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Synthesis and structure–activity relationship study of saponin-based membrane fusion inhibitors against SARS-CoV-2

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ABSTRACT

We previously discovered that triterpenoid saponin platycodin D inhibits the SARS-CoV-2 entry to the host cell. Herein, we synthesized various saponin derivatives and established a structure–activity relationship of saponin-based antiviral agents against SARS-CoV-2. We discovered that the C3-glucose, the C28-oligosaccharide moiety that consist of (−3)-β-α-Xyl-(1→4)-α-β-Rham-(1→2)β-α-Ara-(1→ ) as the last three sugar units, and the C16-hydroxyl group were critical components of saponin-based coronavirus cell entry inhibitors. These findings enabled us to develop minimal saponin-based antiviral agents that are equipotent to the originally discovered platycodin D. We found that our saponin-based antiviral agents inhibited both the endosomal and transmembrane protease serine 2-mediated cell surface viral entries. Cell fusion assay experiment revealed that our newly developed compounds inhibit the SARS-CoV-2 entry by blocking the fusion between the viral and host cell membranes. The effectiveness of the newly developed antiviral agents over various SARS-CoV-2 variants hints at the broad-spectrum antiviral efficacy of saponin-based therapeutics against future coronavirus variants.
distinct pathways (Fig. 1). The first is the endosomal entry mechanism. Dynamin and clathrin mediate the internalization of endosomal vesicles that further mature to endosomes and lysosomes. Acidification of the internal endosomes triggers the activation of cysteine protease cathepsin L for the proteolysis of S2' cleavage site and exposure of the S2 domain for subsequent membrane fusion [14]. The second non-endosomal pathway is based on the cell surface entry mechanism. Upon binding of RBD to ACE2, the host cell protease, transmembrane protease serine 2 (TMPRSS2) cleaves the S2' site at the cell surface and liberates the S2 domain for consequent membrane fusion [15,16]. Notably, chloroquine and hydroxychloroquine had emerged as potential drugs due to their ability to elevate the lysosomal pH and hence inactivate cathepsin L during endosomal viral entry [17,18]. On the other hand, TMPRSS2 inhibitors such as camostat and nafamostat have been investigated as potential drugs for COVID-19 due to their ability to block the non-endosomal cell surface viral entry [19]. However, these drugs have shown limitations as they can block only one of two viral entry pathways, respectively [19,20].

The last step of viral entry for both endosomal and non-endosomal pathways involves membranes fusion. After protease-mediated (either cathepsin L or TMPRSS2) S2' cleavage (pre-fusion conformation), the exposed S2 domain undergoes extensive conformational changes and unfolded heptad repeat 1 (HR1) domain drives fusion peptide insertion into the host cell membrane (extended conformation) [21]. Folding back of HR2 places the fusion peptide and transmembrane segments at the same end of the molecule to proximity leading to the hemifusion state, and eventually resulting in the fusion pore [22]. Markedly, the S2 domain is one of the most conserved motifs among various coronaviruses. Hence, S2 domain-mediated membrane fusion is an attractive intervention point for the development of broad-spectrum antiviral therapeutics [11].

Recently, we reported that platycodin D (1), a saponin-type natural product isolated from Platycodon grandiflorum, prevents both endosomal and cell-surface SARS-CoV-2 infection and proposed the inhibition of membrane fusion as a mechanism of action [23]. Molecular modeling of membrane-inserted platycodin D (1) in an explicit lipid bilayer model predicted the orientations of the partly embedded platycodin D (1) in which the hydrophobic triterpenoid backbone is located within the

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**Fig. 1.** Saponins as promising antiviral agents against SARS-CoV-2 that operate via inhibition of viral entry.
membrane in an analogous manner to cholesterol (Fig. 1B) [24], whereas hydrophilic sugar moiety sticks out of the lipid bilayer. The sugar moiety attached at C28 creates a protrusion on the surface of the membrane that might hinder the membrane fusion. Even though we could not provide direct evidence that platycodin D (1) blocks the S2 protein-mediated membrane fusion, we unearthed the potential of saponin compounds as effective broad-spectrum antiviral agents.

