6th International Electronic Conference on Medicinal Chemistry
1-30 November 2020
sciforum.net/conference/ECMC2020
sponsored by pharmaceuticals

Identification of novel compounds from *Neocarya macrophylla* against toxins from *Naja nigricollis* using computational approach

Amina Jega Yusuf[1]*, Musa Ismail Abdullahi[2], and Aliyu Muhammad Musa[2]

[1] Department of Pharmaceutical & Medicinal Chemistry, Usmanu Danfodiyo University, Sokoto, Nigeria
[2] Department of Pharmaceutical & Medicinal Chemistry, Ahmadu Bello University, Zaria, Nigeria

* Corresponding author: amina.yusuf@udusok.edu.ng

Graphical abstract: Identification of novel compounds from *Neocarya macrophylla* against toxins from *Naja nigricollis* using computational approach

N. macrophylla

Isolation

- Catechin
- Epicatechin
- Catechin-3-rhamnoside
- quercetin

Molecular Docking

- PLA_2
- Neurotoxin
- Cardiotoxin

Table 1: Docking scores of the compounds against three toxins from *Naja nigricollis*

		Docking scores (kcal/mol)		
Compound name	**Compound ID**	**Phospholipase A_2**	**Neurotoxin**	**Cardiotoxin**
Catechin	9064	-8.5	-5.0	-5.4
Catechin-3-rhamnoside	21626704	-7.3	-5.8	-6.0
Epicatechin	72276	-8.2	-5.0	-5.2
Quercetin	528043	-8.5	-5.6	-5.2

Abstract: Envenomation resulting from snakebite especially *N. nigricollis* constitutes a frequent medical emergency in many tropical and sub-tropical countries. The unavailability and side effects associated with the only definitive treatment for snakebite victims necessitated the search for alternative available agents with lesser side effects. The aim of this study was to investigate the inhibitory action of compounds isolated from *N. macrophylla* against toxins (phospholipase A_2, neurotoxin and cardiotoxin) from *N. nigricollis* venom using computational approach.

Phytochemical constituents of *N. macrophylla* (catechin, epicatechin, catechin-3-rhamnoside and quercetin) were screened against three toxins from *N. nigricollis* using AutoDock tools in PyRx software and post docking analysis was conducted using the Chimera 1.14 and BIOVIA Discovery studio visualizer 2020.

The results have shown that, the compounds from *N. macrophylla* can bind with high affinity (ranging from -7.3 to -8.5 kcal/mol) to the active sites of phospholipase A_2 compared to the other toxins. The docking scores of the compounds against neurotoxin and cardiotoxin ranges from (-5.2 to -6. 6) and (-5.2 to -6.0), respectively.

The outcome of this study revealed that, phytoconstituents from *N. macrophylla* can effectively inhibit toxins from *N. nigricollis* venom and thus, could serve as lead compounds for further analysis.

Keywords: *Neocarya macrophylla*, flavonoids, *in* silico, antivenom

Introduction

- Envenomation resulting from snakebite is a neglected public health issue in many tropical and subtropical countries especially in Africa, Asia and Latin America

- with about with about 5.4 million snake bites occur each year, resulting in 1.8 to 2.7 million cases of envenomings (poisoning from snake bites) and in addition, there are 81 410 and 137 880 deaths and around three times as many amputations and other permanent disabilities each year (WHO, 2019).

- The unavailability and side effects associated with the only definitive treatment (administration of ASVs) for snakebite victims necessitated the search for alternative available agents with lesser side effects.

- Snake venom is a complex mixture of enzymatic and toxic proteins, which include phospholipase A_2 (PLA_2), myotoxins, hemorrhagic metallo-proteineases and other proteolytic enzymes, coagulant components, cardiotoxins, cytotoxins and neurotoxins (Kini, 1997; Aird, 2000; Ameen *et al*., 2015).

- Pathology induced by envenomation is due to the collective effect of myotoxic phospholipases A_2, neurotoxins, hyaluronidases and cytotoxins among others.

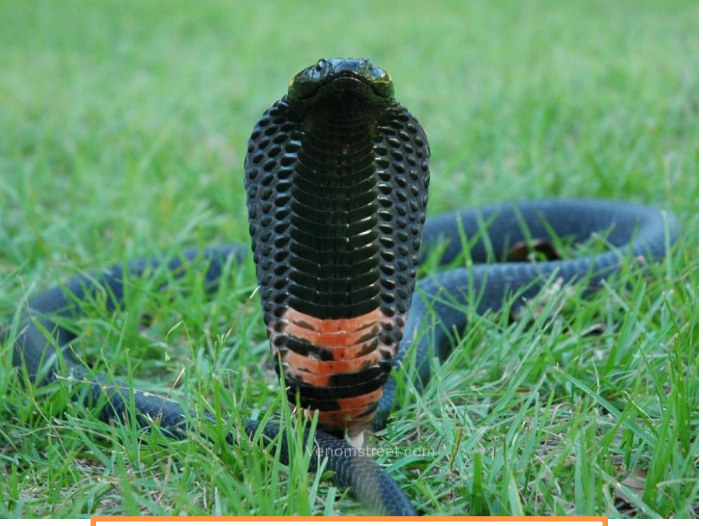
Introduction con't

- *Neocarya macrophylla* (Family; Chrysobalanaceae) commonly known as gingerbread plum has been used in traditional medicine to treat snake bites, cancer, breathing disorders among other (Yusuf *et al*., 2015).

