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Identification of Potential *Aedes aegypti* Juvenile Hormone Inhibitors from Methanol Extract of Leaves of *Solanum erianthum*: An *In Silico* Approach

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Abstract: *This study explores the potential of phytoconstituents from the methanol extract of Solanum erianthum leaves as inhibitors of juvenile hormones in Aedes aegypti using an in silico approach. Gas Chromatography-Mass Spectrometry (GC-MS) analysis identified key compounds in the extract, including γ-sitosterol (40.25%), Ergost-5-en-3-ol (8.75%), and Stigmasterol (8.17%). Molecular docking simulations with the juvenile hormone-binding protein (PDB ID: 5V13) revealed that Ergost-5-en-3-ol (−8.316 kcal/mol) and 9,19-cycloergost-24(28)-en-3-ol (−8.388 kcal/mol) exhibited superior binding affinities compared to the standard juvenile hormone inhibitor Pyriproxyfen (−6.081 kcal/mol). Additionally, Phenol, 2,4-bis(1,1-dimethylethyl) (−7.063 kcal/mol) and DL-α-Tocopherol (−6.411 kcal/mol) showed moderate binding affinities. The physicochemical properties of these compounds, including their potential for intestinal absorption and blood-brain barrier penetration, were favourable. These findings suggest that the identified compounds may serve as promising bioinsecticides for controlling Aedes aegypti and mitigating the spread of vector-borne diseases*.

Keywords*: Health challenge, Aedes aegypti, insecticide, Solanum erianthum, Docking*

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1.0 Introduction

The dengue fever epidemic, driven primarily by the *Aedes aegypti* mosquito, is a growing concern for global health due to its extensive distribution in tropical and subtropical regions. *A. aegypti* is a vector for multiple viral diseases, including dengue virus, Zika virus, chikungunya virus (CHIKV), and Mayaro virus (MAYV) (Nwangwu *et al*., 2024). With over 100 million cases of dengue fever annually and a significant portion of the world's population residing in areas affected by *A. aegypti*, the impact of these diseases is profound (Hahn *et al*., 2001; Paixão *et al*., 2017). The mosquito's capacity to breed rapidly in areas with an inadequate water supply and poor waste disposal, coupled with its nearly imperceptible bite and daytime feeding behaviour, further complicates control efforts (Ruiz-Díaz *et al*., 2017; Gubler, 2002; Knudsen, 1995).

Traditional insecticides, including carbamates, organophosphates, and pyrethroids, have been employed to manage mosquito populations with varying degrees of success. However, their effectiveness is increasingly undermined by issues such as high toxicity and the development of insecticide resistance (Turchen *et al*., 2020). This resistance problem necessitates the development of novel insecticides that are both effective and environmentally benign. One promising approach is to target the juvenile hormone (JH) system, which regulates critical developmental processes in mosquitoes, including metamorphosis and reproduction (Wu *et al*., 2016). Given that juvenile hormones are specific to insects and not present in vertebrates, targeting this system offers the potential for developing insecticides with reduced toxicity to non-target organisms (Riddiford, 1994).

Recent research underscores the potential of plant-derived compounds as viable alternatives to synthetic insecticides. Plants from the *Solanum* genus, such as *Solanum erianthum*, are known for their diverse biological activities, including insecticidal effects. For instance, various *Solanum* species have demonstrated efficacy in controlling mosquito larvae and other insect pests (Singha and Chandra, 2011; Chowdhury *et al*., 2008). These natural compounds offer several advantages, including lower toxicity to humans and rapid decomposition in the environment, which minimizes ecological impact (Borges *et al*., 2021).

In silico methods have become instrumental in identifying and optimizing potential bioactive compounds from plant extracts. These computational techniques allow for the prediction of interactions between plant-derived compounds and specific biological targets, such as the juvenile hormone-binding protein in mosquitoes. Advances in structural biology have provided detailed 3D models of these proteins, which facilitate virtual screening and molecular docking studies to identify promising candidates (Kim *et al*., 2017).

