HPLC-Based Metabolomics in Stroke and Alzheimer's Disease: A Review of Shared Pathophysiology

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Abstract: Stroke and Alzheimer's disease (AD) are two major neurological disorders with increasing global prevalence, affecting approximately 15 million and 55 million individuals respectively. Despite their distinct clinical presentations, both conditions share overlapping pathophysiological mechanisms, including oxidative stress, mitochondrial dysfunction, and neuroinflammation. This review synthesizes current literature on the application of high-performance liquid chromatography (HPLC)-based metabolomics to identify shared metabolic signatures between stroke and AD. HPLC remains a widely accessible and reliable platform for quantifying disease-relevant metabolites in cerebrospinal fluid, plasma, and brain tissue. Key metabolites such as homocysteine, glutamate, kynurenine, lactate, and myo-inositol, linked to excitotoxicity, inflammation, and bioenergetic failure, demonstrate consistent alterations across both diseases and show diagnostic potential, with area under the ROC curve (AUC) values ranging from 0.70 to 0.83. By mapping these biochemical changes, HPLC-based metabolomics offers a practical approach for early detection, disease monitoring, and mechanistic understanding of neurodegeneration. Beyond the biomedical implications, this interdisciplinary review contributes to evidence-based research management by demonstrating how analytical platforms can be leveraged to support translational goals across clinical and public health systems. The findings underscore the importance of integrating biochemical profiling into broader diagnostic and healthcare strategies aimed at aging-related neurological conditions.

Keywords: Alzheimer's disease, HPLC, metabolomics, stroke, biomarkers

1. Introduction

Stroke and Alzheimer's disease (AD) represent two of the most prevalent causes of neurological disability and cognitive decline globally (1-3). Stroke affects approximately 15 million individuals each year, with around 5 million survivors experiencing permanent functional impairment (2). Meanwhile, AD accounts for 60–70% of all dementia cases and currently affects over 55 million people worldwide, a figure expected to rise to more than 130 million by 2050 (3). These diseases place a growing burden on healthcare systems and societies, especially as populations age. Although traditionally studied as distinct entities, there is increasing evidence that stroke and AD are not entirely separate but may converge at multiple pathophysiological levels. Shared risk factors such as aging, hypertension, hyperlipidemia, and type 2 diabetes are well-documented, but emerging data point to a deeper molecular overlap, particularly in metabolic dysfunction (4).

Neurodegeneration in both conditions is strongly associated with oxidative stress, mitochondrial failure, and chronic inflammation (5). Stroke induces rapid ischemic injury, triggering excitotoxicity and energy failure, while AD follows a more insidious course characterized by progressive synaptic loss, protein aggregation, and neuroinflammation (6). However, both disease states involve disruption of central metabolic pathways, including altered glucose metabolism, amino acid imbalances, and redox disturbances. Importantly, these biochemical changes are not merely consequences of tissue damage but are increasingly recognized as drivers of disease progression. Identifying and quantifying such metabolic alterations offers a unique opportunity to uncover early molecular signatures, which could enable more accurate diagnosis and timely therapeutic intervention.

In this context, metabolomics has emerged as a key approach for investigating disease-associated metabolic phenotypes. By analyzing small molecules involved in cellular metabolism, metabolomics captures dynamic

biochemical changes in response to pathological processes. Among available analytical platforms, high-performance liquid chromatography (HPLC) stands out for its accessibility, reproducibility, and suitability for routine clinical samples such as cerebrospinal fluid (CSF), plasma, serum, and tissue homogenates (7). HPLC enables targeted or semi-targeted quantification of low-molecular-weight compounds, particularly polar metabolites relevant to energy metabolism, neurotransmission, and oxidative stress. When coupled with appropriate detection methods, including UV, fluorescence (FLD), refractive index (RI), or mass spectrometry (MS), HPLC offers sufficient sensitivity to detect pathophysiologically relevant changes even in early disease stages (8).

Several studies have demonstrated the utility of HPLC in detecting specific metabolites altered in both stroke and AD. For example, glutamate, the principal excitatory neurotransmitter, is consistently elevated in acute stroke and has also been reported at higher levels in AD, particularly in patients with rapid cognitive decline (9). Homocysteine, an intermediate of the one-carbon metabolism pathway, is associated with vascular dysfunction and amyloid accumulation and is elevated in both conditions (10). Kynurenine, part of the tryptophan degradation pathway, links immune activation to neurotoxicity and has been found to be upregulated in both AD and post-stroke inflammation (11). Additionally, lactate and myo-inositol, markers of mitochondrial dysfunction and glial activation, respectively, are detectable via HPLC and exhibit disease-specific alterations (12). These findings support the notion that common metabolic pathways are disrupted in both diseases and that HPLC-based profiling can reveal clinically meaningful patterns.

