Research Article

In Silico, Study of Natural Alkaloids as Rage Inhibitor for the Treatment of Meningitis

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ABSTRACT

Meningitis is a critical condition of CNS, which may include long-term neurological complications, such as hearing impairment or focal neurological deficits. Receptor for advanced glycation end products (RAGE) regulates metabolism, inflammation and survival of epithelium in stress determination. As mentioned in literature, natural alkaloids have great significance as RAGE inhibitors. Molecular docking study was performed on a series of 25 natural alkaloids showing anti-inflammatory, antioxidants, and neuro-protective action in the brain. The docking technique was used to dock a set of representative compounds within a target site of 6XQ3 using PyRx virtual screening software. Molecular docking has become a significant parameter of in-silico drug development in current conditions, which involves interactions between ligands and proteins at atomic levels. Molecular docking aims to analyze the ligands proteins complex through computational techniques.

Keywords: Meningitis, RAGE, Inflammation, Alkaloids, ADMET, Molecular Docking.

INTRODUCTION

Meningitis is an infection that leads to swelling and inflammation of the cerebro-spinal fluid and the meninges, which are the protective membranes encasing the brain and spinal cord.[1] The exterior membrane of the meninges is dura mater, succeeded by the arachnoid mater and the pia mater. The two inner layers, referred to as the lepto-meninges, are separated by lepto-meningeal space which accommodates spinal fluid.[2] This condition can arise from various bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Listeria monocytogenes*.[3]

Meningitis can lead to severe and potentially fatal outcomes if not adequately addressed, presenting various symptoms that may include long-term neurological damage and hearing impairment. Streptococcus pneumoniae accounts for approximately 72% of cases, while non-groupable *E-coli* and *S.agalactiae* are responsible for around 35% of meningitis cases in newborns.[3]

Pathogens can access cerebro-spinal fluid (CSF) through two primary mechanisms: by infecting immune cells that subsequently relay the pathogen to the nervous system, or by traversing blood capillaries to enter the CSF as free pathogens.[4] Various pattern recognition receptors (PRRs), including toll-like receptors (TLRs), nucleotide oligomerization domain (NOD) proteins, and RAGE, have been identified on both immunocompetent cells and those within the brain.[5,6] In the context of our biological systems, glycotoxins, Maillard reaction products, and Maillard browning products can form as an outcome of hyperglycemia or oxidative stress induced by the Browning reaction, which involves the non-enzymatic glycation of free amine groups in proteins, lipids, or nucleic acids by carbohydrate with a free aldehyde or ketone group and reactive aldehydes.[7] While the formation of AGEs is a normal aspect of metabolic processes, elevated levels can infiltrate tissues and the blood stream, leading to pathological conditions.[8] The toxic effects of AGEs are primarily linked to heightened free radical damage, and swelling, which occur through their interaction with cell surface receptors or through the modification of body proteins, thereby modifying their configuration and proportions.

RAGE is a unit of the immuno gamma globulin superfamily, encoded within class III of the major histo-compatibility complex.[9] RAGE can exist as either a tissue-bound or soluble protein, and its expression is notably influenced by pressure in covering cells, thereby modulating their metabolic processes and enhancing the functionality of the epithelial barrier.[9] The initiation of RAGE by its bio-active ligand promotes cell survival. Continuous signaling through RAGE-mediated survival pathways, particularly in environments with restricted nutrients or oxygen, results in increased autophagy, decreased apoptosis, and, under conditions of cellular exhaustion, necrosis. This cascade of events contributes to chronic inflammation and is often associated with the development of epithelial malignancies.

RAGE and its isoform play a crucial role in maintaining catabolism & anabolism, swelling, the survival of epithelial cells during stress responses.[10] The binding of RAGE, similar as other receptors, leads to several biological effects, including the activation of macrophages, the induction of TNF-α and IL-6, growth of dendritic cells, cellular responses, the activation of $CD4^+$ and $CD8^+$ T-cells & enhancement of responses to local cytokines.[11] Inhibit the RAGE has express to prevent the elevation of these cytokines. Furthermore, inflammation to CNS and elevated levels of pro-

inflammatory cytokines are linked to the disruption of the blood-brain barrier.[12] Inhibition of RAGE has been associated with decreased levels of RAGE and AP1-42, a reduction in cytokines, a decrease in microglial cell activation in CNS as output of improvement in cognitive deficits observed in meningitis cases.[13] Inhibition of RAGE by natural alkaloids is shown in below figure.

