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Review article

Metabolomics on depression: A comparison of clinical and animal research

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ABSTRACT

Background: Depression is a major cause of suicide and mortality worldwide. This study aims to conduct a systematic review to identify metabolic biomarkers and pathways for major depressive disorder (MDD), a prevalent subtype of clinical depression.
Methods: We searched for metabolomics studies on depression published between January 2000 and January 2023 in the PubMed and Web of Science databases. The reported metabolic biomarkers were systematically evaluated and compared. Pathway analysis was implemented using MetaboAnalyst 5.0.
Results: We included 26 clinical studies on major depressive disorder and 78 metabolomics studies on depressive-like animal models. A total of 59 and 86 high-frequency metabolites were reported consistently in two-thirds of clinical and murine studies, respectively. In the comparison between murine and clinical studies, we identified 9 consistently changed metabolites (tryptophan, tyrosine, phenylalanine, methionine, fumarate, valine, deoxycholic acid, pyruvate, kynurenic acid) in the blood, 1 consistently altered metabolite (indoxyl sulfate) in the urine and 14 disturbed metabolic pathways in both types of studies. These metabolic dysregulations and pathways are mainly implicated in enhanced inflammation, impaired neuroprotection, reduced energy metabolism, increased oxidative stress damage and disturbed apoptosis, laying solid molecular foundations for MDD.
Limitations: Due to unavailability of original data like effect-size results in many metabolomics studies, a meta-analysis cannot be conducted, and confounding factors cannot be fully ruled out.
Conclusions: This systematic review delineated metabolic biomarkers and pathways related to depression in the murine and clinical samples, providing opportunities for early diagnosis of MDD and the development of novel diagnostic targets.

1. Introduction

Depression is one of the most important public health concerns, accounting for 125 million disability-adjusted life-years worldwide and representing a major cause of suicide (Lancet, 2022). It is predicted by the World Health Organization (WHO) that depression will become the main cause of the global burden of disease by 2030 (WHO, 2010). Among the complex types of depressive disorders (Messent, 2013), major depressive disorder (MDD), sometimes called major depression, is a highly prevalent subtype of clinical depression (McCarron et al., 2021). In current practice, diagnosis and treatment of MDD depend on relatively subjective assessments of diverse symptoms representing multiple endophenotypes (Schmidt et al., 2011). Routine medical and behavioral examinations based on interviews conducted by mental health specialists serve as the practical method for diagnosing MDD (Bentley et al., 2014). However, this diagnostic method is not cost-effective, and an accurate diagnosis requires extensively trained doctors, longer time to administer, and interview based psychometric examination (Kawamura et al., 2018). Therefore, it is necessary to find an objective and convenient standard to diagnose MDD, such as metabolic biomarkers. Identifying novel biomarkers can provide more reliable diagnosis and an improved understanding of disease pathogenesis, which is instructive for favorable clinical management of MDD.

Metabolomics is a powerful tool for discovering small molecular metabolic markers in system biology, which plays an important role in the diagnosis and mechanism exploration of human diseases (Shen et

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al., 2021). Deranged blood-brain barrier permeability has been reported in depressive disorders (Wu et al., 2022), which implies that small molecule exchange may occur between the brain and peripheral bloodstream. Particularly, metabolomics has notable advantages with regard to biomarker discovery of MDD, due to its ability to detect small-molecule metabolites that easily cross the blood-brain barrier (Qureshi et al., 2017). Moreover, untargeted metabolomics covers a wide range of metabolites and can reflect the underlying complexity of MDD to a large extent (Ke et al., 2019). Therefore, metabolomics can adequately address the problems of the blood-brain barrier and disease heterogeneity in MDD, and thus represents an ideal tool for biomarker discovery of MDD.

In this study, we reviewed all clinical and murine metabolomics studies that were conducted on MDD patients and depressive-like murine models, respectively. Through assessing and comparing metabolomics features related to depression in both clinical and murine studies, we aimed (1) to identify new metabolic biomarkers that warrant further investigation for MDD diagnosis, and (2) to discover the metabolic pathways and dysregulations that underlie the development and progression of MDD.

2. Methods

2.1. Literature search

This systematic review was guided by PRISMA 2020 and there were no deviations to the protocol (Page et al., 2021). We obtained relevant publications by searching the PubMed and Web of Science databases from January 2000 to January 2023. The searching terms were ("metabolomic" or "metabolomics" or "metabolome" or "metabolic profiling" or "metabolic signature" or "metabolic biomarker" or "metabolic profile") AND ("depression" or "depressed" or "depressive") (Fig. 1). Two researchers searched the articles independently and the senior one made a final decision if necessary.

2.2. Inclusion and exclusion criteria

Due to the unclear pathological progress of MDD, various animal models have been used to study the molecular mechanisms of MDD (Liu et al., 2017). Well validated depressive-like animal models, such as the chronic unpredictable mild stress (CUMS) model and chronic social defeat stress (CSDS) model, have been used widely to study clinical MDD (Liu et al., 2017; Willner, 1997; Willner and Mitchell, 2002). These models are targeted at mimicking several human MDD symptoms and are based on a large amount of experimental applications, which can provide a good contrast relationship with MDD (Cryan and Slattery, 2007; Liu et al., 2012). In this study, we included all the relevant metabolomics studies on depression except (1) review articles, (2) articles not utilizing the murine model or clinical samples, (3) articles adopting non-rigorous metabolomics methods, e.g., using clinical chemistry assays, (4) articles without full text, (5) clinical studies not focusing on primary MDD, which is defined as drug-naive MDD and MDD due to other medical conditions. As prospective clinical studies related to risk prediction or prognostic assessment of primary MDD were limited, we only kept 26 case-control clinical studies in this study. Finally, 104 literatures, including 26 clinical studies (e-Appendix 1) and 78 murine (e-Appendix 2) metabolomics studies, were eligible for subsequent analyses.

2.3. Information extraction

After reading the full articles and supplementary materials, the following information was extracted: authors, title, publication date, publication journal, study subject (sample size), analytical platform, biological specimen, study design, and potential metabolic biomarkers with change directions (increase or decrease in concentration levels).

2.4. Statistical analysis

The frequencies on analytical platforms, biological specimens, sample sizes, study designs and repeatedly reported biomarkers among clinical and murine metabolomics studies were calculated and plotted. Pathway analysis, including enrichment analysis and topology analysis, is a standard approach to address and summarize the long lists of analyzed metabolites as a small list of more easily interpretable pathways (García-Campos et al., 2015). Enrichment analysis identifies pathways or metabolite sets that have a higher overlap with a set of molecules of interest than expected by chance (Wieder et al., 2021). In our study, pathways with false discovery rate (FDR) <0.05 were considered statistically significant. Pathway topology analysis can be used for data visualization, exploration, and analysis that are grounded in topology, an area of mathematics that studies abstract notions of shape and connectivity (Skaf and Laubenbacher, 2022) . It not only lists the components of pathways, but also describes how they interact, providing a more detailed picture of how the molecular components of biological processes work together (García-Campos et al., 2015). Impact values present the topology structure's importance of metabolites in their corresponding metabolic pathways. The higher the impact value, the greater the structure's importance of metabolites involved in this pathway (García-Campos et al., 2015). Pathway analysis was performed using the *MetaboAnalyst* 5.0 online software (http://www.metaboanalyst.ca/) (Pang et al., 2022).

3. Results

3.1. Clinical research

3.1.1. Study characteristics

A total of 26 articles were included for final analysis, among which 19 studies were performed with blood (serum or plasma), 5 with urine, and 2 with Cerebro-Spinal Fluid (CSF). Mass-spectrometry based metabolomics studies were reported in 21 articles, while nuclear magnetic resonance (NMR) was adopted in 5 studies. Eleven studies were targeted, and the other 15 studies were untargeted. Study sample sizes summing the cases and controls varied from 16 to 4000, most sample sizes ranged from 100 to 400, and only 1 study had >400 samples.

3.1.2. Analysis of high frequency metabolic biomarkers

In this article, we first summarized high frequency metabolic biomarkers related to the clinical diagnosis of MDD. The trend of one metabolite was considered consistent if it showed the same direction of change in more than two-thirds of the studies. In all, 236 metabolite markers mentioned in these diagnosis-related studies were recorded. We summarized 59 metabolic biomarkers with high frequencies (reported in ≥ 2 studies). Supplementary Table 1 summarized 55 consistent metabolic biomarkers using a two-thirds criterion.

