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Mitragyna inermis (Willd.) O. Kuntze ethnopharmacology and metabolic disorders: An update review and in *silico* study

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ABSTRACT

Mitragyna inermis is a wild plant whose parts are traditionally used. However, there is no particular report on the compounds bioactivity evidence against metabolic disorders. We carried out a literature review of this plant uses and compounds mostly isolated in diabetic and hypertensive states. Following the review, we carried out an *in silico* study on major targets for research into antidiabetic and antihypertensive candidates. From this study, it emerged that the plant is used in the treatment of diabetes and hypertension. The main compounds isolated from this plant were terpenoids and alkaloids. The *in silico* study revealed that these compounds could inhibit α-amylase, α-glucosidase and sodium glucose co-transporter 2 in diabetic status, as well as angiotensin converting enzyme in hypertensive status. Most of these compounds could be absorbed and metabolized on the basis of ADME (Adsorption, Distribution, Metabolism and Excretion) pharmacokinetic prediction. Further studies are

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needed to optimize its activities and conduct *in vitro* trials.

Keywords: *Mitragyna inermis,* metabolic disorders, *in silico* study, diabetes, hypertension

INTRODUCTION

Mitragyna inermis (Willd.) O. Kuntze leaf, fruit, wood, stalk, bark, root and whole plant are used for a variety purposes. Leaves and roots are used in traditional medicine[1]. Several ethnopharmacological studies have been carried out to reveal extracts and some compounds derived from *M. inermis* various parts pharmacological properties in relation to communicable and metabolic disorders.

Indeed, ethnobotanical studies have shown leaf and bark use in the treatment of body pain and diarrhea[2]. In infection cases, leaf or bundles in decoctions are used to treat urinary tract infection[3]. The aqueous extract of the roots stimulates immune defense[4]. Studies have shown that leaf, root stem bark and alkaloids extracts possess antimicrobial properties[5-8]. Also, bark and leaf in decoction are recommended for recovering human immunodeficiency virus patients, herpes simplex virus-1, poliomyelitis and smallpox[9-11]. That plant finds most application especially in malaria disease. For instance, leaves bundles, leaves, stems, roots and compounds as well as ursolic acid, speciophylline and isorhyncophylline isolated from this plant are used to treat malaria fever and against *Plasmodium falciparum*[12,13]. Furthermore, *M. inermis* parts are used in the management of neuronal failure. Indeed, aqueous, ethanolic and ethyl acetate extracts of *M. inermis* stem bark showed significant anti-seizure effects. Extracts flavonoids and alkaloids have these anticonvulsant properties[14].

Today, non-communicable diseases have overtaken infectious diseases as the world's leading cause of death[15]. Among metabolic disorders, special attention is devoted to cardiovascular disease and diabetes[16]. To the best of our knowledge, there are neither potential compounds isolated from *M. inermis* against these diseases, nor synthetic data bringing attention to this plant use in these diseases' treatment. However, the lower adverse effects of *M. inermis* parts and isolated compounds has been reported[17-19]. Furthermore, α-amylase and α-glucosidase through carbohydrate breakdown are involved in diabetes happening[20,21]. Also, kidney sodium glucose co-transporter 2 is involved in diabetes complications[22]. So, these enzymes inhibitors are required for diabetes treatment. Among hypertension management, Angiotensin Converting Enzyme (ACE) inhibitors are mostly required[23]. The implementation of virtual screening of small molecules can be valuable in the search for novel lead compound with potential for further

exploration in new drug discovery studies[22]. So, the present study aims to review the ethnopharmacological and phytochemical studies relating to diabetes and hypertension on the one hand. Then, to carry out an *in silico* study of alkaloids and terpenoids this plant main compounds on these diabetes and hypertension potential targets in order to orient future research and its rational use.

METHODOLOGY

Data sources and research strategy

Two authors (R.J.O. and L.O.) independently searched electronic databases such as Google, Google Scholar, EMBASE, PubMed, PubChem, Scopus and Science Direct. Relevant articles were searched from inception to May 2023. The search strategic term was "*Mitragyna inermis*" or "*Mitragyna africana*". No restrictions were placed on language or study design. Our exclusion criteria were *Mitragyna speciosa*, *Mitragyna africanus*, *Mitragyna parvifolia*, *Mitragyna rotundifolia*, *Mitragyna rubrostipulata*, *Mitragyna ciliata*, *Mitragyna stipulosa*, *Mitragyna tubulosa*, *Mitragyna hirsuta*, *Mitragyna diversifolia*, *Mitragyna ledermannii*, and *Mitragyna savanica*.

Furthermore, in this systematic review after searching for articles, we removed duplicates, examined titles and abstracts and obtained the full text of each article. We included research classified as *M. inermis* ethnobotanical studies[1], phytochemistry studies[2], antihypertensive properties[3], and antidiabetic properties[4]. Review articles were excluded. Accepted articles and articles in press were included in this mini review. Evaluations were carried out by two independent investigators.

In silico study

The *in silico* study focused on potential targets for diabetes namely α-amylase, Sodium-Glucose co-Transporter 2 (SGLT2) and α-glucosidase, and hypertension namely Angiotensin Converting Enzyme (ACE). Studies relating to the various major compounds of *M. inermis* (alkaloids and terpenoids) were diagnosed on PubChem to avoid any duplication in relation to the chosen metabolic disorder's targets.

Molecular docking

The molecular docking studies were conducted to investigate the *in silico* interactions of alkaloids and terpenoids extract from *M. inermis* against the enzyme's α-amylase, α-glucosidase, SGLT2 and ACE. The purpose of the study was to identify potential inhibitors for these four specific enzymes using compounds extracted from the aforementioned. Finally, for comparison we docked

a typical molecule acarbose against α-amylase and α-glucosidase, captopril against ACE and empagliflozin against SGLT2. All molecular docking analyses were performed using the Molecular Operating Environment (MOE).

Ligand dataset preparation

A library consisting of various compounds was created for molecular studies including all alkaloids and all terpenoids. The ligands were draw by using ChemDraw software and saved in MOL file format. Furthermore, the three-dimensional (3D) structure of the ligands was refined through energy minimization using MMFF94x force field implemented in the MOE software.

