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REVIEW: PHYTOCHEMICALS AS INHIBITORS OF THE SPIKE PROTEIN OF OMICRON VARIANT SARS-COV-2

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ABSTRACT

Background: More than 50 mutations have been found in Omicron variant 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 focuses on the uniqueness of SARS-CoV-2 Omicron variants and 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. **Results:** Protodioscin and landomycin A are the most potential phytochemical inhibitors against spike protein, with binding energy of -10.77 kcal/mol and -10 kcal/mol, respectively.
Keywords: *in silico, molecular docking, herbals phytochemical, spike glycoprotein, omicron*

INTRODUCTION

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

The SARS-CoV-2 undergoes mutations that produce several new strains. For surveillance and research purposes, the WHO has classified the strains into four categories: variants of high consequences (VOHC), those of concern (VOC), those of interest (VOI), and those under monitoring (VUM). Among these variants, VOC is linked to high disease severity (high hospitalization and mortality), high transmissibility, pathogenicity, immunologic and vaccine evasion, and poor detectability in diagnostics. Therefore, VOC has emerged as the variant 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]. The Omicron variant has higher transmissibility and resistance toward vaccines and antibodies than other types. 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 years old who are unvaccinated[4,6].

METHODS

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 (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).

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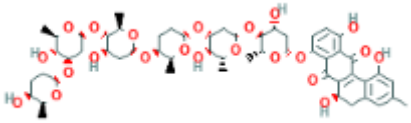
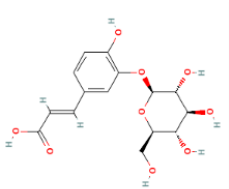
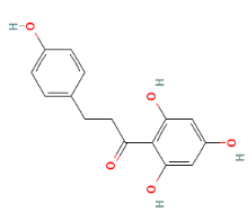
Table 1. Phytochemicals that are potential against spike protein of Omicron variant SARS-CoV-2

Phytochemicals	Binding energy *(kcal/mol)*	Chemical structure	Natural sources	Binding site	IC50 or LD50	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 = 5 g/kg	[25]
Phloretin	-6.3			Tyr501, Ser496, Tyr453, Arg403, Tyr495, Phe497, Thr500, Gly50	LD50 = 0.5 g/kg	[25]

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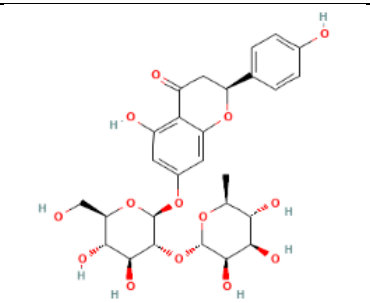
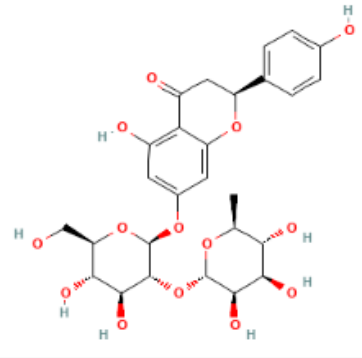
Naringin	-7.5		*Citrus medica Padina boergesenii*	*Ser494, Asp38, Glu35, His34, Lys31, Glu75, Gln76*	NA	[29]
Phyllaemblicin C	-9.1		*Phyllanthus emblica* (Amalaki)	*Tyr453, Gln496, Gln498, Asn501, Tyr449, Ser494, Gln493, Gly496, Thr500, Tyr505, Phe497, Arg403, Tyr495, Leu455, Gln493, Lys417*	IC50 = 11.0 µM	[34]