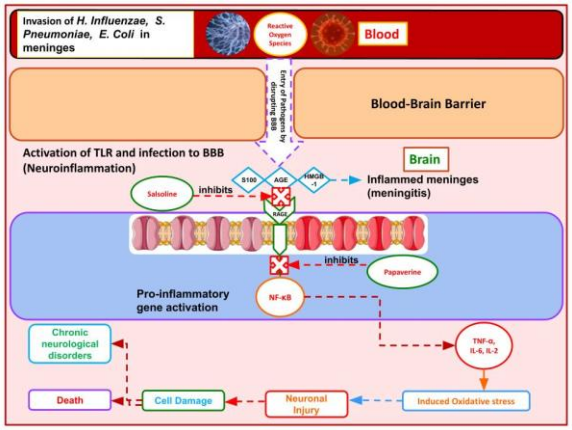

Figure 1: Inhibition of RAGE by Natural Alkaloids.

In the context of bacterial meningitis, the administration of antibiotics and supportive care is essential. This approach ensures the maintenance of respiratory function, supports oxygenation, and includes temperature regulation as fundamental components of meningitis management. The choice of anti-biotic is determined by the suspected causative organism of the infection. Clinicians take the demographic data and medical history of the patient to optimize the selection of antibacterial agents. Recommended treatments include intravenous ampicillin, cefotaxime, gentamicin, acyclovir, meropenem. [14,15,16]

Numerous natural anti-glycation agents exist that can inhibit the generation of AGEs through various natural sources. According to the literature, these natural inhibitors can be sourced from marine environments (such as silymarin and scalarin), herbal remedies (including rosemary, hyperoside, papaverine, and berberine), and dietary components (like resveratrol, vitamin A (retinol), and quercetin).[17]

Research indicates that certain alkaloids, specifically papaverine and berberine, are utilized in the management of meningitis. Studies outside the living body have demonstrated that papaverine hydrochloride can reduce the formation of RAGEs, as well as levels of S100B and HMGB1, which are key players in inflammatory responses.[17]

Generally, patients diagnosed with meningitis may not require hospitalization; instead, they can receive treatment at home, which may include anti-inflammatory and antipyretic medications. However, individuals experiencing seizures necessitate medical supervision.[18] Corticosteroids are typically believed to mitigate the inflammatory effects associated with bacterial meningitis, although their efficacy in viral meningitis remains unproven, warranting further investigation.[19]

Pleconaril, an antiviral agent, functions as an inhibitor of viral replication by targeting the capsid structure of virus.[20] While it is approved for intranasal use in treating common colds, it achieves significantly higher concentrations in the central nervous system, suggesting its potential as a treatment for neurological conditions such as meningitis. Several studies have indicated that pleconaril may effectively shorten the duration of symptoms, particularly headaches.[20,21] However, other research has found no significant differences in outcomes between treatment and placebo groups.[22]

A recently identified drug, psoromic acid, derived from moss, shows potential as a treatment for meningitis caused by HSV by inhibiting the duplication of HSV-1 and HSV-2, as well as affecting DNA polymerase activity.[23] Additionally, valaciclovir has been evaluated in clinical trials for its effectiveness in antiviral suppression related to recurrent meningitis. However, administering valaciclovir twice daily did not prevent the recurrence of meningitis, leading to its recommendation against use for this condition. Furthermore, vaccines have been developed for certain viruses, including EV-71.[24]

