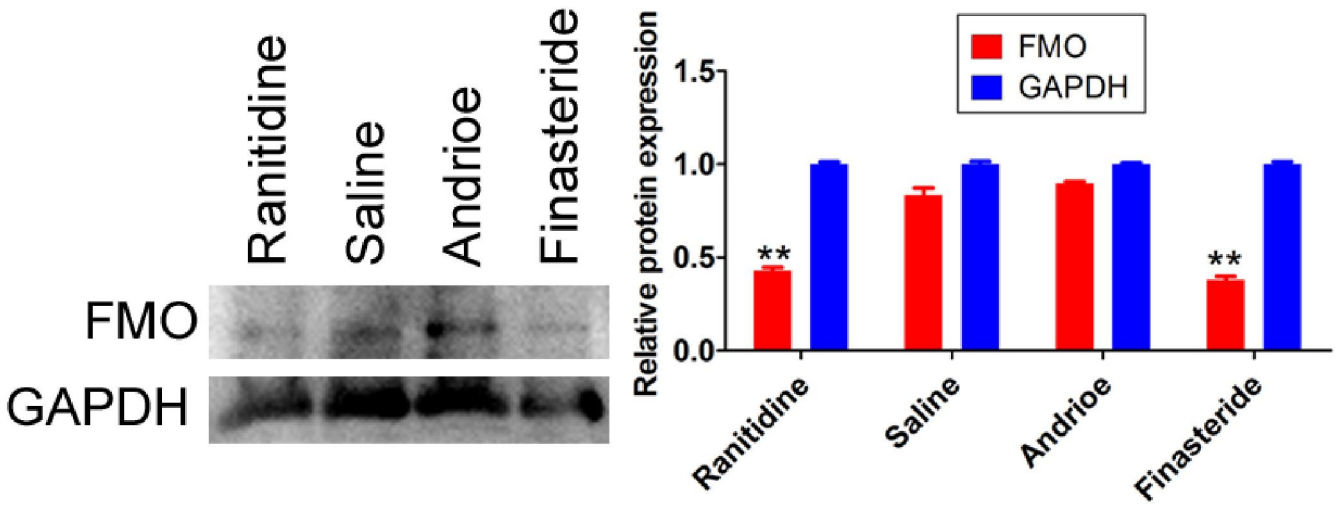


Figure S1 The results of western blot. The result showed that FMO3 expression in the liver tissue of mice treated with ranitidine and finasteride was significantly lower than in the saline-control and Andrioe-treated groups. ** $p<0.01$ vs Saline group; t test.

**Table S1 The results of sample sequencing data processing statistics**

| Sample ID | PE Reads | Raw Tags | Clean Tags | Effective Tags | AvgLen(bp) | GC(%) | Q20(%) | Q30(%) | Effective(%) |
|---|---|---|---|---|---|---|---|---|---|
| A1 | 79882 | 65646 | 57536 | 55953 | 415 | 54.34 | 96.61 | 93.42 | 70.04 |
| A2 | 79873 | 64205 | 55290 | 54009 | 417 | 55.15 | 96.67 | 93.44 | 67.62 |
| A3 | 80158 | 67473 | 59480 | 58151 | 415 | 54.27 | 96.68 | 93.53 | 72.55 |
| A4 | 79944 | 67108 | 59113 | 57672 | 415 | 53.86 | 96.48 | 93.22 | 72.14 |
| A5 | 79778 | 65248 | 56964 | 55605 | 417 | 54.44 | 96.58 | 93.31 | 69.7 |
| A6 | 80127 | 65231 | 56760 | 55491 | 416 | 54.84 | 96.64 | 93.41 | 69.25 |
| A7 | 79802 | 65495 | 57147 | 55230 | 415 | 54.83 | 96.59 | 93.33 | 69.21 |
| A8 | 79817 | 65274 | 56990 | 55560 | 415 | 54.52 | 96.63 | 93.41 | 69.61 |
| FEN1 | 80088 | 67152 | 59822 | 56824 | 415 | 54.46 | 96 | 92.14 | 70.95 |
| FEN2 | 79947 | 67468 | 59875 | 57420 | 418 | 54.32 | 96.07 | 92.29 | 71.82 |
| FEN3 | 80259 | 64784 | 56786 | 55039 | 415 | 54.7 | 96.06 | 92.29 | 68.58 |
| FEN4 | 80168 | 67506 | 60133 | 57973 | 415 | 54.11 | 96.11 | 92.39 | 72.31 |
| FEN5 | 7978 | 6475 | 5670 | 54806 | 415 | 53.87 | 96.02 | 92.21 | 68.69 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 7 | 1 | 3 | | | | | | |
| FEN6 | 79757 | 66671 | 59446 | 57728 | 415 | 54.34 | 96.17 | 92.43 | 72.38 |
| FEN7 | 80036 | 67642 | 60247 | 56580 | 416 | 54.26 | 96.06 | 92.31 | 70.69 |
| FEN8 | 80363 | 66476 | 58623 | 56923 | 416 | 54.37 | 96.02 | 92.17 | 70.83 |
| R1 | 79880 | 66720 | 59074 | 58359 | 413 | 54.24 | 96.59 | 93.43 | 73.06 |
| R2 | 80209 | 66801 | 58929 | 58311 | 414 | 54.29 | 96.65 | 93.47 | 72.7 |
| R3 | 80125 | 69146 | 61848 | 60935 | 412 | 53.73 | 96.59 | 93.45 | 76.05 |
| R4 | 79974 | 67256 | 59662 | 58542 | 412 | 53.82 | 96.45 | 93.16 | 73.2 |
| R5 | 79681 | 69802 | 62870 | 61949 | 411 | 53.44 | 96.58 | 93.42 | 77.75 |
| R6 | 80302 | 69030 | 61638 | 60710 | 412 | 54.25 | 96.56 | 93.37 | 75.6 |
| R7 | 79786 | 65186 | 56758 | 55797 | 416 | 54.41 | 96.52 | 93.22 | 69.93 |
| R8 | 79781 | 67524 | 60009 | 58603 | 413 | 54.27 | 96.57 | 93.39 | 73.45 |
| W1 | 79973 | 68241 | 61037 | 58773 | 418 | 51.61 | 96.6 | 93.43 | 73.49 |
| W2 | 80317 | 70466 | 63381 | 62267 | 418 | 52.17 | 96.62 | 93.44 | 77.53 |
| W3 | 79824 | 70045 | 63173 | 62099 | 416 | 52.08 | 96.63 | 93.46 | 77.79 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| W4 | 79779 | 68859 | 61547 | 60488 | 418 | 51.68 | 96.45 | 93.19 | 75.82 |
| W5 | 79921 | 70445 | 63563 | 62460 | 418 | 51.59 | 96.67 | 93.56 | 78.15 |
| W6 | 79760 | 68691 | 61725 | 60874 | 420 | 51.06 | 96.7 | 93.63 | 76.32 |
| W7 | 79721 | 69411 | 62435 | 61246 | 418 | 51.79 | 96.62 | 93.45 | 76.83 |
| W8 | 80360 | 69787 | 62511 | 61299 | 419 | 51.51 | 96.58 | 93.39 | 76.28 |

