Antigens of Three Medically Important *Schistosoma spp*

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Review Article

ABSTRACT

The present study was carryout to review the antigens of three (3) medically important Schistosomes namely: *Schistosoma mansoni*, *S. haematobium,* and *S. japonicum*. The parasites-host relationship, the antigens, the species that produce the antigens, and the functions of the antigens were discussed. Identified antigens include: Sm-24 kDa, Sm108 kDa, Polymorphic mucins, 28/30 kDa Protease, 47 kDa protease, 60 kDa protease, Cercarial Elastase (CE) also called 28/30 kDa, Cathepsin, 22.6 kDa, 23 kDa, 16 kDa/SLP/SPO-1, Prostaglandin E2 (PGE2), SmEnolase, SmCalp1, 28-kD GST (rSh28GST), 29-kDa, Calpain (Sp80) and SG3PDH. The above mention antigens of the parasites were found to be much important since they enable them to compete with body immunity while carrying out their metabolic activities, reproduction, growth, defense, resistance, and so many other things within the host. Therefore, these antigens are very important in immunological studies; hence, it was recommended that, Since some parasite antigens were found to be promising candidates for developing a vaccine to protect against Schistosoma infection, more parasite antigens should be searched for the best planning and development of numerous strategies that aid in the prevention and control of schistosomiasis.

Keywords: Antigens; S. mansoni; S. haematobium; S. japonicum.

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1. INTRODUCTION

Schistosomes are dioecious parasitic flukes related to the kingdom Animalia and the phylum Platyhelminthes that inflict Schistosomiasis /Bilharziasis, also referred to as Snail fever, in humans and other animals [1]. Schistosomiasis is divided into two types: intestinal and urinary/urogenital schistosomiasis [2].

Infected individuals passed Schistosoma eggs in their feces or urines in a freshwater ecosystem containing snails of the genus *Bulinus* or *Biomphalaria* [3]; under perfect circumstances, they lay eggs and discharge miracidia, which swim and enter a specific snail intermediate host [4]; the miracidia inside the snails developed two generations of sporocysts before emerging to infective [5]. The infectious cercariae swim and penetrate the skin of human hosts while carrying out their activities in the polluted water once the cercariae out from snails are released into the water body [6].

As a result of larger growth in schistosomiasis cases, the global health burden of schistosomiasis is increasingly being compared to that of malaria or tuberculosis in certain analyses [1,5]. Due to the parasites' harboring of numerous resistance antigens, Schistosoma infections can cause lasting damage to different organs, as well as substantial morbidity and disastrous effects on early childhood, adult productivity, and in some cases, death [7].

Because of the sluggish formation of naturally adaptive immunity against pathogens in human bodies, *S. haematobium* causes varying levels of resistance to re-infection in people [8]. This has been ascribed to the need for the immune system to be exposed to enough parasite antigens, as well as the parasites' efficient immune avoidance tactics [9].

Because the primary strategy for schistosomiasis control is the treatment of infected individuals with antihelminth drugs, and praziquantel, which has been widely used, is not 100 percent effective against the three primary Schistosoma species affecting humans (i.e., *S. mansoni, S. japonicum, and S. haematobium*) [10] it is there for important to review on the antigens of schistosomes with their functions as this might help in designing best research that could help in the development of strong and complementary methods of prevention and control of schistosomiasis globally.

2. ANTIGENS OF SCHISTOSOMES DURING PARASITES-HOST RELATIONSHIP

An antigen is any agent that causes an organism's body produces antibodies against it; the substance that causes the immune system to produce antibodies (such as chemicals, bacteria, viruses, or pollen) can come from the outside environment of organisms or even from within the organism's body; antigens can activate lymphocytes, which are the body's infection-fighting white blood cells [11]. Foreign antigens (heteroantigens) come from outside the body, and include parts of or substances produced by parasites (such as bacteria, protozoa, and helminths), as well as substances in snake venom, specified protein molecules in foods, and components of serum and red blood cells from other individuals; while, autoantigens, on the other hand, come from within the body [12].

The body can normally distinguish self from non-self, but in people with autoimmune illnesses, normal physiological substances trigger an immunological response, resulting in the production of autoantibodies; thus, any antigen that triggers an immune response is referred to as an immunogen [13].

Antigenic determinants are areas on the surface of antigens that fit and bind to receptor molecules on the surface of antibodies that have a complementary structure [14]. Antibodies multiply and immune responses such as the formation of new antibodies, the activation of cytotoxic cells, or both against the antigen are triggered when lymphocyte receptors bind to the antigens' surface molecules [15].