In the blood sample, compared with normal controls, MDD patients displayed lower levels of tryptophan, kynurenine, tyrosine, methionine, pyruvate, sarcosine, phenylalanine, taurine, creatinine, valine, fumaric acid, asparagine, PEA, deoxycholate, glutamine, kynurenic acid, 3-hydroxykynurenine, PC(18:0/20:3(5Z,8Z,11Z)), serine and higher levels of glutamate, benzoic acid, aspartic acid, γ-aminobutyric acid, PE (16:0/18:1(9Z)), PE(16:0/18:2(9Z,12Z)), GPC(20:2/0:0), CerP(d18:1/24:1(15Z)), SM(d18:0/22:1(13Z)), LysoPC(17:0) and 5-hexatriacontanone. In the urine sample of MDD patients, we observed lower levels of tyrosine, phenylalanine, hypoxanthine, quinolinic acid, *m*-hydroxyphenylacetate, hippuric acid, *N*-methylnicotinamide, ethanolamine, cysteine, leucine, 1-methylinosine, homovanillic acid, 2,4-dihydroxypyrimidine, 2,3-dihydroxybutanoic acid, indoxyl sulfate,

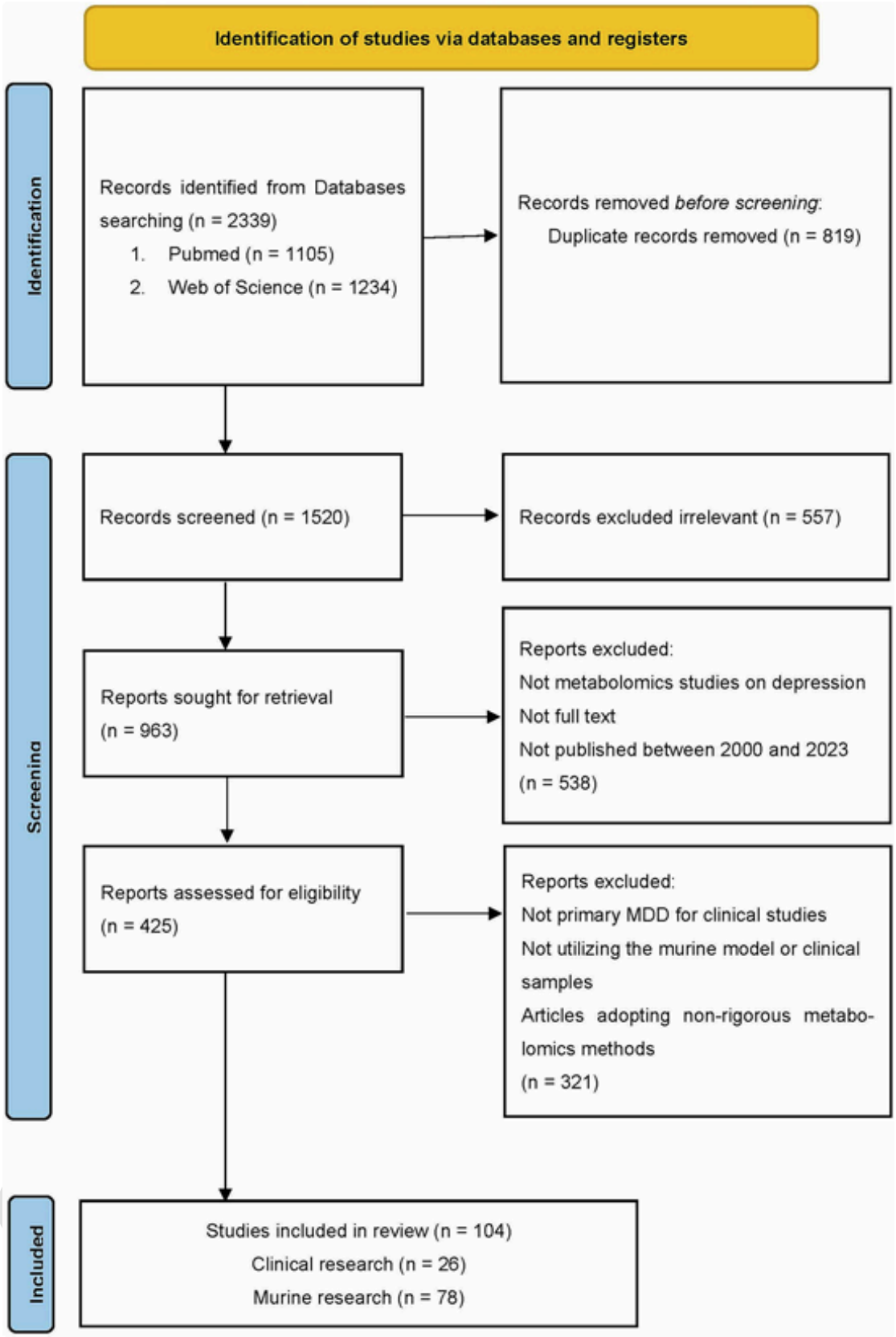

Fig. 1. Flow chart of the literature search and selection.

pseudouridine and higher levels of alanine, α-ketoglutaric acid, succinic acid, azelaic acid, formate, sorbitol, citric acid, lactic acid, sucrose, nicotinate and isobutyrate. Particularly, we found that tyrosine and phenylalanine had the same changing trends in both blood and urine. In addition, we summarized and analyzed the data with a three-fourths criterion, and found that most high frequency metabolites were consistent across two criteria (Supplementary Table 1).

3.1.3. Analysis of metabolic pathways

A total of 236 metabolites were imported to *MetaboAnalyst* for the identification of involved metabolic pathways (Fig. 2A). As a result, 16 significantly enriched metabolic pathways (FDR <0.05) included aminoacyl-tRNA biosynthesis, alanine, aspartate and glutamate metabolism, arginine biosynthesis, glycine, serine and threonine metabolism, butanoate metabolism, tyrosine metabolism, histidine metabolism, valine, leucine and isoleucine biosynthesis, taurine and hypotaurine metabolism, nicotinate and nicotinamide metabolism, glyoxylate and dicarboxylate metabolism, D-glutamine and D-glutamate metabolism, pantothenate and CoA biosynthesis, glycerophospholipid metabolism, citrate cycle (TCA cycle) and beta-alanine metabolism. Notably, taurine and hypotaurine metabolism had the highest impact value (impact = 0.71).

3.2. Animal research

3.2.1. Study characteristics

A total of 78 articles were eligible for final analyses, among which 28 studies were performed with brain tissue, 27 with blood, and 17 with urine. Mass-spectrometry based metabolomics was used in 62 articles, while NMR was utilized in 18 studies. Six studies were targeted, and the remaining 72 studies were untargeted. Study sample sizes summing the cases and controls varied from 9 to 80 and most sample sizes were smaller than 30. Animals of depressive-like symptoms in 58 of the articles were modeled with CUMS, 3 with CSDS, 3 with chronic restraint stress (CRS), and 4 with chronic variable stress (CVS).

3.2.2. Analysis of high frequency metabolic biomarkers

To be consistent with the criteria of clinical studies, the trend of one metabolite was considered consistent if it showed the same change in more than two-thirds of the studies. A total of 578 metabolic biomarkers were reported in the 78 included articles, among which 86 metabolic biomarkers were reported in 3 and more studies. Among them, glutamic acid appeared with the highest frequency with 29 reports, followed by citrate, tryptophan, glycine, proline, myo-inositol, tyrosine, *N*-acetyl-L-aspartic acid, palmitic acid, valine, arachidonic acid and pyruvate. Supplementary Table 2 summarized 77 consistent metabolic biomarkers using a two-thirds criterion.