**Table S2 Alpha diversity index statistics**

| Sample ID | OTU | ACE | Chao1 | Simpson | Shannon | Coverage |
|---|---|---|---|---|---|---|
| A1 | 349 | 356.2348 | 357.5714 | 0.0246 | 4.4439 | 0.9996 |
| A2 | 346 | 352.2343 | 356.2 | 0.0271 | 4.387 | 0.9996 |
| A3 | 359 | 363.8258 | 365.5 | 0.0288 | 4.471 | 0.9997 |
| A4 | 355 | 361.7728 | 364.2308 | 0.0273 | 4.473 | 0.9997 |
| R5 | 354 | 361.0806 | 362.5714 | 0.0339 | 4.4825 | 0.9997 |
| R6 | 338 | 350.8598 | 349 | 0.0419 | 4.1996 | 0.9996 |
| R7 | 349 | 355.8748 | 359 | 0.0195 | 4.5906 | 0.9997 |
| R8 | 349 | 352.3699 | 352 | 0.0508 | 4.1888 | 0.9998 |
| W1 | 54 | 192.1155 | 124 | 0.2482 | 1.8598 | 0.9996 |
| W2 | 40 | 204.223 | 79 | 0.1964 | 2.0594 | 0.9998 |
| W3 | 38 | 119.3596 | 71 | 0.2036 | 1.9729 | 0.9998 |
| W4 | 52 | 123.5124 | 103 | 0.2025 | 2.1266 | 0.9997 |
| W5 | 40 | 107.9454 | 58.3333 | 0.2038 | 2.0666 | 0.9998 |
| W6 | 40 | 72.5537 | 49.3333 | 0.2591 | 1.8963 | 0.9999 |
| W7 | 35 | 60.8773 | 45.5 | 0.2107 | 1.9424 | 0.9999 |
| W8 | 43 | 111.0345 | 65.5 | 0.2583 | 1.8203 | 0.9998 |
| A5 | 359 | 363.9935 | 363.1053 | 0.0228 | 4.4921 | 0.9997 |
| A6 | 363 | 368.4088 | 367.5882 | 0.0208 | 4.5909 | 0.9997 |
| A7 | 353 | 358.7041 | 363.9091 | 0.0225 | 4.467 | 0.9996 |
| A8 | 364 | 368.4355 | 370.5 | 0.024 | 4.5061 | 0.9997 |
| FEN1 | 317 | 331.6806 | 332.4762 | 0.0483 | 4.0035 | 0.9992 |
| FEN2 | 309 | 327.5397 | 335.64 | 0.153 | 3.0112 | 0.9991 |
| FEN3 | 311 | 320.7279 | 320.5 | 0.0384 | 4.2046 | 0.9994 |
| FEN4 | 316 | 328.1112 | 328.0476 | 0.0425 | 4.0977 | 0.9994 |
| FEN5 | 322 | 329.4535 | 330.0526 | 0.0347 | 4.1957 | 0.9995 |
| FEN6 | 322 | 332.3943 | 333 | 0.0571 | 3.9718 | 0.9993 |
| FEN7 | 312 | 327.3241 | 329.6522 | 0.0589 | 3.7382 | 0.9992 |

| | | | | | | |
|---|---|---|---|---|---|---|
| FEN8 | 321 | 330.7174 | 328.9167 | 0.0592 | 3.993 | 0.9995 |
| R1 | 351 | 357.5436 | 358.5 | 0.0194 | 4.6551 | 0.9997 |
| R2 | 355 | 367.3563 | 367.3529 | 0.0205 | 4.612 | 0.9996 |
| R3 | 349 | 356.7963 | 354.7143 | 0.0344 | 4.3975 | 0.9997 |
| R4 | 350 | 354.1829 | 353.2353 | 0.0278 | 4.5348 | 0.9998 |

