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# Investigating Bioactive Compounds from Medicinal Plants for Targeting Nonstructural Proteins of the Chikungunya Virus

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## ABSTRACT

Chikungunya virus (CHIKV) is a major public health problem because it is widely transmitted by Aedes mosquitos and can cause devastating symptoms such as fever, joint pain, and rash. Currently, no particular antiviral medications or vaccines are available for the treatment or prevention of CHIKV infection, highlighting the critical need for alternative therapeutic methods. Medicinal herbs have long been known as rich sources of bioactive chemicals with a wide range of pharmacological activities, including antiviral activity. This study will look into bioactive chemicals derived from medicinal plants and their ability to target nonstructural proteins of the Chikungunya virus, including nsP1, nsP2, nsP3, and nsP4 (Mainly nsP2). A comprehensive literature study and bioinformatics analysis were used to identify medicinal plants renowned for their antiviral activities. The bioactive chemicals found in these plants were tested for their capacity to interact with and inhibit the function of CHIKV nonstructural proteins using molecular docking and molecular dynamics simulations.

Preliminary results showed that some intriguing bioactive chemicals can bind to particular areas of CHIKV nonstructural proteins, potentially affecting the enzymatic activity required for viral replication and propagation. These compounds have high binding affinities and stable interactions with target proteins, indicating that they could be used as lead compounds to create novel antiviral medicines against CHIKV. This study provided insights into the use of bioactive chemicals from medicinal plants as prospective candidates for targeting CHIKV nonstructural proteins, paving the way for the development of efficient antiviral medicines to battle Chikungunya virus infection.

**Key Words:** Bio active chemical, Medicinal plants, Proteins, Virus.

## INTRODUCTION

The tropical disease chikungunya, which is spread by mosquitoes is currently a threat. More than a million people encounter this illness each year, which results in severe joint pain. Kimakonda language which means that which bind up is where the word Chikungunya originates (Zhang et al, 2016). The Chik V virus bears a striking resemblance to the O'nyong-nyong virus, which was discovered in Uganda in 1959 in a patient exhibiting joint pain, fever, and itchy rashes. The virus is spread by 'Anopheles' mosquitoes (Mao et al, 2019). Chikungunya fever is brought on by the Chikungunya virus (CHIKV), which is a member of the Tongoviridae family and genus Alphavirus. This comprises more than thirty species of alphaviruses carried by arthropods. Each of these has seven distinct antigenic complexes in common (Ruiz-Moreno et al, 2012). A few additional alphaviruses, such as the Rose River virus, O'nyong-nyong virus, Bannah Forest virus, and Mayaro virus, are also closely related to CHIKV. This virus group is known to cause

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arthritis. There are three genotypes of CHIKV: West African, East Central South African, and Asian(Lopresti, 2018).

**Chikv Virus Genome**

The Chikungunya virus is a positive single-stranded ribonucleic acid virus that is spherical, enveloped, and has icosahedral symmetry. Its diameter is around 60–70 nm. length of around 11.7 kb, encoding ORF1 and ORF2, two open responding frames. These two open reading frames, which have nucleotide sequences of 7422 and 3744, encode structural and non-structural proteins, respectively. They are linked to a common area (J), which functions as a promoter for the synthesis of sub-genomic RNA. Both proteins were produced as precursors of polyproteins. The four non-structural proteins are encoded by ORF1. At the 5' end of the genome are the non-structural proteins, nsPl, nsP2, nsP3, and nsP4 (Ahola and Merits, 2016). The structural polyprotein, which cleaves into five structural proteins, is encoded by ORF2. At the 3' end of the genome are the genes for the structural protein CP, E3, E2, 6K, and El(Subudhi et al, 2018).

**Medicinal Plants and their Bioactive Compounds**

*Curcuma longa* (curcumin)- Its effectiveness against CHIKV has recently been demonstrated(Mounce et al, 2017). Curcumin, the primary active component of the rhizome of turmeric (Curcuma longa), exhibits antiviral properties against many viruses (Mathew and Hsu, 2018). Its IC50 against CHIKV was 3.89 m. With a CC50 of 11.6 m, the safety index, however, was insufficient. However, demethoxy curcumin, a derivative of it, was more effective and had a better safety record. Because of its lipophilic properties, demethoxy curcumin has the ability to disrupt the CHIKV membrane, which enhances its antiviral efficacy. Because demethoxy curcumin is lipophilic, it can obstruct the CHIKV membrane, which enhances its antiviral properties. Despite curcumin has been demonstrated to be effective in vitro against a range of viral illnesses, its limited water solubility and absorption have mostly prevented the effects from being translated in vivo(Von Rhein et al, 2016). Therefore, before curcumin compounds are employed any further, their in vivo efficacy needs to be confirmed. However, it is possible to derivatized it in order to improve its pharmacokinetics and anti-CHIKV properties.

`*Zingiber officinale* (6-gingerol)- A plant whose rhizome is widely used as a spice and a component of traditional herbal medicine in Asia has been shown to offer numerous health benefits (Akinyemi et al, 2015). Several investigations have documented biological effects, including anti-inflammatory, antibacterial, anticancer, and antioxidant qualities (Ahebwa et al, 2023). Additionally, ginger has been associated with the management and prevention of diabetes, respiratory issues, neurological disorders, and cardiovascular disease(Wahid et al, 2017). [6]-gingerol is one of the components of ginger that has the highest pharmacological activity(Hwu et al, 2015). Fresh ginger has a distinct flavor due to the aromatic ketones that are present in its chemical composition(Abu Bakar and Ng, 2018). This nonvolatile substance possesses a broad spectrum of biological effects, such as anti-oxidation, anticancer, analgesic, and anti-inflammatory abilities, along with a low toxicity profile . It has also been found that [6]-gingerol inhibits the replication of CHIKV once it has infiltrated the host cell(Citronberg et al, 2013).