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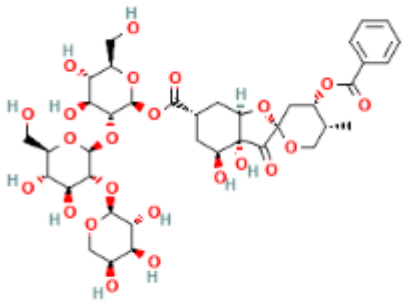
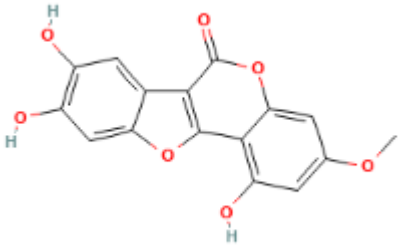
Cinnamtannin B1	-9.0		*Cinnamomum zeylanica* (Tvak)	*Arg403*, *Arg453*, *Gly502*, *Gly496*, *Gln498*, *Ser494*. *Gln406*, *Gln493*, *Tyr505*, *Asn501*, *Tyr495*, *Tyr449*, *Lys417*, *Phe497*	IC50 = 32.9 µM	[35]
Wedelolactone	-7.4		*Coumarins*	Tyr449, Ser494, Arg493, Leu452, Phe49	LD50 = 2.41 mol/kg	[38]

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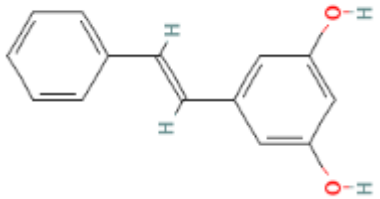
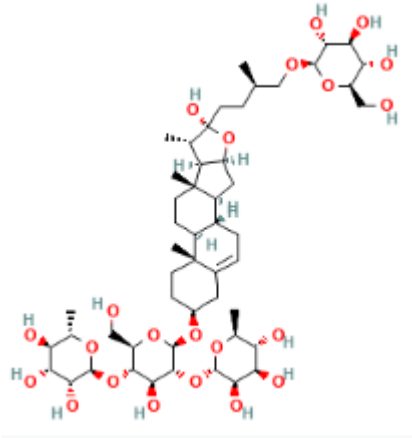
Pinosylvin	-7.0		*Pinus sylvestris*, *Pinus densiflora*)	Phe342, Leu368, Phe375	NA	[40]
Protodioscin	-10.77		*Carica papaya* L.	Leu167, Pro168, Gly170, Phe171, Thy172, Ala173, Pro73, Ile74, Thr76, Gln83, Thr135	NA	[43]

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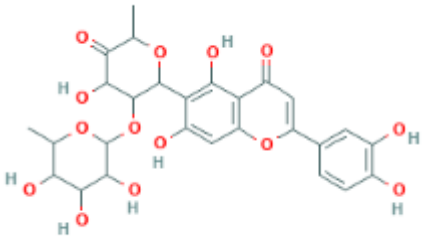
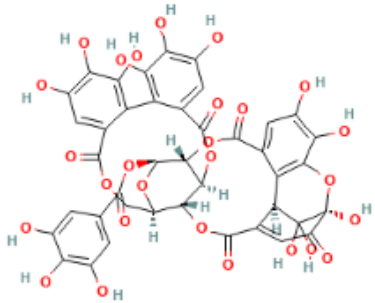
Maysin	-7.5		*C. cujete*	Asp461, Ser655, Val651, Asp40, Lys156, Asp461, Asp185, Ile158, Asp40, Lys156	LD50 = 5 g/kg	[45] [45] [47]
Geraniin	-7.5			Asn157, Asp40, Pro220, Lys652, Asp461, Asp185, Ile158, Asp40, Lys156	LD50 = 300 mg/kg IC50 = 4.2 µM	

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Structure of SARS-CoV-2

The SARS-CoV-2 genome is the largest positive-single-stranded RNA virus (29.9 kb) belonging to the Coronaviridae family[4]. One-third of its genome encodes four structural proteins, which are 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]. The other two-thirds comprise ORF1a and ORF1b, that were translated into polyproteins 1a (pp1a) and 1b (pp1ab). The polyproteins are further split into 16 non-structural proteins (nsp), nsp 1–11 from pp1a and nsp 12–16 from pp1ab[3,4] (Figure 1).