The subgroup analysis of 78 murine studies stratified by biological samples, including the blood, urine and brain tissue, was further performed. In the blood sample, the increased metabolites included D-glucose, glycine, glutamine, D-fructose, myo-inositol, taurine, α-glucose, sphingosine, sphinganine, arachidonic acid, phytosphingosine and phenylacetylglycine, while tryptophan, valine, phenylalanine, palmitic acid, leucine, tyrosine, proline, linoleic acid, oleamide, citric acid, isoleucine, palmitoylcarnitine, pyruvate, methionine, stearamide, TMAO, carnitine, fumarate, pyroglutamic acid, uric acid, arginine, deoxycholic acid, kynurenic acid, indoleacrylic acid, propionylcarnitine, octadecanoic acid, spermidine and lysoPC(18:2(9Z,12Z)) were decreased. In the urine sample, the increases of hippurate, xanthurenic acid, kynurenic acid, cyclic AMP and phenylalanine were frequently reported while citrate, pyruvic acid, phenylacetylglycine, ascorbic acid, glycine, proline, a-ketoglutarate, creatine, glycolic acid, alanine, L-DOPA, lactate, succinate, uric acid, indoxyl sulfate, suberic acid, threonic acid and putrescine were decreased. In the brain tissue, *N*-acetyl-L-aspartic acid, myo-inositol, arachidonic acid, glycine, glycerol, 1-hexadecanoyl-glycero-3-phosphocholine, ascorbic acid, threonine, O-phosphorylethanolamine, leucine, acetylcholine and phosphate were found increased, while glutamic acid, phenylalanine, aspartic acid, cholesterol, proline, taurine, *N*-acetyl-tryptophan, dopamine, glycerophosphocholine, hypoxanthine, pantothenic acid, palmitic acid, 5-HT, oxoproline, 3-phosphoglycerate, valine, threonic acid, benzoic acid, L-allothreonine, phosphomycin, serine and glutathione were reported decreased. The three-fourths criterion to define the change direction also

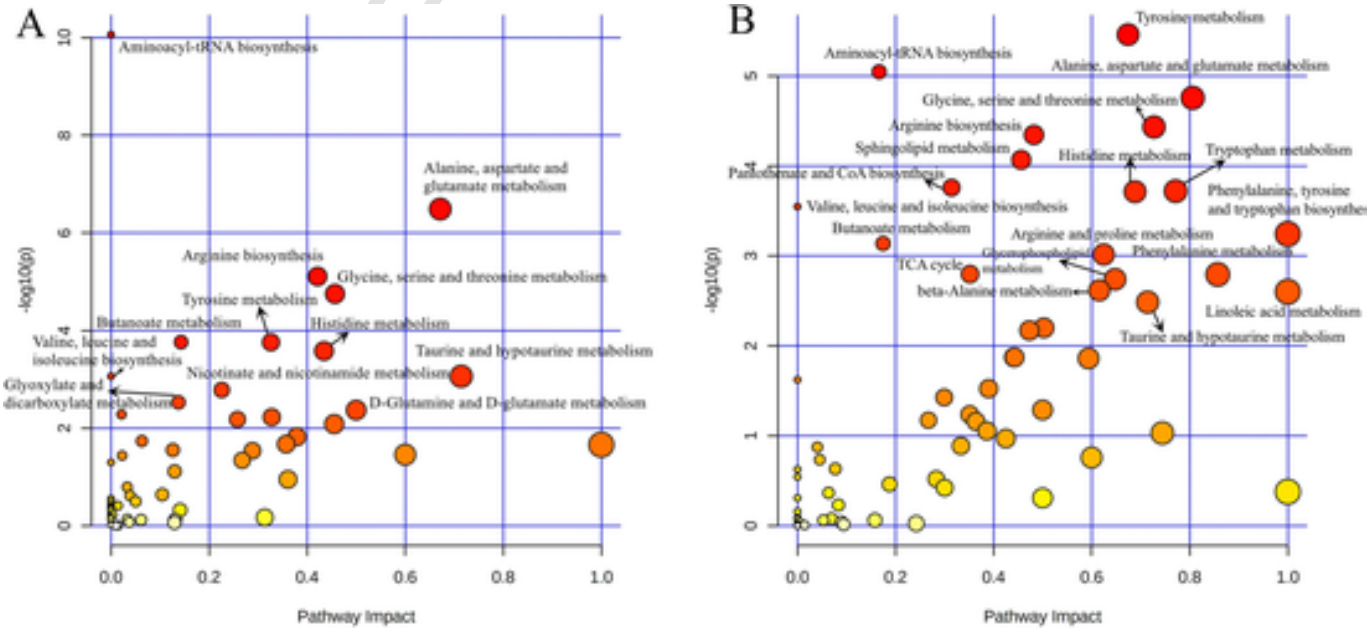

Fig. 2. Pathway analysis for metabolite markers. (A) metabolic pathways in clinical studies; (B) metabolic pathways in murine studies. The X axis shows pathway impact scores, which summarize normalized topology measures of those perturbed metabolites in each pathway. The Y axis shows –log10(*P*) values of the enrichment analysis results. The sizes of the data points are correlated with their X values, and the color gradients correspond to their Y values.

resulted in generally similar results with those from the two-thirds criterion (Supplementary Table 2).

3.2.3. Analysis of metabolic pathways

A total of 578 metabolites were imported to *MetaboAnalyst* for the identification of involved metabolic pathways (Fig. 2B). Finally, 24 pathways were significantly enriched (FDR <0.05), including tyrosine metabolism, aminoacyl-tRNA biosynthesis, alanine, aspartate and glutamate metabolism, glycine, serine and threonine metabolism, arginine biosynthesis, sphingolipid metabolism, pantothenate and CoA biosynthesis, tryptophan metabolism, histidine metabolism, valine, leucine and isoleucine biosynthesis, phenylalanine, tyrosine and tryptophan biosynthesis, butanoate metabolism, arginine and proline metabolism, citrate cycle (TCA cycle), phenylalanine metabolism, glycerophospholipid metabolism, beta-Alanine metabolism, linoleic acid metabolism, taurine and hypotaurine metabolism, glyoxylate and dicarboxylate metabolism, glutathione metabolism, pyruvate metabolism, pentose phosphate pathway, pentose and glucuronate interconversions. Among them, phenylalanine, tyrosine and tryptophan biosynthesis and linoleic acid metabolism had the highest impact value (impact value = 1). Moreover, taurine and hypotaurine metabolism also had a high impact value (impact value = 0.71).

3.3. A comparison between human studies and animal studies

3.3.1. High frequency metabolic biomarkers

By comparing metabolite markers between clinical and murine studies, some metabolites were shared with consistent changing trends in both types of studies. In the blood sample, tryptophan, tyrosine, methionine, fumarate, valine, phenylalanine, pyruvate, deoxycholic acid and kynurenic acid showed a consistently decreasing trend (Table 1). However, taurine and glutamine had the opposite changing directions in the blood of clinical and murine studies.

Table 1
High-frequency metabolites of blood and urine samples in both murine and clinical metabolomics studies.

No.	Metabolite	Clinical		Murine	
		Up[b] (%)	Down[c] (%)	Up[b] (%)	Down[c] (%)
Blood					
1	Tryptophan[a]	0 (0.0 %)	5 (100.0 %)	1 (11.1 %)	8 (88.9 %)
2	Valine[a]	0 (0.0 %)	2 (100.0 %)	1 (14.3 %)	6 (85.7 %)
3	Phenylalanine[a]	0 (0.0 %)	2 (100.0 %)	2 (33.3 %)	4 (66.7 %)
4	Tyrosine[a]	0 (0.0 %)	3 (100.0 %)	0 (0.0 %)	5 (100.0 %)
5	Pyruvate[a]	0 (0.0 %)	3 (100.0 %)	1 (25.0 %)	3 (75.0 %)
6	Fumarate[a]	0 (0.0 %)	2 (100.0 %)	0 (0.0 %)	3 (100.0 %)
7	Deoxycholic acid[a]	0 (0.0 %)	2 (100.0 %)	1 (33.3 %)	2 (66.7 %)
8	Methionine[a]	1 (33.3 %)	2 (66.7 %)	1 (25.0 %)	3 (75.0 %)
9	Kynurenic acid[a]	0 (0.0 %)	2 (100.0 %)	1 (33.3 %)	2 (66.7 %)
10	Glutamine	0 (0.0 %)	2 (100.0 %)	5 (83.3 %)	1 (16.7 %)
11	Taurine	0 (0.0 %)	2 (100.0 %)	3 (75.0 %)	1 (25.0 %)
Urine					
1	Indoxyl sulfate[a]	0 (0.0 %)	2 (100.0 %)	0 (0.0 %)	3 (100.0 %)
2	Phenylalanine	0 (0.0 %)	3 (100.0 %)	3 (100.0 %)	0 (0.0 %)
3	Citric acid	3 (100.0 %)	0 (0.0 %)	2 (20.0 %)	8 (80.0 %)
4	Hippuric acid	0 (0.0 %)	3 (100.0 %)	6 (66.7 %)	3 (33.3 %)
5	α-Ketoglutaric acid	3 (100.0 %)	0 (0.0 %)	0 (0.0 %)	4 (100.0 %)
6	Lactic acid	2 (100.0 %)	0 (0.0 %)	1 (33.3 %)	2 (66.7 %)
7	Alanine	3 (100.0 %)	0 (0.0 %)	1 (33.3 %)	2 (66.7 %)
8	Succinic acid	3 (100.0 %)	0 (0.0 %)	1 (33.3 %)	2 (66.7 %)

[a] This metabolite was reported with the same changing trend in both types of studies.

