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CHEMICAL COMPOSITION, THEORETICAL STUDIES OF THE OXIDATIVE, NEURAMINIDASE INHIBITORY POTENCY OF *ACANTHUS MONTHANUS* LEAF EXTRACTS USING DFT AND MOLECULAR DOCKING SIMULATIONS.

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Abstract

Historically, plants have provided a reliable alternative to chemically synthesized drugs. This study was designed to investigate the chemical composition, theoretical and Density Functional Theory (DFT) investigations of the antioxidant properties of Acanthus *monthanus* leaf extracts. The was to investigate the mechanisms of the oxidative potency of the leaf extracts. The Gas Chromatographic-Mass Spectroscopy analysis reveals the presence of fourteen compounds. The antioxidant properties were determined theoretically using the Hydrogen Atom Transfer (HAT), Single Electron-Proton Transfer (SET-PT) and Sequential Proton Electron Transfer (SPET). The result suggests that the compounds(AMI-AM9) show comparable and low bond Bond Dissociation Energies(BDE) ionization potentials,(IP), proton dissociation energies(PDE),electron transfer energies(ETE) and low proton affinity (PA) Hence, a greater tendency to donate hydrogen atom to the free radicals, AM3 having the least thermodynamic values(60.72,170.33,193.42, 29.44 and PA of 317.15).This values revealed that molecule AM3(alpha-methyl-4-methylmannoside) is a better antioxidant among the studied compounds.(AM1-AM9). DFT investigations for the compounds were carried out using Highest Occupied Molecular Orbital-Lowest Unoccupied Molecular Orbital (HOMO-LUMO), Molecular electrostatic Potential (MESP) and other global descriptors. The results reveals that the molecules have low energy gaps with AM3 having the least value (-12.34). To justify the traditional application of this plant in the treatment of various diseases such as dry cough, pneumonia and influenza, molecular docking using discovery studio was carried out against neuraminidase an influenza causing protein to check its inhibitory potency on the protein. The docking result shows that molecule AM3 a glycoside can be used pharmaceutically in the manufacture of drugs for the treatment of influenza disease.

Introduction

The plant kingdom constitutes the basis of primary health care for the majority of the world's population. Many plants synthesize substances that are useful in human nutrition. The use of medicinal plants predates written human history [1]. Plants produce bioactive components as part of their normal metabolic activities. The development in the field of modern medicine is contemporary compared to the traditional herbal medicine. But man has made a comeback ad the use of herbal medicine is trending across the world. [2,3]. *Acanthus Montanus* belongs to the family, Acanthaceae and is native to West Africa. A decoction of the leaves of *A. Montanus* is used in the treatment of cardiac dysfunction, dry cough,

influenza, hypertension, threatened abortion, sexually transmitted diseases (STD's), and infection. It is used traditionally in the southern part of Nigeria as a good antioxidant [4]. Antioxidants are frequently known to playing a role in the reduction of symptoms of aging, cardiovascular illness, and neurodegenerative diseases. In recent times, these compounds are considered to be a panacea, promoting certain misconceptions in some cultures [5]. Antioxidants reduces or neutralizes Reactive Oxygen Species (ROS) and thus decreases their oxidative process. Typical examples of ROS are OH^-, OOH, O_2^- etc. Some bioactive compounds are very good antioxidants because of the presence of hydroxy groups [6,7].

New drugs to treat influenza were developed based on the understanding of the oligosaccharide structure on the surface of the virus. The key player is N-acetylneuramic acid which is the N-acetyl derivative of a nine carbon monosaccharide [8]. N-Acetylneuraminic acid also forms a coating on newly emerging virus particles which must be removed from the exterior before the virus can adhere to and infect a new cell [9, 10]. This neuraminic acid is removed by an enzyme known as neuraminidase, that the virus carries on its surface. Consequently, by inhibiting these enzymes, the virus cannot shed its coating of neuraminic acid and is unable to infect new cells [10].

