DOI: https://10.83080/rejost.vol6no8.336

Researchers Journal of Science and Technology (REJOST)

The *Schistosoma mansoni* Phosphatome as a Frontier for Antischistosomal Drug Discovery: Molecular Functions, Target Validation and Therapeutic Perspectives

Sulyman, A.O.[1,2*], Bashar, A.A.[1*], Adewale, S.A.[1], Adetoyi, G.M.[1], Azeez, K.L.[1], Asonibare, K.M.[1], Adebayo, K.A.[1], Singh, K.[2] and Naidoo, K.[2]

Abstract

Schistosomiasis remains a major neglected tropical disease, affecting millions of people worldwide and causing substantial morbidity, particularly in endemic communities. Despite decades of control efforts, treatment still depends largely on praziquantel. Although the drug is highly effective against adult schistosomes, its activity against immature developmental stages is reduced, and it does not prevent reinfection. These limitations highlight the need for alternative therapeutic strategies. Protein phosphatases, which counterbalance protein kinases by regulating reversible phosphorylation, represent an important but comparatively neglected part of the *Schistosoma mansoni* drug-discovery landscape. The *S. mansoni* phosphatome includes diverse phosphatase families, such as serine/threonine phosphatases, protein tyrosine phosphatases, dual-specificity phosphatases, and metal-dependent phosphatases, with potential roles in signalling, development, metabolism, reproduction, stress responses, and parasite survival. The importance of phosphorylation-dependent regulation, together with the identification of essential phosphatases through functional genomic approaches, supports their consideration as potential therapeutic targets. Their catalytic domains, structural features, parasite-specific characteristics, and essential biological functions may offer opportunities for selective pharmacological intervention. Emerging approaches that combine RNA interference, phosphoproteomics, comparative genomics, structural bioinformatics, virtual screening, phenotypic screening, and biochemical target-engagement assays are making systematic target identification and validation in *S. mansoni* increasingly feasible. This review therefore examines the molecular functions and biological significance of the *S. mansoni* phosphatome, evaluates the evidence for phosphatase target validation and druggability, and discusses emerging strategies for inhibitor discovery. Finally, a translational framework linking phosphatase prioritisation, genetic and biochemical validation, structure-guided discovery, selective inhibitor development, and preclinical evaluation is proposed to help advance phosphatases from neglected regulatory enzymes to validated antischistosomal drug targets.

✉ Ayub Ahmed Bashar; ayubahmad110@gmail.com; Phone: +2348184615915

[1]Department of Biochemistry, Faculty of Pure and Applied Sciences, Kwara State University, P.M.B. 1530, Malete, Ilorin, Nigeria

[2]Department of Nature Conservation, Faculty of Applied and Health Sciences, Mangosuthu University of Technology, P.O. Box 12363, Jacobs, 4026, Durban, South Africa.

Keywords: *Schistosoma mansoni*; Phosphatome; Protein phosphatases; Antischistosomal drug discovery; Target validation; Druggability; Phosphoproteomics; Praziquantel

Article history
Received: June 30, 2026
Received in revised form: September 2, 2026
Accepted for publication: September 7, 2026
Available online: September 10, 2026

1.0 Introduction

Schistosomiasis is a neglected tropical disease caused by parasitic blood flukes of the genus *Schistosoma* and remains an important cause of chronic morbidity in endemic populations (Buonfrate et al., 2025). The disease is closely linked to poverty, inadequate sanitation, unsafe water exposure, and limited access to healthcare. Although several *Schistosoma* species infect humans, *Schistosoma mansoni* is particularly important because it is widely distributed across Africa, parts of the Middle East, the Caribbean, and South America and is a major cause of intestinal and hepatosplenic schistosomiasis (Aula et al., 2021). Current control strategies have reduced disease burden in several endemic settings; nevertheless, transmission persists, and continued dependence on chemotherapy remains a major vulnerability in the long-term elimination agenda. Identifying and validating new parasite-specific molecular targets is therefore essential for expanding the antischistosomal drug pipeline.

1.1 Global burden

Schistosomiasis remains a substantial global health problem despite being preventable and treatable. The World Health Organization (WHO) estimates that at least 253.7 million people required preventive treatment for schistosomiasis in 2024, while more than 100.5 million people were reported to have received treatment (Fan et al., 2026). Importantly, approximately 93.9% of those requiring preventive chemotherapy reside in Africa, highlighting the disproportionate burden borne by African populations (WHO, 2026). Transmission has been reported in 79 countries, although population-level preventive chemotherapy is currently required in 50 endemic countries with moderate-to-high transmission.

The burden of schistosomiasis extends beyond infection prevalence. Chronic infection can cause substantial pathological consequences because adult worms reside within the vasculature and continuously release eggs (Mawa et al., 2021). Some of these eggs become trapped in host tissues, where they trigger persistent inflammatory and granulomatous responses. Depending on the infecting species and disease presentation, this can lead to intestinal pathology, hepatosplenic disease, portal hypertension, urinary tract damage, anaemia, impaired growth, and reduced cognitive or educational performance (Colley et al., 2014). Schistosomiasis is therefore not only an infectious disease problem but also a chronic socioeconomic and developmental burden in affected communities.

For *S. mansoni*, the biological complexity of the parasite further complicates disease control. Its life cycle alternates between freshwater snail and mammalian hosts and includes morphologically and physiologically distinct stages, including eggs, miracidia, sporocysts, cercariae, schistosomula, and sexually mature adult worms (Onyekwere, 2022). Each developmental transition involves extensive remodelling of cellular signalling, metabolism, reproduction, and host–parasite interactions. This developmental plasticity creates numerous opportunities for therapeutic intervention, but it also means that a drug effective against one developmental stage may have limited activity against another.

The persistence of transmission despite large-scale treatment highlights the limitations of relying exclusively on chemotherapy. WHO therefore advocates an integrated strategy that combines preventive chemotherapy with access

to safe water, sanitation, hygiene education, behavioural interventions, snail control, and other environmental measures (WHO, 2026). Nevertheless, chemotherapy remains the principal biomedical intervention, making it important to maintain and expand the repertoire of effective antischistosomal drugs.

1.2 Dependence on Praziquantel

Praziquantel (PZQ) has remained the principal drug for schistosomiasis control for approximately four decades because of its broad activity against the major human *Schistosoma* species, favourable safety profile, low cost, and suitability for large-scale administration (Villamizar-Monsalve et al., 2024; Banda and Abere, 2025). Current World Health Organization (WHO) control programmes continue to rely heavily on periodic praziquantel treatment of populations at risk. In 2024, at least 253.7 million people required preventive treatment for schistosomiasis, illustrating the continuing scale of this dependence (WHO, 2026).

Despite its effectiveness, reliance on a single principal antischistosomal drug remains an important limitation to long-term disease control. Praziquantel has relatively limited activity against immature schistosomes, meaning that recently acquired infections may be less susceptible to treatment. As a result, treatment must be repeated in endemic areas where exposure to infective cercariae continues (Villamizar-Monsalve et al., 2024).

This dependence highlights the need to expand the antischistosomal therapeutic pipeline with compounds that act through mechanistically distinct targets and, ideally, show activity against developmental stages that are poorly affected by praziquantel.

1.3 Limitations and Resistance Concerns

The major limitations of praziquantel include its reduced efficacy against immature worms, inability to prevent reinfection, and continued dependence on repeated mass drug administration. A systematic review reported generally high cure and egg-reduction rates following treatment but also documented substantial reinfection after praziquantel administration, with reported reinfection rates varying considerably across studies and geographical settings (Aboagye and Addison, 2023).