The growing body of metabolomic data highlights the importance of viewing stroke and AD through a shared biochemical lens. Investigating the metabolic interface between these disorders could not only advance understanding of their etiology but also provide candidate biomarkers for differential diagnosis, disease staging, and therapeutic monitoring. Importantly, HPLC-based methods are scalable and can be adapted for longitudinal studies, allowing researchers to capture temporal changes in metabolic profiles across disease progression. The reproducibility and quantification potential of HPLC further strengthen its value for translational applications, particularly in clinical environments where high-resolution mass spectrometry may not be feasible.

This review synthesizes current findings on the application of HPLC-based metabolomics to stroke and AD, with a focus on identifying shared metabolic disturbances and evaluating their potential as biomarkers. Special attention is given to methodological considerations that influence data quality, including sample preparation, chromatographic conditions, and detector selection. By integrating insights from clinical and preclinical studies, this work aims to clarify the metabolic crosstalk between cerebrovascular and neurodegenerative pathology and to outline practical strategies for leveraging HPLC in biomarker development. Ultimately, a deeper understanding of these shared metabolic signatures may contribute to earlier diagnosis, improved patient stratification, and more targeted therapeutic interventions in both stroke and Alzheimer's disease.

2. HPLC-Based Metabolomics in Neurological Research

2.1. Mechanisms of Metabolite Detection by HPLC

High-performance liquid chromatography (HPLC) plays a central role in untargeted and targeted metabolomics due to its high resolution, reproducibility, and ability to quantify a wide range of polar and non-polar metabolites (13). In neurological research, this technique is particularly effective for detecting low-molecular-weight compounds implicated in neurodegenerative disorders, including amino acids, organic acids, neurotransmitters, and oxidative stress-related metabolites (14). The fundamental principle of HPLC lies in the differential interaction of analytes with a stationary phase and a mobile phase, resulting in their separation based on physicochemical properties such as polarity, charge, or hydrophobicity (15). Various detection modes can be coupled with HPLC, such as ultraviolet (UV), fluorescence (FLD), refractive index (RI), and mass spectrometry (MS), each suited to specific metabolite classes. For example, UV detection is commonly used for organic acids and nucleotides, while FLD offers high sensitivity for biogenic amines and derivatized amino acids. The versatility of HPLC enables accurate quantification of specific metabolic intermediates that may serve as biomarkers or provide mechanistic insight into pathological processes.

In neurodegenerative diseases like stroke and Alzheimer's disease, metabolic disruptions often manifest as alterations in the central carbon metabolism, redox balance, neurotransmitter turnover, and mitochondrial function (16,17). HPLC-based metabolomics facilitates precise measurement of these changes by separating key compounds such as glutamate, GABA, lactate, citrate, homocysteine, and kynurenine, which are frequently implicated in excitotoxicity, energy dysregulation, and neuroinflammation (18). Importantly, sample preparation is a critical step that affects the reproducibility and accuracy of metabolite detection. Brain tissue and biofluids such as cerebrospinal fluid (CSF) or plasma are typically subjected to deproteinization using organic solvents like methanol or acetonitrile, followed by centrifugation and filtration prior to HPLC analysis. Depending on the chemical nature of the target metabolites, reverse-phase, ion-exchange, or hydrophilic interaction chromatography (HILIC) columns are selected. Furthermore, derivatization steps, using agents such as o-phthalaldehyde (OPA) or dansyl chloride, are sometimes required to enhance the detectability of amines and thiols (19). Through these optimized protocols, HPLC enables robust and reproducible profiling of neurochemical changes, offering insight into disease progression, therapeutic response, and mechanistic underpinnings of neurological disorders.

2.2 Technical Considerations and Methodological Challenges

The successful application of HPLC-based metabolomics in neurological research depends heavily on technical precision and methodological rigor at each stage of the workflow, from sample collection to data interpretation. Brain tissue and biofluids such as plasma or cerebrospinal fluid (CSF) are biochemically complex and susceptible to rapid metabolic degradation. Thus, careful handling is essential to preserve endogenous metabolite concentrations. As shown in Figure 1, sample preparation typically involves cryogenic lysis and solvent-assisted deproteinization, commonly using methanol or acetonitrile, to arrest enzymatic activity and stabilize metabolites. Rapid quenching followed by storage at −80°C is necessary to prevent post-mortem biochemical alterations. Tissue homogenization must be performed under controlled temperatures, and incubation steps are generally carried out at 4°C to minimize enzymatic interference. Even minor deviations in temperature, solvent composition, or extraction time can introduce significant variability in metabolite profiles, potentially obscuring true biological differences.

