLC12A1), for docking study (Denton et al., 2013; Thorn et al., 2013; Garcia and Kaczorowski, 2014; Kehrenberg and Bachmann, 2022) (Figure 1). Accordingly, three chemical structures of the control drugs (VU590, furosemide, or FSM, and torasemide, or TSM)

were also retrieved from PubChem for use in the docking study. Similarly, the 3D X-ray crystallographic protein structures were retrieved from the protein data bank (<https://www.rcsb.org/>). Among the three target enzymes, ACE (PDB ID: 6WTH) and SLC12A1 (7E1Z) were directly retrieved from the PDB, and due to the unavailability of KCNJ1 in the PDB, we generated the theoretical model through a homology modeling approach with a suitable template structure identified through Blastp, and the structure was generated using Swiss Model tools. All ligands, including control drugs, undergo structural optimization and are saved in the.pdb file format. Similarly, all heteroatoms, ligands, and additional chains were removed from the retrieval protein structure, and structural validation was performed for theoretical KCNJ1 and saved in the.pdb file format used in the docking study. The molecular docking study was performed using the PyRx 0.8 platform and AutoDock 4.2 software. The virtual screening was repeated twice to get the most errorless ligand-binding energy or docking scores (kcal/mol.). Based on the docking score (kcal/mol.), the potent phytoconstituents were again docked manually in AutoDock to confirm the ligand's crystallographic binding mode and appropriate docking score through 3-D and two-dimensional (2-D) molecular interactions with targets using the software BIOVIA-DSV-2019 (Swain et al., 2022a; Sahoo et al., 2022b).

Physicochemical or Lipinski rule of five profile

Currently, advanced computational tools are able to predict various drug-likeness-relevant profiles of candidates according to their chemical structure, leading to the selection of potential leads at the primary stage with higher clinical success. So, to see if our compounds would make a good active oral drug candidate, we predicted their physicochemical or Lipinski rule of five (RO5) profiles. We recorded EI_1 to EI_9 along with standard drug profiles individually using the SwissADME tool with reference to the PubChem database (Sahoo et al., 2022b).

Toxicity profile prediction

After biological activity, the toxicity profile is another crucial parameter to select non-toxic candidates for further study, and most of the candidates were eliminated from clinical trials due to higher toxicity even after displaying higher therapeutic activity. Similarly, the possible toxicity profiles, including hepatotoxicity (HT), carcinogenicity (CG), immunotoxicity (IT), mutagenicity (MG), cytotoxicity (CT), toxicity class (TC), and lethal dose (LD₅₀ mg/kg) of EI_1 to EI_9 and three standard drugs, were predicted using the ProTox tool

(http://tox.charite.de/protox_II/) (Sahoo et al., 2021 and Swain et al., 2022b).

was used to predict the ADME/T profiles of all phytoconstituents (EI_1 to EI_9), including blood brain

