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Research Article

Molecular docking and *in silico* ADMET evaluation of compounds from *Erythrina senegalensis*, as potential α-glucosidase and α-amylase inhibitors for the treatment of diabetes mellitus

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Abstract

Inhibition of α-amylase and α-glucosidase, responsible for postprandial glucose levels seems to be crucial in the prevention and management of Diabetes Mellitus (DM). Parts of *Erythrina senegalensis* DC are used for the management of diabetes as a traditional medicine. In this study, isolated compounds from this plant exhibiting previous good *in vitro* activities were docked using Autodock to explore their binding mode on α-glucosidase and α-amylase proteins. Molecular docking is a computational method used for the prediction of the molecule potency against a targeted disease. As the results, compounds showed different types of interactions within the active pocket of enzymes, including hydrogen bonding and hydrophobic interactions. The most potent compound for inhibiting α-glucosidase was kaikasaponin III (**2**) (-10.1 Kcal/mol), while β-amyrin (**5**) (-10.0 Kcal/mol) was the most potent inhibitor against α-amylase. In addition, the pharmacokinetic and drug-likeness studies of the studied compounds were performed. The results suggested that, amongst all the studied compounds, β-amyrin (**5**) has the best potential to be considered as viable candidate for future development as DM drugs. This study confirmed the α-amylase and α-glucosidase inhibitory potential of *E. senegalensis* compounds for managing DM and supports further drug development from this plant.

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1. Introduction

Carbohydrate metabolism is all of the biochemical reactions responsible for the formation, breakdown and interconversion of carbohydrates in living organisms. Disorder of the metabolism of carbohydrates is the cause of the appearance of diabetes mellitus (DM), one of the well-known metabolic diseases. DM, which is characterized by a chronic accumulation of glucose in the bloodstream, occurs when the liver or pancreas do not function properly [1]. In recent years, the number of diabetic patients has continued to increase day by day around the world. According to the International Diabetes Federation (IDF), in 2019, this disease had reached about 463 million individuals worldwide, and just two years later, 74 million new cases were detected [2]. If no practical solution is discovered as soon as possible, then approximately 637 million patients will be diabetic within the next six years. Type 2 diabetes, the most common form of DM is a serious condition that develops when the body does not use insulin (the natural hormone that allows the body's cells to use glucose for energy) effectively and gradually loses the ability to produce enough. In fact, in order to be useful to different cells, the polysaccharides provided by the diet are first broken down into disaccharides by salivary amylase and then by pancreatic amylase; the products of this degradation (disaccharides) are finally transformed into monosaccharides by the α-glucosidases which are maltase, lactase and saccharase [3]. Then, without enough insulin, glucose will build up in the blood and this can be over the long term a source of many health problems. This is why slowing down or completely stopping the activities of α-amylase and especially α-glucosidase is an effective method to reduce the impact of dietary carbohydrates on blood sugar levels [3, 4]. Three medications namely acarbose, voglibose and miglitol are currently present in the clinic to improve the daily lives of patients with diabetes. But because of their numerous harmful effects, their use is increasingly limited, hence the incessant search for an alternative treatment [3, 4]. The most obvious choice for these alternatives would be plants with ethnomedical uses in the treatment of diabetes, since many of them have fewer side effects compared to synthetic products [4]. *Erythrina senegalensis* DC is one of the species among the genus *Erythrina*, which is part of the Fabaceae family and that has a lot of benefits from its parts [5, 6]. This plant has been reported to be a source of a large number of constituents belonging to the triterpene, saponin, pterocarpan, and cinnamate classes [7, 8]. Previously, from the root wood, leaves, and stem bark of this plant, we isolated and characterized secondary metabolites with the inhibitory potential against α-amylase and α-glucosidase [9, 10]. Afterwards, it would be interesting to study the mechanisms of inhibition of both enzymes by these phyto compounds. Virtual screening has offered a new way to identify molecules for therapeutic purposes. It is in this context that the importance of molecular docking appears, aimed at modeling the structure of a protein-ligand complex, allowing a better understanding of the interactions between a potential compound (ligand) and its therapeutic target (protein) [11, 12]. As far as we know, until now there have been no studies conducted to investigate the *in silico* antidiabetic effects of the six known compounds: soyasaponin I (**1**), kaikasaponin III (**2**), sericoside (**4**), sericic acid (**7**), erythrinasinate X (**9a**), erythrinasinate B (**9b**), and the new semisynthetic derivative erythrinamate (**10**). The aim of this study was therefore to use molecular docking and ADMET analysis to evaluate the drug-likeness of these compounds as potential α-amylase and α-glucosidase inhibitors for DM treatment.

2. Materials and methods

2.1. Plant material

The aerial parts of *Erythrina senegalensis*, were harvested from Ngaoundere, in the Adamawa Region of Cameroon, in the 7th month of the year 2020 and taxonomically identified. A voucher specimen (No. 50119 NHC) was recorded at the Yaounde National Herbarium of Cameroon.

2.2. Isolation, compound elucidation and semisynthesis

Investigated samples were isolated and obtained by chemical reaction following the same procedure as already reported by Djoko et al. [9]. The structures of all compounds were established using 1 & 2D NMR data (^{1}H, ^{13}C NMR, HSQC, HMBC) along with MS data as previously reported [9].

2.3. Proteins preparation

Proteins for docking analysis were prepared using MGL tools. α-glucosidase (3PHA) and α-amylase

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(4W93) 3D structures were obtained from the PDB (www.rcsb.org) [13]. PyMOL was used for the identification and visualization of amino acid residues in the active pocket of both enzymes. Subsequently, co-crystallized ligands, co-factors, ions and water molecules were removed and the proteins were saved in pdb format, for docking studies.

2.4. The preparation of ligands

The PubChem database was used to prepare the 3D structures of the isolated compounds and the semisynthetic derivatives from the studied cameroonian antidiabetic plant *E. senegalensis*, in sdf format [14]. The addition of hydrogen atoms and energy minimization were included. All chemical structures were saved in PDB format after conversion.

2.5. In silico molecular docking

Molecular docking was employed to explore the interactions between compounds and specific targeted proteins. The docking protocol involving the elimination of heteroatoms and all water molecules from the active binding site of enzymes, adding polar hydrogen atoms and Kollman charges, and correcting any missing residues [15], was validated before docking studies. The docking protocol was validated by first separating the co-crystal ligand from the active pocket of the complex, and then re-docking was performed to validate its accuracy [16]. After that, compounds were docked using the default genetic algorithm of AutoDock's scoring function. The grid box dimensions were set as follows: (x: 15.749435, y: 0.438618, z: 75.704832,) for 3PHA and (x: -8.019108, y: 20.939272, z: -19.030489) for 4W93. For each protein, a total of 100 different poses were generated, and the pose with the lowest energy and the highest binding affinity (most stable) was selected and was analysed in 2D and 3D designs to understand the interactions between the sample and the targeted protein [17]. The results of this study could facilitate the design of novel compounds with better binding affinities to α-amylase and α-glucosidase.