Against this background, the objectives of this study was to carry out a chemical composition and theoretical study of the antioxidant, the inhibitory ability of some of the identified bioactive compounds. Carry out a molecular docking using the bioactive compounds from the plants against the neuraminidase enzyme. Finally, the chemical reactivity investigation of the compounds using the Density Functional Theory (DFT) study

Experimental and Computational details

Gas Chromatographic-Mass Spectrometry: GC-MS analysis was carried out on Agilent Technologies Intuvo 9000 GC system and Agilent Technologies 5977B Mass Selective Detector (MSD) coupled with 4513A Automatic Liquid Sampler (ALS). The part number of the column used was Agilent 190915 – 483 UI INT Capillary Column with the specification HP – 5MSUI30M, 0.25mm, 0.25µm, Intuvo.

The carrier gas used was Helium at a flow rate of 1.2ml/mm. the infection volume was 1µl. the inlet temperature was maintained at 300^0C. the oven temperature was programmed initially at 50^0C for 5min at the rate of 5^0C. A total of 58mintues run time was used. The MSD transfer line was maintained at a temperature of 250^0C. The source temperature was 230^0C and MS quad at 150^0C. The ionization mode used was electron ionization at 70ev. Total Ion Count (TIC) was used for compound identification and quantification. The spectrum of the separated compounds saved in the NIST05 reference spectra library. Data analysis and peak area measurement was carried out using Agilent Mass Hunter software

Computational Details

Gaussian 09 Software package [11] was used to perform all DFT quantum calculations and the Gaussview 6.0 interface. All the ground state geometries of the compounds were optimized using the DFT/B3LYP methods and 6-311 ++G(d,p) basic set The molecular electrostatic potential (MESP) was carried out using the Multiwfn 3.7(dev) package [15].

Theoretical Determination of Antioxidant Potency

Radical scavenging pathways: Three reaction mechanisms were employed in this study to explain the radical scavenging ability of phenolic antioxidants.

1. Hydrogen Atom Transfer (HAT) from antioxidant molecules to radicals
   $ArOH + F^o \longrightarrow ArO^o + FH$
2. Two – step reaction: Single – electron transfer followed by proton transfer (SPLET)
   $ArOH + R_o \longrightarrow ArOH^{o+} + R^-$
   $\longrightarrow RH + ArO^o$
3. Two – step reaction: sequential proton loss electron transfer (SPLET)

$ArOH \longrightarrow ArO^- + H^+$ $BOE = H^o_{ArO} + H^o_H - H_{ArOH}$

$ArO^- + R^o \longrightarrow ArO^o + R^-$; $R^- + H^+ RH$ $IP = H_{ArOH^{o+}} + He - H_{ArOH}$

BOE, IP, BOE, PA and ETE can be determined by theoretical methods;

$POE = H^o_{ArO} + H_{H^+} - H_{ArOH^{o+}}$

$PA = H_{ArO^-} + H_{H^+} - H_{ArOH}$

$ETE = H^o_{ArO} + He - H_{ArO^-}$

H is molecular enthalpy of different compounds.

