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Research Article

VIRTUAL SCREENING, MOLECULAR DOCKING, AND ADME/T PROPERTIES ANALYSIS OF REPELLENT EFFICACY OF NATURAL COMPOUNDS ON *DERMESTES MACULATUS* OF *PROTOPTERUS ANNECTENS*

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ABSTRACT

Dermestes maculatus is a very important pest of smoke-dried fish that destroys the flesh, eating away the muscles, and leaving the skeletons when cured fish are stored for long period. This necessitates the idea of establishing an alternative repellant from natural plant products. In this article, compounds of *Capsicum annum* will be studied against repellent protein NDS2 of *D. maculatus*. The compounds present in *C. annum*. were docked against The NADH dehydrogenase subunit 2 (NDS2) protein of *D. maculatus*. PyRx-Python prescription 0.8 was used to identify binding affinities of compounds against the proteins. The results we obtained from molecular docking show that among 48 molecules of natural origin from *C. annuum* was downloaded in SDF format from the NCBI PubChem database. Six molecules are the best compounds observed through molecular docking and some hydrogen bonding and hydrophobic interactions are proposed as the efficacy from *C. annuum* on a repellent protein of *D. maculatus*. The molecular docking was performed to establish efficacy and binding affinity of ligands from *C. annum* on the repellent protein of *D. maculatus.* ADMET analysis is performed to establish the possible toxicity of the ligands. Importantly, all six natural compounds present in *C. annum*. may be more potent in new insecticide against NSD2 in *D. maculatus* but needs further experimental research.

Keywords: *Capsicumannuum, Dermestes maculatus, In silico* Analysis, *Protopterus annectens*, Repellent.

INTRODUCTION

Insects of a stored product are known in different agricultural products including smoked fish products (SFPs). The genus *Dermestes* is known for its infestation of dried fish during storage, transportation, and marketing causing qualitative and quantitative damage. Dried fish is readily attacked by several species of dermestid beetle, including *Dermestes maculatus* (*D. maculatus*), *Dermestes frischii* (*D. frischii*), and *Dermestes ater* (*D. ater*). The Dermestid beetle, *D. maculatus*, is a very important pest of smoke-dried fish which destroys the flesh, eating away the muscles, and leaving the skeletons when cured fish arestored for a long period, it accounts for about 71.5% of dried fish infestation recorded in most of the producing areas with a substantial loss in dry weights of about 43-62.7% from both larvae and adults in Nigeria (Babarinde *et al.,* 2012).

Fish serves as one of the major and cheapest sources of animal protein and has been used steadily due to its availability and nutritional values. Fish is also used to correct protein deficiency in human diets in tropical areas. The need to protect smoked fish from pests is imperative because fish plays a crucial role in ensuring food security, income generation, and employment opportunities (Don-Pedro, 1989).

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The West African lungfish (*Protopterus annectens*) or Tana lungfish is a species of lungfish found in a wide range of freshwater habitats in West and Middle Africa, as well as the northern half of Southern Africa (Dalsgaard *et al.*, 2011). Lungfish typically comprised a small proportion of a fisherman's catch. Preservation of this fish prevents the action of microbes that result in spoilage. There are several methods of fish preservations that include freezing, salting, and canning out of which sun or smoke drying to reduce the moisture content of the fish is more appropriate for long term storage and contains more protein on a weight basis (Federal and Agriculture Organization, 1989).

Synthetic chemical insecticides (SCIs) have been an important part of pest management (PM) for many years. Interest is however growing fast in the possible role of plants and minerals as traditional protectants of stored products and as an alternative to pest control (Nwaehujor & Olatunji, 2011). The use of synthetic insecticides was found to be toxic to humans, animals, and the environment. Abolagba *et al.* (2011) reported the toxic effect of 2,2-dichlorovinyldimethylphosphate (DDVP1000 EC) on fish against *Dermestes* beetles and observed that after four weeks of exposure to atmospheric air these pesticides were still present in the fish. All these problems have initiated the development of new types of selective insect-control alternatives to conventional fumigants (Moravvej *et al.*, 2010).

