# Phytochemicals as a potential inhibitor of Spike Protein of SARS-CoV-2 Omicron Variant

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# Phytochemicals as a potential inhibitor of Spike Protein of SARS-CoV-2 Omicron Variant

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***Abstract***

**Background:** More than 50 mutations have been found in Omicron SARS-CoV-2. Most Omicron mutations are located in the spike protein, which plays a pivotal role in virus infection. The mutated spike protein in the Omicron variant increases virus transmissibility and potentially threatens the effectiveness of COVID-19 vaccines and antibody therapies. Herbal plants, such as Indian Ayurveda, African herbal plants, and Traditional Chinese Medicines (TCM), have been studied as SARS-CoV-2 potential therapy in several countries.
**Objective:** This review explores potential phytochemical herbals that target spike protein omicron based on the available molecular docking studies.
**Methods:** We collected research articles on the molecular docking of phytochemicals that target spike protein omicron. Combination of several keywords: in silico OR molecular docking AND spike omicron, were used as input for Google search. Out of 83 articles from Google search, eight articles matched the inclusion criteria and were selected in this review.
**Result:** Protodioscin from *Carica papaya* and Landomycin A from *Aloe vera* are the most potential *phytochemical inhibitors* against spike protein with the free binding energy of -10.77 kcal/mol and -10kcal/mol, respectively.

**Keywords: in silico, molecular docking, herbals phytochemical, spike glycoprotein, omicron**

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## Introduction

A severe case of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the agent responsible for the global pandemic COVID-19 disease. The first COVID-19 case was discovered in December 2019 in Wuhan, China, and has been spread globally ever since. In March 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic [1], and as Mei 2023, there have been 765,903,278 certified COVID-19 cases, with 6,927,378 fatalities documented [2].

SARS-CoV-2 mutation produces several new strains. For surveillance and research, the WHO divided the strains into four categories: variations with high impact (VOHCs), those of concern (VOCs), interest (VOIs), and those being monitored (VUMs). Among these variants, VOC is linked to high disease severity (high hospitalization and death rates), high transmissibility, pathogenicity, immunological and vaccine (therapeutic) evasion, and poor detectability in diagnostics; therefore, have emerged as the variations of most interest to the world. The WHO has identified numerous SARS-CoV-2 variants of concern (VOCs), such as Alpha, Beta, Gamma, Delta, and Omicron[3]. Compared to other varieties, the Omicron variant has higher transmissibility, resistance toward vaccines and antibodies. The ability to escape neutralizing antibodies has caused Omicron reinfection rates to be ten times higher than previous variants [4][5]. Most Omicron symptoms are milder than other variants, but it can be worse in patients with comorbidities, older age and younger than 20 that unvaccinated [4][6]

## Methodology

Research articles on molecular docking of active phytochemicals were collected through the Google search engine. We used a combination of keywords (in silico OR molecular docking AND spike omicron) AND

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(Phytochemical), yielding 83 articles. A specific inclusion criterion was applied to the articles, which should include more than one phytochemical as ligand and spike omicron as the protein target. After applying this inclusion criterion, we found eight research articles reviewed in this study (Table 1). The writer uses Corel and *Pymol* to make the figures.

**Structure of SARS-CoV-2**

The SARS-CoV-2 genome is the biggest positive-sense RNA virus to date (29.9 kb) [4]. The SARS-CoV-2 genome, which makes about one-third of the virus, encodes the four structural proteins, the envelope (E), membrane (M), nucleocapsid (N), and spike (S), as well as nine additional proteins, ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c, and ORF10 [7]. In contrast, two-thirds of the foundation for SARS-CoV-2 is made up of ORF1a and ORF1b, which are translated into polyproteins 1a (pp1a) and 1b (pp1ab). The polyproteins further split into 16 non-structural proteins (nsp), nsp 1–11 from pp1a and nsp 12–16 from pp1ab [3][4] (Figure 1).

