

**Table S1** Comparison of the times of head-scratching of the rats (n=15) in 2 h.

Groups	Times (mean $\pm$ SD)	<i>p</i>
A Control	3.8 $\pm$ 5.5	---
B Model	465.5 $\pm$ 400.1 **	0.000 <sup>a</sup>
C WZY Decoction	216.7 $\pm$ 119.7 **	0.000 <sup>b</sup>
D Flunarizine	220.3 $\pm$ 183.8 **	0.000 <sup>b</sup>

a: compared to group A; b: compared to group B; \*\*p<0.01.

**Table S2** The database information of the potential biomarkers and their trends in headache rat brain tissue.

NO	Metabolite	Formula	HMDB	METLIN	KEGG	Trend in Model
1	Glycerophosphocholine (GPC)	C <sub>8</sub> H <sub>20</sub> NO <sub>6</sub> P	HMDB00086	370	C00670	↑
2	Arginine	C <sub>6</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>	HMDB00517	13	C00062	↓
3	Adenosine monophosphate (AMP)	C <sub>10</sub> H <sub>14</sub> N <sub>5</sub> O <sub>7</sub> P	HMDB03540	63401	C01367	↑
4	Nicotinamide adenine dinucleotide (NAD)	C <sub>21</sub> H <sub>27</sub> N <sub>7</sub> O <sub>14</sub> P <sub>2</sub>	HMDB00902	101	C00003	↑
5	Glutathione (GSH)	C <sub>10</sub> H <sub>17</sub> N <sub>3</sub> O <sub>6</sub> S	HMDB00125	44	C00051	↑
6	Oxidized glutathione (GSSG)	C <sub>20</sub> H <sub>32</sub> N <sub>6</sub> O <sub>12</sub> S <sub>2</sub>	HMDB03337	45	C00127	↑
7	Adenine	C <sub>5</sub> H <sub>5</sub> N <sub>5</sub>	HMDB00034	85	C00147	↑
8	Adenosine	C <sub>10</sub> H <sub>13</sub> N <sub>5</sub> O <sub>4</sub>	HMDB00050	86	C00212	↑
9	Valerolactam	C <sub>5</sub> H <sub>9</sub> NO	HMDB11749	62467	-	↑
10	Butyrylcarnitine	C <sub>11</sub> H <sub>21</sub> NO <sub>4</sub>	HMDB02013	964	C02862	↑
11	Caprolactam	C <sub>6</sub> H <sub>11</sub> NO	-	44753	C06593	↑
12	Cholecalciferol (Vitamin D3)	C <sub>27</sub> H <sub>44</sub> O	HMDB14315	165	C05443	↓

**Table S3** The database information of the potential biomarkers and their trends in headache rat plasma.

NO	Metabolite	Formula	HMDB	METLIN	KEGG	Trend in Model
1	Arginine	C <sub>6</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>	HMDB00517	13	C00062	↓
2	Carnitine	C <sub>7</sub> H <sub>15</sub> NO <sub>3</sub>	HMDB00062	52	C00318	↓
3	5-Hydroxyindoleacetic acid (5-HIAA)	C <sub>10</sub> H <sub>9</sub> NO <sub>3</sub>	HMDB00763	2975	C05635	↓
4	3-Methylindole	C <sub>9</sub> H <sub>9</sub> N	HMDB00466	5453	C08313	↓
5	Hydroxyindole	C <sub>8</sub> H <sub>7</sub> NO	HMDB59805	34514	C02040	↓
6	Indoleacetic acid (IAA)	C <sub>10</sub> H <sub>9</sub> NO <sub>2</sub>	HMDB00197	70	C00954	↓

**Table S4** Principle metabolic pathways of the metabolites in KEGG database.

NO	Metabolite	Pathways
1	Arginine	Arginine and proline metabolism; Arginine biosynthesis; Aminoacyl-tRNA biosynthesis
2	Glutathione	Glutathione metabolism; Cysteine and methionine metabolism
3	Oxidized glutathione	Glutathione metabolism
4	Indoleacetic acid	Tryptophan metabolism
5	5-Hydroxyindoleacetic acid	Tryptophan metabolism
6	3-Methylindole	-
7	Hydroxyindole	-
8	Adenine	Purine metabolism
9	Adenosine	Purine metabolism; cAMP signaling pathway; Sphingolipid signaling pathway
10	Adenosine monophosphate	Purine metabolism
11	Nicotinamide adenine dinucleotide	Nicotinate and nicotinamide metabolism; Oxidative phosphorylation; Vitamin digestion and absorption
12	Carnitine	Lysine degradation; Bile secretion
13	Butyrylcarnitine	-
14	Glycerophosphocholine	Glycerophospholipid metabolism; Ether lipid metabolism
15	Caprolactam	Caprolactam degradation
16	Valerolactam	Valerolactam degradation
17	Cholecalciferol	Vitamin digestion and absorption