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In-Silico Studies on the Inhibitory Potentials of Some Phytochemicals of *Buccholzia coriacea* against Selected Ebola Virus Receptor Proteins

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Abstract

Ebola Virus (EBOV) is a single-stranded, negative-sense RNA virus that causes severe hemorrhagic in humans and non-human primate. It is a virus not receptive to a large portion of known antiviral drugs, and there is no valid treatment for the disease up till now. Looking at the ability of Ebola virus to create a pandemic scenario across globe; there is a paramount need for new drugs and therapeutics to fight this life-threatening infection. This research work dealt with the evaluation of the inhibitory activity of some purified phytochemicals of *Buchholzia coriacea* against five randomly selected Ebola virus receptor proteins, using *in-silico* studies. The viral proteins: Nucleoprotein, Glycoprotein, VP35, VP30 and RNA polymerase L were docked with the lead compounds obtained from the phytochemicals of *B. coriacea*; catechin, limonene, taraxerone, nobiletin and kaempferol-3,7,4'-trimethyl ether. The results showed that ligands; catechin, kaempferol-3,7,4'-trimethyl ether and nobiletin, showed better inhibitory potentials on all the EBOV receptors except on Nucleoprotein receptor when compared with that of the standard compounds. Hence, all the screened ligands that exhibited high potential inhibitory properties can be taken as anti-Ebola drug without delay for clinical trials.

Keywords: Hemorrhagic; Ligands: Pharmacokinetic; Inhibitory; Phytochemicals; *In-silico*

Introduction

Ebola Virus (EBOV) belongs to the family *Filoviridae* and contains a single-stranded, negative sense ~19 kb RNA genome. There are five known species of EBOV: Zaire EBOV, Reston EBOV, Ivory Coast EBOV, Sudan EBOV and Bundibugyo EBOV. Out of these five species of EBOV, it is only Reston EBOV that does not cause disease in humans, while the other four species cause Ebola Hemorrhagic Fever (EHF), with human mortality rates between 40% to 90% [1] and till date antiviral and vaccines are not available. Therapies showing great potential logically would focus on reducing viral load and/or promoting productive immune responses, as the symptoms of the disease are believed to be caused by both replications of the virus and host immune responses [1].

The genome of EBOV encodes seven genes that produce ten mature viral proteins. These proteins include a nucleoprotein, viral proteins 35 and 40 (VP35 and VP40), a Glycoprotein (GP) that is processed by the cellular protease Furin into GP1 and GP2, with the GP1 gene producing two additional Soluble Glycoproteins (sGP and ssGP), viral proteins 30 and 24 (VP30 and VP24), and the viral RNA-dependent RNA polymerase (L). The ribonucleoprotein encapsulates the genome and forms a complex with VP30, VP35 and L, which is required for both genome replication and the transcription of viral genes [2]. VP40 is the matrix protein and the main determinate of viral budding through the host cell plasma membrane [3].

However, there is no up to date collection of scientifically proven information on *B. coriacea* for its folklore claims in medicine as an antiviral agent, which is necessary for the frontier research and drug development. Thus, prompting this research. *B. coriacea* belongs to the family *Capparidaceae* and it was named after R.W. Buchholz who was a collector of plants in Cameroon in the late 1800's [4,5]. It is an evergreen, small to medium-sized tree that grows up to 20 m tall which is distributed in Cameroon, Central African Republic, Gabon, Congo, Angola, Ghana, Nigeria, among others [6,7]. *B. coriacea* has a smooth, blackish-brown or dark green bark with leaves that are dense crown, large glossy leathery and arranged spirally and clustered at the ends of the branches and conspicuous green-white flowers in racemes at the end of the branches [8,9].

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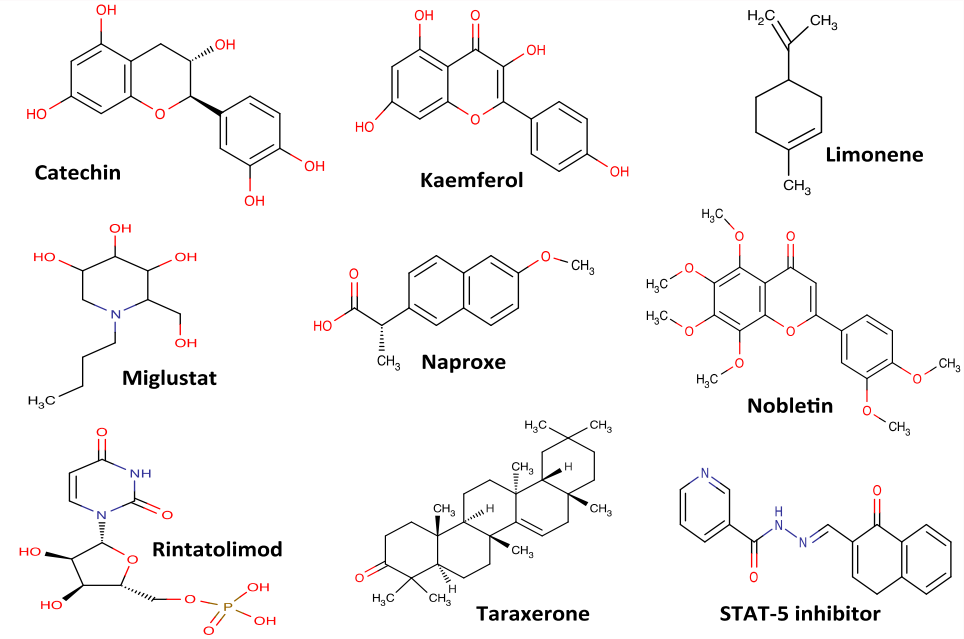

