

# 水蛭素与缺血性脑卒中

2024-04-22

LiChuang Huang



@ 立效研究院

# Contents

|          |   |           |
|----------|---|-----------|
| <b>1</b> | <b>摘要</b>                                     | <b>1</b>  |
| 1.1      | 需求  | 1         |
| 1.2      | 结果  | 1         |
| <b>2</b> | <b>前言</b>                                     | <b>1</b>  |
| <b>3</b> | <b>材料和方法</b>                                  | <b>1</b>  |
| 3.1      | 材料  | 1         |
| 3.2      | 方法  | 1         |
| <b>4</b> | <b>分析结果</b>                                   | <b>2</b>  |
| <b>5</b> | <b>结论</b>                                     | <b>2</b>  |
| <b>6</b> | <b>附：分析流程</b>                                 | <b>2</b>  |
| 6.1      | 养阴通脑颗粒  | 2         |
| 6.1.1    | 成分  | 2         |
| 6.1.2    | 成分靶点  | 3         |
| 6.1.2.1  | GeneCards 获取化合物靶点                             | 3         |
| 6.1.2.2  | 所有靶点  | 4         |
| 6.1.3    | 脑缺血再灌注 cerebral ischemia reperfusion (CIR) 靶点 | 5         |
| 6.1.4    | 网络药理-疾病                                       | 6         |
| 6.1.5    | PPI 网络  | 8         |
| 6.1.6    | 富集分析 (Top30)                                  | 9         |
| 6.2      | 水蛭素 Hirudin                                   | 11        |
| 6.2.1    | 水蛭素-靶点-富集通路                                   | 11        |
| 6.2.2    | 分子对接  | 13        |
|          | <b>Reference</b>                              | <b>13</b> |

# List of Figures

|   |  |    |
|---|--|----|
| 1 | Overall targets number of datasets         | 5  |
| 2 | Network pharmacology with disease          | 7  |
| 3 | Targets intersect with targets of diseases | 7  |
| 4 | HERBS raw PPI network                      | 8  |
| 5 | HERBS Top30 MCC score                      | 9  |
| 6 | HERBS KEGG enrichment                      | 9  |
| 7 | Hirudin targets of disease                 | 11 |
| 8 | HIRU KEGG enrichment                       | 12 |
| 9 | HIRU GO enrichment                         | 12 |

## List of Tables

|   |   |    |
|---|---|----|
| 1 | Herbs information . . . . .                     | 2  |
| 2 | Components of Herbs . . . . .                   | 2  |
| 3 | Hirudin targets from GeneCards . . . . .        | 4  |
| 4 | Tables of Herbs compounds and targets . . . . . | 4  |
| 5 | CIR GeneCards used data . . . . .               | 6  |
| 6 | HERBS KEGG enrichment data . . . . .            | 10 |
| 7 | Compounds contributes to Top30 . . . . .        | 10 |

# 1 摘要

## 1.1 需求

- 复方：地黄 15g、黄芪 15g、葛根 18g、石斛 15g、水蛭 3g、川芎 9g
- 有效成分：水蛭中水蛭素 Hirudin（重点关注）
- 疾病：缺血性脑卒中
- 机制：血管生成
- 目标：找到水蛭素通过 XX 靶点及 XX 靶点涉及的通路 YY 影响缺血性脑卒中的血管生成

请注意，网药有效成分筛选时确认包括水蛭素，如不包括，请及时联系

## 1.2 结果

这是以上一份文档 (名为：养阴通脑颗粒中关键成分对脑缺血再灌注的影响) 为基础修改的 PDF 文档。

# 2 前言

# 3 材料和方法

## 3.1 材料

## 3.2 方法

Mainly used method:

- The `biomart` was used for mapping genes between organism (e.g., `mgc_symbol` to `hgnc_symbol`)<sup>1</sup>.
- R package `ClusterProfiler` used for gene enrichment analysis<sup>2</sup>.
- The Human Gene Database `GeneCards` used for disease related genes prediction<sup>3</sup>.
- Databases of `DisGeNet`, `GeneCards`, `PharmGKB` used for collating disease related targets<sup>3-5</sup>.
- Website `HERB` <http://herb.ac.cn/> used for TCM data source<sup>6</sup>.
- R package `STEINGdb` used for PPI network construction<sup>7,8</sup>.
- The MCC score was calculated referring to algorithm of `CytoHubba`<sup>8</sup>.
- R package `UniProt.ws` used for querying Gene or Protein information.
- R version 4.3.3 (2024-02-29); Other R packages (eg., `dplyr` and `ggplot2`) used for statistic analysis or data visualization.

4 分析结果

5 结论

6 附：分析流程

6.1 养阴通脑颗粒

6.1.1 成分

Table 1 (下方表格) 为表格 Herbs information 概览。

(对应文件为 Figure+Table/Herbs-information.xlsx)

注：表格共有 6 行 18 列，以下预览的表格可能省略部分数据；含有 6 个唯一 ‘Herb\_’；含有 6 个唯一 ‘Herb\_pinyin\_name’。

Table 1: Herbs information

| Herb_     | Herb_p... | Herb_c... | Herb_e... | Herb_l... | Proper... | Meridians | UsePart   | Function  | Indica... |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| HERB00... | CHUAN ... | 川芎        | Chuanx... | Radix ... | Warm; ... | Liver;... | rhizome   | 1. To ... | Cerebr... |
| HERB00... | DI HUANG  | 地黄        | Radix ... | NA        | NA        | NA        | NA        | NA        | NA        |
| HERB00... | GE GEN    | 葛根        | root o... | Radix ... | Cool; ... | Spleen... | tuberoid  | To rel... | Angina... |
| HERB00... | HUANG QI  | 黄芪        | root o... | Radix ... | Warm; ... | Lung; ... | root      | To rei... | Common... |
| HERB00... | SHI HU    | 石斛        | Dendro... | Herba ... | Minor ... | Stomac... | Dendro... | Treatm... | 1. Den... |
| HERB00... | SHUI ZHI  | 水蛭        | Bigflo... | Garden... | Mild; ... | Liver     | fruit     | To cle... | Heat t... |