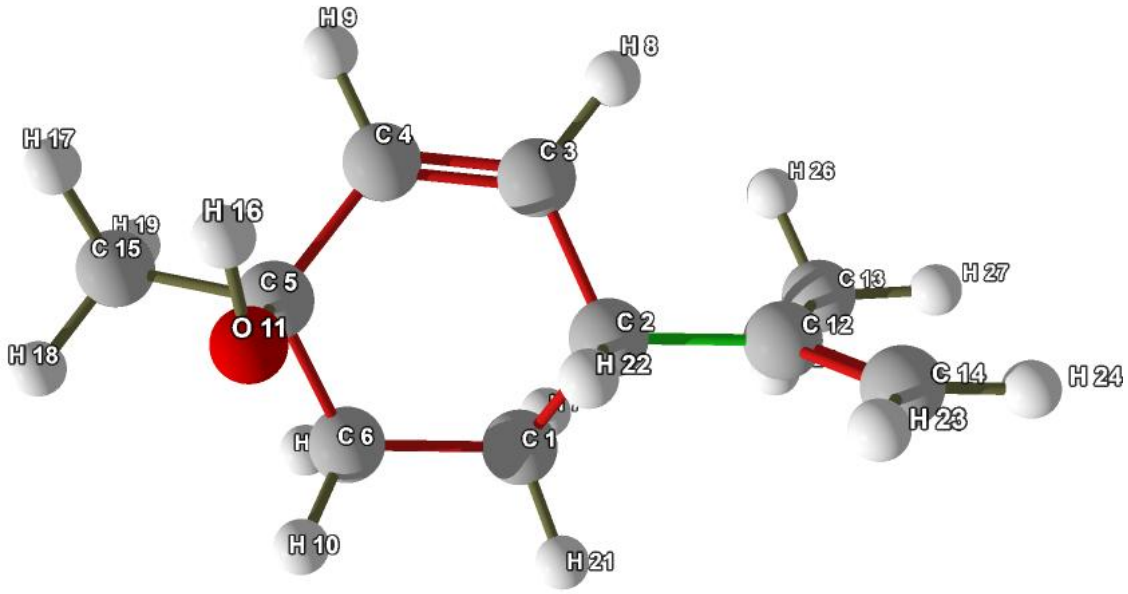
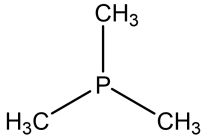
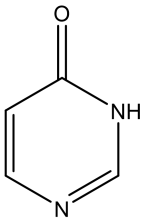


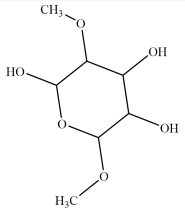
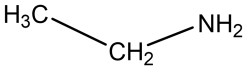
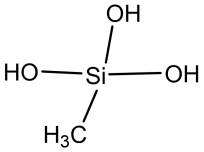
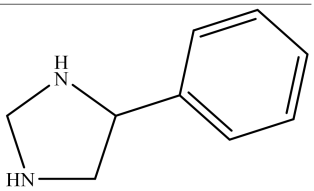
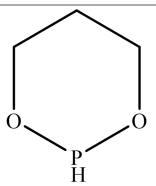
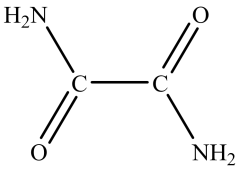
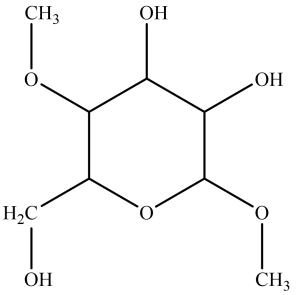
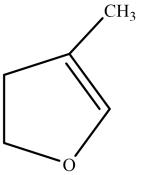
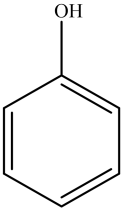
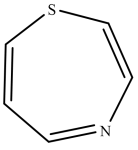
Fig.1. Crystal structure with atoms numbering of studied compound

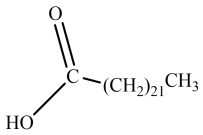
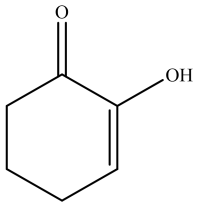
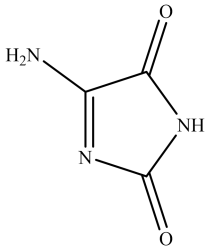
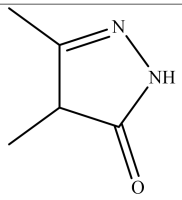
Results and discussion

Chemical Composition of the extract of *A. Montanus* leaf extract is presented in Table 1. The chromatogram of the extract is presented in figure 2. These peaks indicated the presence of different compounds in the extract. The molecular formula, percentage composition, retention time, structure and molecular masses of these compounds are shown in Table 1.

