Statistical Analysis of the Inhibitory Activities of Triterpenoid Derivatives against Two Selected Diseases

Adegoke Afeez B.[1], and Maradesa Adeleke[2] and Afolabi Habeeb[3]
[1,2]*Federal University of Technology Akure, Ondo State,Nigeria*
[3]*Adeleke University, Ede Osun State, Nigeria*

Abstract:- **This research work is based on studying the quantitative properties of the molecular descriptors of ligands that are suitable for curing ulcer and malaria diseases. The data used is computational result of triterpenoids of Lonchocarpus cyanescens with OH and OCH_3 derivation through molecular docking. The statistical significance test of PostHoc Analysis showed that the Molecular weight, Area and volume play crucial role in determining the significant effect of OH and OCH_3 in tackling the malaria and ulcer protein receptors. OH-derivative has uniform effect on both receptors responsible for the diseases while OCH_3 has significant effect on that of Ulcer as compared to that of Malaria protein receptor.**

Keywords: **Factorial Design, PostHOC, Molecular Descriptors, Protein Receptors**

I. INTRODUCTION

Malaria, being a life-threatening disease caused by *Plasmodium* parasites. The parasites are spread to people through the bites of infected female *Anopheles* mosquitoes, called "malaria vectors"[1]. Infected people with malaria usually feel very sick, with a high fever and shaking chills. Each year, approximately 210 million people are infected with malaria, and about 440,000 people die from the disease. Most of the people who die from the disease are young children in Africa [2].

Ulcer is a discontinuity or break in a bodily membrane that impedes the organ of which that membrane is a part from continuing its normal functions. There are various types which includes peptic, gastric, and duodenal ulcers. Stomach ulcers is also known as gastric ulcers which are open sores that develop on lining of the stomach. Ulcers can also occur in part of the intestine just beyond the stomach which is also known as duodenal ulcers. Both are sometimes referred to as peptic ulcers. The most common symptom of ulcer is associated with burning or gnawing pain in the center of the abdomen, indigestion, heartburn and feeling sick .

Triterpenoids is a natural product confirmed effective against various forms of diseases. Lonchocarpuscyanescens is a species of shrub from fabaceae family. Various studies has been carried out on the bioactivity, phythotherapeutic, anti-psychotic . The aims an objective of these work is to compare the effectiveness of two triterpenoidsderivatives (i.e OH and OCH_3) against protein receptor responsible for Malaria and Ulcer diseases using statistical Model and validate the result with the molecular docking studies carried out on it.

Computational Studies

According to Adejoro et al, the pdb files 3QS1, 1LS5 and 1SME for the three malaria receptors and 1AFC, I AXM and 2AXM responsible for Ulcer were obtained from the Protein Data Bank. Both protein receptors were treated using Dicovery studio 4.1.Visualizer, for initial preparation of the pdb files to select the needed chains, delete multiple ligands and non-protein parts. After that OpenBabel GUI version 2.3.2a and Spartan 14 version 1.18 were used to convert the pdb file format and optimize the geometry of the ligands, respectively. AutoDock Tools 1.5.6 and AutoDockVina version were used for molecular docking process and to analyse the output of docking process, EduPymol version 1.7.4.4 was used.