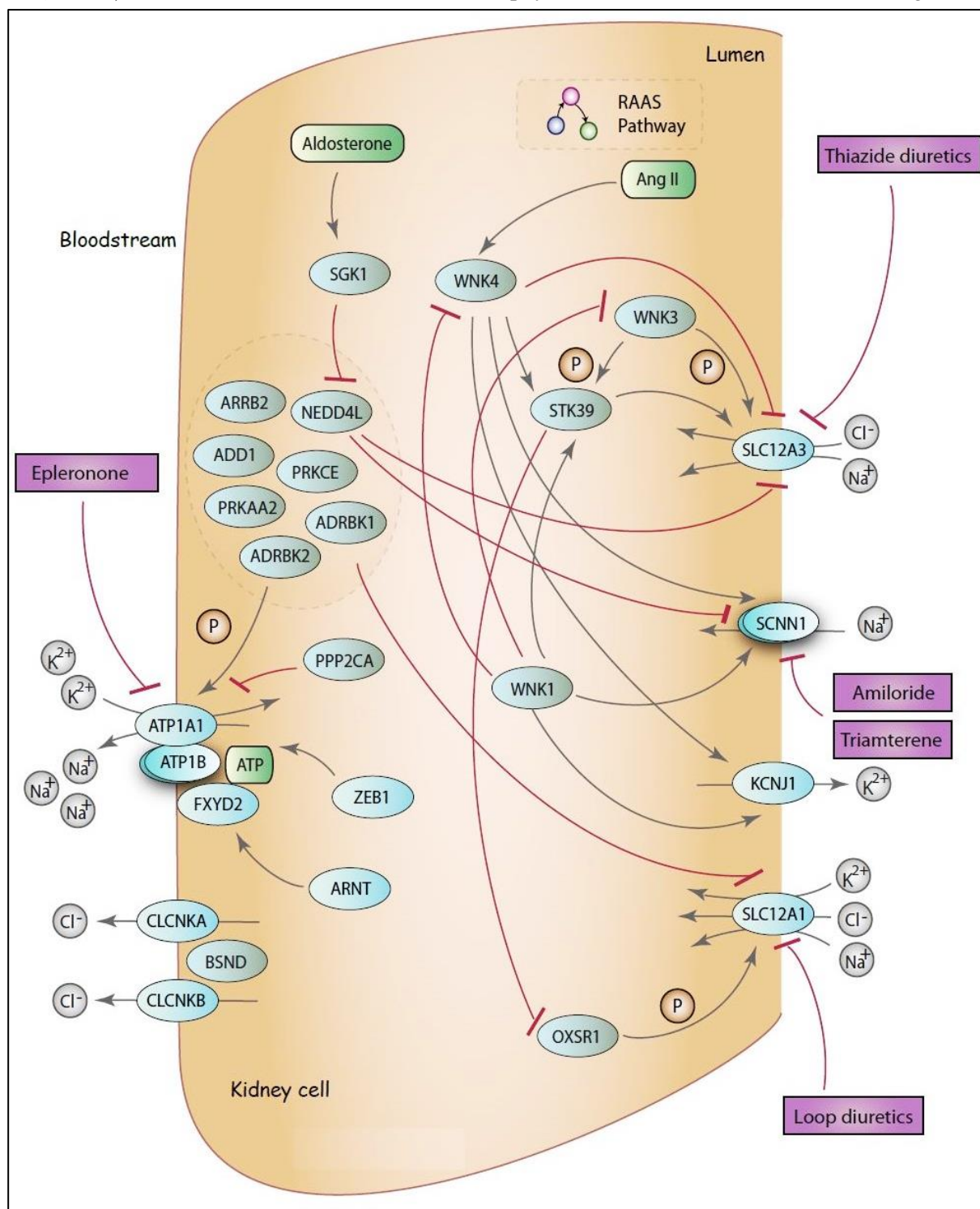


Figure 1. Schematic presentation of diuretic-associated pathways and their putative target enzymes to control the disorder. The above graphical presentation was extracted from the PharmaKGF (<https://www.pharmkgb.org/>) database.

Pharmacokinetics prediction

Pharmacokinetics, also known as ADME/T profiles, is another important factor in choosing possible lead candidates. It examines the metabolization of drugs after oral administration and assists in determining the safest dose for any pharmacological study. The SwissADME tool

barrier (BBB), gastrointestinal absorption (GI-abs.), and P-glycoprotein substrate interactions with cytochrome P450 enzyme interactions (CYP1A2-I, CYP2C19-I, CYP2C9-I, CYP2D6-I, and CYP3A4-I), as well as bioavailability profiles. (Sahoo et al., 2022b and Swain et al., 2022b).

Results and Discussion

GC-MS analyses and phytochemical identification

The quantitative phytochemical study via GC-MS analyses on *E. indica* methanol extracts revealed the presence of a variety of phytoconstituents in different molecular weights (Figure S1). From a large set of constituents, we have selected nine constituents (EI_1 to EI_9) according to higher volume GCMS peaks. Further, selected compounds, EI_1 (2-Trimethylsiloxy-6-hexadecenoic acid, methyl ester), EI_2 (2,5-Diisopropyl-1,3,2-dithiaborinane), EI_3 (2-Methyl-5-t-butyl-1,3-oxathiane), EI_4 ((R)-(-)-(Z)-14-Methyl-8-hexadecen-1-ol), EI_5 (11,14-Eicosadienoic acid, methyl ester), EI_6 (Z,Z-6,28-Heptatriacontadien-2-one), EI_7 (2,6-Diamino-4-hexynoic acid), EI_8 (5-Hydroxymethylfurfural), and EI_9 (7-Ethyl-2-undecen-6-one) were verified and retrieved from PubChem with individual IDs, molecular formula, and other relevant information's of individual compounds (Table 1).

Table 1. Selected nine phytochemicals (EI_1 to EI_9) from GC-MS spectra of *Eleusine indica* alcoholic extracts with their molecular formula, molecular weight, reference PubChem CIDs as physicochemical profiles of phytochemicals.

Sl. No.	Phyto-chemical	PubChem _CID	MF	MW	XLogP (≤ 5)	HBD (≤ 5)	HBA (≤ 10)	tPSA (≤ 142)	MR (≤ 130)	RB (≤ 3)
1.	EI_1	91696378	C ₂₀ H ₄₀ O ₃ Si	356.6	7.92	0	3	35.5	108.02	16
2.	EI_2	557896	C ₉ H ₁₉ BS ₂	202.2	4.52	0	2	50.6	65.26	2
3.	EI_3	552319	C ₉ H ₁₈ OS	174.31	3	0	2	34.5	51.68	1
4.	EI_4	12487634	C ₁₇ H ₃₄ O	254.5	6.6	1	1	20.23	84.52	13
5.	EI_5	5365566	C ₂₁ H ₃₈ O ₂	322.5	8	0	2	26.30	103.40	17
6.	EI_6	5365964	C ₃₇ H ₇₀ O	530.9	16.2	0	1	17.1	179.23	32
7.	EI_7	549875	C ₆ H ₁₀ N ₂ O ₂	142.16	3.8	3	4	89.3	36.30	2
8.	EI_8	237332	C ₆ H ₆ O ₃	126.11	0.6	1	3	50.4	30.22	2
9.	EI_9	91694770	C ₁₃ H ₂₄ O	196.33	4.1	0	1	17.1	17.07	8

Note: MF, molecular formula; MW, molecular weight (g/mol.); H-BD, h-bond donor; H-BA, h-bond acceptor; tPSA, topological polar surface area; MR, molar refractivity; RB, rotatable bonds; EI_1 (2-Trimethylsiloxy-6-hexadecenoic acid, methyl ester), EI_2 (2,5-Diisopropyl-1,3,2-dithiaborinane), EI_3 (2-Methyl-5-t-butyl-1,3-oxathiane), EI_4 ((R)-(-)-(Z)-14-Methyl-8-hexadecen-1-ol), EI_5 (11,14-Eicosadienoic acid, methyl ester), EI_6 (Z,Z-6,28-Heptatriacontadien-2-one), EI_7 (2,6-Diamino-4-hexynoic acid), EI_8 (5-Hydroxymethylfurfural), and EI_9 (7-Ethyl-2-undecen-6-one).