Receptors preparation

The 3D structures of the receptors including α-amylase, α-glucosidase, angiotensin converting enzyme and kidney Sodium Glucose co-Transporter 2 (SGLT2) were retrieved from the RCSB Protein Data Bank using the PDB IDs: 4W93[20], 5NN5[21], 1O8A[23] and 2XQ2[22], respectively. Prior to molecular docking studies, the receptors underwent preparation using a previously described protocol[24]. In case of α-amylase, SGLT2 and α-glucosidase, the binding site for docking was determined by extracting the coordinates of the co-crystallized ligand. On the other hand, for angiotensin converting enzyme, the reported catalytic site was selected as the binding site for docking study[25]. The alkaloids and terpenoids were docked into the proposed binding site of the receptors using triangular matcher as a placement method in combination with an induced-fit docking protocol. For post docking analysis, Chimera software was utilized. The 2D interactions occurring among the specific amino acid residues inherent in the proteins under investigation, which are manifested in 3D interactions and the docked ligands were meticulously illustrated using the computational framework provided by Discovery Studio software.

ADME profile prediction

Gastrointestinal absorption and brain access are two pharmacokinetic behaviors crucial to estimate at various stages of the drug discovery processes[26]. The most scoring compounds Adsorption, Distribution, Metabolism and Excretion (ADME) profile were predicted using the SwissADME web server[27].

RESULTS AND DISCUSSION

Botanical aspects

M. inermis (Wild.) O. Kuntze is a medium-sized tree or bushy shrub with smooth or scaly gray bark (Figure 1 a,d)[28].

The species is distinguished by its elliptical, acuminate, wedge-shaped leaves, solitary and terminal cream flowers (Figure 1 b,c,e)[28,29]. This plant produces spherical and dark-brown fruits (Figure 1f)[29,30].

Figure 1. *M. inermis* different parts (a: young plant; b: leaf arrangement on twigs; c: whole leaf in acuminate form; d: stem bark; e: flowers; f: dry fruit)

M. inermis is common of savannah, forest, marsh banks, temporarily flooded sites and on heavy, clayey and poorly drained soils[31]. It grows in temporarily flooded lowlands, ponds and riverbanks in the Sahelo-Sudanian to Guinean zones as well as from Senegal, Mauritania to Cameroon, the Central African Republic, Chad, the Democratic Republic of Congo and Sudan (Figure 2)[30,32]. In Burkina Faso, the species is found in all regions and sometimes in pure stands[30]. Floristic diversity study has shown that the plant appears as a grouping with monospecific development[33]. It develops in groups associating a variety of biological types such as phanerophytes, lianas, therophytes and hemicryptophytes[34]. The plant is reputed to support carbon and nitrogen stor-

age[35-38]. *M. inermis* is one of the top 20 plant species used in Burkina Faso[39]. That plant is among the woody plants with high ethnobotanical use value and would require large-scale reforestation to improve its availability[40]. There are not currently IUCN (International Union for the Conservation of Nature) data on the species vulnerability[41].

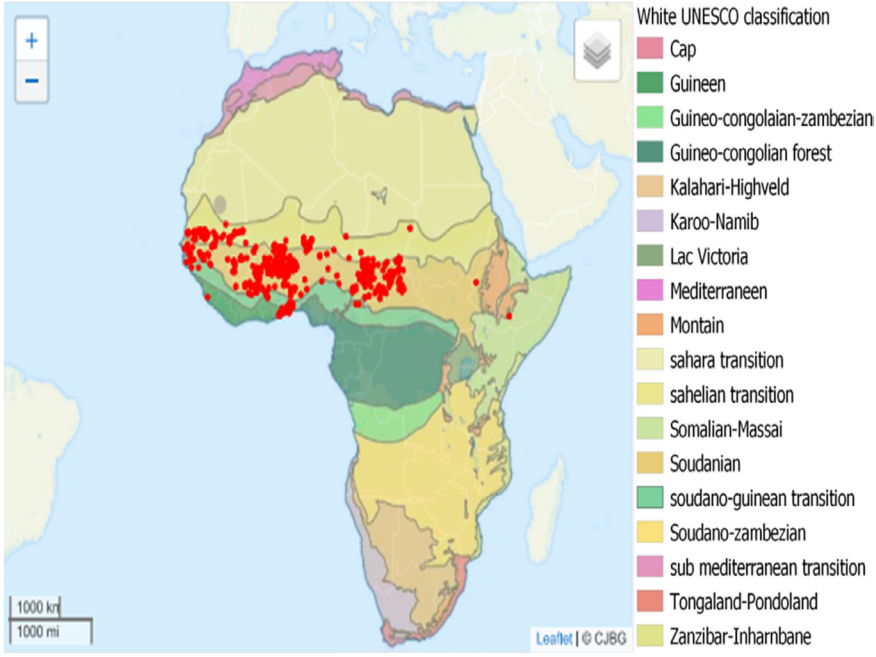

Figure 2. Phytogeography of *M. inermis:* The red dots show the distribution of *M. inermis* plants based on survey data[42].

Phytochemistry

Like other species of Rubiaceae family, *M. inermis* has biochemical potential. However, studies carried out on *M. inermis* have enabled potential compounds or groups of compounds to be identified and highlighted. Their presence is linked to their solvent affinity and the extraction method. Thus, the presence of sterols, triterpenes, polyphenols, flavonoids, catechic tannins, saponosides, quinones and alkaloids has been noted with aqueous leaf decoction[17,43,44]. Also, the presence of tannins, cardiac glycosides, alkaloids, reducing sugars, carbohydrate and flavonoids was reported in leaf methanolic extract[45]. Condensed and gallic tannins, saponin, alkaloids, flavonoids, anthraquinones, glycosides, terpenes and reducing compounds were found in the leaves methanolic and acetone decoction[46,47]. Root and stem bark chloroformic, ethanolic and aque-

ous extracts screening revealed the presence of tannins, reducing compounds, alkaloids, emedols, carotenoids, steroidal and triterpenic saponosides, flavonoids, anthracenosides, leuco-anthocyanins, anthocyanosides, coumarins, phlabotannins and steroids[48-50]. Anthraquinones, mucilage and gums, resin, terpenoids, lignins, steroids, carbohydrates, glycosides, saponins, tannins, alkaloids, flavonoids were screened in the leaves, roots and stem bark[7,51,52]. It has been reported that aqueous leaf decoction total phenolic and flavonoid content are 24.42 mg GAE (Gallic Acid Equivalent)/100 mg, and 0.95 mg QE (Quercetin Equivalent)/100 mg extract, respectively[53]. Total phenolic contents of extracts varying from acetone, ethyl acetate and water of roots, stem bark and leaves ranged from 47.05 to 112.31 mg GAE/g dry matter[54]. *M. inermis* stem bark quantitative phytochemical analysis showed that flavonoids (120 mg/g) was the highest phytochemical detected following alkaloids (62.00 ± 0.33 mg/g), tannins (48.00 ± 0.33 mg/g) and phenols (55.00 ± 0.88 mg/g) while the lowest was saponins (5.0 mg/g)[7]. These results also show solvents leading in bark compounds extraction. In depth, some studies have proceeded to these compounds' isolation and structural elucidation.