Many medicinal plants and spices have been cited as pest control agents for stored grains, legumes, and smoked fish (Lithi *et al.*,2013). Chili peppers (*Capsicum annuum L.*) are used as vegetables, spices, medicinal herbs, and ornamental plants around the world. These plants belong to the family Solanaceae and appear in different forms, shapes, sizes, and colors. Some varieties are pungent and some are not (Andrews, 1999). Its popularity can be traced to its enhancement to food palatability. Chemical analyses revealed that the fruit consists of relatively low content of sodium and calories, but rich in vitamins A, C, E and a good source of folic acid and potassium (Haselow & Osei, 2015). During the last years, new insecticides were developed interfering with mitochondrial electron transport (MET), most of them with the proton-translocating NADH: ubiquinone oxidoreductase complex I. It is worth mentioning that complex I is not a completely new insecticide target since one of the classical complex I inhibitors, rotenone, is known for its weak and limited insecticidal activity. This research is aimed at determining ligands efficacy of *C. annuum.* on repellent NDS2 protein *D. maculatus* of *P. annectens* through *in silico* approach.

MATERIALS AND METHOD

Protein preparation

The structure of target protein NADH dehydrogenase subunit 2(NDS2) was downloaded from the protein data bank (PDB) (https://www.rcsb.org) in .pdb format.

Homology Modeling of NADH dehydrogenase subunit 2 (NDS2)

Homology modeling approaches use experimental protein structure ("templates") to construct suitable receptor proteins. Homology modeling is probably the most effective tool for producing robust tridimensional models of protein structure (Verma *et al.,* 2020). Swiss-model is a web-server of structural bioinformatics devoted to modeling homology for the analysis of 3D protein structures (Kaczanowski & Zielenkiewicz, 2010). The whole protein was modeled by uploading the NADH dehydrogenase subunit 2 (NDS2) protein FASTA sequence into the SWISS-MODEL workspace via automatic mode for the creation of a more reliable protein model (Krieger *et al.,* 2003). The NDS2 protein and its sequence, respectively, were selected as the target protein and query sequence. Global quality estimate, local quality estimate comparison, and NDS2 model template alignment with 5gpn.30. An (NADH: ubiquinone oxidoreductase complex I), were calculated (Figure 1).

Modeled NDS2 protein validation

The NDS2 protein modeled was validated using the Ramachandran plot. Ramachandran plot validated the output using Rampage (Read *et al.,* 2011). The NDS2 based protein plot values for Ramachandran and its 5gpn.30.A template was obtained (Table No. 1). In the NDS2 protein Ramachandran plot, 92.0% of the amino acid residues were found in the favored region, 6.7% residues in the permitted region, and 1.3% percent of the residues in the outer regions (Figure 2). The Ramachandran plot data for the NDS2 modeled protein suggested favorable reliability of the NDS2-modelled protein for subsequent docking studies (Table 1, Figure 2).

Preparation of Ligands

An extensive literature survey was made and 48 different phytochemical extracts of Capsicum extracts were obtained. The 3D or 2D structures of the ligands were downloaded from NCBI PubChem in .sdf formats (Lawal, *et al.,* 2020). the downloaded ligands were combined altogether using OpenBabel software. A standard ligand for the protein was obtained through literature and docked against the protein to check its binding affinity, those phytochemicals that have lower binding affinity than the standard were selected and subjected to visualization.

Virtual screening and molecular docking

The prepared protein was in .pdb format loaded to PyRx software for docking; it was then converted to autodock macromolecule. The prepared ligands were imported into the PyRx software; the ligands were minimized to .mmff4 to reduce their energy and converted to dock-able .pdbqt format. The protein and the ligands were docked to detect their binding energy, the X,Y, and Z dimensions (57.75, 52.9 and 48.60 respectively) of the protein was maximized to cover its grids. The ligands that have lower dock scores

than the control insecticide were saved in .pdb format and their

binding affinities were recorded. Visualization was carried out using Discovery studio 2016 (Abhishek Kumar Verma and Mayadhar Barik, 2020) compounds that show hydrogen and hydrophobic bonds were selected for further analysis, and those without the aforementioned bonds were discarded.