This study aims to identify potential juvenile hormone inhibitors from the methanol extract of *Solanum erianthum* leaves using an *in silico* approach. By employing molecular docking and virtual screening techniques, we seek to discover novel compounds that could interfere with the JH signalling pathway in *Aedes aegypti*. This research has the potential to contribute to the development of innovative and environmentally sustainable strategies for mosquito control, offering a new avenue for tackling vector-borne diseases on a global scale.

2.0 Materials and Methods

2.1 Extraction

Fresh samples of the leaves of *Solanum erianthum* were collected and identified at the Botanical Gardens of the University of Ibadan. The leaves were dried under mild sunlight and ground. A 1kg portion of the powdered sample was extracted successively with hexane, ethyl acetate and methanol. The extracts were concentrated to dryness. The methanol extract was retained for further studies.

2.2 GCMS Analysis of Extract

The extract was analyzed on an Agilent 7890 gas chromatograph (Agilent Technologies, Palo Alto, CA) coupled to a mass detector (Agilent 5975C) in an electron impact mode. The sample components were separated on a 30m x 0.32 mm Chrompack CP-Wax 52 CB capillary column with a film thickness of 0.25 um. A 1uL portion of the diluted sample was injected into the column in the splitless mode at 250^{o}C. Helium at an inlet pressure of 12.936 p.s.i, and a flow rate of 5 ml/min, was used as the carrier gas. The column oven temperature was raised steady at 8^{o}C/min from 50^{o}C to 240^{o}C, the final holding time was 5 minutes. Identification of sample constituents was done by comparing the fragmentation patterns of the compounds with those obtainable in the National Institute of Standards and Technology Mass Spectra Library (NIST 14L) on the GCMS database.

2.3 Molecular Docking

The structures of the compounds detected in the extract and that of the standard (Pyriproxyfen) were downloaded from the PubChem database in the SDF file format and subsequently converted into the mol2 format using the OpenBabel software (O'Boyle *et al*., 2011). The protein (PDB ID: 5V13) was obtained from the Protein databank. The SwissDock Server was used to study the interaction of the ligands with the protein (http://www.swissdock.ch/). The ligands were docked using the Autodock Vina Docking engine option (Bugnon, 2024; Eberhardt *et al*., 2021).

2.4 Prediction of Pharmacokinetic and Toxicological Properties

The physicochemical properties of the compounds demonstrating the best potential as insecticides were predicted using SwissADME (Daina *et al*., 2017) while their absorption and toxicological profiles were assessed using ADMESAR (http://lmmd.ecust.edu.cn/admetsar1/predict/) (Muchmore *et al*., 2010).

3.0 Results and Discussion

The results from the GC-MS analysis (Table 1) and *in silico* binding affinity studies (Table 2) of *Solanum erianthum* leaves methanol extract reveal a diverse phytochemical profile with potential implications for mosquito control. Recent literature supports and contextualizes these findings, highlighting the relevance of these compounds in insecticidal activity.

The GC-MS analysis shown in Table 1 identified several key compounds in the methanol extract, including sterols and fatty acid derivatives. These components are well-documented in recent studies for their biological activities. The identified sterols, notably γ-sitosterol, Ergost-5-en-3-ol, and Stigmasterol, align with recent findings on their biological and insecticidal properties. γ-Sitosterol, which was the most abundant compound (40.25% area), has been shown to possess significant insecticidal and anti-inflammatory properties (Elizalde-Romero *et al*., 2021). Ergost-5-en-3-ol and Stigmasterol have also been highlighted in recent research for their potential as insect growth regulators and their roles in disrupting insect development (Singha *et al*., 2023; Rajkumar *et al*., 2022).

The presence of Hexadecanoic acid and Octadecanoic acid esters is consistent with findings that these compounds can impact insect physiology. For instance, fatty acid esters have been noted for their potential to disrupt the endocrine systems of insects (Chen *et al*., 2022). Their significant presence in the extract supports their potential role in influencing mosquito development.

