doi: 10.12032/TMR20200406172

REVIEW

Traditional Chinese Medicine

The potential application of the traditional Chinese herb *Exocarpium Citri grandis* in the prevention and treatment of COVID-19

Wei-Wei Su[1]*, Yong-Gang Wang[1], Pei-Bo Li[1], Hao Wu[1], Xuan Zeng[1], Rui Shi[1], Yu-Ying Zheng[1], Pan-Lin Li[1], Wei Peng[1]

[1]Guangdong Engineering & Technology Research Center for Quality and Efficacy Reevaluation of Post-Market Traditional Chinese Medicine, Guangdong Provincial Key Laboratory of Plant Resources, School of Life Sciences, Sun Yat-sen University, Guangzhou 510275, China.

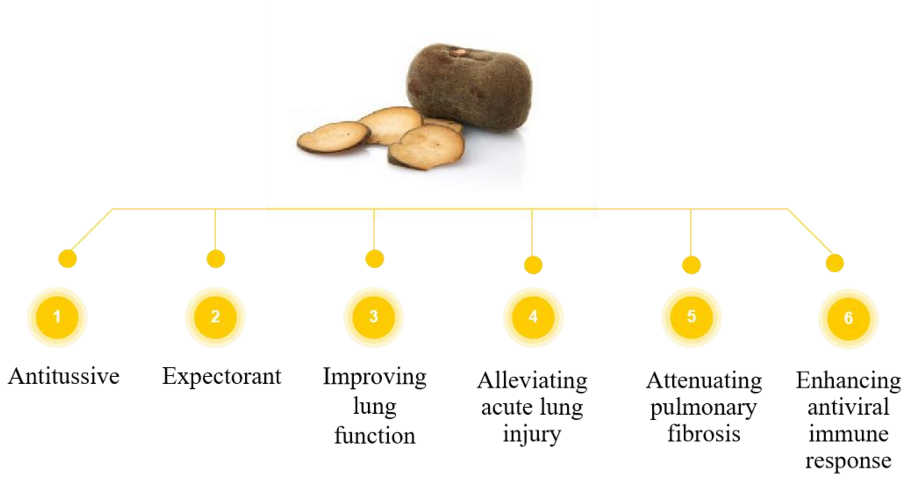
*Corresponding to: Wei-Wei Su. No. 135, Xingang Xi Road, School of Life Sciences, Sun Yat-sen University, Guangzhou 510275, China. E-mail: lsssww@126.com.

Highlights

In this review, the researchers summarized the characteristics and associated mechanisms of naringin, the pharmacologically active compound of the Chinese herb Huajuhong (*Exocarpium Citri grandis,* ECG) in alleviating multiple respiratory diseases, and discussed its potential application in the prevention and treatment of coronavirus disease 2019.

Traditionality

The Chinese herb Huajuhong is the dried epicarp of ECG, an herb that originated from Huazhou town in the Guangdong province of South China. It was first documented in an ancient book of traditional Chinese medicine, *Bencao Gangmu Shiyi* (*Supplement to Compendium of Materia Medica*), which was written in 1765 C.E. It has been used as folk herbal medicine in the treatment of respiratory diseases for hundreds of years in China. ECG was included in the Chinese Pharmacopoeia since 1977 and was a primary ingredient in many famous traditional Chinese medicine prescriptions. ECG contains flavonoids, and naringin is the primary active component.



Abstract

Huajuhong (*Exocarpium Citri grandis*, ECG) is a traditional Chinese herbal medicine and has been used for the treatment of respiratory diseases for hundreds of years. Recently, ECG has been listed in a traditional Chinese medicine formula in the Guidelines for the Diagnosis and Treatment of Coronavirus Disease 2019 (sixth edition) in China. To date, the effect and mechanism of ECG against respiratory diseases have not been systematically reviewed. In this paper, the researchers summarized the effects of ECG and its pharmacologically active compound naringin in functioning as an antitussive and expectorant, improving lung function, alleviating acute lung injury, attenuating pulmonary fibrosis, and enhancing antiviral immune response, so as to provide a reference for its clinical application in the prevention and treatment of multiple respiratory diseases, including coronavirus disease 2019.

Keywords: Huajuhong, *Exocarpium Citri grandis*, Naringin, coronavirus disease 2019, Clinical application

***Acknowledgments*:**

This work was supported by Science and Technology Planning Project of Guangdong Province in China (2018A030313491, 2019B090905002).

