A medicinal plant known as *Holoptelea integrifolia* includes phytoconstituents like betulin and betulinic acid, which have been proven to have potent antiviral properties against the pandemic SARS-CoV-2 virus using in-silico screening study

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Abstract- In the current study, potential inhibitors for many physiologically active compounds discovered in medicinal plants were assessed using molecular docking techniques. The Maestro 12.8 conducted a docking study comparing the antiviral drug Zanamivir with phytoconstituents present in the stem bark of Holoptelea integrifolia, including betulin and betulinic acid. The results demonstrate the effectiveness of this screening methodology, which can speed the creation of new medications for the treatment of developing infectious diseases and other conditions. When compared to the antiviral drug Zanamivir, whose docking score was 3.796, PDB ID (6LU7) is taken as a major binding receptor. Phytoconstituents screening chemicals extracted from the medicinal plant Holoptelea integrifolia, such as betulin (-1.589) and betulinic acid (-1.552), were more effective than the typical antiviral medication zanamivir, whose docking score was 3.796. The docking results show that phytoconstituents in *Holoptelea integrifolia* plants are highly potent against viral diseases, are effective against SARS CoV-2, and can be used to prevent the spread of covid. As a result, they will be a crucial source for new antiviral medications in the future that target various viral diseases.

***Index Terms*: Betulin, Betulinic acid , zanamivir, SARS CoV-2, Zanamivir, Phytoconsitutents.**

I. INTRODUCTION

In Wuhan, China, the COVID-19 was initially discovered in December 2019. The properties of the virus' genomic structure resulted in a kind of viral pneumonia that propagated quickly from person to person. It was categorised as the Middle East Respiratory Syndrome and the acute respiratory syndrome (SARS-2002) (MERS-2012). The coronavirus disease of 2019 (COVID-19) has been classified as a pandemic by the World Health Organization (WHO) [1]. The bacteria known as the coronavirus mainly affects the lungs of people. The Middle East respiratory syndrome (MERS)-COV in 2012 and the severe acute respiratory syndrome (SARS)-COV in 2002 to 2003 are examples of prior coronavirus outbreaks that have been recognised as being substantial threats to public health [2]. According to additional research, this coronavirus and the severe acute respiratory syndrome virus (SARS

COV), middle east respiratory syndrome virus (MERS-COV), and bat coronavirus TG13, respectively, shared 79.5 percent, 50 percent, and 96 percent of their genomes. [3] The audio sounds that the human body produces, such as breath, respiratory sound, heart sound, swallow breathing, pulse sound, pulmonary noises, etc., have been used by medical researchers and doctors to diagnose and monitor human disease. Usually, physical auscultation was used to acquire this information prior to recent patient visits. Digital stethoscopes are being used by researchers and scientists to record noises from the human body, and then the data is automatically analysed to identify diseases, such as wheeze identification in asthma.the use of human speech and voice to assist in the early diagnosis of a variety of disorders (including Parkinson's, depression, Alzheimer's, migraines, dry and wet cough, and voice pathology detection) [4]. The increased infectivity of SARS-CoV-2 was established by the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2, which exhibits 10–20 times higher affinity to the ACE2 receptor than that of SARS-COV [5]. What began as a limited COVID-19 epidemic in December swiftly turned into a worldwide pandemic, as the WHO announced on March 11, 2020. Despite a variety of prevention and containment efforts being used by governments around the world, COVID-19 is still spreading. Worldwide, there have been more than 13.5 million conformed COVID-19 instances as of July 15, 2020, and more than. To stop the spread of the virus to new contacts, isolation must be used first. Mild diseases should be managed at home while keeping the patient's body hydrated, managing their cough and fever, eating nutritious foods, and taking antibiotics on a regular basis. Antivirals should be avoided in short-term treatment, according to China Oseltamivir Guidelines, and corticosteroids can be used to treat acute respiratory distress syndrome (ARDS) Early on in the pandemic, there was little knowledge of COVID-19 and its therapeutic care, making it urgent to use experimental therapeutics and drug repurposing to treat this new viral infection. Since then, because to the tireless efforts of clinical researchers around the world, advancements have been made that have improved our understanding of COVID-19 and its management as well as allowed for the rapid development of novel therapies and vaccines [8]. A significant SARS-CoV-2 variant of concern (VOC) [9] that has spread to at least 200 nations and territories is the Delta variant (PANGO lineage: B.1.617.2), according to the Global Initiative on Sharing All Influenza Data (GISAID) [10]. Additionally, studies have discovered that the Delta variation has a larger secondary attack rate, growth rate, or reproduction number than previous versions, including the Alpha variant (range of the mean estimates: 60-120 [11]In late March 2021, a severe pandemic wave struck India, the country where Delta was initially discovered. However, the Delta wave in India barely lasted three months and decreased quickly after peaking in mid-May, unlike many other locations that saw a protracted Delta pandemic wave. Case numbers stayed low from June through October 2021. (the time of this study). This abrupt epidemic drop has been attributed to a high infection rate following the Delta wave due to low immunisation rates at the time (4.2 percent fully vaccinated at the end of June 2021). Given a predicted basic reproduction number (R0) of 6-7, nevertheless[12].

