

### Supplementary R

**Supplementary table R1: Logistic regression analysis of factors associated with disease severity.**

| Predictor            | $\beta$ (SE)   | Adjusted OR (95% CI) | P value |
|----------------------|----------------|----------------------|---------|
| Age (per year)       | 0.127 (0.030)  | 1.14 (1.07–1.20)     | <0.001  |
| Monocytes (per unit) | 0.0024 (0.001) | 1.002 (1.001–1.004)  | 0.013   |
| Intercept            | −9.56 (2.16)   | —                    | <0.001  |

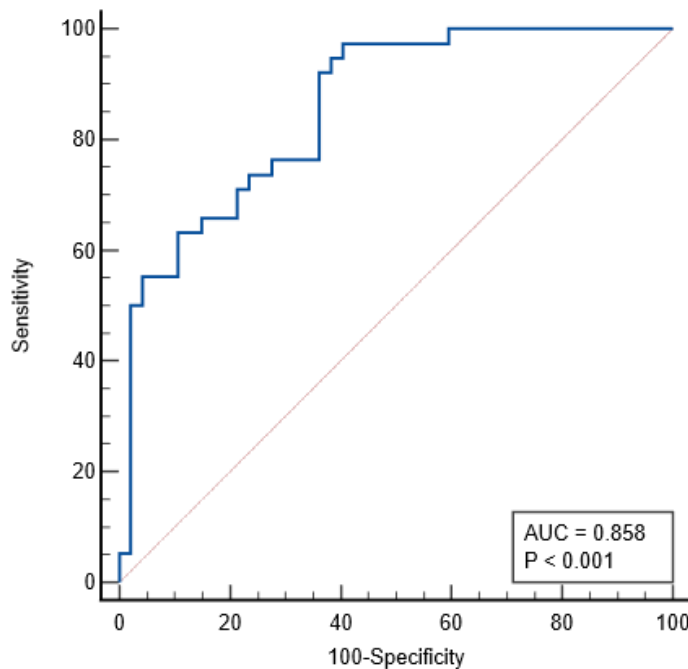
**Cohort:** 85 patients (severe: 38 [44.7%]; non-severe: 47 [55.3%]).

**Model fit:** Likelihood ratio  $\chi^2 = 35.20$  (2 df;  $P < 0.001$ ).

**Discrimination:** AUC = 0.86 (95% CI: 0.77–0.92).

**Variance explained:** Nagelkerke's  $R^2 = 0.45$

**Calibration:** Hosmer-Lemeshow  $\chi^2 = 15.56$  ( $P = 0.049$ ).



**Supplementary Fig. R1.** Receiver operating characteristic (ROC) curve of the logistic regression model for disease severity prediction. The model demonstrates strong discriminative ability with an area under the curve (AUC) of 0.858 (95% CI: 0.77–0.92,  $P < 0.0001$ ). The dashed diagonal line represents random chance (AUC = 0.5), while the solid curve shows model performance. Optimal cutoff ( $>0.235$ , arrow) yields 97.4% sensitivity and 59.6% specificity (Youden's index = 0.57).

**Supplementary table R2. Summary of binding energies ( $\Delta G$ ), origins of natural compounds, and mechanistic profiles of synthetic drugs across target proteins**