Because the immune systems of infected hosts have several life cycle stages of Schistosoma parasites that it must confront [16], schistosomes as helminths internal parasites must rely on and interact with the host for their survival. Cercariae, schistosomula, adult schistosomes, and the eggs generated by adult worms are the life cycle stages that challenge host immunity, and these stages must express various antigens to fit in with the host environment for their metabolic activities [17]. "Many of these antigens may also easily detect and induce cellular, humoral, and immunological responses; some of these responses remain elevated during acute and chronic infection, while others are significantly reduced" [18].

"Even though immunodiagnostics, immunology in *Schistosoma* afflicted people to ascertain resistance to infection or re-infection, immunopathogenesis, and its immunoregulation are the main areas that emerge when looking at human immune responses during schistosomes and host interactions" [19], "such regions mostly focuses on responses to eggs that are either exiting the body via the excreta or are caught in bodily tissues such as the intestine, liver, bladder or blood", [20].

"The availability of urine experimental infection models has aided much understanding of human immune responses to schistosomes" [21]. "*S. haematobium* infections have been less instructive since adult worms do not migrate to the venous plexus and deposit eggs in the bladders of mice, but the development of an *S. haematobium* egg injection model has begun to yield insights into the pathogenesis of this parasite" [22,23].

"Parasite migrations in humans are unknown, but they are expected to be identical to those in experimental animals, with the same end result: adult worm pairs at certain sites, worms that live in those favored venous settings appear to be immune-resistant, multiple mechanisms are thought to be responsible for their long-term survival in an immunological milieu that is hostile (but ineffective). Some of these could be attributed to the schistosomes' ability to replenish their outer tegument through distinct somatic stem cells, as well as their ability to masquerade through molecular mimicry or the acquisition of host antigens" [24].

Some features of *Schistosoma species* survival, such as isotopic alterations in antigen specificities and immunoregulation, may also include modifications of the host's immunological responses [25]. The protective immune response to schistosome infections has already been extensively studied using mouse models, especially using *S. haematobium* as the infecting species, and it has been discovered that both antibodies and T-cells are required for extra safety [26]. Exposure to reduced cercariae that die before reaching maturation provides excellent protection; single exposure to attenuated cercariae results in limited protection, which is principally connected with the generation of IFN-, whereas antibody responses become more essential in the protection of mice that have been treated to attenuated parasites multiple times [27].

"Adult worms generate eggs in their venous sites that are supposed to be taken out of the body via feces or urine and discharged into the environment (from the worms' perspective). However, venous blood flow transports many of the eggs in the opposite direction or makes it difficult for them to leave; the eggs contain a range of proteases antigens, and other potentially harmful moieties, which can cause necrosis once lodged in the tissues" [28]. "Granuloma production is the host's defense against this tissue insult, and it serves to wall off and contain the egg and the proteolytic antigens it releases; immunomodulation of anti-egg antigen responses (granuloma development) develops efficiently in mice and most people during persistent infections to prevent them from overwhelming tissue locations or limiting venous blood flow" [29].

"Soluble worm antigen (SWA) of *S. mansoni* was utilized as a good control; experimental *S. mansoni* infections in T cell defective mice revealed key roles for the immune response in worm maturation and granuloma formation" [30]. Mice have a balanced or Th1 immune response to parasite antigens during the early stages of infection; however, once egg deposition begins around 6 weeks after infection, a dramatic shift to a Th2-type response occurs, this immunologic shift is caused in part by specific schistosome egg antigens interacting with dendritic cells, and in part by the action of certain carbohydrate epitopes [31]. "In humans, uncontrolled production of the Th2 cytokine IL-13 leads to extensive liver fibrosis, which is the functional cause of hepatosplenic disease" [32].

However, "because depletion of Th2 responses, particularly IL-4, leads to internal necrosis and host mortality as a consequence of increased pro-inflammatory Th1-type responses, Th2 reactions also serve as a host protective role, and their proper control reduces overall host pathology. Activated macrophages and IL-10, on the other hand, are part of the Th2-type regulatory feedback that limits the initial granulomatous inflammation, which peaks in size and severity at 8 weeks after *S. mansoni* infection" [33]. "As the infection progresses, these and other immunomodulatory mechanisms further limit granuloma formation, resulting in smaller granulomas and less fibrosis in newly deposited eggs after 12 weeks of infection" [34].