Effective airway management, ensuring adequate oxygenation, administering appropriate intravenous fluids, and controlling fever are essential components in the treatment of meningitis. The choice of antibiotic is determined by the suspected pathogen responsible for the infection. Clinicians must consider the patient's demographic information and medical history to ensure optimal antimicrobial coverage. It is crucial to initiate antibiotic therapy for all patients suspected of having bacterial meningitis. According to *McGill et al. (2016)* [25] third-generation cephalosporins exhibit bactericidal properties against pneumococci and meningococci, making them the empirical choice in most regions where resistance rates are low.[25]

Alkaloids are comprised of one or several nitrogen atoms in a ring structure (true alkaloids). Besides true alkaloids, other alkaloids consist of nitrogen atoms in a side chain.[26] Examples of well-known alkaloids are morphine, codeine and atropine.[27]

MATERIALS AND METHODS

Structure based drug design

This process utilizes an iterative method known as computer-based drug design, which is a crucial component of the drug lead discovery process. This approach aids in the identification of a drug lead, which is defined as a compound that shows at least micro-molar affinity for a specific target, rather than a fully developed pharmaceutical product. During this research, we selected 25 natural compounds, all of which can penetrate the blood-brain barrier and possess properties such as anti-inflammatory, antioxidant, and neuro-protective effects, making them advantageous for the treatment of meningitis. From this selection, we pinpointed one compound that exhibits inhibitory activity against the RAGE receptor, as

well as other receptors, including Toll-like receptors, MARCO, and Caspase-1, all of which are integral to inflammatory responses.

Preparation of data set

A list of 25 natural alkaloids, showing anti-inflammatory and antioxidant action in brain was prepared using different search engines such as Google scholar and Pubmed.

Protein selection and preparation

The protein selection for docking studies is based upon multiple factors like X-ray diffraction, resolution, presence of co-crystallized ligand and the selected protein should not have any protein breaks in their 3D structure. The selected protein should meet requirements of docking studied and it should be downloaded in the form of PDB format from RCSB data bank. The 3-dimensional (3D) structure of the RAGE in complex with a potent inhibitor was obtained from the protein data bank (PDB) *(http://rcsb.org)* with PDB ID: 6XQ3.[28] The downloaded PDB format was not compatible for molecular docking, hence with the help of Discovery Studio Visualizer protein preparation was done. Protein preparation involved exclusion of water molecules, along with complexed inhibitor and addition of hydrogen bonds and missing amino acids. Discovery studio DS 3.5.[29] Using the Auto Dock Vina wizard integrated in the PyRx Virtual Screening tool, the prepared protein was then converted to Protein Data Bank, Partial Charge & Atom Type (PDBQT) format.

Ligand preparation and energy minimization

The 3-dimensional structures of the selected alkaloids showing neuro-protective action in brain were retrieved from the PubChem library *(https://pubchem.ncbi.nlm.nih.gov/)*. The 3-dimensional structure of Co-crystallized ligand of RAGE (PDB ID: 6XQ3) was also retrieved from the Pub-Chem library. All selected alkaloids in SDF format were converted into PDBQT format Using the Open babel tool integrated in the PyRx Virtual Screening software along with energy minimization using the Universal Force Field (UFF).

Receptor-grid generation and molecular docking

The coordinates and size of the full RAGE active site was generated with the help of amino acid at the active site with the use of the receptor grid generation module on PyRx software. The X, Y, and Z grid sizes were -44.083694, -1.743139, 27.439361 respectively. The prepared ligands were then docked into binding pocket of RAGE using the Vina wizard tool embedded on PyRx with exhaustiveness set to 8.

Software Method Validation

Software method validation was performed in PyRx Virtual Screening tool using Protein Data Bank (PDB) protein 6XQ3. The x-ray crystal structure of 6XQ3 complex with co-crystallized ligand was obtained from PDB. The bio active co-crystallized bound ligand was docked with in the active site region of 6XQ3. The resolution of 6XQ3 is 1.71 Å and R value free is 0.220 and R value work is 0.192 indicating that the parameters for docking purpose are good in reproducing X-ray crystal structure.