| Class   |    | Name         | Source                                                                                                                                                             | Energy (Kcal/ Mol) |         |              |               |              |         |           |         |         |
|---------|----|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|---------|--------------|---------------|--------------|---------|-----------|---------|---------|
|         |    |              |                                                                                                                                                                    | S                  | IL17R   | IL17F/IL17RA | IL17AF/IL17RA | IL17A/IL17RA | IL6R    | IL-6/IL6R | CD47    | CD41    |
|         |    |              |                                                                                                                                                                    | (7bnn)             | (5n9b)  | (3jvf)       | (5nan)        | (4hsa)       | (1n26)  | (1p9m)    | (2jjs)  | (3fcs)  |
| Natural | 1. | Phytic acid  | cereals, oil seeds and nuts                                                                                                                                        | -129.83            | -107.12 | -119.23      | -126.4        | -157.76      | -122.57 | -129.4    | -118.63 | -113.11 |
|         | 2. | Amygdalin    | bitter almonds, stone fruits, berries, apricots, plums, peaches, <a href="#">papaya</a> , cherries, rice, sugarcane, sorghum, nuts and <a href="#">Linamarin</a> , | -92.97             | -92.07  | -103.41      | -102.67       | -109.06      | -93.56  | -130.9    | -131.15 | -106.28 |
|         | 3. | Quercetin    | onion, asparagus, and berries                                                                                                                                      | -87.78             | -96.78  | -120.13      | -90.8         | -86.99       | -81.94  | -93.54    | -103.02 | -82.12  |
|         | 4. | Apigenin     | luteolin, parsley, chamomile tea, naringenin, celery, tangeritin, and baicalein, basil,                                                                            | -86.98             | -79.58  | -107.75      | -103.19       | -95.41       | -81.68  | -85.14    | -88.29  | -87.26  |
|         | 5. | Indirubin    | indigo plant, Polygonum tinctorium, Isatis tinctoria and Strobilanthes cusia                                                                                       | -94.13             | -88.3   | -105.27      | -109.12       | -99.02       | -91.96  | -95.05    | -89.31  | -86.64  |
|         | 6. | Kaempferol   | tea, beans, broccoli, apples, and strawberries, Aloe vera, Delile, Euphorbia pekinensis Rupr, Ginkgo biloba L, and Rosmarinus officinalis                          | -96.1              | -79.3   | -102.71      | -106.7        | -103.33      | -91.43  | -89.82    | -93.44  | -92.56  |
|         | 7. | Tryptanthrin | Polygonum tinctorium                                                                                                                                               | -98.5              | -82.01  | -95.53       | -97.26        | -100.1       | -85.67  | -95.55    | -81.45  | -80.01  |

|           |    |                        |                                                                                                                    |         |         |         |         |         |         |         |         |         |
|-----------|----|------------------------|--------------------------------------------------------------------------------------------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|           |    |                        | and Isatis tinctoria                                                                                               |         |         |         |         |         |         |         |         |         |
|           | 8. | Quisqualic             | Quisqualis indica                                                                                                  | -87.39  | -65.71  | -94.3   | -91.91  | -75.31  | -74.17  | -80.36  | -81.66  | -85.37  |
|           | 9. | Ferulic                | rice, wheat, oats, and pineapple, grains, beans, coffee, artichoke, peanut and nuts                                | -72.98  | -66.6   | -94.12  | -93.2   | -78.11  | -60.66  | -85     | -68.13  | -80.46  |
|           | 10 | Acacetin               | <a href="#">Verbascum lych nitis</a> , <a href="#">Odontites viscosus</a> and <a href="#">Robinia pseudoacacia</a> | -83.58  | -73.76  | -88.51  | -85.1   | -91.88  | -78.08  | -80.34  | -91.89  | -86.99  |
|           | 11 | Methionine sulfoximine | Wheat                                                                                                              | -87.78  | -56.76  | -83.3   | -69.29  | -       | -       | -       | -       | -68.87  |
|           | 12 | Artemisinin            | Artemisia annua                                                                                                    | -80.72  | -72.6   | -81.66  | -95.3   | -85.91  | -78.18  | -92.47  | -84.19  | -85.54  |
|           | 13 | Coumarin               | Apiaceae and Rutaceae                                                                                              | -69.93  | -58.8   | -80.71  | -78.16  | -73.44  | -78.01  | -74.29  | -69.62  | -72.86  |
|           | 14 | Ascorbate              | Citrus fruits, strawberries, cantaloupe, green peppers, tomatoes, broccoli, leafy greens, and potatoes             | -76.15  | -73.76  | -79.18  | -76.86  | -76.47  | -60.07  | -85.09  | -       | -64.68  |
|           | 15 | Isoquinoline           | Ranunculales, Menispermaceae, Berberidaceae, Papaveraceae, Hernandiaceae, and Monimiaceae.                         | -64.7   | -57.49  | -69.01  | -68.1   | -73.05  | -73.74  | -69.23  | -62.57  | -62.01  |
|           | 16 | Thymoquinone           | Nigella sativa                                                                                                     | -63.8   | -57.85  | -69.56  | -68.31  | -64.46  | -65.82  | -60.75  | -60.76  | -63.87  |
| Synthetic | 17 | Candesartan            | Block of Angiotensin II receptor                                                                                   | -109.01 | -113.87 | -137.29 | -113.62 | -130.09 | -117.39 | -118.59 | -121.51 | -127.62 |
|           | 18 | aminopterin            | block tetrahydrofolate synthesis by binding to dihydrofolate reductase                                             | -100.13 | -98.1   | -69.005 | -95.46  | -111.95 | -118.9  | -106.7  | -119.69 | -106.66 |