Molecular docking study

The molecular docking score of individual docking scores of selected nine constituents (EI_1 to EI_9) along with three standard drugs (VU590, TSM, and FSM) against three target enzymes (ACE, KCNJ1, and SLC12A1) was recorded (Table 2). According to Auto Dock software, a lower docking score (kcal/mol.) represented higher binding efficacy. For KCNJ1 structure prediction, we have selected a suitable template protein

(PDB ID: 3SPH) with 81% query coverage and 49.84 identity from the Blastp tool. The Ramachandran plot validated the newly generated protein structure of KCNJ1, with 97.08% of regions in favorable regions, indicating its stability and reliability for molecular docking studies (Figure S2). Based on the docking score (kcal/mol.), phytoconstituents exhibited their docking score within -4 to -8 kcal/mol., whereas standard drugs showed a comparatively higher docking score within -4 to -9 against three target enzymes (Table 2). From the individual target enzyme, EI_6 showed a higher docking score of -8.0 kcal/mol., compared to the standard VU590 shower of -9.0 kcal/mol. Similarly, the same EI_6 (-6.6. and -6.63 kcal/mol.) was also the leading candidate against the KCNJ1 and SLC12A1 target enzymes, respectively. When compared to standard, ACE, and SLC12A1 cases, standard had higher docking scores (-9.0 by VU590 and -7.4 by FSM) than EI_6. However, when compared to KCNJ1, the

standard drug TSM (-6.4) had a lower docking score (-6.6 kcal/mol., by EI_6). Overall, based on the recorded docking score, all nine constituents comparatively showed a higher docking score against ACE, and individually, EI_6 (Z, Z-6, 28-Heptatriacontadien-2-one) was the lead candidate among them. The study of the protein-ligand interaction also showed that EI_6 is strongly connected with all target enzymes through H-bonds, van der Wall bonds, and pi-pi alkyl bonds (Figure 2).