Building on these initial findings, we envisioned identifying structural features within saponin that are responsible for the molecular function and corroborating the mode of action, namely the inhibition of...
membrane fusion. We were particularly interested in elucidating the role of C3 and C28 sugar moieties and finding key oxidations in the triterpenoid backbone responsible for the therapeutic efficacy. Eventually, we aimed to develop more potent antiviral agents than the originally discovered platycodin D (1). Herein, we delineate our discoveries enabled by a total synthetic approach to saponin-derivatives that answered all these key questions. We show that our newly developed potent saponin-based anti-SARS-CoV-2 agents act by inhibiting the viral and host cell membranes fusion event.

2. Results and discussion

Inspired by seminal studies by the Gin group and Wang group who developed a minimal vaccine adjuvant based on saponin natural product QS-21 via chemical synthesis [25–27], we embarked on a chemical synthetic approach to design saponin-derivatives that can answer the aforementioned key questions related to the SAR of saponin-based coronavirus entry inhibitors. For the triterpenoid skeleton, we initially utilized commercially available oleanolic acid (2) [28]. We envisioned that the minimal oxidative decorations of 2 only at C3 and C28 would enable facile SAR studies related to the C3 and C28 glycosylations. To investigate the SAR of the sugar moiety, various platycodin D-inspired protected sugar donors ranging from monomeric saccharide 5 to pentameric saccharide 7 were synthesized (See the supporting information for details). Synthesis of 10, devoid of C3 glucose moiety, was achieved via a synthetic sequence that consists of C3-selective protection of oleanolic acid (2), C28 glycosidation with sugar donor 6, and global deprotection (Scheme 1). C3-glucosylated oleanolic acid-based saponin derivatives with different saccharide donors at C28 (11–15) could be synthesized via C28-selective allylative protection of 2, C3-glycosidation with glucose donor 4 [30], C28 allyl deprotection (and subsequent global deprotection in case of compound 11), C28-glycosidation, and final global deprotection.

The first batch of compounds was tested on our previously developed SARS-CoV-2 S-pseudotyped lentiviruses (pSARS-CoV-2 with pHHR-CMV-firefly luciferase, psPAX2 packaging, and SARS-CoV-2 S plasmids) entry assay [23]. For the initial assay, H1299 cells expressing ACE2 (ACE2⁺, the assay system for the endosomal viral entry) were used. The cells were treated with saponin derivatives and the supernatant containing pSARS-CoV-2 virus particles. After 24 h of incubation, pSARS-CoV-2 entry efficiency was quantified by measuring firefly luciferase activity. Our pSARS-CoV-2 cell entry assay revealed that the C3-glucose was essential for the cell entry inhibition exemplified by the lack of efficiency of compound 10 (IC₅₀ > 10 µM) devoid of the C3 saccharide (Fig. 2A, entry 1). We also found that the length and composition of the C28 saccharide were critical for the antiviral activity of the saponin derivatives. 11 with no saccharide moiety at C28 and 12 with a single arabinose moiety at C28 did not show any notable inhibition of pSARS-CoV-2 cell entry (IC₅₀ > 10 µM for both compounds, Fig. 2A, entries 3 and 4). 13 with xylose-based disaccharide connected via a β-1,3-glycosidic bond at C28 and 15 with xylose-based tetrasaccharide connected via β-1,3-glycosidic bonds at C28 showed only moderate viral entry inhibition with IC₅₀ of 7.59 and 8.84 µM, respectively (Fig. 2A, entries 5 and 6). Markedly, saponin derivative 14 which was synthesized by linking glucose at C3 and tetrasaccharide 6 to C28 showed comparable viral entry inhibition (IC₅₀: 1.33 µM, Fig. 2A, entry 6) to platycodin D (1). It is worthwhile to note that the last three sugar units of the C28 tetrasaccharide in 14 ((−→)-β-n-Xyl-(1→4)-α-L-Rham-(1→2)-β-n-Ara-(1→)) were identical to those in platycodin D (1).