2.6. ADMET analysis

The physicochemical and pharmacokinetic attributes of the identified compounds were ascertained through ADMETLAB 3.0 (https://admetlab3.scbdd.com/server/evaluationCal). This computational tool facilitated a comprehensive assessment of several pharmacokinetic parameters, notably absorption, distribution, metabolism, excretion and toxicity (ADMET) [18]. ADMETLAB utilizes an array of sophisticated algorithms and predictive models to prognosticate both drug-likeness and potential toxicity [19]. The algorithms underscoring the bioavailability radar chart are underpinned by advanced machine learning and statistical methodologies, calibrated against vast molecular datasets with delineated properties. Within the confines of the BOILED-Egg model, salient ADME properties, such as blood-brain barrier (BBB) permeation, passive human gastrointestinal absorption (HIA), and designation as either substrate or non-substrate for permeability glycoprotein, were distinctly identified [18].

3. Results

3.1. Isolation procedure

From silica gel column chromatographies of AcOEt and MeOH extracts of the leaves and stem bark of *E. senegalensis*, six pure compounds and two mixtures were isolated and their structures were elucidated by spectral analysis (1 & 2D NMR and MS) and comparison with the published literature. Pure compounds were identified as soyasaponin I (**1**) [20], kaikasaponin III (**2**) [20], daucosterol (**3**) [21], sericoside (**4**) [22], β-amyrin (**5**) [23], oleanolic acid (**6**) [24, 25], sericic acid (**7**). A mixture of two inseparable steroids has also been elucidated as β-sitosterol (**8a**) and stigmasterol (**8b**) [24, 26] along with a mixture of two cinnamates as erythrinasinate X (**9a**) and erythrinasinate B (**9b**) [27]. Compound **10** named erythrinamate was obtained by the esterification of compound **9b**. The structures of those compounds are shown in Fig 4.

3.2. Molecular docking studies

Molecular docking is a computational method used for the prediction of the molecule potency against a targeted disease. We have investigated in this study the binding poses of isolated inhibitors from *E. senegalensis* extracts within the reactive pocket of the active site of α-glucosidase and α-amylase. The results of molecular docking studies against α-glucosidase are given in Table 1 and Fig. 1, while docking studies against α-amylase enzyme are recorded in Table 2, and can be visualized in Fig. 2. Three compounds, **1**,

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Table 1. Binding energy and docking interactions of α-glucosidase with compounds of *E. senegalensis*

Protein (PDB ID)	Compounds	Binding energy (kcal/mol)	Hydrogen bonds residues	Hydrophobic interactions
α-glucosidase	**1**	-9.8	HIS375, ASN70, THR72, SER83	ASP74, ASN352,
(3PHA)	**2**	-10.1	ARG82, SER83, ASN70	PRO354, TYR357, ASN352
	3	-7.9	ASP73	PRO75, PRO354, TYR357
	4	-7.8	VAL351, ASP74, SER83	ASP349, ARG82,
	5	-8.3	No	No
	6	-7.8	No	No
	7	-7.6	ASP73, SER83, ARG82	No
	9a	-4.7	THR72, CYS71	PRO354, TYR357, LYS348, VAL351, ILE68, ARG82, LYS81, ASP80
	9b	-4.0	SER83, THR72, ASN70	PRO75, LYS348, LYS81, PRO354, ARG82
	10	-6.5	LYS108	PRO354, HIS375, ASN70, SER107

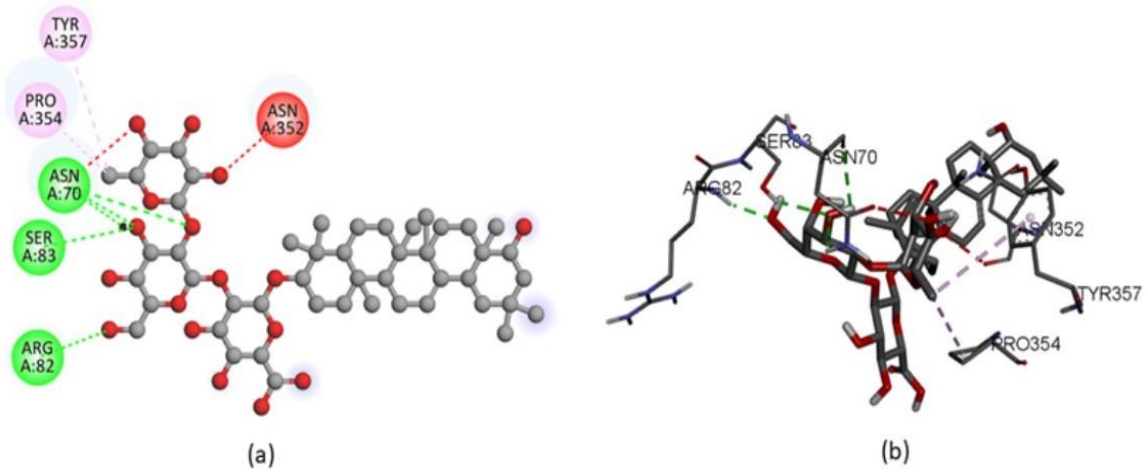

Figure 1. 2D(a) and 3D(b) representations of the α-glucosidase-compound **2** interaction

2 and **5** showed potent inhibition of both α-glucosidase and α-amylase (Tables 1 and 2).

ADMET properties constitute the pharmacokinetic profile of a drug molecule, and refer to the absorption, the distribution, the metabolism, the excretion and the toxicity in and through the human body of a compound. This analysis is very essential in evaluating its pharmacodynamic activities. The results of ADMET analysis, including the values characterizing the physicochemical properties of the considered inhibitors, are presented in Table 3 and Fig. 3.

4. Discussion

α-Glucosidase and α-amylase are two enzymes that breakdown carbohydrates into simple sugars. The inhibition of these enzymes has therefore been a subject of numerous studies on extracts and compounds from antidiabetic plants [9, 28, 29]. α-glucosidase is crucial for the breakdown of degradation of glycogen to glucose [30], but also for the hydrolysis of α-1,6-linked glucans [31]. α-amylase, another digestive enzyme, acts on glycogen or starch, in parotid, urine, serum, pancreas, and sometimes in other tissues or tumours, in smaller amounts [32]. The inhibition of those two enzymes, is a hopeful therapeutic approach, for decreasing PPG (postprandial hyperglycemia) in DM patients [28].