DL-α-Tocopherol, a potent antioxidant, may contribute to the extract's biological activity, as recent studies have linked antioxidants to enhanced insecticidal effects through oxidative stress induction (Borges *et al*., 2022). Sulfurous acid esters, although less studied, have been associated with various bioactivities, adding to the complex bioactivity of the extract (Mishra *et al*., 2023).

The *in silico* studies provided insights into the binding affinities of these compounds (Table 2) with the juvenile hormone-binding protein (5V13). Recent literature supports the potential of these compounds as juvenile hormone inhibitors.

Ergost-5-en-3-ol (−8.316 kcal/mol) and 9,19-cycloergost-24(28)-en-3-ol (−8.388 kcal/mol) exhibited the highest binding affinities. Recent research emphasizes the importance of sterols in disrupting juvenile hormone pathways. For example, β-sitosterol has been reported to affect insect growth and development by interfering with hormone signalling pathways (Hosseinzadeh *et al*., 2023). Similarly, ergosterol has been recognized for its potential to disrupt insect endocrine systems (Elizalde-Romero *et al*., 2021). DL-α-Tocopherol (−6.411 kcal/mol) and Phenol, 2,4-bis(1,1-dimethylethyl) (−7.063 kcal/mol) have moderate binding affinities. Recent studies indicate that compounds with such affinities can still play significant roles in insecticide design. For instance, Tocopherols have been shown to enhance the efficacy of insecticides through synergistic effects (Khan *et al*., 2023). Compounds like β-sitosterol (−3.288 kcal/mol) and γ-sitosterol (−3.241 kcal/mol) showed lower binding affinities. While these affinities suggest weaker interactions with the target protein, recent research suggests that even compounds with lower binding affinities can contribute to insecticidal activity, potentially through combined effects or secondary mechanisms (Turchen *et al*., 2023).

The structures of 3β-Ergost-5-en-3-ol (**1**), 9,19-cycloergost-24(28)-en-3-ol,4,14-dimethyl-, (3β, 4α, 5α) (**2**), Phenol, 2,4-bis(1,1-dimethylethyl) (**3**), and DL-α-tocopherol (**4**),

are shown in Fig. 1. The docking poses of (3β)-Ergost-5-en-3-ol (**1**), 9,19-cycloergost-24(28)-en-3-ol, 4,14-dimethyl, (3β,4α, 5α) (**2**), Phenol, 2,4-bis(1,1-dimethylethyl) (**3**) and DL-α-tocopherol (**4**) within the binding pocket of 5V13 is shown in Fig. 2.

Bioactive compounds must be able to cross biological membranes seamlessly to exert their activity. To evaluate the compounds' ability to cross biological membranes, their physicochemical properties were evaluated using SwissADME. Compounds having PSA less than 140A^{o} have good intestinal absorption; those with PSA values less than 70A^{o} can penetrate the blood-brain barrier (Muchmore *et al*., 2010).

