Scientific Research Publishing

Advances in Bioscience and Biotechnology, 2025, 16(3), 90-102
https://www.scirp.org/journal/abb
ISSN Online: 2156-8502
ISSN Print: 2156-8456

# Antiviral Activity of Natural Compounds Immuno Formula Shiban2/5 against SARS-CoV-2

**Abdulhameed Abdulridha Kodous Al Shaibani, Mohamed Taoubane Maallah, Abderahim Maallah***

Research Department, Shiban Pharma Inc., Laval, Canada
Email: *maallah@shibanpharma.com

**How to cite this paper:** Al Shaibani, A.A.K., Maallah, M.T. and Maallah, A. (2025) Antiviral Activity of Natural Compounds Immuno Formula Shiban2/5 against SARS-CoV-2. *Advances in Bioscience and Biotechnology*, **16**, 90-102.
https://doi.org/10.4236/abb.2025.163005

**Received:** February 8, 2025
**Accepted:** March 17, 2025
**Published:** March 20, 2025



## Abstract

SARS-CoV-2 poses a significant risk to global healthcare systems based on the recent worldwide COVID-19 pandemic. Spike proteins are the hallmark of SARS-Cov-2, which bind to ACE2 receptors that lead to cell and membrane fusion. To address and alleviate respiratory health issues, we at Shiban Pharma have developed a range of natural products derived from plant and herb extracts, recognized for their antiviral activity against SARS-CoV-2, such as propolis extracts. In this study, we are evaluating the effects of the immuno-formula Shiban 2 and Shiban 5 (IF 2/5) on the infection of airway epithelial cells (A549) and primary airway epithelial cell (PAEC) by SARS-CoV-2. The objective is to evaluate the effects of IF 2/5 and of a placebo on viral infection. Our *in vitro* data demonstrates that IF 2/5 inhibits SARS-CoV-2 replication in a dose-dependent manner. Moreover, the compounds in IF 2/5 exhibit synergy, as determined by the Bliss method and Bliss synergy score. The Bliss synergy model was applied to explore the interaction between Propolis and Tannic Acid in modulating SARS-CoV-2 infection inhibition. Finally, our IF 2/5 also displays anti-inflammatory effects on cytokine markers IL-17A, IL-17F, and IL-8, contributing to an antiviral immunomodulatory response in the Propolis and Tannic Acid combination *in vitro*.

## Keywords

SARS-CoV-2, Immuno Formula Shiban 2/5, Natural Plant Extract, Immunity, Therapy, Antiviral, Respiratory

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2 coronavirus. It

was first reported in China and across the world, presenting significant challenges to the Chinese government and to the World Health Organization (WHO) to control the pandemic. SARS-CoV-2 represents serious health issues to healthcare systems around the world [1]. The number of victims is estimated to reach seven million by the end of 2025 [2]. SARS-CoV-2 is characterized by the expression of spike proteins, which bind to ACE2 receptors, leading to cell and membrane fusion [3]. Based on their antibacterial function, human beta defensin (hBD-2) expressed on the surface of epithelial mucus serves as the first defense barrier against infectious pathogen attacks [4].

To date, the targeting of SARS-CoV-2 infection is difficult based on the pathological features and four different clinical phases caused by the virus as a method for measuring the progression and severity of the disease, which makes the treatment not effective. Studies have shown that severe cases of COVID-19 are associated with SARS-CoV-2 infection and are characterized by respiratory distress and/or pneumonia, along with immune system disruptions that lead to a cytokine storm or hyperinflammatory state [5] [6].

Recently, the scientific community has been interested in natural products to solve several limitations and issues regarding the available therapies. They explored the role of diets, supplements, and herbal formulations, to prevent and reduce the severity of pulmonary infection by SARS-CoV-2. However, the potential effectiveness of some plant extracts could act oppositely, exacerbating the effect of the infection [7].

Among the natural compounds derived from plants and herbs that are recognized for their antiviral activity against SARS-CoV-2, we found propolis extracts [8] [9] and tannic acid (TA) [10]. Moreover, two members of the tannin family, punicalagin (PP) and oligomeric proanthocyanidins, are known to inhibit SARS-CoV-2 [11]. The main criticisms raised from the previous report were about the potential toxicity of several plant extracts including propolis [6]. However, to date, the synergistic interaction of PP and TA that can often reduce toxicity and adverse side effects of PP in combination with TA on SARS-CoV-2 viral infection inhibition *in vitro,* has not yet been explored to be used as a natural treatment.

The present study was undertaken to investigate the antiviral and anti-inflammatory properties of IF2/5 prepared by Shiban Pharma and a placebo on the infected airway epithelial cells (A549) by SARS-CoV-2 [12]. Our results demonstrate the antiviral properties of IF2/5 against SARS-CoV-2 infection, as evaluated by immunofluorescence and confocal microscopy without toxicity on the treated cells. The administration of IF2/5 natural products will play a preventive and therapeutic role in the course of SARS-CoV-2 infection, as opposed to other interventions, including addressing the effects of lockdowns and the pro-inflammatory conditions associated with the disease.

Furthermore, the IF 2/5 are patented invention for successful commercialisation due to the therapeutic potential against SARS-CoV-2 infection (Shiban Pharma has 3 patents related to IF2/5 immunoformulations: 1—Canada # 3.151.164, 2—European Union # 21890438.1, 3—PCT: WO 2022/099414 A1). The patents de-

scribe the experimental results including formulations, dosages, novel uses and the developed combinations between the two immune formulations 2 and 5, showing the original properties of the immune formulation 2/5. These patents cover the countries that represent commercial risk of reproducing similar products.