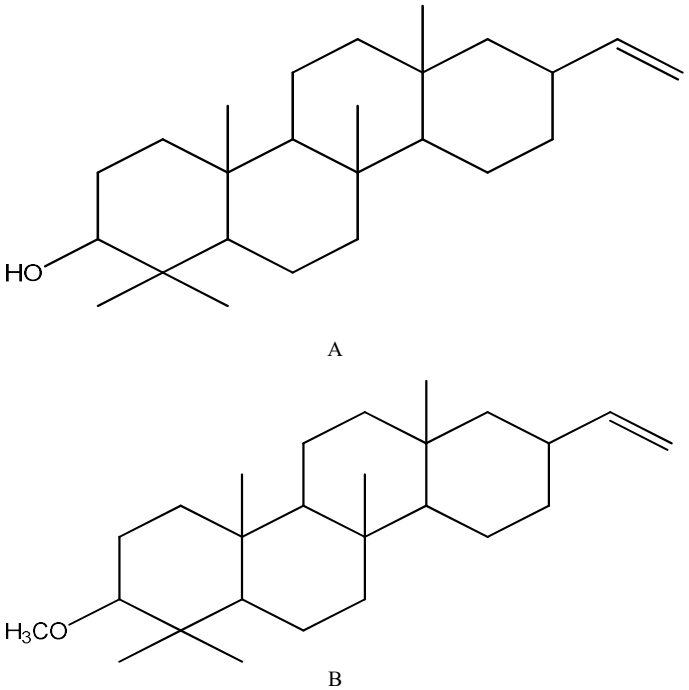

Figure 1: Molecular Structures of the Two Investigated Ligands.

