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Research Article

Identification of Gly/NMDA receptor Antagonist from *Chromolaena odorata's* Derived compounds using Induced Fit Docking and ADME study

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Abstract: The ionotropic activation of N-methyl-D-aspartic acid (NMDA) plays a significant role in different type of neurodegenerative disease, as it is a tetramer with two Glycine binding subunit and two glutamate subunits. NMDA receptor can be inhibited by either blocking of the glycine site or glutamate site. Previously reported inhibitors of NMDA receptor focus on the inhibition of the glutamate subunit, which was reported to be associated with side effects such as ataxia, memory deficits, and neurotoxicity. Therefore, different compounds with antagonistic effect are been explored on Gly/NMDA site. Glide XP docking was employed in screening phyto-constituent of *Chromolaena odorata* against Gly/NMDA receptor for hit compounds with antagonistic properties. The hit compounds were further subjected to Induced fit docking (IFD) and Lipinski rule of five. The final selection was based on Rigid XP docking score using co-crystallized ligand as threshold docking score, interaction with receptor site residues, and IFD score. Ferulic acid, caffeic acid and scutellarein recorded binding affinity of -8.752Kcal/mol, 10.004 Kcal/mol and -9.096 Kcal/mol respectively, which is higher than the binding affinity of co-crystallized ligand. Induced fit score obtained were -614.38, -614.03 and -616.31 for ferulic acid, caffeic acid and scutellarein respectively. The result obtained in this study shows the potency of phytochemical from *C. odorata* to inhibit NMDA receptor. ADME study showed that the drug-like nature of these compounds.

INTRODUCTION

The Activities of the central nervous system (CNS) are being controlled by excitatory and inhibitory amino acids known as neurotransmitters [1, 2]. The balance between the excitatory and inhibitory is important in maintaining a healthy life, whereas an imbalance in the two systems (excitatory and inhibitory) has been recorded in different neurodegenerative disease [3]. Receptors for neurotransmitters can be classified as either ionotropic or metabotropic [4], [5] [6]. N-methyl-D-aspartic acid (NMDA) receptor is an excitatory ionotropic receptor that allows the passage of ions such as sodium, potassium and calcium [1], [7]. The influx of calcium is gated by NMDA receptor which is also known as the glutamate receptor existing in neurons [4], [8], [9], [10], [11]. The activation of NMDA receptor by glutamate induces synaptic plasticity which is responsible for memory formation under normal circumstances [1], [12]. Dysregulation of the receptor as a result of high or low release of glutamate is responsible hypersensitivity or hyposensitivity of NMDA receptor at the post synaptic neurons [2], [13], [14], [15] which has been implicated to a major cause in excitotoxic neuronal damage where there is occurrence of excessive influx of calcium ion into cells leading to neuronal death [16], [17].

NMDA receptor is a tetrameric assembly of different subunit, where the tetramer is formed from two subunit of glycine binding Glu1 and two subunit of glutamate binding Glu2 [18], [19], [20]. Developed Inhibitors are designed to alter the activity of the receptor by interacting with either the glutamate agonist site, glycine agonist site, ion pores or allosteric sites on the amino acid terminal domain [20], [21-23]. Previously used NMDA receptor antagonist was based on interaction with the glutamate agonist site which has been

