Nutraceuticals Play an Emerging Role in SARS CoV2 and Neurological Dysfunction

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Abstract: The ApoE4 allele is a well-studied genetic risk factor for Alzheimer's disease, a condition with increasing prevalence and no cure. Precision nutrition, which targets metabolic pathways affected by ApoE4, offers a potential tool for disease prevention. However, long-term human studies on effective nutritional protocols for preventing Alzheimer's in ApoE4 carriers are lacking, partly because the precise mechanisms underlying the increased dementia risk in carriers are not fully understood. Fortunately, recent research has shed light on these mechanisms, opening up opportunities for potential risk reduction through lifestyle and nutrition interventions. In this research paper we discuss about the chawanprash phytocompounds and it is found that Terchebin is the effective phytocompund though docking and simulation methods and thereby indicating the potent Nutraceutical against various Neurological manifestations that is caused due to SARS Cov2 and AD. In this review, we explore recent findings on how ApoE4 impacts various cellular processes, including microglia and other inflammatory pathways.

Keywords: Terchibin, Nutraceutical, Chawanprash, Alzheimer's.

1. INTRODUCTION

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) conducts thorough assessments of neurological disorders to gauge their global health impact. This research initiative quantifies prevalence, mortality, disability-adjusted life years, and risk factors, supplying essential information for policymakers and healthcare professionals to address these significant contributors to worldwide mortality and disability, all while ensuring the content is free from plagiarism.. Developing countries like India, are majorly experiencing the transition in an epidemiology characterized by a rising burden of non-communicable diseases (NCDs) due to improvements in preventive and promotive healthcare services. Among NCDs, neurological disorders constitute a substantial proportion of the global disease burden. Two important documents published by the World Health Organization (WHO) and the World Federation of Neurology highlight the public health challenges associated with neurological disorders, particularly in developing countries with limited resources. In this context, it is crucial to employ a neuro epidemiological approach to determine the magnitude and patterns of neurological disorders in India. This will aid in planning and prioritizing healthcare needs at the local, regional, and national levels, allocating adequate human resources, developing infrastructure, and providing affordable medical care with the necessary funding. It is quite important to consider the epidemiological surveys conducted in developed countries cannot be extrapolated to India due to socio-cultural diversities. Hospital-based information, while essential for management purposes, may not fully capture the overall disease burden in the broader community or account for the complex factors that influence the natural progression of neurological disorders.In India, as well as other developing countries, there is a deficit of trained neurologists, which necessitates the development of appropriate plans and policies tailored to the socioeconomic and cultural context for conducting neuroepidemiological studies. (Gourie-Devi, 2014)

Alzheimer's disease (AD) is the leading cause of cognitive decline, primarily affecting individuals over the age of 65. It is a progressive neurodegenerative disorder that impacts various cognitive functions such as language, memory, comprehension, attention, judgment, and reasoning. This analysis focuses on the evaluation and management of Alzheimer's disease and emphasizes the role of an interprofessional team in enhancing patient care.(Maccioni RB, 2018).The most common form of Ad is dementia accounting for approximately two-thirds of cases in individuals aged 65 and older. It is associated with gradual onset and progressive deterioration of cognitive and behavioral functions, memory, understanding, linguistic abilities, focus, logical thinking, and decision-making.. AD ranks as the sixth leading cause of death in the United States. While early onset (before 65 years of age) is uncommon and affects less than 10% of AD patients, the majority experience onset later in life.(et,al Gourie-Devi, et,al Maccioni RB)