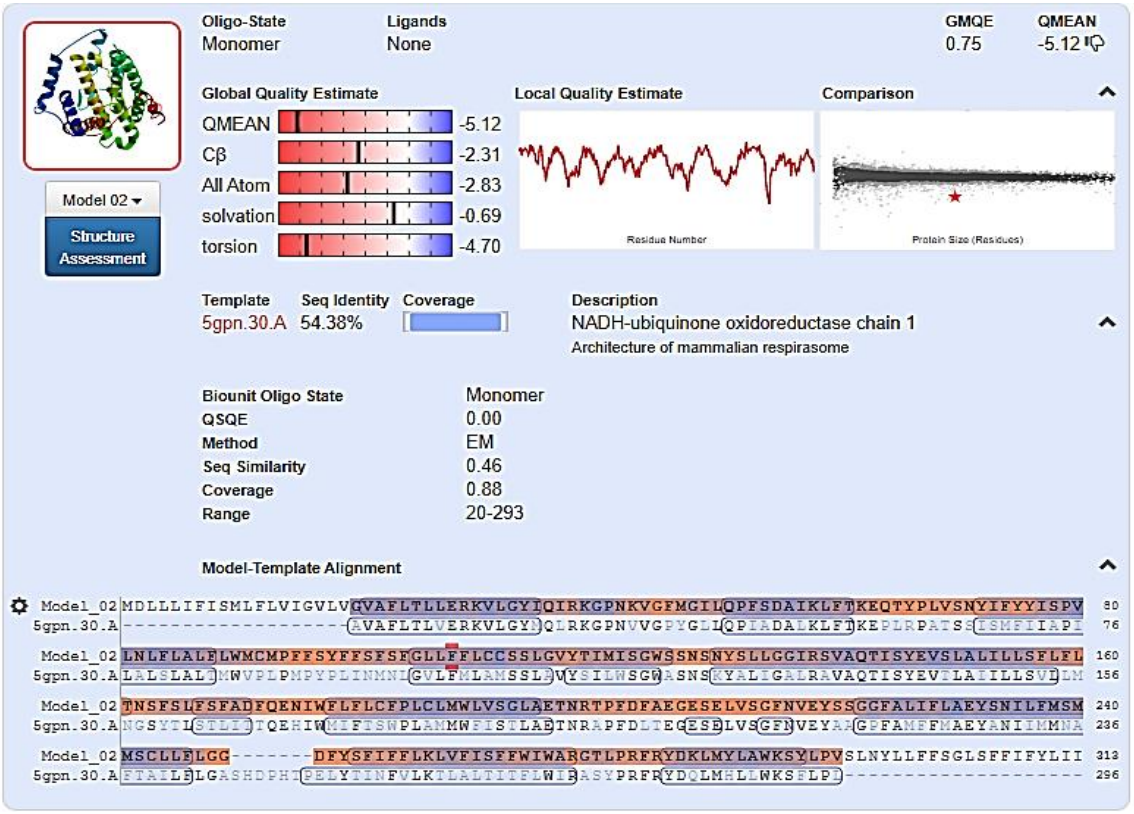


Figure 1. Global quality estimate, local quality estimate comparison, and NDS2 model template alignment with 5gpn.30.A.