**Table S3 Species statistics of different grades of samples**

| Sample | Kindom | Phylum | Class | Order | Family | Genus | Species |
|---|---|---|---|---|---|---|---|
| A1 | 1 | 10 | 16 | 18 | 32 | 85 | 87 |
| A2 | 1 | 10 | 16 | 17 | 32 | 85 | 85 |
| A3 | 1 | 10 | 16 | 17 | 31 | 83 | 86 |
| A4 | 1 | 10 | 16 | 18 | 33 | 85 | 87 |
| A5 | 1 | 10 | 16 | 17 | 32 | 85 | 87 |
| A6 | 1 | 10 | 16 | 17 | 30 | 84 | 86 |
| A7 | 1 | 10 | 16 | 17 | 30 | 82 | 83 |
| A8 | 1 | 10 | 16 | 17 | 31 | 85 | 87 |
| FEN1 | 1 | 10 | 16 | 16 | 29 | 78 | 78 |
| FEN2 | 1 | 10 | 16 | 16 | 30 | 77 | 78 |
| FEN3 | 1 | 10 | 15 | 15 | 28 | 76 | 77 |
| FEN4 | 1 | 10 | 15 | 15 | 26 | 75 | 76 |
| FEN5 | 1 | 10 | 16 | 16 | 30 | 80 | 81 |
| FEN6 | 1 | 10 | 16 | 16 | 29 | 80 | 81 |
| FEN7 | 1 | 10 | 15 | 15 | 29 | 77 | 78 |
| FEN8 | 1 | 10 | 16 | 17 | 31 | 80 | 81 |
| R1 | 1 | 10 | 16 | 17 | 31 | 83 | 84 |
| R2 | 1 | 10 | 16 | 17 | 31 | 82 | 83 |
| R3 | 1 | 10 | 16 | 17 | 32 | 82 | 83 |
| R4 | 1 | 10 | 16 | 17 | 30 | 81 | 82 |
| R5 | 1 | 10 | 16 | 17 | 32 | 82 | 83 |
| R6 | 1 | 10 | 16 | 16 | 31 | 80 | 81 |
| R7 | 1 | 10 | 15 | 16 | 31 | 82 | 83 |
| R8 | 1 | 10 | 16 | 17 | 30 | 82 | 84 |
| W1 | 1 | 7 | 11 | 12 | 20 | 39 | 39 |
| W2 | 1 | 6 | 8 | 9 | 16 | 29 | 29 |
| W3 | 1 | 6 | 9 | 10 | 17 | 27 | 27 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| W4 | 1 | 6 | 8 | 9 | 17 | 39 | 39 |
| W5 | 1 | 7 | 9 | 10 | 16 | 29 | 29 |
| W6 | 1 | 6 | 8 | 9 | 15 | 28 | 28 |
| W7 | 1 | 6 | 8 | 9 | 16 | 28 | 28 |
| W8 | 1 | 8 | 11 | 12 | 19 | 36 | 37 |
| Total | 1 | 10 | 16 | 19 | 34 | 91 | 94 |