proven to be effective but associated with various side effect profile such as neurotoxicity, ataxia and memory deficit [21], [24]. Researches showed that compounds that can target co-agonist Gly/NMDA receptor site might be a way of bypassing side effects associated with the use of glutamate antagonist which is the main advantage of glycine site over glutamate co-agonist site [1], [21]. Recently, Research has shifted from design of synthesized compounds to medicinal plant for promising structures in the discovery of new drugs [25]. Medicinal Plants consist of different chemical structures, which confers different pharmacological properties on them [26]. Literatures has recorded the importance of *Chromolaena odorata* as medical plant with multifunctional activities [27]. Its role cannot be overlooked in treating of infections, arrest bleeding and wound healing [28], [29]. Evidence shows the presence of interesting structures such as flavonoids, glycosides, tannins and alkaloids upon extraction with different solvents which confers different medicinal properties such as anti-inflammatory, antioxidant and analgesic on *C. odorata* [27], [30], [31], [32], [33]. Effort is still been diverted to the development of NMDA receptor inhibitor with low cost, better binding affinity and low side effect profile than current available drugs. Therefore, this study was designed to identify potential lead antagonist of Gly/NMDA receptor from *Chromolaena odorata* compounds by rigid docking and induced fit docking (IFD). IFD This docking approach was employed to allow flexibility of the active site amino acid residue around the lead compounds which will improve accuracy in the prediction of docking score of the antagonist against Gly/NMDA receptor site.

MATERIALS AND METHODS

Ligand preparation

50 Ligands found in the leaf of *Chromolaena odorata* were retrieved from reported journals, and their respective 2D structures of the ligands was downloaded from PubChem compound database in sdf format. The ligands were imported into maestro 11.5 interface where it was prepared using the ligand preparation tool (LigPrep) [34]. LigPrep add missing hydrogen and convert the ligands into their respective 3D structure using OPLS3 force field at a pH of 7±2. On the LigPrep interface, desalt and generate tautomers were selected and left to retain chirality, generating at most 32 per inputted ligands.

Protein preparation and Site Generation

The co-crystallized 3-dimentional structure of Gly/NMDA receptor was acquired from protein data bank (PDB) with PDBid: 1PBQ which was in complex with antagonist 5,7-dichlorokynurenic acid (DCKA) with resolution of 1.90Å [35]. The protein was selected with respect to low resolution and the presence of an antagonist at its active site. The protein was imported into maestro 11.5, where it was prepared using the protein preparation wizard [36]. Protein preparation wizard is important in the filling missing loops, side chains and addition of missing hydrogen atoms at a pH of 7±2. Het state was generated for the ligand which is followed by hydrogen bond assignment and refrain minimization.

Site generation defines the area around the binding site of ligand to receptor where interaction occurs. This was achieved using the receptor generation tool provided on maestro interface [37]. Receptor generation tool maps out the coordinate around the active site of the protein in x, y and z which encircles the bounded antagonist 5,7-dichlorokynurenic acid (DCKA). The grid generates a coordinate of X=5.61, Y=38.0 and Z= -17.16.

Docking using Glide

Glide [38] was employed in analyzing the binding affinity between the library of compounds and the active site. In this case, the active site is held rigidly around the docked ligands with the ligands assuming different pose at the active site. The co-crystallized ligand and prepared ligands were selected from the project table and docked initially using the standard precision algorithm (SP) with ligand sampling selected as flexible, followed by extra precision algorithm (XP) with ligand sampling at none refined only. The binding energy of library of ligands of *Chromolaena odorata* was compared with that of co-crystallized ligand (5,7-dichlorokynurenic acid) with the binding energy of co-crystalized ligand as cutoff binding score.

Induced Fit Docking (IFD)

Induced fit docking protocol was performed on ligands using the induced fit tool in maestro 11.5 [39]. IFD protocol allows the flexibility of both the receptor of the protein and ligand, which has been reported to be robust and very accurate in predicting binding affinity between ligand and active site of a protein [40]. IFD employs the use of glide and prime for ligand docking and protein refinement respectively. The active site was centered on co-ordinate A: 1001 to include the amino acid residues around 5, 7-dichlorokynurenic acid of 1PBQ. The inputted ligand was set to sample ring conformation at an energy window of 2.5kcal/mol. The initial docking protocol was set to employ Van der Waals scaling of 0.5 for both the ligand and receptor and to generate maximum of 20 poses per ligand. Induced fit protein-ligand complexes was generated using prime and further subjected to side chain and backbone refinement. Extra precision algorithm (XP) was employed in re-docking of the ligand with the low energy refined strictures generated by prime. XP glide score, and IFD score was computed for each of the protein-ligand complexes which accounts for the protein-ligand interaction energy and the total energy of the system. Complex with more negative induced fit score has a more favorable binding and the interaction was viewed with 2d interaction diagram tool in maestro 11.5.