***Abbreviations*:**

ECG, *Exocarpium Citri grandis*; COVID-19, coronavirus disease 2019; TCM, traditional Chinese medicine; RARs, rapid adaptation receptors; LPS, lipopolysaccharides; AQP, aquaporin; ACE2: angiotensin-converting enzyme 2; HPPA, 3-(4-hydroxyphenyl) propionic acid.

***Competing interests*:**

The authors declare that they have no conflict of interest.

***Citation*:**

Wei-Wei Su, Yong-Gang Wang, Pei-Bo Li, et al. The potential application of the traditional Chinese herb *Exocarpium Citri Grandis* in the prevention and treatment of COVID-19. Traditional Medicine Research 2020, 5 (3): 160–166.

***Executive Editor*:** Nuo-Xi Pi.

***Submitted*:** 18 March 2020, ***Accepted*:** 3 April 2020, ***Online*:** 13 April 2020.

Background

The coronavirus disease (COVID-19), which broke out in Wuhan at the end of 2019, is rapidly becoming a huge challenge for global public health systems due to its strong infectivity and no specific drug treatment [1, 2]. To date, most COVID-19-infected patients manifest clinical symptoms, such as fever, dry cough, fatigue, and dyspnea. Some severe cases have developed various fatal complications, including acute respiratory distress syndrome, septic shock, metabolic acidosis, and coagulation dysfunction [3, 4]. Clinical imaging shows that multiple small patchy shadows and interstitial changes appear in lung tissue (especially evident in the lung periphery zone) in the early stages of COVID-19 infection. Subsequently, multiple ground-glass infiltration, as well as infiltration shadows and parenchymal lesions, can be observed in the lung tissue in severe cases [5, 6]. The latest autopsy results show that the small airways and alveoli of the dead patients contain a large amount of viscous secretions, which may lead to pulmonary embolism and, eventually, death [7]. The damage of COVID-19 to the human body is multifaceted, especially to the respiratory system, which may lead to serious symptoms, such as pulmonary hypofunction and acute lung injury [8]. Recently, the clinical treatment and prevention of COVID-19 involves administering antiviral and anti-inflammatory drugs, improving lung function, promoting sputum excretion, and alleviating acute lung injury.

Traditional Chinese medicine (TCM) has played an important role in the prevention and treatment of COVID-19 [9]. Huajuhong is the dried epicarp of *Exocarpium Citri grandis* (ECG), which originated from Huazhou town in the Guangdong province of South China [10]. It was first documented in an ancient TCM book, *Bencao Gangmu Shiyi* (*Supplement to Compendium of Materia Medica*), which was written in 1765 C.E. Moreover, ECG has been used as folk herbal medicine in the treatment of respiratory diseases for hundreds of years [11, 12]. ECG was included in the Chinese Pharmacopoeia since 1977 and was a primary ingredient in many famous TCM prescriptions [13]. The flavonoids contained in ECG, especially naringin, have been proven to be the primary active components [14, 15]. The researchers' preliminary studies have revealed that ECG possessed excellent antitussive, expectorant, anti-asthmatic [14], and anti-inflammatory effects [16]. Its antitussive effects are not associated with the central nervous system; that is, it's does not depend on the C fibers in the trachea but are rather related to the discharge of rapid adaptation receptors (RARs) [17]. Furthermore, toxicological studies suggested that ECG has no obvious toxic and side effects on the nervous system, cardiovascular system, and respiratory system of experimental animals [18].

A systematic chemical profiling analysis revealed that naringin is the primary flavonoid in ECG [10, 19]. Naringin (naringenin-7-O-rhamnoglucoside) is a flavanone glycoside that is widely distributed in plant-based food [20]. Evidence from numerous studies supports that naringin possesses pharmacological benefits for the treatment of multiple illnesses [21–23]. Besides, naringin and its metabolite naringenin are systematically evaluated for their therapeutic effects on respiratory diseases [24, 25]. Both are found to be effective in relieving cough, phlegm, and pulmonary inflammation [26–28]. Moreover, the efficacy of naringin against Severe Acute Respiratory Syndromeis also documented (Chinese patent: ZL03126908.7) [29].

Recently, ECG has been listed in a TCM formula in Diagnosis and Treatment Protocol for COVID-19 (Trial Version 6) issued by the National Health Commission of the People's Republic of China [30]. However, the efficacy and mechanism of ECG against respiratory diseases have not been systematically reviewed yet. In this paper, the authors summarized the efficacy of ECG in functioning as an antitussive and expectorant, improving lung function, alleviating acute lung injury, attenuating pulmonary fibrosis, and enhancing antiviral immune response, to show its potential application in the prevention and treatment of multiple respiratory diseases, including COVID-19.