**Table S4 Analysis on the difference of metabolic pathway of KEGG (FEN vs W)**

| Class1 | Class2 | FEN | W | FEN: rel. freq. (%) | W: rel. freq. (%) | p-values (corrected) | Effect size | 95.0% lower CI | 95.0% upper CI |
|---|---|---|---|---|---|---|---|---|---|
| Metabolism | Carbohydrate metabolism | 3101849 | 5511771 | 14.97520522 | 15.92648857 | 0 | -0.951283352 | -0.970906411 | -0.931660293 |
| Metabolism | Lipid metabolism | 765678 | 1434282 | 3.696564592 | 4.144416719 | 0 | -0.447852127 | -0.458353432 | -0.437350821 |
| Metabolism | Metabolism of cofactors and vitamins | 1343061 | 2226544 | 6.484072597 | 6.433690292 | 1.90E-13 | 0.05038 2305 | 0.03698 5362 | 0.06377 9248 |
| Metabolism | Energy metabolism | 1429491 | 2447315 | 6.901342099 | 7.071617159 | 0 | -0.170275061 | -0.184142747 | -0.156407375 |
| Metabolism | Nucleotide metabolism | 1117547 | 1731120 | 5.395328938 | 5.002142306 | 0 | 0.393186632 | 0.381037844 | 0.405335419 |
| Metabolism | Biosynthesis of other secondary metabolites | 280970 | 532746 | 1.356475899 | 1.539391437 | 0 | -0.182915538 | -0.189376017 | -0.176455059 |
| Metabol | Amino acid | 2281 | 3942 | 11.017 | 11.392 | 0 | -0.3749 | -0.3921 | -0.3578 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ism | metabolism | 995 | 521 | 08801 | 07628 | | 88263 | 38135 | 38392 |
| Metabolism | Metabolism of terpenoids and polyketides | 388096 | 696824 | 1.873662208 | 2.013501554 | 0 | -0.139839346 | -0.147330068 | -0.132348624 |
| Metabolism | Xenobiotics biodegradation and metabolism | 418000 | 716849 | 2.01803369 | 2.071364614 | 0 | -0.053330924 | -0.061031796 | -0.045630051 |
| Metabolism | Metabolism of other amino acids | 423180 | 755284 | 2.043041858 | 2.182424124 | 0 | -0.139382265 | -0.147188053 | -0.131576478 |
| Metabolism | Glycan biosynthesis and metabolism | 605924 | 1220926 | 2.925299152 | 3.527915798 | 0 | -0.602616647 | -0.612134406 | -0.593098888 |
| Genetic Information Processing | Translation | 1060066 | 1538206 | 5.117820338 | 4.444709383 | 0 | 0.673110955 | 0.66139012 | 0.68483179 |
| Metabol | Global and | 2853 | 4643 | 13.777 | 13.416 | 0 | 0.36081 | 0.34211 | 0.37950 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ism | overview maps | 768 | 194 | 51188 | 69967 | | 2207 | 6202 | 8213 |
| Human Diseases | Drug resistance | 167613 | 308426 | 0.80920737 | 0.891209588 | 0 | -0.082002218 | -0.086978721 | -0.077025715 |
| Environmental Information Processing | Membrane transport | 953344 | 1468634 | 4.602584474 | 4.243678233 | 0 | 0.35890624 | 0.347649834 | 0.370162647 |
| Environmental Information Processing | Signal transduction | 729407 | 1117801 | 3.521454305 | 3.229931877 | 0 | 0.291522428 | 0.281630372 | 0.301414483 |
| Cellular Processes | Cell motility | 396239 | 257984 | 1.912975242 | 0.745455359 | 0 | 1.167519883 | 1.160953959 | 1.174085808 |
| Genetic Information Processing | Folding, sorting and degradation | 446497 | 757527 | 2.155612412 | 2.188905364 | 2.81E-16 | -0.033292952 | -0.04123028 | -0.025355624 |
| Genetic Information Process | Transcription | 46225 | 69439 | 0.223166525 | 0.200646841 | 0 | 0.022519684 | 0.019991741 | 0.025047626 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ing | | | | | | | | | |
| Genetic Information Processing | Replication and repair | 902255 | 1423866 | 4.355935375 | 4.114319259 | 0 | 0.241616116 | 0.230606005 | 0.252626227 |