"Initial reports on schistosome molecular mimicry in host species was presented in 1965, when it

was discovered that *B. glabrata* had antigens that were similar to those identified in maturing *S. mansoni* larvae" [35]." Polyclonal antibodies to hemolymph from *S. mansoni* resistant (10-R2) and susceptible (M-line) *B. glabrata* strains later proved this, with both interacting extensively with the surface of *S. mansoni* miracidia and sporocysts" [32]. "This relationship lasted for at least 48 hours after the larvae were changed from miracidia to sporocyst, implying that the working to develop larvae share at least certain surface antigens during the first 48 hours of infection, when they are most likely to be targeted by the snail immune response; cross-reactive immunoglobulin tests also suggest some form of molecular mimicry, but such studies lack the specificity required to examine shared antigens" [36].

Glycan mimicry is thought to be aided by larval transformation products (LTPs) generated by the Schistosoma parasite during miracidium-to-sporocyst transformation, however, host hemolymph proteins and systemic hemocytes can react with LTPs because far-western blotting revealed a distinct binding pattern between LTPs and hemolymph proteins isolated from *B. glabrata* strains with varied compatibility with *S. mansoni*. This shows that *S. mansoni* uses various glycan epitopes antigens during larval metamorphosis [37].

When Cercaria intends to penetrate an individual's skin, the process of penetration may be aided by both mechanical movement and antigen that breaks down cell-to-cell adhesions [38]. The head gland, sub-tegumental cell bodies, and acetabular glands are all potential sources of antigen [39]. While each of these sources may play a role in parasite penetration, the acetabular glands, which contain lengthy duct-like cytoplasmic extensions extending to the parasite anterior and are filled with proteases, are the most plausible suspect. Acetabular gland secretions are produced during migration through the skin's collagen-rich basement membrane and have been confirmed to secrete for up to three days after infection [16].

Proteolytic factors responsible for skin penetration have been discovered to use a wide range of serine protease antigens to degrade host structural components [40]. During penetration, *S. mansoni* creates many serine proteases, which are discharged from its acetabular glands [41].

3. SCHISTOSOMA ANTIGENS AND THEIR FUNCTIONS

Antigens from schistosomes are thought to play a role in the pathological physiology of schistosomiasis, Numerous schistosomes antigens have been studied, with the majority of them derived from *S. mansoni, S. haematobium,* and *S. japonicum*; categorization of schistosome antigens recognized by monoclonal antibodies (MoAbs) could improve schistosomiasis influence for two main reasons [42]. Initially, those very antigens may contain specific markers that serve as targets for immune attack, making them possible future candidates for vaccine development; second, where the antigen has the diagnostic possibility, it can be investigated to improve diagnosis and provide useful information on schistosome evolution and classification [43].

When *S. mansoni* enters the snail, it releases venom allergen like protein 9 named SmVAL-9, which causes the up-regulation of *B. glabrata* matrix metalloprotease; this is an important metalloprotease in remodeling tissue, and it is maybe hypothesized that this facilitates parasite entry and penetration into host tissue [44]. A study of excretory/secretary (E/S) product synthesis by sporocysts in vitro identified two more immune modulators. The first is a polypeptide of around 24 kDa that was found to be capable of inhibiting protein synthesis by snail hemocytes in vulnerable M-line snails, but not in the more resistant 10-R2 strain [45]. The existence of a Sperm-coating protein/Tpx-1/Ag5/PR-1/Sc7 (SCP/TAPS) domain in the *S. mansoni* genome was demonstrated to feature 29 of these proteins, which are characterized by the presence of a venom allergen-like protein family [46].

Using mass spectrometry, the SmVALS 4, SmVAL 10, and SmVAL 18 were discovered in the E/S components of cercaria, accounting for around 3% of the normalized proteins detected there [47]. SmVAL24 has been found in the acetabular glands using whole-mount in situ hybridization, although only two of the SmVAL proteins have been functionally described to date [48]. SmVAL4 has the ability to bind lipids and cholesterol, albeit it has yet to be determined how this can affect the host immune response [49].

SmVAL18, on the other hand, has been demonstrated to bind plasminogen and aid in its breakdown into plasmin, a protein involved in

complements element degradation, extracellular protein denaturation, and fibrinolysis. As a result, SmVAL18 could potentially aid parasite migration through the epidermis and prevent blood clotting after venule penetration [50]. Only one VAL, Sj-VAL-1, has been studied in *S. japonicum*, and it has been found to localize to cercariae penetration and head glands, suggesting a probable role in migration into host venules (Chen et al., 2018).

108 kDa is protein that was demonstrated to be able to scavenge superoxide anions produced by phagocytosis-stimulated M-line of *B. glabrata* hemocytes, thus shielding the parasite from this harmful oxygen species [51].