Therefore, there is an urgent need for the exploration of inhibitors of both enzymes and for this purpose,

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Table 2. Binding energy and docking interactions of α-amylase with compounds of *E. senegalensis*

Protein (PDB ID)	Compound	Binding energy (kcal/mol)	Hydrogen bonding residues	Hydrophobic interactions
α-amylase	**1**	-9.1	HIS305, TRP59	GLN63
(4W93)	**2**	-9.6	ASP300, TRP59, ASP356	No
	3	-8.1	LYS200, ILE235	TYR62, TRP59, HIS299
	4	-9.5	GLU233	THR163, HIS305, ARG195
	5	-10.0	GLN63	No
	6	-9.6	GLN63	TRP59
	7	-9.0	ASP197	No
	9a	-5.3	GLN63, ASP197	ILE235, TYR151, ALA307, HIS305, TRP58, TRP59, TRY62, ARG195
	9b	-5.1	HIS299, GLN63	LEU165, GLU233, TRP59, HIS305, ILE235, LYS200, TYR151
	10	-6.2	HIS299	TRP59

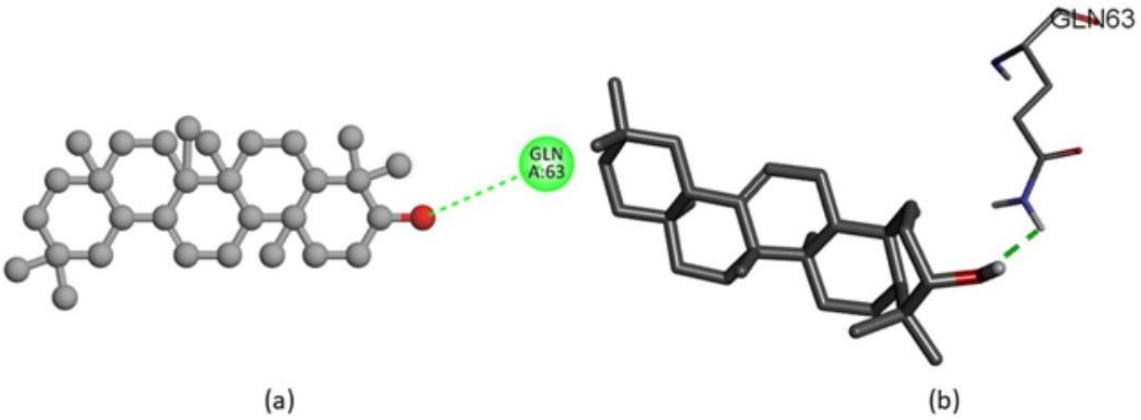

Figure 2. 2D(a) and 3D(b) representations of the α-amylase-compound **5** interaction

molecular docking studies are the most advantageous and convenient crucial computational methods that enable the analysis of ligand-protein interactions. The use of blockers allows to obtain a competitive mode of inhibition. The inactivation of the enzyme leads to the binding of the inhibitor *via* a covalent bond and it depends on concentration and time [30]. The aim of this study was to explore the binding affinities of isolated and semi-synthesized compounds with two different proteins, α-glucosidase and α-amylase. Compounds from ethyl acetate and methanol extracts were then evaluated for their α-amylase and α-glucosidase inhibiting activity *via in silico* molecular docking.

The docking analysis revealed strong and effective interactions between the extracted compounds and the α-glucosidase enzyme. With α-glucosidase, as recorded in Table 1, the decreasing order of the positive binding and potential inhibition was kaikasaponin III (**2**) > soyasaponin I (**1**) > β-amyrin (**5**) > daucosterol (**3**) > sericoside (**4**) = oleanolic acid (**6**) > sericic acid (**7**) > erythrinamate (**10**) > erythrinasinate X (**9a**) > erythrinasinate B (**9b**). Among these compounds, kaikasaponin III (**2**) particularly demonstrated a robust binding with the α-glucosidase enzyme, exhibiting a binding energy of -10.1 kJ/mol, as elaborated in Table 1. In-depth analysis indicated that kaikasaponin III (**2**) established hydrogen bonds

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Table 3. Physicochemical and pharmacokinetic profiles of compounds