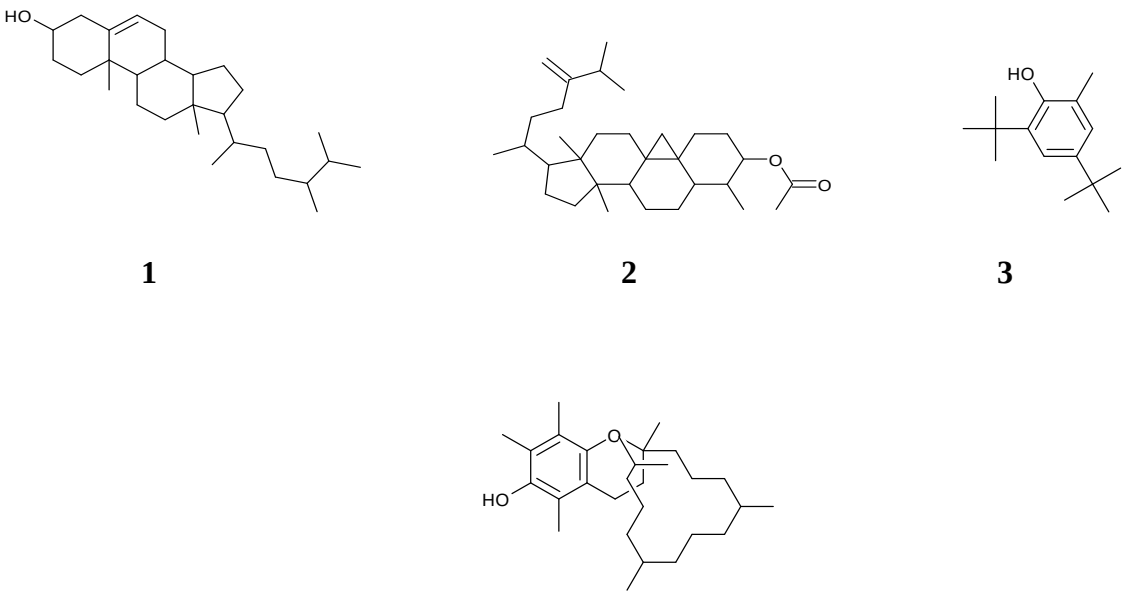
Table 1: **Compounds identified in *Solanum erianthum*leaves methanol extract by GC-MS analysis**

S/N	Retention Time (minutes)	% Area	Compound	Quality
1.	10.992	0.33	α-caryophyllene	97
2.	11.776	0.08	Phenol, 2,4-bis(1,1-dimethylethyl)	90
3.	15.764	0.33	2-pentaecanone, 6,10,14-trimethyl	90
4.	16.622	1.63	Hexadecanoic acid, methyl ester	97
5.	17.326	2.31	Hexadecanoic acid, ethyl ester	93
6.	18.030	0.11	Ethyl heptadecanoate	93
7.	18.316	0.49	9,12-Octadecadienoic acid, methyl ester (Z,Z)	99
8.	18.385	0.57	9,12,15-Octadecatrienoic acid, methyl ester (Z,Z,Z)	98
9.	18.619	0.71	Octadecanoic acid, methyl ester	97
10.	18.963	0.89	Linoleic acid ethyl ester	94
11.	19.026	0.88	9,12,15-Octadecatrienoic acid, ethyl ester (Z,Z,Z)	
12.	19.254	1.26	Octadecanoic acid, ethyl ester	94
13.	19.672	0.10	Nonahexacontanoic acid	90
14.	19.724	0.07	Sulfurous acid,butyl hexadecyl ester	91
15.	19.758	0.16	Sulfurous acid, butyl octadecyl ester	91
16.	20.422	9.55	dl-α-Tocopherol	98
17.	21.154	0.56	Methyl 19-methyl eicosanoate	95
18.	25.011	8.75	Ergost-5-en-3-ol, (3β)-	99
19.	27.540	8.17	Stigmasterol	99
20.	33.295	4.54	β-sitosterol	94
21.	32.478	40.25	γ-sitosterol	96
22.	33.365	2.49	Stigmastanol	91
23.	34.217	2.51	Fucosterol	95
24.	37.405	5.37	Dotriacontane	96
25.	38.526	0.75	9,19-cycloergost-24(28)-en-3-ol, 4,14-dimethyl-, (3β,4α, 5α)	90

In this study, all the compounds investigated have PSA values less than 70 A^o, indicating that they possess good intestinal absorption and would pass through the blood-brain barrier. These results were corroborated by those obtained using ADMESAR, showing the compounds possess good intestinal and CaCo-2 permeability and would penetrate the blood-brain barrier. The physicochemical properties of the compounds are shown in Table 3.