## 2. Material and Methods

### 2.1. Immuno Formula Shiban 2 and Shiban 5 Preparation

Immuno Formula 2 and 5, known under the commercial name of Shibanico 2 and Shibanico 5 from Shiban Pharma (www.shibanpharma.com), are a mixture of extracts from propolis, cinnamon, acacia, tannic acid, and clove. IF2/5 were dissolved in boiled distilled deionized water at a concentration of 200 mg/ml. The water extracts were then filtered using a Whatman No. 4 filter (cat. 1444 110) to create a stock solution, which was further diluted with culture medium to achieve various final concentrations for *in vitro* assays. The placebo control was distilled deionized water.

### 2.2. Cell Culture

A549 (human type II alveolar pneumocyte) [12] and PAEC (Primary Airway Epithelial Cell) cell lines were obtained from the American Type Culture Collection (ATCC, Rockville, MD) [13]. All cells were cultured in Eagle's Modified Essential Medium (EMEM, Life Technologies, CA), supplemented with 10% fetal calf serum, 2 mM L-glutamine, and penicillin/streptomycin, at 37˚C in a 5% $CO_2$ atmosphere.

### 2.3. Virus Preparation and Titration

Lentivirus pseudotyped with the SARS-CoV-2 spike protein was supplied by Creative Diagnostics (catalog number COV-PS02).

### 2.4. Cytotoxicity Assay

Cytotoxicity of IF2 and IF5 was assessed by measuring the growth inhibition of A549 cells. Briefly, A549 cells were seeded at a concentration of $2.5 \times 10^4$ cells/well in 24-well plates and cultured in 5% FCS-EMEM at 37˚C for 2 days. The culture medium was then replaced with fresh medium containing IFs at various concentrations, and the cells were incubated for an additional 3 days. After treatment, the cells were trypsinized, and the number of viable cells was determined using the trypan blue exclusion test. The 50% cytotoxic concentrations (CC50) of IFs, which reduce cell viability, were calculated from a curve relating the percentage of viable cells to the IF concentrations. The antiviral activity of IFs was evaluated in vitro and compared to the activity of each individual compound, as well as their combination.

### 2.5. Pseudovirus SARS-CoV-2 Infection

A549 cells ($10^4$ cells) were seeded in 96-well culture plates. 24 hours after seeding, the cells were incubated in a culture medium containing diluted compounds. The cells were then inoculated with concentrated pseudovirus SARS-CoV-2 for 12 hours in the presence of the diluted compounds. Following this incubation, two-thirds of the

pseudovirus-containing media were replaced with regular EMEM medium, and the cells were incubated for an additional 48 hours. The cells were fixed with 4% paraformaldehyde (PAF) for 10 minutes and washed with PBS. Images were captured using a Confocal Zeiss LSM710 microscope (Oberkochen, Germany). All images were analyzed using Image J (Version 1.53a, National Institutes of Health, USA). SARS-CoV-2-GFP (green fluorescence) was measured and expressed as relative fluorescence units (RFU). The total number of GFP-expressing cells in each condition was normalized to the total number of cells in the respective wells.

### 2.6. Synergy Finder or Bliss Synergy Score

We treated the A549 cells with a mixture of PP and TA using a fixed ratio based on their IC50 values for 48 hours. The treated cells were then incubated with CCK-8 reagent prepared in the culture medium for 4 hours, and absorbance was measured at 450 nm using a Microplate Absorbance Reader (Bio-Rad, iMark, USA). All experiments were repeated three times. The inhibition of cell proliferation was assessed by the absorbance readings. The Bliss synergy score was calculated using SynergyFinder, where a score of 0 indicates an additive effect, < 0 indicates antagonism, and > 0 indicates synergy. The synergism between PP and TA was defined by the Bliss synergy score [14].

### 2.7. Cytokines Expression ELISA

The expression levels of IL-17A, IL-17F, and IL-8 were measured using commercially available cytokine assays purchased from R&D Systems (R&D, MN, USA). Each ELISA analysis was performed in triplicate. To quantify IL-17A, IL-17F, and IL-8 expression, the absorbance of each sample was measured at 490 nm and 680 nm. The 680 nm absorbance, which represents the background signal from the instrument, was subtracted from the absorbance value at 490 nm. Cytokine proteins were quantified relative to serial dilutions of recombinant standards, following the manufacturer's recommendations. The data represents readings from three separate assays.

### 2.8. Immunofluorescence and Confocal Microscopy

We prepared the cell cultures on coverslips for immunofluorescence and processed them in the histology core facility using standard techniques. The coverslips were fixed with 4% paraformaldehyde. After permeabilization with 0.3% Triton X-100 and incubation with goat serum, cells were stained with the appropriate antibody overnight at 4˚C. The cells were then incubated with a secondary antibody at 37˚C for 1 hour and DAPI (0100-20), purchased from Southern Biotech (Birmingham, AL, USA), for 10 minutes. Finally, the samples were examined using a Nikon confocal microscope (Nikon C1-Si, Tokyo, Japan).

### 2.9. Statistical Analysis

Statistical comparisons between the two test groups were evaluated using a one-

way ANOVA or Student's t-test, as appropriate. A P-value of less than 0.05 was considered statistically significant. All values are expressed as mean ± S.E. and analyzed using Prism GraphPad Software Inc. (La Jolla, CA, USA).

## 3. Results

**1) Absence of respiratory cell cytotoxicity side effects of PP and TA compounds.** To evaluate the IF compounds PP and TA, we used Epithelial lung cell line A549, either mock-infected with SARS-CoV-2 or compared to negative control. The cell's treatment with our compounds (PP or TA) was done on an escalating concentration scale from 0 to 200 µg/ml. The cell viability was measured with immunofluorescence. Green fluorescence shows the infection while blue fluorescence was used to show the live cells. Our results showed the absence of a significant difference in cell viability based on immunofluorescence analysis. The PP treatment at (100 µg/ml) for 48 h was able to protect the cells and inhibit the virus replication compared to the infected and untreated control (Figure 1(A)).