Saponosides generally take two forms, depending on whether the aglycone fragment is a triterpene or a steroid[55]. Condensation of an aglycone triterpene with one or more monosaccharides leads to saponosides. Bonding of the saccharide chain to the C-3 of the aglycone leads to monodesmoside-type saponosides; a second bond at position C-28 or C-27 leads to bidesmoside-type saponosides. A rare third bond at any position of the aglycone leads to tridesmoside saponosides. Monodesmosidic and bidesmosidic saponosides with ursane and oleanane-type aglycones are found in *M. inermis* (Figure 3)[18,56-59].

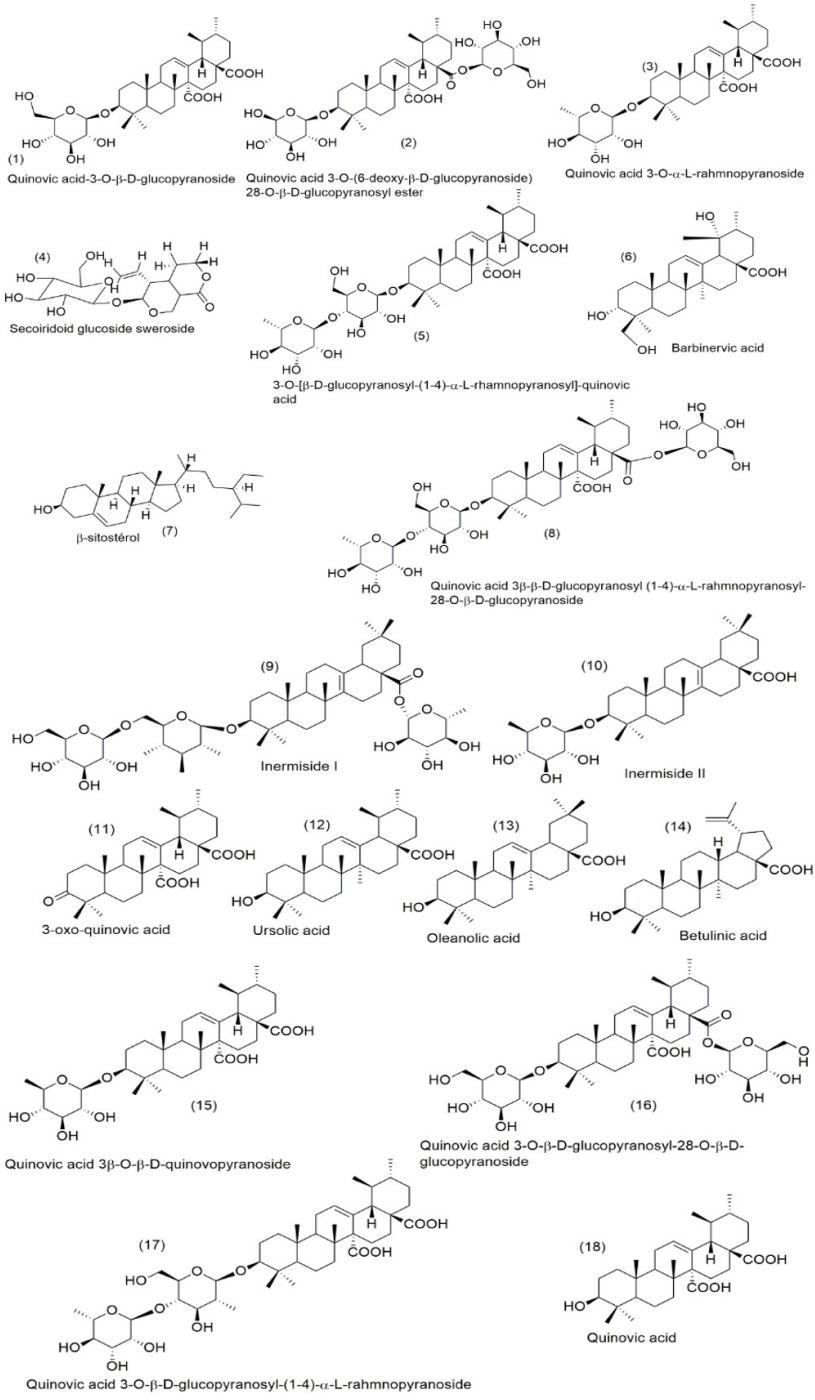

Figure 3. *M. inermis* terpenoids

On the other hand, oxindole alkaloids seem to derive from yohimbine of which secoiridoids are precursors[55]. Tetracyclic oxindoles have four asymmetric centers (C-3, C-7, C-15, and C-20) and pentacyclic oxindoles have five asymmetric centers (C-3, C-7, C-15, C-19, and C-20). Tetracyclic and pentacyclic oxindole and indole alkaloids are found in *M. inermis* (Figure 4)[59-61]. Leaves and barks phytochemistry exhibited these kinds of alkaloids as well as one of their precursors[18]. In addition to alkaloids and saponosides, *M. inermis* leaves, stem bark and roots contain chlorogenic acid and quercetin mono and diglycosides[5]. These data show *M. inermis* various parts may be rich in potentially bioactive compounds.