Validation of Docking Protocol

The docking procedure was validated by calculating the RMSD value of pose obtained before and after docking procedure of 5,7-dichlorokynurenic acid as shown in **Figure 2**.

Pharmacokinetic parameters

The pharmacokinetics properties of the hit compounds were evaluated using the QikProp program embedded in maestro 11.5 [41]. This is crucial in eliminating toxic and compounds with low probability of reaching the target protein.

RESULTS AND DISCUSSION

Molecular docking enables the screening of large database of compounds against target protein to identify possible hit compounds [42]. This procedure is based on the ability of the compounds to interact with amino acid residues, which is based on the protein conformation, and the assumed pose of the ligand [42]. The 50 Library of phytochemicals generated was screened against the target protein, generating 8 ligands that displayed an interesting interaction with binding affinities lesser than the co-crystallized ligand. The extra precision (XP) docked score obtained is because the receptor of the protein is held rigid around the ligands, which might give a result that might not be reliable if the ligands is able to induce a conformational change at the receptor site. Therefore, induced fit docking was employed on the hit compounds to give room for flexibility of the receptor using prime program. The hit induced a significant change on the receptor giving room for a better docking score and interaction with the amino acid residues when compared to result obtained via rigid docking using glide. The sum total of these interactions is used to compute an induced fit score for the bound ligand. In this case, ferulic acid and caffeic acid recorded an induced fit score of -614.38 and -614.03 respectively when compared to the co-crystallized ligand which recorded an induced fit score of -611.13. Admet/tox screening was also recorded for the ligands which indicate their effectiveness as Gly/NMDA antagonist. The docked score, induced fit score and admet/tox screening scores obtained from interaction of hit compounds from library of phytochemicals of *Chromolaena odorata* are shown in Table 1.