Holoptelea integrifolia

Drugs made from plants have been used for many years to treat a variety of illnesses. We still rely on "Ayurveda" for around 75% of our medications nowadays. The recent emergence of Ebola, Swine Flu, Bird Flu, HIV II, and new strains of bacteria with low tolerance to antibiotics raise the prospect of untreatable bacterial diseases and increase the urgency of the quest for new infection-fighting techniques. Recently, herbal remedies have received a lot of attention as an alternative source of effective medications for curing or preventing a variety of disorders. A roadside tree called *Holoptelea integrifolia* performs a variety of biological functions. Plant-based medications have been used for many years to treat a wide range of diseases. Ayurveda continues to be used today for about 75% of our medical needs. The recent advent of diseases like Ebola, Swine Flu, Bird Flu, HIV II, and new bacterial strains with low antibiotic tolerance raise the possibility of incurable bacterial diseases and highlight how urgent it is to find new infection-fighting methods. Herbal medicines are gaining popularity as an alternate source of powerful drugs for treating or preventing a wide range of illnesses. Holoptelea integrifolia, a roadside tree, carries out a number of biological processes. This healing plant

contains a wide range of phytochemicals that can be used to treat a wide range of human and animal illnesses. The plant species is found in temperate and tropical regions of the northern hemisphere and is native to Pacific Islands [13]. It can be found up to 2000 feet in elevation in the outer Himalayas of India. It is a sizable deciduous tree, reaching heights of 30 to 35 metres. The bark is grey and has slightly corky scales. Alternate, sub-coreacious, elliptic-ovate, 5–13 cm long, whole, and pinnately veined leaves. Flowers are greenish-yellow, typically hermaphrodite or male, monochlamydeous or infrequently polygamous, and they bloom from January to February. Typically visible from April to May, the fruits are suborbicular samaras with membrane wings and one tiny kidney-shaped seed [14]. The Indian elm, *Holoptelea integrifolia* (Planch), is a decorative roadside tree whose name is shortened to ho-loh-tee-uh from the Greek words for whole (holos) and ptelea (elm), which indicate totally (undivided). It is a member of the 200 species and 15 genus strong Ulmaceae family. It is also known as Indian Elm Tree in English and Chilbil, Kanju, and Poothigam in Sanskrit [15]. It is a significant Indian pollen allergen, sensitising about 10% of Delhi's atopic residents [16]. The goal of this review is to give current knowledge about this specific plant, covering topics like physicochemical characteristics, phytochemistry, and pharmacology.As a result, the review will be a useful source of knowledge for researchers looking into the product's medicinal and economic potential [17]. There are 200 species in the family Ulmaceae, which has 15 genera. Hindi has the common names Chirmil, Chilbil, Chilla, Dhamna, Kandru, Kanju, Karanji, Kumba, Kunjanali, and Kunj, while Gujarati, Marathi, Tamil, Malayalam, Punjabi, and Telugu also have similar names. Sanskrit has the common name Chirbilva.[18]. According to recent estimates from the WHO (World Health Organization), 80 percent of people globally rely on herbal remedies for some conditions. The world's developing nations have stepped up their efforts to record ethnomedical information and conduct scientific study on medicinal plants. On Earth, there are thought to be between 250,000 and 500,000 different plant species [19] Origin and Distribution. The Pacific Islands were the origin of the plant species.[20]. It is found throughout the northern hemisphere's tropical and temperate regions. The plant has been relegated to Asia's tropical nations, including China, India, Nepal, Sri Lanka, Indo-China, Cambodia, Laos, Myanmar, Vietnam, Burma, and China [21]. It can be found in India in the outer Himalayan region from Jammu eastward up to 2000 ft. extending to Assam and Burma, as well as in the southerly direction from Bengal to Central, Western, and South India to the arid region of Ceylon.

