**Supporting Information**

***Sargassum pallidum* reduces inflammatory response to exert antidepressant effect by regulating intestinal microbial structure and ERK1/2/P38 signaling pathway**

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**[[1]](#footnote-1)**

**Table S1 Reagents**

|  |  |  |
| --- | --- | --- |
| Test Drugs/Reagents | Number | Manufacturer |
| Paroxetine | Y0000578 | Sigma-Aldrich (Shanghai) Trading Co., Ltd. |
| Methanol | F112084 | ACS Corporation |
| Acetonitrile | AS1122-801 | TEDIA Corporation |
| Ethyl Acetate | 3952 | Tianjin Damao Chemical Reagent Factory |
| Kaurenoic acid | AB0300 | Alpha Biological Company (Chengdu, China) |
| 7-Hydroxycoumarin | AB0072 | Alpha Biological Company (Chengdu, China) |
| Nobiletin | AB0864 | Alpha Biological Company (Chengdu, China) |
| Scoparone | AB1701 | Alpha Biological Company (Chengdu, China) |
| Hematoxylin | D1005-1-4 | Nanjing Jiancheng Technology Co., Ltd. (Nanjing, China) |
| Eosin dye | D1006-1-4 | Nanjing Jiancheng Technology Co., Ltd. (Nanjing, China) |
| Isoflurane | 792632-1G | ALDRICHCompany |
| PBS | CBS101.05 | Cellmax Corporation |
| High glucose DMEM medium | CGM102.05 | Cellmax Corporation |
| penicillin-streptomycin | C100C5 | Cellmax Corporation |
| Pancreatin | T1300 | Solarbio Corporation |
| CCK-8 Kit |  | GLPBIO Corporation |
| LPS | L2880 | Sigma Corporation |
| TBST buffer solution | T1082 | Solarbio Corporation |
| TritonX-100 | T8220 | Solarbio Corporation |
| BSA | A8020 | Solarbio Corporation |
| DAPI | TX01025 | Shanghai Yingxin Laboratory Equipment Co., Ltd. |
| TITC-goat anti-rabbit IgG | BA1105 | Boster Biological Co., Ltd. |