Table 1:GC-MS result of *A.Montanus* leaf extracts

SN	Compound	Retention time	% com position	Form ula	Molar mass (g/mol)	Structure
1	trimethylphosphane	5.465	2.44	C_3H_9P	76.08	
2	pyrimidin-4(3*H*)-one	6.026	0.45	$C_4H_4NO_2$	96.089	

3	3,6-dimethoxytetrahydro-2*H*-pyran-2,4,5-triol					
4	ethanamine	8.257	0.25	$C_3H_5NH_2$	45.08	
5	methylsilanetriol	9.343	0.90	CH_6O_3Si	94.01	
6	4-phenylimidazolidine	8.744	0.68	$C_{10}H_{14}N_2$	162.23	
7	1,3,2-dioxaphosphinane	9.579	0.06	$C_3H_7O_2P$	106.06	
8	oxalamide	10.572	0.07	$C_2H_4N_2O_2$	88.06	
9	Alpha methylmanoside	17.338	8.41	$C_8H_{16}O_6$	208	
10	4-methyl-2,3-dihydrofuran	11.181	2.99	C_5H_8O	84.12	
11	phenol	11.456	0.12	C_6H_6O	94.11	
12	1,4-thiazepine	11.456	0.12	$C_5H_5N_5$	111.16	

13	tricosanoic acid	11.753	0.39	$C_{23}H_{46}O_2$	354.6	
14	2-hydroxycyclohex-2-en-1-on	11.834	7.81	$C_6H_8O_2$	112.128	
15	4-amino-1*H*-imidazole-2,5-di	13.310	0.11	$C_3H_3N_3O_2$	113.08	
16	4,5-dimethyl-2,4-dihydro-3*H*-	13.10	0.11	$C_5H_7N_2O$	126.16	