Molecular Docking

Recently investigation, we make use of a docking algorithm called molecular docking. Molecular docking is based on a new hybrid search algorithm, called guided differential evolution. The guided differential evolution algorithm combines the differential evolution optimization technique with a cavity prediction algorithm. We used PyRx virtual screening tool because it showed higher docking accuracy than other stages of the docking products. Non- polar hydrogen atoms were removed from the receptor file and their partial charges were added to the corresponding carbon atoms.

Molecular docking was performed using molecular docking engine of PyRx software. The binding site was defined as a spherical region which encompasses all protein atoms within 15.0 Å of bound crystallographic ligand atom. Default settings were used for all the calculations. Docking was performed using a grid resolution.

ADMET and QSAR analysis

The properties of ADMET is used to predict absorption, distribution, metabolism, secretion and toxicity (ADMET) properties of any molecules to examine compounds with adverse properties at the beginning of the drug development process.[30] According to literature, 90 percent of molecules in the last stage of the discovery of the drug fail due to poor pharmacokinetic profiles: as poor pharmacological effects (40-50%), unfavorable toxicity (30%) and smaller drug (10-15%).[30,31] To overcome this problem, the scientific community focused on improving the process of discovering drugs assessing the properties of ADMET in the early stages of drug development.[32]

The Lipinski law of five so called the law of five pfizers, or simply the law of five (LO5), is to evaluate the form of a drug or determine whether a molecule with a special pharmacological activity action accomplished an oral absorbable in humans. *Christopher A. Lipinski* in 1997 invented law of five based on observation that most drugs for drugs are proportionally small and lipophilic molecule. The rule describes atomic characteristics that are important for pharmacokinetics of medicines in the host, containing its "ADME". However, law of five does not describe whether the molecules are pharmacologically active.[33,34,35] The biologically significant molecule must execute five states to be potentially used as a drug for oral administration. Insufficient absorption or penetration are most likely if:

➢Molar mass > 500,

➢Number of H-bond acceptors > 10,

➢Number of H-bond donors > 5,

➢CLogP > 5.[33]

The prediction of the Quantitative Structure and Activity Relationship (QSAR) depends on the structure of the molecules and atoms present in the compound. Pharmacologically acknowledged in terms of numeric values and presence/absence of the condition (an example of infected/not infected, mutagenic/not mutagenic). Numerous QSAR studies have been implemented to acknowledged biological properties such as pharmacokinetics[36], drug metabolism[37], accumulation[38], transmittance[39], genotoxicity.[40] QSAR models may be categorized according to correlation analysis, which can be either linear or irregular[41], or based on the interaction characteristics between the molecule and the receptor, distinguishing between receptor-dependent and receptor-in dependent models.[42]

Molecular Docking

In recent years, molecular docking has been revealed as a crucial component of computational drug development. This docking technique focuses on predicting the atomic-level influences between small molecules and proteins.[43] It enables researchers to comprehend how small compounds interact with the binding sites of target proteins, thereby elucidating the fundamental biochemical processes underlying these interactions.[44]

The primary aim of molecular docking is to predict the formation of receptor complexes using computational methods.[45] The docking process includes two main stages: ligand sampling and the implementation of a scoring function.[30] A selection algorithm is utilized for finding the most favorable ligand conformation at the protein's catalytic site, considering their catalytic properties. These conformations are then evaluated using the scoring function.[46]