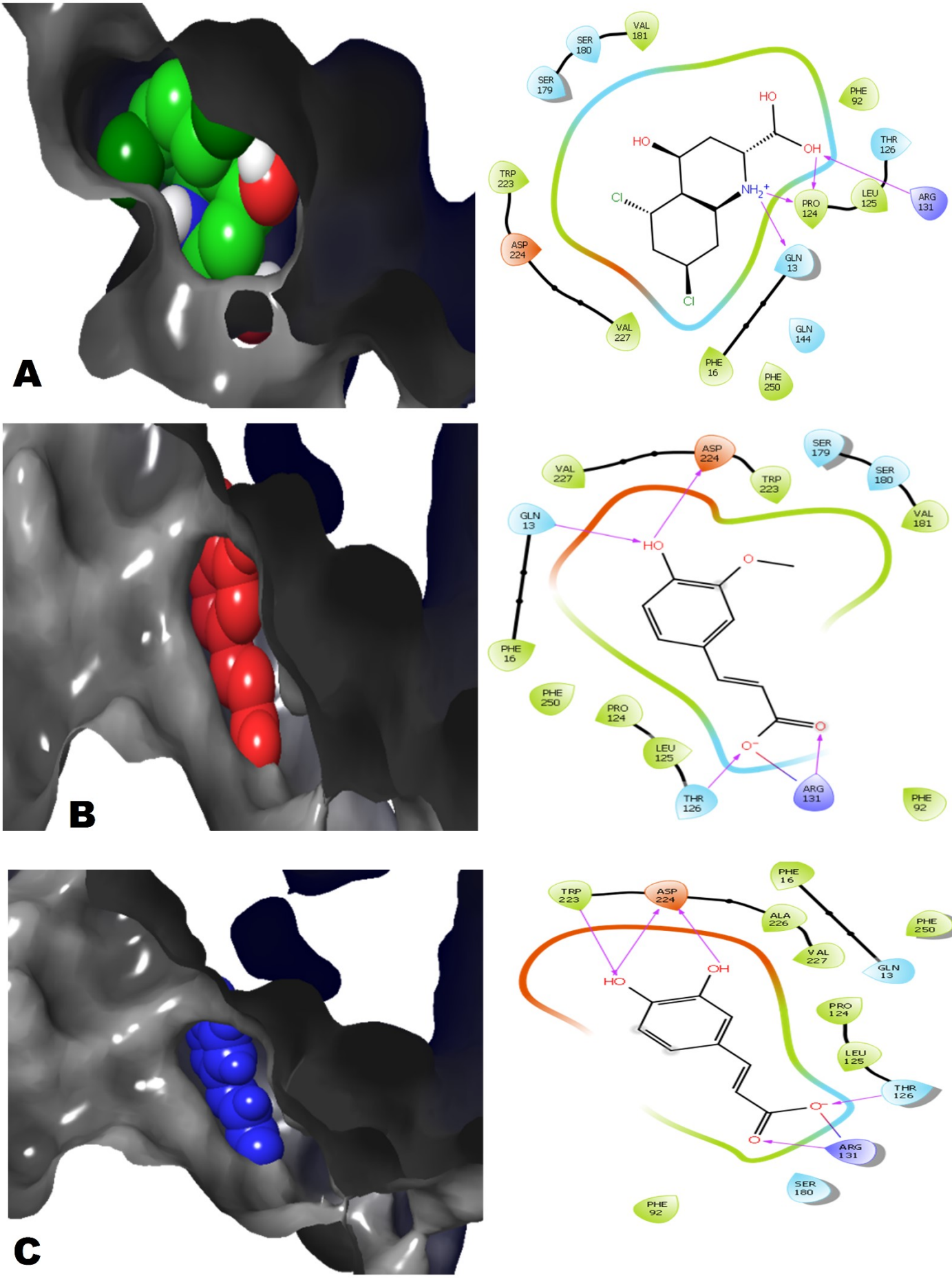
Table 1: Showing the IFD, ADME screening and XP rigid docking of *Chromolaena odorata* to Gly/NMDA receptor

Compounds	Docked Scores	Induced fit docking		ROF	QlogBB	$QlogK_{hsa}$	HOA	MW
		Glide XP	IFD Scores					
Ferulic acid	-8.752	-11.835	-614.38	0	-1.177	-0.613	3	194.187
Caffeic acid	-10.004	-11.733	-614.03	0	-1.547	-0.807	2	180.16
Quercetin	-8.071	-10.627	-616.63	0	-2.294	-0.353	2	302.24
Scutellarein	-9.096	-10.218	-616.21	0	-1.825	-0.208	3	286.24
Garlic acid	-7.797	-9.947	-611.51	0	-1.667	-0.984	2	170.121
protocatechuic	-9.089	-9.836	-611.06	0	-1.225	-0.903	2	154.122
Vanillic acid	-7.785	-9.312	-610.84	0	-0.886	-0.745	3	168.149
Aromadendrin	-8.673	-9.189	-616.7	0	-1.699	-0.33	3	288.256
5,7-dichlorokynurenic acid	-7.476	-8.202	-611.13	0	-0.107	-0.557	2	270.155

ROF Viol: Rule of Five Violation. The rules are: mol. MW < 500, QPlogPo/w < 5, donorHB ≤ 5, accptHB ≤ 10. Maximum is 4; HOA: Human Oral Absorption. 1, 2, or 3 for low, medium, or high. M.W: Molecular Weight of compounds. Normal range 130.0-725.0. QlogKhsa: Prediction of binding to human serum albumin. Normal range between -1.5 to 1.5; QlogBB: Normal range between -3.0 to 1.