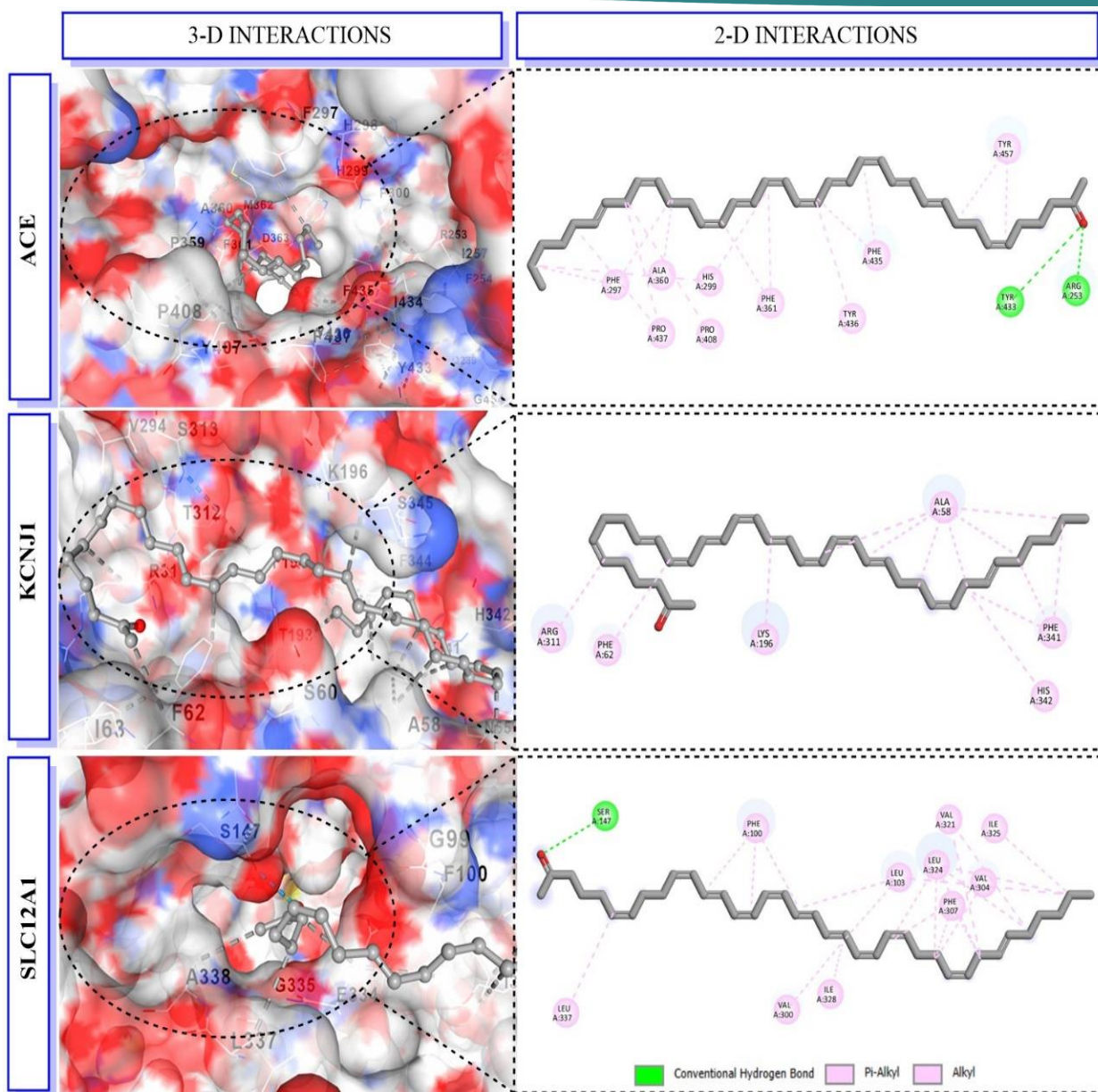


Figure 2. Protein-ligand interaction of EI_6 against selected three target enzymes in 3D and 2D views during the docking study. We generated and represented the images using BIOVIA-Discovery Studio Visualizer and ChemDraw software.

The synergistic nature of all compounds in the form of crude extract is expected to have more potential and requires further experimental study with crude extracts as well as with leading EI_6 for more confirmation.

Physicochemical or Lipinski rule of five profile

Recorded physicochemical profiles or standardized RO5 revealed that all phytoconstituents (EI_1 to EI_9) with standard drugs displayed ideal profiles except the XlogP value (Table 1). Briefly, RO5 hypothesized that if a chemical bearing the molecule weight ≥ 500 g/mol., the water-octanol of the partition coefficient (LogP) ≥ 5 , the number of hydrogen donor (H-bd) groups ≥ 5 , the number of hydrogen acceptor (H-ba) groups ≥ 10 with topological polar surface area (tPSA) within ≥ 140 Å, then the candidate could be considered an active oral candidate and

might have a higher chance of clinical success. Therefore, identified constituents that followed the RO5 except the ideal XlogP value indicated that they could be considered active oral candidates with any nanocarrier for further experimental success. In other hand, recorded toxicity profiles indicated that phytoconstituents are highly safe with a non-toxin profile (Table 2). Among all, EI_8 with the standard drug VU590 showed a higher risk of mutagenicity with EI_3, a class-III toxicity chemical (higher in toxicity class and higher in safety at higher doses). The higher LD₅₀ (mg/kg) indicated that the candidate could be used at a higher concentration without any toxicity risk. The potential EI_6 proved itself as a potential non-toxic profile, with higher LD₅₀ values (15000 mg/kg) and a higher toxicity class VI to consider as a lead candidate (Figure 3).

Pharmacokinetics and overall drug likeness prediction

displayed high GI-abs. similar to standard drug. Similarly, except EI_2, EI_3, EI_4 and EI_9, rest of constituents

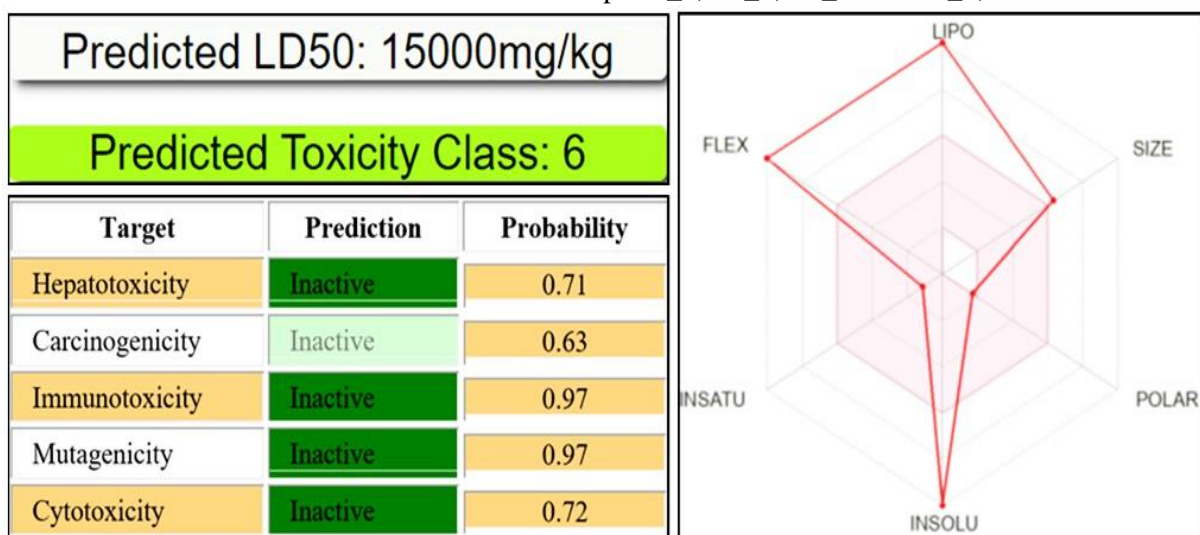


Figure 3. Graphical illustration of toxicity and physicochemical profile prediction of EI_6 from ProTox and SwissADME tools.