Resistance is an additional concern, although it should be described cautiously. Widespread clinically established praziquantel resistance has not been conclusively demonstrated. However, reduced susceptibility has been reported in some settings, and laboratory experiments have shown that praziquantel resistance can be selected under drug pressure. The prolonged use of praziquantel therefore provides a rationale for continued resistance surveillance and, importantly, for developing alternative treatments before resistance becomes a major clinical problem (Eastham et al., 2024).

The therapeutic gap is particularly relevant to drug discovery because the limitations of praziquantel cannot be completely overcome simply by increasing treatment frequency. Repeated treatment can reduce morbidity, but individuals remain vulnerable to subsequent infection. Consequently, new compounds with different molecular targets, complementary stage activity, or potential for combination therapy are needed to strengthen future schistosomiasis control.

1.4 Why Phosphatases?

Protein phosphorylation is a central regulatory mechanism that controls cellular signalling, metabolism, development, differentiation, and stress responses (Zhong et al., 2023). Protein kinases add phosphate groups to target proteins, whereas protein phosphatases remove them, making both enzyme classes essential components of phosphorylation-dependent signalling networks (Ke et al., 2026).

In *S. mansoni*, large-scale phosphoproteomic studies have demonstrated extensive phosphorylation across proteins involved in

diverse biological processes (Hirst et al., 2020). However, identifying phosphorylated proteins does not necessarily reveal which phosphatase controls a particular phosphorylation event. This creates an important opportunity to investigate the parasite phosphatome as a relatively underexplored component of schistosome biology.

Phosphatases are also attractive from a drug-discovery perspective because their catalytic domains and regulatory mechanisms provide potential sites for pharmacological intervention. Major phosphatase groups include the PPP (phosphoprotein phosphatase), PPM (protein phosphatase Mg^{2+}/Mn^{2+}-dependent), protein tyrosine phosphatase (PTP), and dual-specificity phosphatase (DUSP) families (Thiriet, 2012). Their involvement in essential cellular processes makes individual members potential targets; however, predicted druggability alone cannot establish therapeutic validity.

Importantly, evidence from a kinase pathway or phosphorylation-dependent process should not automatically be taken as evidence for the involvement of a particular phosphatase. Such information is useful for generating hypotheses, but phosphatase-specific genetic, biochemical, cellular, or pharmacological evidence is required for target validation.

1.5 Knowledge Gap

Despite extensive characterisation of the schistosome kinome and growing phosphoproteomic resources, the identity, developmental expression, cellular localisation, biochemical activity, substrate specificity, essentiality, and parasite-selective druggability of many *S. mansoni* protein phosphatases remain poorly defined. As a result, the relationship between individual phosphatases and parasite phenotypes is still largely inferential.

The existing literature frequently provides information on kinase signalling, MAPK pathways, phosphoproteomic changes, or host pathology that may suggest phosphatase involvement. However, these observations should not be considered direct evidence of phosphatase function unless supported by phosphatase-specific experimental investigation. Thus, an important gap remains between phosphatase prediction or association and experimentally validated phosphatase function.

This gap is particularly important for drug discovery. A useful therapeutic target must not only be biologically relevant but also demonstrate sufficient essentiality, pharmacological tractability, and parasite selectivity. Systematically identifying and prioritising *S. mansoni* phosphatases according to these criteria could therefore reveal previously underexplored targets for antischistosomal intervention.

1.6 Objectives

This review aims to critically examine the *S. mansoni* phosphatome as a potential resource for antischistosomal drug discovery. Specifically, it seeks to:

1. characterise the major phosphatase families present in *S. mansoni* and summarise their molecular organisation.
2. Evaluate their reported or predicted biological functions in parasite development, reproduction, tegumental biology, stress responses, metabolism and host–parasite interactions.
3. Assess the strength of existing evidence for therapeutic targeting, distinguishing genetic, biochemical, phenotypic and structural evidence from indirect pathway-based inference.
4. prioritise candidate phosphatases according to biological essentiality, druggability and parasite - selectivity evidence.
5. Examine emerging approaches for phosphatase inhibitor discovery, including small-molecule screening, natural products, structure-based approaches, drug repurposing and allosteric inhibition.

6. compare phosphatome - related information across *S. mansoni*, *S. japonicum* and *S. haematobium* to identify conserved and parasite - specific opportunities.
7. propose a translational framework for advancing promising phosphatases from biological candidates to experimentally validated antischistosomal drug targets.

2.0 Review Methodology

This review was designed as a structured narrative review to evaluate the *Schistosoma mansoni* phosphatome from the perspectives of molecular classification, biological function, target validation, and therapeutic potential (Figure 1). Particular emphasis was placed on recent evidence published between 2021 and 2026, while earlier studies were retained where they provided essential foundational information. The methodology was structured to distinguish experimentally demonstrated phosphatase functions from predictions and indirect evidence derived from related signalling pathways.

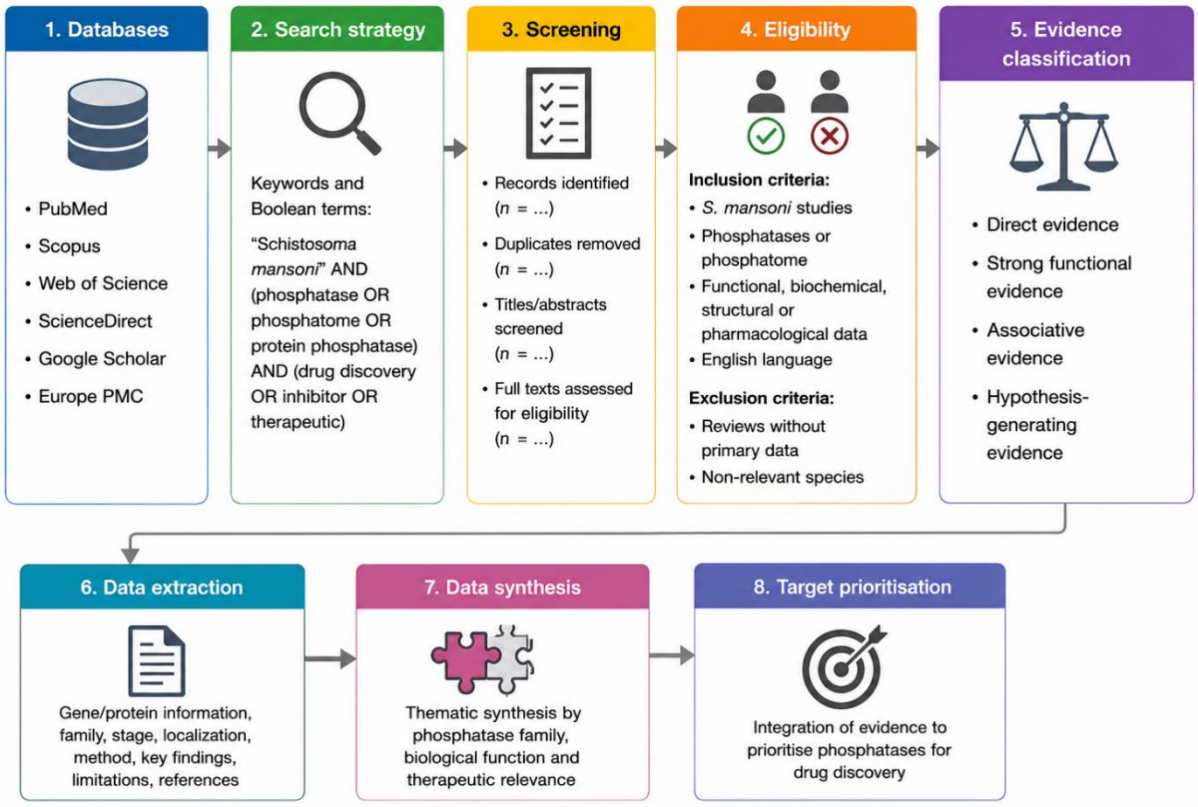

Figure 1: Review methodology (Page et al., 2021)

2.1 Databases

A comprehensive literature search was conducted using major biomedical and multidisciplinary databases, including PubMed/MEDLINE, Web of Science, Scopus, ScienceDirect, Google Scholar, and Europe PMC. Additional information was obtained from authoritative resources, including the World Health Organization (WHO) and relevant parasite genomic and protein databases. Particular attention was given to publications addressing *S. mansoni* phosphatases, phosphorylation - dependent signaling, functional genomics, phosphoproteomics, antischistosomal drug discovery, protein structures, and inhibitor development.

