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Chemical profiling and *in-silico* study of *Phragmanthera incana* (Schum.) Balle species Growing on *Albizia lebbeck* (L.) Benth in the management of type 2 diabetes

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Abstract

Synthetic drugs have relatively attained its optimal significant potency to manage various diseases but with series of side effects that emanates from its administration. Hence, the need to exploit safer alternative therapies, like the use of medicinal plants, for newer compounds with therapeutic potential to manage type 2 diabetes. Ethnobotanical study has claimed that *Phragmanthera incana* leaves have antidiabetic potential. Thus, this study focuses on investigating *P. incana* for its phytochemicals as well as isolating bioactive compounds for docking studies. Extraction using a cold maceration method with solvents of varying polarities, including hexane, chloroform, ethyl acetate, methanol, and a butanol/water mixture was done to afford PH, PC, PE, PM, and PB as the respective extracts. The study found that these leaves contain a diverse range of compounds, including alkaloids, saponins, tannins, phenols, and others. The hexane extract was partitioned by column chromatography to isolate bioactive compounds, which were subsequently characterised using FTIR, NMR, and MS spectroscopic techniques. This led to the identification of Friedelin and 1-octadecene. The *in silico* studies showed Friedelin as the most promising compound with a binding energy of -10.2 kcal/mol. It was revealed to be a potential antidiabetic agent but immune-toxic. The study also designed derivatives of Friedelin to mitigate this immunotoxicity, particularly two compounds coded BAM2 and BAM4 were derived and found to be non-toxic. In summary, the study highlights the potentials of Friedelin isolated from *Phragmanthera incana* leaves for the management of diabetes and the development of its safer derivatives of as potential drug candidates.

Keywords: *Phragmanthera incana*; Chemical profiling; *in-silico* study; Friedelin; Diabetes

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Introduction

Phragmanthera incana (Schum.) Balle (syn. *Phragmanthera capitata* (Sprengel) Balle, is commonly known as 'mistletoe' and 'Afomo onisaana' in Yoruba (South-West, Nigeria), is a semi-parasitic plant characterized by its yellow flowers with red or purple tips (Ibrahim and Ayodele, 2013). This plant exists in varying forms, with its young parts and perianth densely covered in hairs and bearing red berries. It can be found in secondary jungles, bushy savannas, and as a shrub with long stems reaching about 2 meters in length (Adesina *et al.,* 2013). The host trees for *P. incana* identified in Nigeria include: *Psidium guajava, Cola acuminata, Anacardium occidentale* and *Mangifera indica* (Ogunmefun *et al.,* 2013).

The healing versatility of *P. incana*, has been widely reported in the treatment of various conditions such as insomnia, diabetes, cancer, gastrointestinal disorders, microbial infections, infertility and hypertension (Afolayan *et al*., 2016; Ogunmefun *et al*., 2016). In a report by Sanni *et al.* (2018), the antidiabetic potential

of *P. incana* hot infusion and its possible inhibitory effects on carbohydrate digesting enzymes, promotion of muscle glucose uptake, and the antioxidative potentials in Fe^{2+}-induced oxidative stress in hepatic tissue were investigated and results showed that the hot water infusion of *P. incana* leaf did not only exhibit antidiabetic potentials by decreasing the activities of carbohydrate digesting enzymes and increasing muscle glucose uptake, it also abated oxidative stress in hepatic tissues. The report concluded that the protective effects of the leaf infusion against oxidative damages related to T2D was attributed to the constituents of *P. incana.* (Sanni *et al.,* 2018). Herein, we report on the extraction, isolation and investigation of phytochemicals from *P. incana* leaves growing on *Albizia lebbeck* (L.) Benth., and their potential as antidiabetic agents. Also, the docking studies of the isolated bioactive compounds from *P. incana* was reported. The limited reports on the isolation of compounds from *Phragmanthera incana* (Schum.) Balle drives this study, we report the first isolation of friedelin and octadecene from *Phragmanthera incana* which was specifically growing on *Albizia lebbeck* (L.) Benth.

Diabetes mellitus is a global concern to public health and development, specifically for its secondary complications (Guerra *et al.*, 2021). Optimal glycemic control is the aim of diabetes care (Malik *et al.,* 2022). Oral drugs for treatment have been reported, as well as their efficacy in managing diabetes but the side effects are worrisome, this includes, weight gain, extreme erratic hypoglycemia and resistance to drugs (Padhi *et al.*, 2020). Hence, the need to explore alternative safer approach with little or no side effects. Alternative therapeutic approaches, such as medicinal plants, which offer affordability, widespread availability, easy accessibility, minimal risk of adverse effects, and demonstrated effectiveness in delivering dependable antidiabetic benefits to individuals have been explored. Structural bioinformatics, molecular docking as well as pharmacophore modeling are some computational approaches that have been identified (Angadi *et al.*, 2013). Bioinformatics tools have been useful to precisely identify target proteins for different ligands related to diabetes (Sharma *et al.,* 2020)

In this study, we report on the extraction, isolation and investigation of phytochemicals from *Phragmanthera incana* leaves growing on *Albizia lebbeck* (L.) Benth., and their potential as antidiabetic agents. Also, the docking studies of the isolated bioactive compounds was reported.

Materials and Methods

Chemicals and reagents utilised were of analytical grade and were procured from Sigma Aldrich and Merck.

