**Supporting Information**

**Exploring the pharmacological mechanism of the widely used Huashi Baidu Decoction against SARS-CoV-2 by in silico simulations and in vitro assays**

Zhaoyin Zhoua,b, Yaxin Tianb,c,Feng Lia,d,eYan Zhangf,g, Shizhao Chena,d,e, Bo Fengd,e, Leyun Wub, Hongyan Yaoa,b, Jia Lia,d,e, Xiangrui Jiangh,f,g, Jingshan Shenf,g, Haiyu Xui, Luqi Huangi,\*\*\*, Weiliang Zhua,b,c,\*\*, Zhijian Xua,b,c,\*

*aSchool of Chinese Materia Medica, Nanjing University of Chinese Medicine, 210023, Nanjing, PR China.*

*bState Key Laboratory of Drug Research; Drug Discovery and Design Center; Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China.*

*cSchool of Pharmacy, University of Chinese Academy of Sciences, No.19A Yuquan Road, Beijing 100049, China.*

*dShanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, and University of Chinese Academy of Sciences, Beijing 100049, China.*

*eState Key Laboratory of Chemical Biology, Shanghai Institute of Materia Medica, Chinese Academy of Sciences.*

*fState Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China*

*gUniversity of Chinese Academy of Sciences, No.19A Yuquan Road, Beijing 100049, China*

*hShandong Laboratory of Yantai Drug Discovery, Bohai Rim Advanced Research Institute for Drug Discovery, Yantai, Shandong 264117, China*

*iState Key Laboratory of Dao-di Herbs, National Resource Center for Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China.*

|  |  |
| --- | --- |
| **Contents** | **Page** |
| Table S1. Core targets in PPI network. | S2 |
| Table S2. Core nodes in the component-target-pathway network. | S3 |
| Table S3. HSBD’s potential anti-SARS-CoV-2 targets predicted by deep learning methods. | S4 |
| Table S4. HSBD’s potential anti-SARS-CoV-2 targets predicted by ligand-based approach. | S5 |
|  | |

**Table S1.** Core targets in PPI network.

|  |  |  |  |
| --- | --- | --- | --- |
| name | BetweennessCentrality | ClosenessCentrality | Degree |
| TP53 | 0.36 | 0.45 | 46 |
| HSP90AA1 | 0.09 | 0.40 | 24 |
| STAT3 | 0.11 | 0.42 | 22 |
| CTNNB1 | 0.07 | 0.39 | 22 |
| EGFR | 0.08 | 0.39 | 22 |
| PTPN11 | 0.03 | 0.35 | 20 |
| EP300 | 0.12 | 0.39 | 19 |
| HSP90AB1 | 0.03 | 0.38 | 17 |
| MAPK1 | 0.05 | 0.39 | 17 |
| KRAS | 0.06 | 0.38 | 15 |
| HIF1A | 0.04 | 0.39 | 14 |
| BCL2L1 | 0.06 | 0.37 | 13 |
| IGF1R | 0.04 | 0.35 | 13 |
| MDM2 | 0.02 | 0.37 | 11 |
| TNF | 0.05 | 0.34 | 11 |
| PTGS2 | 0.09 | 0.35 | 10 |
| CASP3 | 0.07 | 0.38 | 10 |
| PRKACA | 0.03 | 0.32 | 10 |
| KDR | 0.03 | 0.34 | 10 |
| CDK1 | 0.03 | 0.34 | 9 |
| CALM3 | 0.03 | 0.32 | 9 |
| MET | 0.03 | 0.33 | 9 |
| PLK1 | 0.03 | 0.34 | 8 |
| IKBKB | 0.04 | 0.35 | 8 |
| RUNX1 | 0.02 | 0.32 | 7 |
| APP | 0.15 | 0.32 | 6 |

**Table S2.** Core nodes in the component-target-pathway network (top5 nodes for each category: components, targets, and pathways, ranked by degree). ​