- The antisnake venom of the plant have been validated against *Naja nigricollis* venom in animal models (Yusuf *et al*., 2019; Yusuf *et al*., 2020).

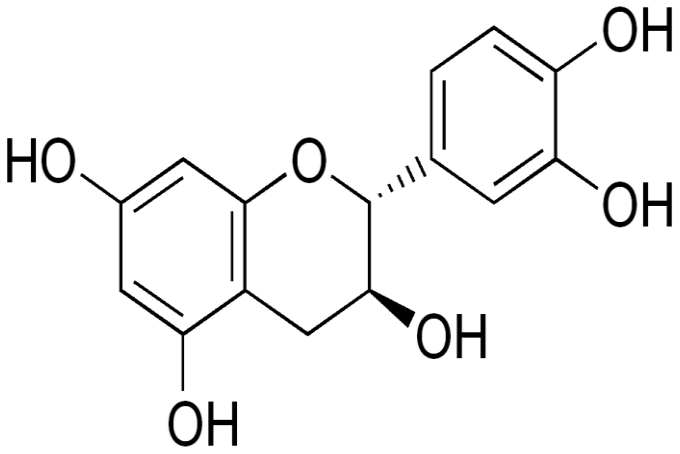
- Catechin, catechin-3-rhamnoside, epicatechin and quercetin were previously isolated from the stem bark and leaves of *N. macrophylla* (Figure 1) (Yusuf *et al*., 2019; Yusuf *et al*., 2020).

- The aim of the study was to investigate the inhibitory action of compounds isolated from *N. macrophylla* against toxins (phospholipase A_2, neurotoxin and cardiotoxin) from *Naja nigricollis* venom using computational approach