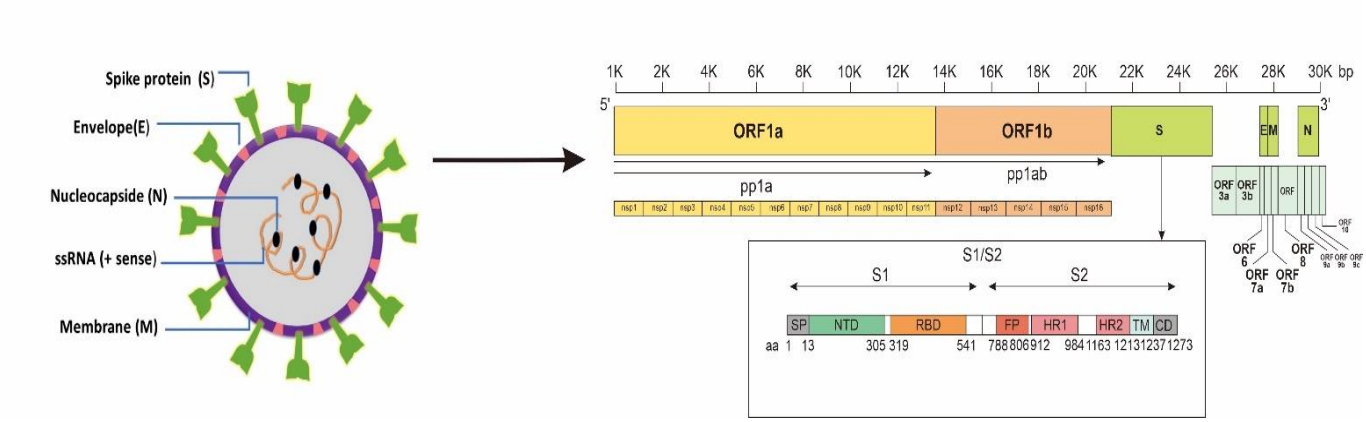

Figure 1. Genomic structure of SARS-CoV-2

Spike protein (S), which is involved in receptor recognition, viral attachment, and membrane fusion, consists of 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 the translation of host protein. Nsp1 mediates RNA replication, processing, and mRNA degradation. Nsp2 modifies signaling 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 as an ssRNA-binding protein and Nsp10 is involved in the mRNA's methylation. Coronavirus replication and transcription require Nsp12, also called RNA-dependent RNA polymerase (RdRp). Nsp13 participates in transcription and replication by binding to ATP via its zinc-binding domain. Nsp14, a domain of an exoribonuclease, served as the proofreader. The endoribonuclease activity in Nsp15 is dependent on Mn^{2+}. Finally, Nsp16 is an enzyme that methylates 2'-O-ribose[8].

Pathogenesis and entry process of the virus

Spike proteins (S proteins) facilitate coronavirus entry into host cells. The spike protein binds to Angiotensin-converting enzyme-2 (ACE2) receptor, which resides on the surface of human cells. Host proteases cleave the trimeric spike protein into two subunits during infection, leaving the N- and C-terminal S1 and S2 regions intact. The RBD of S1 is responsible for ACE2 receptor recognition and contact, while S2 fuses with host cell membranes. The interplay between S proteins and the ACE2 receptor allows the viral RNA to enter the host cell cytoplasm, release the genomic material, and initiate 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

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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 onset of the replication cycle will occur[7].