**Table S2 chromatography and mass spectrometry conditions**

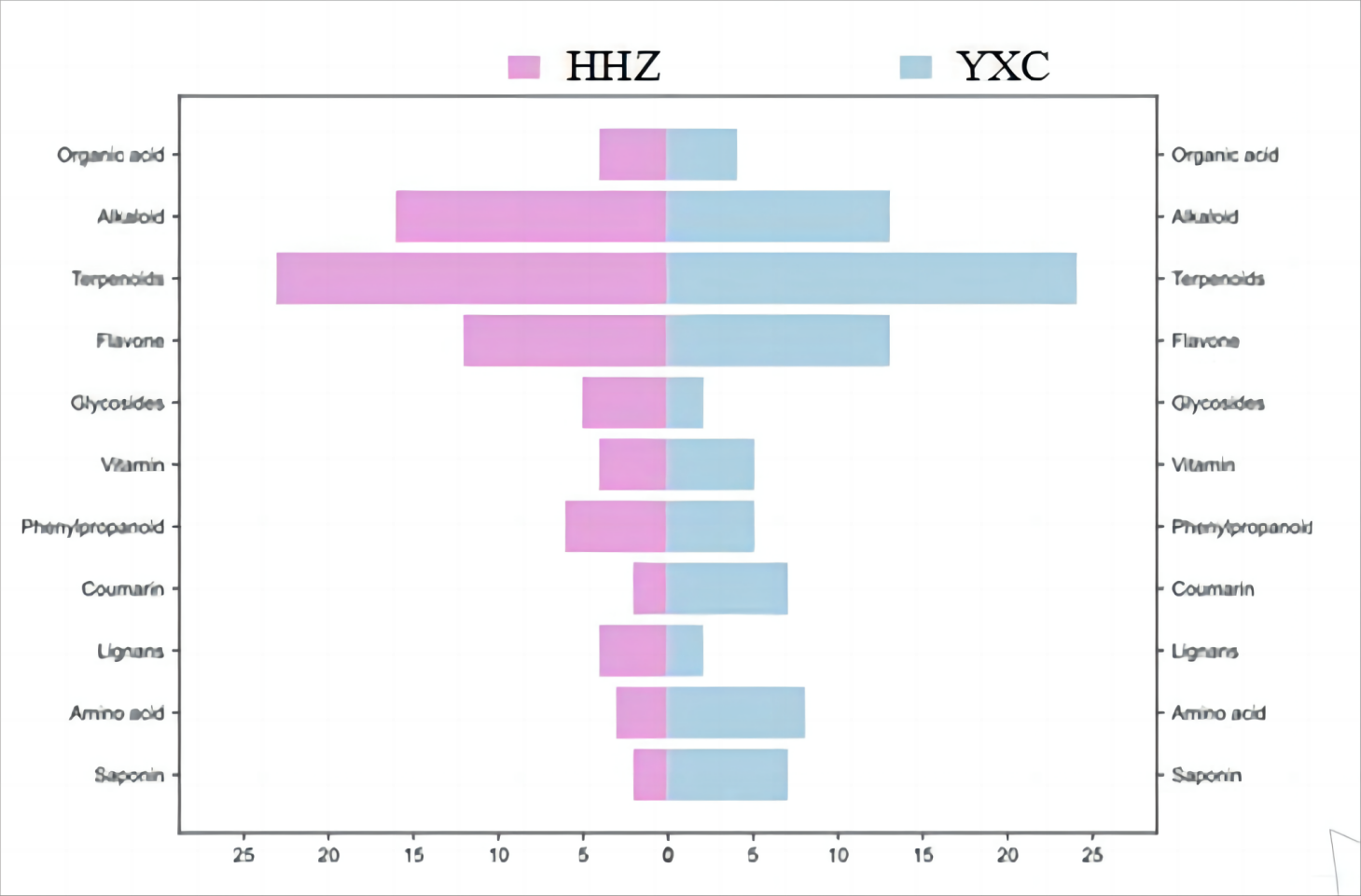
|  |  |
| --- | --- |
| UPLC | |
| Column | Acquity UPLC BEH C18 chromatographic column (100 mm×2.1 mm, 1.7 μm, Waters company) |
| Column temperature（℃） | 40 |
| Mobile phase | A= 0.1% formic acid aqueous solution B= 0.1% formic acid acetonitrile |
| Gradient conditions | 0~15 min(5 %~55 %B), 15~45 min( 55 %~95 %B), 47~47.10min(95 %~5 %B) |
| Flow rate（mL/min） | 0.3 |
| Injection volume （uL） | 3 |
| Mass spectrometer | |
| Lon Source Temp （°C） | 500 |
| Declustering Voltage（V） | 100 |
| Voltage(V) | 4500 |
| Scan Range | 50~1550 |
| Curtain Gas(psi) | 40 |
| Atomizing gas and Auxiliary gas(psi) | 50 |
| Collision Energy(ev) | 40±10 |