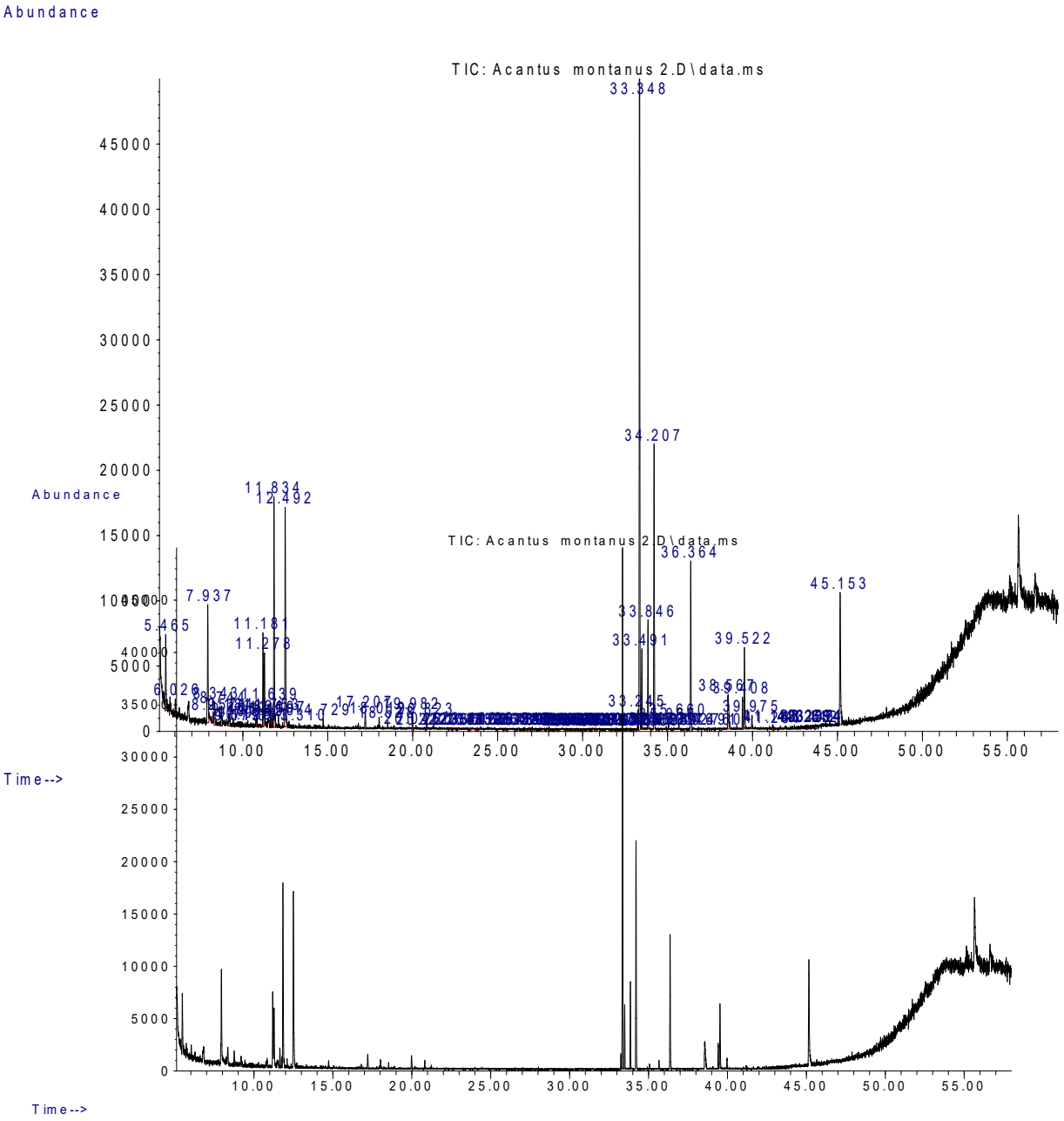


Fig. 2: GC-MS Chromatogram of *A. Montanus* leaf extracts

Antioxidant Activity

Theoretical Evaluation: To determine the antioxidant activity theoretically of the leaf extracts, some compounds were selected based on the presence of OH group in the molecule. Parameters such as the Bond Dissociation Energies (BDE), Ionization Potentials (IP's), Electron Affinity (EA), Proton Dissociation Energy (PDE) and Electron Transfer Energy were calculated.

The antioxidant activity properties of all compounds are reported in Table2. Three different mechanisms were considered.

Hydrogen Atom Transfer (HAT) Mechanism: The BDE is a very reliable thermodynamic parameter to describe the HAT mechanism. This involves the H atom transfer from a hydroxyl group of antioxidant compound to as free radical. The weakest O-H bond with lowest BDE is expected to be abstracted easier, hence high antioxidant potency.

$$Rx - H \longrightarrow Rx^{o} + H^{o}$$

$$\Delta_f H^{o}(Rx^{o}) + \Delta f H^{o}(H^{o}) - \Delta f H^{o}(Rx\text{-}H)$$

The result showed that AM3(60.72) has higher radical scavenging activity than other molecules. This is in agreement with [17].

Singlet electron transfer- proton transfer (SET-PT) Mechanism. The singlet electron transfer followed by proton transfer (SET – PT) is a mechanism in which electron is transferred from the antioxidant to the free radical, resulting to the radical cation ion formation, which it deprotonates subsequently. Ionization potential and PDE are the most important parameters in describing the feasibility of this mechanism. Generally, lower IPs are more subjected to ionization hence, easier electron-transfer tendency between the antioxidant and the free radical. The calculated IP_S in this study reveals that compounds have comparable IP values close to each other. The order showed that molecule AM3 is the most active antioxidant. The PDE which measures the tendency of deprotonation of radical cations formed from the IP. The lowest PDE is for molecule. AM3 which indicates it has higher tendency to deprotonate. However, it is observed that the IP trend appears to be slightly different from that of BDE, the PDE value and sum of IPs + PDEs obey the same trend as BDE energies and molecule AM3 shows lower energies than others. Confirming that it has higher activities with respect to another molecule.

SPLET Mechanism: This is sequential proton loss electron transfer (SPLET) in table 2, reported PA and ETEs show that the first step (PA) extremely

requires much more energy to perform than the second step (ETE). By analyzing both SET-PT and SPLET reaction mechanisms, it is evident that both pathways involve greater energies required to occur with respect to HAT. From the above calculated parameters, it is evident that molecule AM3 is the most active antioxidant and all the above natural products obey the same trends in the three proposed mechanisms.

