***Morinda citrifolia* (noni) fruit juice inhibits SARS-CoV-2 spike protein binding of angiotensin-converting enzyme 2 (ACE2)**

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Abstract

Covid-19 is a global pandemic that has claimed millions of lives. This disease is caused by a coronavirus, SARS-CoV-2, which requires the binding of its spike protein to angiotensin-converting enzyme 2 (ACE2) for infection of the host cell. *Morinda citrifolia* (noni) fruit juice has antiviral activity that involves enhancement of immune system function. SARS-CoV-2 spike-ACE2 interaction experiments were carried out to further investigate the antiviral properties of noni juice and its major iridoids. Noni juice inhibited binding by approximately 69%. Scandoside was the most active of the three iridoids evaluated, reducing average spike protein-ACE2 interaction by 79.25%. The iridoids worked synergistically towards inhibiting spike protein binding when assayed together, improving activity by more than 22% above the expected level. But the modest activity of the most abundant iridoid, deacetylasperulosidic acid, indicates that other phytochemicals (i.e. scopoletin, quercetin, rutin and kaempferol) are also involved. Our results suggest that the presence of several biological active phytochemicals in noni juice enhances resistance to SARS-CoV-2 by interfering with its ability to bind ACE2. This is a new and significant anti-viral mechanism of noni juice that does not directly involve its immunomodulatory properties.

Key words: Coronavirus, Covid-19, SARS-CoV-2, spike protein, *Morinda citrifolia*, Noni, Iridoid

Introduction

Coronaviruses are a group of viruses known for the characteristic glycoprotein projections, or spike proteins, from the viral envelope which give them the crown-like (corona in Latin) appearance from which their name is derived (Lai et al. 1997). First isolated in the 1960s, coronaviruses were originally associated with nasopharyngitis, or the common cold (Tyrrell et al. 1965). However, these RNA viruses have since been found to be responsible for producing much more severe symptoms in the upper respiratory tract as well as adversely affecting other organs throughout the body, often with lethal outcomes (Chen et al. 2020). The recent coronavirus disease 2019 (Covid-19) pandemic was caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), resulting in more than 4.18 million deaths worldwide as of July 2021 (Mohanty et al. 2020; World Health Organization 2021).

More than 20 years ago, angiotensin-converting enzyme 2 (ACE2) was discovered (Tipnis et al. 2000; Donoghue et al. 2000). This enzyme is attached to cell membranes and converts angiotensin II to angiotensin (1–7), thereby influencing blood pressure (Keidar et al. 2007). This enzyme is distributed widely throughout many organs of the human body. But they are especially abundant in the epithelia of the lungs and small intestine (Hamming et al. 2004). In 2003, ACE2 was reported to be a functional receptor for SARS-CoV, which preceded the appearance of SARS-CoV-2 by 16 years (Li et al. 2003). Since then, SARS-CoV-2 was also found to have an ACE2 receptor-binding domain on its spike protein (Lu et al. 2020; Yan et al. 2020). Infection of the cell relies on the binding of ACE2 by the spike protein, which must first undergo proteolytic activation by host transmembrane protease, serine 2 (TMPRSS2) and furin (Benton et al. 2020; Bestle et al. 2020). The role of the SARS-Cov-2 spike protein and ACE2 interaction was confirmed in experiments in which polyclonal antibodies inhibited spike protein-mediated entry of viral RNA into the cell (Walls et al. 2020).

Plant-derived foods support human health by providing nutrients and phytochemicals, which are biologically active secondary plant metabolites (Efferth and Koch 2011). *Morinda citrifolia*, commonly known as noni, is a tropical tree that produces fruit year-round (Morton 1992). It has a well-documented history of traditional use as both food and medicine, has been rigorously evaluated for safety, and has receiving official approval as a safe food by governmental agencies (West 2006). Some of the perceived health benefits of noni juice, both historical and modern, have been substantiated by human intervention studies. Among these are antioxidant, anti-inflammatory and immunomodulatory properties (West et al. 2018). For example, increased serum interleukin-2 (IL-2) concentrations and natural killer (NK) cell activity was observed in healthy volunteers who drank noni juice daily for two-months, demonstrating enhanced innate and adaptive immune system function (Ma et al. 2008). The same effects were observed in immunosuppressed mice that were fed noni fruit juice extract and its major phytochemical constituent, deacetylasperulosidic acid (Murata et al. 2014). In another clinical trial, four weeks of daily noni juice ingestion reduced DNA adduct formation in the lymphocytes of cigarette smokers, thereby preserving immune function against the damaging effects of tobacco smoke (Wang et al. 2013). These findings demonstrate the potential of noni juice in preventing and mitigating viral infections.