Plant collection, authentication, and preparation

Fresh leaves of *P. incana* were obtained in October, 2017, from the Lagoon front, University of Lagos, Akoka, Lagos State, Nigeria (latitude between 6.28° and 6.46°, Longitude between 3.37° and 3.67°). The plant was authenticated at the Herbarium of the Department of Botany, University of Lagos, by Mr. Daramola and Mr. Odewo. Voucher specimen was deposited with reference number LUH 1863.

Leaves were rinsed and air-dried at ambient temperature for two weeks. They were pulverised using an electric hammer mill model TRAPP TRF 80 Hammer mill foliage. The pulverised leaves were stored in a sealed container until required for further use.

Extraction of Plant Samples

Plant preparation and extraction were carried out as described by Cowan (1999) with some modifications. Pulverised leaves of *P. incana* plant (1.5 kg) were extracted exhaustively in 2 L solvents of different polarities using the cold maceration method. The solvents were n-Hexane (100%), chloroform (100%), Ethyl acetate (100%), methanol (100%) and butanol/ water (50: 50). The maceration was done at room temperature for 3 days with repeated agitation. The process of extraction was repeated thrice. PH (*P. incana* in hexane), PC (*P. incana* in chloroform), PE (*P. incana* in ethyl acetate), PM (*P. incana* in methanol) and PB (*P. incana* in butanol/water) extracts were obtained. The dried crude extracts were kept in amber bottles and refrigerated at 4°C for further analyses. The weight of each crude extracts were as follows: PH 250.3 g, PC 370.3 g, PE 186.9 g, PM 215.3 g and PB 526.2 g, respectively.

Qualitative Phytochemical Analysis

Phytochemical screening of *Phragmanthera incana* leaf followed the protocol described by Roghini and Vijayalakshmi (2018) and Harborne (1998) methods to detect the presence of saponins, tannins, flavonoids, steroids, anthocyanin and alkaloids, terpenoids, glycosides, quinones, cardiac glycosides, coumarins, phlobatannins, anthraquinones, phenols.

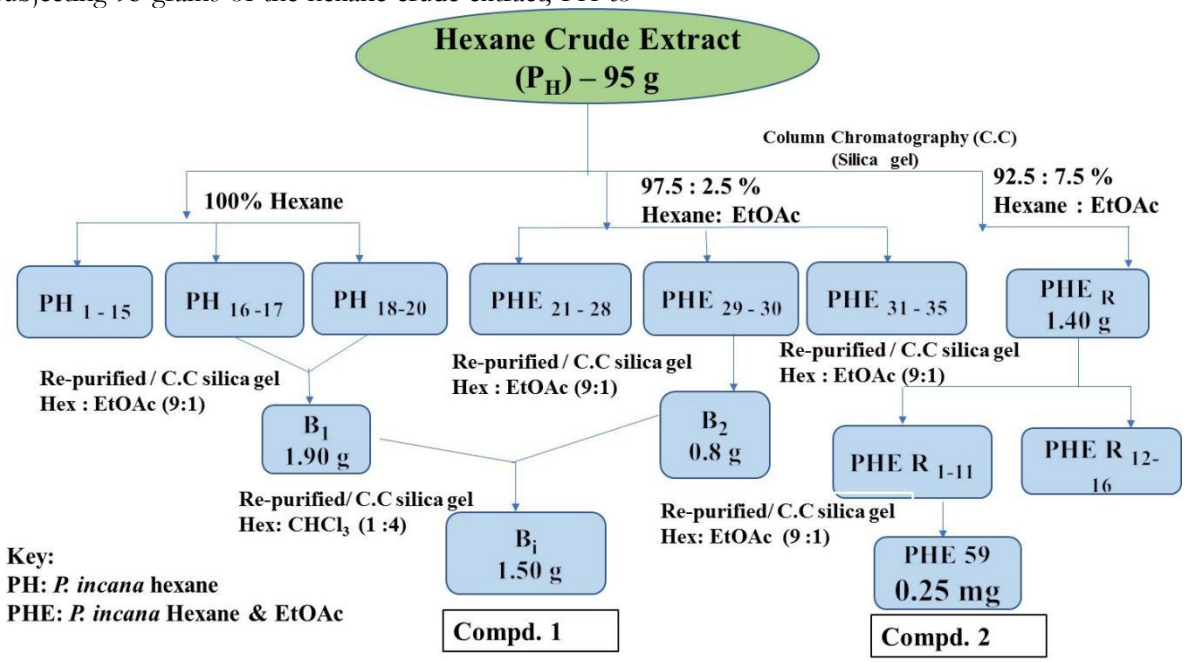
Quantitative Phytochemical Analysis

Quantitative phytochemical screening was carried out on the extracted leave samples using standard

procedures by UV-visible spectrophotometer (UV–VIS spectrophotometer (Spectrumlab 752S).(Roghini and Vijayalakshmi, 2018).

Isolation

The isolation process of *P. incana* leaves involved subjecting 95 grams of the hexane crude extract, PH to column chromatography. This crude fraction yielded, PH_{1-15}, PH_{16-17} and PH_{18-20} from 100% Hexane; PHE_{21-28}, PHE_{29-30} and PHE_{31-35} from 97.5% : 2.5% Hexane : Ethyl acetate; and PHE_{59} (R) from 92.5% : 7.5% Hexane : Ethyl acetate. The fractions were further partitioned and purified to give Compounds 1 and 2 as described in Scheme 1.