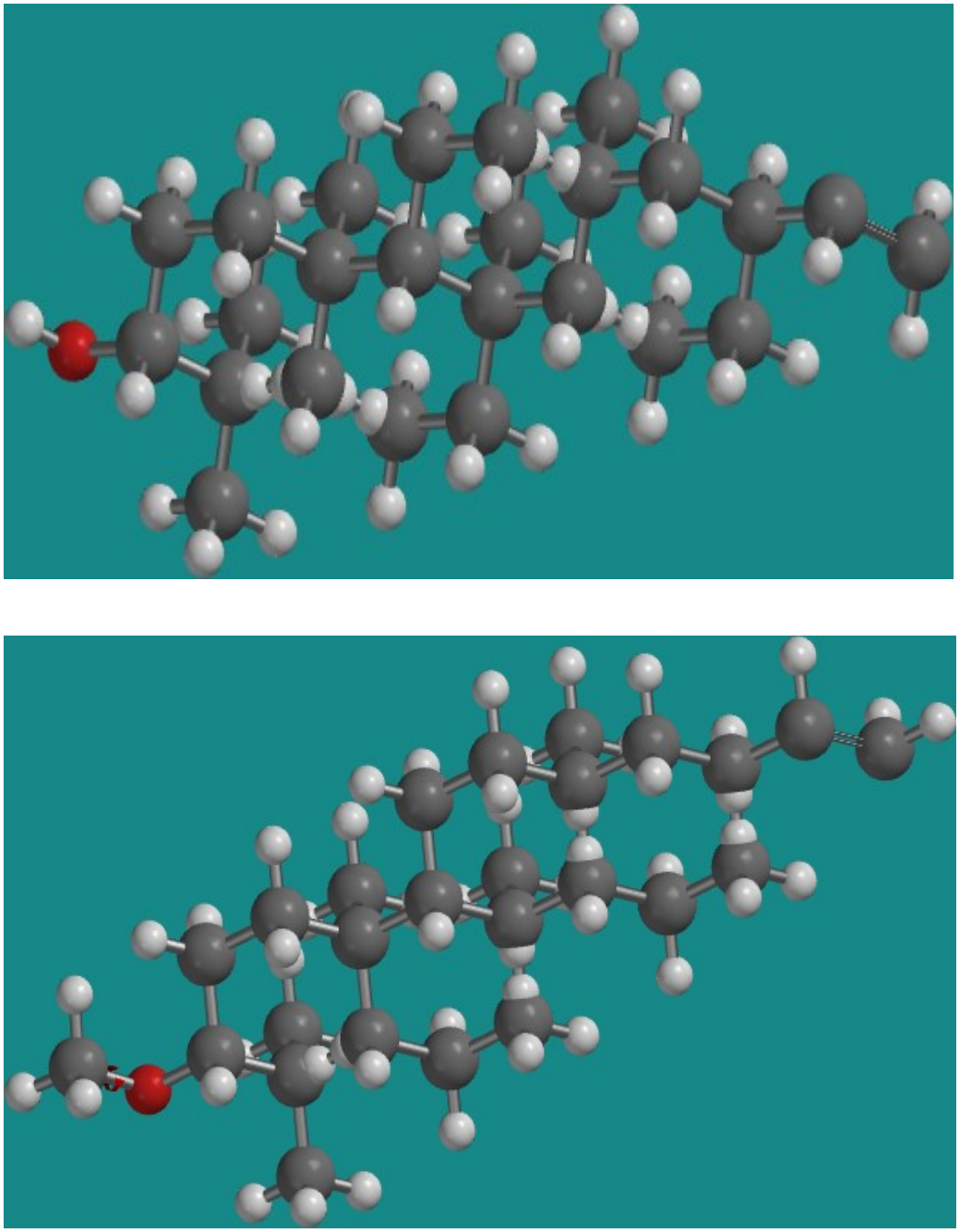

Figure 2. Optimized structure of the two Ligands A and B respectively (ball and stick model).

The chemical and optimized structures of the Triterpenoids derivatives chosen for the study are presented in Figs. 1 and 2 respectively.

II. METHODOLOGY

The data used in this research work was purely secondary data generated via molecular docking of triterpenoid with Ulcer and Malaria protein using the Docking result of Isaiah A.J., et al (2017). Factorial model is built to study the marginal mean effect and statistical of the molecular properties of the Ligands segmented by OH and OCH_3 derivative.

III. RESULT AND DISCUSSION

Table 1: Test Between Subject Effect

Source		Type II Sum of Squares	df	Mean Square	F	Sig.
Intercept	Hypothesis	690901.115	1	690901.115	291.710	.037
	Error	2368.451	1	2368.451[a]		
disease	Hypothesis	4206.752	1	4206.752	1.010	.498
	Error	4166.034	1	4166.034[b]		
properties	Hypothesis	949993.604	7	135713.372	34.130	.000
	Error	27834.856	7	3976.408[c]		
derivative	Hypothesis	2368.451	1	2368.451	.611	.622
	Error	2622.952	.677	3876.794[d]		
disease * derivative	Hypothesis	4166.034	1	4166.034	.977	.036
	Error	29859.531	7	4265.647[e]		
disease * properties	Hypothesis	29818.011	7	4259.716	.999	.501
	Error	29859.531	7	4265.647[e]		
properties * derivative	Hypothesis	27834.856	7	3976.408	9.32	.036
	Error	29859.531	7	4265.647[e]		

From table 1 above, we can say that there is significant effect of the molecular properties of the ligands in determining the potency of such ligand. This is because the p-value (0.00) < α (0.05). With this we can say that efficacy of the ligands of both derivative-family, that is, OH and OCH_3 with respect to its respective molecular properties as significant factors in remedying ulcer and malaria. Also there is interaction in the molecular behavior of molecular properties with respect to its derivative (OH and OCH_3) as it affects Malaria and Ulcer, p-value (0.036) < α (0.05). There is no significant difference in the role OH and OCH_3 played in the triterpenoidand the way triterpenoid attacked Ulcer and Malaria when it comes to OH and OCH_3 case, p-value (0.356) > α (0.05).

Table 2: Test the linearly independence and Pairwise comparisons among estimated marginal means

	Sum of Squares	df	Mean Square	F	Sig.
Contrast	949993.604	7	135713.372	31.815	.000
Error	29859.531	7	4265.647		

From table 2 above, we can say that since, p-value (0.00) < α (0.05), we have statistical reasons to conclude that there is linearly independence and the statistical significance of the molecular properties is pronounced. This makes the estimate of the model to be reliable.