Other in vivo and in vitro studies further our understanding of how noni juice influences immune responses to viral exposure. Chickens fed noni juice experienced increased humoral immune response as determined by the hemagglutination assay following infectious bursal disease virus challenge (Sunder 2007). Neonatal bovine CD4⁺ and CD8⁺ T cell activation increased when animals were fed noni fruit puree from French Polynesia for two weeks (Brooks et al. 2009). A follow-up study revealed that noni puree supplementation for the first three weeks of life also reduced respiratory treatments by 61% (Brooks et al. 2013). After three weeks of Tahitian Noni® Juice ingestion, peripheral blood CD4⁺/CD8⁺ ratio and IL-2 levels increased significantly (Yang et al. 2011). Noni fruit extracts also stimulated

splenocyte proliferation in vitro and increased the humoral immune response of immunosuppressed rats (Nayak et al. 2010). Finally, 16-days of Tahitian Noni Juice ingestion increased interferon-gamma expression in splenocytes and peritoneal exudate cells (Palu et al. 2008).

The studies discussed above have centered largely on the ability of noni juice to mount an immune response to infected cells. The purpose of our present investigation was to evaluate additional antiviral properties of noni juice and its major phytochemical constituents (iridoids), with specific interest in SARS-CoV-2. Accordingly, we focused on the mechanism whereby this virus enters host cells, spike protein binding of ACE2.

Materials and Methods

Noni fruit was harvested by hand in French Polynesia and allowed to fully ripen. The fruit was then processed into a puree by mechanical removal of the seeds and skin with a micro-mesh screen in a commercial fruit pulper. This puree was then pasteurized at 87 °C for 3 seconds at a good manufacturing certified fruit processing facility in Mataiea, Tahiti. This is the same source of noni fruit puree that was approved by the European Commission in 2003 as a safe novel food for use in pasteurized beverages (European Commission 2003). The puree was then filtered through a 0.45 µm PTFE filter to produce a clarified noni juice for testing.

Previously, we identified iridoids as the major phytochemical constituents of noni fruit. We confirmed the presence of these iridoids (deacetylasperulosidic acid, asperulosidic acid and scandoside) according to our validated method (Deng et al. 2011; West et al. 2011). The filtered puree was diluted with methanol-H₂O (1:1), and chromatographic separation was performed using a C-18 column (4.6 mm x 250 mm; 5 µm, Waters Corporation, Milford, MA, USA) and two mobile phases: A; acetonitrile (MeCN), and B; 0.1% formic acid in H₂O (v/v). A linear gradient of 100% B for 0-5 minutes was followed by 70% B

and 30% A for 40 minutes at an elution rate of 0.8 mL/min. Eluted compounds were detected by photodiode array (PDA) within 210-400 nm. Pure deacetyl asperulosidic acid, asperulosidic acid and scandoside were also obtained for use in the spike protein binding experiments.