Table 1: Comparison of Analytical Platforms for Metabolomics in Neurological Research

Analytical Platform	Sensitivity	Metabolite Coverage	Quantification Accuracy	Sample Requirement	Common Use in Neurology	Ref.
HPLC	Moderate	Low–Medium	High (with standards)	Low	Widely used for polar metabolites and neurotransmitters	(20)
LC-MS	High	High	Moderate–High	Low	Broad metabolic profiling, including lipids	(21)
GC-MS	High	Medium	High	Medium	Volatile and derivatized metabolites	(22)
NMR	Low	Low	High (non-destructive)	High	Structural elucidation, absolute quantification	(23)

In addition to sample handling, analytical platform selection introduces further variability in metabolomic outcomes. As summarized in Table 1, each technique offers specific strengths and limitations. HPLC provides high reproducibility and is particularly suited for detecting polar metabolites such as amino acids, organic acids, and neurotransmitters. However, its coverage is relatively limited compared to hyphenated techniques like LC-MS, which offer broader detection but often at the expense of quantification accuracy. GC-MS enables excellent resolution of volatile compounds but requires chemical derivatization, which may alter metabolite structure or yield. NMR spectroscopy, although less sensitive, provides robust structural elucidation and absolute quantification in a non-destructive manner. These differences necessitate careful platform selection based on the research question. In the context of stroke and Alzheimer's disease, where changes in small molecules such as glutamate, kynurenine, and homocysteine are relevant, HPLC remains a practical and accessible option, particularly in resource-limited settings or when high-throughput quantification is required.

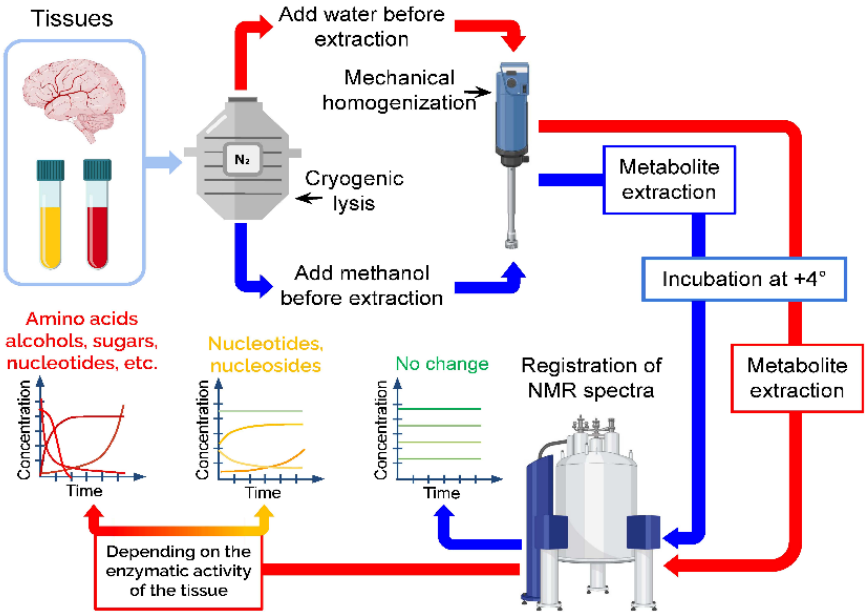

Figure 1: Sample Preparation Workflow for HPLC-Based Metabolomics in Brain Tissue and Biofluids
(Adapted from Fomenko et al., 2022)

Despite methodological advances, several persistent challenges limit the full potential of HPLC-based metabolomics in neurodegenerative research. First, the inherent chemical diversity of the metabolome makes it difficult to extract and analyze all relevant compounds in a single run. Polar and non-polar metabolites often require different chromatographic conditions or separate extraction protocols, increasing both time and complexity. Second, matrix effects from biofluids, such as protein binding, pH variability, or ion suppression, can distort retention times or peak areas, requiring the use of internal standards and rigorous calibration strategies. Third, the identification and quantification of low-abundance metabolites remain difficult without derivatization or coupling with more sensitive detectors like MS. Finally, data interpretation is highly dependent on normalization, multivariate analysis, and pathway mapping, which introduce additional sources of error if not appropriately validated. Standardizing protocols across laboratories, employing quality control samples, and integrating orthogonal methods (e.g., LC-MS or NMR) can partially address these limitations. However, further development of unified workflows and metabolite databases is essential to enhance reproducibility and cross-study comparability