Table 2. Recorded potency in form of molecular docking against three putative diuretics associated target enzymes with predicted five various toxicity profiles, toxicity class and LD₅₀ (kg/mg.) profiles of nine EI_1 to EI_9 of *Eleusine indica* with used standard drugs.

Phyto- & Std.	Docking score (Kcal/mol.)			Predicted five types of toxicity profiles, overall toxicity class							
	ACE	KCNJ1	SLC12A1	HT	CG	IT	MG	CT	TC	LD ₅₀	BA
EI_1	-5.2	-5.3	-5.1	IA(0.76)	IA(0.66)	IA(0.86)	IA(0.79)	IA(0.71)	IV	2000	0.55
EI_2	-6.4	-5.8	-6.0	IA(0.77)	IA(0.78)	IA(0.99)	IA(0.64)	IA(0.82)	IV	500	0.55
EI_3	-5.3	-4.5	-4.8	IA(0.82)	IA(0.57)	IA(0.99)	IA(0.67)	IA(0.87)	III	210	0.55
EI_4	-5.6	-5.2	-5.2	IA(0.84)	IA(0.56)	IA(0.95)	IA(0.96)	IA(0.83)	VI	5600	0.55
EI_5	-5.4	-5.2	-6.0	IA(0.59)	IA(0.56)	IA(0.86)	IA(0.98)	IA(0.70)	VI	20000	0.55
EI_6	-8.0	-6.6	-6.3	IA(0.71)	IA(0.63)	IA(0.97)	IA(0.97)	IA(0.72)	VI	15000	0.17
EI_7	-4.8	-4.5	-5.0	IA(0.92)	IA(0.67)	IA(0.99)	IA(0.54)	IA(0.65)	IV	365	0.55
EI_8	-5.2	-4.5	-4.7	IA(0.80)	IA(0.52)	IA(0.99)	IA(0.73)	IA(0.78)	V	2500	0.55
EI_9	-5.8	-4.9	-6.2	IA(0.70)	IA(0.65)	IA(0.98)	IA(0.95)	IA(0.72)	V	5000	0.55
VU590*	-9.0	NA	NA	IA(0.76)	IA(0.58)	IA(0.97)	IA(0.89)	IA(0.59)	IV	470	0.55
TSM*	NA	-6.4	NA	IA(0.80)	IA(0.60)	IA(0.84)	IA(0.95)	IA(0.73)	V	5000	0.55
FSM*	NA	NA	-7.4	IA(0.51)	IA(0.62)	IA(0.99)	IA(0.89)	IA(0.59)	IV	2000	0.56

Note: * Std., standard; NA, not applicable; FSM, furosemide; TSM, torasemide used against individual target; HT, hepatotoxicity; CG, carcinogenicity; IT, immunotoxicity; MG, mutagenicity; CT, cytotoxicity; TC, toxicity class; BA, bioavailability; LD₅₀, fifty percent lethal dose (mg/kg); ACE, angiotensin-converting enzyme; KCNJ1, potassium inwardly rectifying channel subfamily J member 1; SLC12A1, sodium channel epithelial 1 subunit alpha.

The predicted pharmacokinetics profiles were recorded in Table S1. From records, except EI_5 and EI_6 all are showed no BBB permits like standard drugs. In addition, from each profiles some phytoconstituents showed some

deviated profiles along with three standard drugs, but EI_6 showed ideal pharmacokinetics profiles with similar to standard drugs (Table S1). However, EI_6 showed lower bioavailability profiles (0.17) due to higher Xlop value (16.2) than rest of compounds including standard drugs (0.55). In overall analyses, EI_6 could be consider as lead candidate among all identified phytochemical from *E. indica*.

Current clinical practice widely uses diuretic agents to primarily increase urine production and excrete electrolytes, particularly sodium and chloride ions, without affecting the absorption of protein, vitamins, carbohydrates, or amino acids (Cheng et al., 2017; Arumugham and Shahin, 2023). In addition, it is applicable to adjuvant therapies for cardiac failure, hypercalcemia, cataracts, prime hyperaldosterism, etc. (Blowey et al., 2016; Cheng et al., 2017; Escudero et al., 2022). However, long-term use in clinical practice of such agents induces carcinomas, has a phototoxic impact, and has several adverse effects on the body (Sica et al., 2004; Gupta et al., 2022). Therefore, researchers focus on exploring potential regimens, especially natural regimens, and their molecular mechanisms. Although we use cucumber, ginger, coffee, and tea as diuretic agents, we are unable to explore the most potential candidates and their doses for mainstream applications. The current study is also a cost-effective approach to exploring the diuretic potency of identified phytoconstituents of *E. indica* through various computational approaches. The overall approach showed that the plant extracts might have ethnomedicinal effects because they contained such active phytoconstituents. This made researchers want to focus on individual compounds.

