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Metabolomics assays applied to schistosomiasis studies: a scoping review

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Abstract

Background Metabolomics is an analytical approach utilized to explore the metabolic profiles of biological systems. This process typically involves the application of techniques such as nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). In the case of schistosomiasis, metabolomics has been employed to identify potential diagnostic biomarkers, examine the host's metabolic response, and explore more effective therapeutic strategies. The objective of this scoping review is to assess the scope and characteristics of metabolomic research on schistosomiasis conducted over the past decade.

Methods To identify relevant original publications, a systematic search was conducted in the PubMed and Web of Science databases using the following search terms: ("Metabolomics" OR "Metabolomic" OR "Metabonomics" OR "Metabonomic") AND ("Schistosomiasis" OR "*Schistosoma*"). These terms were applied to the titles and abstracts of the publications, with a focus on the period from January 2014 to December 2024.

Results The initial search yielded 48 articles. However, after a thorough evaluation of the abstracts, 14 articles were selected based on the established inclusion criteria. The selection process is visually depicted in the PRISMA flowchart. The majority of the studies included in this review were conducted in China (7 articles) and Brazil (3 articles). Approximately two-thirds of the studies utilized animal models, with serum serving as biofluid in 66% of the studies. The findings of this scoping review suggest that chromatographic techniques coupled with mass spectrometry are predominantly used in metabolomic research on schistosomiasis, accounting for 75% of the studies. The identified metabolites are associated with metabolic pathways related to glycolysis, the TCA cycle, and amino acid metabolism, as well as demonstrating alterations resulting from intestinal dysbiosis observed during the infection. As exemplified by succinate and citrate, which are present in the alterations of energy pathways in *Schistosoma mansoni* and *Schistosoma japonicum* species. The serum levels of these metabolites are modified, reflecting the host's metabolic and immunological responses induced by the infections.

Conclusions These studies successfully elucidated the metabolic pathways and key metabolites involved in schistosomiasis. The findings are significant for the future identification of diagnostic biomarkers and the development of novel antiparasitic agents targeting *Schistosoma* species.

Clinical trial Not Applicable.

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Keywords Metabonomics, Schistosomiasis, Biomarkers, Diagnostic technique

Background

Metabolomics is an analytical approach used to characterize and quantify metabolites in biological systems, providing insights into metabolic states under various physiological and pathological conditions [1, 2]. This approach is based on the principle of homeostasis, where external disturbances alter endogenous metabolite profiles, serving as fingerprint for these changes. Some researchers use the term "metabonomics" to emphasize the identification of metabolite profiles correlated with the biochemical state of samples, without requiring absolute quantification [3–5].

Metabolomics has made significant advancements over the past decades, offering valuable insights into the metabolic profiles of organisms and their potential applications in health and disease. However, several challenges continue to limit the full realization of its potential. One major hurdle lies in the lack of standardization across methodologies, which affects the reproducibility and comparability of results. Factors such as biological variability, complex data processing, and technical biases introduced during sample collection, preparation, and analysis further complicate the field. Addressing these issues is critical to enhancing the reliability of metabolomics studies [6, 7].

Therefore, the Metabolomics Standards Initiative (MSI) has emerged as a cornerstone effort to establish robust guidelines and standards for metabolomics research. MSI focuses on ensuring consistency and transparency in data acquisition, analysis, and reporting. It promotes the use of standardized protocols, data formats, and repositories, which are essential for fostering collaboration and enabling data sharing among researchers. These efforts are pivotal in driving progress and reliability in metabolomics, paving the way for its application in diverse areas of science and medicine [8, 9].

Despite these initiatives, a key limitation remains the translation of metabolomics discoveries into clinical practice. Currently, very few metabolic biomarkers and panels have been validated and implemented in clinical settings. This is due to several reasons, including the stringent regulatory requirements for clinical validation, high costs of large-scale studies, and challenges in demonstrating clinical utility and cost-effectiveness. Additionally, the complexity of metabolomic data often requires advanced computational tools and expertise, which can represent a barrier to the widespread dissemination of these techniques [10, 11].

Schistosomiasis is a neglected tropical disease characterized by its debilitating effects, caused by specific trematodes of the genus *Schistosoma* [12]. This disease affects over 250 million individuals globally, with a disproportionate burden in tropical and developing regions [13]. Transmission occurs through direct contact with freshwater bodies contaminated with cercariae, the infectious larval stage of the parasite [14]. While the administration of the anthelmintic drug.

Praziquantel (PZQ) has been effective in reducing both the prevalence and intensity of schistosomiasis infections through mass treatment programs over the past three decades, low-intensity infections persist, particularly in areas with poor sanitation and inadequate hygiene facilities. These persistent infections highlight the need for continued efforts in surveillance, prevention, and control strategies to combat schistosomiasis in endemic regions [15].

The distribution of schistosomiasis species exhibits significant variability contingent upon geographic location and each species affects different organic systems. Among the six recognized species of schistosomes that infect humans, *Schistosoma haematobium* (S. *haematobium*) and *Schistosoma mansoni* (*S. mansoni*) serve as the principal etiological agents of urogenital and hepatointestinal schistosomiasis, respectively [16]. Timely and accurate diagnosis of schistosomiasis is crucial for facilitating effective treatment and for interrupting the disease's natural progression before the onset of its most severe manifestations [17, 18].