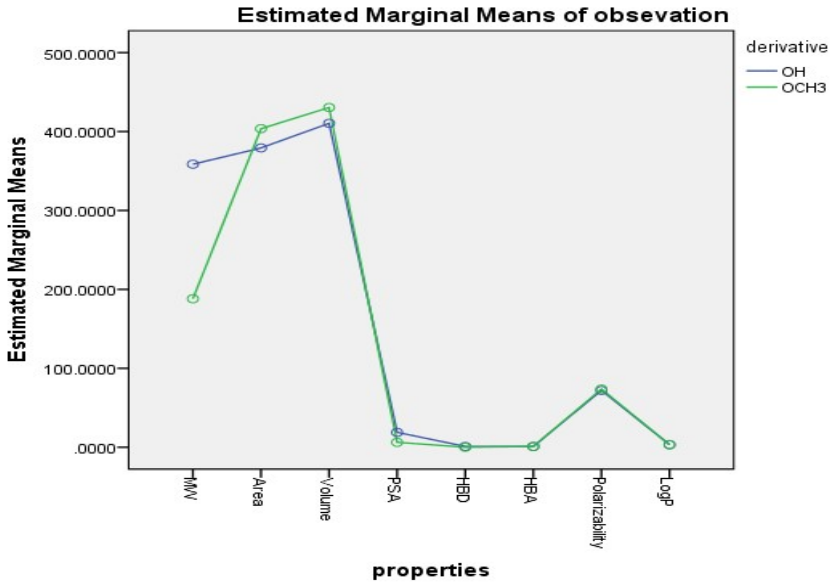

Fig 3: Marginal Mean Effect of the Molecular Properties

From the fig 3 above, we can say that there is significant different in molecular properties of triterpenoid and the derivatives with respect to molecular weight. The OH-derivative tends to have higher mean effect in the behavior of the Ligands with Molecular weight, while OCH_3-derivative has lower molecular weight as compared to the OH-derivative. There is significant interaction in the molecular behavior of OH and OCH_3 at HBD, HBA Polarizability and LogP. PSA of OH is higher than that of OCH_3 and this suggest that OH-derivative will have high penetrating power as compared to OCH_3. Since LogP determine to great extent if the drug can be administered orally, the LogP is so low (less than five and closer to zero), this means both drugs (OH and OCH_3 derivative) can be administered orally. OCH_3 have Area and Volume that have superceded the OH-derivative when basing on estimated mean effect.

Table 4: Multiple Comparisons

	properties	N	Subset		
			1	2	3
Duncan[a,b]	HBD	4	.500000		
	HBA	4	1.000000		
	LogP	4	3.310000		
	PSA	4	12.557500		
	Polarizability	4	72.850000		
	MW	4		273.395843	
	Area	4			391.440000
	Volume	4			420.447500
	Sig.		.184	1.000	.550
Waller-Duncan[a,c]	HBD	4	.500000		
	HBA	4	1.000000		
	LogP	4	3.310000		
	PSA	4	12.557500		
	Polarizability	4	72.850000		
	MW	4		273.395843	
	Area	4			391.440000
	Volume	4			420.447500

From the table 4 above, we can say that the statistical significance of molecular weight, area and volume are immense as compared to other properties that define molecular properties of the Ligands with respect to OH and OCH_3.

Table 5: LSD (Multiple Comparisons)

	(I) properties	(J) properties	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
LSD	MW	Area	-118.044157*	46.1825034	.038	-227.248425	-8.839890*
		Volume	-147.051657*	46.1825034	.015	-256.255925	-37.847390*
		PSA	260.838343*	46.1825034	.001	151.634075	370.042610*
		HBD	272.895843*	46.1825034	.001	163.691575	382.100110*
		HBA	272.395843*	46.1825034	.001	163.191575	381.600110*
		Polarizability	200.545843*	46.1825034	.003	91.341575	309.750110*
		LogP	270.085843*	46.1825034	.001	160.881575	379.290110*
	Area	MW	118.044157*	46.1825034	.038	8.839890	227.248425*
		Volume	-29.007500	46.1825034	.550	-138.211768	80.196768
		PSA	378.882500*	46.1825034	.000	269.678232	488.086768*
		HBD	390.940000*	46.1825034	.000	281.735732	500.144268*