TABLe 1: Vernacular names of *Holoptelea integrifolia*

S.No	Language	Vernacular name
1	Hindi	Papri, Chilbil, Kanju, Banchilla, Bawal, Poothigam, Dhamna, Begana, Chirabil
2	English	Indian elm, Jungle cork tree, Monkey biscuit tree, Indian beech tree
3	Sanskrit	Chirivilva, Pootikaranja, Udakirya, Hasthivaruni, Markati, Vayasi, Karabhanji
4	Malayalam	Aavil, Njettaval, Aval
5	Nepali	Sano pangro
6	Siddha	Iya

A. Vernacular Names.

Depending on the languages used in a particular place, Holoptelea integrifolia goes by a variety of common names. Table 1 displays the names used in several languages.

B. Cultivation:

The plant is often grown by transplanting seedlings raised in nurseries. Seeds are sown in lines 12–20 cm apart to produce seedlings in the nursery. When the seedlings are 10 cm long and the spacing is 22.5 22.5 cm, transplantation is carried out. After two years on the transplant beds, the seedlings are planted during the monsoon season. On lines that are three metres apart, fresh seeds are also sown directly at a rate of two seeds per stake. In both situations, continuous watering is necessary.

C. Diseases and Pest:

The plant is often disease-free, however some pests do

attack it. Tree borers of the families Bostrichidae, Buprestidae, Cerambycidae, and Platypodidae, which frequently infest the stem and young leaves, are significant pests of the tree. Traditional uses of the plant *Holoptelea integrifolia* include the treatment of rheumatism, leprosy, gastroenteritis, dyspepsia, colic, intestinal worms, vomiting, wound healing, and inflammation.[22].

TABLE 2: Pharmacological activities of various extracts of Holoptelea integrifolia

S.No.	Activity	Plant Part	Extract	References
1.	Antibacterial	Stem Bark	Pet. Ether, benzene, chloroform, ethanolic acid and aqueous	23
2	Antifungal	Leaf and stem	Methanolic	24
3	Anti-inflammatory	Leaves	Ethanolic and aqueous	25
4	Antioxidant	Stem bark	Methanolic and aqueous	26
5	Antidiabetic	Leaves	Ether, chloroform, ethanolic acid and aqueous	27
6	Analgesic	Leaves	Ethanolic, ethyl acetate	28
7	Hepatoprotective	Leaves	Methanolic	29

Antiviral activity

A virus is either eliminated by an antiviral drug or its capacity to multiply is suppressed. The antiviral effects against Herpes simplex type 1, influenza FPV/Rostock, and ECHO 6 viruses are attributed to betulinic acid and betulin, which were extracted from the stem bark of Holoptelea integrifolia. Betulinic acid may reduce HIV-1 protease or reverse transcriptase activity or HIV-1 entrance [30].