In the field of metabolomics, particularly in the context of parasitic infections, techniques such as capillary electrophoresis coupled with mass spectrometry (CE-MS), liquid chromatography coupled with mass spectrometry (LC-MS), and nuclear magnetic resonance (NMR) spectroscopy are widely used to examine dynamic alterations in metabolite profiles. These infections often disrupt key metabolic pathways, including energy metabolism, immune responses, glucose uptake, lipid biosynthesis, amino acid metabolism, and the metabolism of the gut microbiota. Specifically, schistosomiasis induces significant metabolic changes that generate distinct biochemical profiles, which can be associated with biochemical status allowing schistosomiasis diagnosis [18, 19].

This article aims to review metabolomic studies on schistosomiasis over the past decade, highlighting analytical platforms such as MS, NMR spectroscopy, and chromatographic techniques used to investigate metabolic alterations. By reviewing the landscape of these studies, this article seeks to contribute to a deeper insight into the metabolic mechanisms underlying schistosomiasis and, in turn, provide valuable information for future research as well as the development of more effective diagnostic and therapeutic strategies.

Materials and methods

This scoping review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [20], which was developed by the Joanna Briggs Institute [21]. The research question was meticulously formulated, employing broad terminology within its components to avoid imposing overly stringent restrictions on the inclusion criteria. The central research question articulated was: "What is the extent and nature of metabolomic studies on schistosomiasis conducted globally over the past decade?" This methodological approach facilitated the inclusion of diverse perspectives and the potential contributions of metabolic studies on schistosomiasis within a global context.

Search strategy

The investigation for original and comprehensive publications was conducted using two prominent electronic databases: PubMed and Web of Science. The temporal scope of the analysis encompassed the years 2014 to 2024. A systematic search strategy was implemented utilizing Boolean operators "AND" and "OR" to facilitate the combination of relevant descriptors. The selected key terms for this search included: ("Metabolomics OR Metabolomic OR Metabonomics OR Metabonomic") AND ("Schistosomiasis OR *Schistosoma*"). These terms were specifically searched within the titles and abstracts of the identified works, covering the period from January 1, 2014, to December 31, 2024.

Eligibility criteria

For inclusion in this review, studies were required to conduct comprehensive metabolomic analyses utilizing samples from humans or animals infected with schistosomiasis, including cases of co-infection. Eligible studies needed to employ at least one of the following analytical techniques: Nuclear Magnetic Resonance (NMR), Liquid Chromatography-Mass Spectrometry (LC-MS), Gas Chromatography-Mass Spectrometry (GC-MS), or Electrospray Ionization Mass Spectrometry (EC-MS). The focus of these studies should be on identifying metabolite alterations in infected subjects, as well as exploring promising models for the diagnosis, prognosis, or staging of schistosomiasis. Exclusion criteria comprised review articles, gray literature—including book chapters, theses, dissertations, reports, and similar documents—and studies that involved direct examinations of the parasite or treatments with a primary research focus.

Data selection

The articles identified through the searches were compiled, and key information—including the title, abstract, authors, publication year, and journal—was exported into an Excel spreadsheet, from which duplicate entries were subsequently removed. Following this, two reviewers (M.L.R. and A.R.S.G.) independently conducted a screening process by reviewing the titles and abstracts to assess eligibility based on the predetermined criteria. Instances of disagreement between the reviewers were addressed through discussion, culminating in a consensus. In cases where consensus could not be reached, a third reviewer (R.O.S.) was involved in the final decision-making process.

Data extraction and synthesis of results

Data extraction was conducted by the same reviewers responsible for the study selection. The included studies were thoroughly read in their entirety, and the following information was systematically collected: country and year of publication, study population, species responsible for the infection, sample size, sample type, analytical techniques employed, multivariate statistical analyses used, main metabolites and metabolic pathways identified, results, limitations, and conclusions.

This information was synthesized and discussed in subsequent sections. This methodological approach aims to provide a comprehensive understanding of research trends and focal areas within the field, highlighting the evolution of literature over time and the specific nuances associated with various methodologies and parasitic species.

Results

The searches conducted on PubMed and Web of Science yielded 36 and 47 articles, respectively, resulting in a total of 83 articles. Following the removal of duplicates, 48 articles were retained for the selection process. Based on the established exclusion and eligibility criteria, 14 articles were ultimately selected for analysis. A detailed depiction of the article selection process is presented in Fig. 1.

Characteristics of selected studies

The studies selected for inclusion in this review, in alignment with its objective, focus on two primary themes: metabolomics and schistosomiasis. Essential details, such as the study location, participant characteristics (human or animal), sample size, type of samples analyzed, as well as the analytical techniques and statistical strategies employed, are critical for offering a comprehensive overview of the progress in this area of research over the past decade. These factors are integral to understanding methodological advancements and the evolution of the field in relation to schistosomiasis [22–35].