## MATERIALS AND METHODS

The docking of *Curcuma longa* (turmeric) and *Zingiber officinale* (ginger) derived composites against the nsp2 protein of the chikungunya virus is the focus of this work. Docking was performed using the CB-Dock (Cavity-detection guided Blind Docking) software program.

**Preparation of Chikv Nsp2 Protein**

Utilizing the Protein Data Bank (PDB), the macromolecule's three-dimensional structure was discovered. This investigation used the Chikv nsp2 protein. Using PDB ID: 4ZTB, the Nsp2 protein structure was obtained from PDB. The PDB format was used to store the three-dimensional structure. The Py-Mol viewer was used to view the downloaded protein.

**Table 1. Chemical and physical properties of various compounds from turmeric (*Curcuma longa*) and ginger (*Zingiber officinale*).**

| Sr.No | Ligand name | Pub chem ID | Molecular wt. (g/mol) | Hydrogen bond | Hydrogen bond donor | Log p | Binding energy ligand +target(nsP2) |
|---|---|---|---|---|---|---|---|
| 1 | α-Pinene | 6654 | 136.23 | 0 | 0 | 2.8 | -6.2 |
| 2 | β-Pinene | 14896 | 136.23 | 0 | 0 | 3.1 | -6 |
| 3 | Myrcene | 31253 | 136.23 | 0 | 0 | 4.3 | -5.7 |
| 4 | α-Phellandrene | 443160 | 136.23 | 0 | 0 | 3.2 | -6.4 |
| 5 | α-Terpinene | 7462 | 136.23 | 0 | 0 | 2.8 | -6.4 |
| 6 | p-Cymene | 7463 | 134.22 | 0 | 0 | 4.1 | -6.4 |
| 7 | Terpinolene | 11463 | 136.23 | 0 | 0 | 2.8 | -6.6 |
| 8 | Curcuphenol | 360253 | 218.33 | 1 | 1 | 5.3 | -7.5 |
| 9 | Tricyclene | 79035 | 136.23 | 0 | 0 | 3.2 | -6.2 |
| 10 | Camphene | 6616 | 136.23 | 0 | 0 | 3.3 | -5.7 |
| 11 | Hexanal | 6184 | 100.16 | 1 | 0 | 1.8 | -4.1 |
| 12 | n-octane | 356 | 114.23 | 0 | 0 | 3.9 | -4.6 |
| 13 | n-decane | 15600 | 142.28 | 0 | 0 | 5 | -5.1 |

**Preparation of Ligands**

For this investigation, ligands from *Zingiber officinale* (ginger) and *Curcuma longa* (turmeric) were used. Downloads of ligand chemical structures are available from the MAPS Database, PubMed, Pubmed Central, Pubchem, Zinc Database, and ChEMBL. These ligands' three-dimensional structure was obtained from PubChem.

**Docking**

The software CB-Dock (Cavity- detection guided Blind Docking) was used to conduct docking investigations. For post-analysis and docking, CB-Dock was employed. The protein and ligand structures were uploaded, and the docking procedure was started. The outcome of the docking was examined.

## RESULTS AND DISCUSSION

A technique named molecular docking, sometimes referred to as molecular anchoring, gives researchers estimates of the free energy binding between a protein and ligand in several spatial conformations. Every spatial conformation has its free energies of binding (between the binder and its target) computed, and the conformation with the lowest energy is deemed to be the most advantageous or best-fitted conformation. The RSCB Protein Data Bank repository, which is associated with PDB Id 4ZTB and has X-Diffraction 2.59 A, is where the NsP2 structure was discovered. The structures of the ligands were obtained from a variety of software programs, including MAPS Database, Pubchem, Zinc Database, Pubmed Central, and ChEMBL.

13 ligands were used in the docking studies, and the target protein was nsP2. The ligands such as α-Phellandrene, α-Terpinene, p-Cymene, Terpinolene, and Curcuphenol exhibit increased affinity for the nsP2 protein in their binding conformation modes. The ligand binding site predicted by the docking approach was examined while examining the binding interaction and location of ligands with the nsP2 protein. Every ligand molecule's binding position to the chikv virus nsP2 protein was examined, and the pose with the lowest binding energy was

produced. In comparison to greater energy scores, the lowest energy score indicated better target protein-ligand binding affinity (best protein-ligand complex). Out of the thirteen ligands, it was discovered that α-Phellandrene, α-Terpinene, p-Cymene, Terpinolene, and Curcuphenol had ligand binding energy values that were lower than those of the other ligands. Ligand Curcuphenol has the lowest binding energy value (-7.5 kcal/mol) when it's bound to the chikv virus nsP2 protein, followed by ligand Terpinolene (-6.6 kcal/mol) and ligands α-Phellandrene, α-Terpinene, and p-Cymene (-6.4 kcal/mol).

## CONCLUSION

Using molecular docking, this work examined the potential of bioactive compounds from Zingiber officinale and Curcuma longa to inhibit the Chikungunya virus's (CHIKV) nsP2 protein. Curcuphenol had the highest binding affinity (-7.5 kcal/mol) among the 13 ligands that were examined. Terpinolene came in second (-6.6 kcal/mol), followed by α-Phellandrene, α-Terpinene, and p-Cymene (-6.4 kcal/mol). These findings imply that these substances may interfere with the enzymatic activity of nsP2, which is necessary for viral replication. The results set the stage for additional experimental validation and medication development by identifying the potential of natural chemicals as antiviral options against CHIKV. This research advances the investigation of plant-based treatments for viral diseases.

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