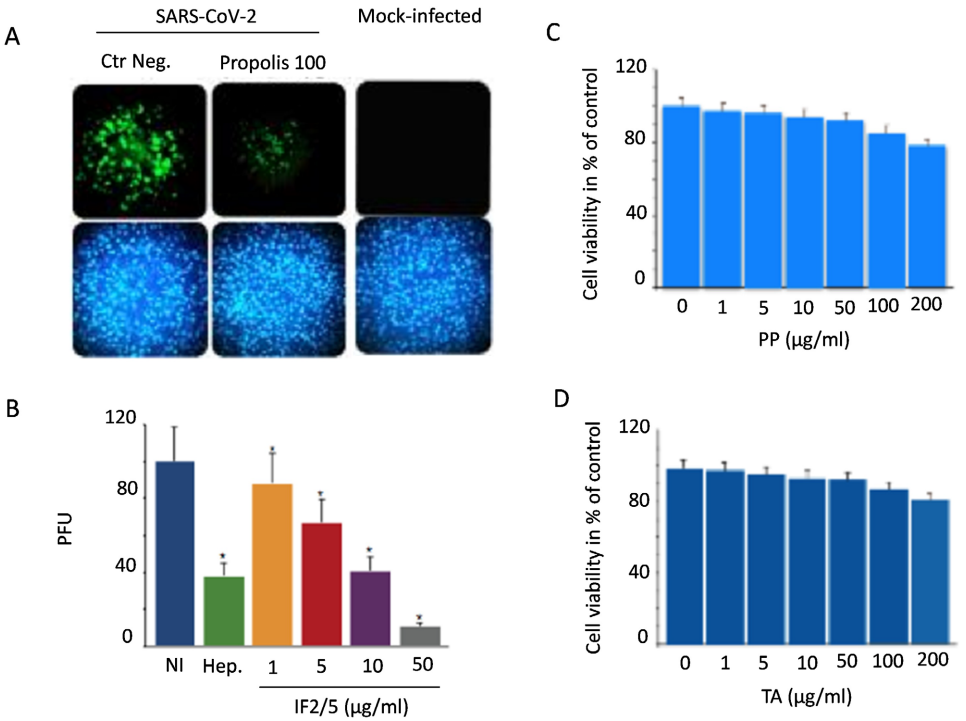


**Figure 1.** ***In vitro*** **Effect of immune formula compounds PP and TA on cell viability SARS-Cov-2 infected.** Morphological features of epithelial lung cell line A549 Mock-infected and infected with SARS-CoV-2 exposed to 0 (vehicle) and 100 µg/ml of Propolis for 48 h (A). A549 cells infected with SARS-Cov-2 at an MOI of 2 containing a serially diluted compound. At 48h post infection, SARS-Cov-2-GFP, green fluorescence was measured. The results are expressed as a mean ± SD for three independent experiments (NI: non-infected, RFU: Relative fluorescence units), (B). Cell viability of uninfected A549 exposed to 0 (vehicle) 1, 5, 10, 50, 100 and 200 µg/ml of Propolis for 48 h (C). Cell viability of uninfected A549 exposed to 0 (vehicle) 1, 5, 10, 50, 100 and 200 µg/ml of TA for 48 h (D). Green fluorescence shows the infection while blue fluorescence was used to show the live cells. The data presented mean ± SEM. All data were repeated three times.

In addition, to examine the dose effect of PP and TA, we exposed for 48 h the infected cells and the control groups. At the highest dose of 200 µg/ml of PP, the cell viability decreased to (78.57% ± 3.36%) compared to controls (Figure 1(B)). In parallel, the impact of TA at the same dose of 200 µg/ml on the cell viability was similar to PP (79.52% ± 3.61%) (Figure 1(C)).

**2) The inhibitory effect on SARS-CoV-2 infection with increasing concentration of PP and TA plant extract in A549 and PAEC.** To examine the effect of PP and TA on the replication of SARS-CoV-2 using A549 and PAEC, we used the IC50 approach. The cells were treated at 50 µg/ml and 100 µg/ml compared to untreated control of PP (Figure 2(A)), TA (Figure 2(B)) and in combination of both of them (Figure 2(C)). The logarithmic graph of the PP (Figure 2(D)) or the TA (Figure 2(E)) concentrations related to the inhibition of SARS-CoV-2 in the infected A549 cells. The concentration required to reach an inhibition rate of 50% was 55.67 µg/ml of PP. However, the required concentration to achieve a 50% inhibition rate was 23.30 µg/ml.