The majority of the selected studies were conducted in Asia ($n = 9$). Additionally, three studies were conducted in Brazil [22–24], two studies were carried out in Thailand

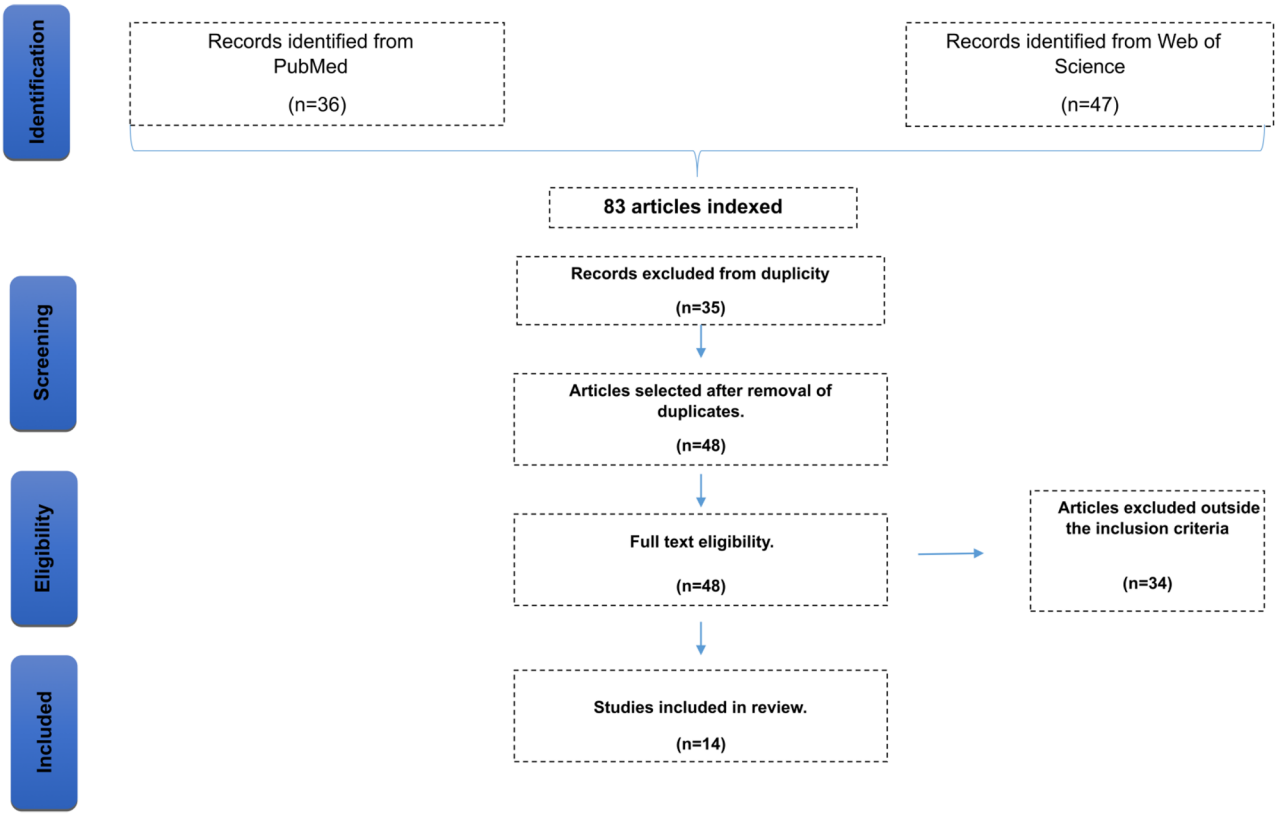

Fig. 1 The PRISMA diagram for the scoping review, using the terms ("Metabolomics OR Metabolomic OR Metabonomics OR Metabonomic") AND ("Schistosomiasis OR *Schistosoma*"), published between Jan/2014 and Dec/2024

[26, 35].One study in Botswana [25], and another in The United State of America [33], while seven studies were performed in China [27–32, 34].

Regarding the sample size of the selected studies, five studies were conducted using human samples [22, 23, 25, 32, 34]while nine studies utilized animal models [24, 26–31, 33, 35]. Among the human studies, three exhibited relatively small sample sizes, ranging from 40 to 65 participants. However, the study by Ndolo et al. [25], was an exception, as it involved a much larger cohort of 527 children, investigating *Schistosoma haematobium (S. haematobium)* infection. In contrast, the studies involving animal models, primarily using mice, showed greater variability in sample sizes, ranging from 9 to 70 participants, with a median of 28 samples (IQR: 15–50).

The primary species of *Schistosoma* responsible for causing schistosomiasis include *S. haematobium*, *S. mansoni* e *S. japonicum* [12]. However, in addition to these commonly studied species, infection by *Schistosoma Mekongi* was also investigated in two of the studies selected for this review. Only a single study simultaneously analyzed three species (*S. mansoni*, *S. japonicum*, and *S. mekongi*) during the early stages of infection [35].

Given the variety of sample types, including urine, feces, serum, tissues, and even bone marrow, a range of analytical techniques were employed in the selected studies. LC-MS was the most commonly used technique, present in eight of the studies reviewed, [26,27,28,29,30,32,34,35]; followed by NMR, used in three studies [22, 23, 31], and GC-MS also employed in three studies [24, 25, 33]. In summary, 75% of the selected studies utilized chromatography in conjunction with mass spectrometry, while 25% used NMR spectroscopy without the use of a chromatographic separation tool.