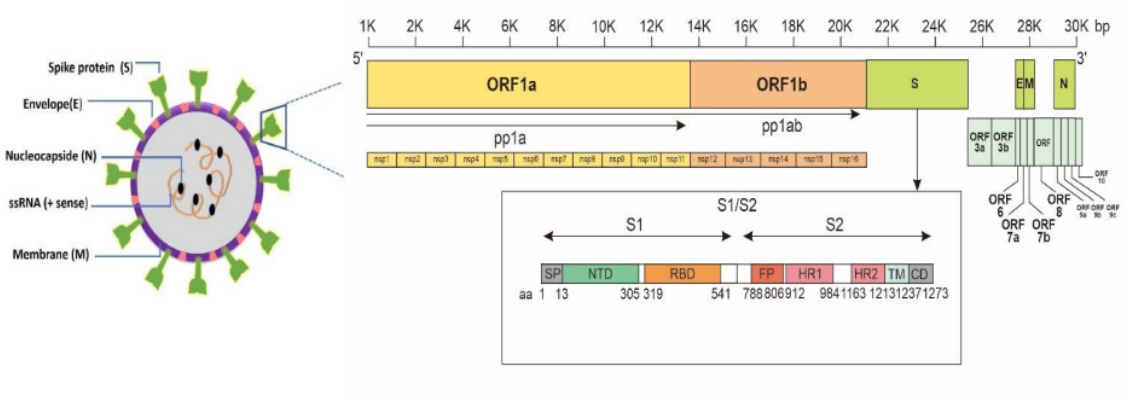


Figure 1. Genomic structure of SARS-CoV-2

Spike protein (S), which is involved in receptor recognition, viral attachment, and membrane fusion, contains two subunits, S1 and S2. The S1 subunit has an N-terminal domain (NTD) and a receptor-binding domain (RBD). In contrast, the S2 subunit consists of the fusion peptide (FP), heptapeptide repeat 1 (HR1) (heptapeptide repeat 2 (HR2), transmembrane (TM), and cytoplasmic domain (CP) [7].

The nsps of the SARS-CoV-2 virus serve a variety of purposes. Nsp1 acts to prevent host proteins from being translated. Nsp1 mediates RNA replication, processing, and mRNA degradation. Nsp2 modifies signalling pathways involved in host cell survival, while Nsp3 acts as a protease. As an anchor for the viral replication-transcription complex to the endoplasmic reticulum membrane, Nsp4's transmembrane 2 (TM2) domain serves as a membrane component. The Main protease (Mpro), or Nsp5, is involved in the replication process. A putative transmembrane domain called Nsp6 is thought to be involved in endoplasmic reticulum autophagosome. Nsp12, Nsp7, Nsp8, and a hexadecameric super-complex, activate RNA polymerase. Nsp9 functions ssRNA-binding protein, and Nsp10 involves in the methylation of the mRNA. Coronavirus replication and transcription need Nsp12, also called RNA-dependent RNA polymerase (RdRp). Nsp13 participates in transcription and replication by binding to ATP via its zinc-binding domain. Nsp14 is a domain of an exoribonuclease for proofreading. Endoribonuclease activity in Nsp15 is reliant on Mn (2+). Nsp16 is an enzyme that methylates 2'-O-ribose [8].


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**Pathogenesis and entry process of the virus**

Spike proteins (S proteins) facilitate coronavirus's entrance into host cells. Spike protein binds to Angiotensin-converting enzyme-2 (ACE2) receptor, which resides on the surface of human cells. The trimeric spike protein will be split into two subunits by host proteases during infection, with the N- and C-terminal S1 and S2 regions remaining intact. The S1 RBD carries out ACE2 receptor identification and contact, while S2 fuses host cell membranes. This process allows the viral RNA to enter the host cell cytoplasm, release the genomic material, and begin the replicative cell cycle in the host cell [9] (Figure 2). S2 incorporates the hydrophobic fusion peptide (FP), which helps the viral and host membranes fuse into the target cell membrane, while S1 separates and detaches. Once HR1 and HR2 of S2 have combined to form a stable six-helix bundle (6-HB) core, FP and transmembrane colonization, viral RNA entry into the host cell cytoplasm, and the beginning of the replication cycle will occur [7].