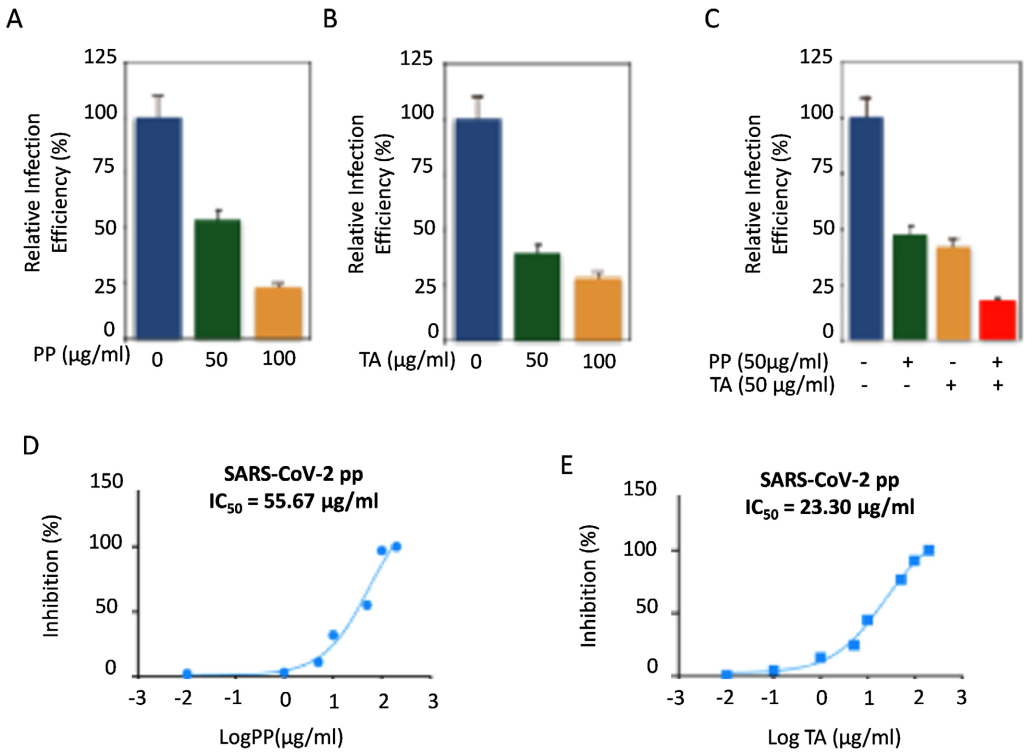


**Figure 2. IC50 of Epithelial lung cell line A549 inhibition of under SARS-CoV-2 infection without/with immune formula compounds PP and TA.** Percentage of relative infection of A549 with SARS-CoV-2 and exposed to 0 (vehicle), 50 and 100 µg/ml of Propolis (A), or TA (B), and with combination of Propolis (50 µg/ml) and TA (50 µg/ml) (C). The data presented mean ± SEM. All data were repeated three times.

**3) Required IC 50 of PP and TA synergy against SARS-Cov-2 infection.** To calculate the concentration of product needed to decrease the relative efficiency rate to 50%, we treated the infected cells with SARS-Cov-2 with the immune for-

mula compound PP and TA. To monitor the inhibition dynamic, the cells were labelled in green fluorescence (Figure 3(A)). The IC50 concentration in A549 cells is 32.59 μg/ml of IF2 (Figure 3(B)) and 26.41 μg/ml in PAEC cells (Figure 3(C)). The combination of PP and TA was synergistic. Although PP or TA alone could inhibit SARS-Cov-2 infection in lung cells, the combination of them could further enhance the infection inhibition. The results of toxicity parameters showed that the combination was safe *in vitro*.

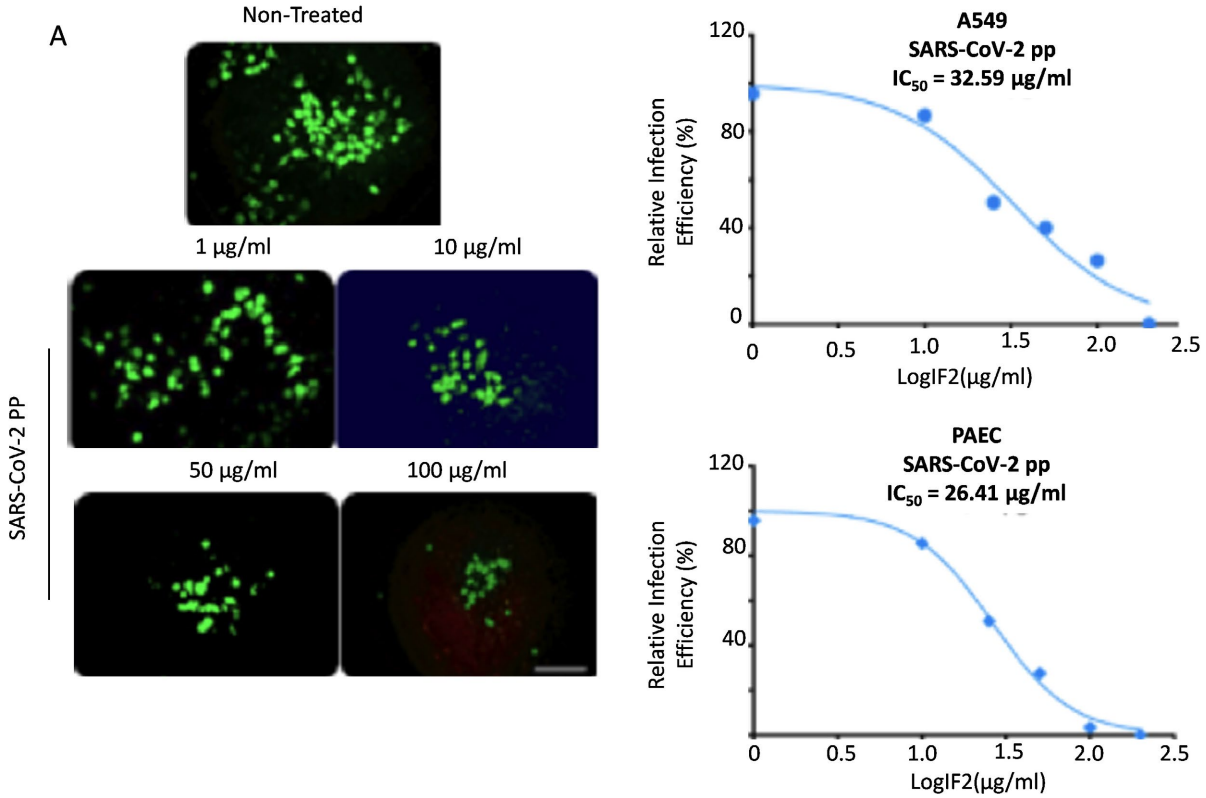


**Figure 3. Calculation and visualisation of synergy score using Bliss method.** PP synergizes with TA to suppress SARS-CoV-2 viral replication in PAEC cells, in a dose-response matrix (inhibition) to compounds combination (TA-Prop) for synergy score of 22.14 (A) and providing the most synergistic area score (MSA) of 22.139 (B). The data presented mean ± SEM. All data were repeated three times.