Application prospect of ECG against COVID-19

Antitussive efficacy

ECG was found to exert significant antitussive effects on pathological cough caused by smoking and ovalbumin-induced cough-variant asthma in guinea pigs [31, 32].

Gao et al. investigated the antitussive mechanism of naringin in a guinea pig cough model [26]. Naringin was found to be a peripheral antitussive. Further studies suggested that the mechanism of action of naringin did not associate with either the sensory neuropeptide system or the modulation of ATP-sensitive K^+ channels. It is considered to exhibit its peripheral antitussive effects through RARs, which were the main afferent nerve fibers to stimulate cough [33]. Shi et al. evaluated the relaxant effect of naringin on rat tracheal smooth muscle by measuring the muscular tension in rat tracheal rings using a mechanical recording system [34]. Naringin was observed to relax tracheal smooth muscle by opening large conductance Ca^{2+}-activated K^+ channels, which mediate plasma membrane hyperpolarization and reduces Ca^{2+} influx. The obtained results revealed the therapeutic potential of naringin against cough-variant asthma.

doi: 10.12032/TMR20200406172

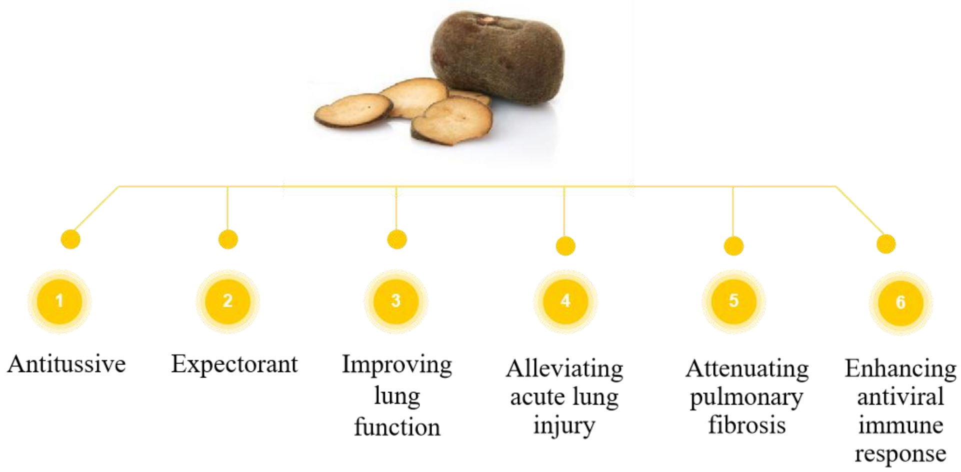


Figure 1 The therapeutic effects of *Exocarpium Citri grandis* against multiple respiratory diseases.

Expectorant efficacy

Naringin has a regulating effect on mucus and serous components in sputum [35, 36]. On the one hand, naringin can significantly inhibit the synthesis and secretion of rat airway mucin 5AC induced by lipopolysaccharides (LPS) and the proliferation of airway epithelial goblet cells, while significantly inhibiting the high secretion of mucin induced by epidermal growth factor [35]. On the other hand, the expression and function of cystic fibrosis transmembrane conductance regulator in the basal parietal membrane promotes the secretion of Cl^- to the airway cavity. This then activates aquaporin (AQP) through osmotic pressure to promote the secretion of serous fluids in the airway, while upregulating the expression of AQP1 and AQP5, which are inhibited by LPS and particulate matter (PM) 2.5 [36].

Improving lung function

Naringin was proven to improve lung function and regulate pulmonary secretion [24]. Shi et al. revealed that naringin improved lung function in mice with lung injury caused by cigarette smoke and PM 2.5 [37]. Naringin can increase dynamic lung compliance, decrease static lung compliance, reduce lung resistance, increase peak expiratory flow rate, increase FEV20/FVC, and improve total lung air volume. These results suggest that naringin not only improves the elasticity of respiratory muscles and affect elastic resistance, but also increases the size of the respiratory tract and reduce airway resistance.