Interaction profiling of the Hit Compounds

Ligands at the active site of proteins are stabilized by interactions with the amino acid residues in which this interaction contributes significantly to the binding energy of the ligands [42]. The 2d and 3d interaction of hit ligand at the active site of Gly/NMDA receptor is shown in **figure 1.** Compounds from *C. odorata* exhibited similar interaction with the co-crystallized ligand with respect to hydrogen bond, hydrophobic interactions and pi-pi interactions [20]. Ugale and Bari reported that amino acid residues Arg131, Pro124 and Thr124 is important in the inhibition of Gly/NMDA receptor [3]. These interactions were validated by Sharma and Gupta [1] which recorded similar interactions and some additional interactions with Thr126 and Trp223. Compounds of C. odorata; Ferulic acid and caffeic acid assumes similar orientation, being enclosed by hydrophobic site residues. Ferulic acid, Quercetin, vanillic acid, caffeic acid and scutellarein forms hydrogen bond with hydroxyl group attached to the phenyl ring at residue Arg244, Gln13 and Thr126, which is also similar to residue interactions of 5,7-dichlorokynurenic acid (crystallized ligand). The carboxyl group of the acidic ligand (ferulic acid, caffeic acid, garlic acid, vanillic acid and protocatechuic) is buried deep within the hydrophobic pocket forming hydrogen bond and a salt bridge with positively charge residue Arg131, and hydrogen bond acceptor from polar side Thr124.This is different in 5,7-dichlorokynurenic acid as it receives proton to form hydrogen bond with Arg131. The phenylic ring of garlic acid, vanillic acid, protocatechuic and scutellarein forms pi-pi stacking with hydrophobic side residue Phe92 that might be crucial for the stability of the ligands at the binding site. Quercetin, scutellarein and aromadenderin shares a common structure with two phenyl rings joined by heterocyclic ring, forming hydrogen bond using their