**4) PP synergizes with TA to suppress SARS-Cov-2 infection of respiratory cells based on Bliss interaction scores.** To study the antiviral effect of combining the two compounds PP and TA of IF2, we need to show the synergistic effect of IF2 combination using a heat map based on the percent excess the Bliss prediction with the average response taken at each combination dose. We used the in vitro dose response matrix to analyze the inhibition of SARS-Cov-2 under PP and TA. The percentage of PAEC inhibition of SARS-Cov-2 viral infection by PP exhibiting an IC50 = 55.67 μg/ml (Figure 4(A)), and by TA with an IC50 = 23.30 μg/ml which corresponds to a bliss synergy score between PP and TA. The Bliss synergy score [14] was calculated using SynergyFinder, where a score of 0 indicates an additive effect, <0 indicates antagonism, and >0 indicates syn-

ergy. The synergism between PP and TA was defined by the Bliss synergy score determined from the heat map was 21,139 (Figure 4(B)).

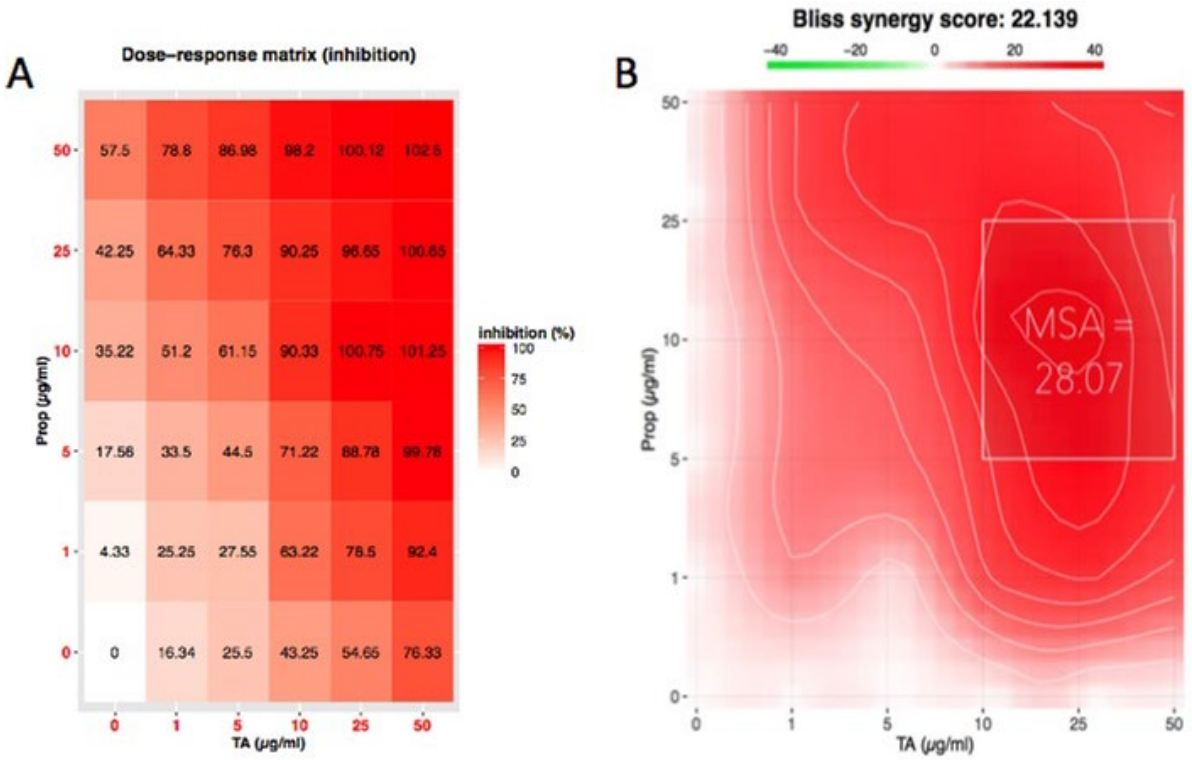


**Figure 4.** ***In vitro*** **Antiviral impact of PP and TA synergy on primary airway epithelial cells (PAEC) SARS-CoV-2 infected.** Percentage of PAEC inhibition of SARS-CoV-2 viral infection by PP exhibiting an IC50 = 55.67 µg/ml (A), and by TA with an IC50 = 23.30 µg/ml (B). Bliss synergy plots describing the synergy between PP and TA, COB. Bliss synergy was calculated and visualized using the SynergyFinder R package[14]. The data presented mean ± SEM. All data were repeated three times. The data presented mean ± SEM. All data were repeated three times.