Scheme 1: Flow chart of isolation of Compounds 1 and 2 from hexane extract (PH) of *P. incana* leaf

Docking Studies

The *in-silico* studies which is the drug-likeness characteristics of compounds was carried out on the two isolated compoundsfrom this study, in addition to six previously documented compounds (Sanni *et al.*, 2018) from *P. incana*. The compounds were specifically assessed for their potential antidiabetic effect and toxicity. The compounds used were Friedelin, 1-octadecene, S-methyl-L-cysteine, 5-methy-1*H*-indole-2,3-dione, 1-methyl-isoquinoline, nicotinic acid, L-cysteine and 2-methoxythiazole.

The protein crystals that contribute to diabetes pathogenesis utilised include; human HLA-DQ8 for immune system (PDB ID: 5UJT), alpha-amylase hydrolase oxidoreductase (PDB ID: 1U2Y), human multidrug resistance protein 1 nucleotide binding domain 1 transport (PDB ID: 2CBZ), human glucose-fructose-6-phosphate amidotransferase (PDB ID: 2ZJ3), activated insulin receptor tyrosine kinase (PDB ID: 1IR3), human cytochrome P450 oxidoreductase (PDB ID: 3LC4), RNA-dependent polymerase (PDB ID: 6M71), human insulin degrading enzyme (IDE) hydrolase (PDB ID: 4RE9), dual binding AMP fructose 1,6- bisphosphatase hydrolase (PDB ID: 2JJK) and monomeric allosteric enzyme human glucokinase transferase (PDB ID: 1V4S), these crystals were obtained from the RCSB Protein Data Bank (http://www.rcsb.org).

Docking calculations were carried out on the eight compounds. AutoDock parameter set and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively (Harley *et al.*, 2021). This was followed by determination of binding sites of selected target receptors using Discovery Studio software to predict the ligand binding sites.

The characteristics of the components of *P. incana* and Friedelin modified structure needed for virtual screening were retrieved from Pubchem data base at http://pubchem.ncbi.nlm.nih and drawn using Chemdraw 14.0 respectively. All ligands were saved in sdf format and the docking analyses were carried out by means of the Autodock tools (Angadi, 2013; Rani *et al.,* 2022) (ADT) v1.5.4 and Autodock v4.2 program; (Autodock, Copyright-2020) to predict their drug likeness. The conformations with the lowest energy

were selected for further analysis. The 2D interactions of the complex protein-ligand structure, including hydrogen bonds and the bond lengths, were analyzed. The Absorption, Distribution, Metabolism, Excretion, and Toxicity of ligands in the human body (ADMET) was used to predict the behaviour of the phytochemicals. To assess toxicity, Protox II webserver was used to ascertain the compounds' toxicity level, their hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity and cytotoxicity were assessed.

Seven hypothetical derivatives of Friedelin were designed through structure activity relationships to checkmate toxicity issues. This involves the addition reaction between Friedelin and aniline, 2-methoxy-5-methylaniline, 4-methylaniline, 2-iodoaniline, 2-chloroaniline, benzylaniline and 2-iodo-5-chloroaniline. The 2D structures were subjected to toxicity test using Protox II webserver.

Results and Discussion

Yield of Extracts

The extractive process of 1.5 kg of pulverized leaves of *P. incana* plant using solvents of different polarities with cold maceration afforded five crude matrices, of which the butanol/ water extract had the highest yield of 526.2 g (10.52 %), followed by chloroform extract 370.3 g (7.41 %), hexane 250.3 g (5.01 %), methanol 215.3 g (4.31 %), and ethyl acetate 186.9 g (3.74 %).

Qualitative and Quantitative Phytochemical Analyses

Phytochemicals such as alkaloids, glycosides, terpenoids, steroids, anthocyanins, and resins were present in all the extracts except for phlobatannins. The quantitative analysis results obtained revealed that *P. incana* leaves contained a high percentage of total alkaloid (64%) followed by total tannins (57%)(Table 1).

Table 1: Quantitative Phytochemistry Results of *P. incana* (mg/100g)

S/N	Phytochemical constituents (mg/ 100g)	Concentration in (mg/ 100g) of leaf extract Methanolic extract
1	Total Tannins	56.74 ± 0.34
2	Total Phenols	24.40 ± 0.25
3	Total Reducing sugar	24.91 ± 0.16
4	Total Alkaloid	64.20 ± 1.01
5	Total Flavonoid	8.90 ± 0.13
6	Total Saponin	7.62 ± 0.59
7	Total Cardiac glycosides	18.01 ± 0.11

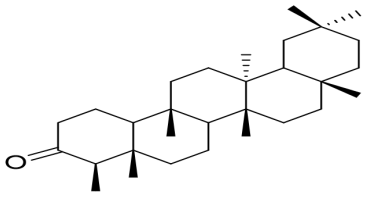
The mean values and standard error mean (S.E.M) are presented.