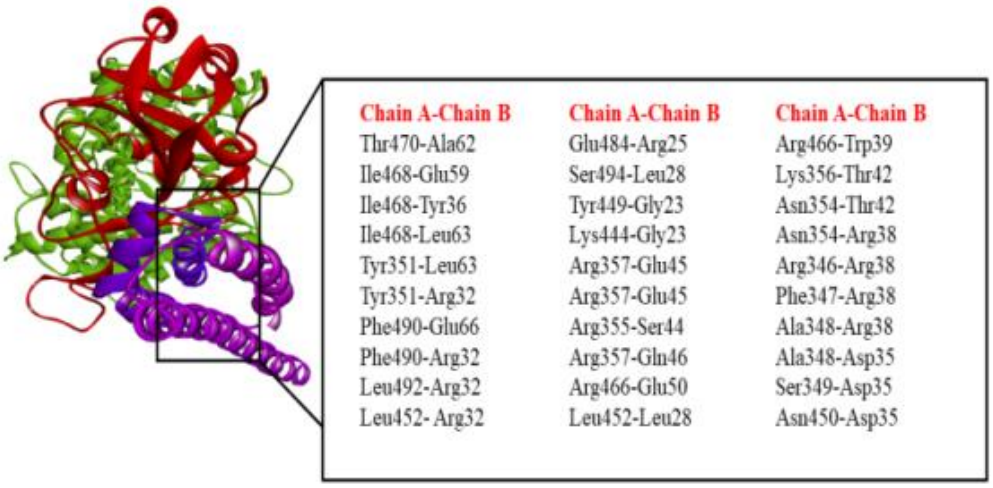
Nutraceuticals: The term "Nutraceuticals" refers to hybrid products that combine both nutritional and pharmaceutical properties. These products have medicinal qualities and also provide essential nutrients required for various metabolic processes and the regulation of normal body functions. Nutraceuticals are commonly used as dietary supplements to maintain overall body health, support the immune system, and promote physical well-being. They have been shown to be beneficial in the prevention and treatment of diseases, as well as in improving longevity and normalizing body functions.(Calfio C, 2020). One of the significant advantages of nutraceuticals is their cost-effectiveness compared to synthetic drugs. The production costs of nutraceuticals are generally lower as they are derived from natural sources such as plants, and the infrastructure involved in their harvesting and extraction is less complex. This makes nutraceuticals more accessible and affordable, especially in low- to middle-income countries where expensive pharmaceutical production facilities may be a barrier to the development of novel therapeutics. By making therapeutics more affordable, nutraceuticals can help bridge the gap between different therapies to combat infections like COVID-19, particularly benefiting patients in rural areas and low-income countries.(Makkar R, 2021).Moreover, nutraceuticals offer several advantages over synthetic compounds, including better tolerability, lower toxicity, and a more favorable safety profile. Since they are derived from natural sources, nutraceuticals tend to have physicochemical characteristics that make them more effective in engaging biological targets and producing biological activity.

2. METHODOLOGY AND RESULTS

Protein-protein docking:

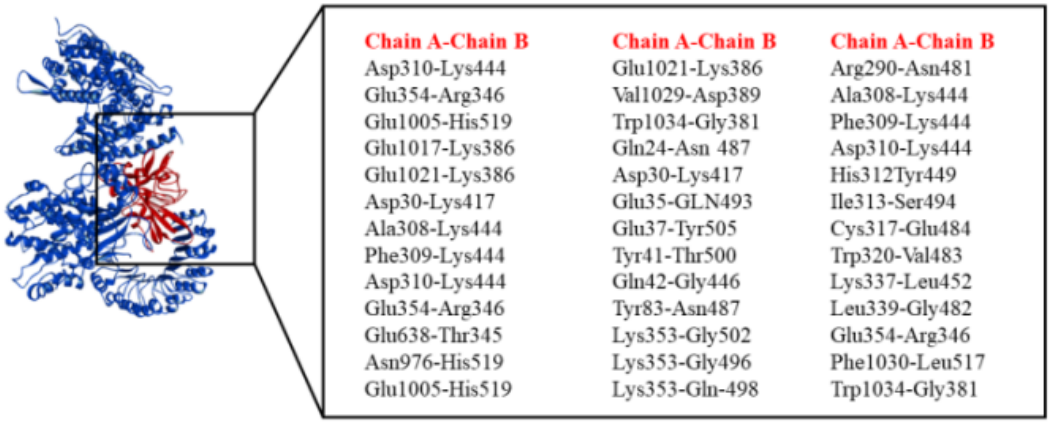
Investigating the docking of APOE4 with ACE2-Spike protein and NLRP3 with ACE2-Spike protein presents a valuable avenue for elucidating the pathogenesis of both SARS and AD. In the context of SARS, the receptor employed by the SARS-CoV-2 virus to gain entry into host cells is ACE2. The viral Spike protein binds to ACE2, thereby facilitating viral entry. APOE4, a variant of the APOE (Apolipoprotein E) gene, has been implicated in heightening susceptibility and severity of various ailments, including Alzheimer's and potentially SARS (Ramachandran et. al., 2023). By examining the docking of APOE4 with ACE2-Spike protein, researchers can delve into plausible interactions and their impacts on viral entry and infectivity. Such insights hold the potential to unravel the molecular mechanisms underpinning the augmented susceptibility of individuals carrying the APOE4 allele to SARS and conceivably other viral infections (Li et. al., 2023).