The databases were selected to provide broad coverage of biomedical literature, parasitology, molecular biology, phosphoproteomics, structural biology, and drug-discovery research. Reference lists of relevant publications were also examined to identify additional studies that were not retrieved through the primary database searches. Using multiple information sources is

recommended because no single database provides complete coverage of the scientific literature (Page et al., 2021).

2.2 Search Strategy

Searches combined terms relating to *S. mansoni*, phosphatases, phosphorylation, biological function, and drug discovery. Representative search combinations included:

- "*Schistosoma mansoni* and phosphatase"
- "*S. mansoni* and phosphatome"
- "*Schistosoma mansoni* and protein tyrosine phosphatase"
- "*Schistosoma mansoni* and serine/threonine phosphatase"
- "*Schistosoma mansoni* and PPM or PPP or DUSP"
- "*Schistosoma mansoni* and phosphoproteomics"
- "*Schistosoma mansoni* and drug target"
- "*Schistosoma mansoni* and phosphatase inhibitor"
- "*Schistosoma* and praziquantel resistance"

The search placed particular emphasis on publications from 2021–2026, consistent with the objective of providing an up-to-date assessment of the phosphatome. Earlier studies were retained when they provided foundational genomic, biochemical, functional, or pharmacological evidence. Search strategies were documented to improve transparency and reproducibility, consistent with current guidance for evidence-based reviews (Page et al., 2021).

2.3 Inclusion/Exclusion Criteria

Studies were included when they provided information relevant to *S. mansoni* phosphatases, phosphorylation-dependent signalling, phosphatome organisation, biological function, functional genomics, target validation, structural characteristics, or antischistosomal drug discovery. Priority was given to peer-reviewed original research articles, systematic reviews, relevant narrative reviews, and authoritative genomic or proteomic studies, with particular emphasis on literature published between 2021 and 2026. Studies were excluded when they lacked meaningful relevance to the review objectives, contained insufficient experimental information, or duplicated previously reported findings without providing additional evidence. Studies involving *S. japonicum* or *S. haematobium* were retained selectively for the comparative analysis in section 8.

Evidence obtained from other organisms was not treated as direct evidence of *S. mansoni* phosphatase function. Instead, such studies were used only when they provided useful mechanistic context or helped generate hypotheses. Clearly defined inclusion and exclusion criteria are important because they determine which evidence contributes to a review and improve transparency in study selection.

2.4 Evidence Classification

Because a major objective of this review is to distinguish established phosphatase biology from prediction, evidence was classified into four broad categories (Table 1). This classification is particularly important for the *S. mansoni* phosphatome because a phosphorylation event, kinase pathway, or phosphoproteomic association does not independently establish which phosphatase regulates the event. Therefore, indirect evidence was not presented as definitive evidence of phosphatase function.

2.5 Data Synthesis

Information extracted from the selected literature was organised according to phosphatase family, developmental stage, cellular localisation, biological function, experimental evidence, and therapeutic relevance. Findings were synthesised qualitatively rather than through meta-analysis because the available studies differ substantially in experimental design, parasite developmental stage, molecular target, and outcome measures.

For candidate therapeutic targets, evidence was considered across several domains, including genetic essentiality, biochemical activity, parasite phenotype, structural information, inhibitor availability, and potential parasite

selectivity. This approach allows candidates to be compared according to the strength and breadth of available evidence and provides the basis for the target-prioritisation framework presented in Chapter 6. The synthesis also follows the principle that evidence should be presented according to its experimental strength rather than simply according to the number of publications supporting a particular hypothesis. Contemporary review methodology recommends clearly describing how studies are selected, how information is extracted, and how evidence is synthesised (Page et al., 2021).

Table 1: Evidence Classification

Evidence category	Definition
Direct evidence	Phosphatase-specific biochemical, genetic, localization, substrate, inhibitor or phenotypic evidence
Strong functional evidence	Multiple experimental observations supporting a specific biological function
Associative evidence	Expression, phosphoproteomic, pathway or co-expression data suggesting involvement without direct functional validation
Hypothesis-generating evidence	Evidence inferred from kinases, MAPK pathways, other organisms, structural prediction or related biological systems

3.0 The *S. mansoni* Phosphatome

The *S. mansoni* phosphatome comprises enzymes and regulatory proteins involved in reversing phosphorylation-dependent signalling events (Selzer, 2013) (Figure 2). Interpreting this phosphatome is complicated by the fact that genomic annotation can identify candidate phosphatases more readily than it can establish their biochemical activity or physiological substrates. Available phosphoproteomic resources nevertheless show that phosphorylation is widespread in the parasite. A deep phosphoproteomic analysis identified 15,844 unique phosphopeptides mapping to 3,176 proteins, providing a substantial resource for investigating phosphorylation-dependent regulation (Hirst et al., 2020).

3.1 Genomic Landscape

The availability of chromosome-level *S. mansoni* genome assemblies and updated annotations has improved the identification of genes encoding catalytic and regulatory proteins (Freire et al., 2026). Current genome resources such as WormBase ParaSite provide manually curated and computationally annotated phosphatase-related genes and their orthologues. For example, Smp_126680 is annotated as a protein phosphatase 1 regulatory subunit, illustrating that the phosphatome includes both catalytic enzymes and proteins that regulate phosphatase complexes.

However, genomic annotation should be regarded primarily as a means of identifying candidates rather than as functional validation. Sequence similarity can establish membership in a phosphatase family, but it does not necessarily establish catalytic competence, substrate specificity, developmental importance, or druggability.

3.2 PPP

The PPP family includes major serine/threonine phosphatases such as PP1, PP2A, and calcineurin/PP2B. These enzymes regulate fundamental cellular processes, including cell-cycle progression, cytoskeletal dynamics, metabolism, and intracellular signalling (Fréville et al., 2022; Brauer, 2022).

Experimental work has demonstrated the presence of PP1-related machinery in *S. mansoni*. SmPP1 interacts with the regulatory protein SmSds, and this interaction can influence PP1 activity, providing direct evidence that phosphatase regulation is integrated into parasite cellular processes (Daher et al., 2006).

More recent studies have also identified PP2B/calcineurin-related proteins within phosphorylation-associated networks. For example, SmPP2B (Smp_126260) occurs among proteins associated with CaMKII-dependent signalling and neuromuscular regulation. However, this association should not be interpreted as proof that PP2B directly regulates all of the associated phosphorylation events (Hirst et al., 2022).

3.3 PPM

PPM phosphatases are Mg^{2+}/Mn^{2+}-dependent enzymes that constitute another major group of serine/threonine phosphatases (N'Guessan-Koffi et al., 2026; Perla et al., 2026). Their catalytic activity depends on conserved metal-binding residues, and members of the family participate in signalling, metabolism, and stress responses in other eukaryotes (Aulakh et al., 2022).

Evidence for PPM members in *S. mansoni* is currently stronger at the annotation and phosphoproteomic levels than at the level of individual biochemical characterisation (Hirst, 2019). Protein phosphatase 2C-related proteins have been detected in *S. mansoni* phosphoproteomic and kinomic datasets, including differential phosphorylation of a PP2C-γ-associated peptide between adult male and female extracts (Hirst et al., 2020).