Alleviating acute lung injury

Naringin possesses a significant inhibitory effect on LPS-induced acute lung inflammation [38–40]. In addition, naringin also significantly inhibits cigarette smoke-induced symptoms of chronic obstructive pulmonary disease, such as chronic airway inflammation, high secretion of mucus, cough hyperresponsiveness, and airway hyperresponsiveness [28, 31]. On the one hand, naringin can significantly inhibit the level of pro-inflammatory factor interleukin 8 in alveolar lavage fluid, reduce neutrophil infiltration, inhibit the decrease of anti-inflammatory factor interleukin 10, and promote the expression of lipoxin A_4 receptor. On the other hand, by regulating the release of nitric oxide and metabolism of pro-oxidant homocysteine, naringin can reduce lung inflammation and damage to lung tissue, as well as promote inflammation resolution [41].

Attenuating pulmonary fibrosis

Pulmonary fibrosis is a severe diffuse pulmonary inflammatory disease caused by a variety of factors. Its pathogenesis includes damage to alveolar epithelial cells, aggregation and activation of inflammatory cells, apoptosis, fibroblast proliferation, and collagen production [42]. Chen et al. evaluated the protective effects of naringin against paraquat-induced acute lung injury and pulmonary fibrosis in mice. The results showed that naringin reduced the levels of tumor necrosis factor-α, transforming growth factor-β1, matrix metalloproteinase-9, tissue inhibitors of metalloproteinases-1, hydroxyproline, and malonaldehyde; while it also significantly increased the activities of several antioxidant enzymes (superoxide dismutase, glutathione peroxidase, and heme oxygenase) [43].

Enhancing antiviral immune response

In a preliminary study, the researchers evaluated the potential of naringin in the supportive treatment of severe acute respiratory syndrome (Chinese patent: ZL03126908.7) [29]. Recently, Cheng et al.

investigated the effects of several flavonoids on immunoregulation and its use in potential targeting ACE2 (angiotensin-converting enzyme 2), which is a receptor of the coronavirus [44]. Naringin was found to inhibit the expression of the proinflammatory cytokines induced by LPS in raw macrophage cell lines, showing its effects for preventing a cytokine storm. Further molecular docking revealed that naringin had stronger binding affinity to ACE2, suggesting its potential in preventing coronavirus infection.

Moreover, some metabolites derived from naringin are also found to possess antiviral activities. For example, 3-(4′-hydroxyphenyl) propionic acid (HPPA) is the primary metabolite of naringin that is catabolized by gut microbiota [45–47]. HPPA is absorbed by the intestinal tract into the blood circulatory system and then reach the lungs and trachea [48]. Recently, HPPA was found to enhance the type I interferon signal, enhance the immune response of macrophages, and regulate the function of antigen-presenting cells and T cells, thereby opening up and enhancing the entire body [49]. The antiviral immune response can enhance type I interferon signaling to prevent influenza infection before it occurs [50], given that naringin is eventually degraded into HPPA [51]. Hence, naringin intake can probably enhance antiviral immune response.

Conclusions

In summary, ECG is a pharmacologically active folk herb which can be used for the treatment of respiratory diseases (Figure 1). It contains flavonoids that have been assigned as the primary active components, especially naringin. To be specific, its therapeutic effects in respiratory diseases are described above: (1) naringin is a peripheral antitussive and exerts its efficiency through RARs; (2) naringin has a regulating effect on both mucus and serous components in sputum; (3) naringin can improve lung function and regulate pulmonary secretion; (4) naringin can alleviate acute lung injury by inhibiting the secretion of pulmonary inflammatory factors and promote inflammation resolution; (5) naringin possesses therapeutic effects in attenuating pulmonary fibrosis; (6) naringin can enhance the antiviral immune response through its catabolite HPPA. These results suggest that naringin has a great potential for application in alleviating the respiratory symptoms caused by COVID-19.