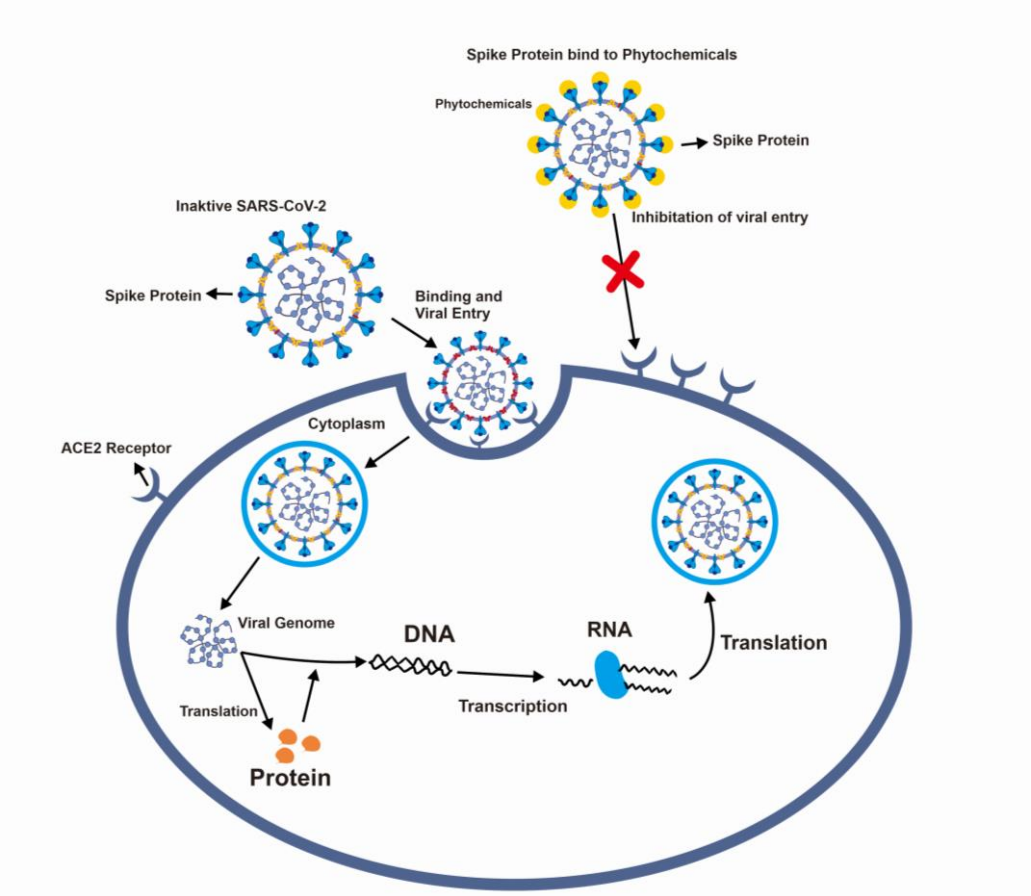

Figure 2. Phytochemicals (colored yellow) can inhibit viral entry to the host cell by binding to the S protein and thus blocking the recognition of the ACE2 receptor.

RBD-ACE2 Complex

Spike protein 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 the human ACE2 (hACE2) receptor can recognize viral cells. Therefore, RBDs are often designated as therapeutic targets and vaccine candidates. The trimeric spike glycoprotein extends 15 nm beyond the virus particle to identify hACE2 throughout the viral infection phase[10]. The spike protein has two conformational modes (open and closed); NTD and RBD are responsible for this conformational flexibility. Spike protein in the closed RBD conformation cannot bind to the ACE2 receptor. The down or closed conformation, sometimes called the perfusion state, is a stable shape in which the RBD is surrounded by NTD, limiting the engagement of the receptor-binding site with the ACE2 receptor. In contrast, the open conformation is less stable, in which 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 pathogenic mechanisms of SARS-CoV-2[11].

Viral cell entrance and membrane fusion are both facilitated by the S2 subunit. A small non-polar fragment called S2 FP, mainly made of the amino

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acids Gly and Ala, may interact with the coronavirus membrane. The 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 initiate 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 allows the fusing process. The S2 TM and CP domains assist the S protein's tethering to the host cell[7].

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

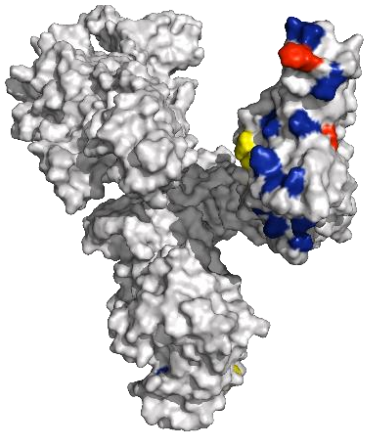

Figure 3. Schematic representation of Spike protein of SARS-CoV-2 (PDB ID: 7Z3Z). Mutations on the S protein of BA.1-BA.4/5 Omicron were shown in color. Blue: mutations BA.1-BA.4/5, yellow: mutations BA.2 and BA.4/5, red: mutations BA.4/5.