Regarding multivariate statistical analyses, nearly all the selected studies employed Principal Component Analysis (PCA) as an unsupervised technique, alongside Partial Least Squares Discriminant Analysis (PLS-DA) or Orthogonal PLS-DA (OPLS-DA) as supervised methods (Table 1). Additionally, HeatMaps were used as an exploratory analysis in five studies [28, 30, 33–35]. These pattern recognition techniques enabled the comprehensive identification and evaluation of the key metabolites responsible for the observed discriminatory patterns in the metabolomic data.

Table 1 presents a summary of the characteristics of the 14 studies evaluated. It includes the following variables: the number of samples (n), the model organism (human or animal), the sample type, the worm species, the country of study, the analytical technique employed,

Table 1 Information for this scoping review was extracted from fourteen articles retrieved from PubMed and Web of Science

Study	Total (*n*=)	Human or animal model	Sample	Worm specie	States	Analytical technique	Multivariate Statistical Analysis	Identified Metabolites
GOUVEIA et al., 2017 [22]	40	Human	Serum	*S. mansoni*	Brazil	NMR	PCA/PLS-DA	Lactate; HDL
RODRIGUES et al., 2022 [23]	41	Human	Serum	*S. mansoni*	Brazil	NMR	PCA /PLS-DA	Alanine; Glycolaldehyde; N-acetylglucosamine; Valine
TAWANA-NDOLO et al., 2023 [25]	527	Human	Urine	*S.haematobium*	Botswana	GC-MS	PLS-DA	3-Chloropropionic; Heptadecyl ester
ZHOU et al., 2023 [32]	41	Human	Feces	*S. japonicum*	China	UHPLC-MS	PCA / (O)PLS-DA	2-Oleoyl-1-palmitoyl-sn-glycero-3-phosphoserine; Indoleacrylic acid; Nicotinic acid; Histidine-Leucine
Li et al.,2024 [34]	65	Human	Serum	*S. japonicum*	China	UHPLC-MS	PCA / PLS-DA/(O) PLS-DA/ Heatmap	Glycocholic acid, Gycochenodeoxycholate, Taurochenodeoxycholic acid.
HU et al., 2020 [30]	70	Mice	Serum, Urine and Tissue	*S. japonicum*	China	UHPLC-MS	PCA / (O)PLS-DA / Heatmap	Phosphatidylcholine; Colfosceril palmitate; Pimelylcarnitine
HU et al., 2017 [27]	28	Mice	Serum	*S. japonicum*	China	LC-MS	PCA / (O)PLS-DA	N-acetylglucosamine-6-phosphate; Carnitine, Amino acids
RONG et al., 2019 [28]	40	Mice	Serum	*S. japonicum*	China	UHPLC-MS	PCA / PLS-DA / Heatmap	Arachidonic acid; Glycerophospholipids, phenylalanine; linoleic acid; Sphingolipids
HUANG et al., 2020 [29]	53	Mice	Serum	*S. japonicum*	China	UHPLC-MS	PCA / PLS-DA	D-Glucuronic acid; Selenomethionine; Muramic acid; Dimethyl D-malate; N-Acetyl-D-glucosamine.
CHIENWICHAI et al., 2022 [26]	10	Mice	Serum	*S. mekongi*	Thailand	UHPLC-MS	PCA / PLS-DA	Heptadecanoyl ethanolamide; Picrotin; Theophylline
CHIENWICHAI et al.,2024 [35]	9	Mice	Feces	*S. mansoni/ S. japonicum/ S. mekongi*	Thailand	UHPLC-MS	PCA / PLS-DA/ Heatmap	25-hydroxyvitamin D2;1α-hydroxy-2β-(3-hydroxypropoxy) Vitamin D3;Ganoderic acid Md.
ZHU et al., 2017 [31]	36	Mice	Urine, Serum e Tissue	*S. japonicum*	China	NMR	PCA / OPLS-DA	Creatinine; Taurine; 3-Ureidopropionate (3-UP); Trimethylamine-N-oxide (TMAO); Hippurate; N-Acetylglutamate; Succinate; Fumarate.
LOYO et al., 2021 [24]	24	Mice	Urine	*S. mansoni*	Brazil	GC-MS	PCA	Hippurate; Malonate; Succinate; Citrate; Alanine; Lysine.
CORTES-SELVA et al., 2021 [33]	10	Mice	Bone marrow	*S. mansoni*	United States	GC-MS	PLS-DA / Heatmap	Glucose; Palmitate; Fatty acids; Cholesterol esters

the application of multivariate statistical analysis, and the metabolites identified.

Discussion

This review covered 14 studies that employed metabolic tools to investigate schistosomiasis, highlighting various metabolic pathways and metabolites with potential as biomarkers for different schistosomiasis species. The studies included both human and mice models, primarily utilizing serum and urine samples, which were analyzed using a range of analytical techniques.

Schistosomiasis occurs mainly in underdeveloped and developing countries [13] with the highest incidence observed in Africa. However, cases are also reported in other regions, including Asia, Latin America, and the Middle East [36]. The geographic distribution of schistosomiasis cases is further illustrated by the study conducted by Tawana-Ndolo [25], which evaluated 527 individuals, a sample size notably larger than that of other human-based studies included in this review.

