Supplementary materials

**Supplementary Figure 1.** Chromatograms of Lvjiaobuxue granule (LBG) (A) and Astragaloside IV (B).

**Supplementary Table 1.** Active ingredients and ADME parameters of formula LBG.

| No. | Name               | OB (%) | DL  | Herb                                      |
|-----|--------------------|--------|-----|-------------------------------------------|
| 1   | Formononetin       | 69.67  | 0.21| *Astragalus membranaceus* Bunge           |
| 2   | Calycosin          | 47.75  | 0.24| *Astragalus membranaceus* Bunge           |
| 3   | Caffeic acid       | 54.97  | 0.05| *Astragalus membranaceus* Bunge           |
| 4   | Astragaloside I    | 46.79  | 0.11| *Astragalus membranaceus* Bunge           |
| 5   | Astragaloside II   | 46.06  | 0.14| *Astragalus membranaceus* Bunge           |
| 6   | Bifendate          | 31.10  | 0.67| *Astragalus membranaceus* Bunge           |
| 7   | Astragaloside IV   | 22.50  | 0.15| *Astragalus membranaceus* Bunge           |
| 8   | Ononin             | 11.52  | 0.78| *Astragalus membranaceus* Bunge           |
| 9   | Acteoside          | 2.94   | 0.62| *Astragalus membranaceus* Bunge, Rehnjannia glutinosa (Gaertn.) DC. |
| 10  | Perlolyrine        | 65.95  | 0.27| *Codonopsis pilosula* (Franch.) Nannf.    |
| 11  | Frutinone A        | 65.90  | 0.34| *Codonopsis pilosula* (Franch.) Nannf., *Angelica sinensis* (Oliv.) Diels, Rehnjannia glutinosa (Gaertn.) DC. |
| 12  | Taraxerol          | 38.40  | 0.77| *Codonopsis pilosula* (Franch.) Nannf.    |
| 13  | Luteolin           | 36.16  | 0.25| *Codonopsis pilosula* (Franch.) Nannf.    |
| 14  | Herbacetin         | 36.07  | 0.27| *Codonopsis pilosula* (Franch.) Nannf.    |
| 15  | Protocatechuic acid| 25.37  | 0.04| *Codonopsis pilosula* (Franch.) Nannf., *Angelica sinensis* (Oliv.) Diels |
| 16  | Lobetolin          | 18.81  | 0.35| *Codonopsis pilosula* (Franch.) Nannf.    |
| 17  | Rehmannioside A    | 25.95  | 0.87| *Rehnjannia glutinosa* (Gaertn.) DC.      |
| 18  | Rehmaionoside C    | 12.89  | 0.34| *Rehnjannia glutinosa* (Gaertn.) DC.      |
| 19  | Catalpol           | 5.07   | 0.44| *Rehnjannia glutinosa* (Gaertn.) DC.      |
| 20  | Purpureaside C     | 3.14   | 0.38| *Rehnjannia glutinosa* (Gaertn.) DC.      |
Atractylenolide II  47.50  0.15  *Atractylodes macrocephala* Koidz.
Atractylon  41.10  0.13  *Atractylodes macrocephala* Koidz.
3β-acetoxyatractylone  40.75  0.22  *Atractylodes macrocephala* Koidz.
Atractylenolide I  37.37  0.15  *Atractylodes macrocephala* Koidz.
Atractylenolide III  31.15  0.17  *Atractylodes macrocephala* Koidz.
Biatractylolide  17.45  0.81  *Atractylodes macrocephala* Koidz.
Atract yolol  -  -  *Atractylodes macrocephala* Koidz.
Honokiol  60.67  0.15  *Angelica sinensis* (Oliv.) Diels
Ferulic acid  39.56  0.06  *Angelica sinensis* (Oliv.) Diels
β-sitosterol  33.94  0.70  *Angelica sinensis* (Oliv.) Diels
Ligustilide  23.50  0.07  *Angelica sinensis* (Oliv.) Diels
Chlorogenic acid  11.93  0.33  *Angelica sinensis* (Oliv.) Diels

**Supplementary Table 2.** The related targets predicted by the major active ingredient of LBG

| No. | Uniport ID | Gene names | Protein names                          | Degree |
|-----|------------|------------|----------------------------------------|--------|
| 1   | Q96RQ9     | IL4I1      | L-amino-acid oxidase                    | 35     |
| 2   | P54687     | BCAT1      | Branched-chain-amino-acid aminotransferase, cytosolic | 32     |
| 3   | O15382     | BCAT2      | Branched-chain-amino-acid aminotransferase, mitochondrial | 32     |
| 4   | P47712     | PLA2G4A    | Cytosolic phospholipase A2              | 32     |
| 5   | Q8NC3      | LYPLA3     | Group XV phospholipase A2              | 32     |
| 6   | P15121     | AKR1B1     | Aldo-keto reductase family 1 member B1  | 31     |
| 7   | P20132     | SDS        | L-serine dehydratase/L-threonine deaminase | 27     |
| 8   | P35575     | G6PC       | Glucose-6-phosphatase                  | 25     |
| 9   | P00439     | PAH        | Phenylalanine-4-hydroxylase            | 23     |
| 10  | O60516     | EIF4EBP3   | Eukaryotic translation initiation factor 4E-binding protein 3 | 22     |
| 11  | P54577     | YARS       | Tyrosine--tRNA ligase, cytoplasmic      | 21     |
| 12  | P23946     | CMA1       | Chymase                                | 19     |
| 13  | P35557     | GCK        | Glucokinase                            | 19     |
| 14  | P20231     | TPSB2      | Tryptase beta-2                        | 17     |
| 15  | P19367     | HK1        | Hexokinase-1                           | 17     |
| 16  | P29218     | IMPA1      | Inositol monophosphatase 1             | 16     |
| 17  | O14732     | IMPA2      | Inositol monophosphatase 2             | 16     |
| 18  | P00491     | NP         | Purine nucleoside phosphorylase        | 16     |
| 19  | P40939     | HADHA      | Trifunctional enzyme subunit alpha, mitochondrial | 15     |
| 20  | P30613     | PKLR       | Pyruvate kinase PKLR                   | 15     |
| 21  | P07195     | LDHB       | L-lactate dehydrogenase B chain        | 11     |
| 22  | P09622     | DLD        | Dihydrolipoyl dehydrogenase, mitochondrial | 6      |
| 23  | P09110     | ACAA1      | 3-ketoacetyl-CoA thiolase, peroxisomal  | 5      |
Supplementary Table 3. The PDB ID information of 6 targets included in BCAAs catabolism

| No | Gene names | PDB ID |
|----|------------|--------|
| 1  | ACAA2      | 4C2J   |
| 2  | BCAT1      | 2ABJ   |
| 3  | BCAT2      | 1KT8   |
| 4  | DLD        | 1ZMC   |
| 5  | HADHA      | 5ZQZ   |
| 6  | IL411      | 5C3L   |

Supplementary Figure 2. “chemical components-targets-differential metabolites” regulatory network of Valine, leucine and isoleucine degradation pathway. Yellow nodes (▲) represent the chemical components, green nodes (●) represent the targets, and pink node (■) represent differential metabolites.
Supplementary Figure 3. 95 pairs of target-compound combinations were possessed great binding activity.