Table 2: Calculated thermodynamic antioxidant properties of *A. Montanus* leaf constituents

Molecule	BDE	IP	PDE	PA	ETE
AM1	63.44	170.42	194.21	317.01	38.19
AM2	64.53	170.48	194.51	317.27	33.20
AM3	60.72	170.33	193.42	317.15	37.66
AM4	65.11	169.52	193.86	317.10	39.16
AM5	68.32	188.74	206.66	347.48	39.78
AM6	67.43	188.42	207.89	347.19	39.56
AM7	66.18	189.66	301.72	347.66	39.42
AM8	61.94	171.56	317.18	351.52	39.51
AM9	67.45	190.44	311.15	328.19	39.06

3.4 Global Reactivity Descriptors: The chemical reactivity indices like chemical hardness (n), is directly correlated with the molecule stability, softness (s) gives an insight into molecule chemical reactivity. Molecules with OH^- are more favorable in the charge – transfer mechanism than other molecules. The common feature of electron – scavenging mechanisms is attracting electrons [18]. To explain the charge – transfer mechanism, electronegativity (x) is studied. The negative of electronic chemical potential, μ shows the ability of molecules to attract electrons. From the results in table 3, molecules with OH^- has lower electronegativity, hence, they are more likely to transfer electrons easily which is an indication of their more antioxidant ability with molecule AM3 showing the least value. The tendency of an electron to escape is measured by its chemical potential. The more negative it is, the more difficult to donate an electron but more favoured to gain. Therefore, the lower μ of molecules with OH^- indicates their more tendency to lose electrons. This chemical reactivity descriptor shows that all molecules with OH^- groups are better targets for electron scavenging reactions [19, 20].

Table 3: Calculated quantum descriptors of the studied compound

compound	E_{HOMO}	E_{LUMO}	ΔE(ev)	η	S	μ	*x*	Ω
AM1	-0.300	-0.195	-2.88	0.053	15.334	-0.234	0.326	0.172
AM2	-0.306	-0.170	-3.73	0.057	14.106	-0.235	0.344	0.413
AM3	-0.617	-0.166	-12.34	0.078	11.546	-0.246	0.351	0.076
AM4	-0.322	-0.167	-4.25	0.064	16.551	-0.251	0.312	0.121
AM5	-0.318	-0.173	-3.84	0.054	12.802	-0.293	0.316	0.077
AM6	-0.293	-0.179	-3.13	0.056	14.591	-0.288	0.314	0.028
AM7	-0.299	-0.194	-2.88	0.044	17.662	-0.291	0.318	0.051
AM8	-0.299	-0.194	-2.88	0.044	17.636	-0.296	0.317	0.062
AM9	-0.283	-0.195	-2.39	0.072	17.651	-0.290	0.247	0.068
AM10	-0.286	-0.187	-2.71	0.038	18.124	-0.291	0.246	0.026

Global Reactivity Descriptors for compounds AM1 – AM9(ev)

3.5 Frontier Molecular orbitals

The electron donating and receiving ability of a molecule can be determined by considering their frontier molecular orbitals, their energy depicts their reactivity. The HOMO and LUMO of molecule AM1-10 were investigated. It is observed that the distribution pattern of frontier molecular orbitals with their corresponding energies was comparable especially with those with the same functional group. HOMO – LUMO energy gap (ΔE gap) is an established parameter to measure the extent of the intramolecular change transfer [21,22,23]. The compounds under investigation exhibits different energy gaps according to the functional group i.e – OH and NH. The HOMO/LUMO energies of the compounds are presented in table 3. Compound am3 showed the lowest HOMO-LUMO energy gap (-12.34)

