ARTICLE

Characterizing metabolomic and proteomic changes in depression: a systematic analysis

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Despite the widespread use of metabolomics and proteomics to explore the molecular landscape of depression, there is a lack of consensus regarding dysregulated molecules with replicable evidence. Thus, this study aimed to identify robust metabolomic and proteomic features in depression by integrating evidence from large-scale studies. In this study, a knowledge base-mining approach was adopted to compile a list of dysregulated molecules derived from metabolomic and proteomic studies. A vote-counting approach was performed to identify consistently altered molecules in the blood and urine samples of patients with depression. A total of 2398 molecular entries were selected, comprising 857 unique metabolites and 468 unique proteins from 143 metabolomic and 23 proteomic studies in depression. The results of vote-counting analyses revealed that 11 metabolites in blood and 5 metabolites in urine exhibited consistent disturbances across studies. Circulating levels of glutamic acid and phosphatidylcholine (32:0) were elevated in depressive patients, whereas the levels of tryptophan, kynurenic acid, kynurenine, acetylcarnitine, serotonin, creatinine, inosine, phenylalanine, and valine were lower. Urinary levels of isobutyric acid, alanine, and nicotinic acid were higher, whereas the levels of N-methylnicotinamide and tyrosine were lower. Moreover, analysis of the proteomic dataset identified only one circulating protein, ceruloplasmin, that was consistently dysregulated. Convergence comparison prioritized tryptophan as the top-ranked circulating metabolite, followed by kynurenic acid, acetylcarnitine, creatinine, serotonin, and valine. Collectively, robust evidence of metabolomic changes was observed in patients with depression, pointing to a role as potential biomarkers. Further investigation of consensus proteomic features for depression is necessitated.

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INTRODUCTION

Depression, a growing global health concern, is characterized by persistent feelings of sadness, lack of enjoyment, and loss of interest [1]. Epidemiological surveys have estimated that the global prevalence of depression is as high as 3 to 10%, making it a leading cause of disability [2–4]. Its pathogenesis involves a multifaceted interaction of biological, environmental, and psychological factors, yet a complete understanding of the mechanisms by which these factors contribute to depression remains elusive [5]. At present, while expanding our systematic knowledge of molecular alterations associated with depression is challenging, it holds promise for the identification of potential biomarkers and therapeutic targets [6–8].

Metabolites and proteins are the main biomolecules in peripheral fluid samples, thus detecting their alterations offers promising avenues for basic and translational research in psychiatric diseases. Metabolomics and proteomics have emerged as powerful tools for delineating the molecular landscape of diseases because they are more relevant to disease compared to transcriptomics and genomics [9, 10]. With rapid advancements in mass spectrometry platforms, these approaches have been widely used to identify the molecular profiles of depression, yielding a substantial quantity of data. For example, our previous research compared the metabolomic and proteomic profiles of patients with depression and control subjects [11–13]. Further observations from other studies also suggested alterations in the proteome and metabolome of depressive patients [14–16]. Overall, these studies offer novel perspectives in the identification of potential biomarkers, as well as in elucidating the biological mechanisms underlying depression.

There is an increasing interest in combining evidence from an abundance of metabolomics and proteomics studies. Currently, several solutions have been proposed in the context of data integration. Combining patient level data is the ideal way to compare molecular profiles across omics studies. A previous study investigated metabolomic profile in the plasma of depressive patients by aggregating patient level data from 9 population-based studies [17]. However, the lack of raw datasets from the same profiling approach hampers the further application of this method. Currently, combining mean concentrations is the most popular method for the joint analysis of molecular studies. Our prior meta-analysis encompassed 46 metabolomics studies and

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identified 23 differential metabolites in the blood of patients with depression [18]. Strengths of our study include a large number of eligible studies and integrating data from different metabolomic platforms. Despite these promising results, discrepancies in methodological designs and technological platforms have led to inconsistent results in previous metabolomic and proteomic studies [19]. It is worth noting that there is a lack of consensus concerning dysregulated molecules with replicable evidence across these large-scale studies, raising doubt on their clinical utility in depression [20]. Indeed, several peripheral biomarker candidates that exhibited a consistent trend of dysregulation across studies, including gamma-aminobutyric acid and kynurenine [21, 22], have been validated in our previous diagnostic research [23], hinting at future applications in this field. The vote-counting procedure is an alternative option to identify conserved and consistent candidate biomarkers for integrating such large-scale omic datasets. A key strength of this method is that it is generally convenient for systematic "big data" analyses because most omics studies provided lists of significantly dysregulated molecules [24]. Therefore, it has been utilized in our previous studies that explored metabolomic alterations in animal models of depression [25, 26].

The aim of the present study was to identify robust molecular features for depression from metabolomic and proteomic studies. Therefore, a knowledge base-driven approach was applied to compile a large list of candidate metabolites and proteins associated with depression. This was followed by vote-counting analyses to identify molecules consistently upregulated or downregulated in the blood and urine of patients with depression. Finally, we compared the altered circulating metabolites identified in this study with those from our previous clinical and preclinical studies, to prioritize candidate biomarkers. We anticipated that this systematic investigation would provide a novel perspective on the metabolomic and proteomic profiles associated with depression.