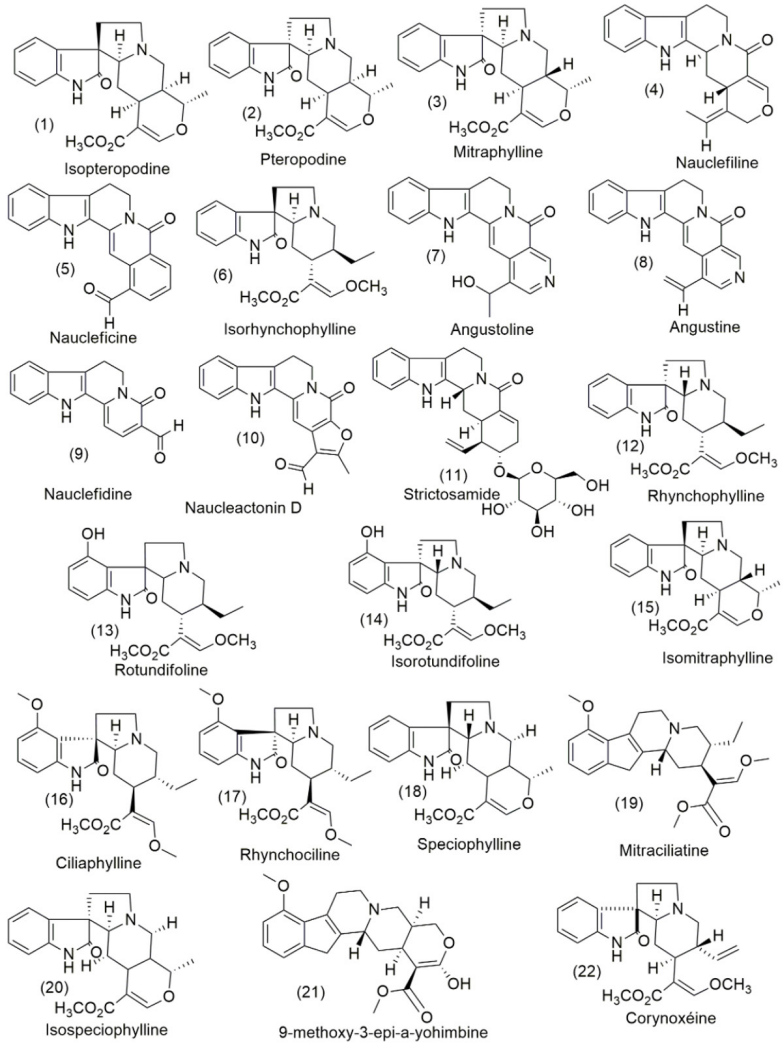

Figure 4. *M. inermis* alkaloids

Ethnobotanical study related to metabolic disorders

Various surveys have been carried out on *M. inermis* traditional knowledge. Leaves and roots are used in liver disease management[62]. Bark decoction and leaves in beverages are used to treat obesity[63]. Leaves and stem barks in decoction or infusion are used in traditional medicine for the treatment of diabetes[64]. In view of this ethnobotanical wealth, a number of studies have reported evidence of its parts use in traditional medicine, both *in vivo* and *in vitro*. Biological properties including, antihypertensive and antidiabetic properties have been reported[44,50,65-67].

M. inermis ingredients antihypertensive capacity

The aqueous extract of *M. inermis* stem bark has hypotensive, cardiotropic and vasodilatory properties. Evidence was provided that aqueous extract from *M. inermis* possess cardiac inotropic effect and induces an increase in coronary flow without inducing tachycardia in isolated heart[68].

M. inermis ingredients antidiabetic capacity

M. inermis parts extracts are reported for their potential to prevent or even treat chronic hyperglycemia and failures leading to diabetes. Thus, Alamin et al.[69] reported *M. inermis* fruits aqueous extract extensive antidiabetic potential. From this study, they showed chronic antihyperglycemic activity at a dose of 400 mg/kg b.w. in streptozotocin-induced diabetic rats orally (p.o.). An improvement in lipid metabolism was also observed suggesting regulation of the NAD+/NADH ratio. However, the aqueous extract of these fruits had no effect on the oral glucose tolerance test. Adoum et al.[58] showed that the anti-diabetic effect of ethanolic stem bark extract *in vivo* at 350 mg/kg b.w. was comparable to that of glibenclamide in diabetic rats induced with intraperitoneal (i.p.) alloxane. These results suggest an increase in insulin production by β–cells, or reduction of glucose absorption in the gastrointestinal tract. In addition, the PBS-buffered extract and aqueous maceration of the leaves resulted in up to 75% inhibition of α-amylase *in vitro*[53,70]. Fruits, stem bark and leaves could be used in the management of diabetes. A recent study reported that plant's properties on diabetes complications. Fractions varying from ethyl acetate, acetone, water and butanol significantly inhibited the formation of glycation end products (AGEs) with IC_{50}s low at the 250 µg/mL. Although, the isolated and individually tested compounds did not show inhibitory activity in AGEs formation[18].

In silico results

Docking analysis of α-amylase inhibitors

Total compound including alkaloids and terpenoids were docked into the active site of α-amylase receptor. Interestingly, the terpenoids exhibited better docking score compared to alkaloids when interacting with the α-amylase receptor. Table 1 displays the five terpenoids and alkaloids that demonstrated best docking scores. Terpenoids 8 and 9 and alkaloids 11 and 19 exhibited docking score -9.66, -9.45, -7.99, and -7.44 kcal/mol, respectively. Notably, terpenoids exhibited superior docking scores in comparison to acarbose, a standard compound with a docking score of -8.49 kcal/mol as shown in Table 1.

Table 1. Docking score of the alkaloids and terpenoids compounds targeting α-amylase receptor

Terpenoids	Docking Score (kcal/mol)	Alkaloids	Docking Score (kcal/mol)
Compound: 1	-8.14214	Compound: 1	-6.44666
Compound: 2	-9.27166	Compound: 2	-6.76994
Compound: 3	-8.14667	Compound: 3	-6.79497
Compound: 4	-6.86704	Compound: 4	-6.62143
Compound: 5	-8.55486	Compound: 5	-6.29868
Compound: 6	-7.81493	Compound: 6	-7.0353
Compound: 7	-7.95475	Compound: 7	-6.21035
Compound: 8	-9.45146	Compound: 8	-6.32868
Compound: 9	-9.66477	Compound: 9	-5.59693
Compound: 10	-7.29294	Compound: 10	-6.30043
Compound: 11	-7.00118	Compound: 11	-7.99939
Compound: 12	-6.92443	Compound: 12	-7.29308
Compound: 13	-6.81734	Compound: 13	-7.2743
Compound: 14	-7.05732	Compound: 14	-7.22914
Compound: 15	-7.73642	Compound: 15	-6.85529
Compound: 16	-8.88075	Compound: 16	-7.09234
Compound: 17	-8.82677	Compound: 17	-7.14176
Compound: 18	-7.53447	Compound: 18	-6.77523
		Compound: 19	-7.44077
		Compound: 20	-6.60598
		Compound: 21	-6.64555
		Compound: 22	-6.94727
Acarbose	-6.89	Acarbose	-6.89