With an ultimate goal to develop a minimal saponin coronavirus membrane fusion inhibitor based on platycodin D (1), we next turned our attention to additional oxidations at the triterpenoid skeleton. Compared to the triterpenoid framework of oleanolic acid, platycodin D (1) has additional hydroxyl groups at C2, C16, C23, and C24. Hence, we sought to investigate the pharmaceutical importance of these hydroxyl groups. Practically, commercial availability of echinocystic acid (1) has additional hydroxyl groups at C2, C16-hydroxyl group compared to oleanolic acid (2) led us to start the second phase synthetic campaign using it as the starting

### A. IC₅₀ for pSARS-CoV-2 entry inhibition to ACE2⁺

| Entry | Compound | IC₅₀ in ACE2⁺ (µM) |
|-------|----------|-------------------|
| 1     | Platycodin D (1) | 1.03 |
| 2     | 10       | > 10              |
| 3     | 11       | > 10              |
| 4     | 12       | > 10              |
| 5     | 13       | 7.59              |
| 6     | 14       | 1.33              |
| 7     | 15       | 8.84              |
| 8     | 16       | > 10              |
| 9     | 17       | 3.86              |
| 10    | 18       | > 10              |
| 11    | 19       | 0.68              |
| 12    | 20       | 0.65              |
| 13    | 21       | > 10              |

### B. Summary of the SAR studies in ACE2⁺

![Fig. 2. Structure-activity relationship of saponin-based ACE2⁺ entry inhibitors against pSARS-CoV-2.](image)
material. Using orthogonal protection/deprotection conditions for C3-, C16-hydroxyls and C28-carboxylate and their selective glycosylation, we synthesized echinocystic acid-based saponin derivatives 16–21 (Scheme 1). pSARS-CoV-2 cell entry inhibition of these compounds was investigated using the aforementioned ACE2− cells. Compound 16, devoid of the C3-sugar unit, did now show any viral entry inhibition activity consistent with results from compound 10, also lacking the C3-glucose moiety. Compounds 17 with the benzylation C3 hydroxyl group was designed to enhance the hydrophilicity around the C3 site and increase its energetic stability within the lipid bilayer (Fig. 1B). However, compound 17 did not show any notable bioactivity against viral entry. Compound 18, decorated with glycosylations at both C3 (derived with glucose donor 4) and C28 (derived with tetrasaccharide donor 6) and acetylation at C16, did not affect the pSARS-CoV-2 cell entry. To our delight, however, when we unmasked the C16 acetyl group, the resulting compound 19 inhibited the cell infection by pSARS-CoV-2 with an IC_{50} of 0.64 µM. Importantly, 19 is natural product asterlingulatoside D originally isolated from the whole plant of Aster lingulatus, which has been traditionally used for the treatment of fever, cold, tonsillitis, snake bite, and bee sting [31]. After identifying compound 19 which is a more potent coronavirus entry inhibitor than platycodin D (1), we synthesized its derivative 20 with an additional xylose moiety at the C28 oligosaccharide group. Compound 20 showed a comparable IC_{50} of 0.65 µM against pSARS-CoV-2 cell entry. Saponin 21, designed to enhance metabolic stability by reducing the C28 ester moiety to an ether group did not show any inhibitory effect probably due to a drastic conformational distortion [27].

Two hit compounds 19 and 20, the most potent inhibitors of pSARS-CoV-2 entry in ACE2−, were then tested using H1299 cells that over-express both ACE2 and TMRPSS2 (ACE2/TMRPSS2−). ACE2/TMRPSS2− was designed to probe the TMRPSS2-mediated cell surface entry of pSARS-CoV-2 (Fig. 1A). Pleasantly, both 19 and 20 inhibited the ACE2/TMRPSS2− entry of pSARS-CoV-2 with IC_{50} of 0.65 and 0.61 µM, respectively (Fig. 3). These compounds showed ~2-fold higher antiviral efficiency than previously discovered platycodin D (IC_{50}: 1.34 µM). These results revealed that 19 and 20 block both the endosomal and the TMRPSS2-mediated cell surface entry pathways of the coronavirus. Hence, we learned that compounds 19 and 20 are targeting a common step in the endosomal and the TMRPSS2− mediated cell surface entry pathways. Two possible events that are common to both entry pathways are: 1) the binding of the S protein to ACE2 and 2) the fusion between viral and host cell membranes. In our previous study, we showed that platycodin D (1) does not inhibit the interaction between the S protein and ACE2 [23]. Considering the structural relevance between platycodin D (1) and 19/20, we speculated that 19 and 20 are blocking the coronavirus entry to the cell by inhibiting the fusion between viral and host cell membranes.