**5) Anti-inflammatory effect on cytokines markers of the antiviral immunomodulatory immune response for PP and TA combination.** The inflammatory response was evaluated based on the expression of IL-17A, IL-17F, and IL-8 cytokines by the infected cells under the effect of IF2 at different concentrations. Treatment of infected cells with IF2 inhibited the release of IL-17A compared to the infected, untreated control (141 ± 7.81 pg/ml) (Figure 5(A)). We found that increasing the concentration of IF2 was able to downregulate the release of IL-17A, with a concentration of 50 µg/ml reducing it to 14.51 ± 2.23 pg/ml compared to the negative control. A similar pattern was observed for IL-17F and IL-8. IF2 treatment at 50 µg/ml also downregulated the expression of IL-17F, reducing it to 9.22 ± 1.78 pg/ml compared to the negative control (Figure 5(B)). Finally, the expression pattern of IL-8 followed that of IL-17A and IL-17F as part of the inflammatory response. Infection upregulated the expression of IL-8 compared to the uninfected control (297.37 ± 28.95 pg/ml). However, IL-8 production was inhibited under IF2 treatment at 50 µg/ml (30.26 ± 5.26 pg/ml) (Figure 5(C)).

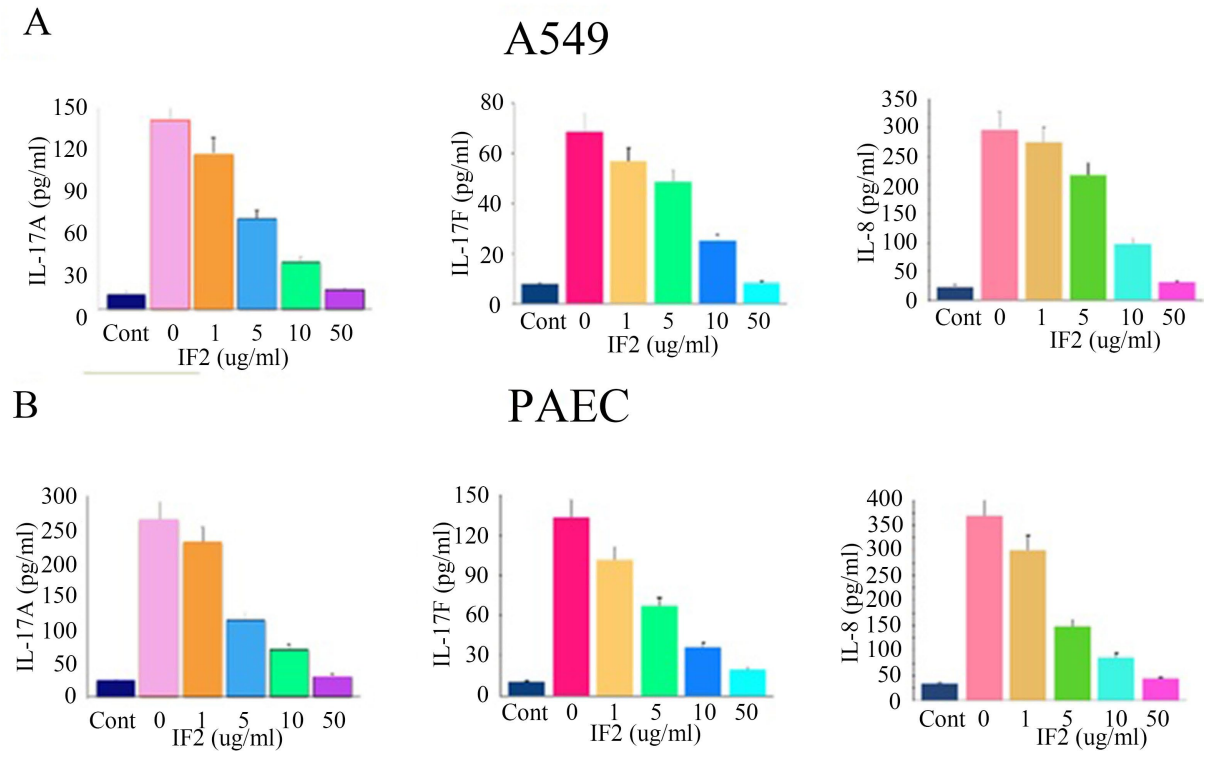


**Figure 5. Cytokines signature of the antiviral immunomodulatory immune response A549 and PAEC cell line models SARS-CoV-2 infected and treated with IF2.** Unexposed (vehicle) and mock infected (control) cell lines A549 (A) and PAEC (B), used to monitor the inflammatory immune response to SARS-CoV-2 infection without exposure to IF2 (0 µg/ml). We targeted the main cytokines of the inflammatory response in A549 and PAEC to 1, 5, 10, 50 µg/ml of IF2 exposure such as IL-8, IL-17A and IL-17F. The data presented mean ± SEM. All data were repeated three times.

## 4. Discussion

PP and TA are known to have various effects in the context of infectious diseases. These compounds exhibit anti-inflammatory and antiviral properties, as reported in the literature [10] [12]. The goal of our study was to harness their synergistic potency to address the health issues posed by SARS-CoV-2, aiming to avoid the side effects associated with other recommended medications [15]-[17]. To achieve this, we determined the required doses of PP and TA, respectively, to demonstrate a significant *in vitro* inhibition of SARS-CoV-2 infection in lung cells.

Several reports interested in natural products or plant extracts explored the role of diets, supplements, and herbal formulations, to prevent and reduce the severity of pulmonary infection by SARS-CoV-2. However, the potential effectiveness of some plant extracts could act oppositely, exacerbating the effect of the infection [7]. The other limitation of the use of PP was the potential toxicity of propolis [6].

Those limitations were taken into consideration, and we addressed the in vitro cytotoxicity of PP and TA on respiratory cells in the present study, which was not detected based on our data. However, the combination of PP and TA was able to disrupt SARS-CoV-2 viral replication in respiratory cells, as reported by others, although not in formulations sitting [18].