Table 1: ADMET Analysis of Natural Compound

ADMET Prediction of Selected Natural Alkaloids with the help of SWISS ADME

Sr.no.	Alkaloids	PubChem ID	Molecular Weight (g/mol)	Hydrogen Bond Donor	Hydrogen Bond Acceptor	C Log P	Lipinski Rule
1.	Arecoline	2230	155.19	0	3	0.80	Yes
2.	Allicine	65036	162.27	0	1	1.61	Yes
3.	Aromoline	362574	594.70	2	8	4.81	Yes
4.	Ajmalicine	441975	352.43	1	4	2.67	Yes
5.	Berberine	2353	336.36	0	4	2.53	Yes
6.	Caffeine	2519	194.19	0	3	0.08	Yes
7.	Capsaicin	1548943	305.41	2	3	3.43	Yes
8.	Chelerithrine	8713432	348.37	0	4	3.02	Yes
9.	Galantamine	9651	287.35	1	4	1.92	Yes
10.	Harmine	5280953	212.25	1	2	2.78	Yes
11.	Lobeline	101616	337.46	1	3	3.47	Yes
12.	Morphine	5288826	285.34	2	4	1.44	Yes
13.	Montanine	11087935	400.47	2	6	1.76	Yes
14.	Nicotine	89594	162.23	0	2	1.48	Yes
15.	Physostigmine	5983	275.35	1	3	1.65	Yes
16.	Piperine	638024	285.34	0	3	3.03	Yes
17.	Palmitine	19009	355.43	0	5	3.08	Yes
18.	Papaverine	4680	339.39	0	5	3.32	Yes
19.	Reserpine	5770	608.68	1	10	3.68	No
20.	Rivastigmine	77991	250.34	0	3	2.34	Yes
21.	Salsoline	46695	193.24	2	3	1.51	Yes
22.	Theacrine	75324	224.22	0	3	-0.16	Yes
23.	Vinpocetin	443955	350.43	0	3	3.50	Yes
24.	Vasicinone	442935	202.21	1	3	0.94	Yes

Table 2: Determination of Drug score and Drug likeness of natural alkaloids using OSIRIS Software

Sr No	Name of compound	Molecular formula	TPSA	Drug score	Drug likeness	Solubility	Toxicity
1.	Arecoline	$C_8H_{13}NO_2$	29.54	0.35	3.1	0.26	Mutagenic
2.	Allicine	$C_6H_{10}OS_2$	61.58	0.48	-6.13	-1.22	-
3.	Aromoline	$C_{36}H_{38}N_2O_6$	83.86	0.23	5.36	-6.71	-
4.	Ajmalicine	$C_{21}H_{24}N_2O_3$	54.56	0.82	3.2	-3.14	-
5.	Capsaicin	$C_{18}H_{27}NO_3$	58.44	0.2	2.59	1.14	Mutagenic, Tumorigenic and reproductive effective
6.	Galantamine	$C_{17}H_{21}NO_3$	41.93	0.91	6.2	-2.67	-
7.	Harmine	$C_{13}H_{12}N_2O$	37.91	0.58	0.35	-3.23	Mutagenic
8.	Lobeline	$C_{22}H_{27}NO_2$	40.54	0.46	-1.1	-3.96	-
9.	Morphine	$C_{17}H_{19}NO_3$	52.93	0.91	5.14	-2.55	-
10.	Montanine	$C_{22}H_{28}N_2O_5$	51.16	0.89	4.42	-2.9	-
11.	Nicotine	$C_{10}H_{14}N_2$	16.13	0.97	5.07	-0.79	-
12.	Physostigmine	$C_{15}H_{21}N_3O_2$	44.81	0.86	2.19	-2.7	-
13.	Piperine	$C_{17}H_{19}NO_3$	38.77	0.39	0.6	-3.61	Reproductive Effect
14.	Papaverine	$C_{20}H_{21}NO_4$	49.81	0.71	3.37	-4.23	-
15.	Reserpine	$C_{33}H_{40}N_2O_9$	117.7	0.27	7.63	-4.45	Reproductive Effect
16.	Rivastigmine	$C_{14}H_{22}N_2O_2$	32.78	0.87	1.81	-1.62	-
17.	Salsoline	$C_{11}H_{15}NO_2$	41.49	0.56	2.77	-1.63	Tumo-origenic
18.	Theacrine	$C_{11}H_{15}NO_2$	64.17	0.72	1.91	-1.53	Reproductive Effect
19.	Vinpocetine	$C_{22}H_{26}N_2O_2$	34.47	0.56	0.35	-3.7	-
20.	Vasicinone	$C_{11}H_{10}N_2O_2$	52.9	0.96	4.61	-1.66	-
21.	Caffeine	$C_8H_{10}N_4O_2$	58.44	0.2	2.59	-1.14	Mutagenic