MATERIALS AND METHODS

Data source

The data for this investigation were sourced from the ProMENDA database (https://menda.cqmu.edu.cn). Details of the database design and data curation have been described in our prior publications [27, 28]. Briefly, ProMENDA is a comprehensive resource developed to collect and present available information on metabolomics and proteomics in depressive patients and animal models. A more detailed description of the ProMENDA database is given in the Supplementary Methods. To date, 22,519 differential metabolite entries and 20,847 differential protein entries have been meticulously curated from 1370 studies that investigated molecular changes in humans, rats, mice, and non-human primates.

Data selection

In the current study, several criteria were applied in the selection of candidate metabolite and protein sets. This study focused on studies that explored metabolomic and proteomic alterations between depressive patients and controls, excluding animal studies or those focusing on treatment effects. Studies that recruited patients with a diagnosis of depressive disorders according to standardized diagnostic criteria or clinician assessment were included, those that recruited patients with depressive symptoms based on depression rating scales were excluded. In addition, studies wherein all patients presented with a specific disease (stroke, diabetes, eating disorder, etc.) were excluded. Data from peripheral blood (plasma or serum) or urine samples, which are commonly used in clinical metabolomics and proteomics analyses, were selected for analysis, whereas other tissues were excluded due to limited molecular data. Lastly, molecular data presented by the ratios of two molecules were excluded.

Data analytic strategy

In the current study, molecular changes in the blood and urine samples of patients with depression were explored. To examine potential biological functions of all identified metabolites and proteins, pathway analyses were conducted using MetaboAnalyst 6.0, with pathways having false discovery rates < 0.05 considered as significantly enriched [29]. Then vote-counting test was performed based on these identified molecules. It tests whether the levels of differential molecules are consistently increased or decreased across independent studies, with the assumption that a robust molecule would be reproducibly identified as dysregulated in independent validation studies [30, 31]. In the current study, metabolomic changes in the blood and urine samples of patients with depression were characterized using the vote-counting procedure. Proteomic alterations in blood and urine samples were then analyzed. As antidepressants could modulate metabolomic and proteomic alterations, secondary analyses were performed based on antidepressant usage (antidepressant-free or not). Given that these molecules were presented in different formats, metabolites were mapped to compound names, whilst proteins were mapped to gene symbols in the ensuing analyses.

Convergence comparison of metabolomic changes in blood

A comprehensive comparison was conducted to systematically synthesize existing evidence on altered metabolite levels in blood. To examine the common metabolites shared by different analytical approaches, the current data were compared with our previous meta-analysis that explored blood-based metabolomic changes in patients with depression by combining mean metabolite concentrations [18]. Next, to integrate cross-species evidence, the common metabolites shared by human and rodent models were examined. The current data were compared with our previous vote-counting studies that specifically investigated metabolomic alterations induced by depression phenotypes and antidepressants in animal models [25, 26].

Statistical analysis

In this investigation, vote-counting analyses were conducted according to the following steps. Based on the selected metabolomic and proteomic datasets, lists of dysregulated metabolites and proteins were compiled. The frequency of dysregulation for each molecule was recorded in these analyses, and candidate molecules with a minimal frequency of four were introduced into the vote-counting procedures [25]. For each candidate molecule in each study, a value of 1 was assigned to upregulation, while a value of −1 was assigned to downregulation. The vote-counting statistic (VCS) for each candidate molecule was calculated by summing total scores, providing an overall trend of dysregulation. The null hypothesis of the vote-counting procedure assumes that the frequency of dysregulation is binomially distributed, signifying that the probabilities of significant upregulation and downregulation for each molecule are both 50% [24]. A binomial probability test was then performed in R software (version 4.3.0) with the function binom.test. Statistical significance was set at $P < 0.05$. All P values referred to one-tailed tests.

RESULTS

Data sets

The flowchart for the current study is depicted in Fig. 1A. Briefly, 2398 molecular entries were selected in blood and urine samples from the ProMENDA database. The metabolomic dataset comprised 1495 metabolite entries derived from 143 studies that compared metabolite levels between depressive patients and controls. The reasons for study exclusion are summarized in Table S1. Comprehensive information on the included metabolomic studies, such as study design, depression criteria, sample size, and citation, is listed in Supplemental Dataset 1. Among these metabolomics studies, blood and urine samples were employed in 130 and 18 studies, respectively. Information on the metabolite entries included in the data analysis, including molecular IDs, comparison groups, tissues, depression category, platform, and dysregulated direction is detained in Supplemental Dataset 2.

The proteomic dataset consisted of 903 protein entries derived from 23 studies. The reasons for data exclusion are outlined in Table S1. Detailed information on the proteomic studies and protein entries can be found in Supplemental Datasets 3 and 4, respectively. Blood and urine samples were used in 22 studies and 1 study, respectively.