carbonyl group attached to their heterocyclic with positively charged Arg131 and Thr126 in case of scutellarein. Hydrogen bond is formed between polar Gln13 with hydroxylphenyl group of Gallic acid and aromandedrin. Quercetin and aromandedrin recorded similar orientation at the active site of Gly/NMDA forming hydrogen bond interaction with Pro124 and Thr126 using the hydroxyl group attached to their heterocyclic ring.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LEU 125
ARG 131
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PHE 250
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NH2+
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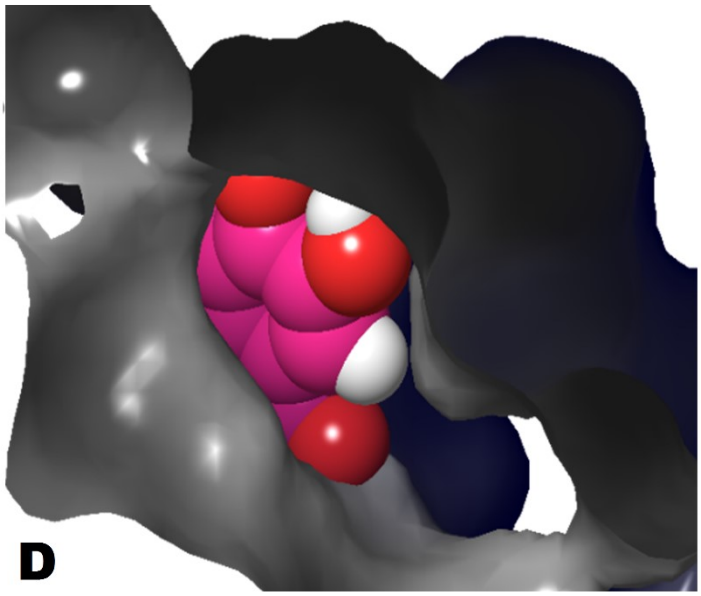
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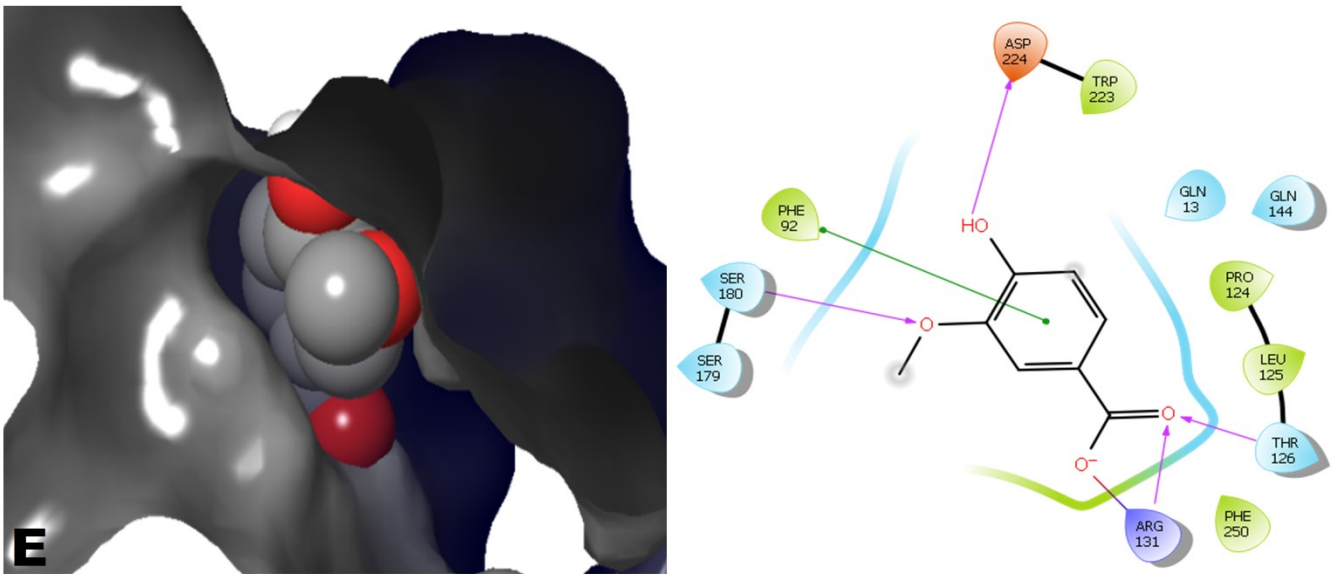
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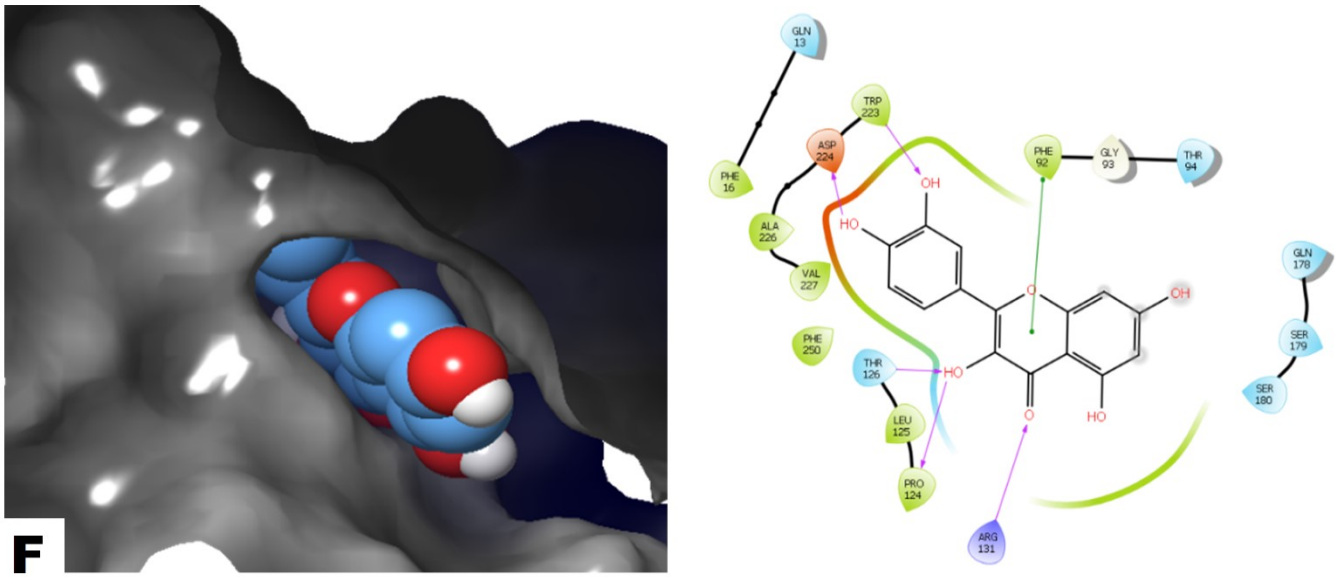
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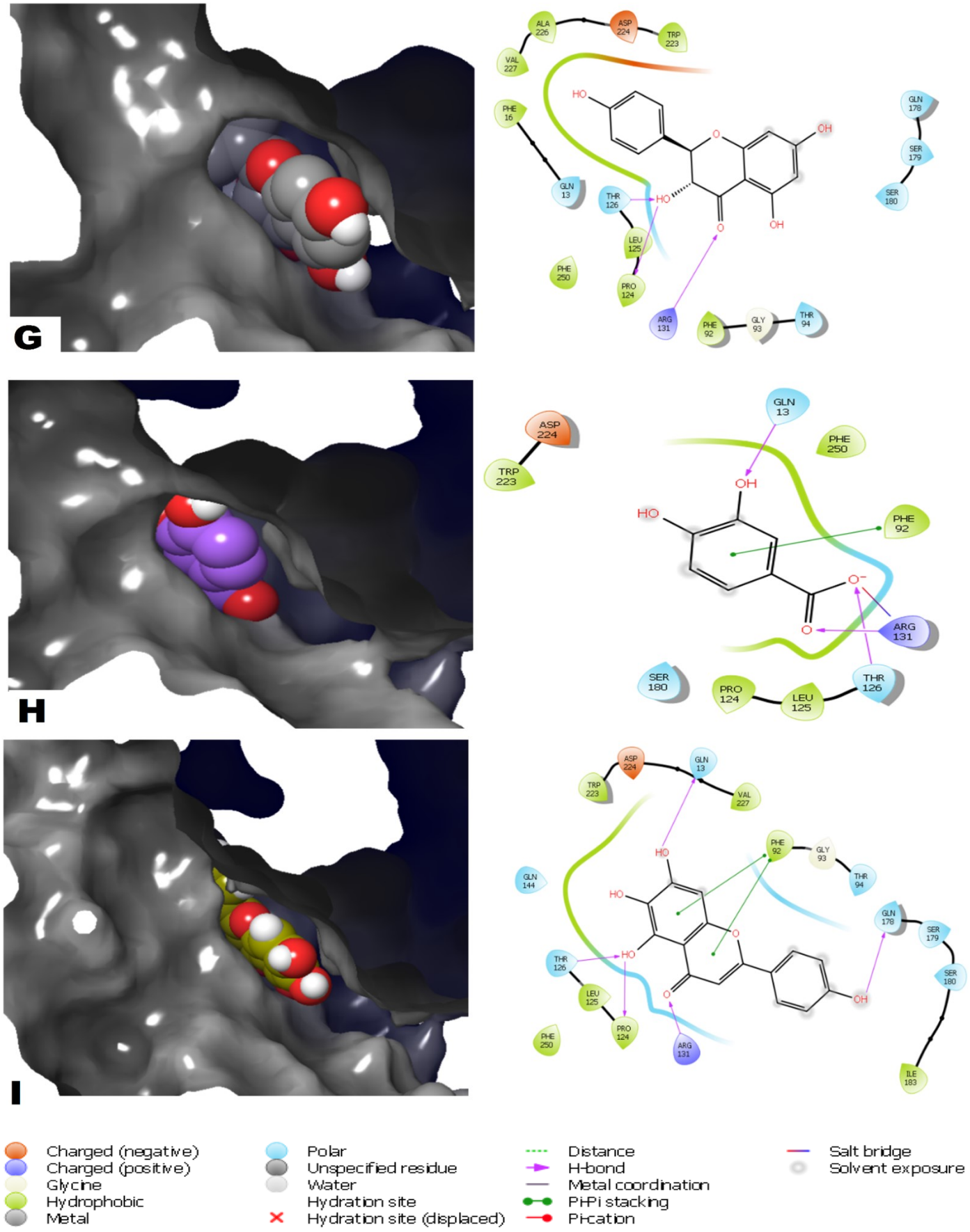