Despite the higher incidence of *Schistosoma* cases in Africa, this review identified only one study conducted in Botswana, in contrast to the greater number of studies from countries such as China and Brazil, which focused on *S. japonicum* and *S. mansoni*. This discrepancy may be attributed to the relatively better socioeconomic conditions in China and Brazil, which could facilitate greater

research funding, infrastructure, and resources for conducting such studies [37].

Characteristics such as these, along with sample size, biofluids, analytical techniques, and multivariate analyses, will be discussed in the following section.

Samples, analytical techniques and multivariate statistical

The studies included in this review can be categorized based on the type of sample investigated. Animal studies offer the advantage of creating controlled environments in which diseases can be induced, allowing for a comprehensive investigation of metabolic implications throughout the organism. As a result, sample sizes in these studies vary depending on the conditions set by the researchers. In contrast, human studies are constrained by the number of individuals available who meet the eligibility criteria, limiting the sample size.

It is important to emphasize that sample size can be a significant limitation in metabolomic studies, as noted in the works of [23, 32]. Additionally, it is crucial to acknowledge that extrapolating findings from mice studies to humans presents challenges, given the anatomical, genetic, and physiological differences between the two species [38]. No animal model currently exists that can fully replicate the clinical conditions observed in humans, underscoring the need for further research involving human subjects.

S. *japonicum* is the most prevalent *Schistosoma* species in China [30] and, as a result, is the most extensively studied in the selected articles. In contrast, *S. haematobium* is one of the main causes of schistosomiasis in Africa [39] and primarily affects the urogenital system. Consequently, the decision to use urine as a sample for analysis in the study by Tawana-Ndolo [25], is likely attributable to the urological involvement associated with this species.

Most studies have analyzed serum samples [22, 23, 26, 27, 28, 29, 30, 31, 34] because blood circulates throughout all tissues and organs, transporting a wide range of information, including disruptions in homeostasis across various systems. Moreover, serum offers a real-time metabolic profile, reflecting the metabolome at the moment of collection, which is valuable for capturing the dynamic biochemical changes associated with disease.

Regarding feces samples, only two studies [32, 35], utilized this type of sample. As an excreted material, feces composition can vary significantly depending on factors such as the patient's diet and intestinal microbiota. It is a multicomponent substance, rich in macromolecules and containing undigested food particles, which can complicate the analysis. These variations pose challenges in obtaining consistent and interpretable metabolic data from feces samples [40].

The diversity of species within the metabolome, along with their distinct physicochemical properties, directly influences the challenges and methods applied in metabolomic research. LC-MS, known for its high resolution and sensitivity, was the most frequently used technique in the reviewed studies. Except for the study by Hu et al. [27], all other studies utilized UHPLC, which enhances column efficiency, peak resolution, sensitivity, and analysis time compared to traditional HPLC [41]. All other studies utilized UHPLC, which enhances column efficiency, peak resolution, sensitivity, and analysis time compared to traditional HPLC [41]. GC-MS was employed less frequently in the studies, possibly because it is a technique used for the separation of volatile and thermally stable compounds, thus being limited to these conditions. Additionally, whether using LC-MS or GC-MS, the preparation of biofluid samples involves a complex process, often including metabolite extraction [25–30, 32, 34, 35] and derivatization steps [24, 33].

NMR spectroscopy, similar to GC-MS, has been employed in a smaller number of studies. This technique is known for its high reproducibility, and, unlike chromatographic methods, it typically does not require the analysis of quality control (QC) samples. Additionally, NMR allows for the analysis of biofluids with minimal sample preparation, often consisting only of dissolving the biofluid in deuterated water [22, 23, 31]. This simplifies the process compared to other techniques that require more labor-intensive steps.

When compared to MS, the main disadvantage of NMR spectroscopy is its lower sensitivity. However, both techniques can complement each other to provide more comprehensive results, as neither can detect all metabolites simultaneously. By combining NMR and MS, researchers can overcome the limitations of each method and achieve a more complete analysis of the metabolome.

Multivariate statistical analyses played a central role in the studies, with PCA, PLS-DA, and OPLS-DA being the most used tools (Table 1). PLS-DA and OPLS-DA formalisms resulted in models with good predictive capacity in most cases. Among the studies investigated, nine carried out cross-validation and reported R^2 and Q^2 values, which are essential for assessing the robustness of the models [22, 23, 25, 28–31, 34, 35]. Q^2 values > 0.5 in most of the studies, reaching up to 0.991 in the model generated by PLS-DA in the study by Rong et al. [28], and a good fit of the models based on the R^2 values highlight metabolomic research as a promising alternative for early diagnosis and the identification of biomarkers associated with schistosomiasis.

The studies did not carry out external validation, which is associated with the limited number of samples in the data sets, a frequent situation in metabolomic studies. However, cross-validation and permutation tests were

used. These are tools often employed to assess the predictive capacity of models and their statistical significance. Both are strategies commonly referred to as resampling, which involves using several randomly generated subsets of the model to evaluate its reliability by calculating confidence intervals [42]. Considering small data sets, resampling is a useful alternative and may be preferable to splitting the data set into calibration and external validation sets. It is important to emphasize that the validation strategy must be defined based on the modeling objective [42].