Table 3: Molecular Docking Analysis of Natural Alkaloids

Sr.No.	Name of compound (Pubchem ID)	Binding Energy (kcal/mol)	Residues Interacted	Bond length		No. of Bonds
				Hydrophobic Bond	Hydrogen Bond	
01	PAPAVERINE (4680)	-6.5	LYS A:110 ARG A:98 LYS A:52 ASN A:112	4.27673 4.10877 4.12766 3.7056	- - - -	04
02	PALMITINE (19009)	-6.5	LYS A:52 LYS A:110 GLN A:100 MET A: 22 ASN A:112 ARG A:98	4.62322 - - 5.05921 - 4.02381	- 3.7447 3.5575 - - -	06
03	SALSOLINE (46695)	-5.5	LYS A:110 ALA A:23 GLN A:24 LYS A:39 ASN A:112	4.29023 4.29023 - - -	- - - 1.78345 2.09347	05
04	CAPSAICIN (1548943)	-5.3	ARG A:98 CYS A:99 LYS A:52 LYS A: 110 ALA A:21	4.04942 - 4.70009 3.8596 4.60347	- 1.89337 - - -	05

A)

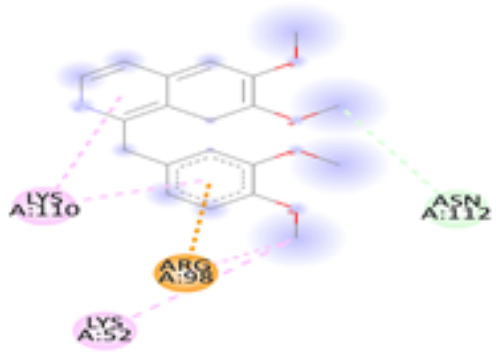

Figure 2: Interaction of Papaverine with the target protein RAGE having the binding energy -6.5 kcal/mol.

B)

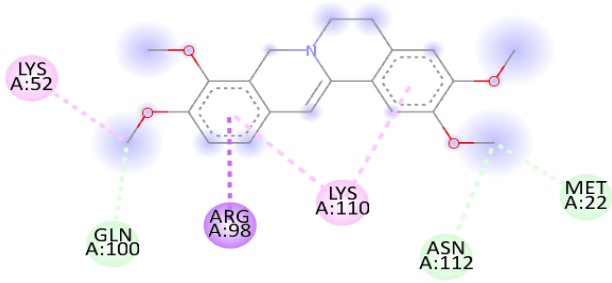

Figure 3: Interaction of Palmitine with the target protein RAGE having the binding energy of -6.5 kcal/mol.

C)

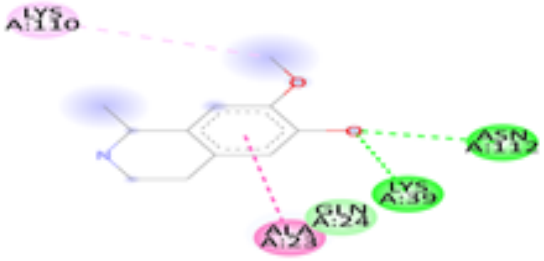

Figure 4: Interaction of Salsoline with the target protein RAGE having the binding energy -5.5 kcal/mol

D)

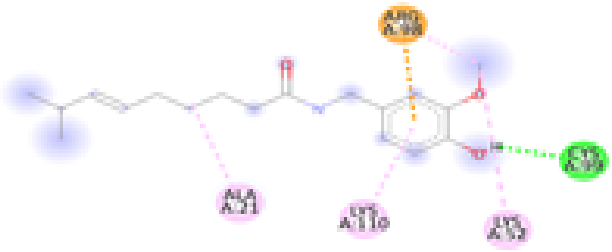

Figure 5: Interaction of Capsaicin with the target protein RAGE having the binding energy -5.3 kcal/mol.