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Betweenness  Centrality | Closeness  Centrality | Degree | Label | Node name | Herb |
| 0.02 | 0.40 | 14 | component | baicalein (TCMID-25849) | Pinelliae Rhizoma, Paeoniae Radix Rubra |
| 0.02 | 0.40 | 14 | component | ombuin (TCMID-05897) | Pogostemonis Herba |
| 0.02 | 0.40 | 14 | component | Kaempferol-7,4′-dimethyl ether (TCMID-05890) | Pogostemonis Herba |
| 0.02 | 0.40 | 14 | component | Nortangeretin (TCMID-27696) | Glycyrrhizae Radix et Rhizoma |
| 0.01 | 0.39 | 13 | component | pollenitin (TCMID-00054) | Ephedrae Herba |
| 0.08 | 0.39 | 22 | target | MCL1 | - |
| 0.08 | 0.44 | 20 | target | EGFR | - |
| 0.08 | 0.38 | 18 | target | PGH2 | - |
| 0.03 | 0.37 | 17 | target | GSK3B | - |
| 0.06 | 0.41 | 16 | target | MK14 | - |
| 0.25 | 0.46 | 32 | pathway | PI3K-Akt signaling pathway | - |
| 0.19 | 0.41 | 26 | pathway | MAPK signaling pathway | - |
| 0.09 | 0.39 | 19 | pathway | Coronavirus disease - COVID-19 | - |
| 0.07 | 0.40 | 18 | pathway | C-type lectin receptor signaling pathway | - |
| 0.10 | 0.40 | 17 | pathway | Th17 cell differentiation | - |

**Table S3.** HSBD’s potential anti-SARS-CoV-2 targets predicted by deep learning methods. ​

|  |  |  |  |
| --- | --- | --- | --- |
| Target Name | UniProt id | Organism | Binding Score |
| RNA-dependent RNA polymerase (RdRp) | P0DTD1 | SARS-CoV-2 | 3.64 |
| Main protease (Mpro) | P0DTD1 | SARS-CoV-2 | 3.06 |
| Helicase | P0DTD1 | SARS-CoV-2 | 3.00 |
| Dihydroorotate dehydrogenase (DHODH) | Q02127 | Human | 2.48 |
| Papain-like protease (PLpro) | P0DTD1 | SARS-CoV-2 | 1.81 |

Note: The binding scores shown in this table represent the highest values for the specified target among all compounds in HSBD.

**Table S4.** HSBD’s potential anti-SARS-CoV-2 targets predicted by ligand-based approach.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Target Name | Reported anti-SARS-CoV-2 compound information in  D3Targets-2019-nCoV | | 2D Similarity | 3D Similarity |
| CAS | Reference (PMID) |
| Main protease (Mpro) | 2257-09-2 | 33350010 | 1.00 | 1.00 |
| Papain-like protease (PLpro) | 20347-71-1 | 33526482 | 1.00 | 1.00 |
| Helicase | 481-49-2 | 33052685 | 0.90 | 0.71 |
| RNA-dependent RNA polymerase (RdRp) | 483-18-1 | 32251767 | 0.78 | 0.60 |
| Dihydroorotate dehydrogenase (DHODH) | 1256565-36-2 | 33249060 | 0.62 | 0.64 |

Note: The 2D/3D similarity values shown in this table represent the highest values for the specified target among all compounds in HSBD.