ID	1	2	3	4	5	6	7	8a	8b	9a	9b	10
Physicochemical Properties												
MW	942.5	926.5	576.4	666.4	456.4	426.4	504.4	414.4	412.4	588.5	584.5	346.2
Vol	923.3	914.5	621.2	671.3	505.8	490.8	532.1	482.1	479.4	670.7	687.7	382.6
Dense	1.0	1.0	0.9	1.0	0.9	0.9	0.9	0.9	0.9	0.9	0.8	0.9
nHA	18.0	17.0	6.0	11.0	3.0	1.0	6.0	1.0	1.0	5.0	3.0	4.0
nHD	11.0	10.0	4.0	8.0	2.0	1.0	5.0	1.0	1.0	2.0	1.0	0.0
nRot	9.0	8.0	9.0	5.0	1.0	0.0	2.0	6.0	5.0	31.0	32.0	14.0
nRing	8.0	8.0	5.0	6.0	5.0	5.0	5.0	4.0	4.0	1.0	1.0	1.0
MaxRing	22.0	22.0	17.0	22.0	22.0	22.0	22.0	17.0	17.0	6.0	6.0	6.0
nHet	18.0	17.0	6.0	11.0	3.0	1.0	6.0	1.0	1.0	5.0	3.0	4.0
fChar	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
nRig	45.0	45.0	26.0	33.0	27.0	26.0	27.0	20.0	21.0	8.0	8.0	9.0
Flex	0.2	0.2	0.3	0.2	0.0	0.0	0.1	0.3	0.2	3.9	4.0	1.6
nStereo	25.0	24.0	14.0	16.0	8.0	8.0	11.0	9.0	9.0	0.0	0.0	0.0
TPSA	295.0	274.8	99.4	197.4	57.5	20.2	118.2	20.2	20.2	76.0	46.5	52.6
LogS	-4.1	-4.9	-5.0	-3.9	-5.0	-6.4	-4.3	-6.7	-5.4	-8.0	-8.6	-6.3
LogD	2.3	3.1	4.9	2.2	3.4	4.6	2.6	5.0	4.4	4.4	4.8	3.7
LogP	1.8	2.8	5.3	2.0	4.0	5.7	2.6	7.2	5.7	8.2	9.1	5.6
mp	251.3	271.1	187.2	235.6	246.4	202.6	253.1	158.1	154.9	109.9	86.8	20.1
bp	351.4	352.1	343.5	288.1	318.1	295.2	281.5	354.7	314.5	427.2	429.2	319.7
pka_acidic	4.1	5.2	7.7	6.2	5.3	8.9	5.5	9.7	9.0	6.9	7.2	8.5
pka_basic	4.4	3.4	5.2	6.8	4.1	6.0	4.7	5.6	6.0	3.8	5.1	2.5
Medicinal Chemistry Properties												
QED	0.1	0.1	0.3	0.2	0.4	0.4	0.4	0.4	0.5	0.1	0.1	0.2
Synth	6.0	6.0	4.0	5.0	4.0	4.0	5.0	4.0	4.0	2.0	2.0	2.0
Fsp^3	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.8	0.8	0.5
MCE-18	176.2	176.2	90.6	133.5	105.4	102.2	110.8	68.5	69.0	7.0	6.0	7.0
Lipinski	1.0	1.0	1.0	1.0	0.0	0.0	0.0	0.0	0.0	1.0	1.0	0.0
Pfizer	0.0	0.0	0.0	0.0	1.0	1.0	0.0	1.0	1.0	0.0	1.0	1.0
GSK	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Golden	1.0	1.0	1.0	1.0	0.0	0.0	1.0	1.0	0.0	1.0	1.0	0.0
Triangle												
Excretion												
$t_{1/2}$	3.5	3.6	1.3	2.3	0.8	0.2	1.5	0.5	0.5	3.6	4.5	0.4
CL-plasma	0.0	0.1	3.9	1.0	4.2	10.4	3.2	14.0	13.0	4.2	4.2	5.5
BCRP	0.0	0.0	0.0	0.1	0.0	0.4	0.0	0.0	0.3	1.0	1.0	0.3
BSEP	0.0	0.0	0.0	0.0	0.7	1.0	0.0	0.0	1.0	0.9	1.0	1.0
MRP1	0.9	0.8	0.0	0.2	1.0	1.0	1.0	0.3	0.2	1.0	1.0	0.0
OATP1B1	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.9	0.9	1.0
OATP1B3	1.0	1.0	1.0	1.0	0.9	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Absorption properties (Probability of meeting the assumed boundary conditions for selected parameters, within the range of 0 to 1).												
Pgp_inh	0.0	0.0	0.0	0.0	0.0	0.7	0.0	0.0	0.6	0.0	0.0	0.4
Pgp_sub	0.4	0.1	0.0	0.3	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
HIA	0.8	0.6	0.0	0.2	0.0	0.0	0.0	0.0	0.0	1.0	1.0	0.6
F_{20}	0.9	0.8	0.0	1.0	0.1	0.6	0.6	0.0	0.2	1.0	1.0	1.0
F_{30}	1.0	1.0	0.5	1.0	0.0	0.0	0.1	0.1	0.3	1.0	1.0	1.0
F_{50}	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
$Caco_2$	-6.2	-6.0	-5.3	-6.6	-5.3	-5.0	-5.8	-5.1	-5.2	-5.1	-5.1	-5.0
MDCK	-5.2	-5.2	-5.1	-5.1	-5.0	-4.9	-5.0	-4.9	-4.9	-4.9	-5.0	-4.7
PAMPA	1.0	1.0	0.9	1.0	1.0	0.9	1.0	0.4	0.0	0.0	0.0	0.0
Distribution Properties												
BBB	0.0	0.0	0.1	1.0	0.8	1.0	0.9	0.1	0.0	0.0	0.0	0.0
logVDss	-0.5	-0.5	-0.5	-0.2	-0.3	0.1	-0.2	-0.2	-0.1	1.3	2.8	0.3
Fu	18.1	17.4	14.6	18.5	8.3	3.5	16.2	18.6	1.1	0.4	0.1	0.9
PPB	72.6	74.1	80.6	73.3	90.9	97.2	81.3	75.5	98.6	100.4	104.5	98.8
Metabolism of considered drugs by enzymes from the human cytochrome P450 group												
CYP1A2-inh	2.1E-16	6.3E-18	4.8E-10	4.4E-11	1.4E-09	1.1E-06	4.7E-12	2.8E-07	1.0E-05	1.0E+00	1.0E+00	1.0E+00
CYP1A2-sub	2.0E-09	9.3E-10	4.6E-06	2.3E-07	8.5E-06	6.6E-02	5.6E-09	7.0E-08	2.3E-10	5.6E-01	4.6E-05	2.0E-06
CYP2C19-inh	2.5E-14	3.0E-13	5.6E-06	8.7E-08	1.6E-02	2.4E-01	1.8E-08	9.6E-05	4.4E-04	6.4E-01	9.9E-01	1.0E+00
CYP2C19-sub	8.3E-06	1.8E-04	8.1E-01	2.0E-04	1.0E+00	1.0E+00	4.6E-04	1.3E-03	1.7E-07	2.8E-01	3.2E-03	3.1E-06
CYP2C9-inh	1.3E-08	2.3E-08	4.5E-02	1.9E-04	5.6E-01	9.2E-01	1.7E-05	6.5E-02	1.8E-04	5.2E-01	2.4E-01	2.5E-03
CYP2C9-sub	1.9E-04	1.1E-05	1.5E-04	5.1E-06	2.6E-01	3.6E-01	4.4E-02	5.3E-05	3.2E-06	2.9E-01	7.3E-01	9.3E-01
CYP2D6-inh	2.0E-07	7.7E-07	2.5E-07	1.1E-05	2.7E-05	1.2E-01	3.1E-06	1.0E-03	2.5E-04	1.0E-01	6.5E-01	3.8E-02