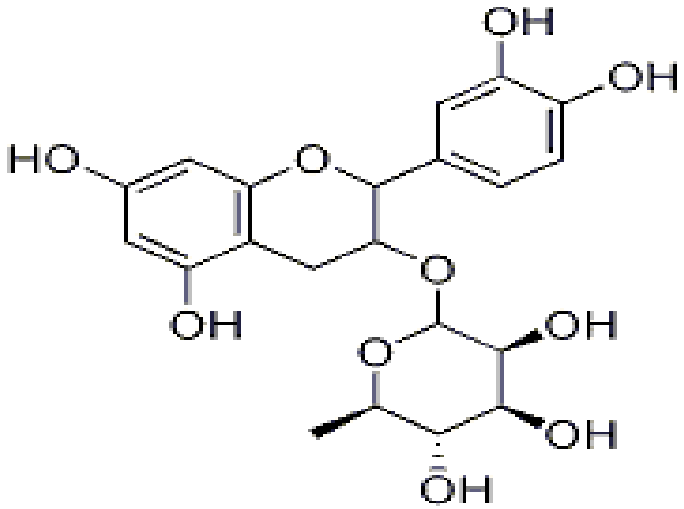


Naja nigricollis

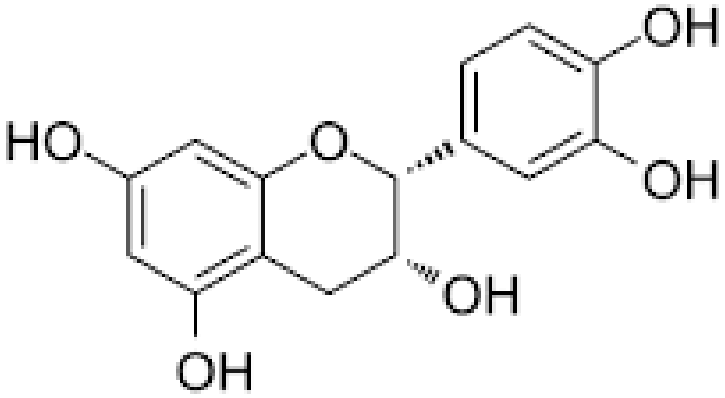
Snake bite



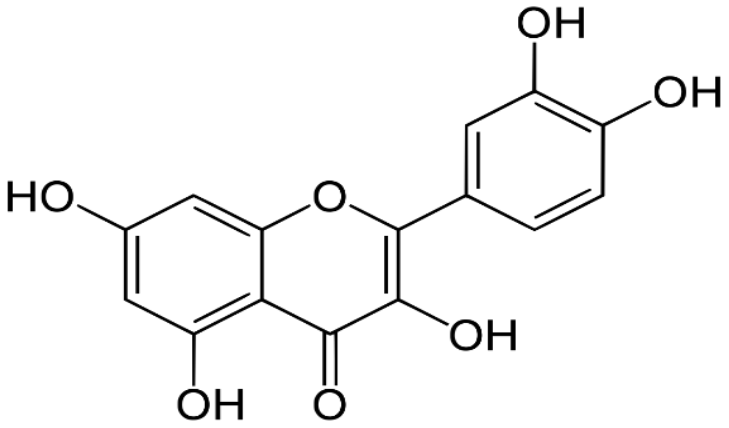
Catechin



Catechin-3-rhamnoside



Epicatechin



Quercetin

Figure 1: 2D structures of compounds isolated from *Neocarya macrophylla*

METHODOLOGY

Isolation

- Catechin
- Epicatechin
- Catechin-3-rhamnoside
- quercetin

- PLA_2
- Neurotoxin
- Cardiotoxin

- **Ligand preparation**
- **Protein preparation**

<u>Molecular Docking analysis</u>

- AutoDock tools in PyRx software