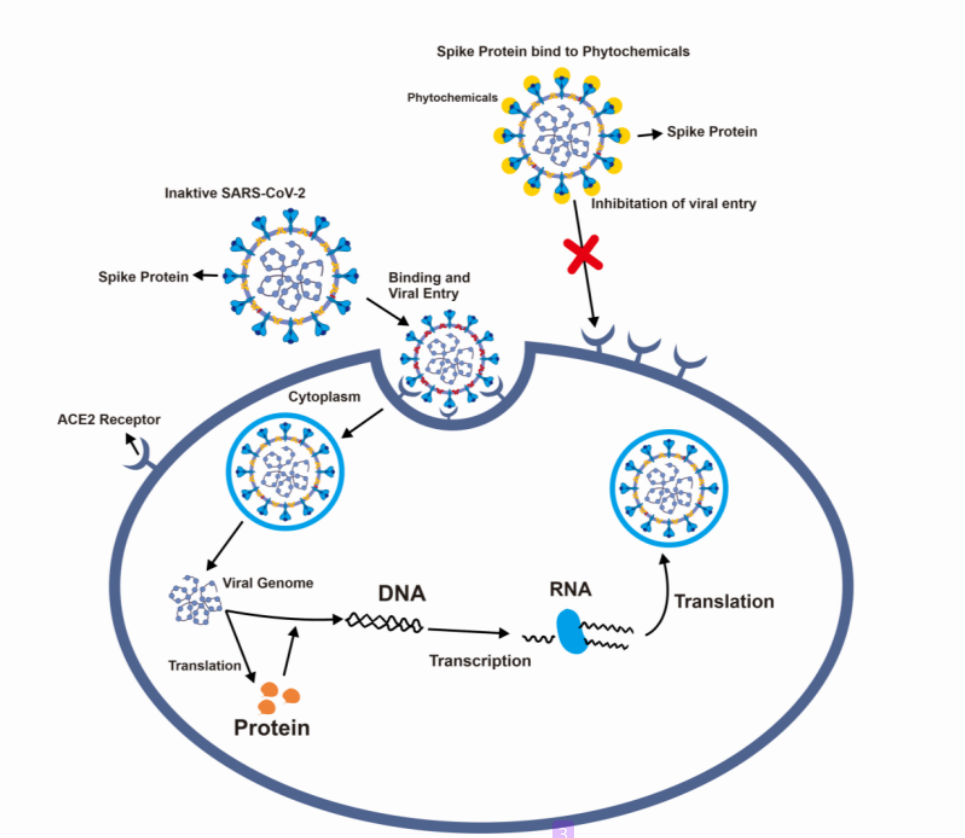


**Figure 2.** Phytochemicals (colored yellow) can inhibit viral entry to the host cell by binding to the S protein and thus blocking the recognition of the ACE2 receptor.

**RBD-ACE2 Complex**

Spike protein (or s protein) is vital for cell adhesion, membrane fusion, and receptor recognition of the host cell. Moreover, glycosylation of the S protein is essential for infection-related host antibody evasion [10]. The RBD of S1 has a shape that protrudes outward so that the human ACE2 (hACE2) receptor can recognize viral cells. Therefore, RBDs are often assigned as therapeutic targets and vaccine candidates. The trimeric spike glycoprotein extends 15 nm beyond the virus particle to recognize hACE2 throughout the viral infection phase [10]. There are two variations of the spike protein: open and closed. NTD and RBD make this conformational flexibility feasible. Therefore, the ACE2 receptor cannot be contacted by spikes in closed RBD conformation.

The down or closed conformation, sometimes called the perfusion state, is a stable shape in which the RBD is encased by S1-NTD, limiting the engagement of the receptor-binding site with the ACE2 receptor. Contrarily, the up or open conformation is less stable where one or more RBDs expose the receptor-binding site to bind with ACE2. The SARS-CoV-2 RBD is the least predictable part with receptor-binding motif (RBM) variations. These variations can be directly linked to different pathogenesis mechanisms of SARS-CoV-2 [11].

Viral cell entrance and membrane fusion are both facilitated by the S2 subunit. A tiny apolar fragment called S2 FP, mainly made of the amino acids Gly and Ala, may interact with the coronavirus membrane. The two times-repeated patterns of the FP domains were included in HR1 and HR2. The amino acid residues in these amphipathic sequences are hydrophobic and hydrophilic, enabling various membrane-bound binding interactions. As a result of their interaction, HR1 and HR2 create fusion cores that cause S2 to penetrate the cell membrane and begin the fusion process [10]. For the viral particle to bind to the host cell, the viral and host cells must fuse, and this core shape causes this to occur. The S2 TM and CP domains aid the S protein's tethering to the host cell [7].

**Mutation of Omicron BA.1-BA.4/5 SARS-CoV-2**

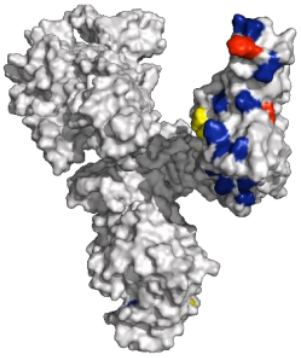

**Figure 3**. Schematic representation of Spike protein of SARS-Cov2 (PDB ID: 7Z3Z) generated by Pymol. Mutations on S protein of BA.1-BA.4/5 Omicron were shown in color. Blue: mutations BA.1-BA.4/5, yellow: mutations BA.2 and BA.4/5, red: mutations BA.4/5.

Thirty amino acid changes, six amino acid deletions, and three amino acid insertions exist in Omicron compared to ancestral strains. The thirty non-synonymous substitutions of Omicron are A67V, T95I, Y145D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F, including deletions residues inH69/V70, 142/V143/Y144, and N211and positions 211, 214, and 214EPE were each given an amino acid insertion [3][12].

The RBD S protein of omicron contains the important mutations G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, and Y505H that increase the affinity to ACE2 and, hence the transmissibility. Mutations of H655Y, N679K, and P681H play a role in enhanced transmissibility and infectivity of the Omicron.[3].

Wuhan-Hu-1 (WT) strain contains 1273 amino acids, compared to the 1270 amino acids found in Omicrons BA.1, BA.1.1, and BA.2. BA.3 has 1267 amino acids, whereas BA.4/5 contains 1268 amino acids. In the spike protein, there are 39 mutations for BA.1, 40 for BA.1.1, 31 for BA.2, 34 for BA.3., and 36 mutations for BA.4/5 that the researcher has discovered. Although the BA.4/5 spike protein contains additional mutations at amino acids 69-70, L452R, F486V, and R498Q, it still shares certain amino acids with other omicron variations [13].