**Table S5.** Potential bioactive HSBD compounds screened by molecular docking.

|  |  |  |  |
| --- | --- | --- | --- |
| Compound Name | Target Name | docking score | Cluster |
| TCMID-27541 | PLpro | -11.36 | 1 |
| TCMID-27726 | PLpro | -10.58 | 1 |
| TCMID-27453 | PLpro | -10.57 | 1 |
| TCMID-27745 | PLpro | -10.49 | 1 |
| TCMID-27314 | PLpro | -10.47 | 1 |
| TCMID-27448 | PLpro | -10.44 | 1 |
| TCMID-27525 | Mpro | -10.14 | 1 |
| TCMID-27550 | Mpro | -9.94 | 1 |
| TCMID-27451 | PLpro | -9.88 | 1 |
| TCMID-27481 | Mpro | -9.86 | 1 |
| TCMID-27578 | Mpro | -9.84 | 1 |
| TCMID-27693 | Mpro | -9.84 | 1 |
| TCMID-27712 | PLpro | -9.82 | 1 |
| TCMID-27511 | Mpro | -9.79 | 1 |
| TCMID-27725 | PLpro | -9.79 | 1 |
| TCMID-27727 | Mpro | -9.76 | 1 |
| TCMID-27317 | Mpro | -9.57 | 1 |
| TCMID-22240 | Mpro | -9.56 | 1 |
| TCMID-27450 | Mpro | -9.56 | 1 |
| TCMID-27600 | Mpro | -9.55 | 1 |
| TCMID-27346 | Mpro | -9.42 | 1 |
| TCMID-27423 | PLpro | -9.41 | 1 |
| TCMID-27601 | Mpro | -9.34 | 1 |
| TCMID-27597 | Mpro | -9.32 | 1 |
| TCMID-27444 | Mpro | -9.11 | 1 |
| TCMID-27576 | Mpro | -9.01 | 1 |
| TCMID-27439 | Mpro | -8.95 | 1 |
| TCMID-27361 | Mpro | -8.94 | 1 |
| TCMID-27362 | Mpro | -8.94 | 1 |
| TCMID-27364 | Mpro | -8.94 | 1 |
| TCMID-27319 | PLpro | -8.63 | 1 |
| TCMID-26940 | Mpro | -8.62 | 1 |
| TCMID-27452 | Mpro | -8.43 | 1 |
| TCMID-22246 | PLpro | -11.28 | 2 |
| TCMID-05947 | PLpro | -11.01 | 2 |
| TCMID-22270 | PLpro | -10.84 | 2 |
| TCMID-19525 | Mpro | -10.78 | 2 |
| TCMID-22216 | PLpro | -10.67 | 2 |
| TCMID-19547 | PLpro | -10.65 | 2 |
| TCMID-05909 | Mpro | -10.62 | 2 |
| TCMID-19495 | PLpro | -10.51 | 2 |
| TCMID-19497 | PLpro | -10.51 | 2 |
| TCMID-19493 | Mpro | -10.15 | 2 |
| TCMID-27440 | Mpro | -10.14 | 2 |
| TCMID-22342 | Mpro | -10.14 | 2 |
| TCMID-27657 | PLpro | -10.12 | 2 |
| TCMID-22248 | Mpro | -10.05 | 2 |
| TCMID-22290 | Mpro | -10.02 | 2 |
| TCMID-27401 | Mpro | -9.86 | 2 |
| TCMID-22341 | Mpro | -9.75 | 2 |
| TCMID-22156 | Mpro | -9.69 | 2 |
| TCMID-22154 | Mpro | -9.69 | 2 |
| TCMID-22317 | Mpro | -9.69 | 2 |
| TCMID-27557 | Mpro | -9.67 | 2 |
| TCMID-27691 | Mpro | -9.13 | 2 |
| TCMID-27411 | Mpro | -10.61 | 3 |
| TCMID-27363 | PLpro | -10.50 | 3 |
| TCMID-27701 | PLpro | -10.19 | 3 |
| TCMID-27564 | Mpro | -10.16 | 3 |
| TCMID-27521 | PLpro | -10.14 | 3 |
| TCMID-27682 | PLpro | -10.14 | 3 |
| TCMID-27537 | PLpro | -10.03 | 3 |
| TCMID-27491 | Mpro | -9.97 | 3 |