References

1. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). Int J Surg 2020, 76: 71–76.
2. Lake MA. What we know so far: COVID-19 current clinical knowledge and research. Clin Med (Lond) 2020, 20: 124–127.
3. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020.
4. Jiang F, Deng L, Zhang L, et al. Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). J Gen Intern Med 2020: 1–5.
5. Xu X, Yu C, Qu J, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. Eur J Nucl Med Mol Imaging 2020: 1–6.
6. Dai WC, Zhang HW, Yu J, et al. CT imaging and differential diagnosis of COVID-19. Can Assoc Radiol J 2020, 71: 195–200.
7. Liu Q, Wang R, Qu G, et al. General anatomy report of novel coronavirus pneumonia death corpse. J Forensic Med 2020, 36: 19–21.
8. Lai CC, Shih TP, Ko WC, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents 2020, 55: 105924.
9. Ren JL, Zhang AH, Wang XJ. Traditional Chinese medicine for COVID-19 treatment. Pharmacol Res 2020, 155: 104743.
10. Li P, Liu M, Hu J, et al. Systematic chemical profiling of *Citrus grandis* 'Tomentosa' by ultra-fast liquid chromatography/diode-array detector/quadrupole time-of-flight tandem mass spectrometry. J Pharm Biomed Anal 2014, 90: 167–179.
11. Jiang K, Song Q, Wang L, et al. Antitussive, expectorant and anti-inflammatory activities of different extracts from *Exocarpium Citri grandis*. J Ethnopharmacol 2014, 156: 97–101.
12. Yuan YP, Zhai HQ, Guo ZJ, et al. Analysis of historical origin and standardization system construction of *Citri Grandis Exocarpium*. Chin J Chin Mater Med 2017, 42: 2214–2218.
13. Committee for the Pharmacopoeia of Peopl's Republic of China. Pharmacopoeia of People's Republic of China, Part 1. Beijing: Chemical Industry Publishing House, 2015.
14. Li P, Ma Y, Wang Y, et al. Experimental studies on antitussive,expectorant and antiasthmatic effects of extract from *Citrus grandis* var. tomentosa. Chin J Chin Mater Med 2006, 31: 1350–1352.
15. Zhu Z, Wu H, Su W, et al. Effects of total flavonoids from *Exocarpium Citri Grandis* on air pollution particle-induced pulmonary inflammation and oxidative stress in mice. J Food Sci 2019, 84: 3843–3849.
16. Li P, Ma Y, Yang H, et al. Anti-inflammatory effects of *Exocarpium Citri grandis* extract. Chin Tradit Herb Drug 2006, 37: 251–253. (Chinese)