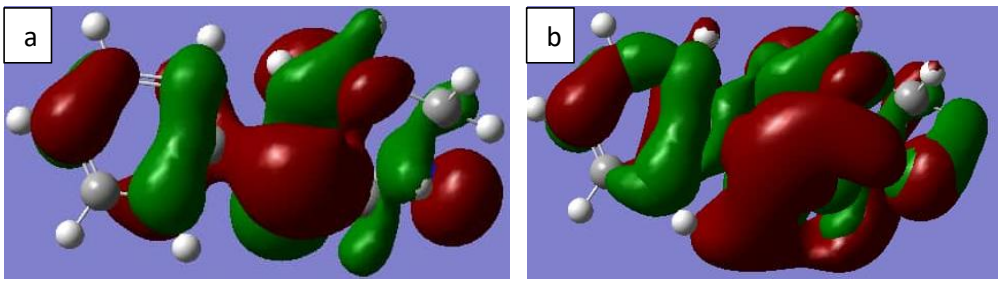


Fig. 4. HOMO[a]-LUMO[b] plot for AM3

3.6 Molecular Electrostatic Potential

The molecular electrostatic potential (MESP) is an important parameter to validate the results of reactivity of a molecular system. The three-dimensional MEP surface gives us an indication about position, shape, and size of the positive, negative and the neutral electrostatic potentials.[24] This provides a better understanding of the physicochemical properties and their relationship with molecular structure and reactivity toward electrophilic and nucleophilic attacks. The red color is the preferred site for electrophilic attack while the blue indicates the positive electrostatic potential and which will be attracted by the charged molecules or radicals. As indicated in figure 5. the positions of oxygen and hydroxy groups showed high electrostatic potential regions.

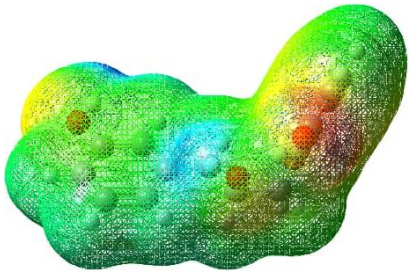


Fig. 5: Molecular Electrostatic Potential surface for AM3

1.7 Molecular docking: Molecular docking is the most useful technique to explore the possible binding mode between ligand and protein complex. The re-docking of nature ligand into the crystal complex is a measure of accuracy of a molecular docking.

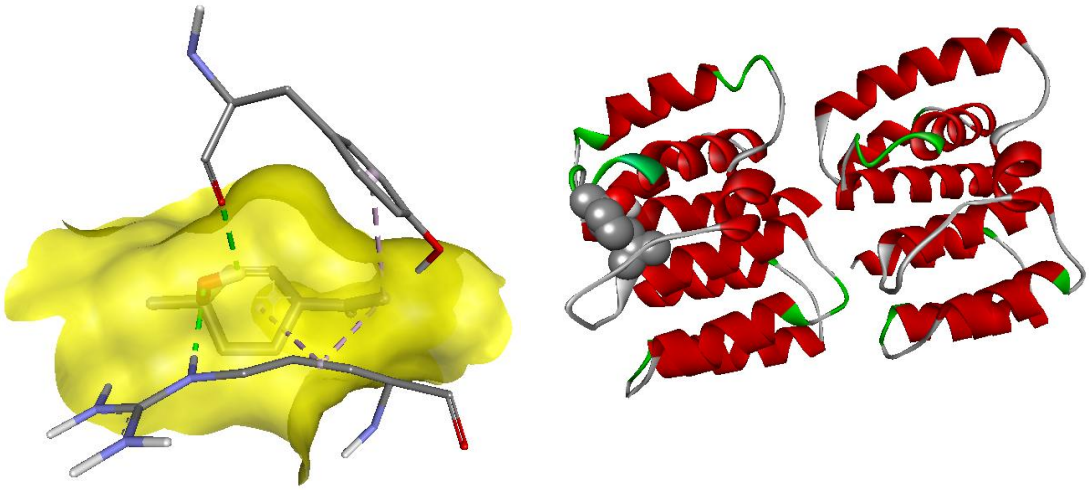


Fig. 6: Binding Mode of the Studied Compound at the binding site of neuraminidase

In this study, an attempt has been made to study the interactions of alpha-methyl-4-methylmannoside, a glycoside with neuraminidase. Neuraminidase is an influenza causing protein [25,26]. This was done to determine the possible binding sites of the glycoside in the neuraminidase ketch domain, the result shows that alpha-methyl-4-methylmannoside could act as inhibitor of the protein – protein interaction between alpha-methyl-4-methylmannoside and neuraminidase. This inhibitory potency would favor the release of alpha-methyl-4-methylmannoside, this will help in the quenching of the radical species. Coupling mode of the ligand at the binding site of the protein is illustrated in the three dimensional and two-dimensional interactions maps of figure 5. The metabolites are embedded within the protein pocket, through hydrophobic and electrostatic interactions. With the residues with 5 – OH bonding. Conclusively, hydrogen bonds and hydrophobic sources dominates the interaction in the complex.