II. RESEARCH AND METHODOLOGY

A. Molecular docking:

By simulating the interaction between a tiny molecule and a protein at the atomic level, the molecular docking approach enables us to characterise how small molecules behave at the binding site of target proteins and to better understand fundamental biological processes [31]. The completion of the human genome project has opened up a growing number of novel therapeutic targets for drug development. The study of a number of structural characteristics of proteins and protein-ligand complexes has also been aided by the advent of nuclear magnetic resonance spectroscopy, crystallography, and high-throughput protein purification techniques. Due to these advancements, computational approaches can now be applied across the entire drug discovery process [32–36]. Prediction of the ligand structure as well as its placement and orientation within these sites (often referred to as The two essential steps in the docking process are evaluation of the binding affinity and the docking pose. The sample methods and scoring frameworks that will be discussed in the theory section are impacted by these two actions.

Knowing the location of the binding site before doing any docking operations considerably increases the efficiency of those processes. The binding site is typically known before ligands are docked into it; by knowing the binding site's position before docking processes, efficiency is considerably increased. The binding site is typically known prior to docking ligands into it. One can also learn more about the sites by contrasting the target protein with a family of proteins that carry out a similar function or with proteins that have been co-crystallized with various ligands. One can also learn more about the sites by contrasting the target protein with a family of proteins that carry out a similar function or with proteins that have been co-crystallized with various ligands. Cavity detection software or online services like GRID [37–38], POCKET [39], Surf Net [40–41], PASS [42], and MMC [43] can be used without knowing the binding sites.

B. Molecular docking applications in drug development include the following:

Molecular docking has been the approach that has been utilised most frequently. There have been some remarkable accomplishments in this field, despite the fact that its principal application is in structure-based virtual screening to discover novel compounds that are active against a particular target protein [44].

C. Investigations of docking using Maestro 12.8

Molecular docking has been the approach that has been utilised most frequently. There have been some remarkable accomplishments in this field, despite the fact that its principal application is in structure-based virtual screening to discover novel compounds that are active against a particular target protein [45]. It is actually part of a pipeline that includes numerous in silico and experimental approaches and is not a stand-alone procedure [46].

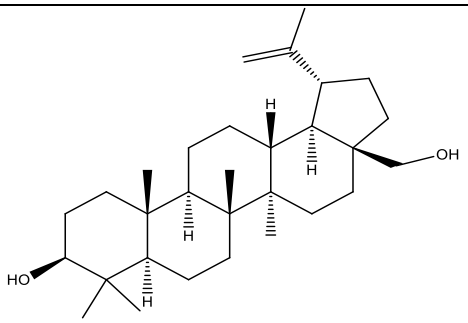
D. Preparing anticipated TPP and ligands for docking

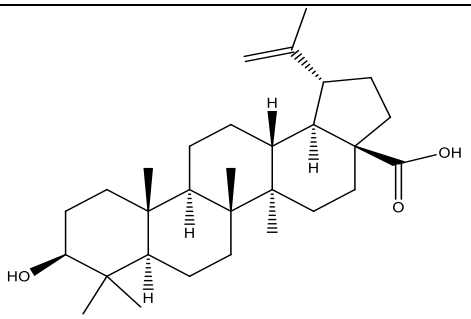
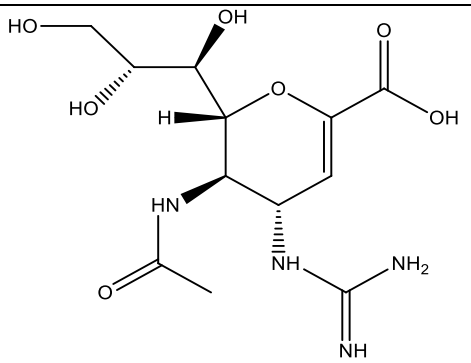
The Maestro 12.8 software includes tools for both protein and ligand optimization, including the ability to modify ligands by adding charge and rotatable bonds, modify proteins by adding atomic charges to make them more polar, calculate the energy contribution of de-solvation during ligand-binding on proteins, and assign grid maps to protein surfaces prior to ligand interaction. The aforementioned abilities enhance molecular docking's speed, accuracy, and docking through the use of a new scoring approach, effective optimization, and multithreading [47].