Isolation and Structural Elucidation of Friedelin and 1-octadecene

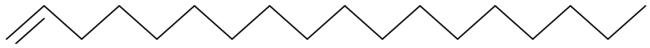
Compound 1 was isolated as a colourless needle-like crystal (0.85 mg, Rf: 0.53) m. pt, 261-263^{o}C, $C_{30}H_{50}O$, molecular weight 426.73 g/mol. Compound 1 was identified by IR, MS and 1D & 2D NMR spectroscopic methods. The IR, ^{1}H, ^{13}C and DEPT as well as MS spectra (Figures 2a-d) are consistent with literature data. The IR spectrum revealed a vibrational stretching absorption at 2922 cm^{-1} and 2848 cm^{-1}, characteristic of CH_2 and C-H stretch of the aliphatic functional group as well as the vibrational frequency of 1715 cm^{-1}, signifying the presence of the characteristic carbonyl ketone (Figure 2d). The ^{1}H NMR indicates that Compound 1 is a saturated steroid-like compound with proton signals between 2.5 and 0.7 ppm. The three signals from 2.4 to 2.2 ppm are from protons that are direct neighbours of the ketone group. The protons of the methyl groups are seen upfield towards the TMS. The ^{13}C NMR reveals the presence of seven quaternary carbon atoms of which the characteristic ketonic group is found at δ C- 213.3 ppm (C-3). Also, similar to that in literature, found at 231.1 ppm are four carbon atoms of the methine groups seen downfield (C-4, 58.2; C-8, 53.1; C-10, 59.5 and C-18, 42.8), eleven methylene carbon atoms and eight methyl carbon atoms where identified to justify 30 carbon atoms of the friedelin skeleton, the mass spectra revealed molecular ion at m/z 426. (Lizazman, *et al.,* 2023; Ambarwati, *et al*., 2019; Sicker, *et al*., 2019).

Compound 2 (1-Octaecene) (Figure 1) was isolated as a colourless liquid; Rf: 0.47, m.pt. 15-18^{o}C, molecular formula $C_{18}H_{36}$ and molecular weight 252.49 g/mol. The IR spectrum revealed vibrational frequencies at 3019 cm^{-1} (the characteristic alkene functional group), 2922 cm^{-1} and 2851 cm^{-1} (representing the vibrational frequencies of CH_2 and C-H stretch of the aliphatic group (Figure 3d). The ^{1}H NMR of Compound 2 (Figure 3a) revealed all the characteristic peaks

in their different environment, the methine protons were observed downfield at δ 5.85 - 4.89 ppm, influenced by the presence of the alkene functional group, which is the characteristic peak of the compound along with the single methyl proton found upfield, δ 0.87 ppm. Likewise, the methylene protons neighbors to the alkene functional group were observed between δ 2.06-1.99 ppm. The ^{13}C NMR showed the characteristic carbon peaks at δ 139.3, 114.1, 37.1, 33.9 and 29.7 ppm due to the presence of the alkene group, the carbon atoms of the methyl group were seen at δ 14.1 ppm (Figure 3b). The ^{135} DEPT NMR displayed two peaks in the positive axis which belonged to the methyl and methine carbon atoms at their respective environment (δ139.3and 14.1 ppm) and the seven methylene carbon atoms seen on the negative axis (Figure 3c). The mass spectrum of 1-octadecene showed a base peak of 43 and molecular ion of 250.0 signifying fragmentation pattern of ($M^+ - H_2$), characteristic of 1-octadecene.

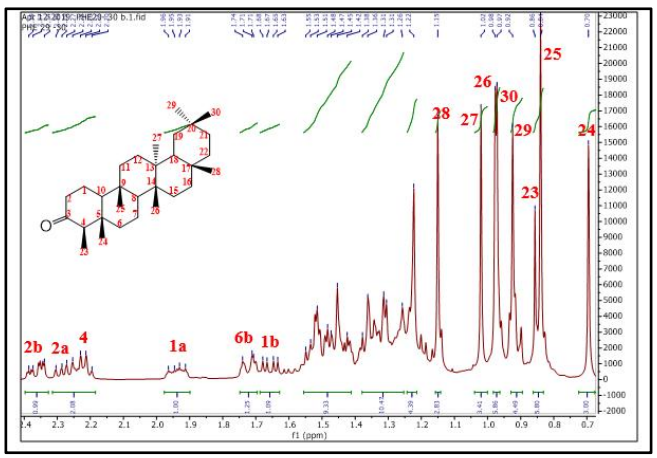


Friedelin

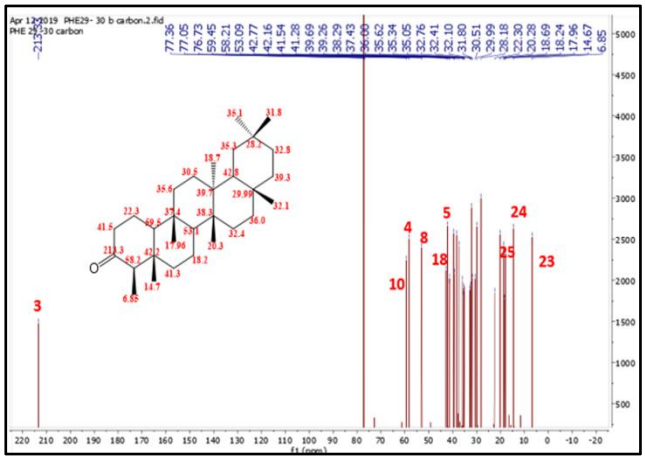


1-Octadecene

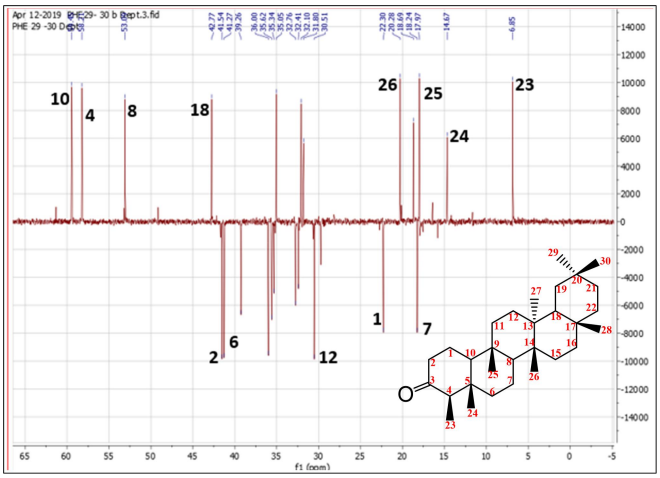
Figure 1: Structures of Friedelin and 1-Octadecene