Table 2 (下方表格) 为表格 Components of Herbs 概览。

(对应文件为 Figure+Table/Components-of-Herbs.xlsx)

注：表格共有 725 行 4 列，以下预览的表格可能省略部分数据；含有 6 个唯一 ‘herb\_id’；含有 696 个唯一 ‘Ingredient.name’。

Table 2: Components of Herbs

| herb_id    | Ingredient.id | Ingredient.name      | Ingredient.alias     |
|------------|---------------|----------------------|----------------------|
| HERB002560 | HBIN001244    | 13-hydroxy-9,11-o... | NA                   |
| HERB002560 | HBIN002016    | 1,7-Dihydroxy-3,9... | 1,7-dihydroxy-3,9... |
| HERB002560 | HBIN003405    | 20-Hexadecanoylin... | 20-hexadecanoylin... |
| HERB002560 | HBIN003436    | 20(r)-21,24-cyclo... | 20(r)-21,24-cyclo... |
| HERB002560 | HBIN004319    | 2',4' -...           | 2', 4'-...           |
| HERB002560 | HBIN005731    | 2'-hydroxy-3         | NA                   |

| herb_id    | Ingredient.id | Ingredient.name      | Ingredient.alias     |
|------------|---------------|----------------------|----------------------|
| HERB002560 | HBIN005735    | 2'-hydroxy-3...      | NA                   |
| HERB002560 | HBIN005744    | 2-hydroxy-3-metho... | NA                   |
| HERB002560 | HBIN006143    | 2-Nonyl acetate      | ANW-21203; SCHEMB... |
| HERB002560 | HBIN006743    | (2S)-4-methoxy-7-... | (2S)-4-methoxy-7-... |
| HERB002560 | HBIN007657    | 3,5-dimethoxystil... | 78916-49-1; TR-03... |
| HERB002560 | HBIN007848    | 3,9-di-O-methylni... | NA                   |
| HERB002560 | HBIN008647    | 3-Hydroxy-2-picoline | BTB 09012; 3-Hydr... |
| HERB002560 | HBIN008667    | 3'-hydroxy-4...      | NA                   |
| HERB002560 | HBIN008668    | 3'-Hydroxy-4...      | 3-(3-hydroxy-4-me... |
| ...        | ...           | ...                  | ...                  |

### 6.1.2 成分靶点

#### 6.1.2.1 GeneCards 获取化合物靶点

HERBs 数据库包含的 Hirudin 靶点较少：

bindingdb, drugbank, 以及预测工具 Super-Pred 等都难以获取更多关于 hirudin 靶点信息。因此，这里使用 GeneCards 搜索。

Table 3 (下方表格) 为表格 Hirudin targets from GeneCards 概览。

(对应文件为 **Figure+Table/Hirudin-targets-from-GeneCards.xlsx**)

注：表格共有 45 行 7 列，以下预览的表格可能省略部分数据；含有 45 个唯一 ‘Symbol’。

**The GeneCards data was obtained by querying :**

hirudin

**Restrict (with quotes) :**

FALSE

**Filtering by Score: :**

Score > 0

**Advance search: :**

[compounds] ( hirudin )

Table 3: Hirudin targets from GeneCards

| Symbol   | Description   | Category      | UniProt_ID | GIFtS | GC_id       | Score |
|----------|---------------|---------------|------------|-------|-------------|-------|
| F2       | Coagulatio... | Protein Co... | P00734     | 59    | GC11P047736 | 2.58  |
| F2R      | Coagulatio... | Protein Co... | P25116     | 55    | GC05P076716 | 2.23  |
| F10      | Coagulatio... | Protein Co... | P00742     | 59    | GC13P113122 | 1.76  |
| FGA      | Fibrinogen... | Protein Co... | P02671     | 58    | GC04M154583 | 1.76  |
| PLAT     | Plasminoge... | Protein Co... | P00750     | 58    | GC08M042174 | 1.76  |
| F3       | Coagulatio... | Protein Co... | P13726     | 54    | GC01M094873 | 1.76  |
| PLG      | Plasminogen   | Protein Co... | P00747     | 58    | GC06P160702 | 1.59  |
| CPA1     | Carboxypep... | Protein Co... | P15085     | 51    | GC07P130380 | 1.12  |
| PLAU     | Plasminoge... | Protein Co... | P00749     | 60    | GC10P073909 | 0.64  |
| CD40LG   | CD40 Ligand   | Protein Co... | P29965     | 59    | GC0XP136649 | 0.64  |
| SERPINC1 | Serpin Fam... | Protein Co... | P01008     | 59    | GC01M174949 | 0.64  |
| SERPINE1 | Serpin Fam... | Protein Co... | P05121     | 59    | GC07P101127 | 0.64  |
| TBXA2R   | Thromboxan... | Protein Co... | P21731     | 59    | GC19M003594 | 0.64  |
| CCL2     | C-C Motif ... | Protein Co... | P13500     | 58    | GC17P034255 | 0.64  |
| CD55     | CD55 Molec... | Protein Co... | P08174     | 58    | GC01P207321 | 0.64  |
| ...      | ...           | ...           | ...        | ...   | ...         | ...   |

### 6.1.2.2 所有靶点

Table 4 (下方表格) 为表格 tables of Herbs compounds and targets 概览。

(对应文件为 Figure+Table/tables-of-Herbs-compounds-and-targets.xlsx)

注：表格共有 13446 行 9 列，以下预览的表格可能省略部分数据；含有 696 个唯一 ‘Ingredient.id’；含有 6 个唯一 ‘Herb\_pinyin\_name’；含有 696 个唯一 ‘Ingredient.name’；含有 2879 个唯一 ‘Target.name’。