To test our membrane fusion inhibition hypothesis, we established a cell fusion assay that consists of HEK293T cells overexpressing S protein (Spike-HEK293T) labeled with GFP and H1299 expressing ACE2/TMRPSS2− (ACE2/TMRPSS2−-H1299) labeled with mRuby as a means to observe direct cell-to-cell fusion between the two cell lines and its inhibition by our newly developed saponin-based compounds. Time-lapse microscopy revealed that Spike-HEK293T gradually moves close to ACE2/TMRPSS2−-H1299 and rapidly fuses with ACE2/TMRPSS2−-H1299 once the contact interaction is initiated. The fused cells displayed S proteins on their surface which caused subsequent fusions with neighboring ACE2/TMRPSS2−-H1299, eventually leading to multinucleated cells. Interestingly, when ACE2/TMRPSS2−-H1299 (labeled with mRuby) was pretreated with 19 and 20, respectively, and subsequently allowed to react with Spike-HEK293T (labeled with GFP), the cell-to-cell fusion event was inhibited (Fig. 4C). Importantly, pre-treatment of ACE2/TMRPSS2−-H1299 with 11, a compound that did not show any inhibition effects in our pSARS-CoV-2 entry assay in ACE2−, did not affect the fusion event (Fig. 4C).

For the quantitative determination of the heterologous cell fusion, Spike-HEK293T (1 × 10^{5} cells) and ACE2/TMRPSS2−-H1299 (2 × 10^{5} cells) were allowed to react for 1 h and subsequently analyzed by flow cytometry (Fig. 4D). The results disclosed that most of GFP-positive Spike-HEK293T were fused with mRuby2-positive ACE2/TMRPSS2−-H1299, generating approximately 4% of double-positive hybrid cells. Control experiment with DMSO or compound 11 did not show any inhibition of cell fusions (Fig. 4D). However, compounds 19 and 20 significantly blocked the formation of hybrid cells, which was comparable to the control experiment in which we added GFP-positive HEK293T (no spike) to ACE2/TMRPSS2−-H1299. Hence, we learned that 19 and 20 are inhibiting the coronavirus entry into the host cells by blocking the S-mediated membrane fusion event. We finally studied the inhibitory effect of the newly synthesized saponin derivatives using viral infectious assay. Firstly, we tested the inhibitory effect of 19 and 20 against the ancestral SARS-CoV-2 in the monkey-derived Vero cells which show abundant expression of ACE2 but lack of expression of TMRPSS2 [23]. Consistent with results from the pseudo-viruses, 19 and 20 showed inhibition of SARS-CoV-2 infection with IC_{50} of 1.04 and 1.42 µM, respectively (Fig. 5A). Notably, 19 and 20 showed more potent inhibition of SARS-CoV-2 entry to the Vero cells than chloroquine (IC_{50}: 5.56 µM) and remdesivir (IC_{50}: 4.67 µM). The newly emerging SARS-CoV-2 variants carry mutations in genes that encode the S protein, leading to enhanced binding to ACE2. Because we showed that our saponin-based compounds block the membrane fusion which is a downstream event that occurs after the S-protein binding to ACE2, we hypothesized that our synthetic saponin derivatives would be effective against various SARS-CoV-2 variants regardless of their affinity to ACE2. Consistent with our hypothesis, compound 20 effectively inhibited the infection of Vero cells against various SARS-CoV-2 variants including alpha (B.1.1.7_UK, IC_{50}: 1.59 µM), beta (B.1.351_South Africa, IC_{50}:...
1.47 µM), gamma (P.1_Brazil, IC₅₀: 1.46 µM), delta (B.1.617.2_India, IC₅₀: 1.67 µM), and omicron (B.1.1.529_multiple countries, IC₅₀: 1.45 µM) variants (Fig. 5B). These results hint at the broad-spectrum antiviral efficacy of saponin-based therapeutics against forthcoming coronavirus variants. We then studied the inhibition of viral entry by compound 20 in A549-ACE2-TMPRSS2 cells that overexpress both ACE2 and TMPRSS2 using SARS-CoV-2-NLuc recombinant virus. Consistent with our biological activity data from the pSARS-CoV-2 system in ACE2/TMPRSS2⁺, 20 effectively inhibited the viral entry with an IC₅₀ of 2.01 µM (Fig. 5C). These observations corroborated that our newly developed saponin-based antiviral agents block both the endosomal and the TMPRSS2-mediated cell surface viral entry pathways.