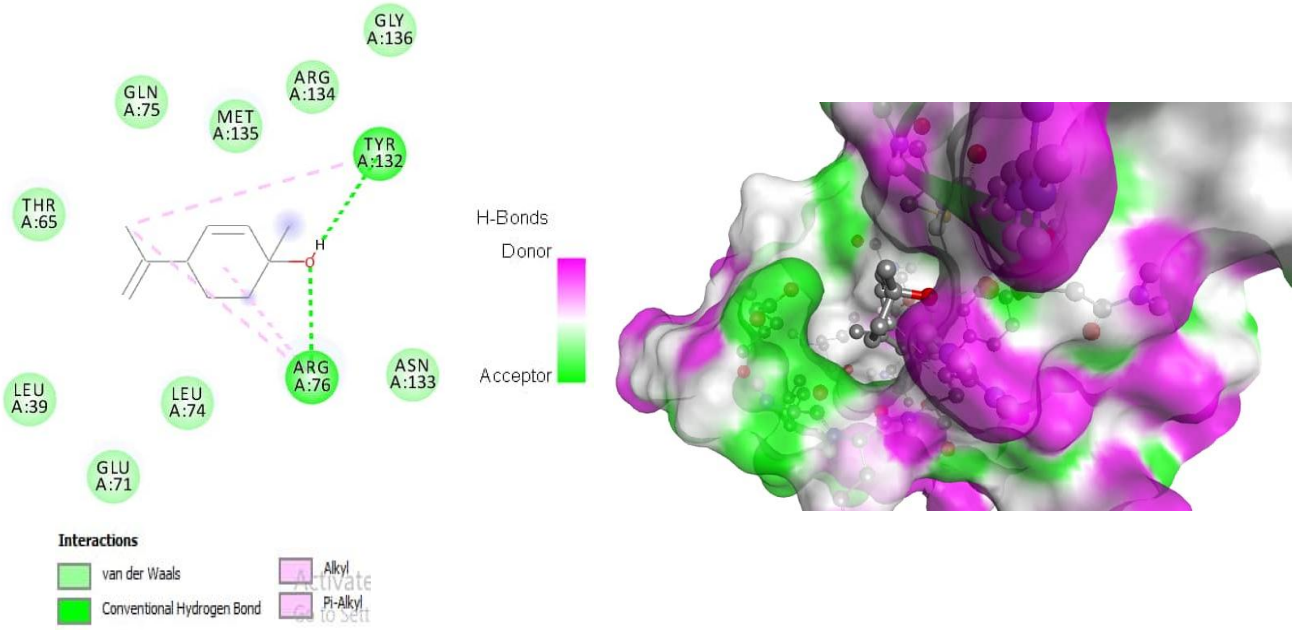


Figure 7: 2-D (left) and 3D (right) ligand-protein interaction

Conclusions

In this study, the chemical composition, oxidative and neuraminidase inhibitory potency of

A.Monatus leaf extracts were considered for investigations. The results showed that the extracts contain bioactive compounds. From the theoretical antioxidant study, it shows that the plant is a good antioxidant and can be used as an alternative to chemically synthesized drugs. The DFT study supports this shown reactivity. This also confirms the traditional usage of this plant in various ways. Molecular docking result predict that alpha-methyl-4-methylmannoside present in *A. Montanus* has a good inhibition activity against neuraminidase which causes the influenza disease. This result suggests that alpha-methyl-4-methylmannoside from *A. monthanus* can be used pharmaceutically in the manufacture of drug as an alternative to chemically synthesized drugs for treatment of diseases of the respiratory tract.

Conflict of interests

The author declares no competing financial interest.

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