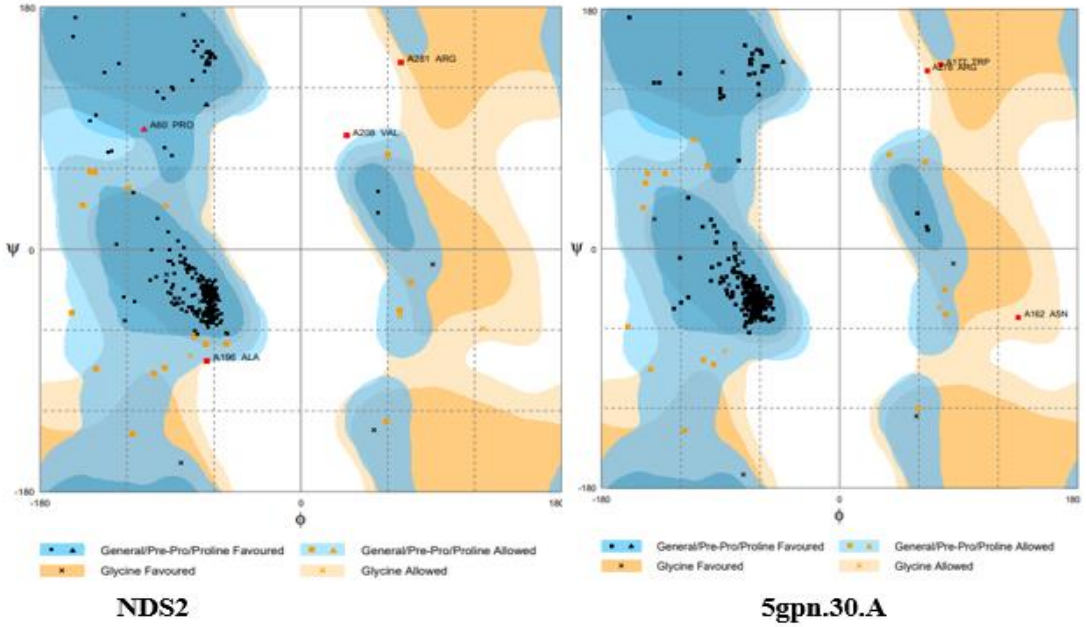


Figure 2. Ramachandran plots for Modeled-NDS2 and 5gpn.30.A.

Table 1. The data from Ramachandran plot of for Modeled-NDS2.

	Percent (%) of residues per region		
Structure	Favored	Allowed	Outline
NDS2	92.0%	6.7%	1.3%
5gpn.30.A	92.3%	6.6%	1.1%

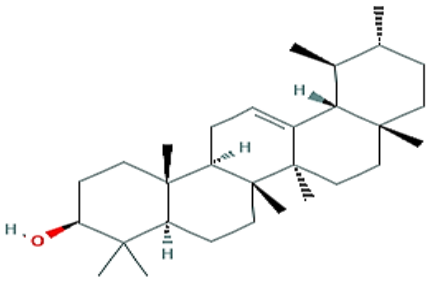
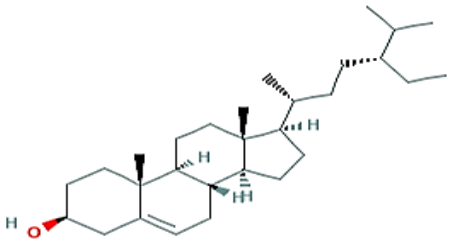
ADMET Properties

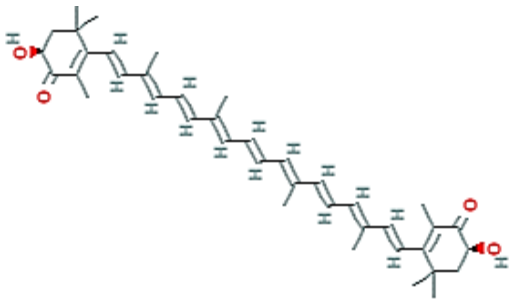
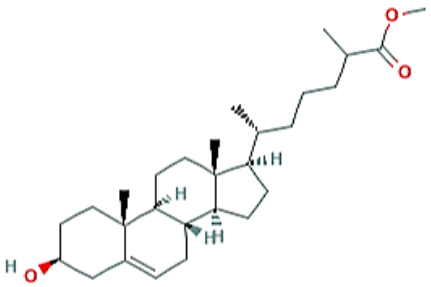
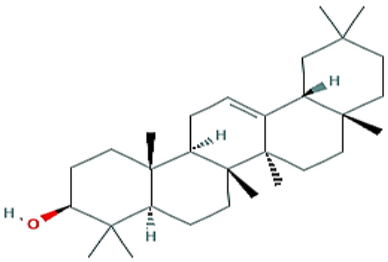
ADMET properties of the selected compounds wereanalyzed using the DruLiTo software. The software can calculate different molecular properties and screen molecules based on drug-likeness rules such asthe Ghose filter, Lipinski's rule, BBB Rule, MDDR-like rule, Veber rule,and CMC-50 like a rule and Quantitative estimate of drug-likeness (QED).Swiss ADME Boiled egg structure method is used for filtering ADME/T properties of compounds (Daina *et al*., 2017) and allows the evaluation of HIA as a function of the position the molecules in the WLOP-Versus-TPSA referential. Several parameters such as the toxicity, number of rotations, number of hydrogen bonds, absorption of the compounds were analyzed (Ertl *et al.*, 2000;9+Verma*., et al.* 2020).