Table 4: Tables of Herbs compounds and targets

| Ingred.....1 | Herb_p... | Ingred.....3 | Ingred.....4 | Target.id | Target... | Databa... | Paper.id | ... |
|--------------|-----------|--------------|--------------|-----------|-----------|-----------|----------|-----|
| HBIN00...    | SHI HU    | 10,12-...    | NA           | HBTAR0... | ATIC      | NA        | NA       | ... |
| HBIN00...    | SHI HU    | 10,12-...    | NA           | HBTAR0... | FPGS      | NA        | NA       | ... |
| HBIN00...    | SHI HU    | 10,12-...    | NA           | HBTAR0... | GART      | NA        | NA       | ... |
| HBIN00...    | SHI HU    | 10,12-...    | NA           | HBTAR0... | MTHFD1    | NA        | NA       | ... |
| HBIN00...    | SHI HU    | 10,12-...    | NA           | HBTAR0... | MTHFD2    | NA        | NA       | ... |
| HBIN00...    | SHI HU    | 10,12-...    | NA           | HBTAR0... | ALDH1L1   | NA        | NA       | ... |
| HBIN00...    | SHI HU    | 10,12-...    | NA           | HBTAR0... | MTHFD1L   | NA        | NA       | ... |
| HBIN00...    | SHI HU    | 10,12-...    | NA           | HBTAR0... | MTFMT     | NA        | NA       | ... |
| HBIN00...    | SHI HU    | 10,12-...    | NA           | HBTAR0... | ALDH1L2   | NA        | NA       | ... |
| HBIN00...    | SHI HU    | 10,12-...    | NA           | HBTAR0... | MTHFD2L   | NA        | NA       | ... |

| Ingred.....1 | Herb_p... | Ingred.....3 | Ingred.....4 | Target.id  | Target... | Databa... | Paper.id | ... |
|--------------|-----------|--------------|--------------|------------|-----------|-----------|----------|-----|
| HBIN00...    | SHI HU    | 10 ,13...    | NA           | NA         | NA        | NA        | NA       | ... |
| HBIN00...    | CHUAN ... | 10-(be...    | 10-( -...    | NA         | NA        | NA        | NA       | ... |
| HBIN00...    | CHUAN ... | 1,1-Di...    | 3658-9...    | NA         | NA        | NA        | NA       | ... |
| HBIN00...    | CHUAN ... | 1,2,3,...    | NA           | NA         | NA        | NA        | NA       | ... |
| HBIN00...    | CHUAN ... | 1,3,8-...    | 1,3,8-...    | HB TAR0... | ACHE      | NA        | NA       | ... |
| ...          | ...       | ...          | ...          | ...        | ...       | ...       | ...      | ... |

### 6.1.3 脑缺血再灌注 cerebral ischemia reperfusion (CIR) 靶点

取下方数据集的合集：

Figure 1 (下方图) 为图 Overall targets number of datasets 概览。

(对应文件为 **Figure+Table/Overall-targets-number-of-datasets.pdf**)

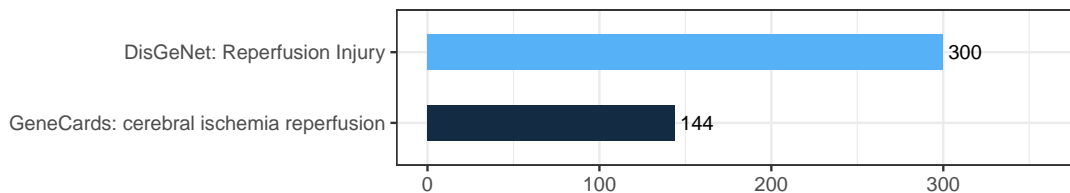


Figure 1: Overall targets number of datasets

Table 5 (下方表格) 为表格 CIR GeneCards used data 概览。

(对应文件为 **Figure+Table/CIR-GeneCards-used-data.xlsx**)

注：表格共有 144 行 7 列，以下预览的表格可能省略部分数据；含有 144 个唯一 ‘Symbol’。

**The GeneCards data was obtained by querying :**

cerebral ischemia reperfusion

**Restrict (with quotes) :**

TRUE

**Filtering by Score: :**

Score > 1



Table 5: CIR GeneCards used data

| Symbol   | Description   | Category       | UniProt_ID | GIFtS | GC_id       | Score |
|----------|---------------|----------------|------------|-------|-------------|-------|
| BDNF-AS  | BDNF Antis... | RNA Gene (...) |            | 29    | GC11P027466 | 11.93 |
| CERNA3   | Competing ... | RNA Gene (...) |            | 19    | GC08P056323 | 6.6   |
| MEG3     | Maternally... | RNA Gene (...) |            | 34    | GC14P116735 | 6.12  |
| SNHG12   | Small Nucl... | RNA Gene (...) | Q9BXW3     | 30    | GC01M031297 | 6.05  |
| MIR211   | MicroRNA 211  | RNA Gene (...) |            | 29    | GC15M031065 | 5.79  |
| SNHG14   | Small Nucl... | RNA Gene (...) |            | 24    | GC15P156537 | 5.68  |
| SOD2-OT1 | SOD2 Overl... | RNA Gene (...) |            | 18    | GC06M159772 | 5.4   |
| H19      | H19 Imprin... | RNA Gene (...) |            | 34    | GC11M001995 | 4.64  |
| GAS5     | Growth Arr... | RNA Gene (...) |            | 31    | GC01M173947 | 4.55  |
| MIR496   | MicroRNA 496  | RNA Gene (...) |            | 16    | GC14P116773 | 4.06  |
| BCL2     | BCL2 Apopt... | Protein Co...  | P10415     | 59    | GC18M063123 | 3.69  |
| TUG1     | Taurine Up... | Protein Co...  | A0A6I8PU40 | 32    | GC22P030969 | 3.69  |
| SCARNA5  | Small Caja... | RNA Gene (...) |            | 23    | GC02P233275 | 3.69  |
| NFE2L2   | NFE2 Like ... | Protein Co...  | Q16236     | 60    | GC02M177227 | 3.64  |
| SOD1     | Superoxide... | Protein Co...  | P00441     | 61    | GC21P031659 | 3.59  |
| ...      | ...           | ...            | ...        | ...   | ...         | ...   |