Further analyses were conducted on the protein-ligand interaction. Figure 5 depicts the interaction pattern analysis of two terpenoids that exhibited good docking score with α-amylase receptor. In case of compound 8, it established hydrogen bonds with Asp-197, Glu-233, Glu-240, Asp-300 and His-305 of the protein. The distance for these hydrogen bonds is 2.29, 3.04, 2.55, 1.98, and 2.12 Å, respectively. For compound 9, it formed hydrogen bonds with Tyr-62, Asp-197, Glu-233, and Glu0-240 residues of the protein. The distance for these hydrogen bonds is 2.20, 2.22, 1.89, and 1.88 Å, respectively. Additionally, hydrophobic interactions are observed between compound and Tyr 151, Leu 162 and Ile 235 residues of the protein. According to the findings, these terpenoids appear to have a greater affinity with target receptor in the docking simulation making them potentially effective candidates for more research in drug development investigations. The molecular interaction analysis of alkaloids 11 and 19 with α-amylase receptor revealed that they fit well within the protein binding site as shown in Figure 5. Compound 11 established hydrogen bonds with Gln-63, Tyr-62, Glu-233, and His-305 amino acids of the corresponding protein with a bond distance of 2.96, 3.20, 2.21, and 3.19 Å, respectively. Additionally, this compound formed hydrophobic interaction with Ile-234. Compound 19 formed two hydrogen bonds with Asp-300, and Ala-307 at a distance of 2.61 and 3.21 Å, respectively. Furthermore, compound 19 engaged in hydrophobic contact with Trp-58, Trp-59, Tyr-62, Leu-162, and Ile-235 amino acid of the protein. 2D interaction shows that these compounds exhibited both hydrogen bonding and hydrophobic interaction with α-amylase receptor (Figure 5). These findings support the plausible inhibitory activity of the high scoring compounds.

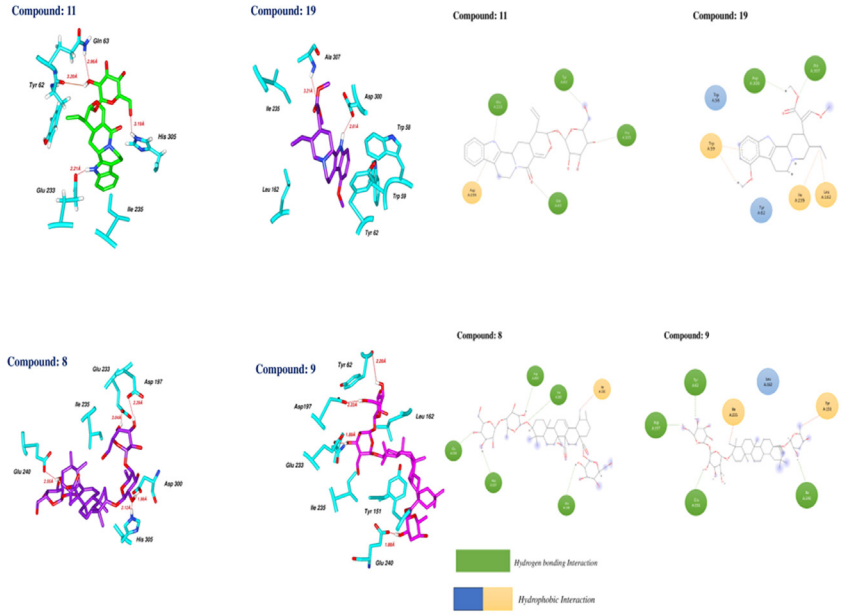

Figure 5. Molecular docking interactions between terpenoids 8 and 9 and alkaloids 11 and 19 with α-amylase (PDB: 4W93). 3D interaction in the right and 2D interactions in the left.

Docking analysis of α-glucosidase

The docking result of the compounds with α-glucosidase disclosed consistent pattern similar to that observed with α-amylase, terpenoids exhibited better docking score than alkaloids. Table 2 displays five compounds, both from terpenoids and alkaloids that demonstrated best docking scores. Additionally, both terpenoids and alkaloids shown higher docking scores than the standard compound acarbose when interacting with α-glucosidase receptor.

Table 2. Docking score of the alkaloids and terpenoids compounds targeting α-glucosidase receptor

Terpenoids	Docking Score (kcal/mol)	Alkaloids	Docking Score (kcal/mol)
Compound: 1	-8.07279	Compound: 1	-6.17872
Compound: 2	-9.19672	Compound: 2	-6.51711
Compound: 3	-8.27856	Compound: 3	-6.19423
Compound: 4	-6.85605	Compound: 4	-5.93376
Compound: 5	-8.93499	Compound: 5	-5.65457
Compound: 6	-5.89858	Compound: 6	-7.15106
Compound: 7	-6.87061	Compound: 7	-5.63317
Compound: 8	-7.35026	Compound: 8	-5.20298
Compound: 9	-8.24143	Compound: 9	-4.97044
Compound: 10	-8.22088	Compound: 10	-5.32063
Compound: 11	-5.75146	Compound: 11	-6.95613
Compound: 12	-5.7025	Compound: 12	-6.30647
Compound: 13	-5.65344	Compound: 13	-5.98386
Compound: 14	-5.13998	Compound: 14	-6.47681
Compound: 15	-7.30929	Compound: 15	-6.62774
Compound: 16	-8.45873	Compound: 16	-6.7234
Compound: 17	-8.78129	Compound: 17	-6.18068
Compound: 18	-5.52423	Compound: 18	-6.78912
		Compound: 19	-6.68291
		Compound: 20	-5.93218
		Compound: 21	-6.5742
		Compound: 22	-6.49402
Acarbose	-6.89	Acarbose	-6.89

Figure 6 displays interaction analysis. Herein, compound 2 which pertains to the terpenoids family, displayed significant interactions, established four hydrogen bonds with Arg-281, Asp-404, Asp-616, and His-674 amino acid of the protein having distances of 2.94, 2.63, 2.63, and 2.72 Å. Compound 5 also formed four hydrogen bonds with distinct residues namely Asp 282, Asp 518, Arg 600, and His 674. The distance for these hydrogen bonds is 2.45, 2.00, 1.96, and 2.12 Å. Both compounds displayed important hydrophobic interac-

tions. Furthermore, alkaloid 6 formed hydrogen bond with Asp-616 amino acid of the protein, with a distance of 2.16 Å. Additionally, Trp-386, Phe-649, and Trp-381 amino acid of the protein formed hydrophobic interaction with compound 6. Alkaloid 11 engaged hydrophobic contact with Asp 282, Ala 555, and leu 650. It established three hydrogen bonds with protein Asp-404, Asp-518 and Arg-600 residues, each having a distance 2.07, 1.95, and 2.16 Å, respectively. 2D interaction shows that these compounds exhibited both hydrogen bonding and hydrophobic interaction with α-glucosidase receptor Figure 6. These findings support the plausible inhibitory activity of the high scoring compounds.