[b] If a metabolite marker is higher in the case group than in the control group, the changing trend is "Up".

[c] If a metabolite marker is lower in the case group than in the control group, the changing trend is "Down".

In the urine sample, a lower level of indoxyl sulfate was found in both clinical and murine studies. However, phenylalanine, citric acid, hippuric acid, α-ketoglutaric acid, lactic acid, alanine and succinic acid showed the opposite trend in clinical and murine urine samples (Table 1).

3.3.2. Significant metabolic pathways

When it comes to significant metabolic pathways related to depression, we discovered that there were 14 shared metabolic pathways. These pathways included aminoacyl-tRNA biosynthesis, alanine, aspartate and glutamate metabolism, arginine biosynthesis, glycine, serine and threonine metabolism, butanoate metabolism, tyrosine metabolism, histidine metabolism, valine, leucine and isoleucine biosynthesis, taurine and hypotaurine metabolism, glyoxylate and dicarboxylate metabolism, pantothenate and CoA biosynthesis, glycerophospholipid metabolism, citrate cycle (TCA cycle) and beta-alanine metabolism. Among these pathways, alanine, aspartate and glutamate metabolism and taurine and hypotaurine metabolism had high impact values in both human and murine studies.

4. Discussion

In this paper, 26 clinical metabolomics studies and 78 murine metabolomics studies on depression were comprehensively reviewed and analyzed. Many metabolites were frequently reported to be altered between the depression group and control group. In the comparison between murine and clinical studies, we identified 9 consistently changed metabolites (tryptophan, tyrosine, phenylalanine, methionine, fumarate, valine, deoxycholic acid, pyruvate, kynurenic acid) in the blood sample, 1 consistently altered metabolite (indoxyl sulfate) in the urine sample and 14 disturbed metabolic pathways in both types of studies.

4.1. Metabolite markers in analytical samples: blood, urine and brain tissue

The identified metabolites in different types of samples could overlap, differ and complement each other, as the abilities to reflect the degree of nervous system damage vary among brain tissue, urine, and blood. Each sample has its advantages and disadvantages. The identified metabolites in the blood and urine samples may have a higher clinical diagnostic value as they are more easily accessible in the human body. In contrast, the changed metabolites in the brain tissue are more suitable for exploring the underlying mechanism of depression, as they can directly reflect the integrity and comprehensiveness of the changed metabolites in the nervous system damage during depression.

When comparing clinical and murine studies, the trends of tryptophan, tyrosine, phenylalanine, pyruvate, deoxycholic acid, kynurenic acid, methionine, fumarate and valine in blood samples were consistent. In addition, 14 metabolic pathways have been identified in clinical and murine studies. The shared metabolites and metabolic pathways hold great potential as biomarkers of MDD and deserve more attention in future research. The murine metabolomics studies on depression could also be supplementary to the clinical studies, as metabolic signatures in the brain tissue could only be obtained in the murine model for ethical reasons.

However, we also observed some inconsistent results in the metabolic changing trends. There could be several reasons for this phenomenon. First, the changes of some metabolites in these samples can vary among different stages of depression because most studies select samples without consideration of stages. In addition, patients at the same stage may also present different metabolite changes in different biological samples. For example, one previous study reported reduced *N*-acetyl-L-aspartic acid in hippocampus but increased in intestine (Yang et al., 2019). Second, diverse lifestyles of MDD patients, such as diet, sleep and exercise may lead to conflicting metabolic changing trends

(Lopresti et al., 2013). Third, the metabolic changes may be affected by various factors such as the region, gender and age of the investigated population. In the investigation of serum metabolomics of Han ethnic group in different regions of China, scientists found up to 22 differential metabolites among different races (Chen et al., 2019). Such factors may interfere with the judgment of MDD as there is no unified standard for the included population in this article. As a result, more studies are needed to clarify the inconsistent relationships of these metabolites with MDD.

4.2. Potential metabolism of MDD

We summarized and analyzed the changes of metabolites from 26 clinical MDD articles and 78 depressive-like animal articles, and then formulated a potential metabolic mechanism map of MDD. It can be found that this map verified some well-studied metabolic pathways related to MDD, such as tryptophan metabolism and TCA cycle. We also found some metabolic pathways less studied in the past, such as the nicotinate and nicotinamide metabolism, valine, leucine and isoleucine biosynthesis, and taurine and hypotaurine metabolism (Fig. 3). To better figure out how they play roles during MDD, we divided them into three biological metabolisms, including glycolysis and TCA cycle, nucleotide metabolism and amino acid metabolism.

4.2.1. Glycolysis and TCA cycle

In our study, we found that the contents of glucose were increased in murine and clinical studies, but pyruvate and related metabolites in the TCA cycle (e.g., fumarate and succinate) were decreased. In accordance with previous metabolomics-based studies, researchers demonstrated that glycolysis and the TCA cycle were related to the occurrence and development of MDD, as they are vital pathways to provide energy for central nervous system (Drevets et al., 2008). Among the metabolites involved in the energy metabolism, glucose is the main energy source for mammals. The abnormal increase in glucose suggests that the body's energy metabolism may be disrupted. Zhu et al. proposed that long-term stress in MDD might lead to excessive secretion of cortisol, converting more lipids, glycogen and proteins into glucose (Zhu et al., 2020), which is in accordance with the phenomenon of increased plasma glucose concentration in CUMS mice (Chen et al., 2021). The rise in glucose is often accompanied by the accumulation of lactic acid. A high concentration of lactic acid in brain tissue can bring about acidosis, aggravate cytotoxic cerebral edema and cause direct damage to nerve cells (Zhang et al., 2020).

Throughout the TCA cycle, we observed a typical increase of alpha-ketoglutaric acid in clinical samples, a ketoic acid product of glutamic acid deamination. After amination, it forms the excitatory neurotransmitter glutamic acid along with glutamine, and glutamic acid can be decarboxylated to form the inhibitory neurotransmitter GABA (Liu et al., 2015). Glutamate and GABA relate to neuro-metabolism during the occurrence of MDD (Humer et al., 2020; Sarawagi et al., 2021). Glutamate is an excitatory neurotransmitter converted into glutamine by astrocytes in brain tissue. Once astrocytes are damaged in the brain, it is easy to cause glutamine-glutamate metabolism disorders. Thus, increasing glutamate can be neurotoxic and cause nerve damage (Abdallah et al., 2014; Mitchell and Baker, 2010). GABA is a metabolite of glutamic acid decarboxylation and is considered an important inhibitory transmitter. An increase in GABA indicates changes in the body's protection against excitatory neurotoxicity (Petroff, 2002).

We also found a significant decrease of fumarate and pyruvate in both clinical and murine models. Ravindran et al. stated that fumarate