#### 6.1.4 网络药理-疾病

Figure 2 (下方图) 为图 Network pharmacology with disease 概览。

(对应文件为 `Figure+Table/Network-pharmacology-with-disease.pdf`)

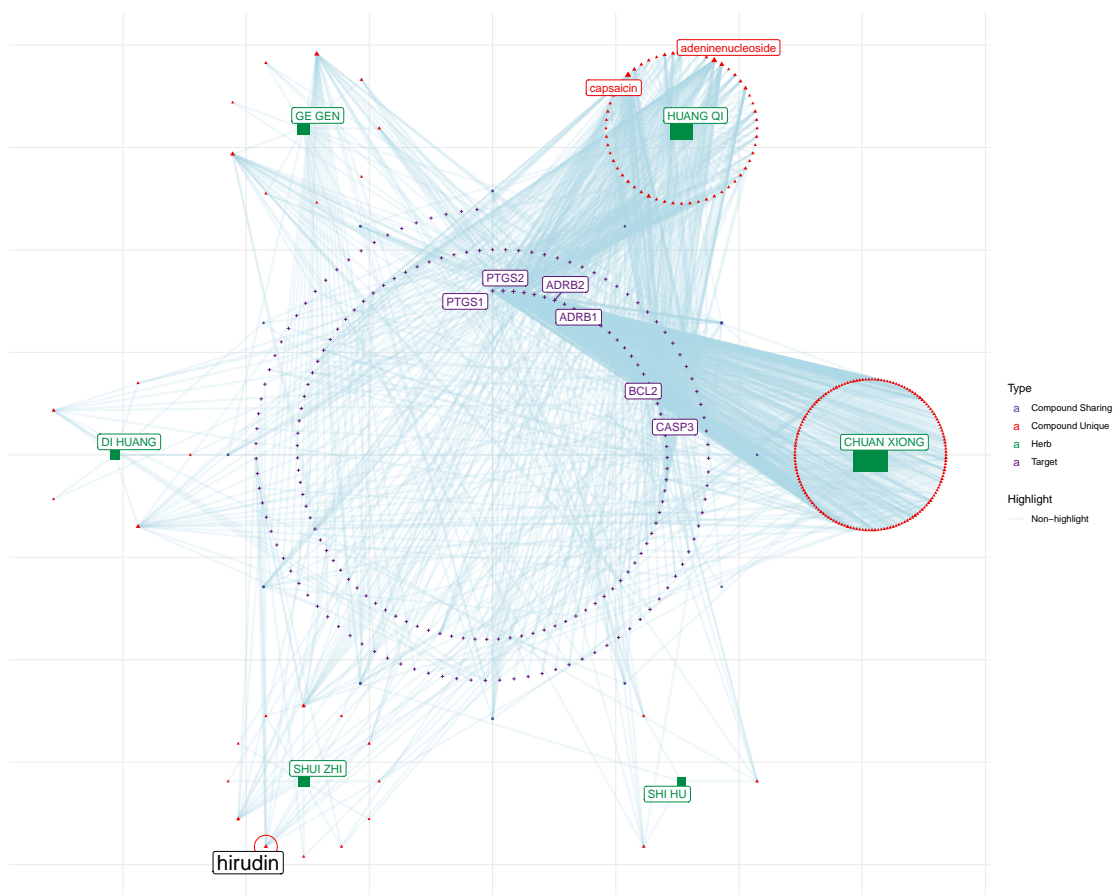


Figure 2: Network pharmacology with disease

Figure 3 (下方图) 为图 Targets intersect with targets of diseases 概览。

(对应文件为 `Figure+Table/Targets-intersect-with-targets-of-diseases.pdf`)

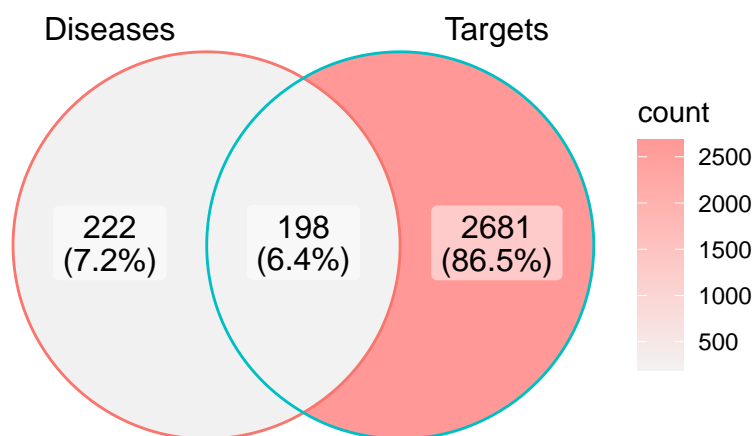


Figure 3: Targets intersect with targets of diseases

**Intersection :**

IL10, HMOX1, MMP9, PTGS2, SOD2, MPO, NOS2, IL6, CAT, CXCL2, TLR4, ALOX5, RELA, CCL2, CASP3, SELE, XDH, FOS, EDN1, TLR2, PLAT, PTEN, MAPK8, PPARA, CDKN1A, KDR, ADORA2A, CXCL1, PLA2, BCL2, SOD1, PPARG, NOS3, TNF, IL1B, MAPK9, ICAM1, THBS1, TERT, JUN, ADORA2B, EFNB2, HGF, CD36, IRAK3, SLPI, IL12A, C...