In the current drug discovery module, molecular docking is the most widely used bioinformatics tool in academia and the pharmaceutical sector, where natural resources are the most alternative drug source and choice for most research work to use on a complementary, alternative, and repurposing basis (Swain et al., 2022a and 2022b; Sahoo et al., 2022a and 2022b). Researchers have implemented several similar types of computational-based approaches to assess the diuretic potency of natural products derived from different natural sources at a preliminary level, prior to expensive experimental studies (Islam et al., 2022; Yang et al., 2022; Yu et al., 2024). Generally, various constituents in crude extracts synergistically show multiple biological activities, but not all compounds are responsible for all diseases. Therefore, the identification of such potent compounds to use against a specific disease is essential to modern drug discovery. However, as a computational-based approach is coding

and programming-dependent, we need proper hypotheses and expertise to get more reliable results. In addition, a computational-based study cannot recommend the candidate for human consumption, but it is a cost-effective, robust platform to explore the potency, predict the toxicity, and study the pharmacokinetics, which guided a systematic way for more clinical success (Swain et al., 2022a and 2022b).

Conclusion

Diuretics or water tablets have been widely recommended for increasing the excretion rate of water or urine from the body to reduce several poisoning substances and are also used for the treatment of hypertension, liver cirrhosis, congestive heart failure, edema, water pinioning, etc., in adjuvant therapy. To search for potential nontoxic diuretic agents, the present study investigates *E. indica* phytoconstituents, followed by bioassay-guided extraction and GC-MS analyses. Selected three potential target enzymes to evaluate the binding efficacy of select nine *E. indica* phytoconstituents (EI_1 to EI_9) against ACE, KCNJ1, and SLC12A1 along with taking three standard drugs (VU590, TSM, and FSM) through molecular docking. Based on recorded docking scores, EI_6 [Z, Z-6,28-Heptatriacontadien-2-one] exhibited higher potency (with docking scores of -8.0, -6.6, and -6.3 kcal/mol.) with nontoxicity toxicity profiles (class VI), higher lethal dose values (LD₅₀=15000 mg/kg), and ideal pharmacokinetics related to standard drugs proved to be the most potent among them. Overall, using low-cost bioinformatics tools to predict these relevant drug-likeness profiles could be a feasible and cost-effective way to move forward with the current drug development module and find new natural drugs that are more likely to work against specific targets.

Acknowledgements

The authors graciously acknowledge Dr. Saurov Dey and his team at CAIF, Guwahati Biotech Park Technology Incubation Centre, for the GCMS study. The authors are also thankful to Dr. A. Leelaveni, Assistant Professor, PG Department of Botany, Berhampur University, Odisha, for the authentication or identification of the plant. The authors also want to thank Salixiras Research Pvt. Ltd., Bhubaneswar, for providing computational facilities and assisting in paper writing and editing.

References

Anbalagan, S., Kanakarajan, Sivakumari, Selvaraj, R., & Kolappapillai, P. (2023). In Silico Molecular Docking Analysis of Flavone and Phytol from Vilvam (*Aegle marmelos*) against Human Hepatocellular Carcinoma

