EXPLORATION FOR ANTI COVID-19 POSSIBLE BIOACTIVE COMPOUNDS IN EDIBLE INSECTS AND SNAILS BY MOLECULAR DOCKING APPROACHES

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**ABSTRACTS**

Numerous FDA-approved medications have been extensively repurposed for COVID-19 treatment following the early onset of the Coronavirus Disease 2019 (COVID-19) pandemic based on molecular docking against chosen protein targets that play critical roles in the replication cycle of the new coronavirus. The edible insects, edible snail and honey bee products contain bioactive compounds that show wide spectrum antiviral effects. The bioactive compounds. We revealed by molecular docking the profound bind affinity of bioactive compounds present in edible insect of *Nipa cineraria, Samia ricini Lethocerus indicus,*  Dragonfly larvae and edible snail *Bellamaya bengalensis*.The chemical components of edible insects and edible snail may act as a potent ligand for COVID-19 therapeutic medication development and as an efficient inhibitor of SARS-CoV-2 Proteins.However, further experimental and clinical research is required to validate their potency.

**I. INTRODUCTION**

Natural bioactive compounds are recognised as one of the major and most diversified sources of a wide range of therapeutic agents, accounting for more than half of the drugs now in clinical use globally [1]. Extra-nutritional substances known as bioactive chemicals can be present in trace levels in food. To ascertain their health consequences, they are the subject of extensive study [2]. According to a number of studies, insects contain bioactive compounds that may reduce health risks and strengthen the immune system. Antimicrobial peptides (AMPs) have been produced in profusion by insects, mammals, reptiles, and plants as a defence against infectious illnesses and environmental changes [3]. To date, thousands of bioactive molecules have been identified from medicinal insects, and a few of them are de novo synthesized, structurally modified and even normalized to the popular pharmaceutical preparations, as represented by cantharidin, mellitin, solenopsin, silk nanofiber, pederin, etc. However, the medicinal role of the insect is still underestimated when compared to the widely prospected plant-derived pharmaceuticals. In two tribal societies of northeast India, it was demonstrated that 12 insect species are deemed therapeutically valuable and are used by local tribes to treat a variety of disorders in humans and domestic animals [4]. These products have several advantageous biological properties, such as anticancer, antibacterial, and antiviral activity. Because natural products are free of toxins or negative side effects, bioactive compounds of natural origin are currently being screened by molecular docking in silico to test their affinity against the molecular targets of COVID-19 [5,6,7,8]. The use of natural compounds with antiviral properties is of great importance due to the ease of production on a large scale and the wide range of available compounds [9,10,11]. Propolis, a resinous bee product, has been reported to have antimicrobial activities, based on its content of phenolic compounds, flavonoids, and esters of aromatic acids [12,13,14]. Specific to antiviral activities, propolis has been shown to inhibit varicellazoster virus, herpes virus, and human immunodeficiency virus [15, 16]. Molluscs are known to be a rich store house of bioactive components and have been used as in age old medicinal practices. They have been used for treating certain respiratory disease such as Tuberculosis both pulmonary and extra pulmonary TB [17,18,19]. Molluscs have also proved to possess antiviral compounds that are effective against Herpes simplex virus [20]. Accounts of molluscan respiratory treatments have been documented as early as 800 BC in Ancient Greece, where the flesh of *Octopus vulgaris* is boiled and given to persons suffering from nasal congestion [21]. Molluscs are also a good source of zinc, and zinc has been proven to suppress virus proliferation in flu and COVID-19 [22].

**II. Molecular docking in drug discovery**

 The biological properties of a large number of compounds can be predicted using computational techniques and can be screened for experimental experiments [23, 24]. Using natural compounds possesses some benefits, including being non-toxic, green, environmentally-friendly, and having supreme biological activities [25,26]. Computational based techniques like molecular modeling and virtual screening represent magic tools that help to understand the molecular aspects of protein ligand interactions during rational drug design process [27]. Among 15 nonstructural proteins (Nsps), the newly emerging Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) encodes a large, multidomain Nsp3. One of its units is the ADP-ribose phosphatase domain (ADRP; also known as the macrodomain, MacroD), which is believed to interfere with the host immune response. Such a function appears to be linked to the ability of the protein to remove ADP-ribose from ADP-ribosylated proteins and RNA, yet the precise role and molecular targets of the enzyme remain unknown. [28]. 6WCF: Crystal Structure of ADP ribose phosphatase of NSP3 from SARS-CoV-2 in complex with MES (PDB: 6WCF). 6Y84: SARS-CoV-2 main protease with unliganded active site (2019-nCoV, coronavirus disease 2019, COVID-19). 6Y84 is receptor protein of SARS-CoV-2 main protease (PDB: 6Y84) [29,28].