Table 2: Binding Affinities of study compounds with 5V13

Compound	Binding Affinity (kcal mol^{-1})	Compound	Binding Affinity (kcal mol^{-1})
α-caryophyllene	-3.704	Sulfurous acid,butyl hexadecyl ester	-4.355
Phenol, 2,4-bis(1,1-dimethylethyl)	-7.063	Sulfurous acid, butyl octadecyl ester	-4.401
2-pentaecanone, 6,10,14-trimethyl	-4.789	DL-α-Tocopherol	-6.411
Hexadecanoic acid, methyl ester	-4.308	Methyl 19-methyl eicosanoate	-4.632
Hexadecanoic acid, ethyl ester	-5.644	Ergost-5-en-3-ol, (3β)-	-8.316
Ethyl heptadecanoate	-4.163	Stigmasterol	-
9,12-Octadecadienoic acid, methyl ester (Z,Z)	-4.572	beta-sitosterol	-3.288
9,12,15-Octadecatrienoic acid, methyl ester (Z,Z,Z)	-4.358	gamma-sitosterol	-3.241
Octadecanoic acid, methyl ester	-5.300	Stigmastanol	-3.342
Linoleic acid ethyl ester	-5.062	Fucosterol	-1.587
Octadecanoic acid, ethyl ester	-4.352	Dotriacontane	
Nonahexacontanoic acid	-	9,19-cycloergost-24(28)-en-3-ol, 4,14-dimethyl-, (3β,4α, 5α)	-8.388
Pyriproxyfen	-6.081		



1 **2** **3**

4

Fig. 1: Structures of 3(β)-Ergost-5-en-3-ol (1), 9,19-cycloergost-24(28)-en-3-ol, 4,14-dimethyl-, (3β,4α, 5α) (2), Phenol, 2,4-bis(1,1-dimethylethyl) (3), and DL-α-tocopherol (4)