(上述信息框内容已保存至 `Figure+Table/Targets-intersect-with-targets-of-diseases-content`)

### 6.1.5 PPI 网络

Figure 4 (下方图) 为图 HERBS raw PPI network 概览。

(对应文件为 `Figure+Table/HERBS-raw-PPI-network.pdf`)

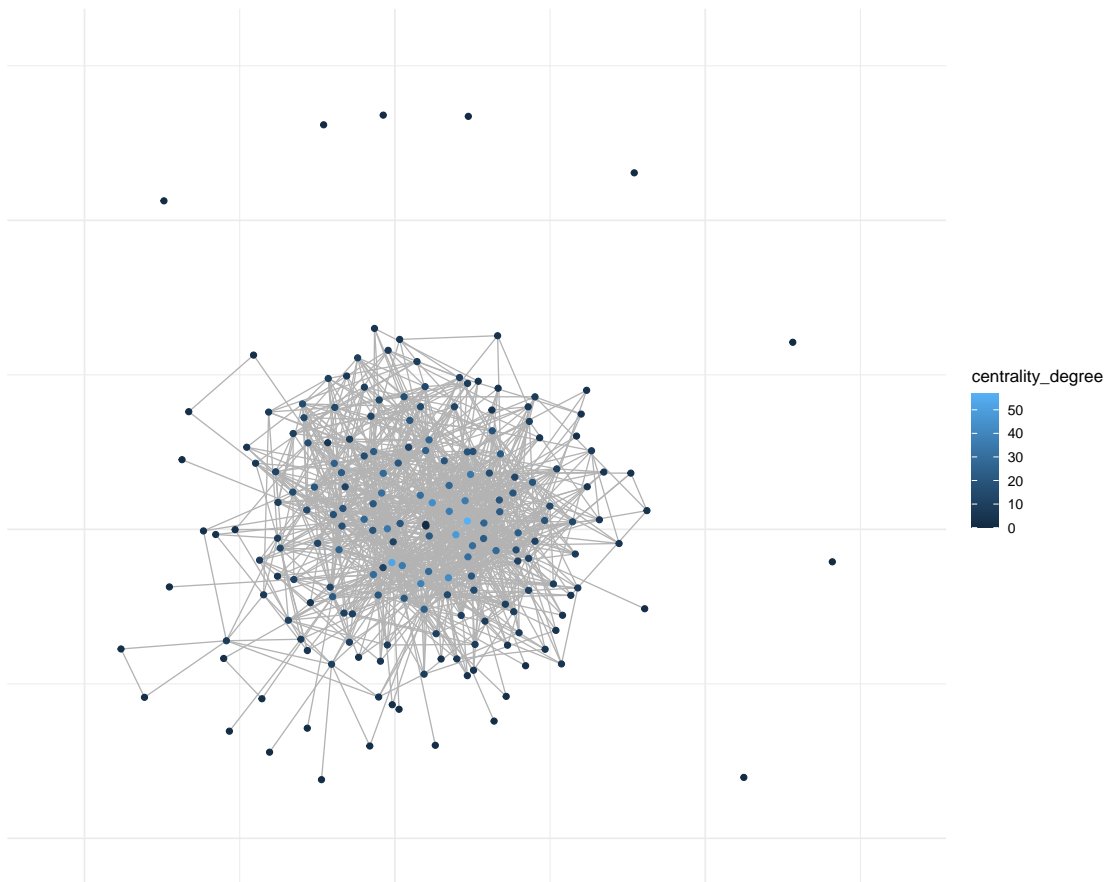


Figure 4: HERBS raw PPI network

Figure 5 (下方图) 为图 HERBS Top30 MCC score 概览。

(对应文件为 `Figure+Table/HERBS-Top30-MCC-score.pdf`)

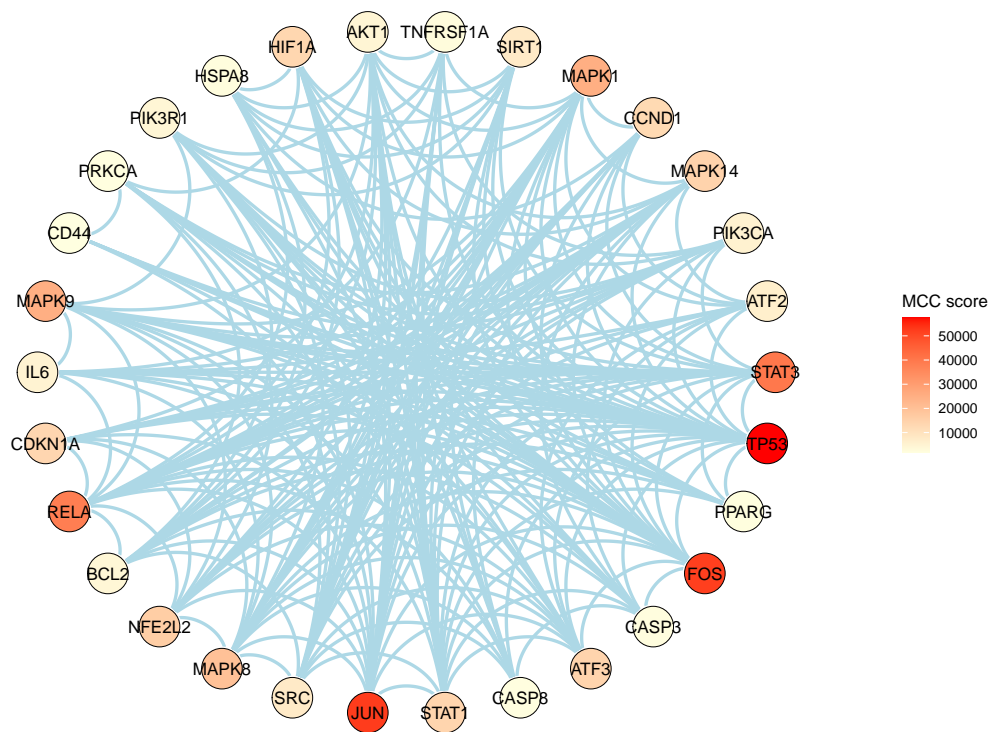


Figure 5: HERBS Top30 MCC score

### 6.1.6 富集分析 (Top30)

Figure 6 (下方图) 为图 HERBS KEGG enrichment 概览。

(对应文件为 `Figure+Table/HERBS-KEGG-enrichment.pdf`)