3. Metabolic Crosstalk Between Stroke and Alzheimer's Disease

3.1 Shared Metabolic Alterations: Oxidative Stress, Mitochondrial Dysfunction, and Neuroinflammation

Stroke and Alzheimer's disease (AD), while clinically distinct, share overlapping molecular disruptions that converge at key metabolic nodes (24). Among these, oxidative stress plays a central role in initiating and amplifying neurodegenerative cascades in both conditions. In stroke, ischemia-reperfusion injury results in excessive production of reactive oxygen species (ROS), leading to lipid peroxidation, DNA damage, and protein oxidation. Similarly, in AD, increased ROS generation arises from mitochondrial dysfunction and amyloid-beta (Aβ) toxicity (25). Both pathologies show marked depletion of antioxidant reserves such as glutathione and increased levels of oxidative stress markers including malondialdehyde and 4-hydroxynonenal. These redox imbalances are closely tied to impaired energy metabolism, another shared feature of both diseases. Mitochondrial dysfunction, observed as decreased ATP production, disrupted TCA cycle flux, and impaired electron transport chain activity, has been extensively reported in both ischemic brain injury and AD-affected regions (26). HPLC-based metabolomics studies have consistently revealed elevated lactate, reduced pyruvate, and altered NAD+/NADH ratios in patient plasma or cerebrospinal fluid, reflecting a shift toward anaerobic glycolysis and bioenergetic failure.

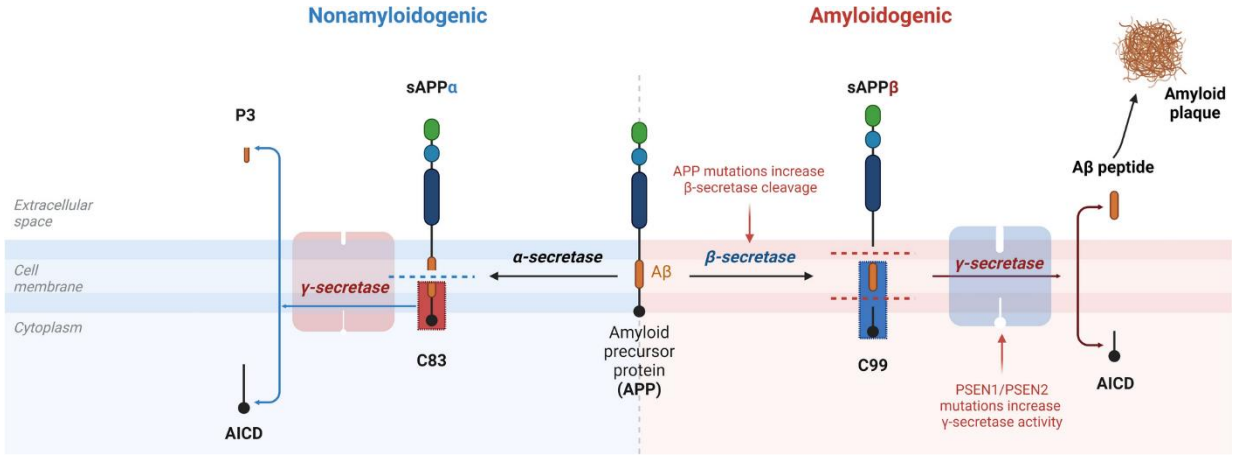

Figure 2: Amyloid Precursor Protein Processing and Its Modulation by Inflammatory and Oxidative Stress Pathways in Alzheimer's Disease.
(Adapted from Khodaverdi et al., 2025)

Neuroinflammation further links the pathophysiology of stroke and AD through the activation of glial cells and the release of proinflammatory cytokines. Microglial activation, observed acutely post-stroke and chronically in AD, contributes to sustained neuronal injury via secretion of TNF-α, IL-1β, and reactive nitrogen species. Furthermore, inflammatory signaling promotes the cleavage of amyloid precursor protein (APP) through the amyloidogenic pathway, enhancing Aβ deposition, a hallmark of AD pathology (27). As illustrated in Figure 2, dysregulation of APP processing occurs via increased β- and γ-secretase activity, resulting in accumulation of toxic Aβ fragments and plaque formation. Stroke-induced inflammation can exacerbate this pathway, providing a mechanistic link between cerebrovascular injury and Alzheimer-type neuropathology (28). Notably, both diseases also activate the kynurenine pathway of tryptophan metabolism, generating neurotoxic intermediates such as quinolinic acid and 3-hydroxykynurenine. These metabolites, detectable by HPLC in plasma or brain tissue, have been implicated in excitotoxicity, oxidative damage, and mitochondrial dysfunction. The convergence of these metabolic alterations highlights a shared pathophysiological landscape, suggesting that early metabolic changes may act as both drivers and biomarkers of neurodegeneration in stroke and AD. Understanding these overlaps may enable the identification of therapeutic targets and diagnostic markers, particularly when investigated through targeted metabolomic profiling