Figure 1: 2-D structure of compounds and standard drug investigated.

Ebola virus is a single-stranded, negative-sense RNA virus that causes severe hemorrhagic fever in humans and nonhuman primates. It is a virus that is not receptive to a large portion of the known antiviral drugs and there is no valid treatment as at date for disease caused by this pathogen. Looking into its prevalence across the globe, there is an urgent need for new drugs and therapeutics to fight this life-threatening infection. The current study dealt with the evaluation of the inhibitory activity of phytochemicals against the five randomly selected Ebola virus receptor proteins, using *in-silico* studies. The viral proteins Nucleoprotein, VP35, VP30, GP and RNA Polymerase L were docked with small molecules obtained from some phytochemicals of *B. coriacea* evaluated on the basis of energetics, stereochemical considerations and pharmacokinetic properties to identify potential lead compounds (Figure 1).

Experimental Section

Selection and preparation of macromolecule

The primary amino acid sequence of each of the five proteins were downloaded from the PubChem database and uploaded to the Swiss Model Server (htpp://swissmodel.expassy.org) where the homology modeling of the five proteins was done. The accession numbers of each protein were noted. The modeled proteins were downloaded and saved in PDB format. The 3D structure of the proteins was modeled using the coordinate file of template from protein data bank (PDB ID: 4GQR).

Selection and preparation of catechin, limonene, taraxerone, nobiletin and kaempferol-3,7,4'-trimethyl ether

The Three-Dimensional (3D) structures of catechin, limonene, taraxerone, nobiletin and kaempferol-3,7,4'-trimethyl ether were obtained from the PubChem database [10]. The optimized ligand molecules were docked into the Ebola virus proteins model using "Ligand Fit" in the AutoDock 4.2.

Molecular docking

The docking of catechin, limonene, taraxerone, nobiletin and kaempferol-3,7,4'-trimethyl ether to the binding site of Ebola virus proteins was done using the AutoDock vina 4.2 [11]. The protein was treated as a rigid body [12], while the rotatable bonds of the ligands were set to be free**.** The grid box size was set at 13.44, 15.14 and 39.44 A° (x, y, and z) to include all the amino acid residues. The spacing between grid points was 0.375 angstroms.

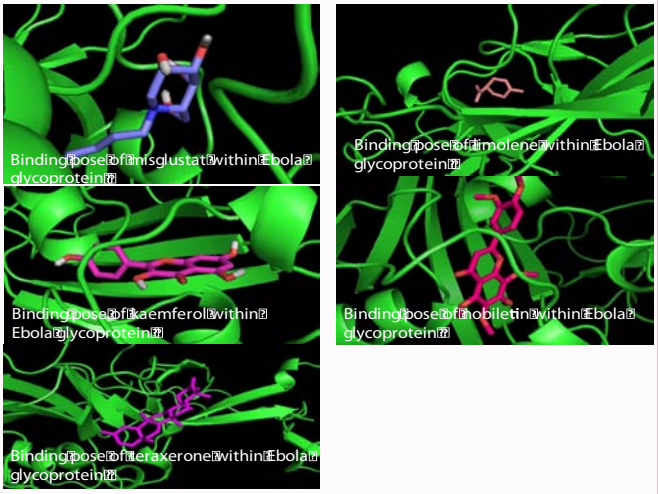

Figure 2: Experimental section 1.