This observation supports biological relevance, but it does not demonstrate that the PP2C protein itself is a validated therapeutic target.

3.4 PTP/DUSP

Protein tyrosine phosphatases (PTPs) and dual-specificity phosphatases (DUSPs) regulate phosphotyrosine and, in the case of DUSPs, selected serine/threonine phosphorylation events (Ku, 2025; De Roo et al., 2025). Earlier genomic analyses identified numerous potential PTP and DUSP domains in *S. mansoni*, demonstrating that the parasite possesses the molecular machinery required for tyrosine-phosphorylation regulation (Abou-El-Naga, 2025; Mughal, 2022; Pereira Moreira et al., 2022).

The main limitation is that the presence of predicted PTP/DUSP domains does not establish their endogenous substrates or physiological functions. Consequently, this group represents an important area for future biochemical and functional investigation rather than a uniformly validated target class.

3.5 Other Phosphatases

The phosphatome also includes phosphatases outside the classical PPP, PPM, and PTP/DUSP groups. These include alkaline phosphatases and other phosphatase or phosphodiesterase activities associated with parasite metabolism and the tegument (Da'dara et al., 2014).

A recent biochemical study demonstrated that the surface enzyme SmNPP5 participates in extracellular FAD metabolism and that suppression of SmAP affects the conversion of FMN to riboflavin. These findings demonstrate that parasite surface phosphatase/phosphodiesterase activities can participate directly in nutrient metabolism (Da'dara et al., 2024).

4.0 Biological Functions

Phosphatases are positioned to influence several processes essential for schistosome survival. However, the strength of evidence differs markedly between biological systems. The functions discussed below should therefore be interpreted according to the evidence-classification framework established in section 6.

4.1 Development

Schistosomes undergo extensive morphological and physiological transitions during their complex life cycle (Cheng et al., 2022). Phosphorylation-dependent signaling contributes to these transitions, but direct functional information for individual phosphatases remains limited. Evidence from phosphoproteomics demonstrates extensive phosphorylation of proteins involved in signaling, metabolism, cytoskeletal organisation, and cellular regulation (Wu et al., 2025; Hirst et al.,

2020; Alli-Shaik et al., 2017). This provides a strong rationale for investigating phosphatases during developmental transitions, but phosphorylation data alone cannot identify the responsible phosphatase.

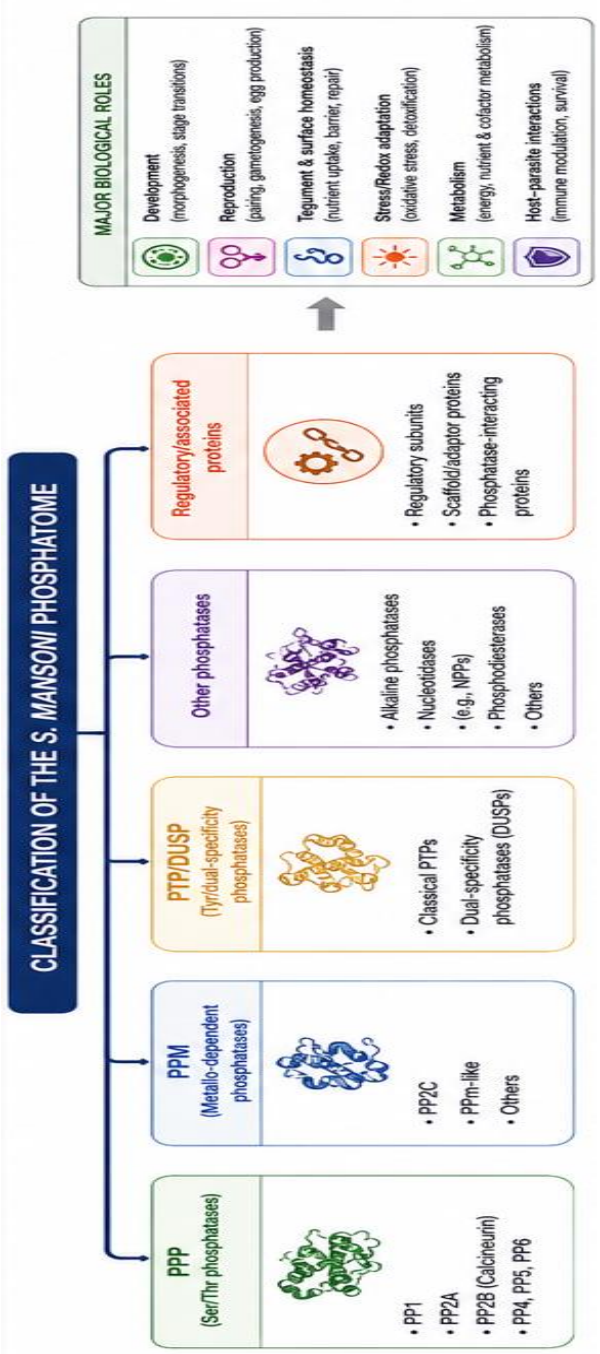

Figure 2: Classification of major phosphatase families in *Schistosoma mansoni* and their potential biological roles (Hirst, et al., 2020)

4.2 Reproduction

Reproductive development is particularly important because adult schistosomes must maintain pairing, sexual maturation, and continuous egg production (Walker et al., 2025; Li et al., 2023). Sex-associated differences in phosphorylation have been detected in adult worms, including differential phosphorylation of PP2C-related proteins (Hirst et al., 2020). These findings suggest that phosphatases may contribute to sex - specific signaling and reproduction, but direct experiments linking individual phosphatases to egg production or pairing remain comparatively limited.

4.3 Tegument

The tegument is essential for nutrient acquisition, immune interaction, and maintenance of the parasite's interface with the host. Surface-associated phosphatases can therefore have functions beyond intracellular signaling (Freitas-Mesquita and Meyer-Fernandes, 2026; Satala et al., 2026). Recent metabolic works demonstrate that suppression of the surface alkaline phosphatase SmAP altered extracellular FMN-to-riboflavin conversion, supporting a direct role for a phosphatase-associated enzyme in parasite surface metabolism (Da'dara et al., 2024). This type of surface accessibility may also be therapeutically attractive because externally exposed proteins could potentially be reached without requiring efficient intracellular drug penetration.

4.4 Stress/Redox

Schistosomes continuously encounter oxidative and metabolic stress generated by their own metabolism and host immune responses. Phosphorylation-dependent signaling is therefore likely to contribute to stress adaptation (Tuazon, 2024; Slovakova & Bilkova, 2021). However, evidence specifically assigning these functions to individual *S. mansoni* phosphatases remains insufficient. Consequently, links between phosphatases and oxidative-stress pathways should currently be treated mainly as hypotheses requiring direct validation rather than as established mechanisms.

4.5 Metabolism

Phosphatases can regulate metabolic enzymes directly through reversible phosphorylation and

can also participate in the metabolism of extracellular phosphorylated metabolites (Zhong et al., 2023). The SmNPP5/SmAP study provides particularly useful direct evidence that phosphatase/ phosphodiesterase activities participate in the parasite's handling of riboflavin-related metabolites. Recombinant SmNPP5 demonstrated measurable enzymatic activity against FAD, while RNAi-mediated suppression altered metabolite processing (Da'dara et al., 2024).

4.6 Host–Parasite Interactions

Phosphatases may influence the parasite's ability to survive within the host by regulating signaling, surface biology, and metabolic adaptation. Nevertheless, the evidence directly connecting individual phosphatases to immune evasion remains limited. Therefore, host - pathology or immune-signaling studies should not be used as direct evidence of a parasite phosphatase function unless the phosphatase itself has been experimentally manipulated.