The ability of noni juice and iridoid samples to inhibit the binding of SARS-CoV-2 spike protein to ACE2 was measured by an enzyme-linked immunosorbent assay kit (Cayman Chemical Company, Ann Arbor, Michigan, USA) involving recombinant rabbit immunoglobulin (Fc)-tagged SARS-CoV-2 spike S1 receptor binding domain (RBD) and His-tagged ACE2. In this assay, a polystyrene 96-microwell plate is precoated with a mouse anti-rabbit monoclonal antibody attached to the rabbit Fc-tagged spike S1 RBD. In the absence of an inhibitor, a recombinant histidine (His)-tagged ACE2 protein binds the spike S1 RBD. The resulting complex is detected with a horseradish peroxidase (HRP)-conjugated anti-His antibody which is quantified by measuring absorbance at 450 nm in a microplate reader (Synergy™ HT, BioTek Instruments, Winooski, Vermont, USA). The absorbance measured without any inhibitor served as the initial activity control, representing 100% spike protein binding. Prior to absorbance measurements, the experiment was performed as follows. A buffer composed of 0.14 M NaCl, 10 mM dibasic sodium phosphate, 0.1% bovine albumin, 1.76 mM monobasic potassium phosphate and 2.68 mM KCl was prepared. 100 µL of this buffer was added to the precoated microwells. Iridoid samples were prepared by dissolving them in the buffer. Next, 50 µL of the dissolved sample solutions, noni juice or buffer (initial activity control) were added to the microwells. Lyophilized His-tagged ACE2 protein (Cayman Chemical Company) was dissolved in the buffer, and 50 µL of this solution was added to each microwell. The Lyophilized SARS-CoV-2 spike RBD (Cayman Chemical Company) was also dissolved in buffer, with the 50 µL of the resulting solution being added to each microwell. The microwell plate was incubated 60 minutes at room temperature on an orbital shaker. Following this initial incubation, the wells were washed three times with 300 µL of a wash buffer composed of 7.61 mM dibasic potassium phosphate and 2.37 mM monobasic potassium phosphate and Polysorbate 20 (500 µL/L). After washing, 150 µL of

HRP conjugated anti-His-antibody solution, prepared with a new buffer (0.4 M NaCl, 75.78 mM dibasic potassium phosphate, 23.51 mM monobasic potassium phosphate, 1.1% bovine albumin and 0.038% EDTA tetrasodium salt), was added to each well. The wells were then incubated a second time at room temperature for 30 minutes on an orbital shaker. Next, the wells were emptied and washed three times again followed by the addition of 175 μ L of 3,3',5,5'-tetramethylbenzidine (TMB) solution, a substrate of HRP and incubation for 10 to 20 minutes at room temperature. 75 μ L of 2.8% sulfuric acid solution was added to each well to stop the enzymatic reaction. Finally, absorbance was read with the microplate reader.

Inhibition percentage was calculated from the difference between control and sample absorbance divided by the absorbance of the control. Replicate samples of the iridoids were prepared and analyzed at 500 μ g/mL. A mixture of the three iridoids, at 167 μ g/mL each in the final assay, was also evaluated. The expected percent inhibition of the mixture was calculated from the result of each replicate test and the ratio of the concentration of each iridoid in the mixture to its concentration in the individual test. Replicate assays were performed with the noni juice.

Results and Discussion

Chromatographic analysis confirmed the presence of iridoids in the noni juice samples (Figure 1). Their concentrations were within the ranges that we had observed previously in pasteurized noni fruit puree (West et al. 2011). Deacetylasperulosidic acid, asperulosidic acid and scandoside contents (mean $\pm$ standard deviation) were, respectively, 1.40 ± 0.12 , 0.41 ± 0.06 and 0.04 ± 0.01 mg/g.

Figure 1. HPLC chromatogram of noni puree juice: 1-deacetylasperulosidic acid, 2-scandoside acid and 3-asperulosidic acid.

The results of the SARS-CoV-2 spike protein binding inhibition experiments are summarized in Table 1. Noni juice exhibited significant anti-spike protein potential by reducing average spike protein-ACE2 binding by 69.14%. Deacetylasperulosidic acid exhibited very modest activity by reducing binding by approximately 8%, with asperulosidic acid reducing it by almost 15%. Scandoside, however, displayed a high degree of biological activity. On average, it prevented 79.25% of spike protein-ACE2 binding. The mixture of these iridoids, with each at lower concentrations, was expected to reduce spike protein-ACE2 interaction by 32.60%. But the mixture was much more active than expected, preventing binding by an average of 55.48%. Deacetylasperulosidic acid is the major phytochemical constituent of noni juice. It has been found to be responsible, to a large degree, for the antioxidant, immunomodulatory and DNA protective properties of noni juice. However, our results suggest that it has a minor role in the ability of noni juice to prevent SARS-CoV-2 binding of the ACE2 receptor. Scandoside displayed very high activity in preventing SARS-CoV-2 binding. But asperulosidic acid and scandoside are present in smaller concentrations in noni juice than those evaluated in our assay. Although it appears that all three iridoids

act synergistically when combined, with an additional 22.88% reduction in spike protein binding beyond the expected levels, they do not appear to be responsible for all the inhibitory activity of noni juice.