Results and Discussion

The EBOV GP is the only critically expressed protein on the virus surface and is important for attachment to host cells and catalysis of membrane fusion. All of the ligands have high binding affinities as compared with Miglustat - the standard drug. Catechin which is known to interact with gene expression has - 7.8 kcal/mol, kaempferol-3,7,4'-trimethyl ether having - 7.6 kcal/mol, taraxerone having - 6.8 kcal/mol, nobiletin having - 6.7 kcal/mol and limonene and Miglustat both having - 5.4 kcal/mol. It can be therefore inferred that the ligands may function as better inhibitors than the standard

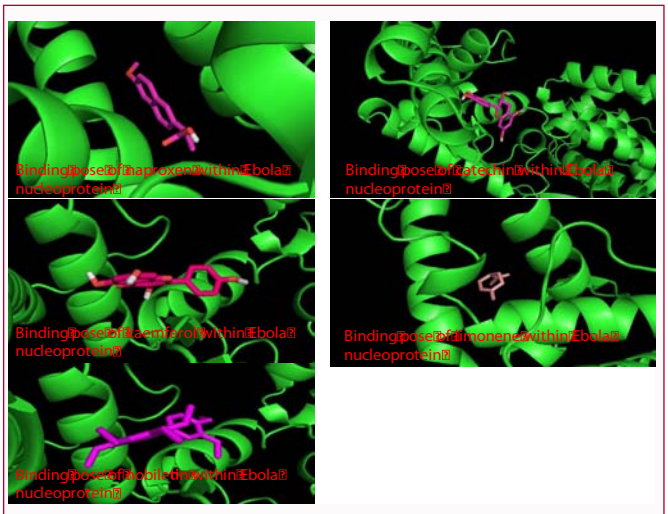

Figure 3: Experimental section 2.

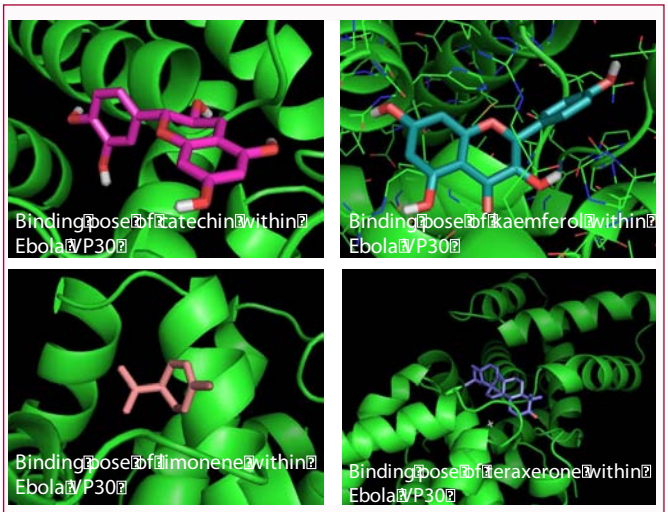

Figure 4: Experimental section 3.

drug (Figures 2-4) (Tables 1-5).

The protein VP30 is an essential transcription factor that is indispensable for viral replication, whose activity is modulated by phosphorylation. Catechin, nobiletin and kaempferol-3,7,4'-trimethyl ether have closer binding affinities of - 7.8 kcal/mol, - 7.6 kcal/mol, and - 7.4 kcal/mol respectively to the standard drug stat-5-inhibitor with binding affinities of - 7.5 kcal/mol. From the table above, it can be concluded that Catechin and nobiletin can serve as better inhibitors of VP30 protein than the standard drug.

Ebola virus VP35 protein is a suppressor of RNA silencing or interference (RNAi) which controls cell differentiation and also acts as an innate antiviral defense response. Catechin, nobiletin and kaempferol-3,7,4'-trimethyl ether have higher binding affinities (7.8 kcal/mol, 7.6 kcal/mol and 7.2 kcal/mol respectively) than rintatolimod (- 6.7 kcal/mol) the standard drug. Hence, they can inhibit the protein better than the standard drug.

EBOV RNA polymerase L is responsible for creation of multiple copies of the RNA genome. Favipiravir which is the standard used is an antiviral drug developed with activity against many RNA viruses and its mechanism of action is thought to be related to the selective

Table 1: Showing Catechin, Limonene, Taraxerone, Nobiletin, Kaempferol- 3, 7, 4' -trimethyl ether and Naproxen (standard drug) with corresponding binding energies obtained from docking with Nucleoprotein Receptor (Ebola virus protein) using AutoDock program.

Compound Name	Binding Energy (Kcal/mol)
Catechin	-5.1
Limonene	-3.3
Taraxerone	-4.6
Nobiletin	-4.7
Kaempferol	-5.2
Naproxen (std)	-6.9

Table 2: Showing Catechin, Limonene, Taraxerone, Nobiletin, Kaempferol- 3, 7, 4' -trimethyl ether and Miglustat (standard drug) with corresponding binding energies obtained from docking with Glycoprotein (Ebola virus protein) using AutoDock program.

Compound Name	Binding Energy (Kcal/mol)
Catechin	-7.8
Limonene	-5.4
Taraxerone	-6.8
Nobiletin	-6.7
Kaempferol	-7.6
Miglustat (std)	-5.4

Table 3: Showing Catechin, Limonene, Taraxerone, Nobiletin, Kaempferol- 3, 7, 4' -trimethyl ether and STAT-5-Inhibitor (standard drug) with corresponding binding energies obtained from docking with VP30 (Ebola virus protein) using AutoDock program.