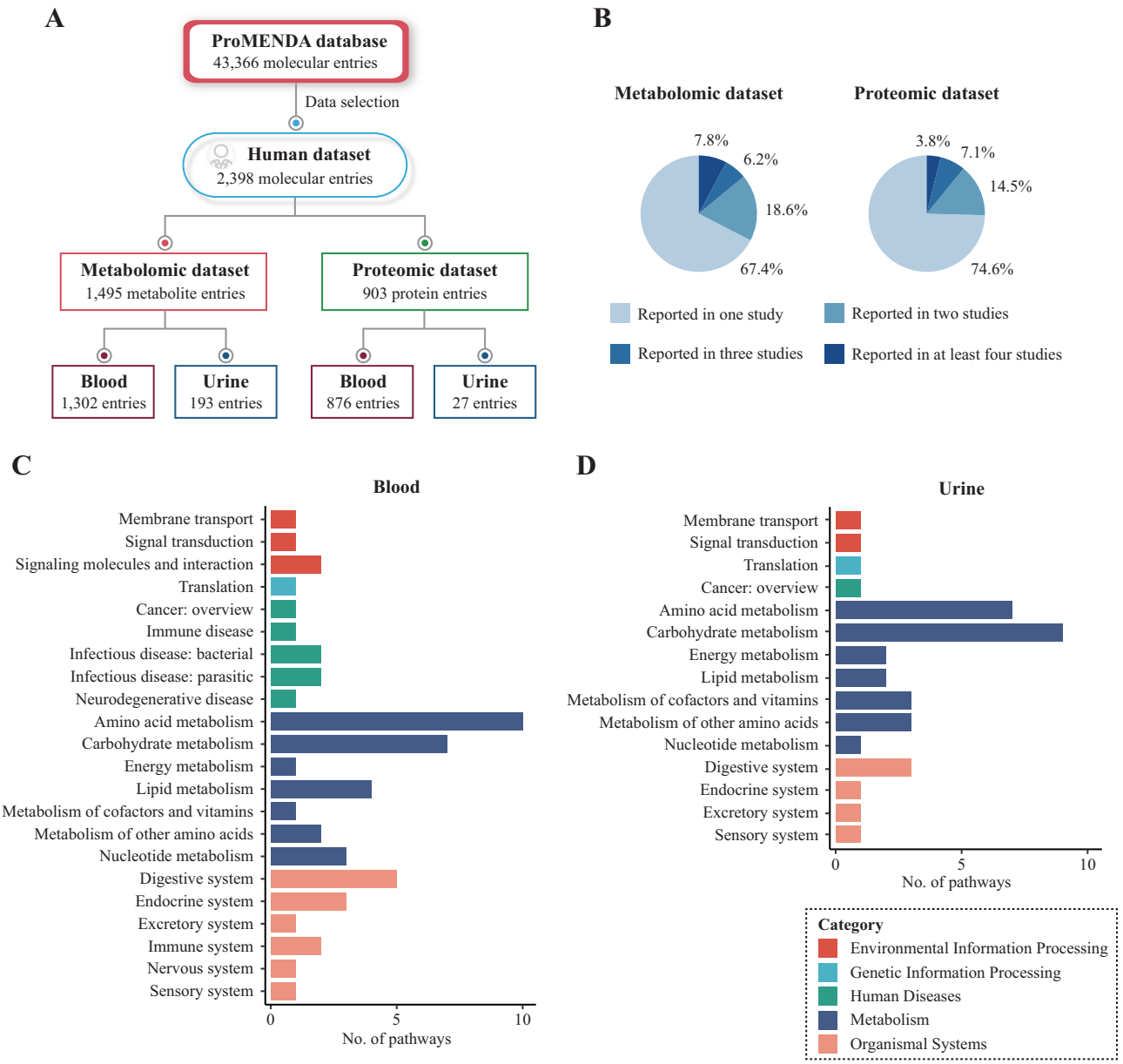

Fig. 1 Study flowchart and data statistics. A Numbers of molecular entries collected from metabolomic and proteomic datasets. **B** Numbers of unique metabolites and proteins and their reported frequencies in metabolomic and proteomic datasets.

In the metabolomic dataset, 857 unique metabolites were reported in at least one study, including 578 in one study, 159 in two studies, and 53 in three studies, respectively (Fig. 1B). Only 67 (7.8%) metabolites were reported in at least four studies. Regarding the proteomic dataset, 468 unique proteins were curated, including 349 in one study, 68 in two studies, and 33 in three studies, respectively. Merely 18 (3.8%) proteins were reported in at least four studies. These results collectively suggested that a small proportion of differential metabolites or proteins were likely to be well replicated across these omics studies.