TMR
doi: 10.12032/TMR20200406172

17. Li P, Su C, Bi F, et al. Study on antitussive effect and mechanism of *Exocarpium Citri grandis* extract. Chin Tradit Herb Drug 2008, 38: 247–250. (Chinese)
18. Li P, Wang Y, Peng W, et al. Safety pharmacological study of the effects of *Exocarpium Citri grandis* extract on central nervous system in mice. Journal of Chinese Medicinal Materials 2007, 30: 1438–1439. (Chinese)
19. Zeng X, Su W, Zheng Y, et al. UFLC-Q-TOF-MS/MS-based screening and identification of flavonoids and derived metabolites in human urine after oral administration of *Exocarpium Citri Grandis* extract. Molecules 2018, 23: 895.
20. Yao H, Su W, Lin L, et al. Comprehensive investigation into the interconversion of C-2 diastereomers of naringin. Chirality 2018, 30: 652–660.
21. Bharti S, Rani N, Krishnamurthy B, et al. Preclinical evidence for the pharmacological actions of naringin: a review. Planta Med 2014, 80: 437–451.
22. Patel K, Singh GK, Patel DK. A review on pharmacological and analytical aspects of naringenin. Chin J Integr Med 2018, 24: 551–560.
23. Salehi B, Fokou PVT, Sharifi-Rad M, et al. The therapeutic potential of naringenin: a review of clinical trials. Pharmaceuticals (Basel). 2019, 12: 11.
24. Li P, Wang Y, Wu Z, et al. The pre-clinical studies of naringin, an innovative drug, derived from *Citri Grandis Exocarpium* (Huajuhong). Acta Sci Nat Univ Sunyatseni 2015, 54: 1–5.
25. Zeng X, Su W, Liu B, et al. A review on the pharmacokinetic properties of naringin and its therapeutic efficacies in respiratory diseases. Mini Rev Med Chem 2019, 22: 286–293.
26. Gao S, Li P, Yang H, et al. Antitussive effect of naringin on experimentally induced cough in Guinea pigs. Plant Med 2011, 77: 16–21.
27. Lin B, Li P, Wang Y, et al. The expectorant activity of naringenin. Pulm Pharmacol Ther 2008, 21: 259–263.
28. Nie YC, Wu H, Li PB, et al. Anti-inflammatory effects of naringin in chronic pulmonary neutrophilic inflammation in cigarette smoke-exposed rats. J Med Food 2012, 15: 894–900.
29. Su W, Wang Y, Fang T, et al. Application of naringin in preparation of supportive treatment for SARS. China patent ZL03126908.7. 2004. (Chinese)
30. National Health Commission of the People's Republic of China. Diagnosis and Treatment Protocol for COVID-19 (trial version 6). Beijing, 2020. (Chinese)
31. Luo YL, Zhang CC, Li PB, et al. Naringin attenuates enhanced cough, airway hyperresponsiveness and airway inflammation in a guinea pig model of chronic bronchitis induced by cigarette smoke. Inter Immunopharmacol 2012, 13: 301–307.
32. Jiao H, Su W, Li P, et al. Therapeutic effects of naringin in a guinea pig model of ovalbumin-induced cough-variant asthma. Pulm Pharmacol Ther 2015, 33: 59–65.
33. Widdicombe J. Neuroregulation of cough: implications for drug therapy. Curr Opin Pharmacol 2002, 2: 256–263.
34. Shi R, Xu JW, Xiao ZT, et al. Naringin and naringenin relax rat tracheal smooth by regulating BKCa activation. J Med Food 2019, 22: 963–970.
35. Nie Y, Wu H, Li P, et al. Naringin attenuates EGF-induced MUC5AC secretion in A549 cells by suppressing the cooperative activities of MAPKs-AP-1 and IKKs-IκB-NF-κB signaling pathways. Eur J Pharmacol 2012, 690: 207–213.
36. Shi R, Xiao ZT, Zheng YJ, et al. Naringenin regulates CFTR activation and expression in airway epithelial cells. Cell Physiol Biochem 2017, 44: 1146–1160.
37. Shi R, Su WW, Zhu ZT, et al. Regulation effects of naringin on diesel particulate matter-induced abnormal airway surface liquid secretion. Phytomed 2019, 63: 153004.
38. Liu Y, Wu H, Nie Y, et al. Naringin attenuates acute lung injury in LPS-treated mice by inhibiting NF-κB pathway. Inter Immunopharmacol 2011, 11: 1606–1612.
39. Chen Y, Wu H, Nie Y, et al. Mucoactive effects of naringin in lipopolysaccharide-induced acute lung injury mice and beagle dogs. Environ Toxicol Pharmacol 2014, 38: 279–287.
40. Peng Y, Hu M, Lu Q, et al. Flavonoids derived from *Exocarpium Citri Grandis* inhibit LPS-induced inflammatory response via suppressing MAPK and NF-κB signalling pathways. Food Agric Immunol 2019, 30: 564–580.
41. Li P, Liao Y, Liu H, et al. Naringin's influence on the protein expressions in the lung tissues of cigarette smoke induced acute lung inflammation in mice by iTRAQ technology. Acta Sci Nat Univ Sunyatseni 2017, 56: 102–110.
42. Meyer KC. Pulmonary fibrosis, part I: epidemiology, pathogenesis, and diagnosis. Expert Rev Respir Med 2017, 11: 343–359.
43. Chen Y, Nie Y, Luo Y, et al. Protective effects of naringin against paraquat-induced acute lung injury and pulmonary fibrosis in mice. Food Chem Toxicol 2013, 58: 133–140.
44. Cheng L, Zheng W, Li M, et al. *Citrus* fruits are rich in flavonoids for immunoregulation and potential targeting ACE2. Preprints 2020.

45. Zeng X, Bai Y, Peng W, et al. Identification of naringin metabolites in human urine and feces. Eur J Drug Metab Pharmacokinet 2017, 42: 647–656.
46. Zou W, Luo Y, Liu M, et al. Human intestinal microbial metabolism of naringin. Eur J Drug Metab Pharmacokinet 2015, 40: 363–367.
47. Chen T, Su W, Yan Z, et al. Identification of naringin metabolites mediated by human intestinal microbes with stable isotope-labeling method and UFLC-Q-TOF-MS/MS. J Pharm Biomed Anal 2018, 161: 262–272.
48. Zeng X, Yao H, Zheng Y, et al. Tissue distribution of naringin and derived metabolites in rats after a single oral administration. J Chromatogr B 2020, 1136: 121846.
49. Steed AL, Christophi GP, Kaiko GE, et al. The microbial metabolite desaminotyrosine protects from influenza through type I interferon. Science 2017, 357: 498–502.
50. Chen T, Wu H, He Y, et al. Simultaneously quantitative analysis of naringin and its major human gut microbial metabolites naringenin and 3-(4'-hydroxyphenyl) propanoic acid via stable isotope deuterium-labeling coupled with RRLC-MS/MS method. Molecules 2019, 24: 4287.
51. Zeng X, Yao H, Zheng Y, et al. Metabolite profiling of naringin in rat urine and feces using stable isotope-labeling-based liquid chromatography-mass spectrometry. J Agric Food Chem 2020, 68: 409–417.