| TCMID-27602 | PLpro | -9.85 | 3 |
| TCMID-27744 | Mpro | -9.77 | 3 |
| TCMID-27716 | PLpro | -9.74 | 3 |
| TCMID-27403 | Mpro | -9.58 | 3 |
| TCMID-27714 | Mpro | -9.55 | 3 |
| TCMID-27278 | Mpro | -9.55 | 3 |
| TCMID-27575 | Mpro | -9.55 | 3 |
| TCMID-27391 | Mpro | -9.42 | 3 |
| TCMID-27354 | Mpro | -9.40 | 3 |
| TCMID-27279 | Mpro | -9.30 | 3 |
| TCMID-27277 | Mpro | -9.15 | 3 |
| TCMID-27352 | PLpro | -8.89 | 3 |
| TCMID-27404 | PLpro | -8.61 | 3 |
| TCMID-27599 | PLpro | -10.68 | 4 |
| TCMID-27424 | PLpro | -10.46 | 4 |
| TCMID-26919 | Mpro | -9.83 | 4 |
| TCMID-27304 | Mpro | -9.77 | 4 |
| TCMID-27461 | Mpro | -9.60 | 4 |
| TCMID-27579 | Mpro | -9.57 | 4 |
| TCMID-27284 | Mpro | -9.50 | 4 |
| TCMID-27493 | Mpro | -9.45 | 4 |
| TCMID-27400 | Mpro | -9.41 | 4 |
| TCMID-27488 | Mpro | -9.39 | 4 |
| TCMID-27300 | Mpro | -9.39 | 4 |
| TCMID-27496 | Mpro | -9.34 | 4 |
| TCMID-27702 | Mpro | -9.31 | 4 |
| TCMID-27498 | Mpro | -9.27 | 4 |
| TCMID-27474 | Mpro | -9.06 | 4 |
| TCMID-27545 | Mpro | -9.01 | 4 |
| TCMID-27446 | Mpro | -8.90 | 4 |
| TCMID-27522 | PLpro | -8.26 | 4 |
| TCMID-27335 | Mpro | -10.95 | 5 |
| TCMID-27309 | Mpro | -10.44 | 5 |
| TCMID-27334 | Mpro | -10.41 | 5 |
| TCMID-27336 | Mpro | -10.11 | 5 |
| TCMID-27626 | Mpro | -10.10 | 5 |
| TCMID-27659 | Mpro | -9.96 | 5 |
| TCMID-27674 | Mpro | -9.89 | 5 |
| TCMID-27528 | Mpro | -9.80 | 5 |
| TCMID-27667 | Mpro | -9.76 | 5 |
| TCMID-27669 | Mpro | -9.68 | 5 |
| TCMID-27668 | Mpro | -9.68 | 5 |
| TCMID-26518 | Mpro | -9.55 | 5 |
| TCMID-27530 | Mpro | -8.74 | 5 |
| TCMID-27285 | PLpro | -10.24 | 6 |
| TCMID-27286 | PLpro | -10.24 | 6 |
| TCMID-27519 | PLpro | -10.03 | 6 |
| TCMID-27490 | Mpro | -9.76 | 6 |
| TCMID-27287 | Mpro | -9.66 | 6 |
| TCMID-27489 | Mpro | -8.99 | 6 |
| TCMID-27290 | PLpro | -8.75 | 6 |
| TCMID-05954 | PLpro | -8.32 | 6 |
| TCMID-27585 | PLpro | -8.32 | 6 |
| TCMID-28762 | Mpro | -9.79 | 7 |
| TCMID-28761 | Mpro | -9.74 | 7 |
| TCMID-28859 | Mpro | -9.72 | 7 |
| TCMID-28742 | Mpro | -9.63 | 7 |
| TCMID-28738 | Mpro | -9.57 | 7 |
| TCMID-28758 | Mpro | -9.54 | 7 |
| TCMID-28757 | Mpro | -9.54 | 7 |
| TCMID-22089 | Mpro | -9.35 | 7 |
| TCMID-28760 | Mpro | -9.27 | 7 |
| TCMID-27724 | PLpro | -10.47 | 8 |
| TCMID-27546 | Mpro | -9.55 | 8 |
| TCMID-27603 | PLpro | -9.15 | 8 |
| TCMID-27598 | PLpro | -9.07 | 8 |
| TCMID-27393 | PLpro | -8.59 | 8 |
| TCMID-27499 | PLpro | -8.58 | 8 |
| TCMID-27484 | PLpro | -10.82 | 9 |
| TCMID-27487 | PLpro | -10.47 | 9 |