Thirty amino acid changes, six amino acid deletions, and three amino acid insertions exist in Omicron compared to the 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. The deletion mutations occur in three positions: H69/V70 (del 69-70), G142/V143/Y144 (del 142-144), and N211 (del 211) and lastly, three amino acids (E, P, E) inserted in positions 214 (214EPE)[3,12]. Among these mutations, 15 residues (denoted in bold) are important mutations that improve the affinity of S protein towards ACE2, increasing transmissibility. Additionally, 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. Mutations of the spike protein among omicron variants varied: 39 mutations occurred in BA.1, 40 mutations in BA.1.1, 31 mutations in BA.2, 34 mutations in BA.3, and 36 mutations in BA.4/5. Although the BA.4/5 spike protein contains additional mutations at amino acids H69/V70, L452R, F486V, and R498Q, it still shares certain amino acids with other omicron variants[13]. H69/V70 deletion in the spike protein of SARS-CoV-2 allows the virus to evade the immune system. A variant with this kind of mutation was considered the "hidden" version because the H69/V70 deletion is connected to S gene target failure (SGTF), which prevents it from being recognized by specific diagnostic tools that target the S gene[3,13].

Antibody escape is linked to mutations in L452R and F486V. The L452R/Q mutation reduced the virus's polyclonal and monoclonal antibody neutralization susceptibility. A higher affinity for the human ACE2 receptor is also linked to the L452R mutation[3,13]. The reduced antibody-neutralizing activity allows the virus to evade antibodies generated by RBD-targeted vaccine[12,13]. Three regions of S1 are the targets of antibodies; the NTD[14,15], the region near ACE2 receptor binding, and

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specific areas in the RBD that do not implicate the binding of ACE2[12]. Antibodies mainly target the first two regions to stop S protein from interacting with ACE2 on host cells, preventing infection[3].

Phytochemical therapy against SARS-CoV-2

The production of vaccines, the repurposing of existing drugs, and the production of active substances as novel antivirals are among the research being conducted 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 computational power to predict how two molecules will interact and estimate the binding energy of test compounds to their biological target [18,19]. Potential phytochemical compounds against SARS-CoV-2 based on several studies were summarized in Table 1.

Landomycin A

A particular angucycline antibiotic called landomycin was discovered in *Streptomyces* species such as *Streptomyces fradia* and *Streptomyces cyanogenus*[20]. Landomycin A, characterized by four tetracyclic ring skeletons with six saccharide residues attached, is often found in Asian honey and *Apis cerana*. Landomycin A has a potent anticancer effect by inducing apoptosis of 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. Landomycin A stabilizes spike protein and ACE2 receptor interaction through the hydrogen bond of 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 signalings 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, B, and 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 contain the secondary metabolism polyphenol known as caffeine acid, including vegetables, potatoes, carrots, olives, coffee beans, fruits, tea, and medicines like propolis. Phenolic acids and their derivatives exhibit anti-inflammatory, anti-oxidative, and anticarcinogenic properties. 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' defense systems against pests and diseases through the inhibitory effects mechanism. In addition, it protects plant leaves against ultraviolet B (UV-B) radiation. Studies on caffeic acid and its derivatives have shown a wide range of beneficial 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 Omicron spike protein has a binding affinity of -6.4 kcal/mol. Caffeic acid hexoside interacts with the RBD of the spike protein through hydrogen bonds of the following residues: Arg403, Glu406, Asn417, Tyr453, and Ser496. The interaction between caffeic hexoside and residues Asn417, Ser496, Tyr501, and His505 of the RBD inhibits the further interaction of S protein towards the ACE2 receptor. Therefore, caffeic acid hexoside is 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 through several mechanisms, including slowing tumor development and inhibiting lung

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JKD (DMJ), Volume 12, Number 5, September 2023 : 301-316

tumor 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 properties[26].