**III. Molecular Docking of bioactive compounds against COVID-19**

Based on the research, in silico study was to identify potential SARS-CoV-2 cell entry inhibitors from peptides derived from edible insects. Further screening led to 82 high-GI-absorption peptides with unique sequences. Molecular docking revealed 10 promising peptides , predicted to interact with at least one key binding residue on RBD. Notably, VPW had the lowest docking energy score and binding peptides. Highlighting its potency among the ten peptides, binding affinities of the insect peptides were superior to some reported natural products. This study suggests that when consumed, edible insects may be a source of putative SARS-CoV-2 cell entry inhibitors in the form of RBD-binding peptides [30]. A study by Moataz et al., (2021) presented bioactive compounds found in bee products include a variety of natural phenolic acids, flavonoids and terpenes with broad antiviral activity [31]. Using AutoDock, we discovered the strong binding affinity of 14 phenolics and terpenes found in honey and propolis (bees glue) against the main protease (Mpro) and RNA-dependent RNA polymerase (RdRp) enzymes of the novel SARS-CoV-2 virus -the causative agent of COVID-19) [31].(Moataz et al., 2021). Vikas kumar et al., (2021) reported that a total of 2,033 compounds were obtained and were subsequently subjected to molecular docking with 3CLpro, PLpro and RdRp [32]. The docking analyses revealed that a total of 14 compounds displayed better docking scores than the reference compounds and have significant molecular interactions with the active site residues of SARS-CoV-2 virus targeted proteins. Furthermore, the stability of docking-derived complexes was analyzed using molecular dynamic simulations and binding free energy calculations. The analysis revealed two hit compounds against each targeted protein displaying stable behavior, binding affinity and molecular interactions. Christine Toelzer reported (2020) on Corona disease 2019 caused by Severe Acute Respiratory Syndrome coronavirus 2, represents a global crisis. Our 2.85-angstrom cryo-electron microscopy structure of SARS CoV-2 spike glycoprotein reveals that the receptor binding domains tightly bind the essential free fatty acid linoleic acid (LA) in the three composite binding pockets. LA binding stabilizes a locked S conformation, resulting in reduced angiotensin- converting enzymes 2 interaction invitro. In human cells, LA supplementation synergizes with the COVID-19 drug, Remdesivir, suppressing SARS-CoV-2 replication.



**Fig-1: Molecular Docking with SARS CoV2 Protein and Bioactive compounds**

**IV. Anit -COVID-19 compounds form honey based products**

Using molecular docking research with Autodock Vina, this work clarified the antiviral affinity of bioactive natural substances isolated from royal jelly and honey bees against SARS-CoV-2 MPro Molecular docking evaluations were enhanced using Vina, and Discover Studio v. 4.5 was used to capture 3D Visualisations of natural ligands in association with the target protein. Two common pharmaceuticals, Indinavir and Lopinavir, were chosen in order to compare the antiviral potential of these natural compounds with the affinity of commercially available medications. Erlose, Kaempferol glucoside, Iridin, and luteolin glucoside (Cynaroside) were the four natural compounds with the lowest binding energies overall, with values of -10.2, -9.6, -9.0, and -8.4 kcal/mol, respectively. If compounds a and b are successful in completing in vitro and in vivo tests to demonstrate their antiviral potential, the information from molecular docking may potentially be used to designate them as prospective antiviral candidates against SARS-CoV-2 infection.[33].