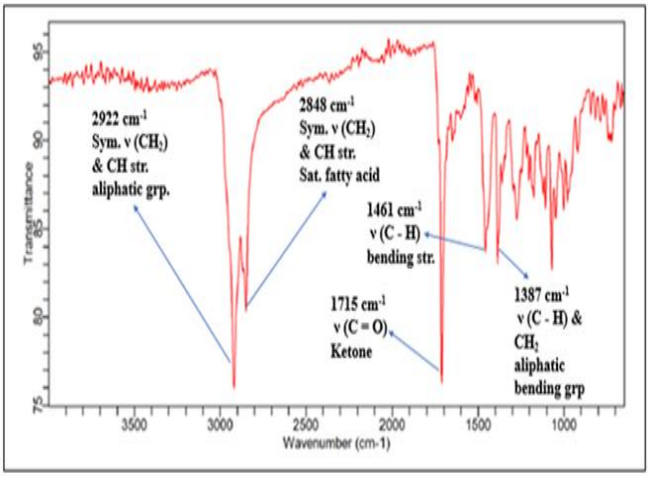
(a)



(b)



(c)



(d)

Figure 2: Spectroscopic data of Compound 1 (a) ^{1}H NMR (b) ^{13}C NMR (c) ^{135}DEPT NMR (d) IR

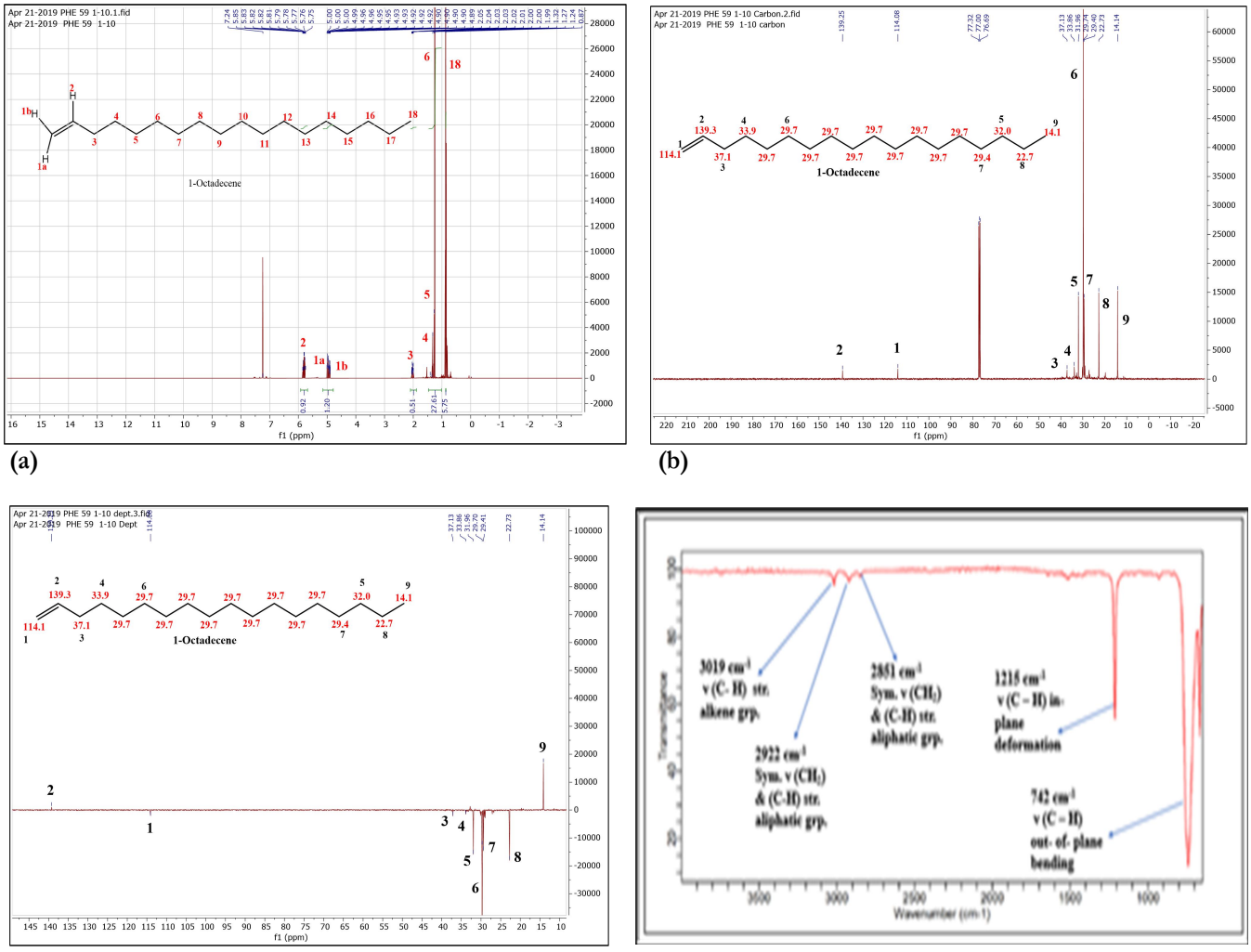


Figure 3: Spectroscopic data of Compound 2 (a) ^{1}H NMR (b) ^{13}C NMR (c) ^{135}DEPT NMR (d) IR

Molecular Docking Analysis

The structures of the eight phytochemicals: Friedelin, 1-octadecene, S-methyl-L-cysteine, 5-methy-1*H*-indole-2,3-dione, 1-methyl-isoquinoline, nicotinic acid, L-cysteine and 2-methoxythiazole from *P. incana* leaves subjected to docking analysis are presented in Figure 4.