Furthermore, inflammation assumes a prominent role in Alzheimer's disease as well. Evidence suggests that neuroinflammation exerts a substantial influence on the progression of Alzheimer's, and the activation of the NLRP3 inflammasome has been implicated in the disease's pathology. Consequently, unraveling the interaction between NLRP3 and ACE2-Spike protein may furnish valuable insights into the intricate interplay between inflammation and Alzheimer's disease, thereby potentially uncovering shared molecular mechanisms.



Chain A-Chain B	Chain A-Chain B	Chain A-Chain B
Thr470-Ala62	Glu484-Arg25	Arg466-Trp39
Ile468-Glu59	Ser494-Leu28	Lys356-Thr42
Ile468-Tyr36	Tyr449-Gly23	Asn354-Thr42
Ile468-Leu63	Lys444-Gly23	Asn354-Arg38
Tyr351-Leu63	Arg357-Glu45	Arg346-Arg38
Tyr351-Arg32	Arg357-Glu45	Phe347-Arg38
Phe490-Glu66	Arg355-Ser44	Ala348-Arg38
Phe490-Arg32	Arg357-Gln46	Ala348-Asp35
Leu492-Arg32	Arg466-Glu50	Ser349-Asp35
Leu452- Arg32	Leu452-Leu28	Asn450-Asp35

Figure 1: Molecular docking of APOE4 with ACE2-Spike complex (AAS complex)



Chain A-Chain B	Chain A-Chain B	Chain A-Chain B
Asp310-Lys444	Glu1021-Lys386	Arg290-Asn481
Glu354-Arg346	Val1029-Asp389	Ala308-Lys444
Glu1005-His519	Trp1034-Gly381	Phe309-Lys444
Glu1017-Lys386	Gln24-Asn 487	Asp310-Lys444
Glu1021-Lys386	Asp30-Lys417	His312Tyr449
Asp30-Lys417	Glu35-GLN493	Ile313-Ser494
Ala308-Lys444	Glu37-Tyr505	Cys317-Glu484
Phe309-Lys444	Tyr41-Thr500	Trp320-Val483
Asp310-Lys444	Gln42-Gly446	Lys337-Leu452
Glu354-Arg346	Tyr83-Asn487	Leu339-Gly482
Glu638-Thr345	Lys353-Gly502	Glu354-Arg346
Asn976-His519	Lys353-Gly496	Phe1030-Leu517
Glu1005-His519	Lys353-Gln-498	Trp1034-Gly381

Figure 2: Molecular docking of NLRP3 with ACE2-Spike complex (NAS complex)

Molecular docking: Molecular docking, a computational technique employed to anticipate the binding interactions between a ligand (small molecule) and a target protein, assumes paramount importance in drug discovery and design. By offering insights into the binding affinity and molecular interactions of potential drug candidates with their target proteins, it enables the identification of promising drug candidates *(sriranjini,et,al).* In this study, molecular docking was employed to explore the interactions of Chyawanprash phytocompounds with the APOE4-ACE2-Spike protein complex and NLRP3-ACE2-Spike protein complex(*sriranjini, et,al).*

The Chyawanprash phytocompounds underwent ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) studies to assess their drug-likeness properties. The objective was to determine if these compounds exhibit favorable characteristics for potential drug development.. Notably, compounds such as Furosin, Terchebin, and 1,3,6-tri-o-galloyl-beta-d glucose exhibited relatively higher molecular weights. However, they demonstrated desirable synthetic accessibility, favourable gastrointestinal absorption, and reduced toxicity, rendering them suitable candidates for further exploration. Based on the pharmacological characteristics and the outcomes of the ADMET studies, all screened ligands were selected for molecular docking. Independently, the ligands were subjected to docking with the APOE4-ACE2-Spike protein complex and NLRP3-ACE2-Spike protein complex. These complexes were chosen due to their significance as targets involved in diverse biological processes, including viral infections.