Immune system evasion mutations that might lower infectivity and increase the likelihood of recurrent infection will be compensated for by the H69/V70 deletion. Some researchers refer to this variation as the "hidden" version because the 69-70 deletion is connected to S gene target failure (SGTF), which prevents it from being identified by SGTF and renders the spike unnoticed [3][13].

The L452R/Q mutation reduced the virus's polyclonal and monoclonal antibody neutralization susceptibility. Antibody escape is linked to mutations in L452R and F486V. A higher affinity for the human angiotensin-converting enzyme-2 (hACE2) receptor is also linked to the L452R mutation [3][13]. The reduced antibody-neutralizing activity caused by mutations in F486 allows the virus to evade antibodies produced by vaccinations that target the virus's RBD [12][13]. Three areas of S1 are the targets of three different antibodies. The NTD is where the initial region is [14][15], and its work is still a mystery. The second area is at or close to where ACE2 binds to the RBD. Antibodies mainly target this area to stop S from interacting with ACE2 on host cells, preventing infection [3]. The last point is that specific antibodies bind to the RBD but do not block ACE2 binding. For instance, the S-trimer becomes unstable due to mAb S309 binding to the N-linked part of the glycan at position 343 [12].

## Phytochemical therapy against SARS-CoV-2

The production of vaccines, the repurposing of existing medications, and the production of active substances as novel antivirals are among the research being done to produce SARS-CoV-2 treatments. Some countries, including China [16] and India [17], have developed herbal medicine for the SARS-CoV-2 infection. African herbal plants, Indian Ayurveda, and Traditional Chinese Medicines (TCM) are some herbal plants utilized in SARS-CoV-2 treatment. The preliminary research on this herbal medicine employs a molecular docking (MD) approach in search of potentially bioactive compounds. MD uses computing power to foretell how two molecules will interact and estimate the binding energy of those compounds toward their biological target[18][19].

## Potential Phytochemical Compounds against SARS-CoV-2 based on several studies

### *Landomycin A*

A particular angucycline antibiotic called landomycin was discovered in *Streptomyces* species like *Streptomyces fradia* and *Streptomyces cyanogenus* [20]. Landomycin A, characterized by four tetracyclic ring skeletons with six saccharides residue attached, is often found in Asian honey and *Apis cerana*. Landomycin A has a potent anticancer effect by inducing apoptosis in the cells with mitochondrial damage [21][22]. A recent study shows that Landomycin A of *Aloe vera* binds to Ser494, Arg 493, Cys488, Gly485, and Ala484 of Spike Protein., likely (Table 1). Landomycin A stabilization interaction of spike protein and ACE2 receptor through the hydrogen bond to Ser484 and Ser493. These mutations alter the ligand-receptor interaction, thus resulting in relatively low binding energy -10 kcal/mol (or high affinity of ligand). Landomycin A also binds to several ROS-dependent cellular signalling's enzymes, such as nitric oxide synthase (NOS), endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase (nNOS), cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and 5-lipoxygenase (5-LOX), with varied binding energy ranging from -11 kcal/mol up to -13.6 kcal/mol. In addition, Landomycin A, landomycin B, and landomycin X, all present in *Aloe vera,* can act as NOS inhibitors. An excessive amount of NOS could induce cell damage; thus, NOS inhibition could promote increased cell count and wound healing [23].

### *Caffeic acid hexoside*

Almost all plant species, including vegetables, potatoes, carrots, olives, coffee beans, fruits, tea, wine, and medications like propolis, produce the secondary metabolism polyphenol known as caffeine acid. Phenolic acids and their derivatives exhibit anti-inflammatory, anti-oxidative, and anticarcinogenic characteristics. Hepatocarcinoma (HCC) preventive effects of caffeic acid have been documented in both *in vitro* and *in vivo* studies. Caffeic acid plays a role in plants' defensive systems against predators, pests, and illnesses through the inhibitory effects of insects, fungi, and bacteria; and its protection role on plant leaves against ultraviolet B (UV-B) radiation. Studies on caffeic acid and its derivatives have shown a wide range of positive effects, including but not limited to hepato- and cardio-protective effects, antiproliferative, anticancer, antiviral, and immunostimulatory effects. [24].

A docking study on Caffeic acid hexoside from *Sargassum wightii* against RBD has a binding affinity of -6.4 kcal/mol and RMSD 2.82Å. It also revealed its interaction towards RBD, mainly through hydrogen bonds with the following residues: Arg403, Glu406, Asn417, Tyr453, and Ser496. The interaction of caffeic acid hexoside with residues the Asn417, Ser496, Tyr501, and His505 of the RBD inhibits the further interaction

of S protein towards the ACE2 receptor (Table 1). These residues are vital for viral recognition by the host cell; thus, Caffeic acid hexoside is considered a potent antiviral agent, especially against omicron B.1.1.529 [25].