Compound Name	Binding Energy (Kcal/mol)
Catechin	-7.8
Limonene	-4.3
Taraxerone	-5.7
Nobiletin	-7.6
Kaempferol	-7.4
STAT-5 inhibitor	-7.5

Table 4: Showing Catechin, Limonene, Taraxerone, Nobiletin, Kaempferol- 3, 7, 4' -trimethyl ether and Rintatolimod with corresponding binding energies obtained from docking with VP35 (Ebola virus protein) using AutoDock program.

Compound Name	Binding Energy (Kcal/mol)
Catechin	-7.8
Limonene	-5.3
Taraxerone	-6.5
Nobiletin	-7.6
Kaempferol	-7.2
Rintatolimod	-6.7

inhibition of viral RNA-dependent RNA polymerase. In comparison with the binding affinities of the ligands of the plant *B. coriacea,* all the phytochemicals exhibited higher binding affinity in the range of -6.5 to -5.6 kcal than that of favipiravir (-4.9 kcal/mol) the standard drug.

Nucleoproteins are proteins that are structurally related with nucleic acid and they occur in all living cells and viruses, where they play vital roles in reproduction and protein synthesis and are often the major antigens for viruses. From this research, the binding affinities

Table 5: Showing Catechin, Limonene, Taraxerone, Nobiletin, Kaempferol- 3, 7, 4' -trimethyl ether and Favipiravir with corresponding binding energies obtained from docking with RNA Polymerase L (Ebola virus protein) using AutoDock program.

Compound Name	Binding Energy (Kcal/mol)
Catechin	-6.4
Limonene	-5.6
Taraxerone	-6.5
Nobiletin	-6.4
Kaempferol	-6.5
Favipiravir	-4.9

of naproxen used as an anti-viral drug was compared with five other ligands of compounds derived from the plant *B. coriacea*. None out of all the five ligands has a binding affinity that is higher than or equal to the standard naproxen, which has a binding affinity of - 6.9 kcal/mol followed by kaempferol-3,7,4'-trimethyl ether with - 5.2 kcal/mol.

Conclusion

Based on the present *in-silico* studies, phytochemicals of *B. coriacea*: Catechin, nobiletin and kaempferol-3,7,4'-trimethyl ether should be studied for its toxicities and biosafety before being considered for clinical trials as Ebola antiviral drugs.

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References

1. Hartman AL, Towner JS, Nichol ST. Ebola and Marburg hemorrhagic fever. Clin Lab Med. 2010;30(1):161-77.
2. Ifemeje JC, Egbuna C, Eziokwudiaso JO, Ezebuo FC. Determination of the anti-nutrient composition of *Ocimum gratissimum*, *Corchorus olitorius*, *Murrayakoenigii spreng* and *Cucurbita maxima*. Int J Innov Sci Res. 2014;3(2):127-33.
3. Feldmann H, Geisbert TW. Ebola haemorrhagic fever. Lancet. 2011;377(9768):849-62.
4. Keay RWJ. Trees of Nigeria. Clarendon press. Oxford. 1989;42-4.
5. Anomi FC, Ike C, Ezeokafor E, Ebere C. The phytochemical, antispamodic and antidiarrhoea properties of the methanol extract of the leaves of *Buchholzia coriacea* family Capparacea. Int J Curr Pharm Res. 2012;4(3):52-5.
6. Ezekiel OO, Onyeoziri NF. Preliminary studies on the antimicrobial properties of *Buchholzia coriacea* (wonderful kola). Afr J Biotechnol. 2009;8(3):472-4.
7. Mbata TI, Duru CM, Onwumelu HA. Antibacterial activity of crude seed extracts of *Buchholzia coriacea* on some pathogenic bacteria. J Dev Biol Tissue Eng. 2009;1(1):1-5.
8. Akpanyung EO, Udoh AP, Akpan EJ. Chemical composition of the edible leaves of *Pterocarpus mildbraedii*. Plant Foods Hum Nutr. 1995;48(3):209-15.
9. Culpeper N. Culpeper's Complete Herbal: A Book of Remedies of Ancient Ills. The Word's Worth Reference Collection Library) Contemporary Publishing Company. 1995.
10. Sayers EW, Barrett T, Benson DA, Bolton E, Bryant SH, Canese K, et al. Database resources of the national center for biotechnology information. Nucleic Acids Res. 2012;40(Database issue): D13-25.
11. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem. 2009;30(16):2785-91.
12. Chitranshi N, Gupta S, Tripathi PK, Seth PK. New molecular scaffolds for the design of Alzheimer's acetylcholinesterase inhibitors identified using ligand- and receptor-based virtual screening. Med Chem Res. 2013;(22(5)):2328-45.