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Table 3. *(Continued).*

ID	1	2	3	4	5	6	7	8a	8b	9a	9b	10
Metabolism of considered drugs by enzymes from the human cytochrome P450 group												
CYP2D6-sub	1.4E-07	1.9E-09	1.5E-05	1.5E-06	1.8E-04	2.7E-02	3.7E-06	1.9E-01	8.1E-03	5.4E-01	7.5E-01	5.1E-02
CYP3A4-inh	6.5E-08	8.2E-07	3.2E-04	1.2E-03	1.9E-03	7.1E-01	2.6E-06	1.1E-03	2.0E-02	7.8E-01	9.5E-01	1.6E-03
CYP3A4-sub	5.1E-07	5.9E-07	5.5E-01	4.0E-03	4.3E-02	1.0E+00	2.9E-04	8.7E-02	6.2E-03	1.9E-02	1.7E-04	1.5E-07
CYP2B6-inh	1.1E-08	1.1E-07	7.9E-01	2.9E-04	1.2E-04	3.9E-03	2.1E-05	9.7E-01	1.0E+00	1.0E+00	1.0E+00	1.0E+00
CYP2B6-sub	6.7E-23	2.6E-25	6.3E-09	5.9E-15	1.2E-05	1.1E-03	2.6E-12	5.7E-07	6.0E-12	4.9E-05	6.0E-04	4.4E-03
CYP2C8-inh	3.0E-03	7.4E-03	9.9E-01	7.4E-01	1.3E-01	6.7E-01	2.7E-03	9.7E-01	1.0E+00	1.0E+00	1.0E+00	1.0E+00
Toxicity characteristics												
BCF	0.9	1.1	3.0	1.2	2.1	3.5	0.8	3.1	2.9	0.2	-0.5	0.9
IGC_{50}	3.6	3.8	5.0	3.9	4.8	5.4	3.7	5.0	4.8	5.3	5.4	4.6
$LC_{50}FM$	4.2	4.6	5.6	4.7	5.6	6.6	4.5	5.8	5.6	4.6	4.6	4.6
$LC_{50}DM$	5.2	5.5	5.5	5.7	6.1	6.0	5.4	5.5	5.6	7.4	7.6	6.2
LM-human	5.1E-06	5.5E-04	7.0E-01	3.7E-02	6.9E-01	6.3E-01	2.1E-03	8.3E-01	2.3E-01	8.4E-01	1.1E-01	9.2E-01
A549	5.8E-01	6.6E-01	9.2E-01	5.7E-01	1.5E-01	4.9E-01	9.5E-02	7.3E-01	5.2E-01	9.0E-01	9.9E-01	2.8E-01
Ames	4.1E-01	4.6E-01	5.9E-01	2.5E-01	8.0E-02	1.2E-01	1.0E-01	1.3E-01	1.5E-01	1.9E-02	9.9E-03	1.7E-01
Carcinogenicity	1.8E-01	1.6E-01	3.0E-01	1.6E-01	7.9E-01	8.7E-01	7.0E-01	6.6E-01	8.5E-01	2.8E-01	1.6E-01	2.9E-01
DILI	7.6E-01	8.6E-01	7.2E-01	1.0E-01	2.1E-01	4.8E-02	2.8E-01	2.1E-01	4.5E-01	1.4E-01	1.7E-01	5.4E-01
EC	2.2E-09	5.5E-09	1.7E-04	8.2E-09	2.5E-03	2.0E-02	1.9E-05	1.7E-01	2.4E-02	3.4E-01	6.5E-01	7.3E-01
EI	4.3E-04	5.7E-04	2.4E-02	8.7E-04	2.8E-01	4.4E-01	4.3E-02	7.9E-01	7.5E-01	9.9E-01	9.9E-01	9.8E-01
FDAMDD	3.2E-02	4.9E-02	1.5E-01	1.3E-01	7.6E-01	8.5E-01	5.4E-01	7.3E-01	8.7E-01	2.4E-01	5.0E-01	1.6E-01
Genotoxicity	3.5E-01	4.0E-01	5.1E-04	2.0E-01	2.7E-01	1.3E-01	6.2E-01	2.1E-04	1.2E-02	4.5E-09	5.0E-10	6.0E-04
H-HT	7.3E-01	6.8E-01	6.4E-01	6.2E-01	7.8E-01	7.3E-01	6.8E-01	6.3E-01	6.5E-01	4.7E-01	4.7E-01	3.5E-01
HEK293	6.1E-01	6.3E-01	6.7E-01	2.2E-01	2.6E-01	6.8E-01	1.6E-01	6.1E-01	7.8E-01	4.5E-01	7.7E-01	2.4E-01
Hematotoxicity	8.7E-02	1.1E-01	1.5E-01	7.9E-02	7.6E-02	9.7E-02	9.6E-02	6.3E-02	1.3E-01	2.4E-02	1.3E-02	9.9E-02
hERG-10um	1.7E-02	2.4E-02	3.7E-01	8.0E-02	1.4E-01	4.7E-01	7.5E-02	5.4E-01	4.2E-01	9.1E-01	9.8E-01	6.4E-01
hERG	4.3E-03	5.4E-03	1.6E-01	1.6E-02	6.7E-02	1.1E-01	4.4E-02	2.9E-01	2.3E-01	8.1E-01	9.6E-01	3.2E-01
Nephrotoxicity-DI	9.2E-01	9.4E-01	2.8E-01	8.0E-01	2.6E-01	1.9E-01	6.2E-01	2.2E-01	2.9E-01	1.4E-01	6.0E-02	1.9E-01
Neurotoxicity-DI	4.3E-04	6.4E-04	2.5E-02	1.1E-03	4.1E-02	1.0E-01	2.1E-02	1.6E-01	2.7E-01	3.6E-03	5.9E-03	2.6E-01
Ototoxicity	1.0E+00	1.0E+00	9.6E-01	9.9E-01	7.6E-01	6.1E-01	9.2E-01	5.8E-01	6.7E-01	1.2E-01	6.4E-02	1.0E-01
Respiratory	3.7E-03	6.6E-03	2.1E-01	3.6E-02	8.4E-01	7.2E-01	7.0E-01	8.3E-01	9.1E-01	9.4E-01	9.7E-01	3.2E-01
ROA	1.4E-02	2.0E-02	4.2E-02	5.5E-02	4.8E-01	5.3E-01	2.7E-01	1.4E-01	1.4E-01	3.2E-02	4.3E-02	1.2E-01
RPMI-8226	1.2E-01	1.3E-01	9.3E-02	1.3E-01	2.3E-02	4.3E-02	3.5E-02	5.9E-02	7.9E-02	6.4E-02	4.9E-02	4.9E-02
SkinSen	1.0E+00	1.0E+00	1.0E+00	9.9E-01	7.5E-01	8.3E-01	8.7E-01	9.7E-01	9.3E-01	1.0E+00	1.0E+00	9.8E-01
NR-AR	2.3E-02	8.1E-03	2.4E-05	1.9E-03	9.4E-03	1.6E-02	6.8E-03	1.7E-05	4.4E-07	3.3E-02	9.4E-02	1.5E-01
NR-AR-LBD	3.9E-04	4.7E-05	1.8E-06	6.8E-05	4.6E-05	9.3E-05	9.1E-05	1.5E-06	7.0E-07	9.5E-02	7.1E-02	2.7E-01
NR-AhR	2.6E-04	1.4E-04	2.6E-06	3.5E-05	4.9E-04	5.3E-04	1.0E-03	2.8E-06	8.7E-09	2.2E-04	1.6E-04	5.9E-03
NR-Aromatase	1.8E-03	1.6E-03	7.5E-04	1.9E-04	3.5E-03	3.7E-02	1.0E-03	1.5E-03	2.6E-01	2.5E-02	5.2E-02	1.8E-02
NR-ER	4.0E-02	2.8E-02	9.9E-01	2.1E-02	6.0E-02	7.6E-02	5.2E-02	9.9E-01	1.0E+00	8.8E-01	9.7E-01	9.4E-01
NR-ER-LBD	1.1E-04	1.4E-04	3.8E-03	2.2E-04	1.3E-01	3.7E-01	9.3E-04	5.1E-02	3.5E-01	6.9E-02	3.8E-01	6.5E-01
NR-PPAR-gamma	2.3E-05	2.4E-05	8.8E-06	5.3E-07	5.4E-02	1.0E-02	3.3E-03	4.6E-04	2.9E-03	6.3E-02	1.6E-01	6.3E-02
SR-ARE	9.1E-03	1.0E-02	1.3E-02	2.9E-02	3.9E-01	5.0E-01	1.2E-01	8.2E-02	9.1E-01	6.4E-01	7.9E-01	7.2E-01
SR-ATAD5	1.8E-05	1.2E-05	2.1E-08	4.7E-05	4.6E-03	1.6E-02	8.7E-04	5.2E-07	3.9E-08	8.6E-03	8.1E-03	2.7E-01
SR-HSE	2.5E-04	3.1E-04	7.5E-04	1.9E-04	7.6E-01	8.4E-01	5.0E-02	1.5E-02	5.3E-02	1.6E-01	5.3E-02	1.9E-01
SR-MMP	1.9E-03	3.1E-03	2.7E-01	9.8E-04	7.0E-01	9.3E-01	2.3E-02	8.8E-01	1.0E+00	2.5E-01	4.7E-01	4.5E-01
SR-p53	3.3E-03	2.6E-03	6.2E-05	2.3E-02	9.0E-03	1.7E-02	6.0E-03	3.4E-04	6.0E-04	2.1E-01	3.7E-01	9.2E-01