Pathway analysis was performed to identify significantly altered pathways based on these identified metabolites and proteins. The results showed that 53 pathways were significantly enriched in the blood of patients with depression, half of which (28 pathways) were involved in the metabolic process, especially for amino acid metabolism (10 pathways) and carbohydrate metabolism (7 pathways; Fig. 1C and Table S2). In urine, 37 pathways were significantly enriched, three-fourths (27 pathways) were involved in the metabolic process, especially for carbohydrate metabolism (9 pathways) and amino acid metabolism (7 pathways; Fig. 1D and Table S3).

Metabolites altered in blood

Metabolites that were consistently increased or decreased in the blood of patients with depression were investigated. Data filtering yielded a total of 1302 differential metabolite entries, corresponding to 814 unique metabolites. Forty-eight of these metabolites that were reported as dysregulated in at least four studies were subjected to vote-counting analyses. The results exposed that the levels of two metabolites, namely glutamic acid (VCS = 7, $P = 0.020$) and phosphatidylcholine (32:0) (VCS = 5, $P = 0.031$), were consistently increased. Conversely, the levels of nine metabolites, namely tryptophan (VCS = −18, $P < 0.001$),

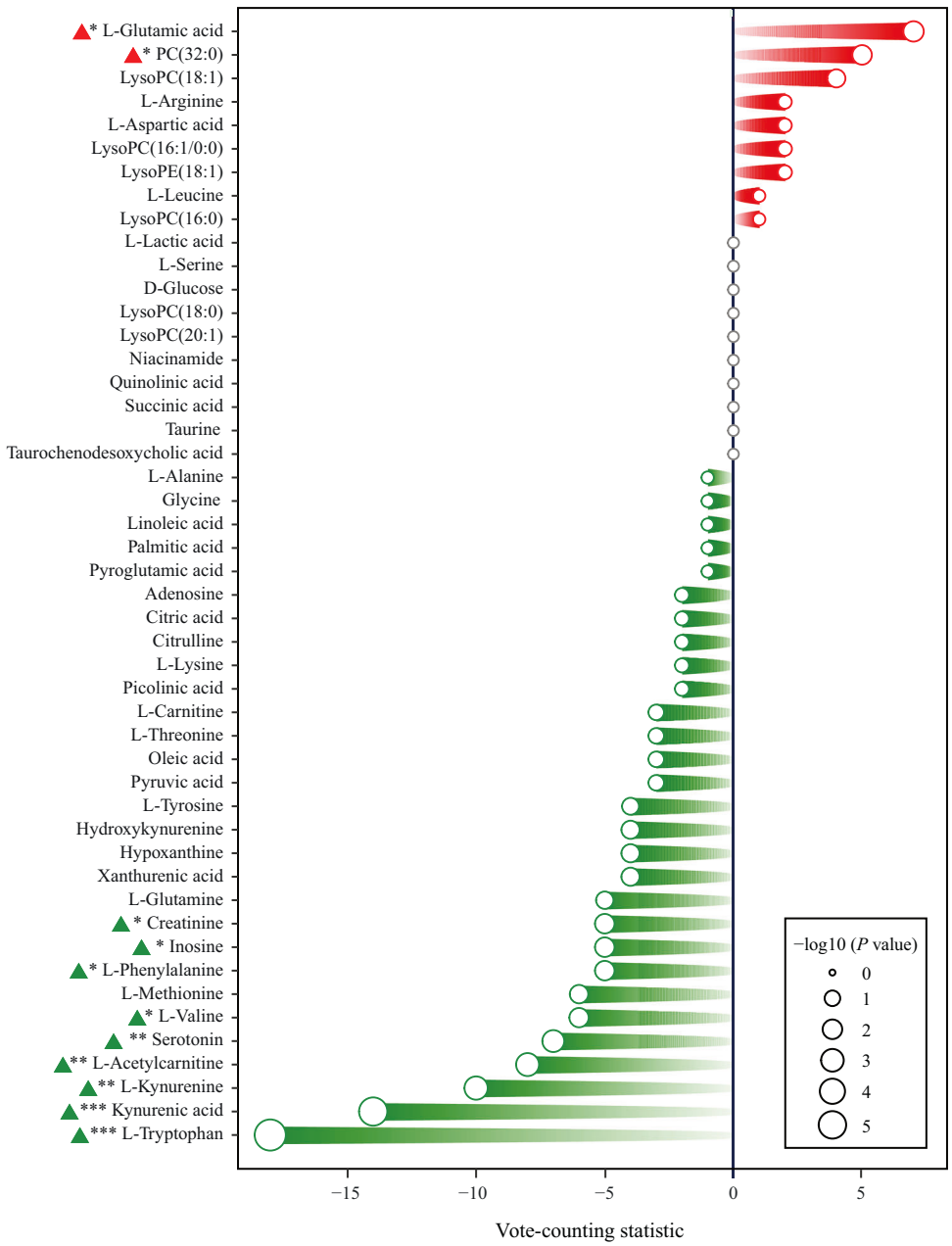

Fig. 2 Vote-counting results for metabolomic changes in the blood of patients with depression. The vote-counting statistics (*x*-axis) for each metabolite (*y*-axis) are presented. Red and green bars represent upregulated and downregulated metabolites, respectively. *, one-tailed $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. *LysoPC* lysophosphatidylcholine; *LysoPE* lysophosphatidylethanolamines; *PC* phosphatidylcholine.