| Organismal Systems | Endocrine system | 99947 | 199848 | 0.482527304 | 0.577469 | 0 | -0.094941696 | -0.09885805 | -0.091025341 |
| Environmental Information Processing | Signaling molecules and interaction | 0 | 0 | 0 | 0 | 1.075 | 0 | -7.56E-06 | 7.56E-06 |
| Cellular Processes | Cell growth and death | 149540 | 236691 | 0.721953966 | 0.683928361 | 0 | 0.038025605 | 0.033453795 | 0.042597416 |
| Cellular Processes | Transport and catabolism | 122564 | 266873 | 0.591718376 | 0.771140489 | 0 | -0.179422113 | -0.183834528 | -0.175009699 |
| Organismal Systems | Circulatory system | 3708 | 225 | 0.0179016 | 0.000650147 | 0 | 0.017251454 | 0.016661517 | 0.01784139 |
| Organismal System | Development | 0 | 0 | 0 | 0 | 1.048780488 | 0 | -7.56E-06 | 7.56E-06 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| s | | | | | | | | | |
| Cellular Processes | Cellular community | 0 | 0 | 0 | 0 | 1.023809524 | 0 | -7.56E-06 | 7.56E-06 |
| Organismal Systems | Immune system | 25437 | 46780 | 0.122805557 | 0.13517273 | 0 | -0.012367173 | -0.014317193 | -0.010417153 |
| Organismal Systems | Environmental adaptation | 43076 | 63132 | 0.207963682 | 0.182422506 | 0 | 0.025541177 | 0.023110793 | 0.027971561 |
| Organismal Systems | Nervous system | 68232 | 135929 | 0.329412619 | 0.392772426 | 0 | -0.063359807 | -0.0665972 | -0.060122413 |
| Organismal Systems | Sensory system | 0 | 0 | 0 | 0 | 1 | 0 | -7.56E-06 | 7.56E-06 |
| Human Diseases | Endocrine and metabolic diseases | 31188 | 50408 | 0.150570418 | 0.145655985 | 4.70E-06 | 0.004914433 | 0.002800861 | 0.007020256 |
| Organismal Systems | Excretory system | 12094 | 32024 | 0.058387798 | 0.092534663 | 0 | -0.034146865 | -0.035606465 | -0.032687265 |
| Organis | Digestive | 4973 | 1734 | 0.0240 | 0.0501 | 0 | -0.0261 | -0.0271 | -0.0250 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| mal System s | system | | 2 | 08808 | 10421 | | 01613 | 0973 | 93497 |
| Human Disease s | Neurodege nerative diseases | 5869 6 | 6645 7 | 0.2833 74415 | 0.1920 3023 | 0 | 0.09134 4185 | 0.08862 2217 | 0.09406 6154 |
| Human Disease s | Substance dependenc e | 9900 | 2375 1 | 0.0477 95535 | 0.0686 2949 | 0 | -0.0208 33955 | -0.0221 24973 | -0.0195 42937 |
| Human Disease s | Infectious diseases: Bacterial | 1667 45 | 2722 20 | 0.8050 16812 | 0.7865 90865 | 9.96E-14 | 0.01842 5947 | 0.01357 3582 | 0.02327 8312 |
| Human Disease s | Infectious diseases: Parasitic | 1144 5 | 2672 1 | 0.0552 54535 | 0.0772 11426 | 0 | -0.0219 56892 | -0.0233 35793 | -0.0205 7799 |
| Human Disease s | Infectious diseases: Viral | 20 | 135 | 9.66E-05 | 0.0003 90088 | 9.43E-12 | -0.0002 93531 | -0.0003 79329 | -0.0002 07734 |
| Human Disease s | Cancers: Overview | 1644 39 | 3067 42 | 0.7938 83832 | 0.8863 43601 | 0 | -0.0924 59769 | -0.0974 02682 | -0.0875 16856 |
| Human Disease s | Cancers: Specific types | 1851 3 | 3779 8 | 0.0893 7765 | 0.1092 18873 | 0 | -0.0198 41223 | -0.0215 42043 | -0.0181 40403 |
| Human Disease s | Immune diseases | 1150 4 | 2319 2 | 0.0555 39377 | 0.0670 14236 | 0 | -0.0114 74859 | -0.0128 13895 | -0.0101 35823 |
| Human Disease | Cardiovas cular | 6 | 45 | 2.90E-05 | 0.0001 30029 | 7.13E-05 | -0.0001 01062 | -0.0001 53129 | -4.90E-05 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| s | diseases | | | | | | | | |