***Phloretin***

An organic dihydrochalcone called phloretin can be found in apples and many other fruits. *Malus doumeri* (Taiwanese crab), *Malus pumila, Malus domestica, Populus candicans, Rosaceae* (lotus), *Etmopterus spinax* (velvet lantern shark), *Colchicum filifolium, Matricaria sabulosa*, etc are a few examples of plants that contain phloretin in large quantities [20]. Phloretin has anticancer potential through its apoptosis and cell cycle arrest mechanisms, antiangiogenic and antimetastatic. It works with several mechanisms, including slowing tumour development and inhibiting lung tumour tissue proliferation. Phloretin was also known to have a synergetic effect with atorvastatin to inhibit the development of colon cancer cells. Moreover, it has anti-inflammatories and antioxidant actions [26].

Phloretin interacted with Tyr501, Ser496, and Tyr453 of RBD through the Hydrogen bond and with Tyr501 and His505 of RBD via the pi-pi-stacking interaction. The calculated binding energy was -6.3 kcal/mol and RMSD of 0.061Å (Table 1). Ser496, Tyr501, and His505 were responsible for the interaction between ACE2 receptors and the RBD of the spike protein of omicron. Phloretin can activate transcription factors that induce antioxidant genes' expression, thus improving the enzymatic antioxidant defence system. Phloretin can also be a penetration enhancer of administered drugs due to its increased fluidity toward binding biological membranes. The predicted toxicity class for phloretin was IV, which means moderate hepatotoxic and mild carcinogenic effects [25]

***Naringin***

Naringenin and Naringin (4',5,7-trihydroxyflavanone-7-rhamnoglucoside) are flavonoids found in citrus fruits, including lemons, oranges, tomatoes and grapefruits. The human body absorbs Naringin via the gastrointestinal tract, mouth cavity, and small intestine, often transforming it into naringenin. The bioavailability of Naringin and naringenin may be decreased in the presence of milk protein and other dietary components. Naringin inhibits cell growth and promotes apoptosis via the ERK pathway, which has anticancer effects [27]. Naringenin can inhibit Hepatitis C virus (HCV) infection by activating peroxisome proliferator-activated receptor α (PPARα) and decreasing VLDL production, which is required for HCV particle secretion [28].

Naringin formed seven hydrogen bonds to S494, D38, E35, H34, K31, E75 and Q76 spike protein omicron with binding affinity -7.483 kcal/mol. Naringenin binds to His164, Glu166, Asp187, Thr190 main protease or 3CLpro of SARS-CoV-2 (PDB ID 6LU7) with binding energy −7.99 kcal/mol. Naringenin binds to 3CLpro as a ligand and blocks its activity [29]. The molecular docking between naringenin and ACE2 revealed a binding energy of −6.05 kcal/mol, with the essential binding sites are Pro146, Leu143, and Lys131. Naringenin work against SARS-CoV-2 by lowering the amounts of inflammatory markers, such as TNF-, IL-1, IL-10, and IFN-γ in COVID-19 patients [30].

***Phyllaemblicin C***

*Phyllaemblicin* can be found in the roots *of Phyllanthus emblica* [20] and demonstrates antiviral properties against coxsackievirus B3 [31] and SARS-CoV-2 by inhibiting the RdRp [32]. Phyllaemblicin B and Phyllaemblicin C from *Phyllanthus emblicalinn* have capabilities as antiproliferative and antiviral substances. The spike protein's ability to attach to the host cell receptor ACE2 may be blocked by phyllaemblicin C, preventing the virus from entering the host cell [33].

In silico study of An Ayurvedic medicine, Phyllaemblicin C from *Phyllanthus emblicalinn* shows hydrogen bond to Y453, G496, Q498, N501, Y449, S494, Q493, G498 and other interactions to Y505, G496, F497, R403, Y495, Y453 spike protein omicron with the lowest binding energy -9.1 kcal/mol. Residues of the spike protein that interacting with ACE2 are K417, G446, Y449, Y453, L455, F456, A475, F486, N487, Y489, Q493, G496, Q498, T500, N501, G502, and Y505. Among these, Phyllaemblicin C interacted too with residues Y449, Y453, Q493, G496, Q498, N501, and Y505 RBD of spike protein [34].

Phyllaemblicin C also bind to Mpro SARS-CoV-2, which form hydrogen bond to N142, Q189, E166, H164, H163, P168, H41 and other non-covalent interaction to L167, Q192, M165, C145, Y54, M49 with affinity -9.7 kcal/mol. Phyllaemblicin C and phyllaemblicin B can be found in Indian gooseberry. Phyllaemblicin C had the highest binding affinity towards spike and Mpro protein targets [34].