At the first step, we evaluated the toxicity of PP and TA on cell viability. The

cell survival remained above 78% for both compounds even at very high dosages, *i.e.* 200 μg/ml. The impact of PP and TA on SARS-CoV-2 was efficient in A549 lung epithelial cells. A significant decrease in viral infection efficiency was observed compared to the controls. The targeting by PP alone, used at 50 μg/ml, reduced infection efficiency to 54%, and at 100 μg/ml, the relative infection efficiency dropped to 24%. On the other hand, TA used alone at 50 μg/ml decreased the infection efficiency to 39%, while at 100 μg/ml it dropped to 28%. The required dose to achieve a 50% inhibition rate for PP and TA in combination were 55.67 μg/ml and 23.30 μg/ml, respectively. Finally, the combination of PP and TA was tested at 50 μg/ml each, which decreased relative infection efficiency from 100% (control) to 17%. This finding strengthens our hypothesis that targeting PP and TA is an effective strategy to inhibit SARS-CoV-2 infection.

In the next step, we explored the necessity of determining the optimal doses of PP and TA to synergize together, which will be the formulation of IF2/5. Based on a dose-response matrix of both components of IF2/5, we found that TA and PP at the doses of 25 μg/ml and 10 μg/ml respectively, achieved an inhibition rate of 100%. The combination of PP and TA proved to be synergistic. While PP or TA alone could inhibit SARS-CoV-2 infection in lung cells, their combination further enhanced the inhibition of infection. Toxicity results indicated that the combination was safe *in vitro*.

IF2 was tested to assess its antiviral and anti-inflammatory properties against SARS-CoV-2 [19] [20]. The required dose of IF2 to achieve 50% inhibition of infection was 32.59 μg/ml. The anti-inflammatory properties of IF2 are evaluated based on the expression of three cytokines that are hallmarks of inflammation: IL-17A, IL-17F, and IL-8 [21] [22]. Treatment with IF2 at varying concentrations showed a decrease in the production of these cytokines, with higher concentrations correlating with greater inhibition of cytokine production. Based on these findings, we concluded that IF2 possesses potent anti-inflammatory properties, as the production of these cytokines significantly decreased when 50 mcg/ml of IF2 was used compared to the controls.

## 5. Conclusions

We found that the two compounds, PP and TA, exhibited potent synergistic inhibitory activity against SARS-CoV-2 infection in lung cells, compared to when TA or PP were used separately, as reported previously. We further assessed the anti-inflammatory effects on cytokine markers such as IL-17A, IL-17F, and IL-8, highlighting the antiviral immunomodulatory immune response of the PP and TA combination against SARS-CoV-2 infection [19]. Moreover, PP and TA synergistically reversed all the symptoms of SARS-CoV-2 infection in patients diagnosed for COVID-19 and treated with IF 2/5 known in the market as Shibanico 2 and Shibanico 5 (data not shown), as demonstrated *in vivo*, to counteract the immune evasion mechanisms and inhibit lung cell infection [21]. The knowledge gained from this novel natural strategy elucidates the scientific mechanisms and supports

the inclusion of this new formulation in health guidelines to help prevent and cover the four stages of SARS-CoV-2 infection course in a safe manner from unexpected side effects of multiple treatments.

The discovery of IF2/5 as a novel promising immunotherapy for COVID-19, it remains that potential off-target effects of this plant extracts natural product have not been fully addressed *in vivo* due to the complexity of COVID-19 pathology and involving several diseases. Our actual efforts to establish the specificity of IF2/5 *in vitro* and *in vivo*, based on a large *in vivo* study to transfer the data from the bench to the bed. Furthermore, our preliminary results (data not shown) confirm the absence of toxicity of the IF2/5 and confirm the therapeutic potential. A large *in vivo* study will be needed to highlight the speculation of potential adverse effects.

## Acknowledgements

The authors would like to thank Bioimmune Solutions (www.bioimmunesolutions.com) for their wonderful scientific work in the manuscript conceptualisation including the formal analysis, writing, review and editing.

## Conflicts of Interest

Shiban Pharma has 3 patents related to IF2/5 immunoformulations (1—Canada # 3.151.164, 2—European Union # 21890438.1, 3—PCT: WO 2022/099414 A1).

## References

[1] Muralidar, S., Ambi, S.V., Sekaran, S. and Krishnan, U.M. (2020) The Emergence of COVID-19 as a Global Pandemic: Understanding the Epidemiology, Immune Response and Potential Therapeutic Targets of SARS-CoV-2. *Biochimie*, **179**, 85-100. https://doi.org/10.1016/j.biochi.2020.09.018

[2] Van Noorden, R. (2022) COVID Death Tolls: Scientists Acknowledge Errors in WHO Estimates. *Nature*, **606**, 242-244. https://doi.org/10.1038/d41586-022-01526-0

[3] Jackson, C.B., Farzan, M., Chen, B. and Choe, H. (2021) Mechanisms of SARS-CoV-2 Entry into Cells. *Nature Reviews Molecular Cell Biology*, **23**, 3-20. https://doi.org/10.1038/s41580-021-00418-x

[4] Bindra, G.K., Williams, S.A., Lay, F.T., Baxter, A.A., Poon, I.K.H., Hulett, M.D., *et al.* (2022) Human β-Defensin 2 (HBD-2) Displays Oncolytic Activity but Does Not Affect Tumour Cell Migration. *Biomolecules*, **12**, Article 264. https://doi.org/10.3390/biom12020264

[5] de la Rica, R., Borges, M. and Gonzalez-Freire, M. (2020) COVID-19: In the Eye of the Cytokine Storm. *Frontiers in Immunology*, **11**, Article 558898. https://doi.org/10.3389/fimmu.2020.558898

[6] Young, T.K. and Zampella, J.G. (2020) Supplements for COVID-19: A Modifiable Environmental Risk. *Clinical Immunology*, **216**, Article 108465. https://doi.org/10.1016/j.clim.2020.108465