**V. Anti COVID-19 Compounds form edible insects**

Bioactive compounds isolated from the *Nipa cineraria* by GC-MS and exploration of anti-COVID-19 potential bioactive compounds were analysed by molecular docking methods. SARS CoV-2 Protein downloaded from PDB (6WCF) and used as a targets. Out 14 compounds these 1,2-Benzenedicarboxylic acid ( -9.99 kcal/mol), Tetradecanoic acid, ethyl ester(-9.06 kcal/mol), Henicosane (-9.38 kcal/mol), 10-Heptadecenoic acid (-10.30 kcal/mol ), 9-Tricosence (-10.77 kcal/mol), Pentadecane,8-hexyl,( -11.27 kcal/mol), Campesterol (-10.53 kcal/mol) are showed low binding energy while comparing stranded drug of Hydroxychloroquine (-8.6 kcal/mol). Beside, 13 bioactive compounds isolated from the edible insects of *Samia ricini* and which was showed low binding energycycloheptanecarboxylic acid (-12.67 kcal/mol), Tetracosanoic acid (-10.96 kcal/mol), Stigmast-5-en-3-ol,oleate (-12.13 kcal/mol), Cyclopentylpropionic acid (-12.16 kcal/mol ), 9-Hexadecenoic acid(-10.79kcal/mol). Two bioactive compound were showed low binding energy against the SARS-CoV2/6WCF: Palmitelaidic acid-10.60 kcal/mol, 5.beta.-Pregnan -3, 2-Oleoylglycerol-10.55 kcal/mol which was identified from the *Lethocerus indicus and*  Dragonfly larvae **:** 2H-benzoxathiol-2-one,5-hydroxy-6-nitro -11.91 kcal/mol. In the present study, The molecular docking analysis of the isolated bioactive compounds was performed from the methanol extract of edible insects. A compounds were selected for docking analysis with COVID-19 /6WCF proteins. 6WCF is a Crystal Structure of ADP ribose phosphatase of NSP3 from SARS-CoV-2. The isolated bioactive compounds bounded well with 6WCF through Carbon hydrogen bonds, Pi- bond interaction, conventional hydrogen bond interaction, pi-pi stacked, pi-akyl interacted bond. Some compounds show highest binding energy when compared to the standard drug Hydroxychloroquine (-8.59 kcal/mol). Highest binding energy values were shown by cycloheptanecarboxylic acid -12.62 kcal/mol. Form the above molecular docking results, we can conclude that insects bioactive compounds can be considered as potential agent against COVID-19/ 6WCF.This study suggests identifying the major bioactive compound of edible insects and screening for its pharmacological properties, which could lead to the development of novel potent natural drugs against COVID-19 that could help counteract the side effects of current synthetic drugs.

**VI. Anti COVID-19 Compounds form edible snail**

For thousands of years Molluscs have been utilised to treat respiratory disorders, however proper research needs to be conducted to support the folkloric claims. Present day study of novel molluscan bioactive components has validated the potential to lead to the development of new antiviral and immunomodulatory drugs. In the present study 13 bioactive compounds were selected out of the 42 screened compounds using GCMS method from *Bellamaya bengalensis*. The binding affinity of these screened compounds in the active sites of SARS-CoV-2 Protein (6WCF). was investigated further. Of these, 4 molecules showed substantial docking scores, higher than the reference compound, a standard drug Hydroxychloroquine prescribed to patients infected with COVID virus. The bioactive molecule from edible snail showed good conformations with the receptors 6wcf and 6Y84 of SARS CoV-2 whereby stable compounds were formed and these complexes showed a more significant number of hydrogen bonds and Vander Waals interaction than the complexes formed with the reference compound. However more confirmatory analysis (both in-vitro and in-vivo) should be conducted for the screened molecules to ascertain the efficacy to be used in the illness treatment.

**Conclusion**

Molecular docking has been the most widely employed technique. Though the main application lies in structure-based virtual screening for identification of new active compounds towards a particular target protein, in which it has produced a number of success stories [34]. The structural databases of molecules are simple to visualise for medicinal chemists. It correctly predicts how ligands will attach to receptors. These medications use the molecular docking technique in their pharmacological development. It saves time and money. It is employed in the creation of new drugs [35, 36, 37, 38, 39]. Edible snail, honey, and insect species may be sources of novel bioactive compounds that address significant global health issues in both high- and low-income countries. Future research should be conducted to better understand the potential advantages of bioactive compounds for COVID-19 prevention and therapy.

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