**Table S3 UPLC-QTOF-MS/MS Identification Results of Compounds in *Sargassum pallidum***

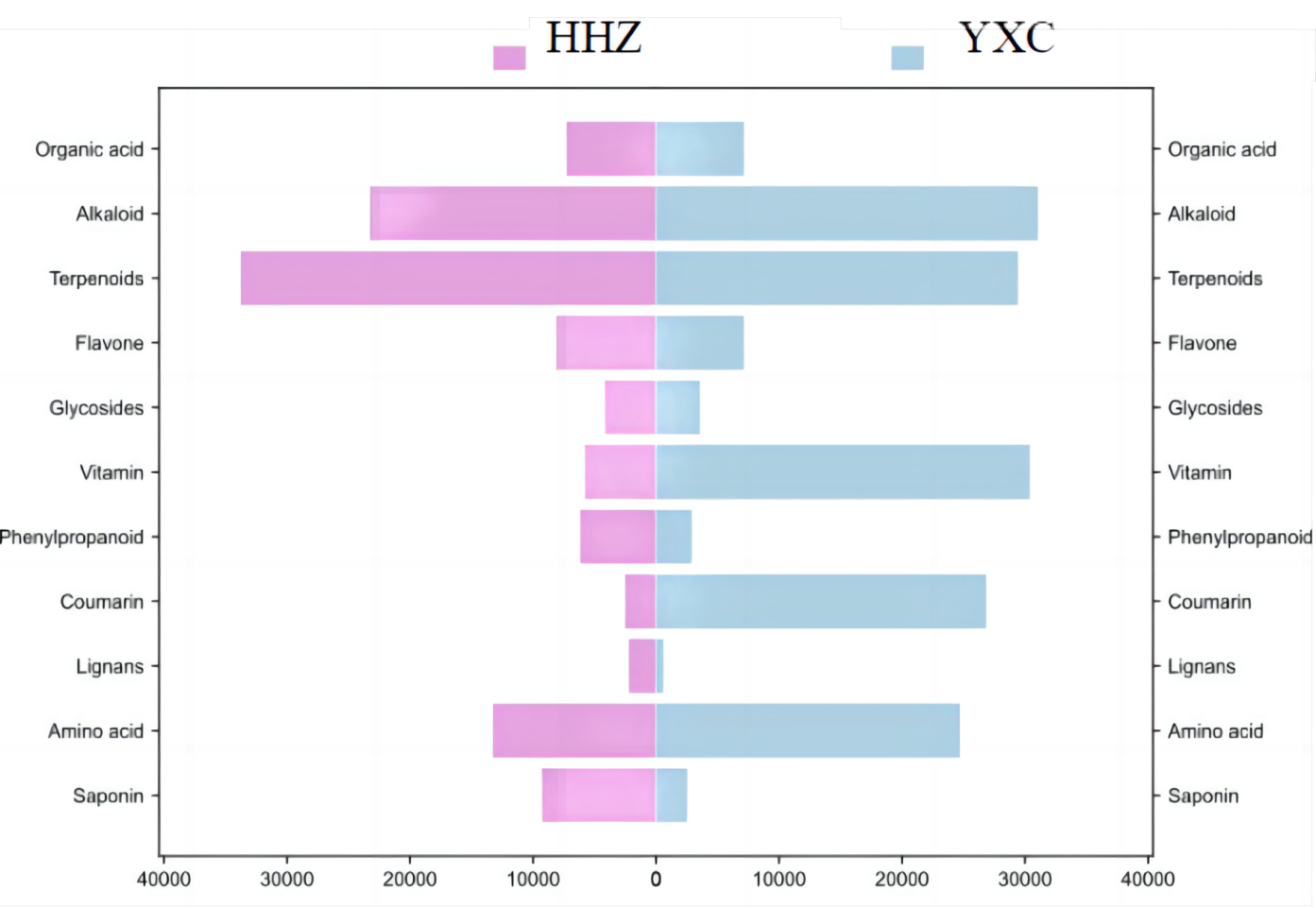
|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| NO. | identity | Molecular formula | Found At RT (min) | Adduct | E.M (Da) | Error(ppm) | MS/MS | Types | **HHZ Original medicinal materials** | **YXC Original medicinal materials** | **HHZ**  **Freeze**  **dried**  **powder** |
| 1 | linoleic acid | C18H32O2 | 31.8 | -H | 279.233 0 | 2.5 | 261.2246 | OA | *√* | *√* | *√* |
| 2 | betaine | C5H11NO2 | 12.68 | +H | 118.086 3 | 2.8 | 59.07 0，58.063 | ALK | *√* | *√* | *√* |
| 3 | adenosine | C10H13N5O4 | 1.87 | +H | 268.104 | -0.8 | 136.0624，119.0350，57.0476 | ALK | *√* | *√* | *√* |
| 4 | adenine | C5H5N5 | 1.67 | +H | 136.0618 | 0.6 | 136.0618，119.0357，92.0261，65.0157 | ALK | *√* | *√* | *√* |
| 5 | protopine | C20H19NO5 | 8.29 | +H | 354.133 6 | 0.8 | 336.1247，275.0714，247.078，206.0826，188.0710，165.0560，149.0576 | ALK | *√* | *√* | *√* |
| 6 | l-carnitine | C7H15NO3 | 11.53 | +H | 162.112 5 | 0.5 | 102.0918，85.0297，60.0840，  58.0682 | ALK | *√* | *√* | *√* |
| ALK |  |  | *√* |
| 7 | uridine | C9H12N2O6 | 1.76 | -H | 243.0623 | 3.7 | 243.0213 | ALK | *√* | *√* |  |
| 8 | thymine | C5H6N2O2 | 2.02 | +H | 127.0502 | 2.1 | 110.0274，84.0466，82.0306，54.0389 | ALK | *√* | *√* | *√* |
| 9 | trichosanatine | C27H28N2O4 | 16.02 | +H | 445.2121 | 0.9 | 252.1035，224.1076，105.0345，91.0558 | ALK | *√* | *√* | *√* |
| 10 | sophoridine | C15H24N2O | 3.59 | +H | 249.1961 | 2.6 | 249.1962，231.1880，148.0776，136.1130，98.0982，96.0826，84.9616，79.0564，70.0678 | ALK | *√* |  | *√* |
| 11 | tetrahydropalmatine hydrochloride | C21H25NO4 | 8.85 | +H | 356.1856 | 1.1 | 356.1858，340.1550，192.1021，176.0712，165.0915，150.0673，148.0774 | ALK | *√* |  | *√* |
| 12 | 6-hydroxypurine | C5H4N4O | 1.74 | +H | 137.0458 | 1.5 | 137.0456，119.0360，110.0355，94.0406，82.0414，67.0309，65.0165，55.0333 | ALK | *√* |  | *√* |
| 13 | roburic acid | C30H48O2 | 38.6 | +H | 441.3726 | 0.6 | 441.3740，357.2881，245.1864，205.1936，189.1620，163.1483，149.0950，135.1173，107.0868 | TRI | *√* | *√* | *√* |
| 14 | 18β-glycyrrhetinic acid | C30H46O4 | 36.03 | -H | 469.3323 | -1 | 425.3408，407.3357，392.3089，381.3278 | TRI | *√* |  | *√* |
| 15 | 3-acetyl-11-keto-beta-boswellic acid | C32H48O5 | 16.33 | +H | 513.3574 | 0.3 | 513.3496，453.3395，435.3266，269.2296，201.1668，185.1357，149.0984，95.0870 | TRI | *√* |  | *√* |