[7] Gasmi, A., Chirumbolo, S., Peana, M., Noor, S., Menzel, A., Dadar, M., *et al.* (2021) The Role of Diet and Supplementation of Natural Products in COVID-19 Prevention. *Biological Trace Element Research*, **200**, 27-30.

https://doi.org/10.1007/s12011-021-02623-3

[8] Anand, A.V., Balamuralikrishnan, B., Kaviya, M., Bharathi, K., Parithathvi, A., Arun, M., *et al.* (2021) Medicinal Plants, Phytochemicals, and Herbs to Combat Viral Pathogens Including SARS-CoV-2. *Molecules*, **26**, Article 1775. https://doi.org/10.3390/molecules26061775

[9] Berretta, A.A., Silveira, M.A.D., Cóndor Capcha, J.M. and De Jong, D. (2020) Propolis and Its Potential against SARS-CoV-2 Infection Mechanisms and COVID-19 Disease. *Biomedicine & Pharmacotherapy*, **131**, Article 110622. https://doi.org/10.1016/j.biopha.2020.110622

[10] Haddad, M., Gaudreault, R., Sasseville, G., Nguyen, P.T., Wiebe, H., Van De Ven, T., *et al.* (2022) Molecular Interactions of Tannic Acid with Proteins Associated with SARS-CoV-2 Infectivity. *International Journal of Molecular Sciences*, **23**, Article 2643. https://doi.org/10.3390/ijms23052643

[11] Chen, H.F., Wang, W.-J., Chen, C.-Y., Chang, W.-C., Hsueh, P.-R., Peng, S.-L., *et al.* (2023) The Natural Tannins Oligomeric Proanthocyanidins and Punicalagin Are Potent Inhibitors of Infection by SARS-CoV-2. *eLife*, **12**, e84899. https://doi.org/10.7554/elife.84899

[12] Al-Qahtani, A.A., Pantazi, I., Alhamlan, F.S., Alothaid, H., Matou-Nasri, S., Sourvinos, G., *et al.* (2022) SARS-CoV-2 Modulates Inflammatory Responses of Alveolar Epithelial Type II Cells *via* PI3K/AKT Pathway. *Frontiers in Immunology*, **13**, Article 1020624. https://doi.org/10.3389/fimmu.2022.1020624

[13] Okoloko, O., Vanderwall, E.R., Rich, L.M., White, M.P., Reeves, S.R., Harrington, W.E., *et al.* (2021) Effect of Angiotensin-Converting-Enzyme Inhibitor and Angiotensin II Receptor Antagonist Treatment on ACE2 Expression and SARS-CoV-2 Replication in Primary Airway Epithelial Cells. *Frontiers in Pharmacology*, **12**, Article 765951. https://doi.org/10.3389/fphar.2021.765951

[14] Ianevski, A., Giri, A.K. and Aittokallio, T. (2020) Synergyfinder 2.0: Visual Analytics of Multi-Drug Combination Synergies. *Nucleic Acids Research*, **48**, W488-W493. https://doi.org/10.1093/nar/gkaa216

[15] Finsterer, J. (2021) Neurological Side Effects of SARS-CoV-2 Vaccinations. *Acta Neurologica Scandinavica*, **145**, 5-9. https://doi.org/10.1111/ane.13550

[16] Akhvlediani, T., Bernard-Valnet, R., Dias, S.P., Eikeland, R., Pfausler, B. and Sellner, J. (2023) Neurological Side Effects and Drug Interactions of Antiviral Compounds against SARS-CoV-2. *European Journal of Neurology*, **30**, 3904-3912. https://doi.org/10.1111/ene.16017

[17] Piekarski, F., Steinbicker, A.U. and Armann, J.P. (2021) The Multisystem Inflammatory Syndrome in Children and Its Association to SARS-CoV-2. *Current Opinion in Anaesthesiology*, **34**, 521-529. https://doi.org/10.1097/aco.0000000000001024

[18] Augustus, A.R., Radhakrishnan, Y., Bhaskar, J.P., Ramamurthi, S. and Shunmugiah, K.P. (2025) Tannic Acid Modulates SARS-CoV-2 Pathogenesis by Curbing Key Host Receptors and Oxidative Stress. *Toxicology in Vitro*, **103**, Article 105971. https://doi.org/10.1016/j.tiv.2024.105971

[19] Yosri, N., Abd El-Wahed, A.A., Ghonaim, R., Khattab, O.M., Sabry, A., Ibrahim, M.A.A., *et al.* (2021) Anti-Viral and Immunomodulatory Properties of Propolis: Chemical Diversity, Pharmacological Properties, Preclinical and Clinical Applications, and in Silico Potential against SARS-CoV-2. *Foods*, **10**, Article 1776. https://doi.org/10.3390/foods10081776

[20] Carabelli, A.M., Peacock, T.P., Thorne, L.G., Harvey, W.T., Hughes, J., de Silva, T.I., *et al.* (2023) SARS-CoV-2 Variant Biology: Immune Escape, Transmission and Fitness. *Nature Reviews Microbiology*, **21**, 162-177. https://doi.org/10.1038/s41579-022-00841-7

[21] Adamopoulos, I.E. and Kuchroo, V. (2023) IL-17A and IL-17F in Tissue Homeostasis, Inflammation and Regeneration. *Nature Reviews Rheumatology*, **19**, 535-536. https://doi.org/10.1038/s41584-023-01004-5

[22] Pease, J.E. and Sabroe, I. (2002) The Role of Interleukin-8 and Its Receptors in Inflammatory Lung Disease. *American Journal of Respiratory Medicine*, **1**, 19-25. https://doi.org/10.1007/bf03257159