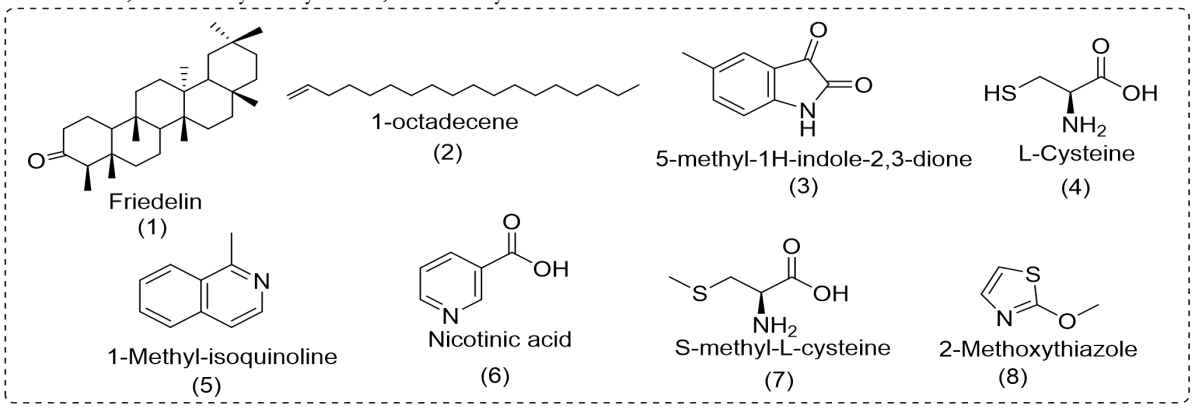


Figure 4: Structure of phytochemicals from *Phragmanthera incana* leaves (Sanni, *et al.,* 2018)

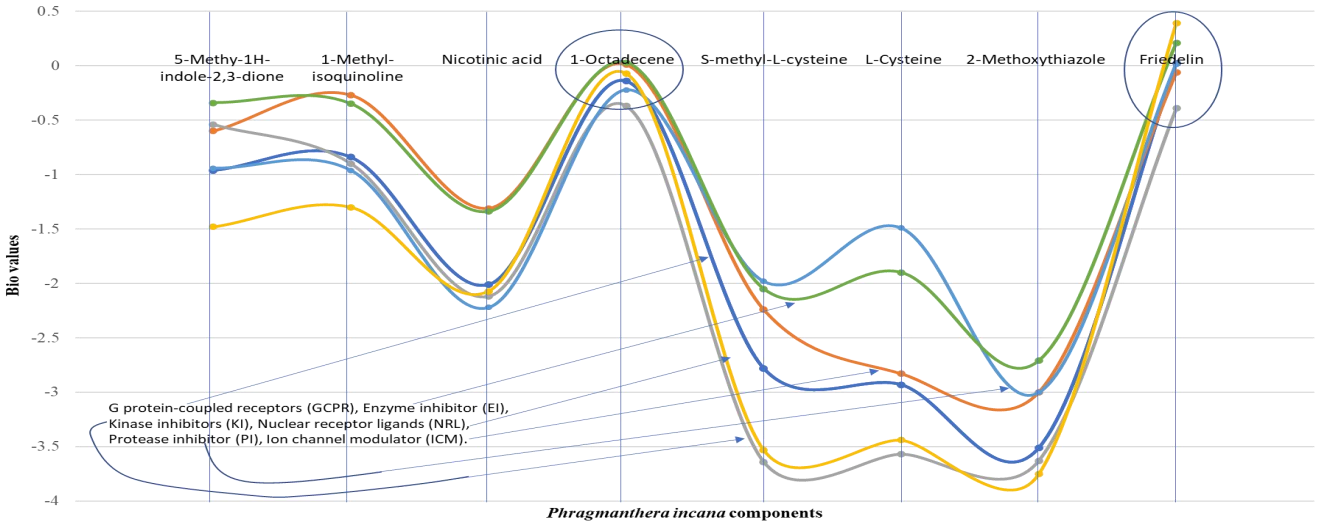


Figure 5: Bioactivity scores of the compounds tested

The potential candidacy of drug leads can be assessed by evaluating their bioactivity scores. Figure 5 reveals the bioactivity scores of the eight phytochemicals from the leaves of *P. incana*. Good activity was observed from above 0.0, while moderate activity was established within the range -5.0 to 0.0. Inactive molecules are found at values below -5.0 (Khan *et al.*, 2017).

From Figure 5, it is obvious that friedelin is the most bioactive component of *P. Incana*, followed by 1-octadecene. Friedelin acting as nuclear receptor ligand (NRL) showed good activity at 0.4, followed by its bioactivity as enzyme inhibitor and G-protein coupled receptor at values above 0.0.