Table 1. Percent inhibition (mean $\pm$ standard deviation) of SARS-Cov-2 spike protein binding to ACE2.

Sample	% Inhibition
Noni juice	69.14 $\pm$ 9.27
Deacetylasperulosidic acid (500 μ g/mL)	7.99 $\pm$ 0.95
Asperulosidic acid (500 μ g/mL)	14.82 $\pm$ 2.15
Scandoside (500 μ g/mL)	79.25 $\pm$ 1.70
Mixture of the iridoids (167 μ g/mL each)*	55.48 $\pm$ 5.25

*The expected % inhibition of the mixture, determined from individual iridoid results and concentration ratios, is 32.60 $\pm$ 1.89.

Other phytochemicals in noni juice may also be contributing to its anti-spike protein binding activity. Scopoletin, rutin, quercetin and kaempferol are present in noni fruit and juice (Deng et al. 2007 JNP; Deng et al. 2010 Food Chem). In silico studies (computer modeling or simulation) have revealed that scopoletin and related compounds have structural properties that allow it to bind to and inhibit SARS-CoV-2 main protease (Mpro) as well as interact with ACE2, thereby interfering with spike protein-ACE2 recognition (Abdelmohsen et al. 2021; Ikanovic et al. 2021; Khan et al. 2021). Rutin exhibited potent spike protein binding and anti-Mpro activity in molecular docking studies (Rahman et al. 2021; Rizzuti et al. 2021). Quercetin and kaempferol demonstrated high binding affinity for the spike protein-ACE2 complex, potentially perturbing effective binding (Pandey 2020). Thus, it is likely that the combination of multiple phytochemicals in noni juice act synergistically to prevent the binding of SARS-CoV-2 to ACE2.

Our current experiment focused solely on binding interactions between SARS-CoV-2 spike S1 RBD and ACE2 and did not evaluate inhibition of cellular proteases. As host cell proteolytic priming of S1 RBD enhances binding affinity, inhibition of furin and serine proteases by noni juice and its phytochemical constituents may further impede the ability of SARS-CoV-2 to infect cells. Scopoletin is reported to be a potent furin inhibitor (De et al. 2012). Molecular docking studies found that quercetin also inhibits furin (Milanovic 2021). Geniposide, an iridoid with a chemical structure very similar to deacetylasperulosidic acid and scandoside, displayed a high degree of interaction with TMPRSS2 in silico (Rahman 2020). This suggests that phytochemicals in iridoids in noni juice may also limit spike protein priming.

Conclusion

Noni juice reduced the ability of SARS-CoV-2 to bind ACE2 in vitro. The iridoids in noni juice are also capable of this. But it appears that other phytochemical constituents also contribute to the level of activity observed in noni juice. Synergistic inhibition of spike protein-ACE2 interaction occurs amongst the iridoids, and further synergies can be expected with scopoletin, quercetin and rutin. These findings provide additional insight into biological activities of noni juice that are not mediated by the immune system but may still improve resistance to SARS-CoV-2 infection.

References

Abdelmohsen UR, Albohy A, Abdulrazik BS, Bayoumi SAL, Malak LG, Khallaf ISA, Bringmann G, Salwa FF. 2021. Natural coumarins as potential anti-SARS-CoV-2 agents supported by docking analysis. *RSC Adv.* 11(208): 16970-16979.