***Cinnamtannin B1***

Cinnamontannin B1 I is a bioactive compound in several plants, such as *Cinnamomum sp*, *Laurencia disticophylla*, *Gnidia lamprantha*, and *Parameria laevigata*. *In vitro*, study revealed that cinnamon tannin B1 exhibited pro-apoptotic effects, antioxidant protection, platelet aggregation, and Cyclooxygenase-2 (COX-2) inhibition. Through the absorption of glucose in 3T3-L1 cells, Cinnamontannin B1 may also prevent platelet aggregation and has the potential to be an antidiabetic drug. By killing melanoma cells and causing cell cycle arrest and death in hepatocellular carcinoma and cervical cancer cells, Cinnamontannin B1 has also been studied as an anticancer agent. Cinnamontannin B1 is potential as an adjuvant treatment to enhance colon cancer prognoses [35].

In silico study, Cinnamontannin B1 from *Cinnamomum zeylanica* shows binding to Y453, G502, G496, Q498, Q493, Y505, N501, and K417 of RBD spike protein with binding energy, -9.0 kcal/mol contributing to inhibit viral entry. Cinnamontannin B1 also bind to E166, N142, T190, P168, F140, and Q189 Mpro with binding affinity -8.385 kcal/mol [34]. Cinnamontannin B1 can binding both RBD spike protein and Mpro SARS-COV-2.

***Wedelolactone***

Wedelolactone can be found in fresh leaves of *Wedelia spp and Eclipta spp*. Wedelolactone has several pharmacological effects, such as anticancer, anti-inflammatory, antidiabetic, antiobesity, and organ protection [36]. Wedelolactone, from *Wedeliaccalendulacea*, is bound towards crucial binding sites of Omicron's spike protein. It interacts through Hydrogen bonds with Tyr449 and Ser494 and hydrophobic interaction with Phe490, Arg493 and Leu452. The drug score of wedelolactone was predicted to be 0.30. An adverse drug score indicates that a compound is unlikely to be developed into a drug. Pharmacokinetic analyses on wadelactone showed the compound is highly water-soluble, increasing its absorption and bioavailability even through other parenteral routes. LD50 Wedelolactone is 2.41 mol/kg, indicating minimal lethal impacts [37].

***Pinosylvin***

Pinosylvin (3,5-dihydroxy-trans-stilbene) is a pre-infectious stilbenoid toxin found mainly in the Pinaceae family. It has advantageous effects on human health, such as anti-inflammatory, anticancer, antioxidant, neuroprotectant, and antiallergic. Pinosylvin derivatives also have antibacterial characteristics towards both Gram-positive and Gram-negative bacteria, such as *Staphylococcus aureus, Escherichia coli, Listeria monocytogenes, Lactobacillus plantarum, Salmonella infantis, Pseudomonas fluorescens, Campylobacter jejuni,* and *Campylobacter coli* [38]. Pinosylvin acts on nuclear factor erythroid-related factor 2 (Nrf2), which regulates gene expression related to oxidative stress homoeostasis [38]. A docking study on Pinosylnin on Omicron; spike protein revealed its calculated affinity as -7.0 kcal/mol with the apparent binding site involving residues Phe342, Leu368, Phe375 RBD (PDB ID 7QNW) [39].

***Protodioscin***

Protodioscin is a bioactive compound that alters free testosterone levels and sperm characteristics. It is usually found in *Tribulus terrestris* and *Trigonella foenum-graecum*. Protodioscin extract may prevent HL-60 in human leukemic cells from proliferating [40]. Furthermore, Methyl protodioscin (MPD) may prevent pancreatic cancer cell lines from developing tumours. The inhibition of tumour development occurred via apoptosis stimulation and cell proliferation inhibition. MPD also control aerobic glycolysis, which supplies energy and nutrients to malignant cells, by blocking the Akt1/c-Myc axis [41].

In silico molecular docking, studies show the ability of Protodioscin to bind with multiple different SARS–CoV–2 proteins. The target protein of Protodioscin, including the RNA binding domain of nucleocapsid, main protease (Mpro), RNA dependent RNA polymerase (RdRp), and spike protein of some variants. Protodioscin binds to Leu167, Pro168, Lys169, Gly170, Phe171, Tyr172, Ala173, Pro73, Ile74, Thr76, Gln83, and Thr135 of RNA binding domain of nucleocapsid with binding energy -13.83 kcal/mol. Protodioscin also bind to Asn496, Asn497, Lys500, Lys577 RdRp with BFE –11.62 kcal/mol. Protodioscin shows Hydrogen bond interaction with residues Leu167, Phe171 and Thr135 N protein were others interaction with Pro168, Lys169, Gly170, Tyr172, Ala173, Pro73, Ile74, Thr76 and Gln83 N protein. Protodioscin also interacted with Asn496, Asn497, Lys500 and Lys577 of RdRP with binding energy -11.62 kcal/mol. Furthermore, it also targeted the Main protein (Mpro) by binding to residues Thr24, Met165, Glu166, Leu167, Pro168, Gln189 and His41 with binding energy -13.19 kcal/mol [42].