**Table S5 Analysis on the difference of metabolic pathway of KEGG (R vs W)**

| Class1 | Class2 | R | W | R: rel. freq. (%) | W: rel. freq. (%) | p-values (corrected) | Effect size | 95.0% lower CI | 95.0% upper CI |
|---|---|---|---|---|---|---|---|---|---|
| Metabolism | Carbohydrate metabolism | 4869911 | 5511771 | 15.71715663 | 15.92648857 | 0 | -0.209331947 | -0.227025874 | -0.19163802 |
| Metabolism | Lipid metabolism | 1070975 | 1434282 | 3.456466005 | 4.144416719 | 0 | -0.687950714 | -0.697201626 | -0.678699802 |
| Metabolism | Metabolism of cofactors and vitamins | 1933746 | 2226544 | 6.240974169 | 6.433690292 | 0 | -0.192716123 | -0.204527452 | -0.180904794 |
| Metabolism | Energy metabolism | 2012550 | 2447315 | 6.495306294 | 7.071617159 | 0 | -0.576310866 | -0.588492336 | -0.564129395 |
| Metabolism | Nucleotide metabolism | 1742909 | 1731120 | 5.625066605 | 5.002142306 | 0 | 0.6229243 | 0.612029644 | 0.633818956 |
| Metabolism | Biosynthesis of other secondary metabolites | 427351 | 532746 | 1.379233132 | 1.539391437 | 0 | -0.160158305 | -0.165968443 | -0.154348168 |
| Metabol | Amino acid | 3330 | 3942 | 10.750 | 11.392 | 0 | -0.6419 | -0.6571 | -0.6267 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ism | metabolism | 889 | 521 | 11517 | 07628 | | 61108 | 65739 | 56476 |
| Metabolism | Metabolism of terpenoids and polyketides | 523753 | 696824 | 1.690361063 | 2.013501554 | 0 | -0.323140491 | -0.329665894 | -0.316615088 |
| Metabolism | Xenobiotics biodegradation and metabolism | 601689 | 716849 | 1.941891803 | 2.071364614 | 0 | -0.12947281 | -0.136270264 | -0.122675356 |
| Metabolism | Metabolism of other amino acids | 642897 | 755284 | 2.074886552 | 2.182424124 | 0 | -0.107537572 | -0.114535481 | -0.100539662 |
| Metabolism | Glycan biosynthesis and metabolism | 843420 | 1220926 | 2.722054724 | 3.527915798 | 0 | -0.805861075 | -0.814269909 | -0.79745224 |
| Genetic Information Processing | Translation | 1610639 | 1538206 | 5.198178248 | 4.444709383 | 0 | 0.753468865 | 0.743059014 | 0.763878716 |
| Metabol | Global and | 4303 | 4643 | 13.888 | 13.416 | 0 | 0.47208 | 0.45542 | 0.48874 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ism | overview maps | 396 | 194 | 78543 | 69967 | | 5758 | 9782 | 1734 |
| Human Diseases | Drug resistance | 218333 | 308426 | 0.704648187 | 0.891209588 | 0 | -0.186561401 | -0.190866108 | -0.182256694 |
| Environmental Information Processing | Membrane transport | 1509030 | 1468634 | 4.870245239 | 4.243678233 | 0 | 0.626567006 | 0.616434496 | 0.636699516 |
| Environmental Information Processing | Signal transduction | 1066990 | 1117801 | 3.443604811 | 3.229931877 | 0 | 0.213672934 | 0.204953858 | 0.222392009 |
| Cellular Processes | Cell motility | 808152 | 257984 | 2.608230738 | 0.745455359 | 0 | 1.862775379 | 1.856468103 | 1.869082656 |
| Genetic Information Processing | Folding, sorting and degradation | 614923 | 757527 | 1.984603231 | 2.188905364 | 0 | -0.204302134 | -0.211227795 | -0.197376473 |
| Genetic Information Process | Transcription | 68083 | 69439 | 0.219731156 | 0.200646841 | 0 | 0.019084315 | 0.016855496 | 0.021313134 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ing | | | | | | | | | |
| Genetic Information Processing | Replication and repair | 1374190 | 1423866 | 4.435062461 | 4.114319259 | 0 | 0.320743201 | 0.310922059 | 0.330564344 |
| Organismal Systems | Endocrine system | 143039 | 199848 | 0.461644241 | 0.577469 | 0 | -0.115824759 | -0.119304934 | -0.112344584 |
| Environmental Information Processing | Signaling molecules and interaction | 0 | 0 | 0 | 0 | 1.075 | 0 | -5.99E-06 | 5.99E-06 |
| Cellular Processes | Cell growth and death | 219593 | 236691 | 0.708714713 | 0.683928361 | 0 | 0.024786352 | 0.020747487 | 0.028825216 |
| Cellular Processes | Transport and catabolism | 174803 | 266873 | 0.564159413 | 0.771140489 | 0 | -0.206981076 | -0.210917547 | -0.203044606 |
| Organismal Systems | Circulatory system | 5082 | 225 | 0.016401653 | 0.000650147 | 0 | 0.015751506 | 0.015286676 | 0.016216336 |
| Organismal System | Development | 0 | 0 | 0 | 0 | 1.048780488 | 0 | -5.99E-06 | 5.99E-06 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| s | | | | | | | | | |
| Cellular Processes | Cellular community | 0 | 0 | 0 | 0 | 1.023809524 | 0 | -5.99E-06 | 5.99E-06 |
| Organismal Systems | Immune system | 37758 | 46780 | 0.121860215 | 0.13517273 | 0 | -0.013312516 | -0.015052687 | -0.011572344 |
| Organismal Systems | Environmental adaptation | 69906 | 63132 | 0.225614709 | 0.182422506 | 0 | 0.043192203 | 0.04099257 | 0.045391836 |
| Organismal Systems | Nervous system | 92265 | 135929 | 0.297776172 | 0.392772426 | 0 | -0.094996254 | -0.097834824 | -0.092157683 |
| Organismal Systems | Sensory system | 0 | 0 | 0 | 0 | 1 | 0 | -5.99E-06 | 5.99E-06 |
| Human Diseases | Endocrine and metabolic diseases | 45984 | 50408 | 0.148408817 | 0.145655985 | 0.004266266 | 0.002752832 | 0.000888971 | 0.004616692 |
| Organismal Systems | Excretory system | 7686 | 32024 | 0.024805806 | 0.092534663 | 0 | -0.067728857 | -0.068889691 | -0.066568023 |
| Organis | Digestive | 7238 | 1734 | 0.0233 | 0.0501 | 0 | -0.0267 | -0.0276 | -0.0258 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| mal System s | system | | 2 | 5993 | 10421 | | 50491 | 75994 | 24988 |
| Human Disease s | Neurodege nerative diseases | 8377 2 | 6645 7 | 0.2703 65854 | 0.1920 3023 | 0 | 0.07833 5624 | 0.07599 0748 | 0.08068 05 |
| Human Disease s | Substance dependenc e | 3267 | 2375 1 | 0.0105 4392 | 0.0686 2949 | 0 | -0.0580 8557 | -0.0590 3601 | -0.0571 3513 |
| Human Disease s | Infectious diseases: Bacterial | 2414 79 | 2722 20 | 0.7793 49615 | 0.7865 90865 | 0.0010 68603 | -0.0072 4125 | -0.0115 19192 | -0.0029 63307 |
| Human Disease s | Infectious diseases: Parasitic | 8287 | 2672 1 | 0.0267 45474 | 0.0772 11426 | 0 | -0.0504 65953 | -0.0515 6185 | -0.0493 70055 |
| Human Disease s | Infectious diseases: Viral | 87 | 135 | 0.0002 80784 | 0.0003 90088 | 0.0178 15056 | -0.0001 09304 | -0.0002 03679 | -1.49E-05 |
| Human Disease s | Cancers: Overview | 2302 24 | 3067 42 | 0.7430 25215 | 0.8863 43601 | 0 | -0.1433 18386 | -0.1476 71194 | -0.1389 65579 |
| Human Disease s | Cancers: Specific types | 2305 0 | 3779 8 | 0.0743 91598 | 0.1092 18873 | 0 | -0.0348 27275 | -0.0362 93621 | -0.0333 60929 |
| Human Disease s | Immune diseases | 1731 1 | 2319 2 | 0.0558 69542 | 0.0670 14236 | 0 | -0.0111 44694 | -0.0123 48871 | -0.0099 40516 |
| Human Disease | Cardiovas cular | 25 | 45 | 8.07E-05 | 0.0001 30029 | 0.0566 11348 | -4.93E-05 | -0.0001 04772 | 6.08E-06 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| s | diseases | | | | | | | | |