Benton DJ, AG, Pengqi Xu, Roustan C, Martin SR, Rosenthal PB, Skehel JJ, Gamblin SJ. 2020. Receptor binding and priming of the spike protein of SARS-CoV-2 for membrane fusion. *Nature* 588(): 327-

Bestle D, Heindl MR, Limburg H, Van Lam van T, Pilgram O, Moulton H, Stein DA, Hardes K, Eickmann M, Dolnik O, Rohde C, Klenk HD, Garten W, Steinmetzer T, Böttcher-Friebertshäuser E. 2020. TMPRSS2 and furin are both essential for proteolytic activation of SARS-CoV-2 in human airway cells. *Life Sci Alliance* 3(9): e202000786.

Brooks VJ, Schafer M, Sharp P, Xu J, Cai J, Keuler NS, Godbee RG, Peek SF, Schultz RD, Suresh M, Darien BJ. 2009. Effects of *Morinda citrifolia* (Noni) on CD4+ and CD8+ T-cell activation in neonatal calves. *Prof Animal Scientist* 25(3):262–265.

Brooks VJ, De Wolfe TJ, Paulus TJ, Xu J, Cai J, Keuler NS, Godbee RG, Peek SF, McGuirk SM, Darien BJ. 2013. Ethnoveterinary application of *Morinda citrifolia* fruit puree on a commercial heifer rearing facility with endemic salmonellosis. *Afr J Tradit Complement Altern Med.* 10(1): 1-8.

Chen B, Tian EK, He B, Tian L, Han R, Wang S, Xiang Q, Zhang S, El Arnaout T, Cheng W. 2020. Overview of lethal human coronaviruses. *Signal Transduct Target Ther.* 5(1):89.

De UC, Mishra P, Pal PR, Dinda B, Basak A. 2012. Non-peptide inhibitors of proprotein convertase subtilisin kexins (PCSKs): An overall review of existing and new data. *Colloquium Series on Protein Activation and Cancer* 1(3):1-76.

Deng S, Palu AK, West BJ, Su CX, Zhou BN, Jensen JC. 2007. Lipxygenase Inhibitory Constituents of the Fruits of Noni (*Morinda citrifolia*) Collected in Tahiti. *J Nat Prod.* 70 (5): 859-862.

Deng S, West BJ, Jensen CJ. 2010. Simultaneous characterization and quantitation of flavonol glycosides and aglycones in noni leaves using a validated HPLC-UV/MS method. *Food Chem.* 111(2):526-529.

Deng S, West B, Palu A, Jensen J. 2011. Determination and comparative analysis of major iridoids in different parts and cultivation sources of *Morinda citrifolia*. *Phytochem Anal.* 22(1):26-30.

Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, Acton S. 2000. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res.* 87(5):E1-E9.

Efferth T, Koch E. 2011. Complex interactions between phytochemicals. The multi-target therapeutic concept of phytotherapy. *Curr Drug Targets.* 12(1):122-132.

European Commission. 2003. Commission decision of 5 June 2003 authorising the placing on the market of "noni juice" (juice of the fruit of *Morinda citrifolia* L.) as a novel food ingredient under regulation (EC) No 258/97 of the European parliament and of the council. *Official J. Eur. Union L* 144, 12/06/2003.

Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* 203(2):631-637.

Ikanovic T, Sehercehajic E, Saric B, Tomic N, Hadziselimovic R. 2021. In silico analysis of scopoletin interaction with potential SARS-CoV-2 target. NT 2021: New Technologies, Development and Application IV, pp 897-903. Springer, New York City

Keidar S, Kaplan M, Gamliel-Lazarovich A. 2007. ACE2 of the heart: From angiotensin I to angiotensin (1-7). *Cardiovasc Res.* 73(3):463-469.

Khan J, Sakib SA, Mahmud S, Khan Z, Islam MN, Sakib MA, Emran TB, Simal-Gandara J. 2021. Identification of potential phytochemicals from Citrus Limon against main protease of SARS-CoV-2: molecular docking, molecular dynamic simulations and quantum computations. *J Biomol Struct Dyn.* Epub 19 Jul 2021.

Lai MM, Cavanagh D. 1997. The molecular biology of coronaviruses. *Adv Virus Res.* 48:1-100.

Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. 2003. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 426(6965):450-454.

Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. 2020. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 395(10224):565-574.