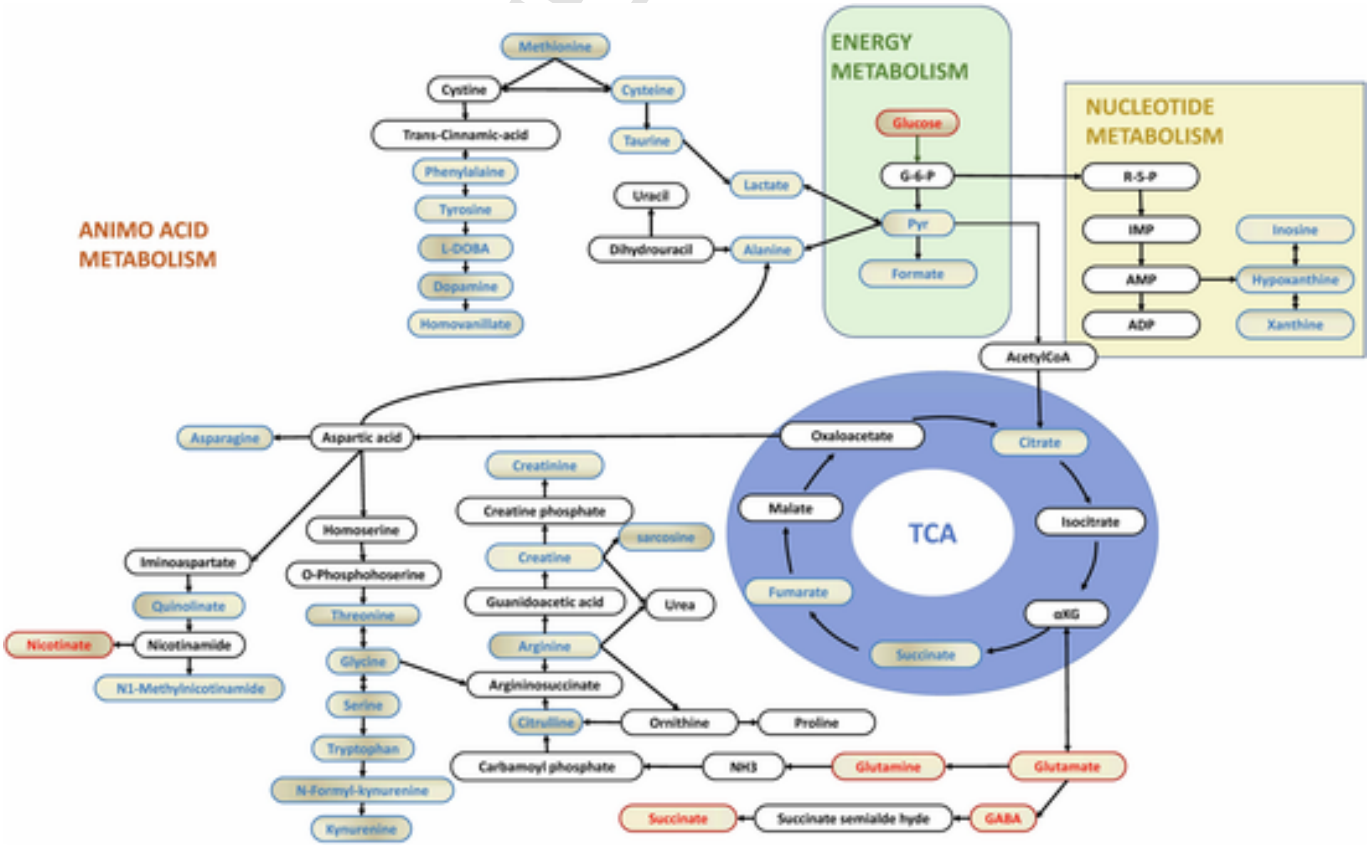

Fig. 3. Abnormal metabolism in major depressive disorder. Red fonts indicate high-frequency metabolites with an upward trend. Blue fonts represent downward high-frequency metabolites. Black fonts represent unreported metabolites. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

augmentation produced a great improvement for MDD patients, which indicates the protective function of fumarate (Ravindran et al., 2022). Fumarate could influence gene expression associated with neuroprotection in microglia (Kronenberg et al., 2019) rather than astrocytes (Pars et al., 2019). Similarly, fumarate could upregulate nuclear factor-like 2–dependent antioxidant reactions and ultimately protect against inflammation and oxidative stress in neurons and astrocytes (Wu et al., 2021). Pyruvate have been proved that it can be used to eliminate excess toxic glutamate and improve depressive symptoms (Teichberg, 2007). It is convinced that pyruvate helps to inhibit oxidative stress (Lee et al., 2004), stimulates pyruvate dehydrogenase activity (Sharma et al., 2009), improve cell energy function and produce adenosine trisphosphate (Izumi and Zorumski, 2010). In previous studies, fumarate and pyruvate was scarcely associated with MDD. Therefore, it is of great significance to explore whether they could be new biomarkers for the diagnosis of MDD.

4.2.2. Nucleotide metabolism

We found that inosine, uric acid, hypoxanthine, xanthine and other substances involved in nucleotide metabolism were decreased to varying degrees in MDD patients and depressive-like murine samples. It is suggested that inosine can increase adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), adenosine, hypoxanthine, xanthine and uric acid levels in CSF, further influencing the energy metabolism (de Oliveira et al., 2016). Gonçalves found that inosine could activate PKA, PI3K/Akt, ERK1/2 and CaMKII pathways while inhibiting GSK-3β pathway, which promotes the expression of the brain derived neurotrophic factor and cell proliferation in the hippocampus (Goncalves et al., 2017). In addition, it is reported that inosine can reduce the activity of acetylcholinesterase and increase that of choline acetyltransferase, which is associated with the decline of memory ability in MDD patients (Gutierres et al., 2014; Pacheco et al., 2018). To sum up, inosine can affect the development of MDD by affecting energy metabolism, cholinergic system and signal transduction pathway.

As the final product of the purine metabolism, uric acid has a significant antioxidant effect (Ali-Sisto et al., 2016), which is involved in the prevention of inflammation and tissue damage in the central nervous system (Hooper et al., 2000). Fang et al. stated that the decrease of uric acid can weaken the antioxidant effect of neurons (Fang et al., 2013). Since the brain is highly susceptible to oxidative stress, any oxidative damage to neurons in the brain may result in changes in membrane structure and function (Sobczak et al., 2004), thus influencing the expression of membrane receptors (Maes et al., 2011). Meanwhile, low levels of antioxidants and high levels of reactive oxygen species can cause the oxidative damage of lipids, proteins and DNA. These two reasons explain the connection between oxidative stress and the risk of MDD. Increased free radical production and decreased levels of antioxidant defense can raise the risk of MDD (Ozcan et al., 2004). High levels of uric acid protect the integrity and function of neurons, thus decreasing the risk of MDD. However, Bartoli et al. pointed out that the decrease of uric acid levels might be due to decreased turnover and increased adenosine activity (Bartoli et al., 2018), which requires further research. To conclude, the decrease of uric acid mainly causes oxidative stress and mediates inflammatory damage to neurons, eventually facilitating the development of MDD.

4.2.3. Amino acid metabolism

Compared with the control group, we found many metabolites involved in amino acid metabolism disturbed, such as tryptophan, valine, and kynurenic acid. Most studies have shown that MDD patients have significantly lower levels of tryptophan compared to controls, and scientists often associate reduced levels of tryptophan with a higher risk of MDD (Pu et al., 2021). In our study, kynurenine, a metabolite of tryptophan (Bender, 1983), was also altered. Previous studies have reported that MDD patients have lower levels of kynurenic acid and kynurenine and a significantly lower kynurenic acid/quinolinic acid ratio than the control group (Allen et al., 2018; Doolin et al., 2018). Metabolites of the kynurenine pathway are involved in inflammatory diseases due to immunomodulatory effects. The kynurenine pathway has two main branches, one of which generates kynurenic acid with neuroprotective effects (Cervenka et al., 2017). Another branch generates 3-hydroxyaminobenzoic acid and quinolinic acid, eventually generating NAD + (Foster et al., 1984). NAD + promotes the occurrence and development of MDD by affecting mitochondrial function and energy synthesis. Quinolinic acid is a NMDA receptor agonist that can additionally inhibit glutamate reabsorption by astrocytes, leading to neurotoxicity (Stone and Perkins, 1981). Quinolinic acid can also induce astrocytes to produce pro-inflammatory mediators (Guillemin et al., 2003), which may contribute to the etiology of MDD (Thomas et al., 2021). Moreover, quinolinic acid activates microglia, which then mediates the death of nerve cells (Kaindl et al., 2012). Therefore, decreased kynurenine may influence the central nervous system through weakening neuroprotective effects, causing neurotoxicity, and mediating inflammation and apoptosis.

In our pathway analysis, taurine and hypotaurine metabolism had a notable high impact value. Taurine was also decreased in clinical blood samples and murine brain tissue samples. Taurine has antioxidant activity and plays a role as a potential antioxidant in the brain cell defense. It also has a protective effect against glutamate-mediated excitatory toxicity by inhibiting glutamate delivery (Pasantes-Morales and Hernández-Benítez, 2010). Moreover, taurine activates GABA receptors to exert its neuronal inhibitory effect, whose changes are proved associated with MDD (Ochoa-de la Paz et al., 2019). Therefore, the decrease of taurine may participate in the development of MDD by aggravating oxidative stress and cytotoxicity.