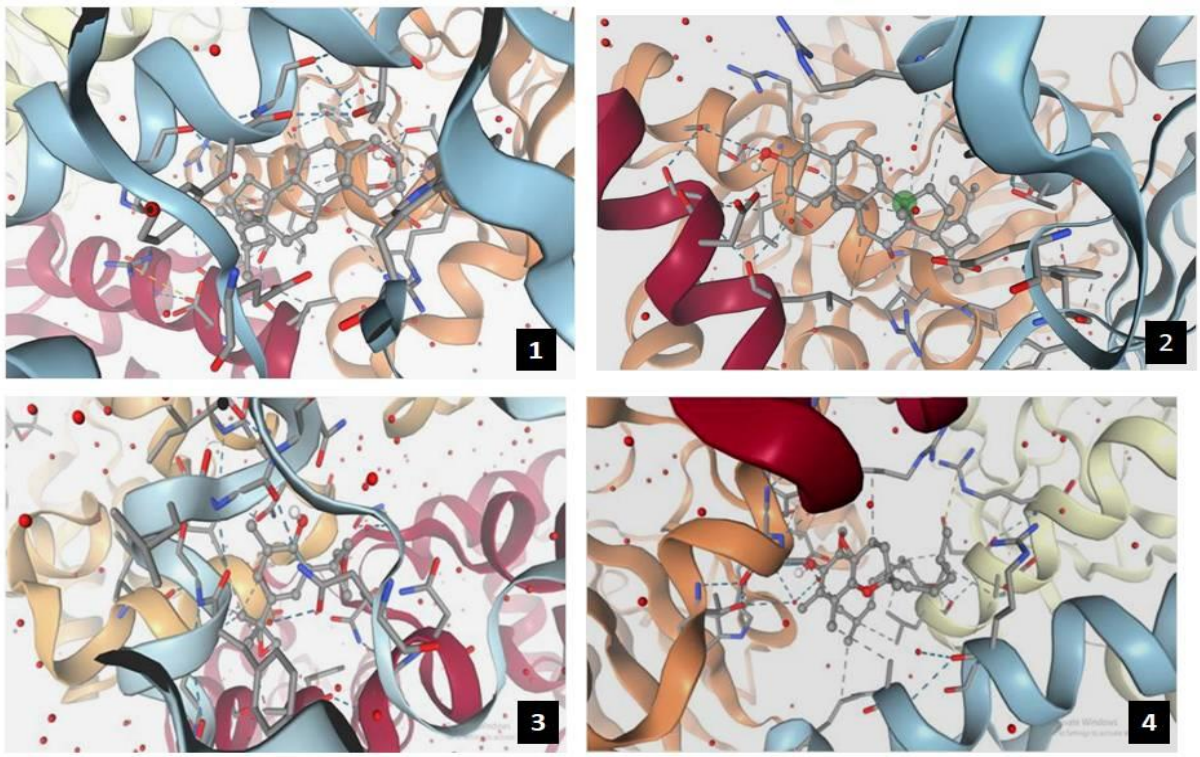


Fig. 2: Docking poses of 3(β)-Ergost-5-en-3-ol (1), 9,19-cycloergost-24(28)-en-3-ol, 4,14-dimethyl-, (3β,4α, 5α) (2), Phenol, 2,4-bis(1,1-dimethylethyl). (3), and dl-α-tocopherol (4)

Table 3: Prediction of Physicochemical Parameters

Property	MW	NRB	HBA	HBD	TPSA (A^o)	iLogP	Log Kp (skin permeation) cm/s
1	400.68	5	1	1	20.23	4.92	-2.50
2	426.72	5	1	1G	20.23	5.00	-1.87
3	206.32	2	1	1	20.23	3.08	-3.87
4	430.71	12	2	1	29.46	5.92	-1.33
5	306.48	15	2	0	26.30	4.82	-3.44

MW=molecular weight; iLog Po/w=octanol/water partition coefficient; PSA= polar surface area; HBD = hydrogen bond donor; and HBA = hydrogen bond acceptor.

Table 4: Toxicity Prediction by the ADMESAR

Ligand	hERG Inhibition	AMES Toxicity	Carcinogens	FT	TPT	HBT	Biodegradation
1	Weak inhibitor	Non-AMES toxic	Non-carcinogens	High FHST	High TPT	High HBT	Not readily biodegradable
2	Weak inhibitor	Non-AMES toxic	Non-carcinogens	High FHST	High TPT	High HBT	Not readily biodegradable
3	Weak inhibitor	Non-AMES toxic	Non-carcinogens	High	High TPT	High HBT	Not readily biodegradable
4	Weak inhibitor	NON-AMES toxic	Non-carcinogens	High	High TPT	High HBT	Not readily biodegradable

****FT – Fish toxicity; TPT - Tetrahymena Pyriformis Toxicity; HBT – Honey Bee Toxicity**

4.0 Conclusion

The study investigated the potential of phytoconstituents from the methanol extract of *Solanum erianthum* leaves as juvenile hormone inhibitors for controlling *Aedes aegypti*, a major vector for several dangerous diseases. Using molecular docking techniques, the binding affinities of the identified compounds with the juvenile hormone-binding protein (5V13) were evaluated. GC-MS analysis revealed a diverse range of compounds including sterols, fatty acids, and antioxidants. Ergost-5-en-3-ol and 9,19-cycloergost-24(28)-en-3-ol exhibited the highest binding affinities, surpassing that of

the standard inhibitor Pyriproxyfen. The results suggest that these compounds could effectively interact with the juvenile hormone pathway, potentially leading to effective mosquito control.

The findings indicate that the methanol extract of *Solanum erianthum* leaves contains bioactive compounds with promising juvenile hormone inhibitory potential. Ergost-5-en-3-ol and 9,19-cycloergost-24(28)-en-3-ol, in particular, demonstrated strong binding affinities, suggesting their potential as effective bioinsecticides. These compounds, along with others identified in the extract, show good physicochemical properties for bioavailability, including the ability to cross biological membranes.

Based on the results, further research is recommended to validate the *in silico* findings through *in vivo* studies. Laboratory and field trials should be conducted to assess the efficacy of these compounds in real-world mosquito control applications. Additionally, exploring the synthesis and optimization of these compounds could enhance their insecticidal properties and ensure their safety and effectiveness in diverse environmental conditions.

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