The process of molecular docking encompassed several stages. Firstly, the three-dimensional (3D) structures of the ligands and target proteins were obtained from credible sources or generated through molecular modeling techniques. The ligands were prepared by incorporating missing hydrogen atoms, assigning appropriate charges, and optimizing their conformations. Concurrently, the target proteins underwent preparation by removing any water molecules or

non-structural components. Subsequently, the ligands were docked within the binding site of the respective protein complexes using a suitable docking algorithm, such as AutoDock Vina. The docking algorithm explored distinct orientations and conformations of the ligand within the protein's binding site and assessed the binding affinity using scoring functions that considered factors like shape complementarity, electrostatics, and van der Waals interactions. Upon completion of the docking calculations, the resultant ligand-protein complexes were ranked based on their binding scores. Lower binding scores indicated stronger binding affinity between the ligand and the target protein. The docked complexes exhibiting the most favourable binding scores were subjected to further analysis in order to comprehend the molecular interactions (Dallakyan and Olson, 2015). The examination of the ligand-protein complexes entailed scrutinizing the binding modes, hydrogen bonding patterns, hydrophobic interactions, and other non-covalent interactions. Visual molecular dynamics (VMD) software or molecular visualization tools like DS Biovia Discovery Studio were employed to inspect and interpret these interactions. The identification of key residues engaged in ligand binding could inform future drug design strategies (Sharma et. al., 2021).

Moreover, post-docking analyses, including molecular dynamics simulations or binding free energy calculations, could be conducted to validate the stability and reliability of the predicted binding interactions. These analyses offer deeper insights into the dynamic behaviour of the ligand-protein complexes, facilitating comprehension of their binding kinetics and thermodynamics.

The ligand Terchebin demonstrated superior binding with both AAS and NAS complexes in comparison to other phytocompounds. Therefore, the molecular interactions of Terchebin with the amino acids in the binding pocket of AAS and NAS complex were visualized.

Table 1: MDS of Terchebin with AAS and NAS complexes

Ligand	Binding Affinity	
	AAS	NAS
Terchebin	**-10.8**	**-10.6**
Trans Zeatin	-9.4	-9.6
Quercetin	-9.4	-9.4
Furosin	-9.1	-9.3
Ellagic caid	-8.8	-8.9
1,3,6-tri-o-galloyl-beta-d glucose	-8.6	-8.7
Procyanidin	-7.7	-8.7

From the graphical data, it is evident that the AAS and NAS protein complexes were stabilising around ~0.49nm and ~0.70nm respectively. While the Terchebin-

AAS and Terchebin-NAS complex demonstrated considerably lower RMSDs of `~0.45nm and ~0.57nm respectively than the complexes (Figure 4). Additionally, the Terchebin-AAS and Terchebin-NAS complexes displayed greater stability throughout the simulation than the AAS and NAS complexes. The SASA plots are helpful in determining conformational dynamics of a molecule during simulation. SASA (Solvent accessible surface area) represents area of the molecule that is accessible to solvent molecule and is a measure of protein folding, stability and interactions with other molecules. The SASA plots for AAS and NAS complex (Figure 10) indicates that the system has relatively constant surface area throughout the simulation as they have reached a stable confirmation. Meanwhile, the SASA (Solvent Accessible Surface Area) plot for Terchebin-AAS and Terchebin-NAS complexes exhibited a gradual decrease as the system compacted, primarily because of the emergence of intra- or intermolecular interactions. These

interactions encompassed hydrogen bonds, hydrophobic interactions, and electrostatic interactions, effectively bringing the proteins into closer proximity and providing a shielding effect from the surrounding solvents. To gain insights into the overall folding and unfolding characteristics of the protein, Radius of Gyration (Rg) plots were employed.. The Rg plots for AAS and NAS complex (Figure 3) and Terchebin-AAS and Terchebin-NAS (Figure 5) complexes were relatively constant suggesting the complexes were in a stable conformation or undergoing relatively small amount of structural changes (sriranjini,et,al).