RESULT AND DISCUSSION

The Crystal Structure of the NADH dehydrogenase subunit 2 (NDS2) protein of *Dermestes maculatus* was used for docking purposes. Molecular docking has been performed using the extra precision (XP) mode of grid-based ligand docking with energetics. We used known natural compounds for docking purposes (Figure 3). We selected the top six compounds with show good dock score, which were docked with NADH dehydrogenase subunit 2 (NDS2) protein of *D. maculatus*. Our result highlighted that; α-amyrin, campesterol, β-sitosterol, Astaxanthin, Methyl (25RS)- 3beta-hydroxy-5-cholesten-26-oate, and β- amyrin yielded a preeminent dock score with the NDS2 protein (Table 2).

Table 2. Dockscore (Kcal/mol) of the target protein with selected natural compounds detected by molecular docking.

Sr. No.	Compounds Name	PUBCHEM ID	Structure	Docking Score (Kcal/mol)
1.	α- amyrin	73170		-8.8
2.	Campesterol	173183		-8.7
3.	β- sitosterol	222284		-8.6

4.	Astaxanthin	5281224		-9.7
5.	Methyl (25RS)-3beta-hydroxy-5-cholesten-26-oate	22213559		-8.4
6.	β- amyrin	73145		-9.3

There is some interaction like hydrophobic interactions and hydrogen bonding between amino acids of target proteins and selected natural compounds. Mostly it has been found that hydrophobic interaction plays a very important role in strongly bind atoms of ligands and amino acids of proteins (Table 3).Mostly it has been found that hydrophobic interaction plays a very important role in strongly binding atoms of ligands and amino acids of proteins. NDS2 protein molecule creates hydrophobic interactions with the help of Leu190(A), Phe277(A), Phe202(A), Leu285(A), Val191(A), Ala270(A), Phe266(A), Leu187(A) amino acids and hydrogen bond with the help of Tyr290 (A) amino acids.The protein interacts with the compounds with the help Tyr 290(A) and Leu190(A), Trp267(A), Phe266(A), Ala270(A), Leu194(A), Val191(A), Phe202(A), Phe277(A), Leu285(A) in hydrogen bonds and hydrophobic interactions respectively (Figure 4 and Table 3).Selected proteins are found to show good hydrophobic interaction and some hydrogen bonding with the amounts of selected natural compounds. These hydrophobic interactions formed between the proteins and compounds show the strength of the interaction.