E)

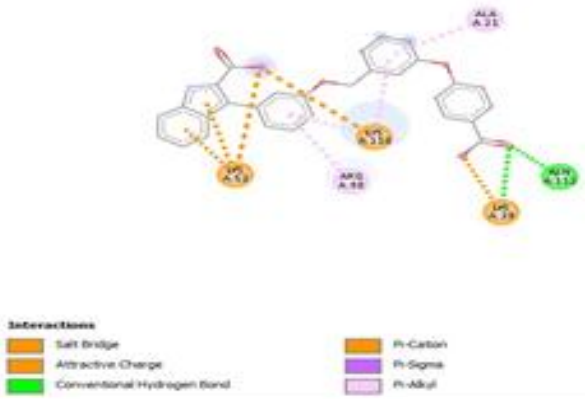

Figure 6: Interaction of Co-crystallize with the target protein RAGE.

The figure (A-E) represents the 2D-molecular complex of the docked compounds against RAGE after visualization using Discovery Studio. A) Papaverine B) Palmitine C) Salsoline D) Capsaicin E) Co-crystallized ligand (PDB 6XQ3).

RESULTS AND DISCUSSION

ADMET analysis

The physicochemical properties of the ligands were determined, and ligands were screened using Lipinski's rule of five. (http://www.swissadme.ch/)[47] This rule is employed to evaluate lipophilicity, polar surface area, hydrogen bond acceptors, hydrogen bond donors, water solubility, and refractivity. Table no. 1 represents the corresponding values that were obtained. Using OSIRIS Software (https://osirissoftware.com/)[48] properties of natural alkaloids such as Drug score, Drug likeliness, TPSA, Solubility these parameters (show in Table 2) were calculated, which are essential for any drug molecule.

Molecular Docking Analysis:

All selected natural alkaloids were submitted for molecular docking study and among all, Papaverine, Palmitine, Sasoline, and Capsaicin were found with good binding affinity. The key interaction of co-crystallized ligand with target protein (6XQ3) were ASN 112, ALA 21, LYS 110, ARG 98, LYS 39, and LYS 52. These natural compounds are suggested for further clinical investigation supporting using selected natural alkaloids as a natural therapeutic agent against meningitis. The primary aim of this study is to endorse to the incorporation of this ancient medicine into modern clinical practice.

CONCLUSION

In this study, we conclude that the alkaloids of the study demonstrate potential neuroprotective activity by virtue of binding to certain key targets to RAGE for that purpose we performed bioinformatics and computational studies to identify, design, and propose anti-glycation properties of natural bioactive compounds (alkaloids) which provides future scope for prevention or intervention related to AGEs complications. The ligand-protein molecular docking simulation was performed preliminarily to investigate and to confirm the potential molecular target for the designed ligands. Binding energies of the drug–enzyme (receptor) interactions are essential to describe how suitably the drug binds to the target molecule. Based on our molecular docking studies, the alkaloids such as papaverine, palmitine, salsoline, and capsaicin present the best results against RAGE with comparable binding energies of co-crystallized ligands. This in silico study on meningitis was inferred that among the 4 best alkaloids, salsoline has the best docking score of -5.5 kcal/mol, which showed the excellent binding affinities with the target protein, and the predicted ADME properties and drug-likeness, thus suggesting a better remedy for meningitis.

We proposed that these 4 natural alkaloids found to be effective in treatment of meningitis and other neurodegenerative disorders by inhibiting AGE-RAGE interactions, but full potential of plant products has still not been explored and also requires further comprehensive investigation of the mechanism of actions in in-vitro and in-vivo biological models to upgrade our knowledge of antiglycation phytomolecules. Thus, inhibition of RAGE and formation of AGE restriction becomes essential, and it can be accomplished by natural sources as RAGE inhibitors from simple integrated strategies to preserve health welfare. So, we believe that in the future, these phytomolecules will work against the meningitis efficiently and accurately.

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Conflict of Interest:

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Abbreviations:

- RAGE - Receptor for Advanced Glycation End Products
- QSAR - Quantitative Structure-Activity Relationship
- ADMET - Absorption, Distribution, Metabolism, Excretion, and Toxicity
- RCSB PDB - Research Collaboratory for Structural Bioinformatics Protein Data Bank
- CNS - Central Nervous System

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