<u>Post docking analysis</u>

- Chimera 1.14
- BIOVIA Discovery studio visualizer 2020

Results and discussion

Table 1: Docking scores of the compounds against three toxins from *Naja nigricollis*

		Docking scores (kcal/mol)		
Compound name	**Compound ID**	**Phospholipase A_2**	**Neurotoxin**	**Cardiotoxin**
Catechin	9064	-8.5	-5.0	-5.4
Catechin-3-rhamnoside	21626704	-7.3	-5.8	-6.0
Epicatechin	72276	-8.2	-5.0	-5.2
Quercetin	528043	-8.5	-5.6	-5.2

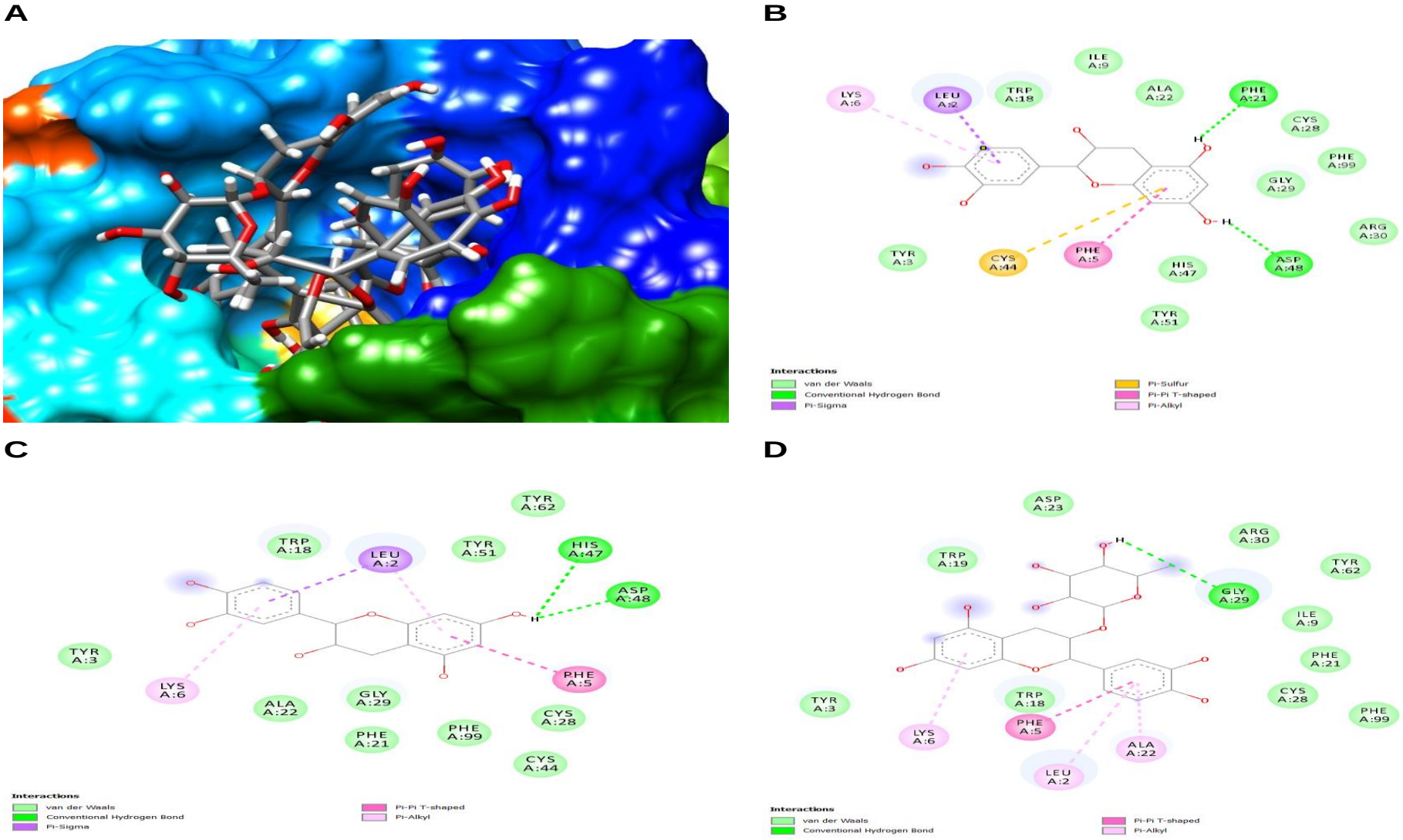
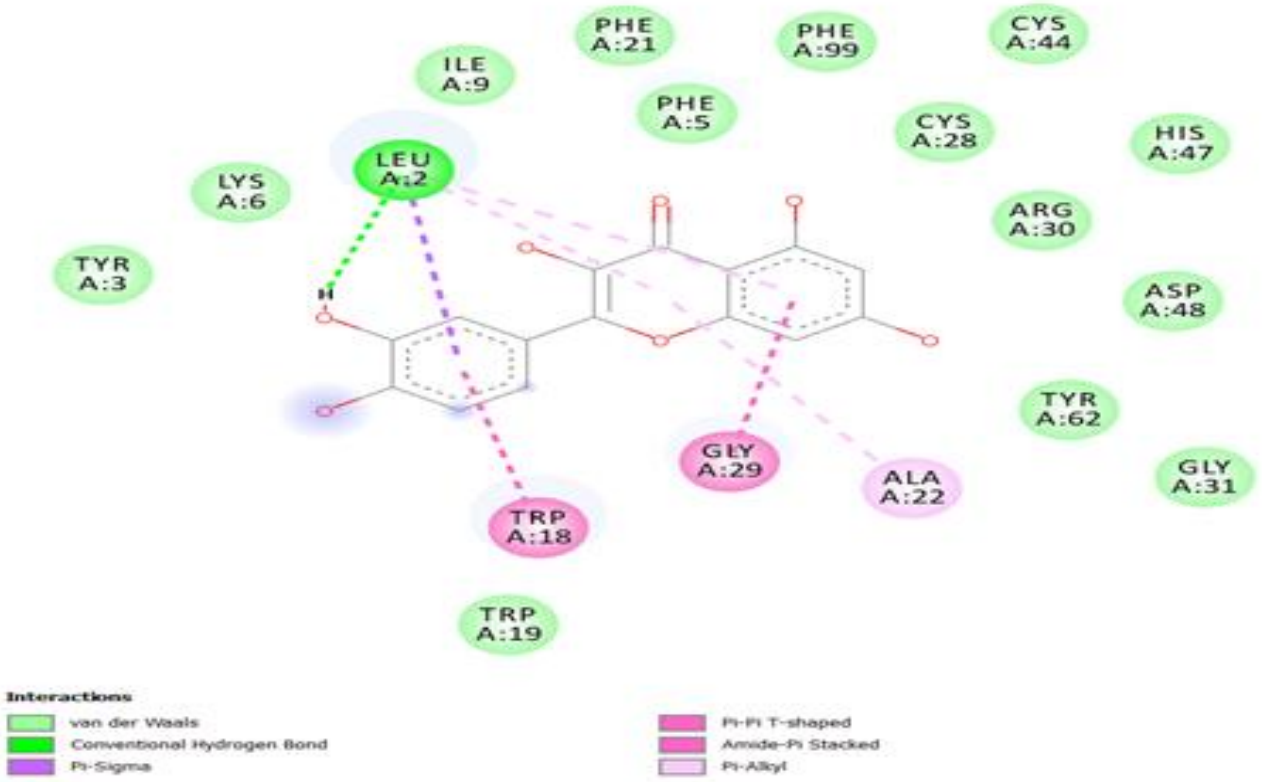