kynurenic acid (VCS = −14, $P < 0.001$), kynurenine (VCS = −10, $P = 0.003$), acetylcarnitine (VCS = −8, $P = 0.004$), serotonin (VCS = −7, $P = 0.008$), valine (VCS = −6, $P = 0.035$), creatinine (VCS = −5, $P = 0.031$), inosine (VCS = −5, $P = 0.031$), and phenylalanine (VCS = −5, $P = 0.031$), were decreased (Fig. 2 and Table S4).

Further analyses were performed based on antidepressant usage. Among thirteen metabolites that were voted in antidepressant-free patients, only tryptophan (VCS = −6, $P = 0.016$) was consistently downregulated (Table S5). For antidepressant-treated patients, the vote counting procedure revealed that three of eight candidate metabolites were downregulated, including kynurenic acid (VCS = −12, $P < 0.001$), tryptophan (VCS = −11, $P < 0.001$), and serotonin (VCS = −5, $P = 0.031$; Table S6).

Metabolites altered in urine

Concerning metabolomic alterations in urine, 87 unique metabolites were identified from 193 differential metabolite entries. Among them, fifteen metabolites, each with a minimal count of four, were subjected to vote-counting analyses. The results showed that the levels of isobutyric acid (VCS = 6, $P = 0.016$), alanine (VCS = 6, $P = 0.016$), and nicotinic acid (VCS = 5, $P = 0.031$) were increased. Conversely, the levels of N-methylnicotinamide (VCS = −6, $P = 0.016$) and tyrosine (VCS = −5, $P = 0.031$) were decreased (Fig. 3 and Table S7).

As most of urinary studies recruited antidepressant-free patients, secondary analyses were only performed in this subpopulation. The results of antidepressant-free patients were similar with those of all populations, except that tyrosine did not show consistent changes (Table S8).

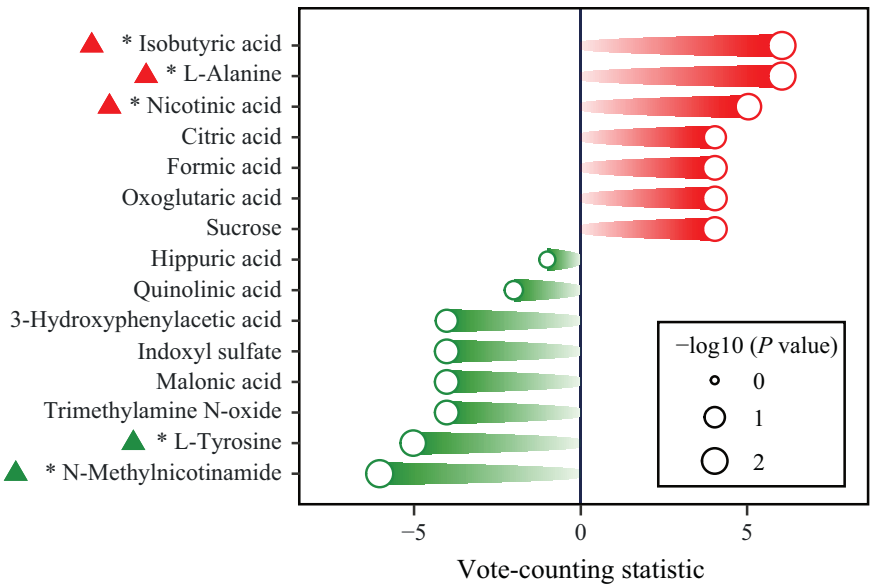

Fig. 3 Vote-counting results for metabolomic changes in the urine of patients with depression. The vote-counting statistics (*x*-axis) for each metabolite (*y*-axis) are presented. Red and green bars denote upregulated and downregulated metabolites, respectively. *, one-tailed $P < 0.05$.

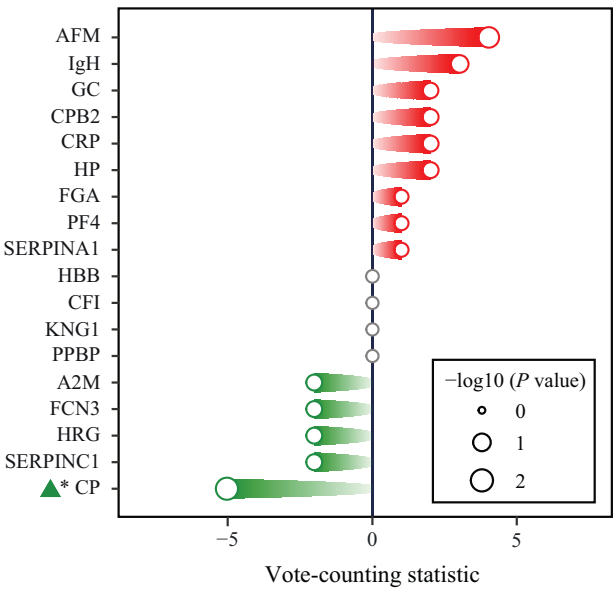

Fig. 4 Vote-counting results for proteomic changes in the blood of patients with depression. The vote-counting statistics (*x*-axis) for each protein (*y*-axis) are presented. Red and green bars indicate upregulated and downregulated metabolites, respectively. *, one-tailed $P < 0.05$.