Valine, leucine and isoleucine biosynthesis was also highlighted in our pathway analysis, and valine presented a consistent downward trend in both clinical and murine studies. Leucine and isoleucine are able to increase the expression levels of brain-derived neurotrophic factor in hippocampal nerve cells, which has been suggested to play a leading role in the depression-related cell signal transduction pathway (Furukawa-Hibi et al., 2011). As a result, this metabolic pathway may accelerate MDD by inhibiting the expression of brain-derived neurotrophic factor. Meanwhile, we discovered that deoxycholic acid, a bile acid, showed a decreasing trend in both two models. Primary bile acids are direct products of cholesterol metabolites in hepatocytes and play an important role in lipid metabolism. Currently, it is recognized that lipid metabolism is altered in psychiatric disorders (Zhong et al., 2022). For example, increased lipid peroxidation, derived from increased oxidative stress and inflammatory states, can induce changes in lipid profile and lipid metabolism of the brain, which is involved in the signaling of MDD (Di Gioia and Zanoni, 2021). For this reason, primary bile acids may take part in boosting oxidative stress and inflammation, thus promoting the development of MDD.

4.3. Limitations of current metabolomics studies on MDD

Several limitations of the existing metabolomics studies on MDD should be noted. First, the clinical biological samples are confined to blood or urine samples in the majority of studies, so other types of samples (e.g., CSF) should be analyzed to allow researchers to obtain a more comprehensive understanding of metabolic signatures. Aberrant CSF circulation is linked with many neurological, neurodegenerative, and psychiatric disorders, such as anxiety and depression (Seo et al., 2021). Second, confounding factors like medications and the course of disease may interfere with the accuracy of the results. In our analysis, we cannot rule out the influence of medications, as most studies did not account for medications. Third, durations of MDD in most patients in clinical studies were unclear, which may affect the metabolic changes

in vivo. Su et al. reported that the clinical manifestations and inflammatory responses of early and late MDD were different, which can be attributed to tryptophan/monoamine dysregulation (Su et al., 2019). Fourth, due to unavailability of original data like effect-size results in many metabolomics studies, we were not able to conduct a traditional meta-analysis. Fifth, there were quite limited metabolomics studies on the risk prediction and prognosis of MDD, so metabolic biomarkers related to the occurrence and prognosis of MDD were not investigated, which calls for more metabolomics studies on risk prediction and prognosis. Last, different metabolomics studies used different specimens, analytical platforms and parameter settings, which result in partial overlap in identified biomarkers and relatively small frequencies for many biomarkers. Future studies are still needed to further validate these findings and translate them into practice.

5. Conclusion

In summary, this study presents a systematic review and analysis of clinical MDD research and depressive-like animal research. Many consistent metabolites (e.g., tryptophan, tyrosine, phenylalanine, pyruvate, deoxycholic acid, kynurenic acid, methionine, fumarate and valine) and shared metabolic pathways (e.g., alanine, aspartate and glutamate metabolism, aminoacyl-tRNA biosynthesis, and taurine and hypotaurine metabolism) were identified altered in both clinical MDD patients and depressive-like murine models. These metabolic dysregulations and pathways, involved in enhanced inflammation, impaired neuroprotection, reduced energy metabolism, increased oxidative stress damage and disturbed apoptosis, could provide a solid molecular foundation for MDD. The findings in this review may provide important opportunities for early diagnosis of MDD and the identification of novel therapeutic targets in the future.

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CRediT authorship contribution statement

Yibo Wang: Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Conceptualization. **Xinyi Cai:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Conceptualization. **Yuchen Ma:** Formal analysis, Data curation, Writing – original draft. **Yang Yang:** Formal analysis, Data curation, Writing – original draft. **Chen-Wei Pan:** Funding acquisition, Project administration, Supervision, Writing – review & editing, Methodology. **Xiaohong Zhu:** Writing – review & editing, Data curation, Methodology, Funding acquisition, Project administration. **Chaofu Ke:** Conceptualization, Data curation, Funding acquisition, Writing – original draft, Writing – review & editing, Project administration, Supervision.

Declaration of competing interest

The authors report no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

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References

Abdallah, C.G., Jiang, L., De Feyter, H.M., Fasula, M., Krystal, J.H., Rothman, D.L., Mason, G.F., Sanacora, G., 2014. Glutamate metabolism in major depressive disorder. Am. J. Psychiatry 171, 1320–1327. https://doi.org/10.1176/appi.ajp.2014.14010067.

Ali-Sisto, T., Tolmunen, T., Toffol, E., Viinamaki, H., Mantyselka, P., Valkonen-Korhonen, M., Honkalampi, K., Ruusunen, A., Velagapudi, V., Lehto, S.M., 2016. Purine metabolism is dysregulated in patients with major depressive disorder. Psychoneuroendocrinology 70, 25–32. https://doi.org/10.1016/j.psyneuen.2016.04.017.

Allen, A.P., Naughton, M., Dowling, J., Walsh, A., O'Shea, R., Shorten, G., Scott, L., McLoughlin, D.M., Cryan, J.F., Clarke, G., Dinan, T.G., 2018. Kynurenine pathway metabolism and the neurobiology of treatment-resistant depression: comparison of multiple ketamine infusions and electroconvulsive therapy. J. Psychiatr. Res. 100, 24–32. https://doi.org/10.1016/j.jpsychires.2018.02.011.

Bartoli, F., Trotta, G., Crocamo, C., Malerba, M.R., Clerici, M., Carra, G., 2018. Antioxidant uric acid in treated and untreated subjects with major depressive disorder: a meta-analysis and meta-regression. Eur. Arch. Psychiatry Clin. Neurosci. 268, 119–127. https://doi.org/10.1007/s00406-017-0817-7.

Bender, D.A., 1983. Effects of a dietary excess of leucine on the metabolism of tryptophan in the rat: a mechanism for the pellagragenic action of leucine. Br. J. Nutr. 50, 25–32. https://doi.org/10.1079/bjn19830068.

Bentley, S.M., Pagalilauan, G.L., Simpson, S.A., 2014. Major depression. Med. Clin. North Am. 98, 981–1005. https://doi.org/10.1016/j.mcna.2014.06.013.

Cervenka, I., Agudelo, L.Z., Ruas, J.L., 2017. Kynurenines: tryptophan's metabolites in exercise, inflammation, and mental health. Science 357. https://doi.org/10.1126/science.aaf9794.

Chen, J.J., Xie, J., Li, W.W., Bai, S.J., Wang, W., Zheng, P., Xie, P., 2019. Age-specific urinary metabolite signatures and functions in patients with major depressive disorder. Aging (Albany NY) 11, 6626–6637. https://doi.org/10.18632/aging.102133.

Chen, H., Xie, H., Huang, S., Xiao, T., Wang, Z., Ni, X., Deng, S., Lu, H., Hu, J., Li, L., Wen, Y., Shang, D., 2021. Development of mass spectrometry-based relatively quantitative targeted method for amino acids and neurotransmitters: applications in the diagnosis of major depression. J. Pharm. Biomed. Anal. 194, 113773. https://doi.org/10.1016/j.jpba.2020.113773.

Cryan, J.F., Slattery, D.A., 2007. Animal models of mood disorders: recent developments. Curr. Opin. Psychiatry 20, 1–7. https://doi.org/10.1097/YCO.0b013e3280117733.

de Oliveira, E.D., Schallenberger, C., Boehmer, A.E., Hansel, G., Fagundes, A.C., Milman, M., Silva, M.D.P., Oses, J.P., Porciuncula, L.O., Portela, L.V., Elisabetsky, E., Souza, D.O., Schmidt, A.P., 2016. Mechanisms involved in the antinociception induced by spinal administration of inosine or guanine in mice. Eur. J. Pharmacol. 772, 71–82. https://doi.org/10.1016/j.ejphar.2015.12.034.

Di Gioia, M., Zanoni, I., 2021. Dooming phagocyte responses: inflammatory effects of endogenous oxidized phospholipids. Front. Endocrinol. (Lausanne) 12, 626842. https://doi.org/10.3389/fendo.2021.626842.

Doolin, K., Allers, K.A., Pleiner, S., Liesener, A., Farrell, C., Tozzi, L., O'Hanlon, E., Roddy, D., Frodl, T., Harkin, A., O'Keane, V., 2018. Altered tryptophan catabolite concentrations in major depressive disorder and associated changes in hippocampal subfield volumes. Psychoneuroendocrinology 95, 8–17. https://doi.org/10.1016/j.psyneuen.2018.05.019.

Drevets, W.C., Price, J.L., Furey, M.L., 2008. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct. Funct. 213, 93–118. https://doi.org/10.1007/s00429-008-0189-x.

Fang, P., Li, X., Luo, J.J., Wang, H., Yang, X.F., 2013. A double-edged sword: uric acid and neurological disorders. Brain Disord. Ther. 2, 109. https://doi.org/10.4172/2168-975x.1000109.