with ARG82, SER83, and ASN70 residues of the enzyme, underscoring the noteworthy involvement of these specific residues in the binding mechanism of kaikasaponin III to *α*-glucosidase, as illustrated in Fig. 1. Additionally, amino acid residues PRO354 and TYR357 were found to engage in interactions with kaikasaponin III through alkyl and *pi*-alkyl interactions, respectively.

The outcomes of the molecular docking analysis underscore a pronounced interaction between the extracted compounds and the *α*-amylase enzyme. With *α*-amylase, the decreasing order of the positive binding and potential inhibition was as follows: *β*-amyrin (**5**) > kaikasaponin III (**2**) = oleanolic acid (**6**) > sericoside (**4**) > soyasaponin I (**1**) > sericic acid (**7**) > erythrinamate (**10**) > erythrinasinate X (**9a**) > erythrinasinate B (**9b**) (Table 2). *β*-amyrin (**5**), in particular, exhibited a potent binding affinity towards *α*-acarbose and is a competitive inhibitor of *α*-glucosidase kJ/mol as indicated in Table 2.

The significance of this interaction is further accentuated by the formation of hydrogen bond between *β*-amyrin (**5**) and the enzyme's GLN63 residue. This interaction pattern, elucidated in Fig. 2,

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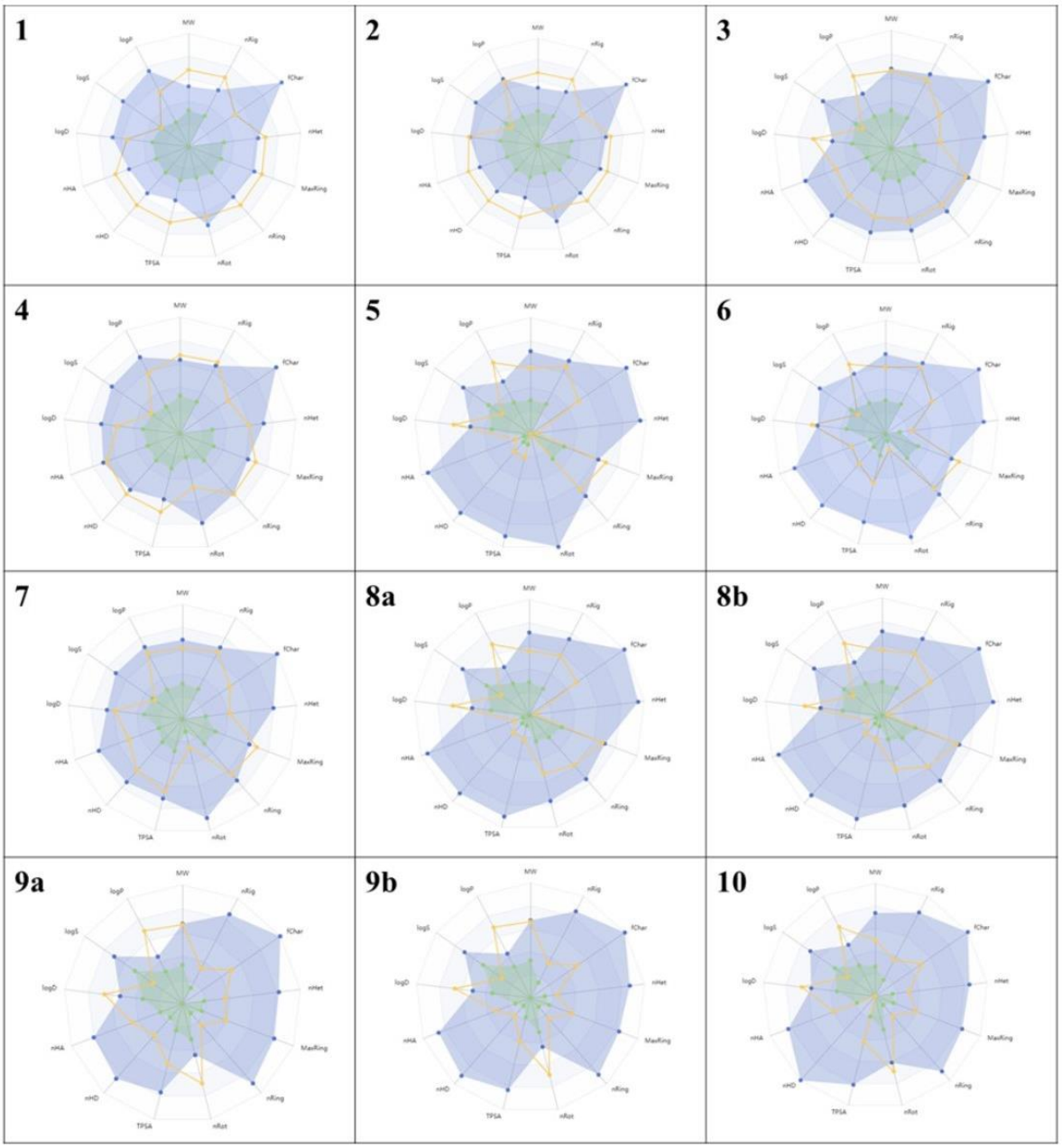