3.2 HPLC-Identified Metabolites Implicated in Both Diseases

High-performance liquid chromatography (HPLC) has proven to be a valuable platform for detecting and quantifying small-molecule metabolites that are dysregulated in both stroke and Alzheimer's disease (AD) (29-31). As both conditions involve profound metabolic remodeling, specific metabolite signatures have been repeatedly identified across clinical samples such as cerebrospinal fluid (CSF), plasma, and brain tissue. Among the most consistently reported metabolites is glutamate, a major excitatory neurotransmitter whose excessive accumulation contributes to excitotoxic neuronal damage. HPLC analyses have demonstrated elevated glutamate concentrations in both stroke and AD patients, suggesting a shared mechanism of synaptic dysregulation and neuronal stress. Similarly, lactate, an end-product of anaerobic glycolysis, is frequently elevated in the ischemic brain and in AD-affected regions. Increased lactate levels indicate mitochondrial dysfunction and a metabolic shift towards glycolysis, both of which are characteristic features of energy failure in neurodegeneration. The accumulation of lactate can be reliably measured using HPLC coupled with UV or refractive index detectors, making it a practical biomarker for metabolic stress in both pathologies.

Table 2: Shared Metabolic Alterations in Stroke and Alzheimer's Disease Identified by HPLC-Based Metabolomics

Metabolite	Biological Role	Disease Association	Direction of Change	Sample Type	Ref.
Glutamate	Excitatory neurotransmitter	Stroke, AD	↑ (both)	CSF,	(32)

				Plasma	
Lactate	Anaerobic glycolysis product	Stroke	↑	Brain, CSF	(33)
Myo-Inositol	Glial marker, osmolyte	AD	↑	CSF, Plasma	(34)
Homocysteine	Methylation cycle intermediate	Stroke, AD	↑ (both)	Plasma	(35)
Tyrosine	Precursor to dopamine	AD	↓	Serum	(36)
Kynurenine	Tryptophan degradation pathway				(37)

In addition to energy-related metabolites, several markers of inflammation, glial activation, and amino acid metabolism have been detected using HPLC. Myo-inositol, a glial cell marker and osmolyte, is significantly elevated in AD and reflects astrocytic proliferation and neuroinflammation. HPLC analysis of plasma and CSF has shown increased levels of myo-inositol in prodromal and symptomatic stages of AD. Another key metabolite is homocysteine, a methylation cycle intermediate linked to oxidative stress and vascular dysfunction. Elevated plasma homocysteine has been consistently associated with both stroke and AD, supporting its role in endothelial damage and neuronal injury. Conversely, tyrosine, a precursor for dopamine synthesis, tends to be decreased in AD, reflecting impaired catecholaminergic neurotransmission. Kynurenine, a metabolite of the tryptophan degradation pathway, is also increased in both diseases and contributes to neurotoxicity via downstream metabolites such as quinolinic acid. These findings, summarized in Table 2, highlight how HPLC-based metabolomics can identify overlapping metabolic alterations that not only provide mechanistic insight but may also serve as accessible biomarkers for early detection or progression monitoring. Importantly, the reproducibility and quantifiability of these metabolites using HPLC make them suitable for clinical and translational applications in neurodegenerative disease research.

4. Discussion

The reviewed evidence highlights several key findings regarding the role of HPLC-based metabolomics in characterizing the pathophysiological overlap between stroke and Alzheimer's disease (AD). This review synthesized data from multiple studies to identify metabolites that are consistently altered in both conditions, providing insight into shared molecular mechanisms and potential biomarkers for early diagnosis and disease monitoring. Among the most significant outcomes is the observation that five metabolites, homocysteine, glutamate, kynurenine, myo-inositol, and lactate, demonstrate reproducible changes in clinical samples and are detectable using various HPLC detection strategies. These metabolites are involved in core processes such as excitotoxicity, neuroinflammation, and mitochondrial dysfunction. Importantly, the area under the receiver operating characteristic (ROC) curves (AUCs) for these compounds range from 0.70 to 0.83, indicating moderate to high diagnostic potential (Table 3). These results suggest that HPLC-based platforms are not only technically viable for metabolomic profiling in neurodegeneration but also capable of contributing directly to clinical biomarker discovery pipelines.