Gouveia et al. [22]) and Rodrigues et al. [23]) validated the statistical accuracy of the models using permutation tests, which showed values of $p < 0.01$. In turn, Zhu et al. [31] used CV-ANOVA tests, which also showed statistical significance, with values of $p < 0.05$. Sensitivity and specificity of the models were assessed using ROC curves and AUC, with the study by Tawana-Ndolo et al. [25) achieving a maximum AUC of 0.875, indicating the model's effectiveness.

From the models, it was possible to obtain the most important variables for projection (VIP), which were responsible for discriminating between classes. These are the metabolites responsible for discriminating the classes in the models and are related to the alterations caused by the infectious process. VIP values were applied in most of the studies in this review to select the metabolites investigated [22–24, 28, 29, 34, 35].

All the studies identified the possible metabolites related to the classes analyzed, but studies such as those by Chienwichai et al. [26, 35], Hu et al. [27], Hu et al. [30], Huang et al. [29]), Rong et al. [28], Zhou et al. [32], Loyo et al. [24] and Li et al. [34] investigated the potential of these metabolites as biomarkers in greater depth. To this end, they applied additional statistical tools, such as Student's t-test, FDR, Fold-Change, Pearson's correlation, and ROC curve, to determine their statistical relevance and discriminatory capacity. In the context of the ROC curve, the studies by Chienwichai et al. [26, 35] and Hu et al. [30] are noteworthy for their application in the early diagnosis of potential biomarkers, in which the work by Hu et al. [30] identified xanthurenic acid and naphthalene sulfonic acid as markers with 100% sensitivity and specificity, demonstrating their high discriminatory power.

The studies investigated in this paper can be divided into two complementary lines: one focused on developing diagnostic models and the other on identifying biomarkers with clinical potential. Both approaches not only broaden the understanding of the metabolic processes involved but also provide valuable contributions for practical application in the clinical field, with emphasis on early diagnosis and monitoring of specific conditions.

Thus, the findings reinforce the importance of multivariate analyses and statistical tools in clinical research, indicating promising avenues for advancing diagnostic strategies and the study of metabolic biomarkers. However, future studies should focus on the experimental validation of these findings to consolidate their practical applicability and increase the benefits for human health.

Metabolomics signatures

The findings from the studies included in this scoping review collectively suggest that schistosomiasis infection is associated with significant disruptions in various physiological processes. These include alterations in the Tricarboxylic Acid (TCA) cycle, disturbances in glucose and lipid metabolism, modifications to the intestinal microbiota, immune system responses, and reactive effects on genetic material [22–35].

The parasite-host interaction mechanism necessitates the maintenance of balance to mitigate the deleterious effects of infection. In this context, metabolic signatures of bone marrow-derived macrophages have been investigated in a mouse model predisposed to metabolic alterations and infected with *Schistosoma mansoni (S. mansoni)* [33].

It was demonstrated that macrophages from infected mice exhibited enhanced mitochondrial respiration compared to their uninfected counterparts. This alteration is linked to the TCA cycle, with increased glucose and palmitate transfer, heightened accumulation of free fatty acids, and a reduction in cholesterol esters [33]. These results align with most studies reviewed, which consistently indicate significant disruptions in the TCA cycle during schistosomiasis infection [24–26, 31].

In contrast to laboratory animals under controlled conditions, humans and other free-living animals are often exposed to multiple infections simultaneously, caused by a variety of pathogens including viruses, bacteria, and parasites. The concurrent presence of these pathogens in the same host can influence the severity of infections and disrupt the host's normal metabolic processes. Previous studies have highlighted that metabolomics serves as a valuable tool for monitoring metabolic changes, particularly in cases of co-infection [22, 31].

Periportal fibrosis (PPF) is one of the most severe complications associated with *S. mansoni* infection and has been the focus of metabolomic studies aimed at elucidating the metabolic patterns associated with PPF. These studies have revealed key metabolic pathways that are critical for monitoring and understanding the progression of PPF in humans [22, 23].

In a study aimed at diagnosing PPF due to *S. mansoni* in patients co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV), as well as in those mono-infected with HBV or HCV, Gouveia et al. observed several key findings. Lactate and high-density lipoprotein (HDL) were identified as the primary factors responsible

for distinguishing between the groups. Serum lactate levels were found to be elevated in samples from the co-infected group, while serum HDL levels were higher in individuals' mono-infected with either HBV or HCV. The authors suggested that the presence of liver disease alters aerobic metabolism, shifting glucose metabolism towards glycolysis, which subsequently leads to an increase in serum lactate levels [22].

The assessment of PPF is essential for monitoring disease progression and prognosis in patients with *S. mansoni* infection. Metabonomic models utilizing ^{1}H NMR spectroscopy were developed to differentiate between mild and significant PPF and to identify variations in metabolite profiles. In these models, serum levels of N-acetylglucosamine, alanine, and glycolaldehyde were found to be elevated in more advanced cases, whereas serum levels of valine and carbohydrates were higher in patients with milder forms of the disease. Wang et al. conducted a study using an animal model and identified similar metabolites in the classification of PPF patterns associated with *S. mansoni*, emphasizing the role of amino acid metabolism [43]. These findings are consistent with disruptions in amino acid metabolism in hepatocytes, which occur as a response to fibrogenesis and liver damage induced by schistosomiasis [23, 44]. The identification of specific metabolites linked to schistosomiasis-associated PPF underscores the importance of conducting further research across different stages of the disease to establish a comprehensive and accurate metabolic profile [34, 45, 46].