Fig. 4. Compounds 19 and 20 block viral membrane fusion with the host cell membrane. (A) Schematic illustration of the SARS-CoV-2 S protein-mediated cell fusion. (B) Experimental timeline for cell fusion assay using time-lapse imaging. (C) Still images at different time points from time-lapse imaging of S-mediated cell fusion. (D) The fusion between Spike-HEK293T and ACE2/TMPRSS2⁺-H1299 was determined by counting the number of cells double-positive for GFP and mRuby by flow cytometry. H1299 cells expressing only GFP (no spike) were used for the control experiment. All compounds were used at the concentration of 10 µM. The data were representative of three independent experiments.
3. Conclusions

To sum up, we established a structure–activity relationship of oleanolic and echinocystic acid-based synthetic saponin derivatives against SARS-CoV-2. Our studies showed that the C3-glucose, the C28-polysaccharide that consists of \((\rightarrow 3)\)-\(\beta\)-D-Xyl-(1 \(\rightarrow\) 4)-\(\alpha\)-L-Rham-(1 \(\rightarrow\) 2)-\(\beta\)-D-Ara-(1 \(\rightarrow\) ), and the C16 free hydroxyl moieties were pivotal for the antiviral activity of saponin derivatives. These SAR studies identified...
two echinocystic-based synthetic saponins 19 and 20 that exhibit 2-fold potency against pSARS-CoV-2's cell entry into ACE-TMPRSS2 compared to the originally identified hit compound platycodin D. Our cell fusion assay experiment revealed that newly identified synthetic saponins 19 and 20 inhibit the membrane fusion between the coronavirus and host cells, the common downstream event for both endosomal and TMPRSS2-based cell surface viral entry pathways into the cell. Importantly, our structurally minimal synthetic saponins inhibited the membrane fusion of various SARS-CoV-2 variants, consistent with the conserved nature of the S2 domain which is the key protein during membrane fusion. These observations hint at the broad-spectrum antiviral efficacy of our saponin-based therapeutics that is not limited to SARS-CoV-2 but applicable to other impending coronaviruses.

4. Experimental

Materials and methods for biological assays, general procedure, materials, and instrumentalations for the synthesis of chemical compounds are provided in the Supporting Information. Detailed synthetic procedure, physical data, and copies of 1H and 13C NMR spectra of newly synthesized compounds are also provided in the supplementary materials.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

Tay Young Kim, C. Justin Lee, and Sunkyu Han conceived and designed the overall study. Youngho Jang, Tai Young Kim, C. Justin Lee, and Sunkyu Han analysed the data and wrote the manuscript with input from co-authors. Youngho Jang and Hyeonggeun Lim synthesized all compounds designed in this manuscript. Tay Young Kim performed all the SARS-CoV-2 pseudovirus-related experiments. Sangeun Jeon and Jinah Lee performed the authentic SARS-CoV-2 experiments under the supervision of Seungtaek Kim.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbior.2022.105985.