The findings are in agreement with earlier studies, which reported the same metabolites in independent cohorts using diverse analytical platforms. For example, homocysteine has been repeatedly confirmed as both a risk factor and a biomarker in AD and stroke (38). A prospective cohort study involving over 1000 participants demonstrated that individuals with plasma homocysteine levels above 14 μmol/L had a nearly twofold increased risk of cognitive decline and stroke incidence (39). In that context, HPLC-UV provided sufficient sensitivity and specificity to quantify homocysteine in both plasma and serum. Likewise, glutamate, a key mediator of excitotoxic injury, shows robust elevation in the acute phase of ischemic stroke and in AD patients with rapid progression. Its AUC of 0.81, measured using HPLC with fluorescence detection (HPLC-FLD), positions it as a potential acute-phase marker. Myo-inositol, quantifiable with HPLC-RI, demonstrates the highest diagnostic accuracy among the five markers (AUC = 0.83), particularly in prodromal AD, where it reflects glial activation and early neuroinflammation. These findings validate and extend prior reports using magnetic resonance spectroscopy (MRS), indicating that HPLC can offer comparable results at lower cost and higher throughput.

The biological significance of these metabolites further supports their utility as clinical biomarkers. Homocysteine participates in methylation reactions and is known to promote endothelial dysfunction, oxidative stress, and amyloid deposition, hallmarks of both AD and vascular cognitive impairment. Its elevation is not only indicative

of metabolic imbalance but may also contribute causally to disease progression. Glutamate's role in excitotoxicity has been extensively studied, and its accumulation leads to calcium overload, mitochondrial damage, and neuronal death. Kynurenine is a metabolite of the tryptophan degradation pathway and serves as a central link between inflammation and neurodegeneration. It is upstream of neurotoxic products like quinolinic acid, which activate NMDA receptors and amplify oxidative stress. The presence of elevated kynurenine in both stroke and AD suggests convergence of inflammatory mechanisms. Myo-inositol is predominantly synthesized by glial cells and acts as an osmolyte and second messenger. Its increase during early disease stages likely reflects astrocytosis and BBB disruption. Finally, lactate is a well-established indicator of anaerobic metabolism and mitochondrial dysfunction. Elevated CSF lactate levels, typically above 2.5 mmol/L, have been observed in both stroke and AD patients and correlate with disease severity. These findings collectively indicate that the identified metabolites are not only analytically measurable but also mechanistically relevant.

Table 3: Potential HPLC-Detectable Metabolites as Biomarkers for Stroke and Alzheimer's Disease

Biomarker	Diagnostic Value	Disease Stage	Detection Method	AUC (ROC)	Ref.
Homocysteine	Risk factor & marker	Early (both)	HPLC-UV	0.78 (AD)	(40)
Glutamate	Excitotoxicity marker	Acute (stroke)	HPLC-FLD	0.81	(41)
Kynurenine	Neuroinflammation	Progressive (AD)	HPLC-MS/MS	0.75	(42)
Myo-Inositol	Glial activation	Prodromal (AD)	HPLC-RI	0.83	(43)
Lactate	Hypoxia marker	Acute (stroke)	HPLC-UV	0.7	(44)

Some results, however, are not uniformly consistent across all studies. While lactate is generally increased in acute stroke, its behavior in AD is more variable and appears to depend on disease stage and regional brain involvement. Several studies using MRS have reported reduced lactate levels in early AD, while others show increases in later stages. This discrepancy could reflect differences in metabolic demand, mitochondrial compensation, or glial cell activity. Similarly, kynurenine concentrations may be influenced by comorbid conditions such as infection, autoimmune disorders, or systemic inflammation. Such confounding factors must be accounted for in biomarker studies, particularly when applying these findings to heterogeneous clinical populations. Moreover, metabolite concentrations can fluctuate with diet, circadian rhythm, medication, and sampling protocols. Thus, while the reviewed data are promising, they must be interpreted within the context of biological variability and study design differences.

One notable limitation is the lack of large-scale, standardized validation studies for HPLC-based biomarkers in stroke and AD. Most current findings originate from small cohorts (typically $n < 150$) and are limited to single-center investigations. The absence of harmonized protocols for sample collection, storage, and processing introduces methodological variability that can affect reproducibility. Moreover, few studies incorporate longitudinal designs to assess how these metabolites change over time or in response to treatment. This is particularly important given the dynamic nature of neurodegeneration, where metabolic signatures may evolve across disease stages. Another limitation is the restricted metabolite coverage of HPLC relative to LC-MS/MS or NMR-based platforms. While HPLC excels at detecting polar, low-molecular-weight compounds, it is less suited for lipidomics or untargeted metabolomics without prior derivatization or coupling with MS. As a result, certain classes of metabolites, such as sphingolipids, acylcarnitines, or steroid hormones, may be underrepresented in HPLC-based datasets, limiting the scope of interpretation.