5.0 Evidence for Therapeutic Targeting

The therapeutic value of a phosphatase depends on more than its presence in the parasite. A convincing target requires evidence that perturbing the protein compromises parasite survival and that its biochemical characteristics allow selective pharmacological intervention. RNA interference has provided an important route for testing gene function in *S. mansoni*. Large-scale functional-genomic studies have shown that systematic RNAi can identify genes whose suppression produces severe parasite phenotypes (Rinaldi et al., 2024). A recent genome-scale drug-discovery study identified 63 additional genes with fitness effects, including genes encoding kinases and phosphatases, and integrated these findings with earlier RNAi data to generate a larger target set (Stephens et al., 2025). However, a phosphatase should only be classified as genetically validated when perturbation of that phosphatase itself produces a reproducible phenotype.

5.1 Biochemical Evidence

Biochemical validation requires demonstration of catalytic activity and, ideally, identification of physiological substrates or inhibitors. Such evidence remains much less extensive for the *S. mansoni* phosphatome than for its kinome. This represents a major research opportunity because recombinant expression, phosphatase assays, phosphoproteomics, and substrate-trapping approaches could help connect predicted phosphatases to specific biochemical pathways.

5.2 Phenotypic Evidence

Phenotypic evidence becomes particularly persuasive when phosphatase perturbation causes measurable effects such as impaired motility, pairing, attachment, development, reproduction, or survival. The recent genome-scale screening framework demonstrates the value of combining RNAi phenotype severity with other druggability criteria rather than treating essentiality alone as sufficient for target selection (Dayanc et al., 2025; Stephens et al., 2025).

5.3 Structural Evidence

Structural information can establish whether a phosphatase contains an accessible catalytic pocket, regulatory site, or parasite-specific structural feature suitable for selective ligand binding. Protein structures, homology models, and AlphaFold predictions can be combined with molecular docking and molecular dynamics to prioritise compounds. Importantly, computational binding predictions should be regarded as lead-generation evidence rather than proof of inhibition. Experimental enzymatic and parasite assays remain necessary.

5.4 Selectivity

Selectivity is critical because phosphatases are common in mammalian cells. A useful schistosome target should ideally contain sequence or structural differences that can be exploited to obtain preferential parasite inhibition (Skelly & Da'dara, 2025). The genome-scale drug-discovery framework explicitly incorporated mammalian essentiality, assayability, druggability, and parasite selectivity alongside RNAi

phenotype severity when prioritising targets (Stephens et al., 2025).

6.0 Target Prioritisation

Target prioritisation should integrate multiple independent characteristics rather than relying on a single measure such as gene expression or predicted essentiality. For the *S. mansoni* phosphatome, particular attention should be given to evidence demonstrating that a phosphatase is essential for parasite survival or development, has measurable biochemical activity, is sufficiently characterized at the structural level, and can potentially be selectively inhibited without unacceptable effects on the host. Recent genome-scale studies of *S. mansoni* have similarly emphasized the integration of genetic essentiality, druggability, assayability and parasite selectivity when identifying promising therapeutic targets (Stephens *et al*., 2025).

Table 2 summarizes the qualitative evidence framework proposed in this review for prioritising *S. mansoni* phosphatases according to the strength and relevance of available experimental evidence. The framework is intended to distinguish well-supported candidates from phosphatases for which evidence remains primarily predictive or associative.

Table 2: Proposed qualitative evidence framework for prioritising *S. mansoni* phosphatases

Criterion	Strong evidence	Intermediate evidence	Limited evidence
Genetic essentiality	Reproducible severe phenotype after phosphatase-specific perturbation	Moderate phenotype	Prediction only
Developmental relevance	Stage-specific expression + phenotype	Differential expression	Annotation only
Biochemical activity	Recombinant enzyme activity demonstrated	Conserved catalytic motifs	Sequence prediction
Substrate relationship	Experimentally confirmed substrate	Phosphoproteomic association	Pathway prediction
Structural tractability	Experimental structure + ligandable pocket	High-confidence model	Domain prediction
Druggability	Validated inhibitor with on-target evidence	Predicted ligandability	No chemical evidence
Selectivity	Parasite-selective inhibitor/site	Parasite-specific residues	Conserved mammalian orthologue
Phenotypic validation	Genetic + pharmacological phenotype	Genetic phenotype	No phenotype
Overall priority	High	Moderate	Low/currently speculative

Note: The scoring system is a proposed qualitative framework for this review and is not intended to represent a validated universal scoring system. Higher scores indicate stronger supporting evidence, but target prioritisation should consider the quality and independence of the underlying evidence rather than numerical score alone.

Identification of a phosphatase within the *S. mansoni* genome is not sufficient to establish its value as a therapeutic target. Target prioritisation requires integration of evidence from several independent domains, including genetic essentiality, biochemical activity, developmental relevance, substrate or pathway association, structural tractability, druggability, parasite selectivity and phenotypic validation. Figure 3 presents the proposed evidence-integration

framework used in this review to rank phosphatases according to their potential suitability for antischistosomal drug discovery. Greater weight is assigned to evidence that directly demonstrates biological or pharmacological relevance, while prediction or indirect association contributes less strongly to target priority.

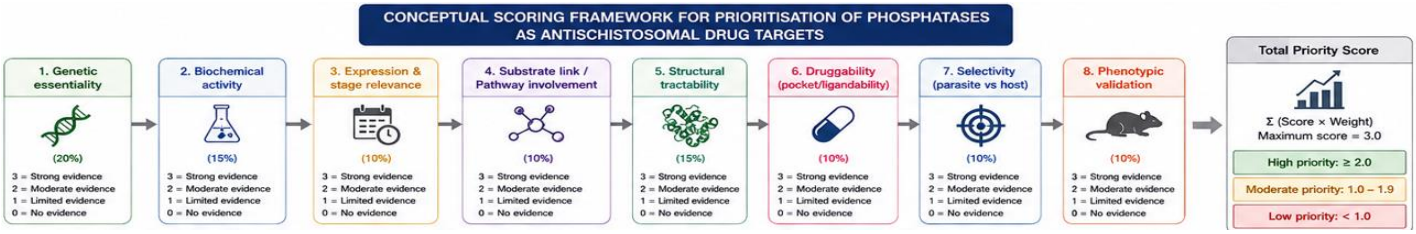

Figure 3: Conceptual framework for prioritising *S. mansoni* phosphatases as potential antischistosomal drug targets (Stephens et al., 2025)

The framework emphasizes that target priority should emerge from convergent evidence rather than from a single experimental observation. For example, a phosphatase with demonstrated genetic essentiality, measurable catalytic activity, structural tractability and parasite-selective inhibition would warrant substantially greater attention than a protein supported only by sequence annotation or pathway association. The scoring system is therefore intended as a qualitative decision-support framework for this review, rather than as a validated universal scoring system.

7.0 Drug Discovery Strategies

The identification of a promising phosphatase target represents only the initial stage of antischistosomal drug discovery. Translating target information into a viable therapeutic candidate requires a sequential process involving target validation, structural and biochemical characterisation, compound identification, screening, optimisation and assessment of parasite selectivity and drug-like properties. Chemical and bioactivity resources such as ChEMBL can complement schistosome drug discovery by supporting compound identification, target–compound relationships and drug-repurposing efforts (Padalino *et al*., 2023). Figure 4 presents a proposed integrated pipeline that combines these approaches to guide the progression from phosphatase target identification to validated inhibitor candidates.