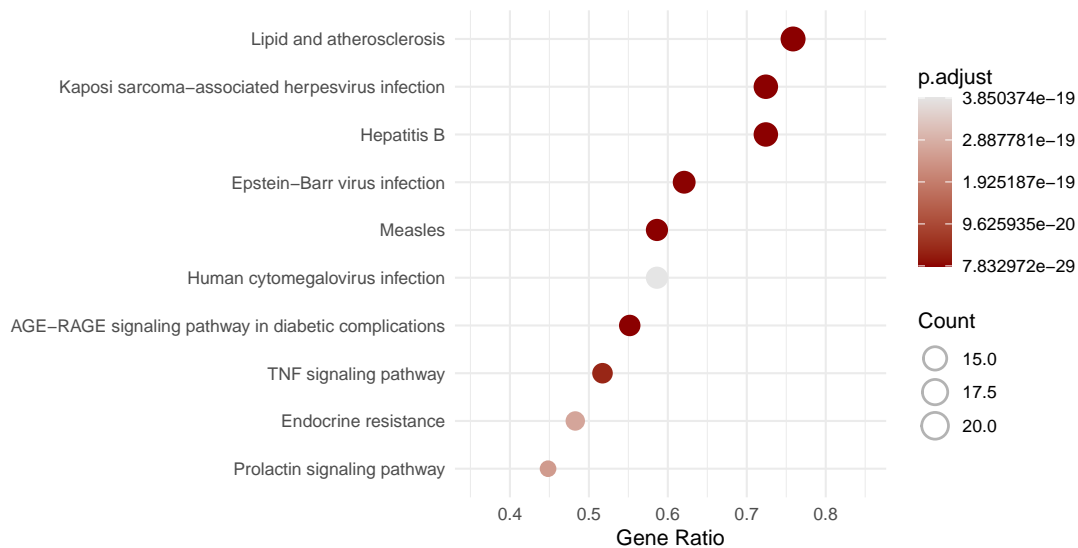


Figure 6: HERBS KEGG enrichment

Table 6 (下方表格) 为表格 HERBS KEGG enrichment data 概览。

(对应文件为 Figure+Table/HERBS-KEGG-enrichment-data.xlsx)

注：表格共有 195 行 9 列，以下预览的表格可能省略部分数据；含有 195 个唯一 ‘ID’。

1. pvalue: 显著性 P。

Table 6: HERBS KEGG enrichment data

| ID       | Descri... | GeneRatio | BgRatio  | pvalue    | p.adjust  | qvalue    | geneID    | Count |
|----------|-----------|-----------|----------|-----------|-----------|-----------|-----------|-------|
| hsa05161 | Hepati... | 21/29     | 162/8764 | 4.0169... | 7.8329... | 1.1416... | 207/13... | 21    |
| hsa05417 | Lipid ... | 22/29     | 215/8764 | 1.7025... | 1.6599... | 2.4194... | 207/59... | 22    |
| hsa05167 | Kaposi... | 21/29     | 194/8764 | 2.1692... | 1.4099... | 2.0550... | 207/83... | 21    |
| hsa04933 | AGE-RA... | 16/29     | 100/8764 | 1.4213... | 6.9289... | 1.0098... | 207/59... | 16    |
| hsa05162 | Measles   | 17/29     | 138/8764 | 3.6237... | 1.4132... | 2.0598... | 207/59... | 17    |
| hsa05169 | Epstei... | 18/29     | 202/8764 | 4.3574... | 1.4161... | 2.0640... | 207/59... | 18    |
| hsa04668 | TNF si... | 15/29     | 114/8764 | 1.3331... | 3.7136... | 5.4126... | 207/13... | 15    |
| hsa04917 | Prolac... | 13/29     | 70/8764  | 1.0206... | 2.4877... | 3.6258... | 207/59... | 13    |
| hsa01522 | Endocr... | 14/29     | 98/8764  | 1.2349... | 2.6756... | 3.8997... | 207/59... | 14    |
| hsa05163 | Human ... | 17/29     | 225/8764 | 1.9745... | 3.8503... | 5.6118... | 207/13... | 17    |
| hsa05210 | Colore... | 13/29     | 86/8764  | 1.8209... | 3.2280... | 4.7048... | 207/59... | 13    |
| hsa04210 | Apoptosis | 14/29     | 135/8764 | 1.3592... | 2.2088... | 3.2193... | 207/59... | 14    |
| hsa05142 | Chagas... | 13/29     | 102/8764 | 1.9039... | 2.8558... | 4.1623... | 207/84... | 13    |
| hsa05418 | Fluid ... | 14/29     | 139/8764 | 2.0751... | 2.8903... | 4.2126... | 207/59... | 14    |
| hsa04625 | C-type... | 13/29     | 104/8764 | 2.4816... | 3.2261... | 4.7020... | 207/84... | 13    |
| ...      | ...       | ...       | ...      | ...       | ...       | ...       | ...       | ...   |

Table 7 (下方表格) 为表格 Compounds contributes to Top30 概览。

(对应文件为 Figure+Table/Compounds-contributes-to-Top30.xlsx)