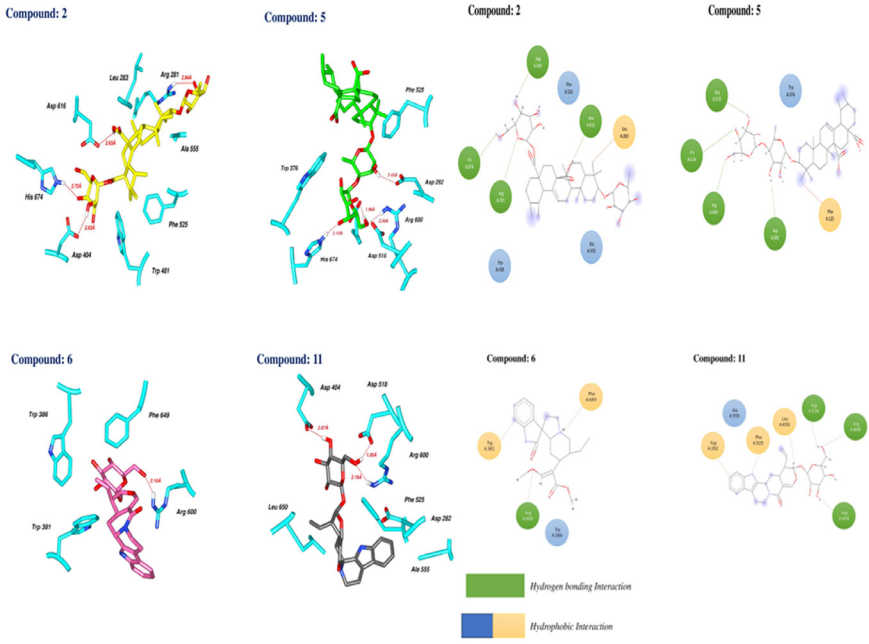

Figure 6. Molecular docking interactions between terpenoids 2 and 5 and alkaloids 6 and 11 with α-glucosidase (PDB: 5NN5). 3D interaction in the right and 2D interactions in the left.

The biochemical basis of most anti-diabetic drugs involves inhibiting the catalytic activities of carbohydrate metabolizing enzymes such as human pancreatic α-amylase and α-glucosidase, which reduces blood sugar levels by suppressing carbohydrate digestion and glucose uptake, making them the primary targets in controlling blood glucose in diabetes mellitus patients[71]. Thus, terpenoids 2, 5, 8, 9, 16, 17, and alkaloids 1, 6, 11, 13, 14, 16, 17, 19 might be potent antidiabetic drugs.

Docking analysis of Angiotensin Converting Enzyme (ACE)

Both alkaloids and terpenoids resided well in the binding site of ACE receptor, virtually show similar docking score as shown in Table 3. In general, terpenoids and alkaloids had higher docking scores when interacting with the ACE receptor than captopril, which is recognized inhibitor of this receptor.

Table 3. Docking score of the alkaloids and terpenoids compounds targeting ACE receptor

Terpenoids	Docking Score (kcal/mol)	Alkaloids	Docking Score (kcal/mol)
Compound: 1	-4.20691	Compound: 1	-6.52445
Compound: 2	-5.3765	Compound: 2	-5.38772
Compound: 3	-4.19894	Compound: 3	-5.98851
Compound: 4	-8.53989	Compound: 4	-6.90636
Compound: 5	-5.55693	Compound: 5	-7.18063
Compound: 6	-3.88615	Compound: 6	-6.27578
Compound: 7	-6.54263	Compound: 7	-7.35921
Compound: 8	-8.765	Compound: 8	-6.86186
Compound: 9	-5.55732	Compound: 9	-6.23907
Compound: 10	-4.87211	Compound: 10	-7.52613
Compound: 11	-4.60608	Compound: 11	-7.48866
Compound: 12	-4.72709	Compound: 12	-5.82266
Compound: 13	-4.32381	Compound: 13	-7.16123
Compound: 14	-5.36818	Compound: 14	-6.22365
Compound: 15	-4.45572	Compound: 15	-6.31605
Compound: 16	-4.71778	Compound: 16	-6.64717
Compound: 17	-6.45235	Compound: 17	-6.71206
Compound: 18	-3.15279	Compound: 18	-5.97653
		Compound: 19	-8.30466
		Compound: 20	-6.14573
		Compound: 21	-8.13562
		Compound: 22	-6.47229
Captopril	-5.31	Captopril	-5.31

The interaction pattern of terpenoids 4 and 7 and alkaloids 19 and 10 have been analyzed and presented in Figure 7. Compound 4 established three hydrogen bonds with the protein's Ala-354, Gln-369 and Asp-377 residues, with bond distances measuring 2.60, 3.08, 2.00 Å, respectively. On the other hand,

compound 7 exhibited only hydrophobic interaction with Pro-163, Ala-354, Glu-376, Val-380, Phe-457, and Tyr-523 amino acid receptor. Compound 19 and 10 demonstrated favorable interaction pattern with ACE receptor. Herein, Compound 19 exhibited hydrogen bonds with Trp-279, Gln-281 and Ala-354 amino acid of the protein with a bond distance of 2.65, 2.79, and 2.82 Å, respectively. Further, hydrophobic interaction also observed between receptor and compound 19. Also compound 10 manifested two hydrogen bonds with Ala-354 and His-513 with bond distance 2.11, and 3.00 Å, respectively. Additionally compound 10 also engaged in hydrophobic interactions with Glu-162, Trp-279, Gln-369, Val-380 and Phe-457 amino acids of the protein. 2D interaction shows that these compounds exhibited both hydrogen bonding and hydrophobic interaction with ACE receptor (Figure 7). These findings support the plausible inhibitory activity of the high scoring compounds.