Phloretin interacted with Tyr501, Ser496, and Tyr453 of spike's RBD through the hydrogen bond and with Tyr501 and His505 of RBD via the π-stacking interaction. The calculated binding energy was -6.3 kcal/mol. Ser496, Tyr501, and His505 were responsible for the interaction between the ACE2 receptor and the RBD of the Omicron's spike protein. Phloretin can activate transcription factors that activate pro-antioxidant gene expression, thus improving the enzymatic antioxidant defense system. Phloretin can also be a penetration enhancer of administered drugs due to its increased fluidity toward binding biological membranes. Lastly, the predicted toxicity class for phloretin was IV, indicating 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, oral cavity, and small intestine, often converting it into naringenin. The bioavailability of naringin and naringenin may be reduced in the presence of milk protein and other dietary components. Naringin inhibits cell growth and promotes apoptosis via the extracellular signal-regulated kinase (ERK) pathway, thus exhibiting 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 towards S494, D38, E35, H34, K31, E75, and Q76 of the Omicron's spike protein with an affinity of -7.48 kcal/mol[29]. Naringenin also binds to His164, Glu166, Asp187, and Thr190 main protease (3CLpro) of SARS-CoV-2 with binding energy −7.99 kcal/mol and blocks its activity[30]. Moreover, it also binds to the ACE2 receptor with a binding energy of −6.05 kcal/mol, with the essential binding sites Pro146, Leu143, and Lys131. Furthermore, naringenin acts against SARS-CoV-2 by lowering inflammatory markers, such as TNF-, IL-1, IL-10, and IFN-γ in COVID-19 patients[31].

Phyllaemblicin C

Phyllaemblicin can be found in the roots of *Phyllanthus emblica*[20] and demonstrates antiviral properties against coxsackievirus B3[32] and SARS-CoV-2 by inhibiting the RdRp[33]. 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 ACE2 receptor may be blocked by phyllaemblicin C, preventing the virus from entering the host cell[34]. Phyllaemblicin C and phyllaemblicin B can be found in Indian gooseberry. Phyllaemblicin C had the highest binding affinity towards spike and Mpro protein targets[35].

In silico study of 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 Omicron's spike protein (binding energy -9.1 kcal/mol). Phyllaemblicin C also interacted with residues Y449, Y453, Q493, G496, Q498, N501, and Y505 of RBD, which are important for ACE2 receptor recognition [35]. Phyllaemblicin C also binds to Mpro SARS-CoV-2, which form hydrogen bond to N142, Q189, E166, H164, H163, P168, H41 and other non-covalent interaction with L167, Q192, M165, C145, Y54, M49 with affinity -9.7 kcal/mol.

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 cinnamontannin B1 exhibited pro-apoptotic effects, antioxidant protection, platelet aggregation, and cyclooxygenase-2 (COX-2) inhibition. Through the uptake 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 potentially serves as an adjuvant to enhance colon cancer prognosis[36].

JURNAL KEDOKTERAN DIPONEGORO
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JKD (DMJ), Volume 12, Number 5, September 2023 : 301-316

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 binds to E166, N142, T190, P168, F140, and Q189 Mpro with a binding affinity of -8.385 kcal/mol[35]. Cinnamontannin B1 can bind both RBD spike protein and Mpro SARS-COV-2.

Wedelolactone

Wedelolactone can be found in the fresh leaves of *Wedelia sp* and *Eclipta sp.* Wedelolactone has several pharmacological effects, such as anticancer, anti-inflammatory, antidiabetic, antiobesity, and organ protection[37]. Wedelolactone, from *Wedeliaccalendulacea*, is bound towards crucial binding sites of Omicron's spike protein. It interacts through hydrogen bonding 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. The LD50 wedelolactone is 2.41 mol/kg, indicating minimal lethal impacts[38].

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, neuroprotective, and antiallergic properties. 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*[39]. Pinosylvin acts on nuclear factor erythroid-related factor 2 (Nrf2), which regulates gene expression related to oxidative stress homeostasis[39]. A docking study on pinosylnin docking on Omicron's spike protein revealed its affinity to be -7.0 kcal/mol with the apparent binding site involving residues Phe342, Leu368, Phe375 RBD (PDB ID 7QNW)[40].