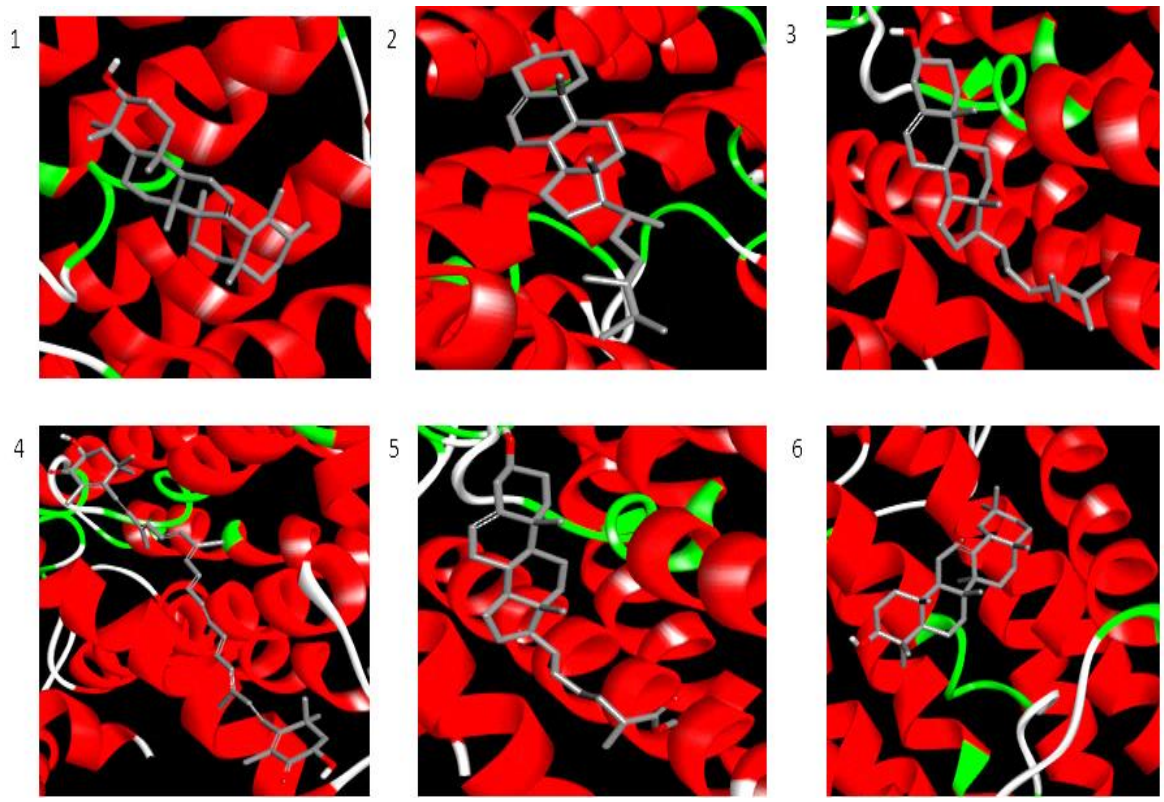


Figure 3. Ribbon representation of NADH dehydrogenase subunit 2 (NDS2) with top selected compounds. 1.α- amyrin; 2. Campesterol; 3.β- Sitosterol; 4.Astaxanthin; 5.Methyl (25RS) - 3beta-hydroxy-5-cholesten-26-oate; and 6.β- Amyrin.

Table 3. Protein-ligand interaction profile of NADH dehydrogenase subunit 2 (NDS2) with selected compounds.

Proteins	Phytochemicals (PUBCHEM ID)	Interaction	Amino acids interactions
NADH dehydrogenase subunit 2 (NDS2)	73170	Hydrogen bonding	Tyr290 (A)
		Hydrophobic interactions	Leu190(A), Phe277(A), Phe202(A), Leu285(A), Val191(A), Ala270(A), Phe266(A), Leu187(A)
	173183	Hydrogen bonding	-
		Hydrophobic interactions	Phe254(A), Phe99(A), Trp90(A)
	222284	Hydrogen bonding	-
		Hydrophobic interaction	Phe 266(A), Leu 190(A), Ile 263(A), Trp 267(A), Leu 187(A), Val 191 (A), Leu 194(A)
	5281224	Hydrogen bonding	-
		Hydrophobic interaction	Ile255(A), Trp177(A), Lys259(A), Leu179(A), Phe262(A), Leu 247(A), Leu 194(A), Val191(A),Ile263(A), Phe266(A), Leu190(A), Ala270(A), Leu187(A), Leu258(A)
	22213559	Hydrogen bonding	-
		Hydrophobic interaction	Phe246(A), Val191(A), Leu194(A), Leu247(A), Leu187 (A), Ile263(A), Phe266(A), Leu190(A), Trp267(A)
	73145	Hydrogen bonding	Tyr290(A)
		Hydrophobic interaction	Leu190(A), Trp267(A), Phe266(A), Ala270(A), Leu194(A), Val191(A), Phe202(A), Phe277(A), Leu285(A)