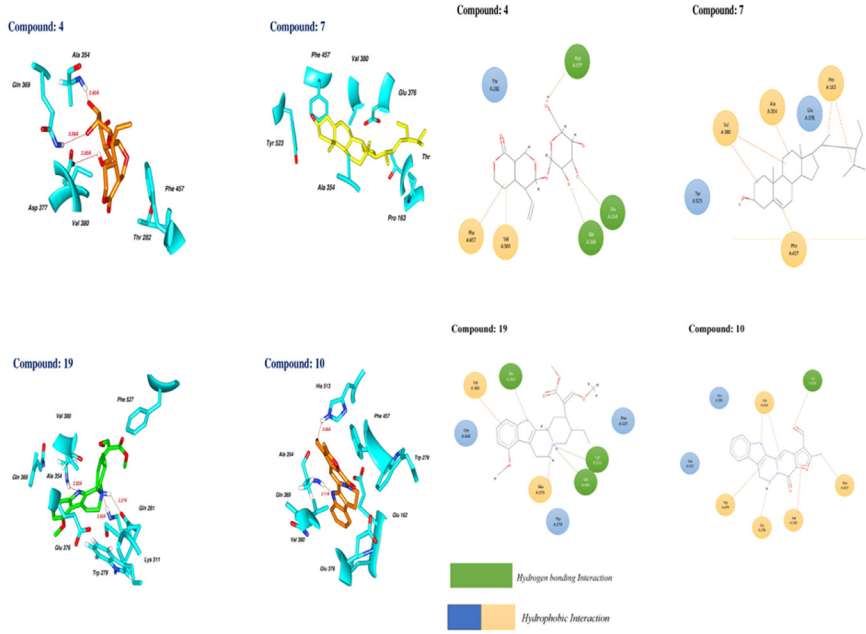

Figure 7. Molecular docking interactions between terpenoids 4 and 7 and alkaloids 19 and 10 with angiotensin converting enzyme (PDB: 108A). 3D interaction in the right and 2D interactions in the left.

ACE is essential for blood pressure regulation and electrolyte homeostasis through the renin–angiotensin–aldosterone system. So, ACE inhibitors are a first line of therapy for hypertension, heart failure, myocardial infarction and diabetic nephropathy[23]. However, terpenoids 4,5,7,8,17 and alkaloids 5,7,10,11, 19 might be potent antihypertensive drug candidates.

Docking analysis of Sodium Glucose co-transporter 2 (SGLT2)

The docking results of terpenoids and alkaloids with SGLT2 receptor shown a lower affinity than the other three suggested receptors namely α-glucosidase, α-amylase and ACE receptors. Table 4 presents docking result of terpenoids and alkaloids with SGLT2 receptor. Interestingly, the terpenoids exhibited better docking score compared to alkaloids when interacting with the receptor.

Table 4. Docking score of the alkaloids and terpenoids compounds targeting SGLT2

Terpenoids	Docking Score (kcal/mol)	Alkaloids	Docking Score (kcal/mol)
Compound: 1	-5.55716	Compound: 1	-4.95916
Compound: 2	-6.5534	Compound: 2	-4.73264
Compound: 3	-5.69784	Compound: 3	-4.91457
Compound: 4	-5.0918	Compound: 4	-4.84715
Compound: 5	-6.4528	Compound: 5	-4.65885
Compound: 6	-5.19954	Compound: 6	-4.84331
Compound: 7	-5.11214	Compound: 7	-4.90466
Compound: 8	-6.40594	Compound: 8	-4.58541
Compound: 9	-6.77291	Compound: 9	-4.49578
Compound: 10	-5.73278	Compound: 10	-4.64818
Compound: 11	-4.92561	Compound: 11	-5.76122
Compound: 12	-4.72267	Compound: 12	-4.81659
Compound: 13	-4.69988	Compound: 13	-5.17577
Compound: 14	-4.77389	Compound: 14	-4.90317
Compound: 15	-5.71305	Compound: 15	-4.91769
Compound: 16	-5.94821	Compound: 16	-4.92341
Compound: 17	-6.37138	Compound: 17	-5.18537
Compound: 18	-4.75509	Compound: 18	-4.75765
		Compound: 19	-4.94668
		Compound: 20	-4.84495
		Compound: 21	-5.48553
		Compound: 22	-4.75224
Empagliflozin	-4.87	Empagliflozin	-4.87

The interaction pattern of terpenoids 2 and 9 with SGLT2 receptor are shown in Figure 8. Compound 2 formed three hydrogen bonds with Tyr 570, Ile 572, and Lys 573 residues with bond distance of 2.45, 2.27, and 2.23 Å. Conversely, compound 9 only engaged in hydrophobic interaction with Tyr 570 and Ile 570 residues of the receptor. The Compound 11 demonstrated formation of one hydrogen bond with Lys 576 residue at a 2.64 Å. In contrast compound 21 form two hydrogen bonds with Ser 569 residue of the receptor, at 2.48 and 2.69 Å. It is noteworthy that both compounds also shown hydrophobic interaction with the SGLT2 receptor as presented in Figure 8. In general, terpenoids and alkaloids had higher docking scores when interacting with SGLT2 receptor than empagliflozin which is recognized inhibitor of this receptor. 2D interaction shows that these compounds exhibited both hydrogen bonding and hydrophobic interaction with SGLT2 receptor (Figure 8). These findings support the plausible inhibitory activity of the high scoring compounds.

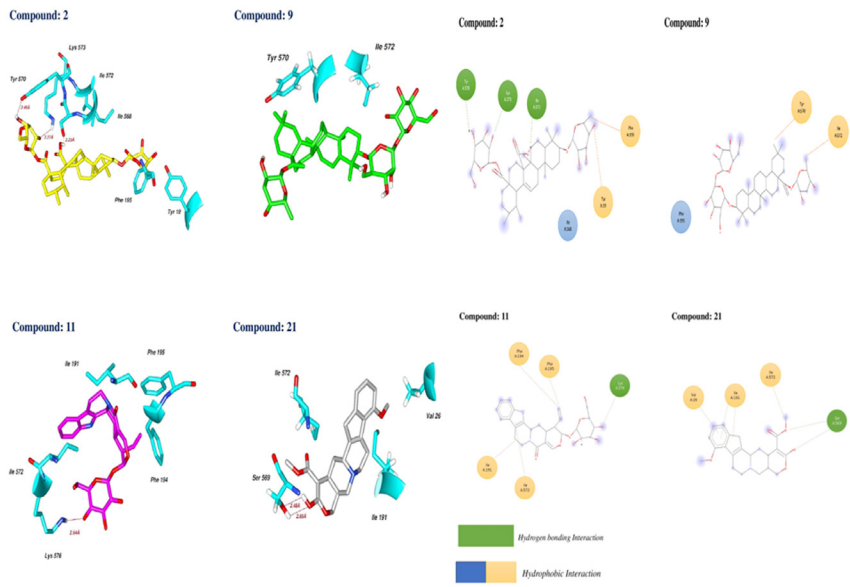

Figure 8. Molecular docking interactions between terpenoids 2 and 9, alkaloids 11 and 21 with sodium-glucose co-transporter 2 (PDB: 2XQ2). 3D interaction in the right and 2D interactions in the left.