Proteins altered in blood

In order to further explore proteomic changes in patients with depression, 876 and 27 differential protein entries from blood and urine samples were selected, respectively. Among the 453 candidate proteins in blood, vote-counting analyses were conducted for 18 candidate proteins. Our results indicated that only one protein, ceruloplasmin (CP), was consistently dysregulated, with decreased expression levels in the proteomic studies (VCS = −5, $P = 0.031$; Fig. 4 and Table S9). Further analyses of antidepressant-free patients revealed similar results (Table S10). Due to the limited amount of data, it was not feasible to conduct vote-counting analyses for proteomic changes in urine samples.

Convergence comparison of metabolomic changes in the blood of depressive patients

The list of perturbed metabolites identified in the current investigation was compared with two lists of dysregulated metabolites from our previously published human and animal model studies (Fig. 5A). Results of the convergence comparison showed that four downregulated metabolites, comprising tryptophan, kynurenic acid, acetylcarnitine, and creatinine, overlapped between the human vote-counting and the combined mean results. Three dysregulated metabolites identified in the current study, comprising tryptophan, serotonin, and valine, were also consistently downregulated in animal model-based blood samples, with evidence indicating that antidepressants could reverse these alterations. Based on these multiple lines of evidence, a panel of common signatures was constructed for the metabolomic profile in the blood of depressive patients (Fig. 5B). Among consistently dysregulated metabolites identified in the current study, tryptophan was the only metabolite that exhibited robust convergent evidence in both human and animal models. Kynurenic acid, acetylcarnitine, and creatinine were validated by an alternative statistical approach, while serotonin and valine were validated by cross-species comparison.

DISCUSSION

To the best of our knowledge, this study has been one of the first attempts to thoroughly examine universally disturbed metabolomic and proteomic profiles in patients with depression using a knowledge base-mining approach. A systematic analysis of 143 metabolomic studies identified 11 metabolites in blood and 5 metabolites in urine that exhibited consistent disturbances in depressive patients. Our findings signaled that the levels of glutamic acid and phosphatidylcholine (32:0) were consistently elevated in the blood of patients with depression, while those of tryptophan, kynurenic acid, kynurenine, acetylcarnitine, serotonin, creatinine, inosine, phenylalanine, and valine were lower. In urine samples, the concentrations of isobutyric acid, alanine, and nicotinic acid were increased, whereas those of N-methylnicotinamide and tyrosine were decreased. A thorough examination of 23 proteomic studies unveiled that only one protein, ceruloplasmin, was consistently altered in the blood of