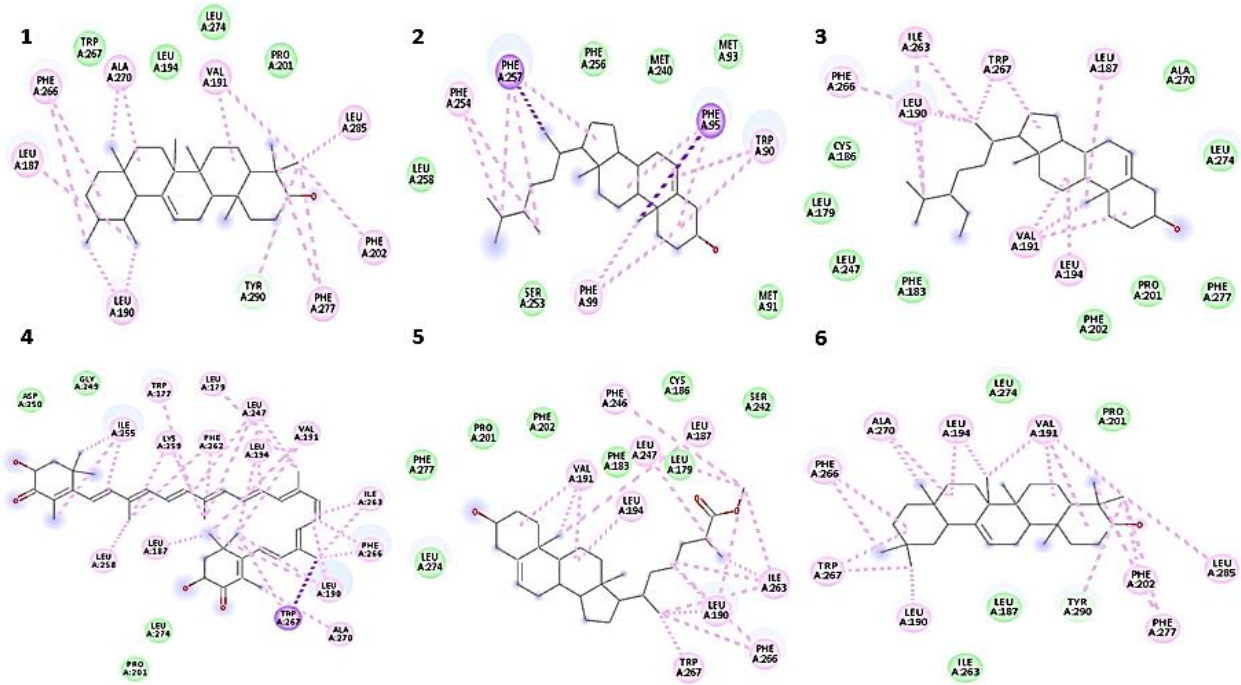


Figure 4. Protein-ligand interactions profile of NADH dehydrogenase subunit 2 (NDS2) with selected compounds.1.α-amyrin; 2.Campesterol; 3.β-Sitosterol; 4.Astaxanthin; 5.Methyl (25RS) - 3beta-hydroxy-5-cholesten-26-oate; and 6.β-Amyrin.

ADMET properties of top compounds

ADME/T properties of the top compounds (Figure 5) were appraised by using the DruLiTo is open-source software. It can calculate different molecular properties and screen the molecules based on drug-likeness rules such as the MDDR-like rule, Lipinski's rule, BBB Rule, Veber Rule, Ghose Filter, and CMC-50 like a rule and Quantitative estimate of drug-likeness (QED).The data obtained were within the range of values for all-natural compounds. The importance of polar surface area (PSA) suggested good oral bioavailability for selected natural compounds. The parameters, such as the number of rotatable No bonds and number of stable bonds correlated with the product of intestinal absorption, revealed that all-natural compounds (α-amyrin, Campesterol, and β-Sitosterol, etc.) are well absorbed (Figure 5 &Table 4).