注：表格共有 291 行 3 列，以下预览的表格可能省略部分数据；含有 6 个唯一 ‘Herb\_pinyin\_name’；含有 106 个唯一 ‘Ingredient.name’；含有 30 个唯一 ‘Target.name’。

Table 7: Compounds contributes to Top30

| Herb_pinyin_name | Ingredient.name                | Target.name |
|------------------|--------------------------------|-------------|
| HUANG QI         | 13-hydroxy-9,11-octadecadie... | PPARG       |
| HUANG QI         | 1,7-Dihydroxy-3,9-dimethoxy... | PPARG       |
| HUANG QI         | 1,7-Dihydroxy-3,9-dimethoxy... | MAPK14      |

| Herb_pinyin_name | Ingredient.name                | Target.name |
|------------------|--------------------------------|-------------|
| CHUAN XIONG      | 1-Acetyl-beta-carboline        | MAPK14      |
| CHUAN XIONG      | 1-beta-ethylacrylate-7-alde... | MAPK14      |
| HUANG QI         | 3,9-di-O-methylnissolin        | PPARG       |
| HUANG QI         | 3,9-di-O-methylnissolin        | MAPK14      |
| CHUAN XIONG      | 3-Butylidene-7-hydroxyphtha... | PPARG       |
| CHUAN XIONG      | 3-butylidene-phalide           | CCND1       |
| CHUAN XIONG      | 3-butylidene-phalide           | CDKN1A      |
| CHUAN XIONG      | 3-butylidene-phalide           | TP53        |
| GE GEN           | 3'-Methoxydaidzein             | PPARG       |
| GE GEN           | 3'-Methoxydaidzein             | MAPK14      |
| CHUAN XIONG      | 4,7-Dihydroxy-3-butylphthalide | PPARG       |
| CHUAN XIONG      | 4-hydroxy-3-butylphthalide     | PPARG       |
| ...              | ...                            | ...         |

## 6.2 水蛭素 Hirudin

### 6.2.1 水蛭素-靶点-富集通路

Figure 7 (下方图) 为图 Hirudin targets of disease 概览。

(对应文件为 Figure+Table/Hirudin-targets-of-disease.pdf)

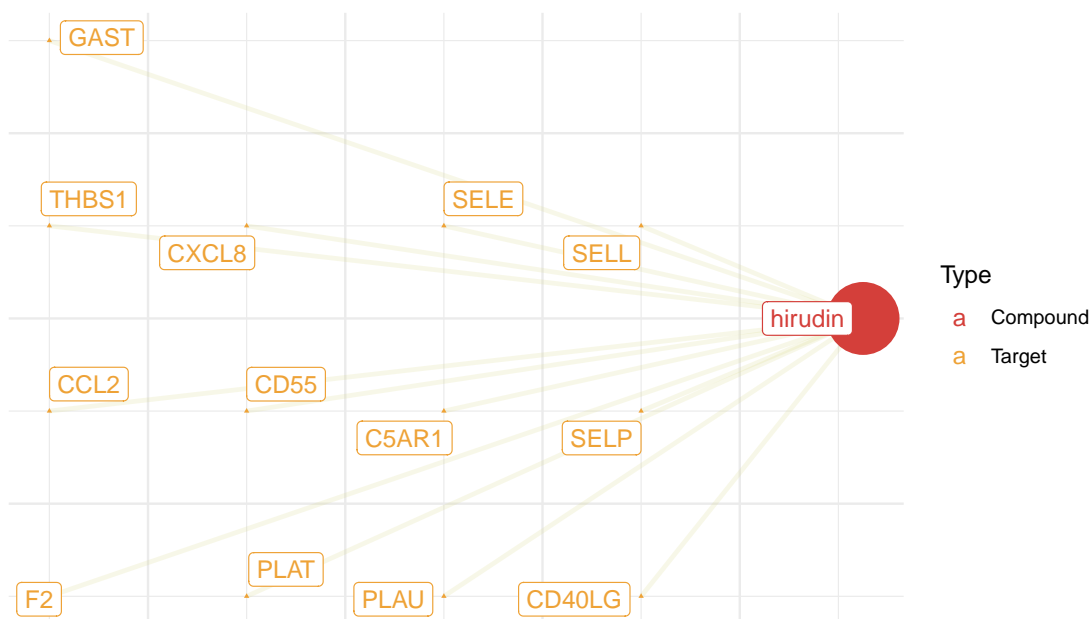


Figure 7: Hirudin targets of disease

Figure @ref(fig:HIRU KEGG enrichment) (下方图) 为图 HIRU KEGG enrichment 概览。

(对应文件为 Figure+Table/HIRU KEGG enrichment.pdf)