- (HepG-2) Mitochondrial Proteins. *Int. J. Exp. Res. Rev.*, 36, 405-414.
<https://doi.org/10.52756/ijerr.2023.v36.035>
- Arumugham, V.B., & Shahin, M.H. (2023). Therapeutic uses of diuretic agents. 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
- Atanasov, A.G., Zotchev, S.B., & Dirsch, V.M. (2021). International Natural Product Sciences Taskforce; Supuran CT. Natural products in drug discovery: advances and opportunities. *Nat. Rev. Drug Discov.*, 20(3), 200-216. <https://doi.org/10.1038/s41573-020-00114-z>
- Bhosale, A., Kokate, A., Jarag, S., Bhise, M., Wagh, V., Chandra, P., Ranjan, R., & Choudante, S. (2023). Targeting COVID-19 through active phytochemicals of betel plant by molecular docking. *Int. J. Exp. Res. Rev.*, 32, 178-187.
<https://doi.org/10.52756/ijerr.2023.v32.015>
- Blowey, D.L. (2016) Diuretics in the treatment of hypertension. *Pediatr. Nephrol.*, 31(12), 2223-2233. <https://doi.org/10.1007/s00467-016-3334-4>
- Cesar, S.A., & Ignacimuthu, S. (2015). Finger millet [*Eleusine coracana* (L.) Gaertn]. *Methods Mol. Biol.*, 1223, 135-42. https://doi.org/10.1007/978-1-4939-1695-5_10
- Cheng, C.J., Rodan, A.R., & Huang, C.L. (2017). Emerging Targets of Diuretic Therapy. *Clin. Pharmacol. Ther.*, 102(3), 420-435.
<https://doi.org/10.1002/cpt.754>
- Chopra, B., & Dhingra, A.K. (2021). Natural products: A lead for drug discovery and development. *Phytother. Res.*, 35(9), 4660-4702.
<https://doi.org/10.1002/ptr.7099>
- Denton, J.S., Pao, A.C., & Maduke, M. (2013). Novel diuretic targets. *Am. J. Physiol. Renal. Physiol.*, 305(7), F931-42.
<https://doi.org/10.1152/ajprenal.00230.2013>
- Dias, D.A., Urban, S., & Roessner, U. (2012). A historical overview of natural products in drug discovery. *Metabolites*, 2(2), 303-36.
<https://doi.org/10.3390/metabo2020303>
- Dorce, A.L.C., Martins, A.D.N., Dorce, V.A.C., & Nencioni, A.L.A. (2017). Perinatal effects of scorpion venoms: maternal and offspring development. *J. Venom. Anim. Toxins Incl. Trop Dis.*, 23, 31. <https://doi.org/10.1186/s40409-017-0121-z>
- Escudero, V.J., Mercadal, J., Molina-Andújar, A., Piñeiro, G.J., Cucchiari, D., Jacas, A., Carramiñana, A., & Poch, E. (2022). New insights into diuretic use to treat congestion in the ICU: Beyond furosemide. *Front. Nephrol.*, 2, 879766. <https://doi.org/10.3389/fneph.2022.879766>
- Garcia, M.L., & Kaczorowski, G.J. (2014). Targeting the inward-rectifier potassium channel ROMK in cardiovascular disease. *Curr. Opin. Pharmacol.*, 15, 1-6. <https://doi.org/10.1016/j.coph.2013.11.005>
- Gupta, A., Zaheer, M.R., Iqbal, S., Roohi, A.A., & Alshammari, M.B. (2022). Photodegradation and in silico molecular docking study of a diuretic drug: Clopamide. *ACS Omega*, 7(16), 13870-13877. <https://doi.org/10.1021/acsomega.2c00256>
- Islam, M.N., Hasan, M.F., Dey, A., Bokshi, B., Das, A.K., Sadhu, S.K., & Biswas, N.N. (2022). Identification of Potential Diuretic and Laxative Drug Candidates from *Avicennia officinalis* L. Bark through *In Vivo* Mice Model Studies and *In Vitro* Gas Chromatography-Mass Spectrometry and Molecular Docking Analysis. *Evid Based Complement Alternat Med.*, 2022, 4409250. <https://doi.org/10.1155/2022/4409250>
- Kehrenberg, M.C.A., & Bachmann, H.S. (2022). Diuretics: a contemporary pharmacological classification? *Naunyn Schmiedebergs Arch. Pharmacol.*, 395(6), 619-627. <https://doi.org/10.1007/s00210-022-02228-0>
- Konappa, N., Udayashankar, A.C., Krishnamurthy, S., Pradeep, C.K., Chowdappa, S., & Jogaiah, S. (2020). GC-MS analysis of phytoconstituents from *Amomum nilgircum* and molecular docking interactions of bioactive serverogenin acetate with target proteins. *Sci. Rep.*, 10(1), 16438. <https://doi.org/10.1038/s41598-020-73442-0>
- Li, J.W., & Vederas, J.C. (2009). Drug discovery and natural products: end of an era or an endless frontier? *Science*, 325(5937), 161-165. <https://doi.org/10.1126/science.1168243>
- Liu, X.L., Wang, D.D., Wang, Z.H., & Meng, da L. (2015). Diuretic properties and chemical constituent studies on *Stauntonia brachyanthera*. *Evid. Based Complement Alternat Med.*, 2015, 432419. <https://doi.org/10.1155/2015/432419>
- Maughan, R.J., & Griffin, J. (2003). Caffeine ingestion and fluid balance: a review. *J. Hum. Nutr. Diet.*, 16(6), 411-20. <https://doi.org/10.1046/j.1365-277X.2003.00477.x>
- Ogbole, O.O., Segun, P.A., & Adeniji, A.J. (2017). *In vitro* cytotoxic activity of medicinal plants from Nigeria ethnomedicine on Rhabdomyosarcoma cancer cell line and HPLC analysis of active extracts. *BMC Complement Altern Med.*, 17(1), 494. <https://doi.org/10.1186/s12906-017-2005-8>