Urine is a biofluid that facilitates noninvasive sample collection, thereby simplifying diagnostic processes, particularly in rural settings. In the study conducted by Loyo et al., hippurate was identified as the metabolite most strongly correlated with the intensity of *S. mansoni* infection. Additionally, methyl malonate was significantly altered in this study, with detectable levels present in both mild and severe cases of *S. mansoni* infection [24]. In contrast, the study by Zhu et al. found that malonate levels were reduced in cases of *S. japonicum* infection, highlighting potential differences in metabolic responses between species [31]. Malonate is a known inhibitor of succinate dehydrogenase, an enzyme that plays a crucial role in regulating mitochondrial oxidative metabolism. This inhibition is particularly significant during the inflammatory response, as it is associated with alterations in the TCA cycle [22, 31].

Rong et al. [28] conducted a study investigating serum metabolites in *S. japonicum* infection in severe combined immunodeficiency (SCID) mice, with BALB mice serving as controls. The analysis revealed differential metabolites across the groups, implicating metabolic pathways involved in arachidonic acid, glycerophospholipids, phenylalanine, linoleic acid, sphingolipids, purines, and glycosylphosphatidylinositol (GPI) anchor biosynthesis. These alterations reflect distinct metabolic shifts in lipid and phospholipid metabolism, suggesting immunological disturbances in response to infection. Moreover, these findings contribute to understanding of the abnormal growth and development of worms in SCID mice, highlighting the impact of immune dysfunction on parasite dynamics.

The study identified several biologically significant pathways, including sphingolipid metabolism, which is crucial for maintaining the integrity of the cell surface, and arachidonic acid metabolism, which plays a key role in cell signaling processes. Both pathways were found to be altered, with a decrease in sphingolipids in male worms and a reduction in arachidonic acid in female worms from SCID mice. The identified and differentiated metabolites are likely associated with abnormalities in the growth and development of the *Schistosoma* worms. In addition to the observed differential changes between male and female profiles, these findings suggest that the host's influence on the parasite may vary depending on the gender of the worm [28].

The study by Li et al. [34] identified significant alterations in metabolic pathways during Schistosoma japonicum infection, with emphasis on steroid hormone biosynthesis, cholesterol metabolism, bile secretion, and primary bile acid biosynthesis, all directly related to the progression of the infection from chronic to advanced stages. The biomarker candidates listed in Table 1 showed gradual increases in concentration as the disease progressed.The reduction in steroid hormone biosynthesis, such as androsterone and its derivatives, was associated with the exacerbation of hepatic damage in advanced stages, while the increase in bile acids suggested toxicity and pro-inflammatory effects in hepatic tissues.

Considering that eleven of forteen selected papers studied *S. japonicum* or *S. mansoni*, the reported metabolites to these ten studies are summarized at Fig. 2. Only two metabolites are present in the two diseases, being associated with TCA cycle (citrate and malonate). However, both species affect the same metabolic pathways, as the metabolism and biosynthesis of protein, TCA cycle, as well as lipids and fatty acids metabolism. These studies reported shared metabolites associated with the TCA cycle, including succinate and citrate, demonstrating consistent disruptions in energy metabolism pathways [24, 31]. Dimethyl-D-malate, an additional intermediate of the TCA cycle, has been linked to the activation of glycolytic pathways, indicating a pronounced metabolic adaptation.

The analysis of amino acids in both species reveals significant effects on protein metabolism and branched-chain amino acids. Glyceraldehyde, a metabolite involved in aldehyde metabolism, reflects biochemical alterations