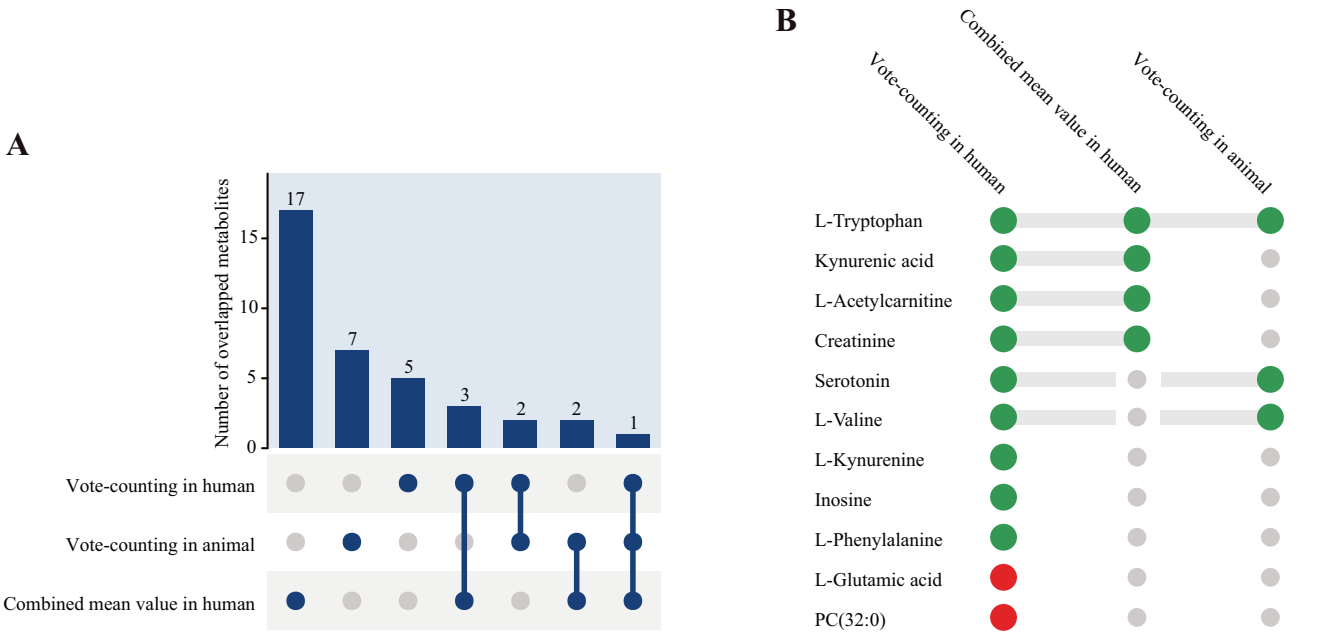

Fig. 5 Convergence comparison of metabolomic changes in the blood of patients with depression. A Upset plot for overlapped dysregulated metabolites identified by convergence comparison. Numbers of dysregulated metabolites resulting from vote-counting of metabolomic data in patients ('vote-counting in human') and animal models ('vote-counting in animal') and from the meta-analysis of metabolomic data in patients ('combined mean value in human') were compared. **B** List of overlapping metabolites. For each metabolite, red and green circles represent upregulated and downregulated metabolites, respectively. *PC* phosphatidylcholine.

patients with depression. Besides, a convergence comparison was also performed to prioritize circulating metabolites. The top-ranked metabolite was tryptophan, followed by kynurenic acid, acetylcarnitine, creatinine, serotonin, and valine. Altogether, these findings enhance our understanding of the panoramic metabolomic and proteomic alterations in depression.

Herein, a decrease in the circulating levels of tryptophan metabolites, including tryptophan, serotonin, kynurenic acid, and kynurenine, was noted in patients with depression. Tryptophan, an essential amino acid exclusively obtained from dietary sources, is chiefly metabolized through three pathways in the human body, namely the serotonin, kynurenine, and indole pathways [32]. Our findings highlighted dysregulated metabolites in both the tryptophan-serotonin and tryptophan-kynurenine pathways. Consistent with the serotonin theory of depression, a decrease in peripheral serotonin levels was observed herein. While the role of serotonin in depression has long been controversial, recent attention has shifted towards the tryptophan-kynurenine pathway [33, 34]. In mammals, over 95% of tryptophan is degraded via the kynurenine pathway, wherein tryptophan is converted to kynurenine, which is in turn further metabolized to kynurenic acid and quinolinic acid [35]. The decreased level of kynurenine metabolites observed in our study supports the role of the tryptophan-kynurenine pathway in depressive patients, in line with the finding of a large-scale meta-analysis examining kynurenine metabolites in major psychiatric diseases [36]. The decreased levels of kynurenic acid indicated attenuated neuroprotective effects, as kynurenic acid is known as a neuroprotective agent that acts on multiple receptors [37]. These findings highlight the importance of tryptophan metabolism in the pathophysiology of depression.

Furthermore, we also found other evidence supporting the disturbance of amino acid metabolism in depression. In this study, the concentrations of three essential amino acids, including valine, phenylalanine, and tryptophan, were significantly decreased, implying a deficiency in dietary intake of amino acids in depressive patients. However, the causal link between altered levels of essential amino acid levels and depression remains to be elucidated, as tryptophan and phenylalanine depletion studies yielded conflicting results regarding the induction of depressive symptoms [38]. Additionally, an increase in the level of glutamic acid was detected in depressive patients. In agreement with our findings, another large-scale meta-analysis reported elevated levels of glutamic acid in postmenopausal women with depression [39]. Likewise, previous studies also identified a significant positive correlation between the level of glutamic acid and the severity of depression, which may be linked to glutamate excitotoxicity [40, 41].

In this study, alterations in the levels of several circulating metabolites, including creatinine, acetylcarnitine, and inosine, were identified. A decrease in the level of creatinine was noted. The negative correlation between creatinine levels and depression is consistent with findings from biochemical studies [42, 43], although other studies have reported contrasting results [44]. Creatinine is synthesized from creatine in muscles. Its reduction may be explained by low muscle mass or insufficient dietary protein intake in individuals with depression [45]. Our study also uncovered a decrease in acetylcarnitine levels, a metabolite involved in energy metabolism via fatty acid oxidation, in depressive individuals, consistent with the results of our previous meta-analysis [18]. Clinical research also pointed out that acetylcarnitine supplementation could alleviate depression [46]. This evidence indicates that deficits in acetylcarnitine play a role in depression and may serve as a potential antidepressant agent. The present study identified decreased inosine levels in depressive patients. Inosine, a derivative of adenosine, fulfils complex biological functions such as mediating translational modification and energy expenditure [47, 48]. Our research, along with prior studies, demonstrated that inosine supplementation could alleviate depressive behaviors in animal models [49–51].