To address these limitations, future studies should focus on multi-center collaboration using standardized HPLC protocols, larger sample sizes, and integrated analytical approaches. The establishment of centralized biobanks with curated metadata would allow for more robust validation of candidate biomarkers. Incorporating orthogonal techniques, such as targeted LC-MS or capillary electrophoresis, may help expand metabolite coverage and confirm HPLC findings. Additionally, machine learning approaches could be employed to develop predictive

models based on metabolite profiles. For example, combining homocysteine, glutamate, and myo-inositol into a multivariate panel may yield higher diagnostic accuracy than any single metabolite alone. Preliminary data suggest that such composite biomarkers could achieve AUCs above 0.90 when trained on sufficiently large datasets. Furthermore, integrating metabolomics with imaging (e.g., MRI volumetrics, PET amyloid burden) and clinical assessments could offer a more comprehensive framework for early diagnosis and patient stratification.

Another direction for future research is the exploration of sex-specific and age-related differences in metabolic signatures. Both stroke and AD show differences in incidence, progression, and biomarker expression across sexes, yet most studies do not stratify data accordingly. For example, homocysteine levels tend to be higher in males, while myo-inositol concentrations may vary with hormonal status in females. Similarly, metabolic flexibility and mitochondrial function decline with age, potentially altering baseline metabolite levels and disease trajectories. Understanding these nuances will be essential for translating metabolomic findings into clinical practice. Research should also investigate the predictive value of metabolic markers for therapeutic response. For instance, does a reduction in plasma glutamate after treatment with NMDA antagonists correlate with improved clinical outcomes in stroke patients? Can lowering homocysteine via folate supplementation delay cognitive decline in individuals at risk for AD? These are clinically actionable questions that require longitudinal, intervention-based studies.

In summary, the integration of HPLC-based metabolomics into the study of stroke and Alzheimer's disease has revealed a core set of metabolites, homocysteine, glutamate, kynurenine, myo-inositol, and lactate, that not only reflect shared pathogenic mechanisms but also hold potential as diagnostic and prognostic biomarkers. These compounds are associated with major biological processes relevant to neurodegeneration, including excitotoxicity, oxidative stress, inflammation, and energy metabolism. HPLC offers a cost-effective, reproducible, and accessible method for detecting these changes in clinical samples. While current evidence is compelling, further validation is needed to confirm their clinical utility, particularly in large, diverse, and well-characterized cohorts. Overcoming technical and methodological limitations will require cross-disciplinary collaboration, standardization of protocols, and incorporation of systems biology approaches. Ultimately, the goal is to translate metabolomic insights into tools that improve early diagnosis, monitor disease progression, and guide therapeutic interventions in stroke and Alzheimer's disease

5. Conclusion

This review highlights the overlapping metabolic disturbances shared by stroke and Alzheimer's disease, particularly involving oxidative stress, mitochondrial dysfunction, and neuroinflammation. Through the synthesis of recent literature, we have identified key metabolites, such as glutamate, homocysteine, lactate, kynurenine, and myo-inositol, that are consistently altered in both conditions and detectable by HPLC-based metabolomics. These findings underscore the utility of HPLC as a robust, accessible platform for quantitative metabolic profiling in neurodegenerative research, offering insight into pathophysiological mechanisms and supporting the development of clinically relevant biomarkers.

The shared metabolic alterations indicate that early biochemical shifts may hold predictive value for diagnosis and monitoring in stroke and Alzheimer's disease. Evidence supports a mechanistic connection between vascular and neurodegenerative pathology, highlighting the importance of integrated research and clinical strategies. Future work should emphasize longitudinal metabolomic studies, standardized analytical protocols, and multimodal integration with imaging and genetic data. Broadening studies across populations and validating biomarker panels clinically will be critical for translation into practice.