|  |  |  |                       |  |  |  |  |  |  |  |  |  |
|--|--|--|-----------------------|--|--|--|--|--|--|--|--|--|
|  |  |  | effects against<br>S. |  |  |  |  |  |  |  |  |  |
|--|--|--|-----------------------|--|--|--|--|--|--|--|--|--|

**Supplementary table R3: Statistical Comparison of Mean Binding Energies ( $\Delta G$ ) of Natural vs. Synthetic Compounds Across Target Proteins (including  $\Delta\Delta G$ , 95% CI, and  $p$  Values)**

| Target | Binding Affinity ( $\Delta G$ ) |                        | $\Delta\Delta G$ | 95% CI          | p    | $I^2$<br>(%) | $\tau^2$ |
|--------|---------------------------------|------------------------|------------------|-----------------|------|--------------|----------|
|        | Natural<br>Compounds            | Synthetic<br>Compounds |                  |                 |      |              |          |
| 7bnn   | -85.83±15.3                     | -91.19 ± 19.03         | -5.36            | -17.91 to 7.19  | 0.39 | 68           | 0.32     |
| 5n9b   | -75.62±14.6                     | -84.16 ± 18.89         | -8.54            | -19.68 to 2.60  | 0.13 | 72           | 0.41     |
| 3jvf   | -93.4±15.23                     | -94.25 ± 21.71         | -0.85            | -15.09 to 13.39 | 0.91 | 65           | 0.29     |
| 5nan   | -91.4±15.98                     | -98.02 ± 18.86         | -6.62            | -18.76 to 5.52  | 0.28 | 58           | 0.22     |
| 4hsa   | -91.35±21.75                    | -96.92 ± 22.45         | -5.57            | -22.09 to 10.95 | 0.50 | 75           | 0.48     |
| 1n26   | -81.17±14.93                    | -87.13 ± 19.97         | -5.96            | -18.25 to 6.33  | 0.33 | 70           | 0.35     |
| 1p9m   | -89.87±18.42                    | -92.08 ± 17.88         | -2.21            | -15.33 to 10.91 | 0.74 | 62           | 0.27     |
| 2jjs   | -87.44±99.75                    | -98.07 ± 19.77         | -10.63           | -59.39 to 38.13 | 0.66 | 80           | 0.63     |
| 3fcs   | -84.71±16.21                    | -88.80 ± 22.31         | -4.09            | -18.36 to 10.18 | 0.57 | 78           | 0.57     |

**$\Delta G$  (kcal/mol):** Mean ± standard deviation of binding energies.  
 **$\Delta\Delta G$**  represents the difference in binding free energy ( $\Delta G$ ) between Natural and Synthetic compounds binding to target proteins.  
**95% CI :** 95% confidence interval for  $\Delta\Delta G$  (Natural – Synthetic).  
 **$I^2$ :** Percentage of total variation due to between-target heterogeneity ( $I^2 > 50\%$  = substantial).  
 **$\tau^2$ :** Estimated variance of true effect sizes (random-effects model applied where  $I^2 > 50\%$ ).