| TCMID-27538 | Mpro | -9.65 | 9 |
| TCMID-27715 | Mpro | -9.56 | 9 |
| TCMID-27365 | PLpro | -8.67 | 9 |
| TCMID-22314 | Mpro | -10.90 | 10 |
| TCMID-22265 | Mpro | -10.66 | 10 |
| TCMID-00033 | PLpro | -10.65 | 10 |
| TCMID-22266 | Mpro | -10.34 | 10 |
| TCMID-22303 | Mpro | -10.29 | 10 |
| TCMID-22148 | Mpro | -9.80 | 11 |
| TCMID-22152 | Mpro | -9.68 | 11 |
| TCMID-22168 | Mpro | -9.56 | 11 |
| TCMID-22098 | PLpro | -8.22 | 11 |
| TCMID-28202 | Mpro | -10.25 | 12 |
| TCMID-28222 | Mpro | -9.78 | 12 |
| TCMID-28271 | Mpro | -9.78 | 12 |
| TCMID-28270 | Mpro | -9.65 | 12 |
| TCMID-22115 | Mpro | -9.36 | 13 |
| TCMID-22167 | Mpro | -9.26 | 13 |
| TCMID-27327 | Mpro | -8.70 | 13 |
| TCMID-27479 | Mpro | -9.88 | 14 |
| TCMID-27347 | Mpro | -9.65 | 14 |
| TCMID-27580 | Mpro | -9.56 | 14 |
| TCMID-27512 | PLpro | -10.63 | 15 |
| TCMID-27513 | PLpro | -10.63 | 15 |
| TCMID-05982 | Mpro | -8.94 | 15 |
| TCMID-37067 | Mpro | -9.84 | 16 |
| TCMID-37096 | Mpro | -9.70 | 16 |
| TCMID-37054 | Mpro | -8.99 | 16 |
| TCMID-19523 | Mpro | -11.85 | 17 |
| TCMID-19522 | PLpro | -11.48 | 17 |
| TCMID-19502 | Mpro | -8.47 | 17 |
| TCMID-27708 | Mpro | -9.99 | 18 |
| TCMID-27390 | Mpro | -9.34 | 18 |
| TCMID-27547 | Mpro | -9.81 | 19 |
| TCMID-27561 | Mpro | -8.38 | 19 |
| TCMID-37102 | Mpro | -10.18 | 20 |
| TCMID-37138 | Mpro | -8.78 | 20 |
| TCMID-37125 | Mpro | -9.90 | 21 |
| TCMID-37121 | Mpro | -9.83 | 21 |
| TCMID-16012 | Mpro | -8.56 | 22 |
| TCMID-16004 | Mpro | -8.45 | 22 |
| TCMID-15972 | Mpro | -9.68 | 23 |
| TCMID-27492 | Mpro | -10.40 | 24 |
| TCMID-28905 | PLpro | -9.81 | 25 |
| TCMID-27566 | PLpro | -9.83 | 26 |
| TCMID-27510 | Mpro | -9.01 | 27 |
| TCMID-27372 | PLpro | -8.21 | 28 |
| TCMID-26609 | Mpro | -9.82 | 29 |
| TCMID-22304 | Mpro | -10.21 | 30 |
| TCMID-27456 | PLpro | -9.89 | 31 |
| TCMID-26495 | Mpro | -10.48 | 32 |
| TCMID-26478 | Mpro | -8.77 | 33 |
| TCMID-05981 | Mpro | -9.44 | 34 |
| TCMID-29623 | Mpro | -8.59 | 35 |
| TCMID-27696 | PLpro | -9.86 | 36 |
| TCMID-27586 | Mpro | -9.60 | 37 |
| TCMID-27457 | PLpro | -10.27 | 38 |
| TCMID-26949 | Mpro | -10.92 | 39 |
| TCMID-26613 | Mpro | -9.65 | 40 |
| TCMID-26517 | Mpro | -8.63 | 41 |
| TCMID-26477 | PLpro | -8.78 | 42 |
| TCMID-25916 | Mpro | -8.40 | 43 |
| TCMID-19514 | PLpro | -9.39 | 44 |
| TCMID-05977 | Mpro | -8.98 | 45 |
| TCMID-05973 | Mpro | -9.13 | 46 |
| TCMID-05972 | Mpro | -8.94 | 47 |
| TCMID-05965 | PLpro | -8.64 | 48 |