Figure 3. Bioavailability radar charts describing the physicochemical and pharmacokinetic properties of E. senegalensis identified compounds.

highlights the pivotal role played by these specific residues in mediating the binding interaction of β-amyrin (**5**) with α-amylase.

The docking analysis revealed a tough and effective interaction between the evaluated compounds and both enzymes. The maximum binding energy was -4 kcal/mol, and the minimum binding energy was -10.1 kcal/mol. Moreover, 71.42% of the binding energy were less than -6 kcal/mol. Indeed, hydrophobic interactions and hydrogen bonds, are quite important in the energetical stabilization of a ligand at the interface of a protein structure. These hydrophobic interactions are optimized by hydrogen bonds at the protein-ligand interface, and this leads to increases the binding affinity of complex molecules. So, drug efficacy and binding affinity related to hydrophobic interactions, can be optimized by including them at the site of the hydrogen bonding [33].

α-Acarbose is a competitive inhibitor of α-glucosidase [34] while montbretin A is a competitive inhibitor of α-amylase [35]. The amino acid residues of active pocket play a physiological role in enzyme activity.

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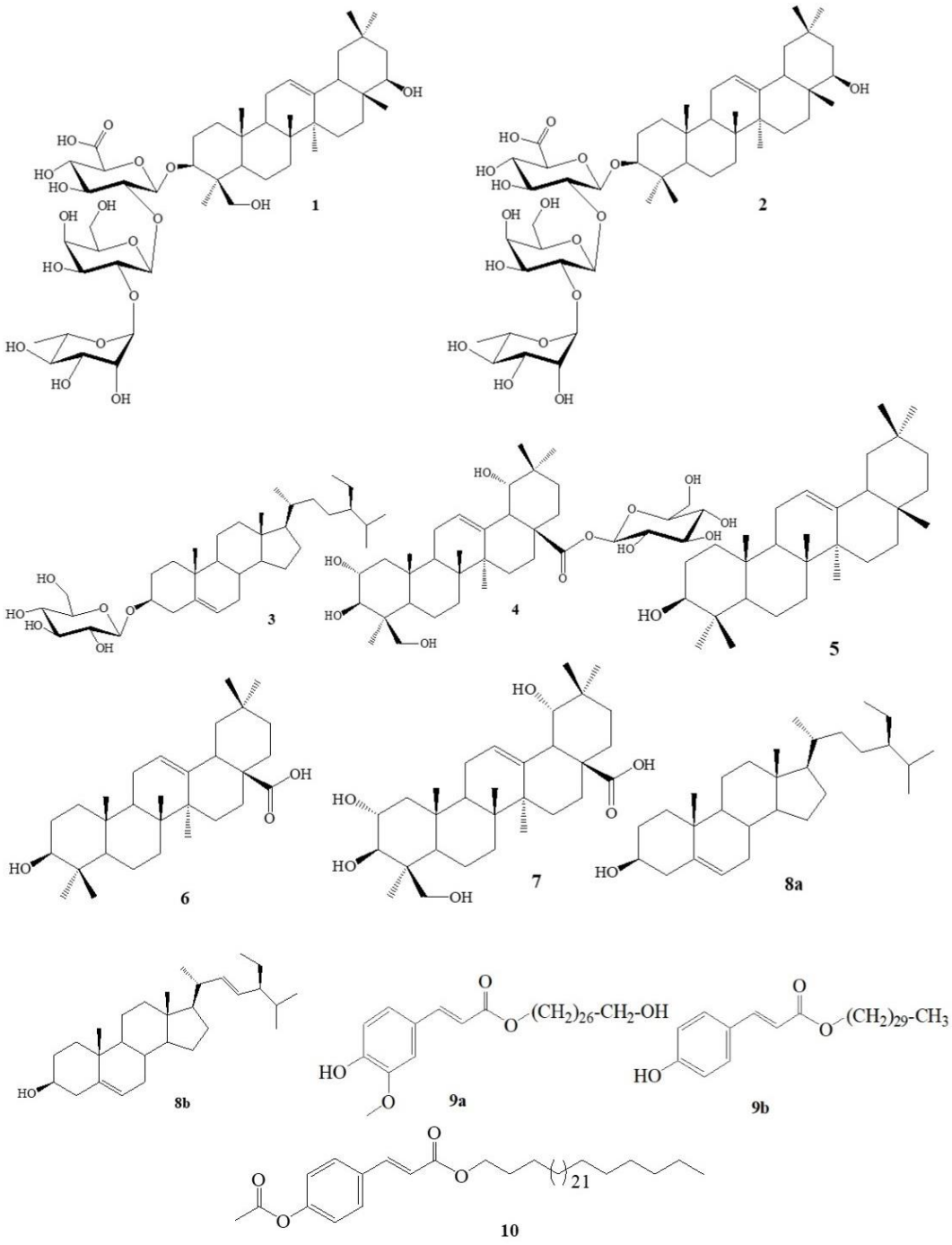

Figure 4. Structures of isolated compounds from *E. senegalensis*

Alpha-acarbose and Montbretin A bind in the active sites of their respective enzymes, inducing conformational changes that lock the enzymes in an inhibited state. The inhibitors prevent the proper binding and processing of the natural substrates by occupying crucial catalytic sites and reducing the flexibility of loops surrounding the active site. These conformational shifts ensure that the enzymes cannot carry out their normal catalytic functions, making them effective inhibitors for regulating carbohydrate digestion and glucose release.

Results of molecular docking analysis corroborate with the previously reported *in vitro* evaluation [10] and allowed to relate saponins triterpenes of oleanane

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classes as potential responsible for the antidiabetic activity of *E. senegalensis* DC.