Figure 2: A) Docking pose of the compounds at the active site of *N. nigricollis* PLA_2. 2D animated poses between the compounds and *N. nigricollis* PLA_2 **B)** catechin, **C)** epicatechin, **D)** catechin-3-rhamnoside, **E)** Quercetin


PHE A:21
PHE A:99
CYS A:44
ILE A:9
PHE A:5
CYS A:28
HIS A:47
LEU A:2
LYS A:6
ARG A:30
TYR A:3
ASP A:48
TYR A:62
GLY A:29
ALA A:22
GLY A:31
TRP A:18
TRP A:19
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Sigma
Pi-Pi T-shaped
Amide-Pi Stacked
Pi-Alkyl

E) Quercetin

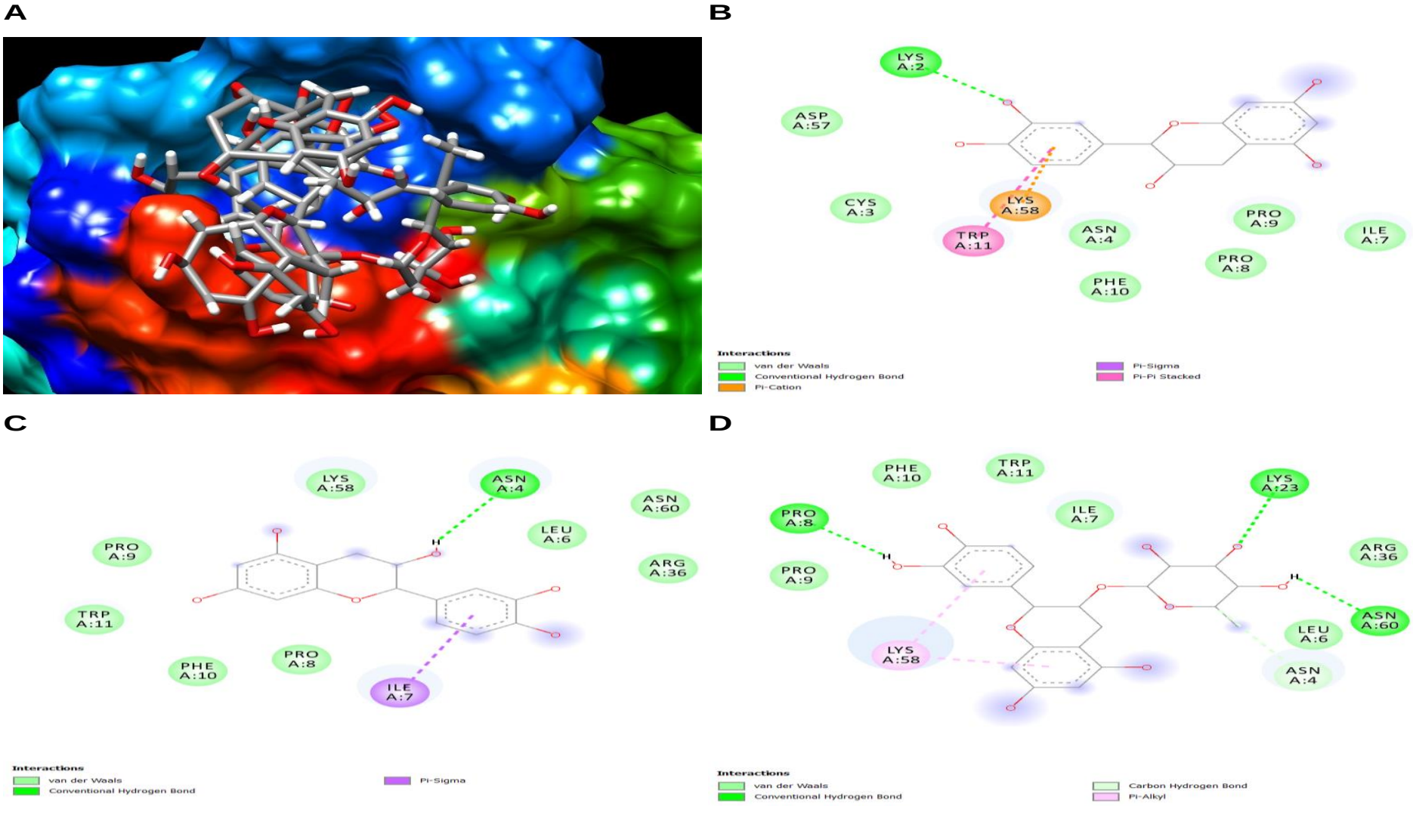
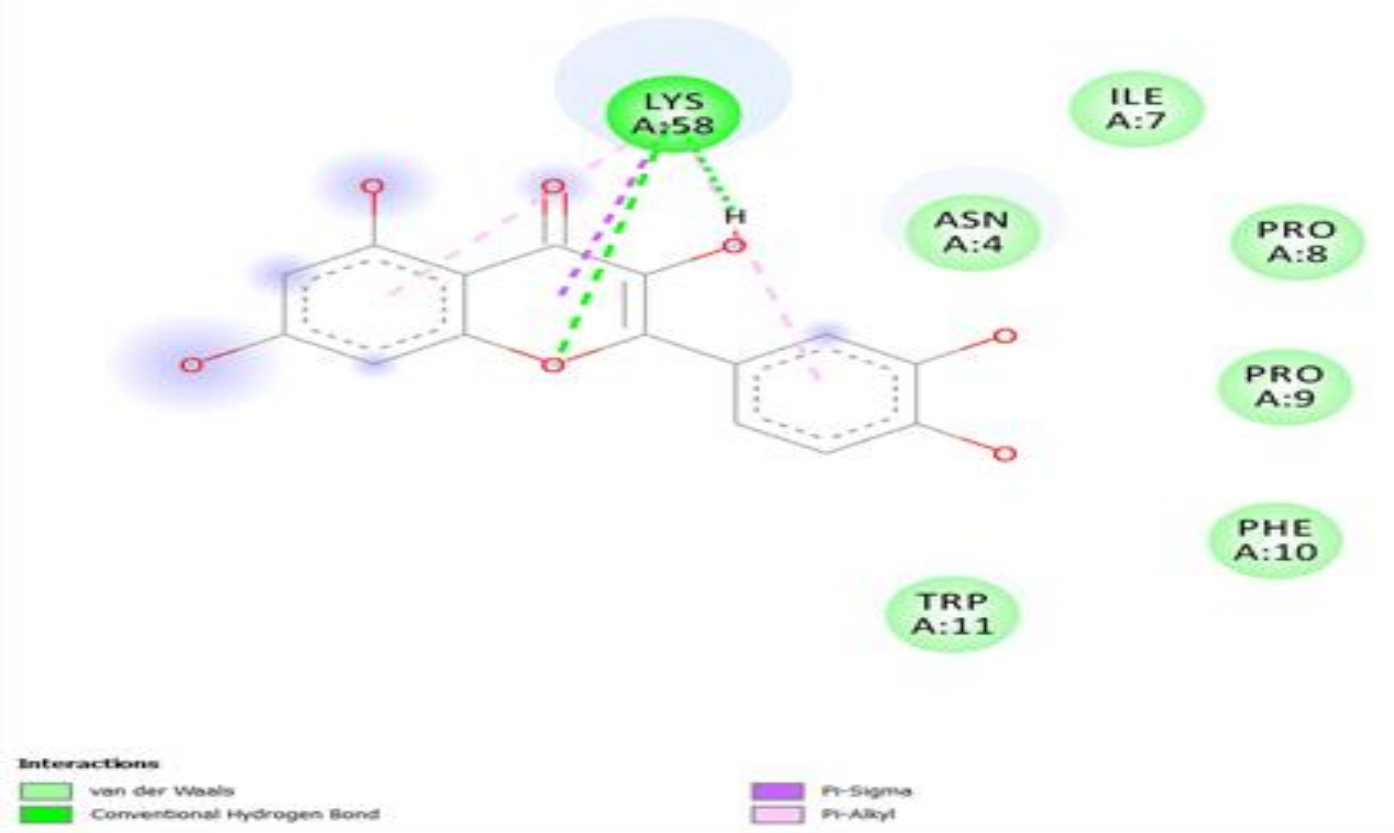