However, sodium-glucose co-transporters are molecular targets for drugs to treat diabetes and obesity[22]. Thus, terpenoids 2,9 and alkaloids 11,21 might be potent antidiabetic drugs. However, all compounds appeared to be non-selective inhibitor of α-amylase, α-glucosidase, ACE, and SGLT2. It has been

reported that in most cases, diabetes is associated with high blood pressure[72]. Thus, these non-selective compounds might be suitable drug candidate for both diabetes and these complications management.

Pharmacokinetic of the most scoring compounds

Physicochemical data shown seven scoring compounds with highest probability of being absorbed by the gastrointestinal tract and to permeate to the brain, six scoring compounds with highest probability to permeate to the brain and seven scoring compounds non-permeant as shown BOILED-Egg prediction in Figure 9 and Table 5.

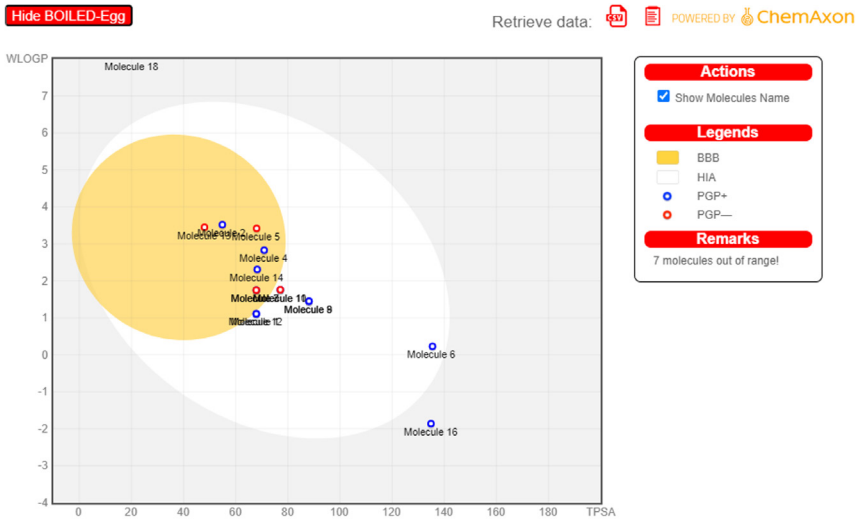

Figure 9. BOILED-Egg (Brain Or IntestinaL EstimateD permeation predictive model) prediction

Table 5. High scoring compounds ADME profiles

Compound	TPSA	Log P	Solubility	GI Absorption	BBB Permeability	CYP2D6 Inhibition
Alkaloid: 1	67.87	1.85	Soluble	High	No	Yes
Alkaloid: 5	54.86	3.09	Moderately	High	Yes	No
Alkaloid: 6	67.87	2.43	Soluble	High	Yes	Yes
Alkaloid: 7	70.91	2.52	Soluble	High	Yes	Yes
Alkaloid: 10	68.00	2.85	Soluble	High	Yes	No
Alkaloid: 11	135.48	0.90	Soluble	High	No	No
Alkaloid: 12	67.87	2.46	Soluble	High	Yes	Yes
Alkaloid: 13	88.10	2.12	Soluble	High	No	Yes
Alkaloid: 14	88.10	2.12	Soluble	High	No	Yes
Alkaloid: 16	77.10	2.41	Soluble	High	No	Yes
Alkaloid: 17	77.10	2.34	Soluble	High	No	Yes
Alkaloid: 18	67.87	1.83	Soluble	High	No	Yes
Alkaloid: 19	48.00	3.50	Moderately	High	Yes	Yes
Alkaloid: 21	68.23	2.47	Soluble	High	Yes	Yes
Terpenoid: 2	253.13	1.38	Moderately	Low	No	No
Terpenoid: 4	134.91	-0.78	Very	Low	No	No
Terpenoid: 5	232.90	2.15	Moderately	Low	No	No
Terpenoid: 7	20.23	7.24	Poorly	Low	No	No
Terpenoid: 8	312.05	0.69	Moderately	Low	No	No
Terpenoid: 9	257.68	1.74	Poorly	Low	No	No
Terpenoid: 16	236.06	2.38	Poorly	Low	No	No
Terpenoid: 17	212.67	3.11	Poorly	Low	No	No

TPSA: Total Polar Surface Area; Log P: Consensus Log P; GI: Gastrointestinal; BBB: Blood Brain Barrier; CYP2D6: Cytochrome P2D6.

Gastrointestinal absorption and brain access are two pharmacokinetic behaviors crucial to estimate at various stages of the drug discovery processes[26]. According to pharmacokinetic study, terpenoids are lowly absorbed by the gut. Then, they might be the good post-prandial drug for digestive enzymes inhibition as well as α-amylase and α-glucosidase. These compounds are probably metabolized and eliminated according to the failing of CYP2D6 inhibition. However, alkaloids are on the high gastrointestinal absorption, so must not be the suitable drug for gut and salivary enzyme inhibition. Alkaloids 5, 10, and

11 might be probably eliminated by cytochrome P450. Therefore, inhibition of cytochrome P450 is certainly one major cause of pharmacokinetics-related drug-drug interactions leading to toxic or other unwanted adverse effects due to the lower clearance and accumulation of the drug or its metabolites[27].

M. inermis ingredients have antihypertensive and hypoglycemic properties supported by its leading chemical composition. The virtual study reveals terpenoids and alkaloids isolated from *M. inermis* are potential various drugs. Our study provides an *in silico* interpretation of the antihypertensive and antidiabetic potential of *M. inermis* metabolites as well as providing sufficient evidence for future research with suitable targets on these agents and linking their pharmacological actions to the host. Thus, assuming that plant is a leading source of promising bioactive compounds. Herein, these various studies show the importance of the species in promoting traditional and complementary medicine. The species is relatively abundant in Burkina Faso and is growing rapidly. However, study reported the vulnerability of this species in its biotope like others due to overexploitation in traditional medicine. Thus, this species deserves to be safeguarded for future generations. Further study may allow identification or any pharmacophores adding for new class drugs with optimizing activities discovery.

STATEMENT OF ETHICS

Not applicable.

CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept – R.J.O, L.O.; Design – R.J.O., N.A.; Supervision – L.O., Z.U., G.A.O.; Data Collection and/or Processing – R.J.O., N.A., L.O.; Analysis and/or Interpretation – R.J.O., N.A.; Literature Search – R.J.O, L.O.; Writing – R.J.O., N.A.; Critical Reviews – L.O., Z.U., G.A.O.

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