The identified compounds underwent evaluation for their physicochemical properties using the Swiss ADME tool. The drug-likeness prediction includes the evaluation of properties like hydrophobicity, electronic distribution, hydrogen bonding, molecular weight, pharmacophore entity, bioavailability, reactivity, toxicity, and metabolic stability. Lipinski's rule is an approach commonly used for the prediction of the viability of compounds as prospective drug candidates. This rule helps to predict if a biologically active molecule is likely to have the chemical and physical properties to be orally bioavailable. Lipinski's rule of five (LRO5) defines four simple physicochemical parameter ranges (molecular weight (MW) ≤ 500 Da, number of hydrogen bond donor (nHD) ≤ 5, number of hydrogen bond acceptor (nHA) ≤ 10 and octanol–water partition coefficient (Log P) ≤ 5 and no more than one violation is allowed) that are associated with acceptable aqueous solubility and intestinal permeability and comprise the first steps in oral bioavailability [36]. Then, according to LRO5 and as shown in Table 3, the MW, nHD, nHA, and Log P values of β-amyrin (**5**), oleanolic acid (**6**), sericic acid (**7**), β-sitosterol (**8a**), stigmasterol (**8b**) and erythrinamate (**10**) are within the acceptable range. Among these compounds, only β-amyrin (**5**) did not violate any LRO5 and for the others, no compound violates more than one rule; therefore, these compounds could be considered as drug-like compounds. Soyasaponin I (**1**) and kaikasaponin III (**2**) that also showed potent inhibition to both α-glucosidase and α-amylase (Tables 1 and 2) have three violations each. Those compounds (**1** and **2**) amongst those parameters, were only in recommended range of the octanol–water partition coefficient (Log P), a parameter used to determine the lipophilicity of the selected compounds. Moreover, only Soyasaponin I (**1**), kaikasaponin III (**2**) and sericoside (4) were not in the recommended range value (20-130 Å) for the Total Polarity Surface Area (TPSA), used here for the examination of the polarity of the compounds.

In the process of advanced therapeutic drug development, a profound understanding of pharmacology and toxicology is crucial. These knowledges serve to reduce the period of medication development and increase the success rate. ADMET properties (pharmacokinetic properties) are frequently used to assess the characteristics of a compound. The ADMET parameters of all compounds were obtained from the ADMETLAB 3.0 tool. From the results presented in Table 3, the values for human intestinal absorption (HIA) indicate that Soyasaponin I (**1**), erythrinasinate X (**9a**) and ery-thrinasinate B (**9b**) possess the highest likelihood of being effectively absorbed through the intestinal membrane. Indeed, greater HIA means that the compound could be better absorbed from the intes-tinal tract upon oral administration. The evaluation of plasma protein binding (PPB) is a crucial determinant in assessing the safety profile of medications. Phar-maceuticals with a low PPB value (50-90%) are generally considered to be safer, while drugs with a high PPB value (> 90%) often exhibit a narrow therapeutic index, indicating a smaller margin of safety. In our study, it appears that soyasaponin I (**1**), kaikasaponin III (**2**), daucosterol (**3**) > sericoside (**4**), sericic acid (**7**) and β-sitosterol (**8a**), showed low plasma protein binding (PPB) values, indicating a wide therapeutic index for them. The Blood-Brain Barrier (BBB) is a layer of cells that acts as a filter, keeping harmful substances and pathogens out, and beneficial chemicals in. The penetration through the BBB was better for sericoside (**4**) and oleanolic acid (**6**), followed by β-amyrin (**5**) and sericic acid (**7**). All those compounds are oleanane-type triterpenoids. Prediction of the efflux by P-glycoprote in (P-gp), revealed that daucosterol (**3**), β-amyrin (**5**), β-sitosterol (**8a**), erythrinasinate X (**9a**) and erythrinasinate B (**9b**) came out as a non-substrate and noninhibitor of P-gp. Soyasaponin I (**1**), kaikasaponin III (**2**), sericoside (**4**) and sericic acid (**7**) were substrates/noninhibitors while oleanolic acid (**6**) and stigmasterol (**8b**) were non-substrates/inhibitors. Not being a substrate of P-glycoprotein (P-gp), indicate the possible safe use of those compounds without any toxicological outcome (Référence imp1). In terms of solubility, all derivatives displayed reduced dissolution due to more lipophilic characters. All the other ADMET parameters showing the comprehensive physicochemical and pharmacokinetic profiles of all the derivatives are presented in Table 3.

According to radar charts displaying the comprehensive picture of lower and upper limits of physi-

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cochemical parameters in comparison with the compound properties (Fig. 3), interestingly, most of the parameters are in an acceptable range describing the promising candidates for biological molecules.

5. Conclusions

In this research, we have investigated in *silico*, the binding poses of some isolated compounds from *Erythrina senegalensis* DC leaves and stem bark within the active site cavity of α-amylase and α-glucosidase. Our results displayed that the identified compounds formed many hydrogen and hydrophobic bonds with amino acids residues of the two enzymes (α-glucosidase and α-amylase) and the calculated Gibbs free energy ($\Delta G < 0$) reflected a spontaneous interaction. Moreover, kaikasaponin III (2) and β-amyrin (5), showed the best binding activity towards the α-glucosidase and α-amylase active sites, respectively. Furthermore, *in silico* ADMET study was performed on all of the compounds under consideration, and predicted favorable drug-likeness properties for some of them, especially β-amyrin (5). This comprehensive exploration offers a promising avenue for further investigation into the efficacy of those compounds as α-glucosidase and α-amylase inhibitors in the context of DM drug development. However, further *in vivo* investigations should be done before the validation of these chemoinformatics investigation's findings. The current study consolidates the fact that *E. senegalensis* is a promising source of bio-compounds, that could be considered as therapeutic candidates for DM drug development.

Authors' contributions

Investigation, methodology, writing - original draft, C.T.D.; Conceptualization, methodology, project administration, writing- reviewing and editing, validation, J.N.N.; Investigation, writing - original draft, P.S.; Investigation, methodology, writing - original draft, A.Y.G.; Software, investigation, methodology, writing - original draft; formal analysis, data curation, S.A.E.; Investigation, writing - original draft; formal analysis, R.K.; Software, investigation, methodology, writing - original draft, G.B.B.N.; Formal analysis, Writing- reviewing and editing, J.D.D.; Formal analysis, writing- reviewing and editing, R.T.F.; Data curation, visualization, formal analysis, writing- reviewing and editing, A.V.; Conceptualization, supervision, validation, E.T.

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Availability of data and materials

All data will be made available on request according to the journal policy.

Conflicts of interest

The authors confirm that there is no conflict of interest to declare.

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