**Table S6 Analysis on the difference of metabolic pathway of COG (FEN vs W)**

| Class1 | Class2 | FEN | W | FEN: rel. freq. (%) | W: rel. freq. (%) | p-values (corrected) | Effect size | 95.0% lower CI | 95.0% upper CI |
|---|---|---|---|---|---|---|---|---|---|
| INFORMATION STORAGE AND PROCESSING | RNA processing and modification | 7950 | 17702 | 0.024210278 | 0.031769065 | 0 | -0.007558787 | -0.008272124 | -0.006845451 |
| INFORMATION STORAGE AND PROCESSING | Chromatin structure and dynamics | 7943 | 17445 | 0.024188961 | 0.031307838 | 0 | -0.007118877 | -0.007829791 | -0.006407963 |
| METABOLISM | Energy production and conversion | 1631110 | 2685347 | 4.967248671 | 4.819283963 | 0 | 0.147964708 | 0.138640832 | 0.157288584 |
| CELLULAR PROCESSES AND SIGNALING | Cell cycle control, cell division, chromosome partitioning | 385875 | 544647 | 1.175111209 | 0.977456006 | 0 | 0.197656084 | 0.19315042 | 0.202161748 |
| METABOLISM | Amino acid transport and | 243776 | 398004 | 7.423775766 | 7.142801907 | 0 | 0.280956696 | 0.269721392 | 0.292191999 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | metabolism | 7 | 1 | | | | | | |
| METABOLISM | Nucleotide transport and metabolism | 834995 | 1254413 | 2.542825318 | 2.251244422 | 0 | 0.291580896 | 0.284930729 | 0.298231063 |
| METABOLISM | Carbohydrate transport and metabolism | 2818152 | 4502184 | 8.582116906 | 8.079888055 | 0 | 0.502281005 | 0.490318641 | 0.514243369 |
| METABOLISM | Coenzyme transport and metabolism | 1302304 | 2300565 | 3.965929835 | 4.128731225 | 0 | -0.162801391 | -0.171282219 | -0.154320563 |
| METABOLISM | Lipid transport and metabolism | 800689 | 1454459 | 2.438352638 | 2.61025891 | 0 | -0.171906272 | -0.178645637 | -0.165166908 |
| INFORMATION STORAGE AND PROCESSING | Translation, ribosomal structure and biogenesis | 1942656 | 2911433 | 5.916005317 | 5.225031389 | 0 | 0.690973928 | 0.681006575 | 0.700941282 |
| INFORMATION STORAGE AND PROCESSING | Transcription | 2618402 | 4231142 | 7.973866786 | 7.593459908 | 0 | 0.380406878 | 0.368816852 | 0.391996904 |
| INFORMATION STORAGE AND | Replication, recombination and repair | 2016463 | 3358575 | 6.140771104 | 6.027499104 | 0 | 0.113272001 | 0.102948548 | 0.123595454 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PROCESSING | | | | | | | | | |
| CELLULAR PROCESSES AND SIGNALING | Cell wall/membrane/envelope biogenesis | 2382023 | 4532924 | 7.254017559 | 8.135055893 | 0 | -0.881038335 | -0.892454763 | -0.869621906 |
| CELLULAR PROCESSES AND SIGNALING | Cell motility | 615110 | 772156 | 1.873205565 | 1.385757233 | 0 | 0.487448333 | 0.481882626 | 0.493014039 |
| CELLULAR PROCESSES AND SIGNALING | Posttranslational modification, protein turnover, chaperones | 1058478 | 1819086 | 3.223402124 | 3.264640282 | 0 | -0.041238158 | -0.048876077 | -0.033600239 |
| METABOLISM | Inorganic ion transport and metabolism | 1555870 | 3178716 | 4.738118943 | 5.70471341 | 0 | -0.966594467 | -0.976080125 | -0.957108808 |
| METABOLISM | Secondary metabolites biosynthesis, transport and catabolism | 383771 | 744720 | 1.168704741 | 1.33651895 | 0 | -0.167814209 | -0.172573237 | -0.163055181 |
| POORLY | General | 383 | 675 | 11.684 | 12.115 | 0 | -0.431 | -0.445 | -0.417 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| CHARACTERIZED | function prediction only | 6868 | 1015 | 48325 | 77436 | | 291108 | 228777 | 353439 |
| POORLY CHARACTERIZED | Function unknown | 2457564 | 4518638 | 7.484063927 | 8.109417385 | 0 | -0.625353458 | -0.636863551 | -0.613843365 |
| CELLULAR PROCESSES AND SIGNALING | Signal transduction mechanisms | 2038226 | 3242537 | 6.20704636 | 5.819250385 | 0 | 0.387795976 | 0.377500958 | 0.398090993 |
| CELLULAR PROCESSES AND SIGNALING | Intracellular trafficking, secretion, and vesicular transport | 791901 | 1487278 | 2.411590383 | 2.669157846 | 0 | -0.257567463 | -0.264313263 | -0.250821662 |
| CELLULAR PROCESSES AND SIGNALING | Defense mechanisms | 907769 | 1404743 | 2.764445291 | 2.52103561 | 0 | 0.243409681 | 0.236448798 | 0.250370564 |
| CELLULAR PROCESSES AND SIGNALI | Extracellular structures | 16 | 735 | 4.87E-05 | 0.001319075 | 1.13E-122 | -0.00127035 | -0.001373397 | -0.001167302 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| NG | | | | | | | | | |
| CELLULAR PROCESSES AND SIGNALING | Nuclear structure | 0 | 0 | 0 | 0 | 1 | 0 | -4.74E-06 | 4.74E-06 |
| CELLULAR PROCESSES AND SIGNALING | Cytoskeleton | 5391 | 10370 | 0.016417309 | 0.018610621 | 5.87E-14 | -0.002193311 | -0.00276401 | -0.001622613 |