E. Protein docking using phytochemical ligand molecules in a simulated TPP

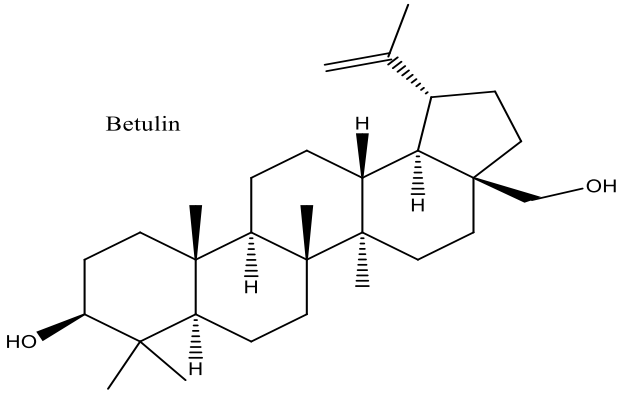
The binding-free energy, also known as docking, was estimated in the current work to represent the binding affinity of two ligands and one prescription drug (Standard Drug Zanamivir) to model TPP. The phytochemicals Betulin and Betulinic acid, which are found in the stem bark of the *Holoptelea integrifolia* plant, have the highest binding affinity and docking scores, respectively. They also have greater binding energies than the prescription drug Zanamivir, whose docking score is -1.589. (3.796). The binding-free energy, also known as docking, was estimated in the current work to represent the binding affinity of two ligands and one prescription drug (Standard Drug Zanamivir) to model TPP. The phytochemicals Betulin and Betulinic acid, which are found in the stem bark of the *Holoptelea integrifolia* plant, have the highest binding affinity and docking scores, respectively. They also have greater binding energies than the prescription drug Zanamivir, whose docking score is -1.589. (3.796).The binding-free energy, also known as docking, was estimated in the current work to represent the binding affinity of two ligands and one prescription drug (Standard Drug Zanamivir) to model TPP. The phytochemicals Betulin and Betulinic acid, which are found in the stem bark of the *Holoptelea integrifolia* plant, have the highest binding affinity and docking scores, respectively. They also have greater binding energies than the prescription drug Zanamivir, whose docking score is -1.589. (3.796). As a result, we chose 2 phytochemical ligand Betulin and Betulinic acid phytoconstitutent that exhibits superior docking energy. The ligands with the highest affinity for the model TPP are listed in Table 2 for further study [48]. The Schrodinger program's Glide energy (Maestro 12.8) drug discovery tool was employed in the study as an alternative to Auto Dock Vina. Maestro 12.8 predicts binding affinity energies between (-1.589 kcal/mole to 3.796 kcal/mole) when docking calcineurin with inhibitors, which is nearly identical to the results of the current study [49].

Table 2: *Holoptelea integrifolia phytoconstituents were screened in silico and compared to common antiviral medications in the following ways:*

S. No	Name of Phytoconstituents	Chemical Structure	Docking score	Glide energy
1.	Betulin		-1.589	-17.899

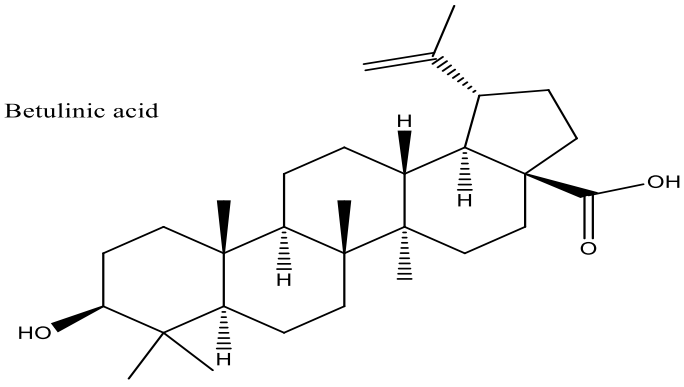
2.	Betulinic acid		-1.552	-26.908
3.	Zanamivir		3.796	-25.04