**Supplementary table R4:** The mean of binding free energy ( $\Delta G$ ) to the studied proteins, half-maximal inhibitory concentration ( $IC_{50}$ ), and corresponding negative logarithm ( $pIC_{50}$ ) for natural and synthetic compounds, derived from molecular docking simulations.

| <b>Drug</b>                   | <b><math>\Delta G</math> (kcal/mol)</b> | <b><math>IC_{50}</math> (nM)</b> | <b><math>pIC_{50}</math></b> |
|-------------------------------|-----------------------------------------|----------------------------------|------------------------------|
| <b>Phytic acid</b>            | -124.89±13.57                           | 2.8e-83                          | 91.554                       |
| <b>Amygdalin</b>              | -106.89±14.11                           | 4.4e-70                          | 78.359                       |
| <b>Quercetin</b>              | -93.67±11.33                            | 4.5e-59                          | 66.378                       |
| <b>Apigenin</b>               | -90.58± 9.04                            | 3.9e-57                          | 64.659                       |
| <b>Indirubin</b>              | -95.42±7.28                             | 1.3e-60                          | 68.237                       |
| <b>Kaempferol</b>             | -95.04±7.89                             | 2.9e-60                          | 67.968                       |
| <b>Tryptanthrin</b>           | -90.67±7.74                             | 3.8e-57                          | 64.699                       |
| <b>Quisqualic acid</b>        | -81.79±8.58                             | 4.0e-50                          | 56.375                       |
| <b>Ferulic acid</b>           | -77.69±11.04                            | 5.5e-47                          | 52.98                        |
| <b>Acacetin</b>               | -84.45±5.83                             | 1.1e-51                          | 59.119                       |
| <b>Methionine sulfoximine</b> | -73.20±11.25                            | 9.2e-45                          | 44.714                       |
| <b>Artemisinin</b>            | -84.06±6.54                             | 2.1e-51                          | 58.796                       |
| <b>Coumarin</b>               | -72.86±6.10                             | 2.1e-44                          | 44.46                        |
| <b>Ascorbate</b>              | -74.03±7.49                             | 4.6e-45                          | 44.878                       |
| <b>Isoquinoline</b>           | -66.65±5.07                             | 1.5e-37                          | 35.842                       |
| <b>Thymoquinone</b>           | -63.90±3.52                             | 2.8e-35                          | 33.896                       |
| <b>Candesartan</b>            | -120.99±8.56                            | 1.1e-80                          | 88.393                       |
| <b>Aminopterin</b>            | -102.97±14.47                           | 1.4 e-64                         | 72.85                        |
| <b>Dexamethasone</b>          | -86.09±5.61                             | 2.7e-65                          | 64.63                        |
| <b>Remdesivir</b>             | -105.80±7.40                            | 1.1e-70                          | 76.086                       |
| <b>Nitazoxanide</b>           | -85.88±7.91                             | 4.3e-63                          | 71.37                        |
| <b>Calcitriol</b>             | -89.64±7.76                             | 1.6e-56                          | 65.637                       |
| <b>Enalapril</b>              | -98.62±9.29                             | 4.7e-64                          | 71.572                       |
| <b>Quinapril</b>              | -87.08±6.89                             | 1.5e-54                          | 62.837                       |
| <b>Molsidomine</b>            | -83.31±8.51                             | 8.5e-53                          | 61.073                       |
| <b>Bromopyruvate</b>          | -57.15±5.83                             | 1.3e-33                          | 41.896                       |

$\Delta G$  values are expressed in kcal/mol,  $IC_{50}$  values in nanomolar (nM), and  $pIC_{50}$  calculated as  $-\log_{10}(IC_{50} [M])$ .