Ma DL, Jun Z, Jianhua G. 2008. The effect of Tahitian Noni Juice on antioxidation and immune function. *Chin Med Res Clin.* 6:8–10.

Mohanty SK, Satapathy A, Naidu MM, Mukhopadhyay S, Sharma S, Barton LM, Stroberg E, Duval EJ, Pradhan D, Tzankov A, Parwani AV. 2020. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19) - anatomic pathology perspective on current knowledge. *Diagn Pathol.* 15(1):103.

Morton JF. 1992. The ocean going noni, or Indian mulberry (*Morinda citrifolia*, Rubiaceae) and some of its “colorful” relatives. *Econ Bot.* 46(3):241-256.

Murata K, Abe Y, Futamura-Masudaa M, Uwaya A, Isami F, Matsuda H. 2014. Activation of cell-mediated immunity by *Morinda citrifolia* fruit extract and its constituents. *Nat Prod Commun.* 9(4):445-50.

Nayak S, Mengi S. 2010. Immunostimulant activity of noni (*Morinda citrifolia*) on T and B lymphocytes. *Pharm Biol.* 48(7):724-731.

Palu AK, Kim AH, West BJ, Deng S, Jensen J, White L. 2008. The effects of *Morinda citrifolia* L. (noni) on the immune system: its molecular mechanisms of action. *J Ethnopharmacol.* 115(3):502-506.

Pandey P, Rane JS, Chatterjee A, Kumar A, Khan R, Prakash A, Ray S. 2020. Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: an in silico study for drug development. *J Biomol Struct Dyn.* 22:1-11.

Rahman N, Basharat Z, Yousuf M, Castaldo G, Rastrelli L, Khan H. 2020. Virtual Screening of Natural Products against Type II Transmembrane Serine Protease (TMPRSS2), the Priming Agent of Coronavirus 2 (SARS-CoV-2). *Molecules* 25(10):2271.

Rahman F, Tabrez S, Ali R, Alqahtani AS, Ahmed MZ, Rub A. 2021. Molecular docking analysis of rutin reveals possible inhibition of SARS-CoV-2 vital proteins. *J Tradit Complement Med.* 11(2):173-179.

Rizzuti B, Grande F, Conforti F, Jimenez-Alesanco A, Ceballos-Laita L, Ortega-Alarcon D, Vega S, Reyburn HT, Abian O, Velazquez-Campoy A. 2021. Rutin is a low micromolar inhibitor of SARS-CoV-2 main protease 3CLpro: implications for drug design of quercetin analogs. *Biomedicines* 9(4):375.

Sunder J, Yasmeeen RBR, Kundu A, Jeyakumar S. 2007. Immunomodulator effect of *Morinda citrifolia* in poultry. *Indian J Animal Sci.* 77(11):1126-1128.

Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. 2000. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. *J Biol Chem.* 275(43):33238-33243.

Tyrrell DA, Bynoe ML. 1965. Cultivation of a novel type of common-cold virus in organ cultures. *Br Med J.* 1(5448):1467-1470.

Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veasler D. 2020. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* 181(2):281-292.e6.

Wang MY, Peng L, Jensen CJ, Deng S, West BJ. 2013. Noni juice reduces lipid peroxidation-derived DNA adducts in heavy smokers. *Food Sci Nutr.* 1(2):141-149.

West BJ, Jensen CJ, Westendorf J, White LD. 2006. A safety review of noni fruit juice. *J Food Sci.* 71(8): R100-R106.

West BJ, Deng S, Jensen CJ. 2011. Nutrient and phytochemical analyses of processed noni puree. *Food Res Int.* 44(7): 2295–2301.

West BJ, Deng S, Isami F, Uwaya A, Jensen CJ. 2018. The Potential Health Benefits of Noni Juice: A Review of Human Intervention Studies. *Foods* 7(4):58.

World Health Organization (2021) Coronavirus (COVID-19) Dashboard. <https://covid19.who.int/>, accessed 30 July 2021.

Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. 2020. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 367(6485):1444-1448.

Yang RB, Liu JX, Zhu KR, et al. 2011. Effect of Tahitian Noni Juice on immune function in mice. *J Chin Med Res.* 11(7):401-403.