Fig. 1: Interactions between the ligands and NMDA receptor. (A) 5,7-dichlorokynurenic acid; (B) Ferulic acid; (C) Caffeic acid; (D) Garlic acid; (E) Vanillic acid; (F) Quercetin; (G) Aromadendrin; (H) protocatechuic; (I) Scutellarein

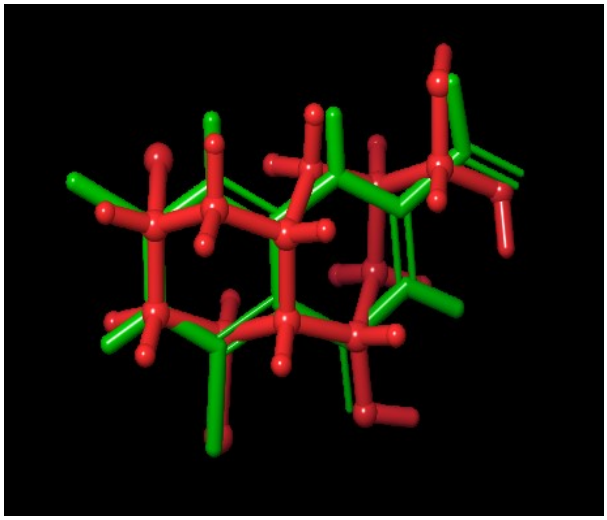

Fig. 2: Showing the validation of the docking protocol employed with co-crystallized ligand (green) before docking and after glide XP docking (Red). The co-crystallized ligand overlaps almost perfectly with an RMSD of 0.8298 indicating accuracy in the docking protocol employed

ADME/TOX

Evaluation of the pharmacokinetic property of ligands is useful in screening a large database of compounds for hit compounds [42]. The tool is also useful in eliminating toxic ligands and evaluating the drug likeness properties of a compound. The hit compounds were evaluated using parameters such as the absorption, distribution, metabolism and elimination (ADME) [43]. These parameters are based on the Lipinski rule of five (ROF) which enlist important criteria needed before a compound to be considered to be drug like. From our ADME study, the hit compounds violated none of the Lipinski rules, which qualifies them to possess drug like properties [42,44s]. Some important parameters were also taken into consideration such as the human oral absorption, binding of the ligands to human serum albumin and blood brain barrier, with most of the ligands recording a high human oral absorption. In addition, the ligands fall between the normal ranges of their binding with human serum albumin which shows their effectiveness in binding to target receptor. The activity of these ligands on the CNS is also crucial, and it was deduced that the ligands recorded a low activity of the CNS which falls within normal range of -3.0-1.0.

CONCLUSION

It is of paramount importance to explore natural sources for compounds with drug like properties, which confers less side effect when compared to synthetic drugs. This study has shown the ability of phytochemicals from *Chromolaena odorata* to act a potent antagonist of Gly/NMDA receptor, which can be utilized in treatment of neurodegenerative diseases. Therefore, it is required that further research be conducted on the ability of these compounds to be a potent antagonist of Gly/NMDA receptor.

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CONFLICT OF INTEREST

The authors declare no financial or commercial conflict of interest.

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