❖ *Chemical composition of phytoconstituents from Holoptelea integrifolia.*



(1*R*,3a*S*,5a*R*,5b*R*,7a*R*,9*S*,11a*R*,11b*R*,13a*R*,13b*R*)-3a-(hydroxymethyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1*H*-cyclopenta[*a*]chrysen-9-ol

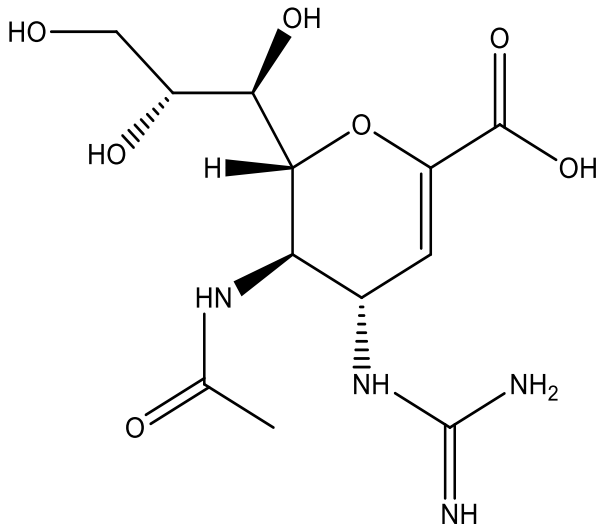
Figure 1: Chemical structure of Betulin



(1*R*,3a*S*,5a*R*,5b*R*,7a*R*,9*S*,11a*R*,11b*R*,13a*R*,13b*R*)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1*H*-cyclopenta[*a*]chrysene-3a-carboxylic acid

Figure 2: Chemical structure of Betulinic acid

Zanamivir



(2*R*,3*R*,4*S*)-3-acetamido-4-guanidino-2-((1*R*,2*R*)-1,2,3-trihydroxypropyl)-3,4-dihydro-2*H*-pyran-6-carboxylic acid

Figure 3: Chemical structure of Zanamivir

III.RESULT AND DISCUSSION

The data from the aforementioned in silico study and experimental evaluation demonstrate that the medicinal plant *Holoptelea integrifolia* contains Betulin and Betulinic Acid, which have the highest binding affinities and docking scores (-1.589 kcal/mol and (-1.552) kcal/mol, respectively), and which bind to receptors with PDB ids (6LUT) and when compared to the phytoconstituents found in the *Holoptelea integrifolia* plant, the antiviral drug Zanamivir International's docking score of (3.796 kcal/mole) is the lowest. This result demonstrates that betulin and betulinic acid phytoconstituents are highly and potent effective not only in the treatment of SARS Cov-2 but also for a various other viral diseases.

6LUT: Crystal structure of Serine Racemase from Dictyostelium discoideum. [50].
Classification: ISOMERASE
Organism(s): Dictyostelium discoideum
Expression system: Escherichia coli
Mutation(s): No
Resolution: 1.35 Å

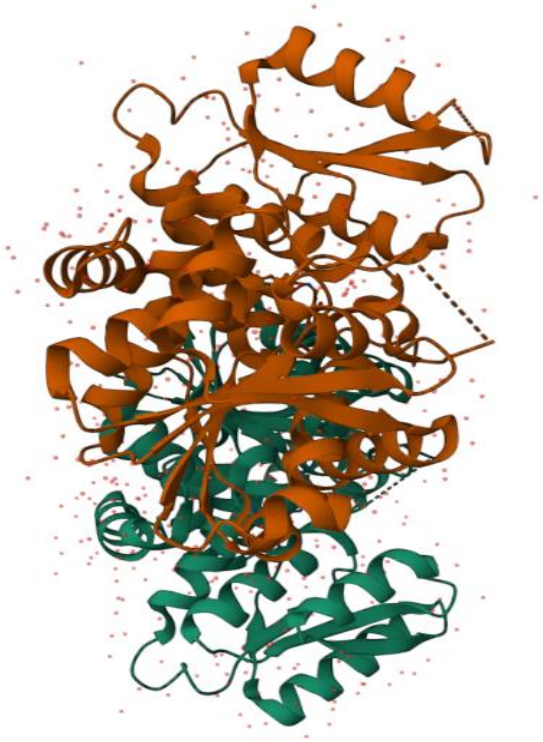


Figure 3: 3D- Structure of protein (6LUT)