The proposed pipeline begins with phosphatase target identification and prioritisation, followed by experimental validation of essentiality, enzymatic activity and structural characteristics. Validated targets can then be subjected to virtual screening, structure-based or phenotypic compound screening, followed by biochemical confirmation of inhibitory activity. Promising compounds require subsequent optimisation through structure–activity relationship studies, assessment of potency and selectivity, and evaluation of physicochemical and pharmacokinetic properties. Finally, candidates should undergo parasite-level validation and appropriate preclinical assessment before further development. This stepwise approach is intended to reduce attrition by ensuring that computational predictions are progressively supported by biochemical, phenotypic, structural and selectivity evidence.

7.1 Natural Products

Natural products provide structurally diverse chemical scaffolds and remain an important source of antischistosomal leads. Recent reviews describe activity from plant-derived compounds, essential oils, alkaloids, flavonoids, terpenoids, and other metabolites against different parasite stages (Azevedo et al., 2023; Mtemeli et al., 2022).

7.2 Small Molecules

Small-molecule discovery can begin with enzyme-based screening against purified phosphatases and then progress through dose-

response, selectivity, and parasite assays. ChEMBL-based approaches have demonstrated how chemical databases can be combined with *S. mansoni* functional-genomic information to identify compounds with ex vivo activity (Padalino et al., 2023).

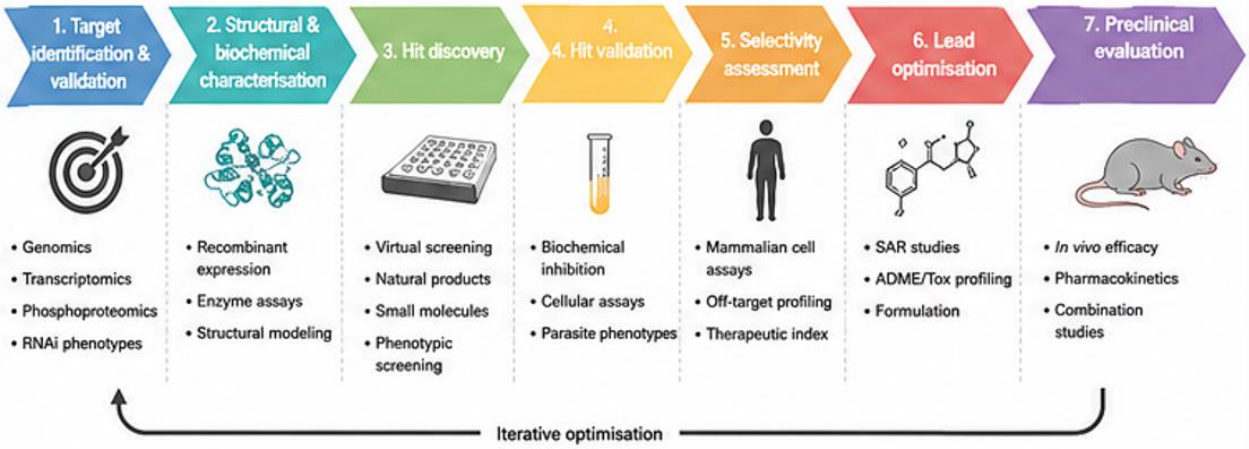

Figure 4: Proposed integrated pipeline for discovery and development of phosphatase inhibitors against *S. mansoni* (Padalino et al., 2023)

7.3 Structure-Based Discovery

Structure-based discovery uses experimentally determined or predicted protein structures to identify compounds capable of occupying catalytic or regulatory pockets. Recent *S. mansoni* studies have demonstrated the feasibility of combining structural modelling, virtual screening, and biochemical assays to identify enzyme inhibitors (Gomes et al., 2023). For phosphatases, structure-based approaches may be particularly useful for identifying non-conserved pockets adjacent to the catalytic site, where parasite selectivity may be easier to achieve.

7.4 Phenotypic Screening

Phenotypic screening measures parasite responses directly rather than beginning with a predefined molecular target. It can identify compounds active against multiple developmental stages and reveal unexpected mechanisms (Marhöfer et al., 2025). Its major limitation is target deconvolution. Consequently, phosphatase candidates identified from phenotypic screens require subsequent biochemical, genetic, or proteomic validation.

7.5 Drug Repurposing

Drug repurposing can shorten early development because existing compounds may already have pharmacokinetic and safety information. Recent work continues to explore repurposing as a strategy for schistosomiasis, although preclinical activity does not establish clinical usefulness (Villamizar-Monsalve et al., 2024).

7.6 Allosteric Inhibition

Allosteric inhibition is particularly attractive where catalytic sites are highly conserved between parasite and host proteins. Binding to regulatory pockets outside the conserved catalytic centre may permit greater selectivity (Odugbemi et al., 2026; Nath et al., 2026). Recent genome-scale work on *S. mansoni* demonstrates the broader feasibility of discovering parasite-selective allosteric pockets, although the published example concerns p97 rather than a phosphatase (Stephens et al., 2025). This provides a useful conceptual model for future phosphatase-directed discovery.

7.7 Combination Therapy

Combination therapy could reduce dependence on praziquantel and potentially limit resistance by simultaneously perturbing mechanistically distinct pathways. An ideal combination would involve compounds with complementary developmental-stage activity and minimal overlapping toxicity. However, phosphatase-based combinations remain largely a future research opportunity because few *S. mansoni*

phosphatases have progressed sufficiently through validation to support rational combination testing.

8.0 Comparative Phosphatomics: *S. mansoni* Versus *S. japonicum* Versus *S. haematobium*

Although *S. mansoni*, *S. japonicum* and *S. haematobium* share a substantial proportion of their molecular machinery, differences in host preference, tissue tropism, developmental biology and disease manifestations may influence the functional importance and therapeutic accessibility of individual phosphatases. Comparative analysis can therefore help distinguish conserved phosphatases that may represent broad-spectrum schistosomal targets from species-specific features that could support selective intervention. Table 3 compares the current phosphatome-related evidence across the three major human schistosome species and highlights areas in which functional characterization remains limited.

Table 3. Comparative phosphatome landscape and therapeutic implications of *Schistosoma mansoni*, *S. japonicum* and *S. haematobium*.

Feature	*S. mansoni*	*S. japonicum*	*S. haematobium*
Major disease presentation	Intestinal/hepatosplenic	Intestinal/hepatosplenic, often high egg output	Urogenital
Phosphorylation machinery	Extensive phosphoproteomic resources	Phosphoproteomic evidence available	Comparative genomic/proteomic resources
Kinome	Extensive	Extensive	Extensive
Phosphatase research	Underdeveloped but increasingly tractable	Less comprehensively characterised	Less comprehensively characterised
Comparative value	Strong model for functional validation	Useful for conserved targets	Important for urogenital disease-specific biology
Drug-discovery opportunity	Target validation and inhibitor discovery	Cross-species target conservation	Species-specific selectivity

Comparative genome resources for the three major schistosomes provide a basis for identifying orthologous drug targets, while updated chromosome-level assemblies improve comparative annotation (Kamara et al., 2023). However, orthology does not guarantee functional equivalence. A conserved phosphatase may perform different functions because of differences in expression, substrate availability, protein partners, or developmental biology. Comparative phosphatomics should therefore combine sequence conservation with expression, localisation, phosphoproteomic, and functional evidence.

9.0 Challenges and Future Directions

Several barriers currently limit the development of phosphatases as antischistosomal targets. First, functional annotation remains ahead of experimental validation. Many predicted phosphatases have identifiable catalytic domains but lack experimentally established substrates, localisation, or essentiality.

Second, phosphatase selectivity is difficult because many catalytic mechanisms are conserved between parasites and mammals. Structural analysis should therefore focus on parasite-specific residues, accessory domains, and allosteric pockets rather than catalytic motifs alone.

