



SEARCHING FOR BIOACTIVE COMPOUNDS AGAINST SARS-COV-2 FROM TRADITIONAL CHINESE MEDICINES

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Traditional Chinese medicine is a treasure in Chinese culture, which has been applied for thousands of years and accumulated numerous knowledge about the usages of herbs to improve human health. Since the breakout of coronavirus disease 2019 (COVID-19), traditional Chinese medicines play an important role in the fight against the infectious disease in China. Starting from traditional Chinese medicines with antivirus effects will greatly increase the possibility to find the lead compounds against COVID-19.

Based on the in-house multi-technology platform, a series of natural compounds with inhibitory activity against 3CL protease (3CLpro) were disclosed from antivirus medicinal herbs and formulas. For example, shuanghuanglian preparation, a Chinese traditional patent medicine (also called proprietary Chinese medicine) used for the treatment of acute respiratory tract infections since 1973, is a classical purified herbal preparation extracted from three Chinese herbal medicines, namely, *Lonicera japonica* Thunb., *Scutellaria baicalensis* Georgi, and *Forsythia suspense* (Thunb.) Vahl. A total of 27 compounds were quickly identified and separated from the three herbs, and assayed their inhibitory activities against 3CLpro. The results showed that nine compounds were identified as lower-micromolar-range inhibitors of 3CLpro. Among these, the binding of baicalin as well as baicalein with 3CLpro was comprehensively characterized, and a crystal structure of SARS-CoV-2 3CLpro in complex with baicalein, the first noncovalent, nonpeptidomimetic small-molecule inhibitor, was also determined. The study provides a good example for exploring the in vitro potency of Chinese traditional patent medicines and identifying bioactive ingredients toward a specific target, and adds scientific evidence to support the clinical potential of Shuanghuanglian preparation, as well as two natural products for COVID-19 treatment.¹ We also discovered myricetin, a flavonoid found in many food sources, as a non-peptidomimetic and covalent inhibitor of the SARS-CoV-2 3CLpro. Crystal structures of the protease bound with myricetin and its derivatives unexpectedly revealed that the pyrogallol group worked as an electrophile to covalently modify the catalytic cysteine. The results provide detailed mechanistic insights into the covalent mode of action by pyrogallol-containing natural products and a template for design of nonpeptidomimetic covalent inhibitors against 3CLpro.² In addition, we tried an efficient discovery of potential inhibitors for SARS-CoV-2 3CL protease directly from the herbal extracts using a native MS-based affinity-selection method. It is a meaningful attempt to search for bioactive molecules in a quick and purposeful way.

Keywords: Traditional Chinese medicine and ethnodrug; Anti-SARS-CoV-2; bioactive compounds

Acknowledgements: We are thankful for the financial support from the Science and Technology Commission of Shanghai Municipality (20430780300).

References

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