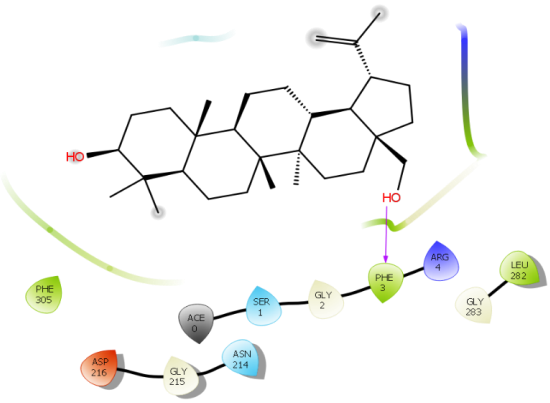


Figure 4: Betulin 2D diagrams of docked conformation compound

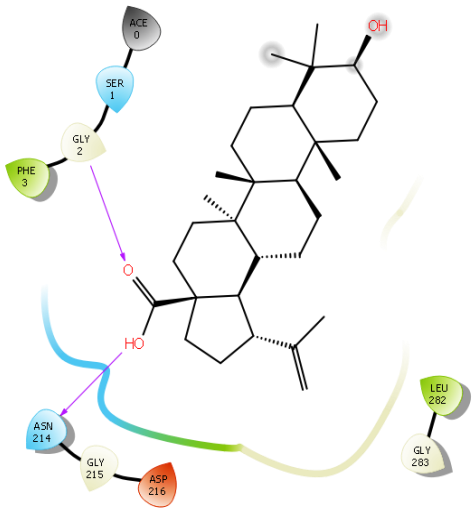


Figure 5: Betulinic acid 2D diagrams of docked conformation compound

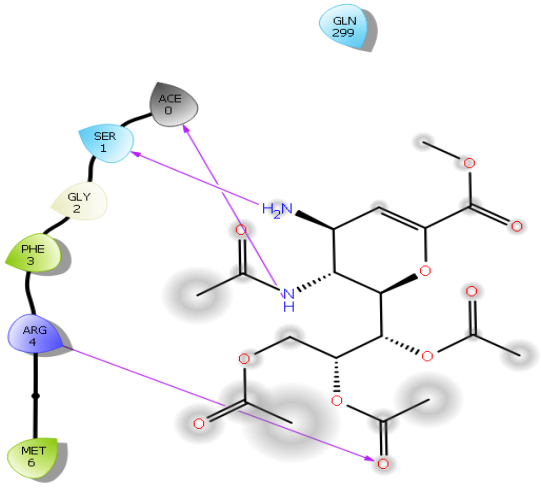


Figure 6: Zanamivir 2D diagrams of docked conformation compound

IV.CONCLUSION

Phytoconstituents present in *Holoptelea integrifolia* stem bark show effective property and potent record against viral diseases especially targeting SARS CoV-2, according to our research, which is based on in-silico study a medicinal plant containing Betulin and Betulinic acid. Though our work is based on computational molecular docking, Maestro 12.8, a scientific tool used for molecular docking analysis, is of great importance. It may be said that the unknown plants of this genus may usher in a new era of viral disease treatment in the future because these plant species and their phytoconstituents were efficient against numerous types of viral infections in our study by molecular docking analysis.

Compliance with ethical standards

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Disclosure of conflict of interest
The authors declare there is no conflict of interest in this study.

Statement of informed consent
Informed consent was obtained from all individual participants included in the study.

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