Foster, A.C., Vezzani, A., French, E.D., Schwarcz, R., 1984. Kynurenic acid blocks neurotoxicity and seizures induced in rats by the related brain metabolite quinolinic acid. Neurosci. Lett. 48, 273–278. https://doi.org/10.1016/0304-3940(84)90050-8.

Furukawa-Hibi, Y., Nitta, A., Ikeda, T., Morishita, K., Liu, W., Ibi, D., Alkam, T., Nabeshima, T., Yamada, K., 2011. The hydrophobic dipeptide Leu-Ile inhibits immobility induced by repeated forced swimming via the induction of BDNF. Behav. Brain Res. 220, 271–280. https://doi.org/10.1016/j.bbr.2011.02.003.

García-Campos, M.A., Espinal-Enríquez, J., Hernández-Lemus, E., 2015. Pathway analysis: state of the art. Front. Physiol. 6, 383. https://doi.org/10.3389/fphys.2015.00383.

Goncalves, F.M., Neis, V.B., Rieger, D.K., Lopes, M.W., Heinrich, I.A., Costa, A.P., Rodrigues, A.L.S., Kaster, M.P., Leal, R.B., 2017. Signaling pathways underlying the antidepressant-like effect of inosine in mice. Purinergic Signal. 13, 203–214. https://doi.org/10.1007/s11302-016-9551-2.

Guillemin, G.J., Croitoru-Lamoury, J., Dormont, D., Armati, P.J., Brew, B.J., 2003. Quinolinic acid upregulates chemokine production and chemokine receptor expression in astrocytes. Glia 41, 371–381. https://doi.org/10.1002/glia.10175.

Gutierres, J.M., Carvalho, F.B., Schetinger, M.R.C., Marisco, P., Agostinho, P., Rodrigues, M., Rubin, M.A., Schmatz, R., da Silva, C.R., Cognato, G.d.P., Farias, J.G., Signor, C., Morsch, V.M., Mazzanti, C.M., Bogo, M., Bonan, C.D., Spanevello, R., 2014. Anthocyanins restore behavioral and biochemical changes caused by streptozotocin-induced sporadic dementia of Alzheimer's type. Life Sci. 96, 7–17. https://doi.org/