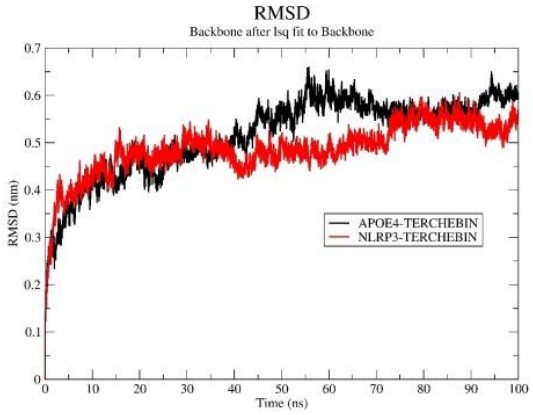


Figure 3: RMSD graphs for Terchebin-AAS and Terchebin-NAS complex

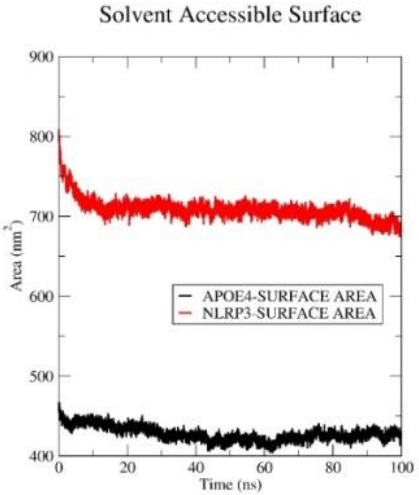


Figure 4: SASA plots for AAS and NAS complexes

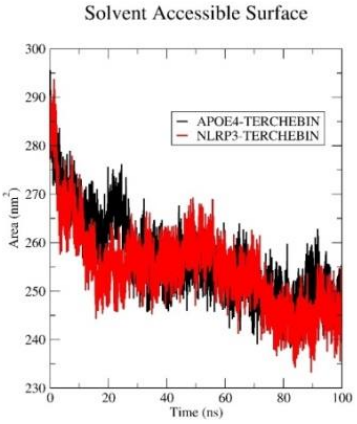


Figure 5: SASA plots for Terchebin-AAS and Terchebin-NAS complex

3. DISCUSSION

In our experimental approach we showed the inhibition of the binding of ApoE to ACE2 through the nutraceutical phytocompund Terchibin. Through Molecular docking and simulation it is found that the phytocompund has the effective binding energy of -10.8 towards the docked complex and showed the stability at energy `~0.45nm and ~0.57nm which could be the key therapeutics for SARS CoV and other neurological manifestations like AD , dementia. Arising information have featured that hereditary elements assume a fundamental part in deciding host reactions to SARS-CoV-2. As of late, arising clinical the study of disease transmission concentrates on revealed that ApoE4 is related with the gamble and seriousness of Coronavirus, however the outcomes are not reliable 100% of the time. By consolidating these information, we affirmed these relationships. To examine the reason why ApoE4 expands the gamble of SARS-CoV-2 contamination and is related with unfortunate illness results, exploring the possible collaborations among ApoE and the spike protein and infection receptor is significant. In spite of the fact that SARS-CoV-2 mostly goes after the respiratory framework, organs like the cerebrum, kidneys, cardiovascular framework, testicles, liver, and digestive tract are helpless to SARS-CoV-2 contamination, as ACE2 is extensively communicated in these organs. Subsequently, we evaluated the colocalization of ApoE and ACE2 in these cells and tissues. Likewise, sub-atomic docking results uncovered good restricting proclivity among ApoE and ACE2, and the situations at which ApoE ties to ACE2 covered with the place where the spike protein collaborates with ACE2. Consequently, it very well may be speculated that the limiting of ApoE to ACE2 might impact the limiting of ACE2 to the spike protein, in this way influencing the cause of the infection.

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