Figure 3: A) Docking pose of the compounds at the active site of *N. nigricollis* cardiotoxin. 2D animated poses between the compounds and *N. nigricollis* cardiotoxin **B)** catechin, **C)** epicatechin, **D)** catechin-3-rhamnoside, **E)** Quercetin


LYS
A:58
ILE
A:7
ASN
A:4
PRO
A:8
PRO
A:9
PHE
A:10
TRP
A:11
H
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Sigma
Pi-Alkyl

E) Quercetin

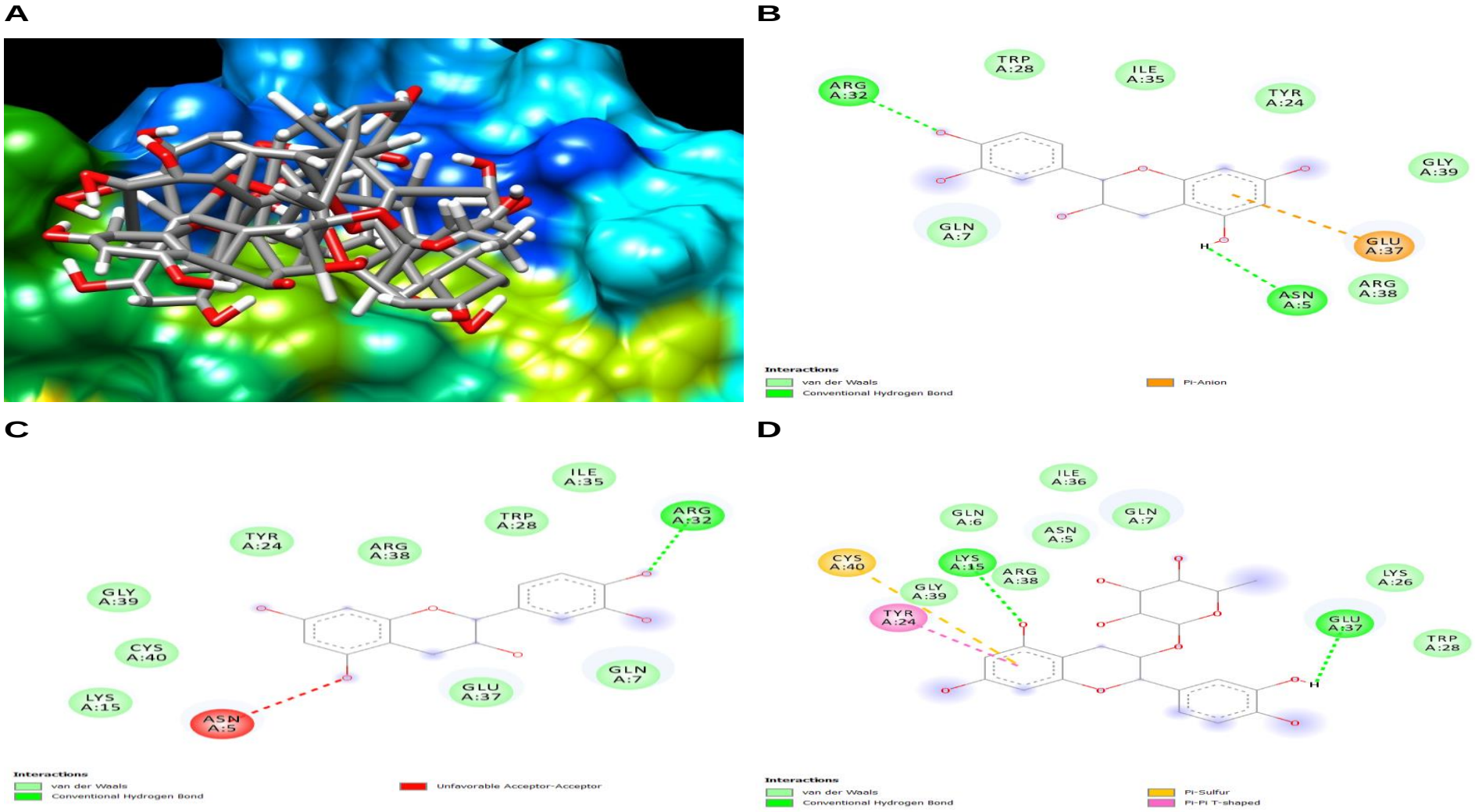
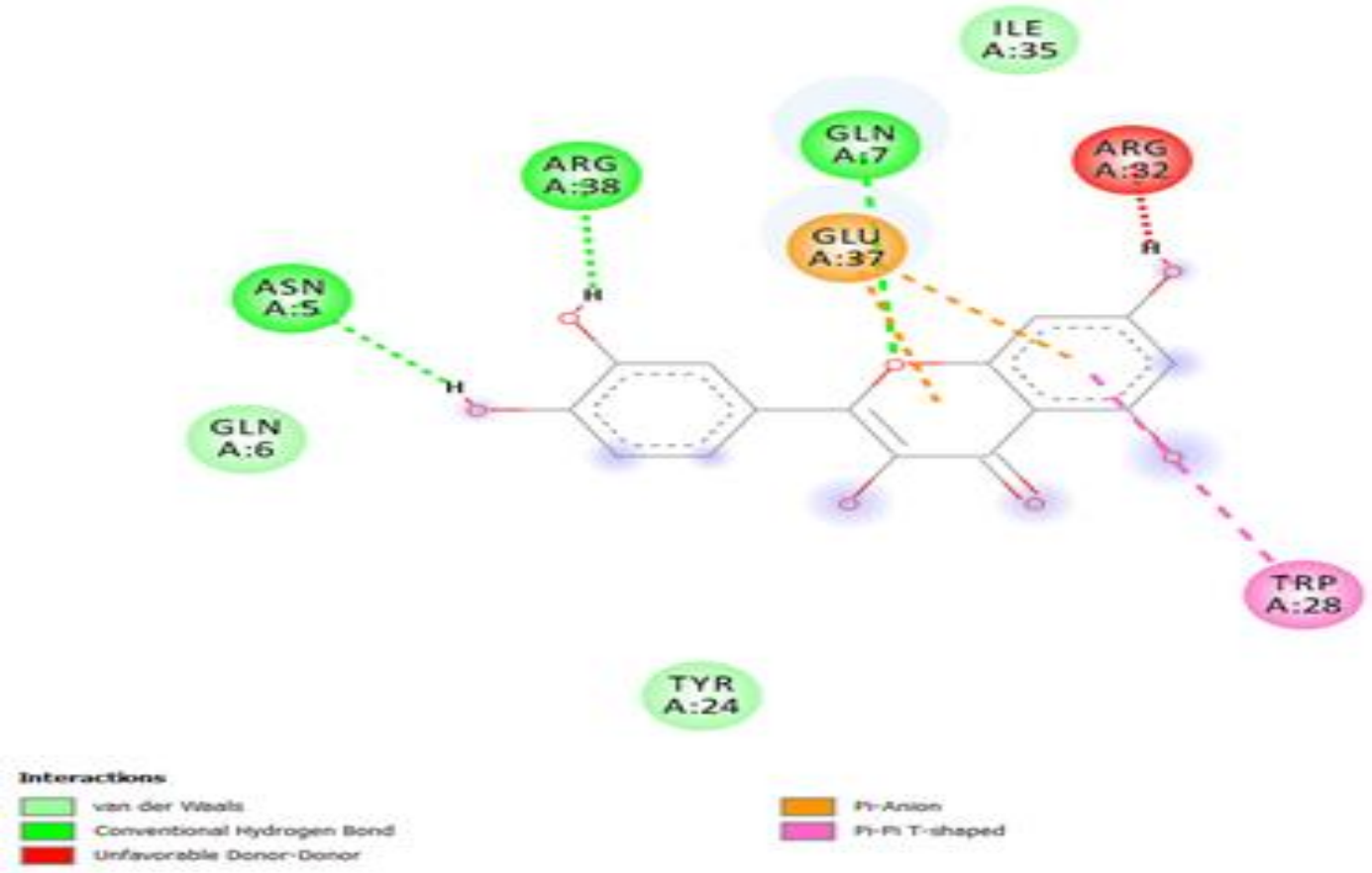


Figure 4: A) Docking pose of the compounds at the active site of *N. nigricollis* neurotoxin. 2D animated poses between the compounds and *N. nigricollis* neurotoxin **B)** catechin, **C)** epicatechin, **D)** catechin-3-rhamnoside, **E)** Quercetin