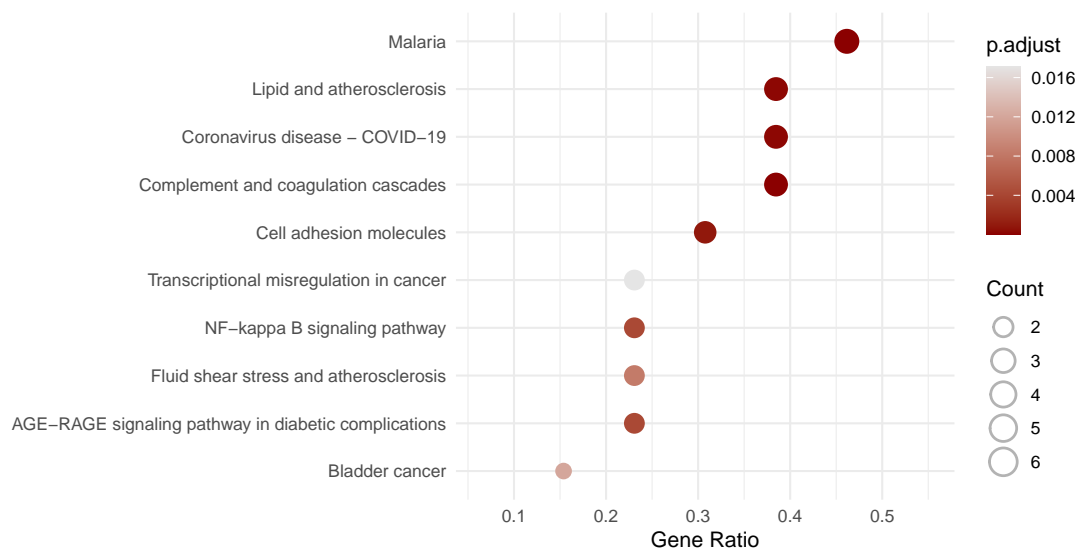


Figure 8: HIRU KEGG enrichment

Figure @ref(fig:HIRU GO enrichment) (下方图) 为图 HIRU GO enrichment 概览。

(对应文件为 **Figure+Table/HIRU GO enrichment.pdf**)

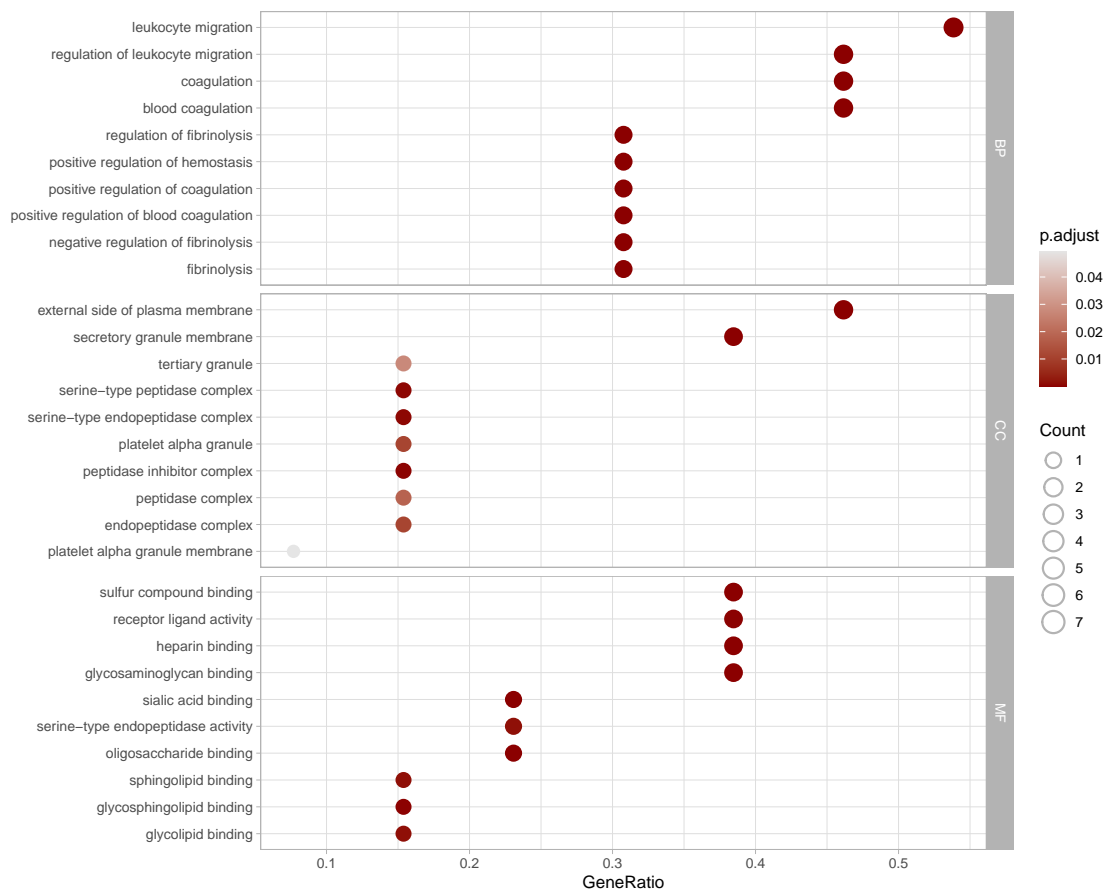


Figure 9: HIRU GO enrichment

### 6.2.2 分子对接

## Reference

1. Durinck, S., Spellman, P. T., Birney, E. & Huber, W. Mapping identifiers for the integration of genomic datasets with the r/bioconductor package biomaRt. *Nature protocols* **4**, 1184–1191 (2009).
2. Wu, T. *et al.* ClusterProfiler 4.0: A universal enrichment tool for interpreting omics data. *The Innovation* **2**, (2021).
3. Stelzer, G. *et al.* The genecards suite: From gene data mining to disease genome sequence analyses. *Current protocols in bioinformatics* **54**, 1.30.1–1.30.33 (2016).
4. Piñero, J. *et al.* The disgenet knowledge platform for disease genomics: 2019 update. *Nucleic Acids Research* (2019) doi:10.1093/nar/gkz1021.
5. Barbarino, J. M., Whirl-Carrillo, M., Altman, R. B. & Klein, T. E. PharmGKB: A worldwide resource for pharmacogenomic information. *Wiley interdisciplinary reviews. Systems biology and medicine* **10**, (2018).
6. Fang, S. *et al.* HERB: A high-throughput experiment- and reference-guided database of traditional chinese medicine. *Nucleic Acids Research* **49**, D1197–D1206 (2021).
7. Szklarczyk, D. *et al.* The string database in 2021: Customizable proteinprotein networks, and functional characterization of user-uploaded gene/measurement sets. *Nucleic Acids Research* **49**, D605–D612 (2021).
8. Chin, C.-H. *et al.* CytoHubba: Identifying hub objects and sub-networks from complex interactome. *BMC Systems Biology* **8**, S11 (2014).