| 16 | ambroxane | C16H28O | 30.31 | +H | 237.2213 | 0.2 | 149.1309，135.1186，121.1109，109.1008，95.0856，93.0707，81.0715，67.0562，55.0581 | DIT | *√* | *√* | *√* |
| 17 | sclareolide | C16H26O2 | 19.3 | +H | 251.200 6 | -0.3 | 233.1979，135.1164，121.1026，  107.086 6，95.0899，79.0548，67.0571 | DIT | *√* | *√* | *√* |
| 18 | kaurenoic acid | C20H30O2 | 22.2 | +H | 303.233 4 | 0.7 | 285.2220，257.1897，175.1483，  161.1318，147.1167，133.1012 | DIT | *√* | *√* | *√* |
| 19 | alpha-cyperone | C15H22O | 12.89 | +H | 219.1743 | -0.6 | 219.1738，145.1021，119.0873，105.0712，91.0556，77.0407，67.0599 | SE | *√* | *√* | *√* |
| 20 | atractylenolide iii | C15H20O3 | 11.75 | +H | 249.1485 | 0.3 | 170.1076，161.0950，155.0861，128.0627，105.0728，91.0545，79.0564，55.0211 | SE | *√* | *√* | *√* |
| 21 | curdione | C15H24O2 | 16.17 | +H | 237.1849 | -0.2 | 201.1675，159.1163，121.0996，105.0718，93.0721，77.0412，67.0561 | SE | *√* | *√* | *√* |
| 22 | parthenolide | C15H20O3 | 11.75 | +H | 249.1485 | 0.3 | 161.0950，142.0790，128.0627，105.0728，91.0545，81.0711，77.0421，55.0211 | SE | *√* | *√* | *√* |
| 23 | galangin | C15H10O5 | 16.64 | -H | 269.0456 | -3 | 269.0400，240.0400，225.0566，210.0345，181.0727 | FLA | *√* | *√* | *√* |
| 24 | apigenin | C15H10O5 | 16.63 | -H | 269.0456 | -1.3 | 269.0468，227.0341，195.0487，171.0428，167.0574，143.0458 | FLA | *√* | *√* |  |
| 25 | nobiletin | C21H22O8 | 13.97 | +H | 403.1388 | 0.7 | 403.1404，373.0936，327.0865，211.0258，183.0283 | FLA | *√* | *√* | *√* |
| 26 | cimifugin | C16H18O6 | 7.11 | +H | 307.1176 | 0.7 | 259.0603，235.0614，221.0451，205.0486，177.0543 | FLA | *√* |  |  |
| 27 | neoeriocitrin | C27H32O15 | 35.02 | -H | 595.1669 | 2 | 459.1838，339.1539 | FLA | *√* |  |  |
| 28 | riboflavin | C17H20N4O6 | 5.24 | -H | 375.131 | 0.8 | 255.0882，241.0716，212.0890 | VIT | *√* | *√* | *√* |
| 29 | retinoic acid | C20H28O2 | 19.8 | +H | 301.2162 | 1 | 283.2111，241.1948，199.1500，185.1328，173.1344，159.1168，145.1013，131.0858，117.0724，105.0713，91.0558，67.0568 | VIT | *√* | *√* | *√* |
| 30 | vitamin d2 | C28H44O | 46.73 | +H | 397.3465 | 0.7 | 379.3454，225.1626，201.1746，161.1329，147.1173，119.0875，109.0665，81.0730 | VIT | *√* | *√* | *√* |
| 31 | nicotinic acid | C6H5NO2 | 1.69 | +H | 124.0393 | 0.8 | 80.0515，78.0351，53.0421，50.0186 | VIT | *√* |  | *√* |