ILE
A:35
GLN
A:7
ARG
A:38
ARG
A:32
GLU
A:37
ASN
A:5
GLN
A:6
TRP
A:28
TYR
A:24
Interactions
van der Waals
Conventional Hydrogen Bond
Unfavorable Donor-Donor
Pi-Anion
Pi-Pi T-shaped

E) Quercetin

Table 2: Interactions of the compounds against the three toxins from *Naja nigricollis*

	Interactions		
Compound name	**Phospholipase A_2**	**Neurotoxin**	**Cardiotoxin**
Catechin	**H-Bond**: PHE21, ASP48 **Others**: TYR3, PHE5, LYS6, ILE9, LEU9, TRP18, ALA22, CYS28, GLY29, ARG30, CYS44, HIS47, TYR51, PHE99	**H-Bond**: ASN5, ARG32 **Others**: GLN7, TYR24, TRP28, ILE 35, GLU37, ARG38, GLY39	**H-Bond**: LYS2 **Others**: CYS3, ASN4, ILE7, PRO8, PRO9, PHE10, TRP11, ASP57, LYS58
Catechin-3-rhamnoside	**H-Bond**: GLY29 **Others**: LEU2, TYR3, PHE5, LYS6, ILE9, TRP18, TRP19, PHE21, ALA22, ASP23, CYS28, ARG30, TYR62, PHE99	**H-Bond**: LYS15, GLU37 **Others**: ASN5, GLN6, GLN7, TYR24, LYS26, TRP28, ILE36, RG38, GLY39, CYS40	**H-Bond**: PRO8, LYS23, ASN60 **Others**: ASN4, LEU6, ILE7, PRO9, PHE10, TRP11, ARG36, LYS58
Epicatechin	**H-Bond**: HIS47, ASP48 **Others**: LEU2, TYR3, PHE5, LYS6, TRP18, PHE21, ALA22, CYS28, GLY29, CYS44, TYR51, TYR62, PHE99	**H-Bond**: ARG32 **Others**: ASN5, GLN7, LYS15, TYR24, TRP28, ILE35, GLU37, ARG38, GLY39, CYS40	**H-Bond**: ASN4 **Others**: LEU6, ILE7, PRO8, PRO9, PHE10, TRP11, ARG36, LYS58, ASN60
Quercetin	**H-Bond**: LEU2 **Others**: TYR3, PHE5, LYS6, ILE9, TRP18, TRP19, PHE21, ALA22, CYS28, GLY29, ARG30, GLY31, CYS44, HIS47, ASP48, TYR62, PHE99	**H-Bond**: ASN5, GLN7, ARG38 **Others**: GLN6, TYR24, TRP28, ARG32, ILE35, GLU37	**H-Bond**: LYS58 **Others**: ASN4, ILE7, PRO8, PRO9, PHE10, TRP11

Conclusion

We have screened four compounds (catechin, catechin-3-rhamnoside, epicatechin and quercetin) isolated from *N. macrophylla* using molecular docking.

The outcome of this study revealed that, phyto-constituents from *N. macrophylla* can effectively inhibit toxins from *N. nigricollis* venom and thus, could serve as lead compounds for further analysis

Some References

- World Health Organization, WHO. 2019. Snake envenomings. WHO Fact sheets; [cited 2019 Aug 23]. Available from: https://www.who.int/news-room/fact-sheets/detail/snakebiteenvenoming.
- Kini, R. M. (1997). Venom Phospholipase A2 Enzymes. Structure, Function and Mechanism,Chichester: John Wiley & Sons Ltd., Chichester, United Kingdom, 155–183.
- Aird, S. D. (2002). Ophidian envenomation strategies and the role of purines, *Toxicon* 40 (59): 35-393.
- Mackessy, S. P. (2002). "Biochemistry and pharmacology of colubrid snake venoms" Toxin Reviews. *Journal of Toxicology*: 21 (1-2): 43–83.
- Robert, A. H., Adam, H., Simon, C. W., Brian, F., David Soares, A M., Fontes, M. R. M and Giglio, J. R (2004). Phospholipases A2 myotoxins from Bothrops snake review. *Current Organic Chemistry*, 8: 1677–1690.
- Ameen, S. A., Salihu, T., Mbaoji, C. O., Anoruo-Dibia, C. A and Adedokun, R. A. M. (2015). Medicinal plants used to treat Snake bite by Fulani Herdsmen in Taraba State, Nigeria. *International Journal of Applied Agricultural and Apicultural Research* 11 (1&2): 10-21.
- Kini, R., Chan, Y., 1999. Accelerated evolution and molecular surface of venom phospholipase A2 enzymes. J. Mol. Evol. 48, 125–132..
- Warrell, D. A. (2003). Injuries, envenoming, poisoning, and allergic reactions caused by animal. In: Warrell DA, Cox TN, Firth JD, Benj J Jr, editors. Oxford Textbook of Medicine. Oxford: Oxford University Press; 2003. pp. 923–45

Acknowledgments

We acknowledged the efforts of Mr. Adeboyega Abayomi of the Department of Biochemistry University of Jos, Nigeria and Jaris Computational Biology Center for providing the necessary softwares for the research work