**Table S7 Analysis on the difference of metabolic pathway of COG (R vs W)**

| Class1 | Class2 | R | W1 | R: rel. freq. (%) | W: rel. freq. (%) | p-values (corrected) | Effect size | 95.0% lower CI | 95.0% upper CI |
|---|---|---|---|---|---|---|---|---|---|
| INFORMATION STORAGE AND PROCESSING | RNA processing and modification | 6762 | 17702 | 0.013342264 | 0.031769065 | 0 | -0.018426801 | -0.018996238 | -0.017857365 |
| INFORMATION STORAGE AND PROCESSING | Chromatin structure and dynamics | 4840 | 17445 | 0.009549992 | 0.031307838 | 0 | -0.021757918 | -0.022298407 | -0.021217429 |
| METABOLISM | Energy production and conversion | 2455957 | 2685347 | 4.845907602 | 4.819283963 | 1.74E-10 | 0.026623639 | 0.018460659 | 0.034786619 |
| CELLULAR PROCESSES AND SIGNALING | Cell cycle control, cell division, chromosome partitioning | 661520 | 544647 | 1.305260962 | 0.977456006 | 0 | 0.327804956 | 0.32374699 | 0.331862923 |
| METABOLISM | Amino acid transport and | 374466 | 398004 | 7.388684288 | 7.14281907 | 0 | 0.245865218 | 0.235982664 | 0.255747771 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | metabolism | 3 | 1 | | | | | | |
| METABOLISM | Nucleotide transport and metabolism | 1379629 | 1254413 | 2.722179036 | 2.251244422 | 0 | 0.470934615 | 0.464994384 | 0.476874845 |
| METABOLISM | Carbohydrate transport and metabolism | 5389660 | 4502184 | 10.63446728 | 8.079888055 | 0 | 2.554579228 | 2.543474335 | 2.565684121 |
| METABOLISM | Coenzyme transport and metabolism | 1879108 | 2300565 | 3.707713019 | 4.128731225 | 0 | -0.421018207 | -0.428394145 | -0.413642269 |
| METABOLISM | Lipid transport and metabolism | 1092155 | 1454459 | 2.154957199 | 2.61025891 | 0 | -0.455301711 | -0.461093976 | -0.449509446 |
| INFORMATION STORAGE AND PROCESSING | Translation, ribosomal structure and biogenesis | 2988494 | 2911433 | 5.896669116 | 5.225031389 | 0 | 0.671637727 | 0.662904824 | 0.68037063 |
| INFORMATION STORAGE AND PROCESSING | Transcription | 4580517 | 4231142 | 9.037927843 | 7.593459908 | 0 | 1.444467934 | 1.433943399 | 1.454992469 |
| INFORMATION STORAGE AND | Replication, recombination and repair | 3065461 | 3358575 | 6.048534548 | 6.027499104 | 5.59E-06 | 0.021035444 | 0.011969606 | 0.030101282 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PROCESSING | | | | | | | | | |
| CELLULAR PROCESSES AND SIGNALING | Cell wall/membrane/envelope biogenesis | 3269816 | 4532924 | 6.451752295 | 8.135055893 | 0 | -1.683303598 | -1.693169778 | -1.673437419 |
| CELLULAR PROCESSES AND SIGNALING | Cell motility | 953023 | 772156 | 1.880432516 | 1.385757233 | 0 | 0.494675283 | 0.489833593 | 0.499516973 |
| CELLULAR PROCESSES AND SIGNALING | Posttranslational modification, protein turnover, chaperones | 1472292 | 1819086 | 2.905014622 | 3.264640282 | 0 | -0.35962566 | -0.366198328 | -0.353052993 |
| METABOLISM | Inorganic ion transport and metabolism | 2181212 | 3178716 | 4.303801659 | 5.70471341 | 0 | -1.40091175 | -1.409179992 | -1.392643508 |
| METABOLISM | Secondary metabolites biosynthesis, transport and catabolism | 482003 | 744720 | 0.951051668 | 1.33651895 | 0 | -0.385467282 | -0.389499754 | -0.38143481 |
| POORLY | General | 566 | 675 | 11.168 | 12.115 | 0 | -0.947 | -0.959 | -0.935 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| CHARACTERIZED | function prediction only | 0255 | 1015 | 38476 | 77436 | | 389596 | 583689 | 195503 |
| POORLY CHARACTERIZED | Function unknown | 3409487 | 4518638 | 6.727340492 | 8.109417385 | 0 | -1.382076894 | -1.392027152 | -1.372126635 |
| CELLULAR PROCESSES AND SIGNALING | Signal transduction mechanisms | 3396240 | 3242537 | 6.701202518 | 5.819250385 | 0 | 0.881952134 | 0.872719511 | 0.891184757 |
| CELLULAR PROCESSES AND SIGNALING | Intracellular trafficking, secretion, and vesicular transport | 978971 | 1487278 | 1.931631136 | 2.669157846 | 0 | -0.737526709 | -0.74321095 | -0.731842469 |
| CELLULAR PROCESSES AND SIGNALING | Defense mechanisms | 1621842 | 1404743 | 3.200009531 | 2.521003561 | 0 | 0.6790597 | 0.672698208 | 0.685421192 |
| CELLULAR PROCESSES AND SIGNALI | Extracellular structures | 7 | 735 | 1.38E-05 | 0.001319075 | 5.98E-193 | -0.001305263 | -0.001404864 | -0.001205662 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| NG | | | | | | | | | |
| CELLULAR PROCESSES AND SIGNALING | Nuclear structure | 0 | 0 | 0 | 0 | 1 | 0 | -3.69E-06 | 3.69E-06 |
| CELLULAR PROCESSES AND SIGNALING | Cytoskeleton | 7139 | 10370 | 0.014086132 | 0.018610621 | 0 | -0.004524489 | -0.005012983 | -0.004035994 |