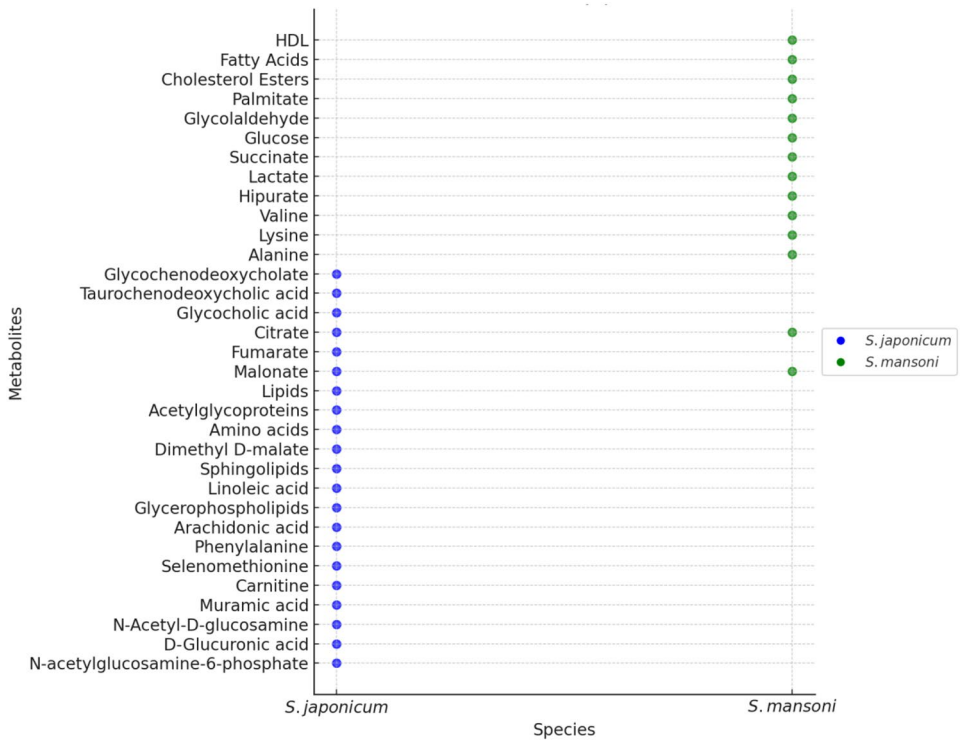

Fig. 2 Relation of altered metabolites in serum or urine of humans and rats induced by *S japonicum* and *S mansoni* observed in 10 published articles

associated with hepatic fibrosis, particularly in infections caused by *S. mansoni* [23]. In contrast, carnitine, which plays a critical role in lipid and fatty acid metabolism, has been identified as a key factor in the immune response during the initial stages of *S. japonicum* infection [27, 30].

Increased lactate concentrations have been reported in cases of coinfection, while metabolites such as hippurate have shown a significant correlation with modifications in the intestinal microbiota, highlighting the intricate relationship between the host's metabolic and immune systems [21, 22, 24]. Furthermore, muramic acid has been proposed as a potential bacterial marker, suggesting an active immune response during infection [29]. Vitamin D, its derivatives, and ganoderic acid have been identified as potential biomarkers for the early diagnosis of intestinal schistosomiasis. These compounds, associated with lipid metabolism, exhibit detectable metabolic alterations in the early stages of infection, underscoring their clinical relevance in the early identification of the disease [35].

The identification of differential metabolites, including succinate, citrate, lactate, glyceraldehyde, and carnitine, establishes a robust framework for the development of innovative diagnostic, prognostic, and therapeutic strategies for schistosomiasis. These observations underscore the intricate complexity of host-parasite interactions and emphasize the necessity for further research integrating metabolomic, genomic, and immunological data. Methodological and conceptual advancements in this domain hold the potential to enhance the management of *Schistosoma*-induced diseases and broaden understanding of metabolic perturbations associated with other parasitic infections, thereby offering novel opportunities for precision-based clinical interventions.

Limitations and future perspectives

This review highlights several gaps in current knowledge, particularly the scarcity of studies involving human subjects. Furthermore, the absence of external validation using independent data sets represents a significant limitation, as this step is essential to ensure the robustness and statistical power of the models developed. Another critical point is the low representation of studies conducted in African regions, where schistosomiasis has the highest global prevalence, potentially compromising the applicability and generalization of the findings on a global scale.

A considerable variation in the identified metabolites was also observed, attributed to the heterogeneity in experimental conditions, including the different types of samples used, such as serum, urine, feces, and tissue, as well as the stage of infection. Moreover, the importance of future studies integrating other omics techniques, such as genomics, lipidomics, and proteomics, is emphasized to provide a more comprehensive understanding of the

metabolic and molecular interactions associated with schistosomiasis.

Conclusions

The articles included in this review describe the metabolic alterations observed in humans and mice infected with *Schistosoma* species, with *S. japonicum* being the most frequently evaluated. Most studies utilized serum samples and employed chromatographic techniques in conjunction with PCA formalism, except for one study. Some articles focused on identifying the potential metabolic pathways associated with infection, considering the site of the disease, while others aimed to classify and monitor the progression of the disease.

The analysis of these specific metabolic alterations, including those in the TCA cycle, amino acid metabolism, and lipid metabolism, is crucial for understanding the relationship between the observed biochemical disturbances and clinical manifestations such as hepatic fibrosis and immune dysfunctions. This integrated approach provides a more comprehensive insight into the pathogenic mechanisms involved, contributing to advancements in the diagnosis and clinical management of schistosomiasis.

Abbreviations

NMR	Nuclear magnetic resonance
MS	Mass spectrometry
PCA	Principal Component Analysis
OPLS	DA-Orthogonal Partial Least Squares Discriminant Analysis
GC	Gas chromatography
LC	Liquid chromatography
CE	MS-Mass spectrometry
PRISMA	ScR-Scoping Reviews
QC	Quality control
ROC	Receiver operating characteristic
TCA	Tricarboxylic Acid
PPF	Periportal fibrosis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
MSI	Metabolomics Standards Initiative

Author contributions

MLR, ARSG, ROS and EPL conceived the study. MLR and ARSG assessed study eligibility and extracted data with consultation from ROS. MLR and ARSG drafted the manuscript, ALCD and all authors reviewed the manuscript and approved the final version for submission.

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Data availability

All data generated and analysed during this study are included in this article and can be requested.

Declarations

Ethics approval and consent to participate

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Competing interests

The authors declare no competing interests.

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