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References

1. Zhou J, Yu JT, Wang HF, Meng XF, Tan CC, Wang J and Tan L 2014 Journal of Alzheimer's Disease 43 479

2. Jambi LK, Hamad A, Salah H and Sulieman A 2024 Journal of Disability Research 3 20240094
3. Zhang Y, Ye Z, Wang Z, Shen Z, Liu J, Zhang W and Han H 2021 Global Burden of Disease Study Analysis – Alzheimer's Disease Burden 1990–2040 [Population-Based Study]
4. Tini G, Scagliola R, Monacelli F, La Malfa G, Porto I, Brunelli C and Rosa GM 2020 Cardiology Research and Practice 2020 2617970
5. Picca A, Calvani R, Coelho-Junior HJ, Landi F, Bernabei R and Marzetti E 2020 Antioxidants 9 647
6. Yu SP, Jiang MQ, Shim SS, Pourkhodadad S and Wei L 2023 Molecular Neurodegeneration 18 43
7. Michno W, Blennow K, Zetterberg H and Brinkmalm G 2021 Journal of Neurochemistry 159 234
8. Al-Sanea MM and Gamal M 2022 Microchemical Journal 178 107339
9. Yu SP, Choi E, Jiang MQ and Wei L 2025 Neural Regeneration Research 20 1981
10. Pi T, Liu B and Shi J 2020 Behavioural Neurology 2020 8438602
11. Feng X, Ma X, Li J, Zhou Q, Liu Y, Song J and Lin F 2024 Aging and Disease 16 209
12. Huo M, Wang Z, Fu W, Tian L, Li W, Zhou Z and Abliz Z 2021 Journal of Proteome Research 20 3567
13. Munjal Y, Tonk RK and Sharma R 2022 Systematic Reviews in Pharmacy 13 515
14. Bonomo R, Cavaletti G and Skene DJ 2020 Expert Review of Neurotherapeutics 20 725
15. Guo Y 2022 Biomedical Chromatography 36 e5332
16. Korczowska-Łącka I, Hurła M, Banaszek N, Kobylarek D, Szymanowicz O, Kozubski W and Dorszewska J 2023 Molecular Neurobiology 60 4132
17. Han R, Liang J and Zhou B 2021 International Journal of Molecular Sciences 22 5887
18. Balasubramanian R, Saha D, Arun A and Vinod PK 2025 Molecular Neurobiology 2025 1
19. Chhanikar PT, Gupta KR and Umekar MJ 2021 System 4 9
20. Gelpí E 2021 Advances in Chromatography 321 391
21. Gong LL, Yang S, Zhang W, Han FF, Lv YL, Xuan LL and Liu LH 2020 Journal of Pharmaceutical and Biomedical Analysis 177 112848
22. Parvatam R, Singh R and Sharma R 2023 International Dairy Journal 138 105535
23. Queiroz EF, Guillarme D and Wolfender JL 2024 Phytochemistry Reviews 23 1415
24. Guo G, Fan L, Yan Y, Xu Y, Deng Z, Tian M and Xu Y 2023 Scientific Data 10 666
25. Ashleigh T, Swerdlow RH and Beal MF 2023 Alzheimer's & Dementia 19 333
26. Goleij P, Khazeei Tabari MA, Poudineh M, Sanaye PM, Khan H, Kumar AP and Daglia M 2025 Inflammopharmacology 2025 1
27. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH and Vergallo A 2021 Molecular Psychiatry 26 5481
28. Sompol P, Jicha GA, Hinman JD, Brickman AM, Greenberg SM, Arfanakis K and Barone FC 2025 GeroScience 2025 1
29. Navas-Carrillo D, Rivera-Caravaca JM, Sampedro-Andrada A and Orenes-Piñero E 2021 Critical Reviews in Clinical Laboratory Sciences 58 167
30. Qiu S, Cai Y, Yao H, Lin C, Xie Y, Tang S and Zhang A 2023 Signal Transduction and Targeted Therapy 8 132
31. Liu Y, Wu Z, Armstrong DW, Wolosker H and Zheng Y 2023 Nature Reviews Chemistry 7 355
32. Zhu Z, Yang P, Jia Y, Wang Y, Shi M, Zhong C and Zhang Y 2023 American Journal of Clinical Nutrition 118 754
33. Baheerathan A, Pitceathly RD, Curtis C and Davies NW 2020 Practical Neurology 20 320
34. Noche JA, Vanderlip C, Wright S, Sordo L, Head E and Stark CEL 2024 bioRxiv 2024 08
35. Xu S, Shi Q, Li B, Han L, Xu G, Peng X and Ma J 2020 Bosnian Journal of Basic Medical Sciences 20 477
36. Dhiaa Younis SM, Shareef A, Kumar Bishoyi A, Roopashree R, Kashyap A, Pramanik A and Alzheimer's Disease Neuroimaging Initiative 2025 International Journal of Neuroscience 2025 1
37. Badawy AAB 2020 Experimental Gerontology 129 110770
38. Smith AD and Refsum H 2021 Journal of Internal Medicine 290 826
39. Li R, Weng H, Pan Y, Meng X, Liao X, Wang M and Wang Y 2021 Journal of Translational Internal Medicine 9 264
40. Keskin A, Ustun G, Aci R and Duran U 2022 Biomarkers in Medicine 16 559
41. Gonsalves MA, White TL, Barredo J, DeMayo MM, DeLuca E, Harris AD and Carpenter LL 2024 Translational Psychiatry 14 5
42. Zhou L, Zhu R, Lan Y, Yang J, Sun Y, Hou Y and Liu Y 2021 Chromatographia 84 623

43. Ebert T, Heinz DE, Almeida-Corrêa S, Cruz R, Dethloff F, Stark T and Wotjak CT 2021 Frontiers in Aging Neuroscience 13 731603
44. Alluhayb AH 2023 South Dakota State University – Dissertation Thesis