The previous docking study reported that the protodioscin formed the strongest binding affinity with Wuhan's spike protein, followed by Delta and Omicron. As with the Wuhan variant, Protodioscin bound to Spike protein via Arg403, Lys417, Tyr453, Leu455, Val483, Glu484, Phe486, Tyr489, Phe490, and Gln493 with binding energy -11.19 kcal/mol. Within these binding site residues, Lys417, Leu455, Glu484, Phe490, and Gln493 are also used to interact with the Delta variant with binding energy -11.57 kcal/mol. Lastly, Protodioscin bind to S protein omicron withresidues Asp405, Tyr453, Ser494, Ser496, Arg498, Tyr501, Gly502, Gly504, and His505 with binding energy -10.77 kcal/mol. These results indicated that protodioscin could strongly interact with spike protein for all variants at critical residues or hotspots for its binding to the ACE2 receptor. Blocking the interaction of ACE2 to spike protein may prevent the entry and fusion of SARS–CoV–2 [42].

***Maysin***

Maysin can be found in *Zea mays* (corn) and *Crescentia cujete*. Previous research on maysin revealed that it can prevent Alzheimer's disease by triggering a cellular immune response. Maysin increases the production of Th2 cytokines to inhibit or reduce amyloid aggregation [43]. An *in-silico* study of 73 plants' secondary -metabolites demonstrated that maysin, geraniin, Kaempferol-7-glucoside, and 6-hydroxy cyanidin-3 had a broad-spectrum affinity toward spike protein of SARS-CoV-2. In addition, maysin and geraniin showed superior advantages against spike protein wild type (WT) and omicron variant than that zafirlukast, the standard drug. Generally, maysin had higher binding free energy towards the spike protein of both wild types (-8.5 kcal/mol) and omicron (-7.5 kcal/mol).

***Geraniin***

Geraniin can be found in *Euphorbia makinoi, Macaranga tanarius, Elaeocarpus sylvestris, Zingiber officinale,* and ***Ne****phelium lappaceum (rambutan)* [20]**.** Geraniin from rambutans' peel extract has strong antioxidant properties minimal with minimal cytotoxicity [44]. Geraniin was docked with the spike protein/hACE2 receptor complex (PDB ID 6M0J) resulting in a docking score of -8.1 kcal/mol and forming eight hydrogen bonds (Arg403, Tyr449, Tyr453, Gln493, Ser494, Gln498, Gly502, and Tyr505), four van der Waals interactions (Tyr495, Gly496, Thr500, and Asn501), and one pi-pi interaction (Tyr505) with the spike protein. The result from the docking study demonstrated that geraniin binds more stably to the spike protein than to the hACE2 receptor, with an RMSD of approximately 0.1–1.0 nm. Using competitive ELISA, geraniin proved can hinder the interaction between the spike protein RBD and the hACE2 receptor. The results showed that geraniin effectively prevented the binding of the spike protein RBD to the hACE2 receptor at a level comparable to the effect of the neutralizing antibody against the spike protein. [43].

**Conclusion and Future prespective**

Eleven probable phytochemical plants are potential inhibitors against spike protein of the SARS-CoV-2 Omicron variant. Based on the predicted binding energy analysis, phytochemicals protodioscin and landomycin A present in *Carica papaya* and *Aloe vera* are the strongest candidates as S-protein inhibitors.

**Conflicts of Interest**

The authors declare no conflict of interest.

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**Author Contributions**

Three authors were involved in this article. "Conceptualization, Tuti Ratnasari and Faizah Fulyani; methodology, Tuti Ratnasari; software, Pymol for students; validation, Tuti Ratnasari, Faizah Fulyani and Endang Mahati; writing—original draft preparation, Tuti Ratnasari; writing—review and editing, Tuti Ratnasari and Faizah Fulyani; visualization, cdr and Pymol for students; supervision, Endang Mahati; project administration, Endang Mahati; funding acquisition, no funding sponsor".

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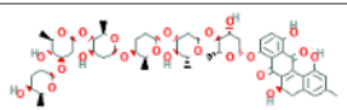
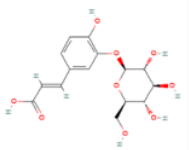
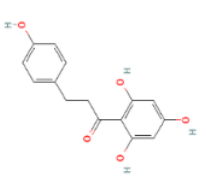
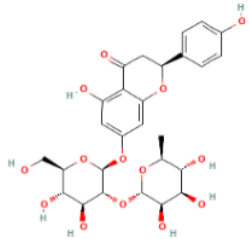
**Table 1. Journals of The Study on Phytochemicals as A Therapy Against Spike Protein Omicron**