Third, target validation requires the integration of multiple technologies. RNAi can establish phenotypes, phosphoproteomics can identify potential substrates, recombinant assays can demonstrate catalytic activity, and structural biology can establish ligandability. No single technique is sufficient.

Fourth, the field needs better integration between functional genomics and chemical

biology. Recent genome-scale studies show that hundreds of *S. mansoni* genes can be experimentally prioritised, but essentiality does not automatically translate into druggability (Stephens et al., 2025).

Future studies should therefore focus on a smaller number of high - confidence phosphatases and systematically establish:
essentiality → localisation → biochemical activity → substrate → structure → inhibitor → selectivity → parasite phenotype → in vivo efficacy.

Following this sequence would help convert predicted phosphatases into experimentally validated therapeutic targets.

10.0 Conclusions

The *S. mansoni* phosphatome represents a potentially valuable but insufficiently explored resource for antischistosomal drug discovery. Extensive phosphoproteomic evidence demonstrates that phosphorylation is deeply integrated into parasite biology, while genomic and functional-genomic resources increasingly permit the systematic identification of candidate phosphatases.

Nevertheless, the current evidence base remains uneven. The existence of a predicted phosphatase, its association with a kinase pathway, or the detection of a phosphorylated substrate does not establish that the enzyme is essential or druggable. Direct biochemical, genetic, phenotypic, and structural validation is therefore required.

The most promising future strategy is an integrated approach combining phosphatome annotation, functional genomics, phosphoproteomics, structural biology, computational screening, and chemical validation. Target prioritisation should favour phosphatases supported by independent evidence of essentiality, assayability, ligandability, and parasite selectivity. Such a framework could help expand schistosomiasis treatment beyond its heavy dependence on praziquantel and establish phosphatases as a new class of experimentally validated antischistosomal targets.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Declaration

The authors hereby declare that the work presented in this review article is original and that any liability for claims relating to the article will be borne by them.

Acknowledgements

The authors are grateful to the Biochemistry Department, Kwara State University, Malete for providing an enabling environment to carry out this research.

References

Aboagye, I. F., & Addison, Y. A. A. (2023). Praziquantel efficacy, urinary and intestinal schistosomiasis reinfection–a systematic review. *Pathogens and Global Health*, *117*(7), 623-630.

Abou-El-Naga, I. F. (2025). Receptors for growth and development of *Schistosoma mansoni*. Journal of Helminthology, 99, e29.

Alli-Shaik, A., Wee, S., Lim, L. H., & Gunaratne, J. (2017). Phosphoproteomics reveals network rewiring to a pro-adhesion state in annexin-1-deficient mammary epithelial cells. *Breast Cancer Research*, *19*(1), 132.

Aula, O. P., McManus, D. P., Jones, M. K., & Gordon, C. A. (2021). Schistosomiasis with a focus on Africa. *Tropical medicine and infectious disease*, *6*(3), 109.

Aulakh, S. K., Varma, S. J., & Ralser, M. (2022). Metal ion availability and homeostasis as drivers of metabolic evolution and enzyme function. *Current opinion in genetics & development*, *77*, 101987.

Azevedo, C. M., Meira, C. S., da Silva, J. W., Moura, D. M. N., de Oliveira, S. A., da Costa, C. J., Santos, E. D. S., & Soares,

M. B. P. (2023). Therapeutic potential of natural products in the treatment of schistosomiasis. *Molecules*, *28*(19), 6807.

Banda, H., & Abere, A. (2025). Determining the mechanisms of praziquantel resistance in schistosomiasis: insights and future directions. *Discover Medicine*, *2*(1), 105.

Brauer, B. L. (2022). *Deciphering Phosphoprotein Phosphatase Signaling Networks Using Proteomics Approaches* (Doctoral dissertation, Dartmouth College).

Buonfrate, D., Ferrari, T. C. A., Adegnika, A. A., Stothard, J. R., & Gobbi, F. G. (2025). Human schistosomiasis. *The Lancet*, *405*(10479), 658-670.

Cheng, S., Zhu, B., Luo, F., Lin, X., Sun, C., You, Y., Yi, C., Xu, B., Wang, J., Lu, Y., & Hu, W. (2022). Comparative transcriptome profiles of *Schistosoma japonicum* larval stages: Implications for parasite biology and host invasion. PLoS neglected tropical diseases, 16(1), e0009889.

Colley, D. G., Bustinduy, A. L., Secor, W. E., & King, C. H. (2014). Human schistosomiasis. *The Lancet*, *383*(9936), 2253-2264.

Da'dara, A. A., Bhardwaj, R., Ali, Y. B., & Skelly, P. J. (2014). Schistosome tegumentalecto-apyrase (SmATPDase1) degrades exogenous pro-inflammatory and pro-thrombotic ucleotides. *PeerJ*, *2*, e316.

Da'dara, A. A., Nation, C. S., & Skelly, P. J. (2024). Metabolism of FAD, FMN and riboflavin (vitamin B2) in the human parasitic blood fluke *Schistosoma mansoni*. BMC Infectious Diseases, 24(1), 636.

Daher, W., Cailliau, K., Takeda, K., Pierrot, C., Khayath, N., Dissous, C., Capron, M., Yanagida, M., Browaeys, E., & Khalife, J. (2006). Characterization of *Schistosoma mansoni* Sds homologue, a leucine-rich repeat protein that interacts with protein phosphatase type 1 and interrupts a G2/ M cell - cycle checkpoint. Biochemical Journal, 395(2), 433-441.

Dayanc, B., Eris, S., Gulfirat, N. E., Ozden-Yilmaz, G., Cakiroglu, E., Coskun Deniz, O. S., Karakülah, G., Erkek-Ozhan, S., & Senturk, S. (2025). Integrative multi-omics identifies AP-1 transcription factor as a targetable mediator of acquired osimertinib resistance in non-small cell lung cancer. *Cell Death & Disease*, *16*(1), 414.

De Roo, C., McLean, E., & Liu, R. (2025). Dual-specificity phosphatases: An update on their activity regulation and roles in metabolic diseases. *Current Opinion in Physiology*, *44*, 100816.

Eastham, G., Fausnacht, D., Becker, M. H., Gillen, A., & Moore, W. (2024). Praziquantel resistance in schistosomes: a brief report. *Frontiers in parasitology*, *3*, 1471451.

Fan, X., Zhou, C., Zhang, P., & Ming, Y. (2026). Effects of Different Living Environ-ments on Intestinal Flora in Patients with *Schistosoma* Japonicum-Induced Liver Fibrosis. MicrobiologyOpen, 15(4), e70366.

Freire, C. F., Souza-Lopes, T., Amaral, M. S., Tahira, A. C., & Verjovski-Almeida, S. (2026). Comprehensive *Schistosoma mansoni* Hierarchical Transcriptome Assembly Points to Novel lncRNAs Associated with Sexual Dimorphism. Non-coding RNA, 12(2), 9.

Freitas-Mesquita, A. L., & Meyer-Fernandes, J. R. (2026). Phosphate Acquisition in Protozoan Parasites: Transport Systems,

and Extracellular Phosphate-Releasing Enzymatic Activities. *International Journal of Molecular Sciences*, *27*(9), 3707.

Fréville, A., Gnangnon, B., Khelifa, A. S., Gissot, M., Khalife, J., & Pierrot, C. (2022). Deciphering the role of protein phosphatases in apicomplexa: the future of innovative therapeutics? *Microorganisms*, *10*(3), 585.

Gomes, B. F., Senger, M. R., Moreira-Filho, J. T., Vasconcellos, F. J. D., Dantas, R. F., Owens, R., Andrade, C. H., Neves, B. J., & Silva-Junior, F. P. (2023). Discovery of new *Schistosoma mansoni* aspartyl protease inhibitors by structure-based virtual screening. Memórias do Instituto Oswaldo Cruz, 118, e230031.