References

[1] C.-Y. Moira, R.-H. Xu, SARS: epidemiology, Respiratory 8 (Suppl) (2003) S9–S14, https://doi.org/10.1046/j.1440-1843.2003.00518.x.
[2] “Middle East respiratory syndrome coronavirus (MERS-CoV),” can be found under https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus-mers.
[3] “Coronavirus Disease (COVID-19) Situation Reports,” can be found under https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
[22] S. C. Chiliveri, J. M. Louis, R. Ghirlando, A. Bax, Transient lipid-bound states of spike protein heptad repeats provide insights into SARS-CoV-2 membrane fusion. Sci. Adv. 7 (2021) eabk2226. https://doi.org/10.1126/sciadv.abk2226.

[23] T.Y. Kim, S. Jeon, Y. Jang, L. Gotina, J. Won, Y.H. Ju, S. Kim, M.W. Jang, W. Won, M.G. Park, A.N. Pae, S. Han, S. Kim, C.J. Lee, Platycodon D, a natural component of Platycodon grandiflorum, prevents both lysosome- and TMPRSS2-driven SARS-CoV-2 infection by hindering membrane fusion, Exp. Mol. Med. 53 (2021) 956–972, https://doi.org/10.1038/s12276-021-00624-9.

[24] D.W. Sanders, C.C. Jumper, P.J. Ackerman, D. Bracha, A. Donlic, H. Kim, D. Kenney, I. Castello-Serrano, F. Douam, R.F. Padera, B.D. Levy, C. Ploss, SARS-CoV-2 requires cholesterol for viral entry and pathological syncytia formation, eLife 10 (2021), e65962, https://doi.org/10.7554/eLife.65962.

[25] P. Wang, Q. Dai, P. Thogaripally, F. Zhang, S.M. Michalek, Synthesis of QS-21-Based Immunoadjuvants, J. Org. Chem. 78 (2013) 11525–11534, https://doi.org/10.1021/jo402118q.

[26] A. Fernández-Tejada, E.K. Chea, C. George, N. Pillarsetty, J.R. Gardner, P.O. Livingston, G. Ragupathi, J.S. Lewis, D.S. Tan, D.Y. Gin, Development of a minimal saponin vaccine adjuvant based on QS-21, Nat. Chem. 6 (2014) 635–643, https://doi.org/10.1038/nchem.1963.

[27] A. Fernández-Tejada, D. S. Tan, D. Y. Gin, Development of Improved Vaccine Adjuvants Based on the Saponin Natural Product QS-21 through Chemical Synthesis. Acc. Chem. Res. 49 (2016) 1741–1756. https://doi.org/10.1021/acs.accounts.6b00242.

[28] T. B. Ayeleso, M. G. Matumba, E. Mukwevho, Oleumollic Acid and Its Derivatives: Biological Activities and Therapeutic Potential in Chronic Diseases. Molecules 22 (2017) 1915. https://doi.org/10.3390/molecules2211915.

[29] A. L. M. Morotti, K. L. Lang, I. Carvalho, E. P. Schenkel, L. S. C. Bernardes, Semi-Synthesis of new glycosidic triazole derivatives of dihydrocucurbitacin B. Tetrahedron Lett. 56 (2015) 303–307. https://doi.org/10.1016/j.tetlet.2014.11.049.

[30] K. Egusa, S. Kusumoto, K. Fukase, Solid-Phase Synthesis of a Phytoalexin Elicitor Pentasaccharide Using a 4-Azido-3-chlorobenzyl Group as the Key for Temporary Protection and Catch-and-Release Purification, Eur J. Org. Chem. 2003 (2003) 3435–3445, https://doi.org/10.1002/1096-0025(20030508)2003:3435<3445::AID-0035>3.0.CO;2-3.

[31] Y. Shao, C.-T. Ho, C.-K. Chin, O. Poobrasert, S.-W. Yang, G. A. Cordell, Asterlingsulatosides C and D, Cytotoxic Triterpenoid Saponins from Aster lingulatus. J. Nat. Prod. 60 (1997) 743–746. https://doi.org/10.1021/np970080t.