

## ORAL PRESENTATIONS

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### COMPONENTS AND ACTION MECHANISMS OF TRADITIONAL CHINESE MEDICINE AGAINST COVID-19

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Traditional Chinese medicine (TCM) has achieved remarkable efficacy in the clinical treatment of coronavirus disease 2019 (COVID-19). Nevertheless, the pharmacodynamic material basis and molecular mechanisms of TCM formulae remain critical scientific questions to be elucidated. Huashi Baidu decoction (Q-14), a clinically approved TCM formula for COVID-19 treatment, exerts dual pharmacological effects of antiviral and anti-inflammatory activities. Using an integrative pharmacological strategy combined with ultra-high-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry, a total of 343 chemical constituents were identified from Q-14, among which 60 prototype compounds that could be absorbed into blood were screened out. Six bioactive monomers exhibiting dose-dependent inhibitory effects against SARS-CoV-2 infection were further obtained. Among them, echinatin and quercetin target the viral main protease ( $M^{\text{pro}}$ ), while glycyrrhisoflavone and licoisoflavone A target viral RNA-dependent RNA polymerase (RdRp). Licochalcone B, echinatin and glycyrrhisoflavone are capable of suppressing SARS-CoV-2-triggered inflammatory responses. Moreover, glycyrrhisoflavone and licoisoflavone A potently inhibit the inflammatory target PDE4. High-resolution crystal structures of PDE4 in complex with these two compounds were solved, clarifying their anti-inflammatory molecular mechanisms at the atomic level.

Qing-Fei-Pai-Du decoction (QFPD) is another well-known TCM formula against COVID-19. Leupeptin, a microbial-derived metabolite discovered from QFPD, can inhibit SARS-CoV-2  $M^{\text{pro}}$  and suppress viral propagation at the cellular level. Produced by medicinal-plant-symbiotic *Streptomyces* species, leupeptin indicates that pharmacologically active substances of TCM herbs do not merely originate from plant tissues. Instead, medicinal herbs, symbiotic microorganisms and microbial metabolites together constitute an ecosystem of bioactive substances for TCM.

Collectively, these studies demonstrate that TCM formulae exert anti-COVID-19 effects via a multi-component and multi-target mode: they directly target key viral proteins to restrain viral replication, and act on host inflammatory pathways to alleviate inflammatory injury. In addition, microbial-originated metabolites constitute a non-negligible source of TCM bioactive components. These findings provide important theoretical support for the modernization research of TCM and the discovery of lead natural compounds against SARS-CoV-2.