10.1016/j.lfs.2013.11.014.
Hooper, D.C., Scott, G.S., Zborek, A., Mikheeva, T., Kean, R.B., Koprowski, H., Spitsin, S.V., 2000. Uric acid, a peroxynitrite scavenger, inhibits CNS inflammation, blood-CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis. FASEB J. 14, 691–698. https://doi.org/10.1096/fasebj.14.5.691.
Humer, E., Probst, T., Pieh, C., 2020. Metabolomics in psychiatric disorders: what we learn from animal models. Metabolites 10. https://doi.org/10.3390/metabo10020072.
Izumi, Y., Zorumski, C.F., 2010. Neuroprotective effects of pyruvate following NMDA-mediated excitotoxic insults in hippocampal slices. Neurosci. Lett. 478, 131–135. https://doi.org/10.1016/j.neulet.2010.04.078.
Kaindl, A.M., Degos, V., Peineau, S., Gouadon, E., Chhor, V., Loron, G., Le Charpentier, T., Josserand, J., Ali, C., Vivien, D., Collingridge, G.L., Lombet, A., Issa, L., Rene, F., Loeffler, J.P., Kavelaars, A., Verney, C., Mantz, J., Gressens, P., 2012. Activation of microglial N-methyl-D-aspartate receptors triggers inflammation and neuronal cell death in the developing and mature brain. Ann. Neurol. 72, 536–549. https://doi.org/10.1002/ana.23626.
Kawamura, N., Shinoda, K., Sato, H., Sasaki, K., Suzuki, M., Yamaki, K., Fujimori, T., Yamamoto, H., Osei-Hyiaman, D., Ohashi, Y., 2018. Plasma metabolome analysis of patients with major depressive disorder. Psychiatry Clin. Neurosci. 72, 349–361. https://doi.org/10.1111/pcn.12638.
Ke, C., Pan, C.W., Zhang, Y., Zhu, X., Zhang, Y., 2019. Metabolomics facilitates the discovery of metabolic biomarkers and pathways for ischemic stroke: a systematic review. Metabolomics 15, 152. https://doi.org/10.1007/s11306-019-1615-1.
Kronenberg, J., Pars, K., Brieskorn, M., Prajeeth, C.K., Heckers, S., Schwenkenbecher, P., Skripuletz, T., Pul, R., Pavlou, A., Stangel, M., 2019. Fumaric acids directly influence gene expression of neuroprotective factors in rodent microglia. Int. J. Mol. Sci. 20. https://doi.org/10.3390/ijms20020325.
Lancet, T., 2022. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry 9, 137–150. https://doi.org/10.1016/S2215-0366(21)00395-3.
Lee, Y.J., Kang, I.J., Bünger, R., Kang, Y.H., 2004. Enhanced survival effect of pyruvate correlates MAPK and NF-kappaB activation in hydrogen peroxide-treated human endothelial cells. J. Appl. Physiol. (1985) 96, 793–801. discussion 792. https://doi.org/10.1152/japplphysiol.00797.2003.
Liu, X.J., Zhou, Y.Z., Li, Z.F., Cui, J., Li, Z.Y., Gao, X.X., Sun, H.F., Zhang, L.Z., Du, G.H., Qin, X.M., 2012. Anti-depressant effects of Xiaoyaosan on rat model of chronic unpredictable mild stress: a plasma metabonomics study based on NMR spectroscopy. J. Pharm. Pharmacol. 64, 578–588. https://doi.org/10.1111/j.2042-7158.2011.01412.x.
Liu, C.C., Wu, Y.F., Feng, G.M., Gao, X.X., Zhou, Y.Z., Hou, W.J., Qin, X.M., Du, G.H., Tian, J.S., 2015. Plasma-metabolite-biomarkers for the therapeutic response in depressed patients by the traditional Chinese medicine formula Xiaoyaosan: a (1)H NMR-based metabolomics approach. J. Affect. Disord. 185, 156–163. https://doi.org/10.1016/j.jad.2015.05.005.
Liu, Y.Y., Zhou, X.Y., Yang, L.N., Wang, H.Y., Zhang, Y.Q., Pu, J.C., Liu, L.X., Gui, S.W., Zeng, L., Chen, J.J., Zhou, C.J., Xie, P., 2017. Social defeat stress causes depression-like behavior with metabolite changes in the prefrontal cortex of rats. PLoS One 12, e0176725. https://doi.org/10.1371/journal.pone.0176725.
Lopresti, A.L., Hood, S.D., Drummond, P.D., 2013. A review of lifestyle factors that contribute to important pathways associated with major depression: diet, sleep and exercise. J. Affect. Disord. 148, 12–27. https://doi.org/10.1016/j.jad.2013.01.014.
Maes, M., Galecki, P., Chang, Y.S., Berk, M., 2011. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35, 676–692. https://doi.org/10.1016/j.pnpbp.2010.05.004.
McCarron, R.M., Shapiro, B., Rawles, J., Luo, J., 2021. Depression. Ann. Intern. Med. 174. https://doi.org/10.7326/aitc202105180. . Itc65–itc80.
Messent, P., 2013. DSM-5. Clin. Child Psychol. Psychiatry 18, 479–482. https://doi.org/10.1177/1359104513502138.
Mitchell, N.D., Baker, G.B., 2010. An update on the role of glutamate in the pathophysiology of depression. Acta Psychiatr. Scand. 122, 192–210. https://doi.org/10.1111/j.1600-0447.2009.01529.x.
Ochoa-de la Paz, L., Zenteno, E., Gulias-Cañizo, R., Quiroz-Mercado, H., 2019. Taurine and GABA neurotransmitter receptors, a relationship with therapeutic potential? Expert. Rev. Neurother. 19, 289–291. https://doi.org/10.1080/14737175.2019.1593827.
Ozcan, M.E., Gulec, M., Ozerol, E., Polat, R., Akyol, O., 2004. Antioxidant enzyme activities and oxidative stress in affective disorders. Int. Clin. Psychopharmacol. 19, 89–95. https://doi.org/10.1097/00004850-200403000-00006.
Pacheco, S.M., Pereira Soares, M.S., Gutierres, J.M., Barbieri Gerzson, M.F., Carvalho, F.B., Azambuja, J.H., Chitolina Schetinger, M.R., Stefanello, F.M., Spanevello, R.M., 2018. Anthocyanins as a potential pharmacological agent to manage memory deficit, oxidative stress and alterations in ion pump activity induced by experimental sporadic dementia of Alzheimer's type. J. Nutr. Biochem. 56, 193–204. https://doi.org/10.1016/j.jnutbio.2018.02.014.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71. https://doi.org/10.1136/bmj.n71.
Pang, Z., Zhou, G., Ewald, J., Chang, L., Hacariz, O., Basu, N., Xia, J., 2022. Using MetaboAnalyst 5.0 for LC-HRMS spectra processing, multi-omics integration and covariate adjustment of global metabolomics data. Nat. Protoc. 17, 1735–1761. https://doi.org/10.1038/s41596-022-00710-w.
Pars, K., Gingele, M., Kronenberg, J., Prajeeth, C.K., Skripuletz, T., Pul, R., Jacobs, R., Gudi, V., Stangel, M., 2019. Fumaric acids do not directly influence gene expression of neuroprotective factors in highly purified rodent astrocytes. Brain Sci. 9. https://doi.org/10.3390/brainsci9090241.
Pasantes-Morales, H., Hernández-Benítez, R., 2010. Taurine and brain development: trophic or cytoprotective actions? Neurochem. Res. 35, 1939–1943. https://doi.org/10.1007/s11064-010-0262-8.
Petroff, O.A., 2002. GABA and glutamate in the human brain. Neuroscientist 8, 562–573. https://doi.org/10.1177/1073858402238515.
Pu, J., Liu, Y., Zhang, H., Tian, L., Gui, S., Yu, Y., Chen, X., Chen, Y., Yang, L., Ran, Y., Zhong, X., Xu, S., Song, X., Liu, L., Zheng, P., Wang, H., Xie, P., 2021. An integrated meta-analysis of peripheral blood metabolites and biological functions in major depressive disorder. Mol. Psychiatry 26, 4265–4276. https://doi.org/10.1038/s41380-020-0645-4.
Qureshi, M.I., Vorkas, P.A., Coupland, A.P., Jenkins, I.H., Holmes, E., Davies, A.H., 2017. Lessons from metabonomics on the neurobiology of stroke. Neuroscientist 23, 374–382. https://doi.org/10.1177/1073858416673327.
Ravindran, N., McKay, M., Paric, A., Johnson, S., Chandrasena, R., Abraham, G., Ravindran, A.V., 2022. Randomized, placebo-controlled effectiveness study of quetiapine XR in comorbid depressive and anxiety disorders. J. Clin. Psychiatry 83. https://doi.org/10.4088/JCP.21m14096.
Sarawagi, A., Soni, N.D., Patel, A.B., 2021. Glutamate and GABA homeostasis and neurometabolism in major depressive disorder. Front. Psychol. 12, 637863. https://doi.org/10.3389/fpsyt.2021.637863.
Schmidt, H.D., Shelton, R.C., Duman, R.S., 2011. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. Neuropsychopharmacology 36, 2375–2394. https://doi.org/10.1038/npp.2011.151.
Seo, J.S., Mantas, I., Svenningsson, P., Greengard, P., 2021. Ependymal cells-CSF flow regulates stress-induced depression. Mol. Psychiatry 26, 7308–7315. https://doi.org/10.1038/s41380-021-01202-1.
Sharma, P., Benford, B., Li, Z.Z., Ling, G.S., 2009. Role of pyruvate dehydrogenase complex in traumatic brain injury and measurement of pyruvate dehydrogenase enzyme by dipstick test. J. Emerg. Trauma Shock 2, 67–72. https://doi.org/10.4103/0974-2700.50739.
Shen, D., Zhao, H., Gao, S., Li, Y., Cheng, Q., Bi, C., Zhou, Z., Li, Y., Yu, C., 2021. Clinical serum metabolomics study on fluoxetine hydrochloride for depression. Neurosci. Lett. 746. https://doi.org/10.1016/j.neulet.2020.135585.
Skaf, Y., Laubenbacher, R., 2022. Topological data analysis in biomedicine: a review. J. Biomed. Inform. 130, 104082. https://doi.org/10.1016/j.jbi.2022.104082.
Sobczak, S., Honig, A., Christophe, A., Maes, M., Helsdingen, R.W., De Vriese, S.A., Riedel, W.J., 2004. Lower high-density lipoprotein cholesterol and increased omega-6 polyunsaturated fatty acids in first-degree relatives of bipolar patients. Psychol. Med. 34, 103–112. https://doi.org/10.1017/s0033291703001090.
Stone, T.W., Perkins, M.N., 1981. Quinolinic acid: a potent endogenous excitant at amino acid receptors in CNS. Eur. J. Pharmacol. 72, 411–412. https://doi.org/10.1016/0014-2999(81)90587-2.
Su, K.P., Lai, H.C., Peng, C.Y., Su, W.P., Chang, J.P., Pariante, C.M., 2019. Interferon-alpha-induced depression: comparisons between early- and late-onset subgroups and with patients with major depressive disorder. Brain Behav. Immun. 80, 512–518. https://doi.org/10.1016/j.bbi.2019.04.032.
Teichberg, V.I., 2007. From the liver to the brain across the blood-brain barrier. Proc. Natl. Acad. Sci. U. S. A. 104, 7315–7316. https://doi.org/10.1073/pnas.0702450104.
Thomas, M., Savitz, J., Zhang, Y., Burrows, K., Smith, R., Figueroa-Hall, L., Kuplicki, R., Khalsa, S.S., Taki, Y., Teague, T.K., Irwin, M.R., Yeh, F.C., Paulus, M.P., Zheng, H., On Behalf Of Tulsa, I, 2021. Elevated systemic inflammation is associated with reduced corticolimbic white matter integrity in depression. Life (Basel) 12. https://doi.org/10.3390/life12010043.
Wieder, C., Frainay, C., Poupin, N., Rodríguez-Mier, P., Vinson, F., Cooke, J., Lai, R.P., Bundy, J.G., Jourdan, F., Ebbels, T., 2021. Pathway analysis in metabolomics: recommendations for the use of over-representation analysis. PLoS Comput. Biol. 17, e1009105. https://doi.org/10.1371/journal.pcbi.1009105.
Willner, P., 1997. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology 134, 319–329. https://doi.org/10.1007/s002130050456.
Willner, P., Mitchell, P.J., 2002. The validity of animal models of predisposition to depression. Behav. Pharmacol. 13, 169–188. https://doi.org/10.1097/00008877-200205000-00001.
Wu, Z., Yu, H., Tian, Y., Wang, Y., He, Y., Lan, T., Li, Y., Bai, M., Chen, X., Chen, Z., Ji, P., Zhang, H., Jin, X., Song, J., Cheng, K., Xie, P., 2021. Non-targeted metabolomics profiling of plasma samples from patients with major depressive disorder. Front. Psychol. 12, 810302. https://doi.org/10.3389/fpsyt.2021.810302.
Wu, S., Yin, Y., Du, L., 2022. Blood-brain barrier dysfunction in the pathogenesis of major depressive disorder. Cell. Mol. Neurobiol. 42, 2571–2591. https://doi.org/10.1007/s10571-021-01153-9.
Yang, X., Wang, G., Gong, X., Huang, C., Mao, Q., Zeng, L., Zheng, P., Qin, Y., Ye, F., Lian, B., Zhou, C., Wang, H., Zhou, W., Xie, P., 2019. Effects of chronic stress on intestinal amino acid pathways. Physiol. Behav. 204, 199–209. https://doi.org/10.1016/j.physbeh.2019.03.001.
Zhang, W., Sun, Q., Jia, L., Li, M., 2020. Ketamine exerts a protective role in a cell-based model of major depressive disorder via the inhibition of apoptosis and inflammation and activation of the Krebs cycle. Bosn. J. Basic Med. Sci. 20, 44–55. https://doi.org/10.17305/bjbms.2019.4222.
Zhong, J., Chen, J., Cao, M., Fang, L., Wang, Z., Liao, J., Chen, D., Zhang, X., Guo, J., Zhao, L., Zhou, C., 2022. Elevated plasma intestinal fatty acid binding protein and

aberrant lipid metabolism predict post-stroke depression. Heliyon 8, e11848. https://doi.org/10.1016/j.heliyon.2022.e11848.
Zhu, Y.L., Li, S.L., Zhu, C.Y., Wang, W., Zuo, W.F., Qiu, X.J., 2020. Metabolomics analysis of the antidepressant prescription Danzhi Xiaoyao Powder in a rat model of Chronic Unpredictable Mild Stress (CUMS). J. Ethnopharmacol. 260, 112832. https://doi.org/10.1016/j.jep.2020.112832.