The plot also revealed 1-octadecene exhibiting good bioactivity as ion channel modulator and as enzyme inhibitor. Other components of the *P. incana*, though with lower values showed moderate activity in the range of 0.0 to -3.75.

The eight phytochemicals were docked against ten diabetic protein crystals of various functions listed earlier to ascertain the diabetic cellular the phytochemicals would inhibit. The results obtained from the docking are summarised in Table 2. It is interesting to note that friedelin, performed optimally, especially as alpha-amylase hydrolase oxidoreductase (PDB ID: 1U2Y) and human insulin degrading enzyme (IDE) hydrolase (PDB ID: 4RE9) with binding energy energies of -10.2 kcal/mol.

All the phytochemicals performed better with Friedelin as the best potential inhibitor of human insulin degrading enzyme (IDE) hydrolase (Table 3). Subsequently, the human insulin degrading enzyme (4RE9) was redocked against the eight compounds and a common diabetic type 2 standard drug, Metformin for comparison. Interestingly, only S-methyl-L-cysteine and L-cysteine showed activities below Metformin. Results of docking of the eight phytochemical constituents of *P. incana* with the binding region of 4RE9 targeted protein in comparison with metformin showed that friedelin interacted with HIS_{112} (2.92 Å and 3.94 Å bond lengths) and PHE_{820} (3.40 Å bond length) while interaction of 4RE9 with metformin revealed HIS_{108}, ALA_{140}, HIS_{112}, ASN_{139} amino acid residues interactions. Notably, these non-polar and polar amino acids respectively interact through carbon-hydrogen and π-σ bonding. This interaction revealed an attractive solubility and permeability potential of friedelin in any medium ensuring its bioavailability compared to that of metformin.

All drug candidates must be non-toxic, hence the need to ascertain the toxic levels of the compounds. To achieve this, Protox II webserver was used to ascertain the compounds' toxicity level, their hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity and cytotoxicity were assessed and results showed that of the eight compounds only 1-octadecene and S-methyl-L-cysteine are non-toxic. Friedelin, the most bioactive component was highly immunotoxic and was subjected to derivatisation.

Table 2: The binding energies of *P. incana* compounds with ten diabetic protein molecules in kcal/mol

Name of the phytochemical	5UJT	1U2Y	2CBZ	2ZJ3	1IR3	3LC4	6M71	4RE9	2JJK	1V4S
Friedelin	-9.1	-10.2	-7.9	-8.7	-8.7	-9.6	-8.9	-10.2	-8	-8.2
5-Methy-1H-indole-2,3-dione	-5.6	-6.1	-5.7	-6.8	-6	-6.4	-5.8	-7.9	-5.5	-5.7
1-Methyl-isoquinoline	-5.4	-6.4	-5.4	-5.3	-5.8	-6.4	-5.8	-7.6	-4.8	-4.8
Nicotinic acid	-4.4	-5.1	-4.5	-5.3	-5.0	-5.6	-4.6	-5.9	-5.0	-5.9
1-Octadecene	-3.8	-4.6	-3.8	-4.1	-4.7	-4.7	-4.7	-5.6	-4.0	-5.9
S-Methyl-L-cysteine	-3.7	-4.2	-4.2	-4.9	-3.6	-4.7	-4.1	-4.8	-3.9	-4.7
L-Cysteine	-3.6	-4.0	-3.9	-4.6	-3.8	-4.4	-3.8	-4.3	-3.8	-4.5
2-Methoxythiazole	-3.3	-3.7	-3.2	-4.4	-3.5	-4.2	-3.6	-4.2	-3.5	-4.4

Table 3: The binding energies of the compounds against human insulin degrading enzyme (4RE9) in kcal/mol

Ligand	Binding Affinity (kcal/mol)
4re9_Friedelin_E= 485.36	-10.2
4re9_5-Methyl-1H-indole-2,3-dione_E= 289.16	-7.9
4re9_1-Methyl-isoquinoline_E = 103.44	-7.6
4re9_Nicotinic acid_E= 58.08	-5.9
4re9_Octadecene_E= 5.89	-5.6
4re9_Metformin_E= 136.80	-5.2
4re9_S-Methyl-L-cysteine_E= 98.88	-4.8
4re9_L-Cysteine_E= 64.65	-4.3

Bioactivity scores play a pivotal role in docking studies as they offer invaluable insights into the potential biological activity of a ligand. These scores aid in comprehending how a ligand interacts with a target protein or receptor and its capability to induce a specific biological response. The utility of binding affinity scores extends to the selection and prioritisation of ligands based on their binding affinities, facilitating the identification of the most promising compounds. Subsequently, compounds with elevated bioactivity scores are often earmarked for further experimental evaluation.

Furthermore, bioactivity scores serve as an essential compass in assessing the impact of chemical modifications employed during drug development (Harley *et al.,* 2021). Friedelin and 1-octadecene has been reported to inhibit cancer cells (Kakinuma *et al.*, 2006), possess the ability to interact with hydrophobic molecules such as fatty acids, cholesterol, and lipophilic hormones (McEwan, 2009), regulate metabolic enzymes and promote proteins (Schwab *et al.*, 2012) and bind to additional sites on the enzymes (Copeland, 2013).