Table 4. Structural; physicochemical; biochemical; pharmacokinetics and toxicity properties of selected natural compounds.

Sr. No.	Compound Id	MW	logp	Alogp	HBA	HBD	TPSA	AMR	nRB	N Atom	N Acidic Group	RC	nRigidB	nAromRing	nHB	SAlerts
1.	5281245	552.4	12.70	10.48	1	1	20.2	199.8	17	97	0	0	23	0	2	2
2.	2221355	430.3	8.75	1.288	3	1	46.5	122.2	7	77	0	4	27	0	4	3
3.	222284	414.3	11.59	1.3	1	1	20.2	123.8	6	80	0	4	27	0	2	1
4.	173183	400.3	11.02	1.976	1	1	20.2	120.8	5	77	0	4	27	0	2	1
5.	73170	426.3	11.44	2.366	1	1	20.2	130.5	0	81	0	5	35	0	2	1
6.	73145	426.3	11.54	3.012	1	1	20.2	132.3	0	81	0	5	35	0	2	1

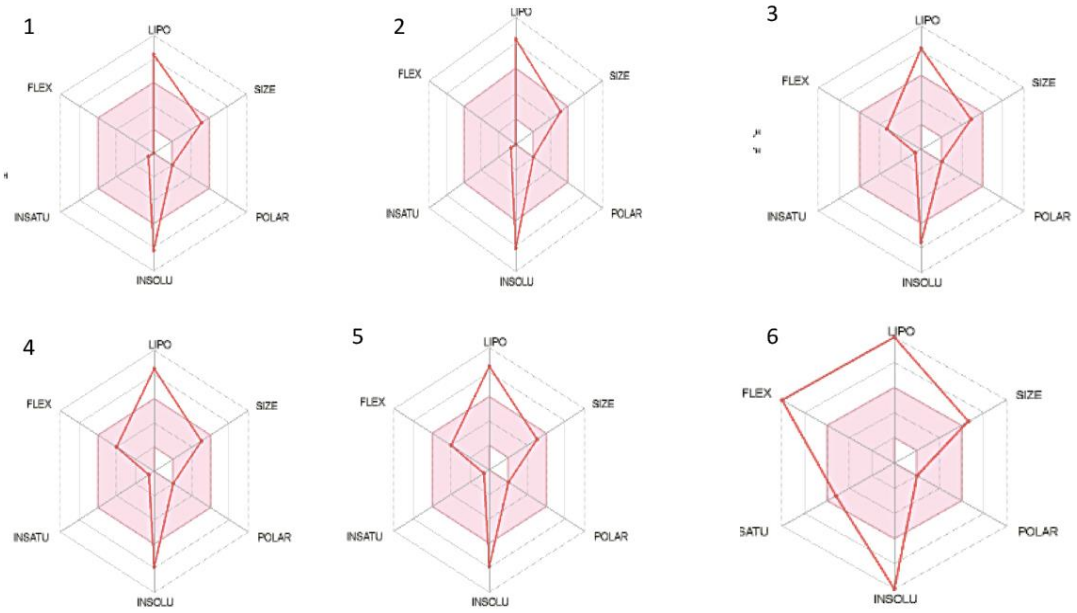


Figure 5. All six compounds show in the colored zone are the suitable physiochemical space for oral bioavailability and show the INSATU (Instauration), LIPO (Lipophilicity), POLAR (Polarity), SIZE (Molecular Weight), INSOLU (Insolubility), and FLIX (Rotatable bond flexibility) parameters.

CONCLUSION

In this study, it has been shown that six selected natural screened compounds present in *C. Annuum* have good docking score and strong hydrophobic interactions and some H-bonding and follows the Lipinski rule of five. Thus, these compounds might have the potential to be utilized against the NSD2 of *D. maculatus.* Here, in this study, we can conclude that the obtained compounds from this *in silico* study may be a good agent to combat new insecticide against *D. maculatus* either alone or in combination but needs further experimental research.

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