Notably, alterations in amino acid metabolism and nicotinic acid metabolism were noted in the urine of patients with depression, with increased levels of alanine, nicotinic acid, and isobutyric acid and decreased levels of N-methylnicotinamide and tyrosine. Alanine and tyrosine are non-essential amino acids whose levels are altered in depressive individuals. Previous studies have reported a positive correlation between alanine concentrations

and depressive symptoms, supporting our finding [40]. As tyrosine is a precursor for catecholamine neurotransmitters, its dysregulation in urine may suggest a deficiency in these neurotransmitters in depressive patients [52]. Our study also identified an increase in the level of urinary nicotinic acid and a concomitant decrease in that of N-methylnicotinamide, both of which participate in nicotinic acid metabolism. A recent large cohort study described that high dietary consumption of nicotinic acid was associated with an increased risk of depression [53]. However, a similar study based on the same cohort reported a U-shaped association between nicotinic acid intake and depression [54]. Animal studies also evinced that N-methylnicotinamide and nicotinamide, two metabolic products of nicotinic acid, could exert anti-depressive effects [55, 56]. Taken together, we hypothesized that an impairment of nicotinic acid metabolism in depression, resulting in the accumulation of nicotinic acid and a decline in N-methylnicotinamide levels. However, additional validation research is still required to confirm this hypothesis. Additionally, the levels of isobutyric acid, a short-chain fatty acid, were increased in depressive patients, consistent with animal studies reporting increased fecal isobutyric acid levels. This observation suggests the potential role of the microbiota-gut-brain axis in depression [57].

Our proteomic analysis determined that only one protein, ceruloplasmin, exhibited consistent alterations in the blood of patients with depression. Contrary to previous studies suggesting an upregulation in the expression of ceruloplasmin in patients with depression [58], its expression was found to be downregulated in this study. This discrepancy underscores the need for further research with larger sample sizes to provide valuable insights into the role of ceruloplasmin in depressive individuals.

An important finding in this study is that most of altered molecules identified in previous metabolomics and proteomics analyses were not reproducible on a wide scale across different cohorts. This highlights the long-standing reproducibility challenge faced by metabolomics and proteomics research [59]. It is globally recognized that both methodological and biological variations can compromise the reproducibility of omics research [60–62]. Therefore, efforts to promote methodological standards, optimize data availability, and improve omics techniques are warranted to enhance the replication of omics results [63]. Additionally, this inconsistency may be ascribed to the phenotypic heterogeneity of depressive patients, as patients exhibit a broad spectrum of psychiatric symptoms. Earlier studies documented clinical factors, including gender, age, and disease severity, significantly impact the molecular profiles of depressive patients, which may contribute to its pathophysiological heterogeneity [64–66]. These findings highlight the need for further independent validation of discovered molecules in larger cohorts with diverse populations, which may yield more well-replicated results.

Nevertheless, several limitations should be acknowledged in the present study. To begin, considering the methodological weaknesses of the vote-counting analysis, we were unable to identify dysregulated molecules beyond those included in the knowledge base. More robust findings could potentially be obtained by combining raw omics datasets, although this remains a challenging task at the current stage. Despite its exploratory nature, the vote-counting method offers valuable insight into molecular profiles of depression, given that it remains the most feasible approach to summarizing such large-scale data. Secondly, potential confounding factors such as age and gender were not adjusted for in this study. Future large-scale studies that collect both demographic and molecular data from individual participants could provide more precise insights into the correlations between complex clinical and molecular profiles in depression. Fourthly, limited data precluded further analyses that explored molecular changes associated with treatment response. Further work is needed to understand the processes that could influence the efficacy of interventions in depression. Lastly, our study was limited to studies using metabolomic and proteomic platforms. Further research employing a broader range of analytic platforms, such as immunoassay kits and Western Blot, could offer a more comprehensive view of the molecular profile in depression.

In summary, this study established a comprehensive framework for detecting dysregulated molecules with replicable evidence across large-scale metabolomic and proteomic studies in depression. Based on the 2398 molecular entries, this study characterized molecular changes associated with depression. The results of vote-counting analyses suggested robust evidence of disturbances in amino acid metabolism, especially for tryptophan metabolites, pointing to a role as potential biomarkers. Future studies are needed to discover proteomic features of depression.

DATA AVAILABILITY

The datasets generated in the current study are available in Supplemental Datasets 1–4, or on the ProMENDA website (https://menda.cqmu.edu.cn).

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with the relevant guidelines and regulations. The study was approved by The Ethics Committee of Chongqing Medical University (IACUC-CQMU-2024-0115). The datasets generated in the current study were collected from publicly available literature or reports, therefore informed consent forms are not applicable.

ADDITIONAL INFORMATION

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