Design of Friedelin derivatives to checkmate toxicity issues

Seven hypothetical derivatives of friedelin were designed through structure activity relationships. This involves the addition reaction between Friedelin and aniline, 2-methoxy-5-methylaniline, 4-methylaniline, 2-iodoaniline, 2-chloroaniline, benzylaniline and 2-iodo-5-chloroaniline. The structures are shown in Figure 6. The 2D structures were subjected to toxicity test using Protox II webserver. Notably, the derivatives of friedelin, BAM-2 and BAM-4 pose non-toxicity issues.

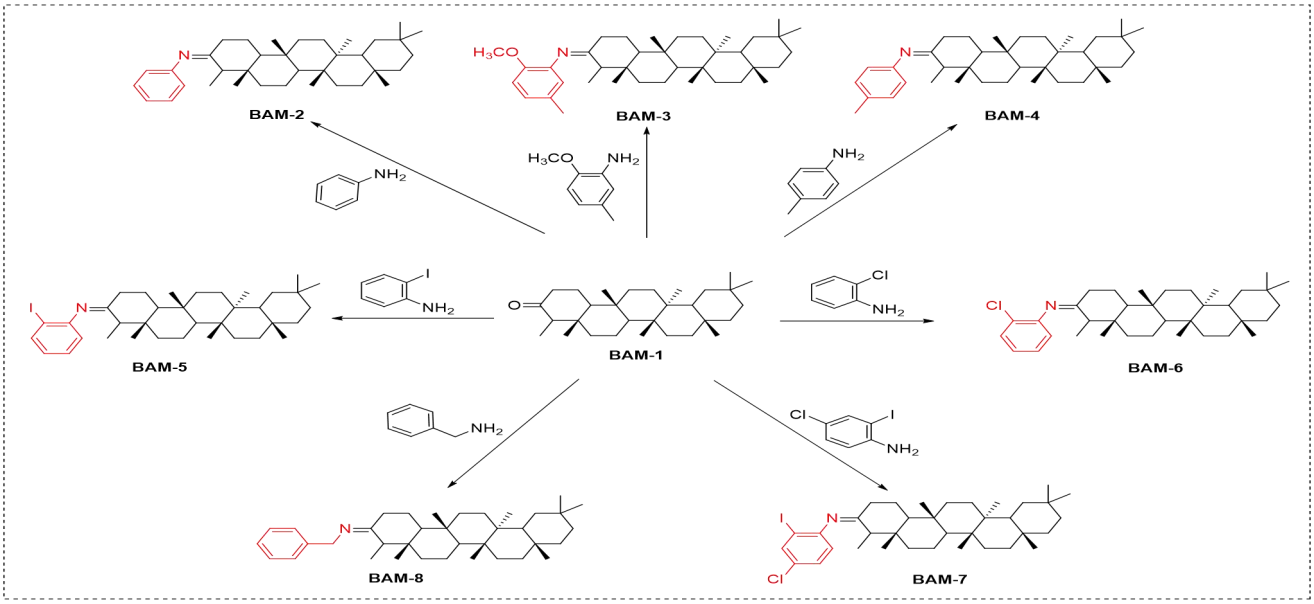


Figure 6: Friedelin (BAM-1) and its hypothetical derivatives as anti-diabetic agents

The derivative, BAM-4 also possessed excellent binding energy, better than all other derivatives and the reference drug, Metformin. The binding interactions in 2D are presented in Figure 7.

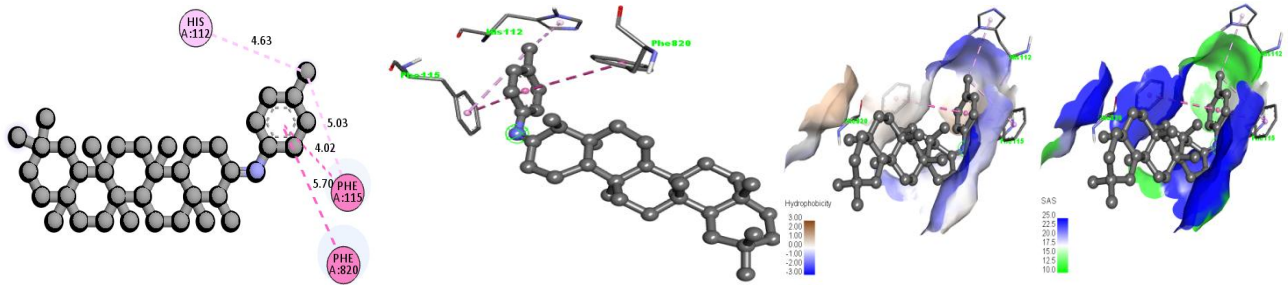


Figure 7: BAM-4 - 4RE9 complex as best interacting ligand (π-π and π-alkyl) exhibiting hydrophobic/hydrophilic interactions and good solvent accessibility surface.

Conclusion

In this study, the bioactive compounds, Friedelin, a triterpenoid, and 1-octadecene were isolated and characterised from *P. incana*. The *in silico* docking and toxicity studies of these compounds and some of friedelin hypothetical derivatives predicted that they possess antidiabetic properties. The *in silico* studies showed Friedelin as the most promising compound with a binding energy of -10.2 kcal/mol. It was revealed to be a potential antidiabetic agent but immune-toxic. The study also designed derivatives of Friedelin to mitigate this immunotoxicity, particularly two compounds coded BAM2 and BAM4 were derived and found to be non-toxic. The study highlights the potentials of Friedelin isolated from *P. incana* leaves for the management of diabetes and the development of its safer derivatives of as potential drug candidates.

Conflict of interest statement

The authors wish to declare that there is no competing interest in this study.

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