| 32 | ethyl 4'-hydroxy-3'-methoxycinnamate | C12H14O4 | 22.31 | +H | 223.0965 | -0.2 | 207.0321，149.0263，121.0295，91.0559，77.0387 | PHE | *√* | *√* | *√* |
| 33 | ethyl-p-coumaric acid (p) | C9H8O3 | 1.53 | +H | 165.0546 | 0.4 | 109.0653，79.0560，77.0412,51.0279 | PHE | *√* |  |  |
| 34 | 7-hydroxycoumarin | C9H6O3 | 10.86 | +H | 163.039 | 0.2 | 149.0223，121.0283，93.0341，65.0416 | COU | *√* | *√* | *√* |
| 35 | scoparone | C11H10O4 | 8.48 | +H | 207.0652 | -1 | 191.0339，163.0400，151.0757，107.0503，91.0556，77.0411，65.0413 | COU | *√* |  | *√* |
| 36 | salvianolic acid | C26H22O10 | 15.36 | +H | 495.1286 | -3.9 | 495.1282，195.0095，131.0877 | LIG | *√* |  | *√* |
| 37 | valine | C5H11NO2 | 1.07 | +H | 118.0863 | 2.8 | 118.0875，59.0770，58.0693 | AA | *√* | *√* | *√* |
| 38 | methyl linoleate | C19H34O2 | 33.99 | +H | 295.2632 | 0.8 | 263.2424，161.1301，133.1033，109.1015，81.0711，55.0601 | FA | *√* | *√* |  |
| 39 | sarsasapogenin | C27H44O3 | 39.92 | +H | 417.3363 | 0.7 | 417.3332，273.2204，161.1352，147.1177 | SAP | *√* | *√* | *√* |
| 40 | diosgenin | C27H42O3 | 35.9 | +H | 415.3207 | 0.9 | 415.2557，271.2077，253.1934，175.1498，147.1171，133.1011，119.0867 | SAP | *√* |  | *√* |
| 41 | muscone | C16H30O | 35.11 | +H | 239.2369 | -0.1 | 109.1014，95.0864，81.0728，67.0575，57.0737，55.0594 | Other | *√* | *√* | *√* |
| 42 | cis-13-docosenoamide | C22H43NO | 41.21 | +H | 338.3417 | 1.1 | 116.1089，97.0659，69.0730，57.0743 | Other | *√* | *√* | *√* |
| 43 | oleamide | C18H35NO | 30.69 | +H | 282.2791 | 0.8 | 111.0814，83.0868，69.0728，55.0581 | Other | *√* | *√* | *√* |
| 44 | (-)-umbelliferamide | C32H30N2O4 | 18.85 | +H | 507.2283 | 1 | 252.1021，224.1072，105.0324，91.0554，77.0406 | Other | *√* | *√* | *√* |
| 45 | -hydroxymethylfurfural | C6H6O3 | 3.63 | +H | 127.0389 | 1.6 | 127.0410，68.9982，59.9335 | Other | *√* |  | *√* |

OA: Organic acid, ALK: Alkaloids, TRI: Triperpenoids, DIT: Diterpenoids, SE: Sesquiterpenes, FLA: Flavonoids, QUI: Quinones, GLY: Glycoside, VIT: Vitamin, PHE: Phenylpropanoids, COU: Coumarin, LIG: Lignans, AA: Amino acid, FA: Fatty acid, SAP: saponin,

**Figure S1 Comparison of the amount of ingredients in various types of HHZ and YXC**



**Figure S2 Comparison of the relative contents of HHZ and YXC HHZ: *Sargassum pallidum* YXC：*Sargassum fusiforme***



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