Hirst, N. (2019). *Schistosoma mansoni*: integration of phosphoproteomics, kinomics and CaMKII (Doctoral dissertation, Kingston University).

Hirst, N. L., Lawton, S. P., & Walker, A. J. (2022). CaMKII regulates neuromuscular activity and survival of the human blood fluke *Schistosoma mansoni*. Scientific Reports, 12 (1), 19831.

Hirst, N. L., Nebel, J. C., Lawton, S. P., & Walker, A. J. (2020). Deep phosphoproteome analysis of *Schistosoma mansoni* leads development of a kinomic array that highlights sex-biased differences in adult worm protein phosphorylation. PLoS neglected tropical diseases, 14 (3), e0008115.

Kamara, I. K., Thao, J. T., Kaur, K., Wheeler, N. J., & Chan, J. D. (2023). Annotation of G - protein coupled receptors in the genomes of parasitic blood flukes. *microPublication Biology*, *2023*, 10-17912.

Ke, D. T., Zhan, Z., Zhang, W., Hu, Z., & Chen, P. H. (2026). Deciphering phosphorylation TACtics: Advances in phosphorylation targeting strategies and bifunctional modalities. *Cell Chemical Biology*, *33*(2), 153-168.

Ku, B. (2025). Structural analysis of dual specificity phosphatases, the only type of protein tyrosine phosphatases found in humans and across diverse microorganisms. *Journal of Microbiology*, *63*(10), e2506006.

Li, X., Weth, O., Haeberlein, S., & Grevelding, C. G. (2023). Molecular characterization of Sm tdc-1 and Sm ddc-1 discloses roles as male-competence factors for the sexual maturation of *Schistosoma mansoni* females. Frontiers in cellular and infection microbiology, 13, 1173557.

Marhöfer, R. J., Noack, S., & Selzer, P. M. (2025). Antiparasitics discovery from genotype to phenotype to compounds. *Trends in Parasitolo-gy*, *41*(6), 431-440.

Mawa, P. A., Kincaid-Smith, J., Tukahebwa, E. M., Webster, J. P., & Wilson, S. (2021). Schistosomiasis morbidity hotspots: roles of the human host, the parasite and their interface in the development of severe morbidity. *Frontiers in immunology*, *12*, 635869.

Mtemeli, F. L., Ndlovu, J., Mugumbate, G., Makwikwi, T., & Shoko, R. (2022). Advances in schistosomiasis drug discovery based on natural products. *All Life*, *15*(1), 608-623.

Mughal, M. N. (2022). Characterization of the autophagy machinery in *Schistosoma mansoni*, a parasite of public health relevance (Doctoral dissertation, Dissertation, Gießen, Justus-Liebig-Universität Gießen, 2022).

N'Guessan-Koffi, C., De Witte, C., Franetich, J. F., Farce, A., Peucelle, V., Silvie, O., Toure, S., Marion, S., Gnangnon, B., Freville, A., Khalife, J., & Aliouat, E. M.

(2026). Molecular and cellular characterization of Plasmodium berghei PPM9 phosphatase, an enzyme dispensable during both asexual and sexual life cycle stages. *Scientific Reports*.

Nath, B., Chakraborty, S., & Biswas, S. (2026). PEG400 regulates Falcipain 2 activity through an allosteric mechanism. *The FEBS Journal*.

Odugbemi, A. I., Mthembu, W., &Zininga, T. (2026). Exploiting ER proteostasis in malaria: protein disulphide isomerases as selective antimalarial targets. *Expert Opinion on Therapeutic Target.*

Onyekwere, A. (2022). *Population genetic structure and hybridization of urogenital schistosomiasis among primary school-age pupils in Nigeria.* Doctoral dissertation, Université de Perpignan.

Padalino, G., Coghlan, A., Pagliuca, G., Forde-Thomas, J. E., Berriman, M., & Hoffmann, K. F. (2023). Using ChEMBL to complement schistosome drug discovery. *Pharmaceutics*, *15*(5), 1359.

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *bmj*, *372*.

Pereira Moreira, B., Weber, M. H., Haeberlein, S., Mokosch, A. S., Spengler, B., Grevelding, C. G., & Falcone, F. H. (2022). Drug repurposing and de novo drug discovery of protein kinase inhibitors as new drugs against schistosomiasis. *Molecules*, *27*(4), 1414.

Perla, S., Pascale, J., Liu, M., Kumar, A., Kuppuswamy, S., Alladi, C. G., & Samara, V. A. (2026). Protein Tyrosine Phosphatases in Cancer: From Oncogenic Drivers to Therapeutic Targets.

Rinaldi, G., Paz Meseguer, C., Cantacessi, C., & Cortés, A. (2024). Form and Function in the Digenea, With an Emphasis on Host–Parasite and Parasite–Bacteria Interactions. *Digenetic Trematodes*, 3-45.

Satala, D., Kowalik, K., &Karkowska-Kuleta, J. (2026). Cell surface shaving-based proteomic profiling of the surfaceome in pathogenic microorganisms. *International Journal of Molecular Sciences*, *27*(2), 1048.

Selzer, P. M. (2013). *Protein Phosphorylation in Parasites: Novel Targets for Antiparasitic Intervention*. John Wiley & Sons.

Skelly, P. J., & Da'dara, A. A. (2025). Expression, characterization and selective chemical inhibition of essential *Schistosoma mansoni* tegumental acetyl-cholinesterase SmTAChE). International Journal of Molecular Sciences, 26(5), 1975.

Slovakova, M., &Bilkova, Z. (2021). Contemporary Enzyme-Based methods for Recombinant proteins in vitro phosphorylation. *Catalysts*, *11*(8), 1007.

Stephens, D. R., Fung, H. Y. J., Han, Y., Liang, J., Chen, Z., Ready, J., & Collins III, J. J. (2025). A genome-scale drug discovery pipeline uncovers therapeutic targets and a unique p97 allosteric binding site in *Schistosoma mansoni*. Proceedings of the National Academy of Sciences, 122(35), e2505710122.

Thiriet, M. (2012). Cytosolic Protein Phosphatases. In *Intracellular Signaling Mediators in the Circulatory and Ventilatory Systems* (pp. 387-463). New York, NY: Springer New York.

Tuazon, J. A. (2024). *The Ikaros zinc finger transcription factor Eos as a novel regulator of STAT5 phosphorylation in CD4+ T helper cells*. The Ohio State University.

Villamizar-Monsalve, M. A., López-Abán, J., Vicente, B., Peláez, R., & Muro, A. (2024). Current drug strategies for the treatment and control of schistosomiasis. *Expert Opinion on Pharmacotherapy*, *25*(4), 409-420.

Walker, A. J., Rinaldi, G., & Shakir, E. M. (2025). Molecular interactions between male and female schistosomes–a role for remote communication? *Trends in Parasitology*, *41*(1), 28-37.

World Health Organization. (2026). *Schistosomiasis*. https://www.who.int/-news-room/fact-sheets/detail/schistos-omiasis

Wu, L., Xu, H., Zhang, X., Zhang, M., Xu, Y., Zhang, Q., Tao, H., Dong, C., Zhang, X., Zhou, M., Yang, J., & Song, Q. (2025). Integrated proteomics and phosphoproteomics profiling dynamic signaling networks underlying two distinct types of macrophage activation. *Cellular Immunology*, *413*, 104972.

Zhong, Q., Xiao, X., Qiu, Y., Xu, Z., Chen, C., Chong, B., Zhao, X., Hai, S., Li, S., An, Z. & Dai, L. (2023). Protein posttranslational modifications in health and diseases: Functions, regulatory mechanisms, and therapeutic implications. *MedComm*, *4*(3), e261.