| Senyawa Fitokimia Terbaik | BFE (kcal/mol) | Stucture | Sources | Binding site | Inhibitory concentration IC50 | Reference |
|---|---|---|---|---|---|---|
| *Landomycin A* | -10 |  | *Aloe vera* | Ser494, Arg 493, Cys488, Gly485, Ala484 | NA | [23] |
| *Caffeic acid hexoside* | -6.4 |  | *Sargassum wightii* | Arg403, Glu406, Asn417, Tyr453, Ser49, Leu455, Tyr495, Ser494, Tyr501, His505 | LD50 (mg/kg) 5000 | [25] |
| *phloretin* | -6.3 |  | | Tyr501, Ser496, Tyr453, Arg403, Tyr495, Phe497, Thr500, Gly50 | LD50 500 | |
| *Naringin* | -7.5 |  | *Citrus medica Padina boergesenii* | Ser494, Asp38, Glu35, His34, Lys31, Glu75, Gln76 | NA | [45] |

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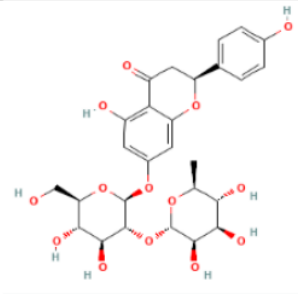
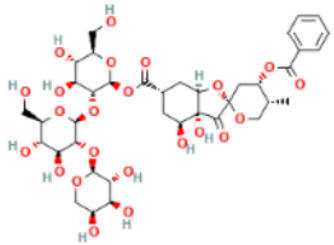
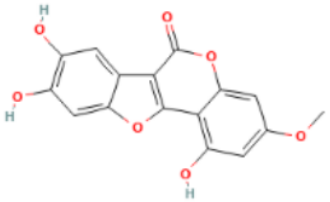
| | | | | | | |
|---|---|---|---|---|---|---|
| *Phyllaemblicin C* | -9.1 |  | *Phyllanthus emblica* (Amalaki) | *Tyr453, Gln496, Gln498, Asn501, Tyr449, Ser494, Gln493, Gly496, Thr500, Tyr505, Phe497, Arg403, Tyr495, Leu455, Gln493, Lys417* | 11.0 mM | [46] |
| *Cinnamtannin B1* | -9.0 |  | *Cinnamomum zeylanica* (Tvak) | Arg403, Arg453, Gly502, Gly496, Gln498, Ser494. Gln406, Gln493, Tyr505, Asn501, Tyr495, Tyr449, Lys417, Phe497 | 32.9 mM | |
| *Wedelolactone* | -7.4 |  | *Coumarins* | Tyr449, Ser494, Arg493, Leu452, Phe49 | LD50 2.41 mol/kg | [37] |

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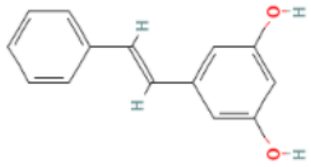
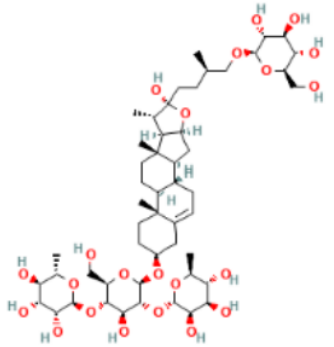
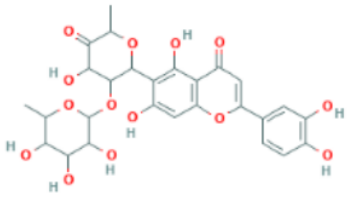
| | | | | | | |
|---|---|---|---|---|---|---|
| *Pinosylvin* | -7.0 |  | *Pinus sylvestris, Pinus densiflora*) | Phe342, Leu368, Phe375 | NA | [39] |
| *Protodioscin* | -10.77 |  | *Carica papaya* L. | Leu167, Pro168, Gly170, Phe171, Thy172, Ala173, Pro73, Ile74, Thr76, Gln83, Thr135 | NA | [42] |
| *Maysin and* | -7.5 |  | *C. cujete* | Asp461, Ser655, Val651, Asp40, Lys156, Asp461, Asp185, Ile158, Asp40, Lys156 | LD50 5000 | [47] |

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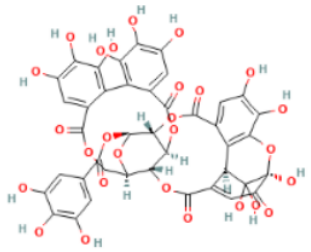
| | | | | | |
|---|---|---|---|---|---|
| *Geraniin* | -7.5 |  | Asn157, Pro220, Asp461, Ile158, Lys156 | Asp40, Lys652, Asp185, Asp40, | LD50 300 IC50 4.2 µM[48] |

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# Phytochemicals as a potential inhibitor of Spike Protein of SARS-CoV-2 Omicron Variant

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