- Ong, S.L., Mah, S.H., & Lai, H.Y. (2016). Porcine pancreatic lipase inhibitory agent isolated from medicinal herb and inhibition kinetics of extracts from *Eleusine indica* (L.) Gaertner. *J. Pharm. (Cairo)*, 2016, 8764274. <https://doi.org/10.1155/2016/8764274>
- Ong, S.L., Nalamolu, K.R., & Lai, H.Y. (2017). Potential lipid-lowering effects of *Eleusine indica* (L.) Gaertn. extract on high-fat-diet-induced hyperlipidemic rats. *Pharmacogn. Mag.*, 13(Suppl 1), S1-S9. <https://doi.org/10.4103/0973-1296.203986>
- Puah, P.Y., Lee, D.J.H., Puah, S.H., Lah, N.A.S.N., Ling, Y.S., & Fong, S.Y. (2022). High-throughput metabolomics reveals dysregulation of hydrophobic metabolomes in cancer cell lines by *Eleusine indica*. *Sci. Rep.*, 12(1), 9347. <https://doi.org/10.1038/s41598-022-13575-6>
- Ralte, L., Khiangte, L., Thangjam, N.M., Kumar, A., & Singh, Y.T. (2022). GC-MS and molecular docking analyses of phytochemicals from the underutilized plant, *Parkia timoriana* revealed candidate anti-cancerous and anti-inflammatory agents. *Sci. Rep.*, 12(1), 3395. <https://doi.org/10.1038/s41598-022-07320-2>
- Roush, G.C., Kaur, R., & Ernst, M.E. (2014). Diuretics: a review and update. *J. Cardiovasc. Pharmacol. Ther.*, 19(1), 5-13. <https://doi.org/10.1177/1074248413497257>
- Sahoo, A., Fuloria, S., Swain, S.S., Panda, S.K., Sekar, M., Subramaniyan, V., Panda, M., Jena, A.K., Sathasivam, K.V., & Fuloria, N.K. (2021). Potential of Marine Terpenoids against SARS-CoV-2: An *in silico* drug development approach. *Biomedicines*, 9(11), 1505. <https://doi.org/10.3390/biomedicines9111505>
- Sahoo, A., Jena, A.K., & Panda, M. (2022a). Experimental and clinical trial investigations of phyto-extracts, phyto-chemicals and phyto-formulations against oral lichen planus: A systematic review. *J. Ethnopharmacol.*, 298, 115591. <https://doi.org/10.1016/j.jep.2022.115591>
- Sahoo, A., Swain, S.S., Panda, S.K., Hussain, T., Panda, M., & Rodrigues, C.F. (2022b). *In silico* identification of potential insect peptides against biofilm-producing *Staphylococcus aureus*. *Chem. Biodivers.*, 19(10), e202200494. <https://doi.org/10.1002/cbdv.202200494>
- Scheen, A.J. (2018). Type 2 diabetes and thiazide diuretics. *Curr. Diab. Rep.*, 18(2), 6. <https://doi.org/10.1007/s11892-018-0976-6>
- Sica, D.A., & Carter, B., Cushman, W., & Hamm, L. (2011). Thiazide and loop diuretics. *J. Clin. Hypertens. (Greenwich)*, 13(9), 639-643. <https://doi.org/10.1111/j.1751-7176.2011.00512.x>
- Sukor, N.S.M., Zakri, Z.H.M., Rasol, N.E., & Salim, F. (2023). Annotation and identification of phytochemicals from *Eleusine indica* using high-performance liquid chromatography tandem mass spectrometry: Databases-driven approach. *Molecules*, 28(7), 3111. <https://doi.org/10.3390/molecules28073111>
- Swain, S.S., & Padhy, R.N. (2015). *In vitro* antibacterial efficacy of plants used by an Indian aborigine tribe against pathogenic bacteria isolated from clinical samples. *J. Taibah Univ. Med. Sci.*, 10, 379-390. <https://doi.org/10.1016/j.jtumed.2015.08.006>
- Swain, S.S., & Padhy, R.N. (2016). Isolated ESBL producing Gram-negative bacteria along with an *in silico* attempt against ESBL enzyme by flavonoids. *J. Taibah. Univ. Med. Sci.*, 11, 217-229. <https://doi.org/10.1016/j.jtumed.2016.03.007>
- Swain, S.S., Singh, S.R., Sahoo, A., Hussain, T., & Pati, S. (2022a). Anti-HIV-drug and phyto-flavonoid combination against SARS-CoV-2: a molecular docking-simulation base assessment. *J. Biomol. Struct. Dyn.*, 40(14), 6463-6476. <https://doi.org/10.1080/07391102.2021.1885495>
- Swain, S.S., Singhm, S.R., Sahoo, A., Panda, P.K., Hussain, T., & Pati, S. (2022b). Integrated bioinformatics-cheminformatics approach toward locating pseudo-potential antiviral marine alkaloids against SARS-CoV-2-Mpro. *Proteins*, 90(9), 1617-1633. <https://doi.org/10.1002/prot.26341>
- Thorn, C.F., Ellison, D.H., Turner, S.T., Altman, R.B., & Klein, T.E. (2013). PharmGKB summary: Diuretics pathway, pharmacodynamics. *Pharmacogenet Genomics*, 23(8), 449-453. <https://doi.org/10.1097/FPC.0b013e3283636822>
- Titko, T., Perekhoda, L., Drapak, I., & Tsapko, Y. (2020). Modern trends in diuretics development. *Eur. J. Med. Chem.*, 208, 112855. <https://doi.org/10.1016/j.ejmech.2020.112855>
- Wright, C.I., Van-Buren, L., Kroner, C. I., & Koning, M.M. (2007). Herbal medicines as diuretics: a review of the scientific evidence. *J. Ethnopharmacol.*, 114(1), 1-31. <https://doi.org/10.1016/j.jep.2007.07.023>
- Yang, L., Zeng, H., Xia, X., Wang, H., Zhao, B., & He, J. (2022). Natural phenylethanoid glycosides diuretics derived from *Lagopsis supina*: Biological activity, mechanism, molecular docking, and structure-

- activity relationship. *Bioorg. Chem.*, 129, 106165. <https://doi.org/10.1016/j.bioorg.2022.106165>
- Yu, Y., Hu, D., Liu, J., Wu, C., Sun, Y., Lang, M., Han, X., Kang, D., Min, J.Z., Cui, H., & Zheng, M. (2024). Constituents of *Chimaphila japonica* and Their Diuretic Activity. *Molecules*, 29(5), 1092. <https://doi.org/10.3390/molecules29051092>
- Zhao, Y., & Cao, E. (2022). Structural pharmacology of cation-chloride cotransporters. *Membranes* (Basel), 12(12), 1206. <https://doi.org/10.3390/membranes12121206>

How to cite this Article:

Tapan Kumar Sahu, Nityananda Sahoo, Gurudutta Pattnaik, Himansu Bhusan Samal, Amulyaratna Behera and Biswakanth Kar (2024). Alcoholic Extracts of *Eleusine indica* as Alternative Diuretic Regimens: A Computational Based Investigation. *International Journal of Experimental Research and Review*, 37(Spl.), 11-21.

DOI : <https://doi.org/10.52756/ijerr.2024.v37spl.002>



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.