	HBA	390.440000*	46.1825034	.000	281.235732	499.644268*
	Polarizability	318.590000*	46.1825034	.000	209.385732	427.794268*
	LogP	388.130000*	46.1825034	.000	278.925732	497.334268*
	MW	147.051657*	46.1825034	.015	37.847390	256.255925*
	Area	29.007500	46.1825034	.550	-80.196768	138.211768
	PSA	407.890000*	46.1825034	.000	298.685732	517.094268*
Volume	HBD	419.947500*	46.1825034	.000	310.743232	529.151768*
	HBA	419.447500*	46.1825034	.000	310.243232	528.651768*
	Polarizability	347.597500*	46.1825034	.000	238.393232	456.801768*
	LogP	417.137500*	46.1825034	.000	307.933232	526.341768*
	MW	-260.838343*	46.1825034	.001	-370.042610	-151.634075*
	Area	-378.882500*	46.1825034	.000	-488.086768	-269.678232*
	Volume	-407.890000*	46.1825034	.000	-517.094268	-298.685732*
PSA	HBD	12.057500	46.1825034	.802	-97.146768	121.261768
	HBA	11.557500	46.1825034	.810	-97.646768	120.761768
	Polarizability	-60.292500	46.1825034	.233	-169.496768	48.911768
	LogP	9.247500	46.1825034	.847	-99.956768	118.451768
	MW	-272.895843*	46.1825034	.001	-382.100110	-163.691575*
HBD	Area	-390.940000*	46.1825034	.000	-500.144268	-281.735732*

From the table 5 above, we can see that there is statistical significant difference in molecular weight, Area and Volume of the Ligands as compared to other properties (p-value< α(0.05)). The test for significant difference between Molecular weight, Area and Volume of the Ligand and other of its molecular properties showed that there is significant difference between molecular weight and other molecular properties of both OH and OCH_3 derivative, this because all the p-values are less that α (0.05), (p-value< α(0.05)). It further showed that there is significant difference between Area and other molecular properties (p-value<α(0.05)) and there is statistical significant difference between Volume and other molecular properties of the Ligands with respect to OH and OCH_3 derivative, (p-value< α(0.05)). The behavior and the effect of other properties are not statistically pronounced as that of MW, Area and Volume.

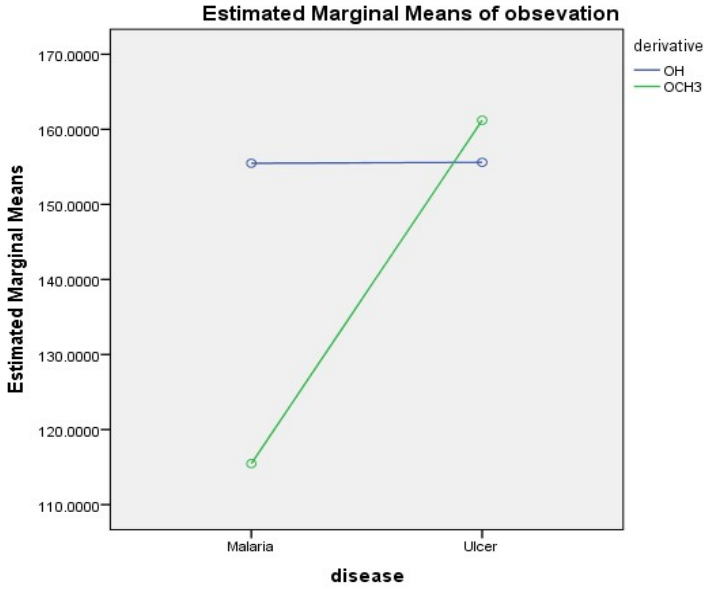

Fig 4: Estimated Marginal Mean of derivative

From the fig 4 above, we can say that there is interaction between the molecular behavior of OH and OCH_3 when docked with triterpenoid. OH-derivative has uniform effect on both Malaria and Ulcer while OCH_3-derivative has significant effect on Ulcer protein as compared to that of OH-derivative.

IV. CONCLUSION

Having analyzed the data generated via studying chemical properties of triterpenoid derivatives, which was used to dock Ulcer and Malaria protein receptor, we discovered that Molecular weight, Area and Volume played a significant role in tackling ulcer and Malaria protein. The potency of this drugs will purely based on Molecular weight, Area and Volume. The OCH_3 derivative is said to have significant effect on Ulcer protein as compared to Malaria Protein, while the OH-derivative is potent for both ailment. The result presented in this research work has complemented and buttressed the fact that OH and OCH_3 derivative played a significant role in determining the potency of the Ligand under investigation as also stated by Adejoro et al (2016).

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