Protodioscin

Protodioscin is a bioactive compound that alters free testosterone levels and sperm characteristics. It is commonly found in *Tribulus terrestris* and *Trigonella foenum-graecum*. Protodioscin extract may prevent the proliferation of HL-60 in human leukemic cells[41]. In addition, methyl protodioscin (MPD) may inhibit tumor development of pancreatic cancer cell lines. The inhibition of tumor development occurred via apoptosis stimulation and cell proliferation inhibition. MPD also controls aerobic glycolysis, which supplies energy and nutrients to malignant cells, by blocking the Akt1/c-Myc axis[42].

A molecular docking study shows Protodioscin's ability to bind with multiple SARS–CoV–2 proteins. The target protein includes the nucleocapsid's RNA binding domain, 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 (N protein) with binding energy -13.83 kcal/mol. Protodioscin also bind to Asn496, Asn497, Lys500, Lys577 RdRp with binding energy of –11.62 kcal/mol. Protodioscin shows hydrogen bond interaction with residues Leu167, Phe171 and Thr135 of the N protein and several others interaction with Pro168, Lys169, Gly170, Tyr172, Ala173, Pro73, Ile74, Thr76 and Gln83 of the N protein. Protodioscin also interacted with RdRP via residues Asn496, Asn497, Lys500, and Lys577 with a binding energy of -11.62 kcal/mol. It also targeted the Main protein (Mpro) by binding to residues Thr24, Met165, Glu166, Leu167, Pro168, Gln189, and His41 with a binding energy of -13.19 kcal/mol[43].

The previous docking study reported that the protodioscin formed the strongest binding affinity with Wuhan~~'s~~ spike protein, followed by Delta and Omicron. Similar to 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 a binding energy of -11.57 kcal/mol. Finally, protodioscin bind to S protein of Omicron with residues Asp405, Tyr453, Ser494,

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JKD (DMJ), Volume 12, Number 5, September 2023 : 301-316

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 with spike protein may prevent the entry and fusion of SARS–CoV–2 [43].

Maysin

Maysin can be found in *Zea mays* (corn) and *Crescentia cujete*. Previous research on maysin has shown 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[44]. 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 (-8.4 kcal/mol) and Omicron (-7.5 kcal/mol)[45].

Geraniin

Geraniin can be found in *Euphorbia makinoi*, *Macaranga tanarius*, *Elaeocarpus sylvestris*, *Zingiber officinale*, and *Nephelium lappaceum (rambutan)*[20]**.** Geraniin from rambutans' rind extract has potent antioxidant properties with minimal cytotoxicity[46]. Docking of geraniin on spike protein Wild type (WT) and Omicron variant generates binding energy of 7.1 kcal/mol and -7.5 kcal/mol, respectively. This result was much better than zafirlukast, the standard drug[45]. Another study showed that docking of geraniin on the spike protein/hACE2 receptor complex involved the formation of eight hydrogen bonds involving Arg403, Tyr449, Tyr453, Gln493, Ser494, Gln498, Gly502, and Tyr505. Additionally, four van der Waals interactions were observed with Tyr495, Gly496, Thr500, and Asn501, along with one pi-pi interaction involving Tyr505. The docking analysis revealed that geraniin has a higher affinity for the spike protein compared to the hACE2 receptor, as evidenced by a more stable binding interaction. The root mean square deviation (RMSD) between geraniin and the spike protein was around 0.1–1.0 nm. Moreover, the ELISA experiment showed that geraniin could impede the interaction between the spike protein receptor-binding domain (RBD) and the human angiotensin-converting enzyme 2 (hACE2) receptor. The findings demonstrated that geraniin had a significant inhibitory impact on the interaction between the spike protein receptor-binding domain (RBD) and the human angiotensin-converting enzyme 2 (hACE2) receptor, equivalent to the efficacy of the neutralizing antibody targeting the spike protein[44]. Geraniin inhibits interaction RBD and hACE2 with LD50 300 mg/kg[45] and IC50 4.2 µM[47].

CONCLUSION AND FUTURE PERSPECTIVE

Eleven probable phytochemical plants are potential inhibitors against the 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

Tuti Ratnasari: Conceptualization, data curation, methodology and validation, writing and editing.
Faizah Fulyani: Conceptualization, methodology and validation, writing and editing, project supervision.
Endang Mahati: Methodology and validation, writing and editing, project supervision.

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