S. mansoni up-regulated an invadolysin 33.2-fold in *B. glabrata* hemocytes 12 hours post infection, and this invadolysin, identified as SmLeish, was revealed to be capable of reducing the velocity of susceptible M-line *B. glabrata* hemocytes. This function is important for reducing the frequency with which sporocysts are encapsulated by hemocytes in vitro, and it was also discovered to be important for *B. glabrat*a survival [52]. *S. mansoni*'s mimicry goes beyond surface epitopes, since sporocysts can create host-like adrenocorticotropic hormone, which is converted by host hemocytes into melanocytestimulating hormone, causing hemocytes to circle up towards the sporocyst [53].

Polymorphic mucins (SmPoMucs) of *S. mansoni* are also group of antigens that were discovered as part of a proteomics screen to find preferentially abundant proteins produced by *B. glabrata*-compatible and incompatible strains of *S. mansoni*, and have since become one of the most intensively studied constituents of resistance polymorphism in the *S. mansoni* system; these antigens have variability that should be considered as a key mechanism [54].

A 28/30 kDa protease capable of cleaving casein, gelatin, C3, C3b laminin, fibronectin, keratin, and collagens IV and VIII; a 47 kDa protease capable of cleaving gelatin, casein, collagen type VI, and elastin; and a 60 kDa protease capable of cleaving casein and gelatin are among these proteases [55].

SmCE (Schistosoma mansoni Cercarial Elastase) which is also called 28/30 kDa variant antigen, is the most important, accounting for around 36% of the total volume of acetabular gland contents [56]. The presence of SmCE throughout the intra-mammalian section of the *S. mansoni* life cycle emphasizes its relevance. Cercariae, lung stage schistosomulae, and adult worms all have a membrane-bound version of the protein [57]. Although *S. haematobium* has a protease similar to SmCE antigen that fulfills the same role as *S. mansoni,* it was long assumed that *S. japonicum* did not produce any serine protease during first penetration events because SmCE antibodies did not react with *S. japonicum* cercarial extracts [58].

Proteomic analysis of the host/parasite molecular interface during *S. japonicum* penetration into mouse skin revealed a single *S. japonicum* cercarial elastase (SjCE2b) produced in cercaria and localized to the acetabular glands, though levels of this protein are low compared to those found in *S. mansoni* and *S. haematobium* [59].

Sm16/SmSLP/SmSPO-1 antigens is an anti-inflammatory protein discovered in *S. mansoni*, it makes up around 3–4% of the protein released by cercariae within the first 3 hours after infection, implying a role in parasite survival [57]. Sm16.8 kDa was shown to change cytokine profiles by inhibiting Il-1a production in keratinocytes, lowering ICAM-1 expression in endothelial cells, preventing LPS-induced neutrophil migration into the dermis, and decreasing LPS-mediated IL-6, TNF-a, and IL-1b production [60]. It reduces the ability of mouse bone marrow derived macrophages to produce Il-12p40, IL-10, and IFN-ginduced NO 2, as well as decreasing antigen processing by phagocytic cells in mice [61].

Sj16 is the Sm16.8 kDa counterpart found in *S. japonicum* that has also been shown to have immunomodulatory properties, including a reduction in macrophage maturation and modulation of cytokine production in thioglycolate-induced peritoneal mouse cells by upregulating IL-10 and IL-1RA while downregulating MIP-2, IL-1b, and IL-12p35 [62]. Sj16.8 kDa has the ability to increase the number of CD4+ CD25+ Foxp3+ regulatory T cells, implying that it can not only suppress inflammatory responses but also help to generate a regulatory response [63].

It was discovered that Schistosome E/S fractions containing a 23 kDa antigen have been shown to specifically target T lymphocytes for apoptosis, a process thought to be mediated by causing an up-regulation of both the Fas Ligand and Fas receptor on CD3+ cells [64]. The inability of

vaccinated mouse lymphocytes to recognize the E/S products of invading parasites may be partly due to the loss of T lymphocytes during early penetration, as a functional T cell driven response would be significantly impeded [65].

S. mansoni can produce prostaglandin E2 (PGE2), as well as an E/S product of less than 30 kDa in size that can up-regulate the production of PGE2 and IL-10 from human keratinocytes; this appears to be important for infection kinetics, as IL-10 deficient mice are able to slow schistosomula travel through the skin and into the lungs [66]. The 23 kDa and 30 kDa immunomodulatory antigens were discovered through filtration of schistosome E/S products, although their specific molecular identities have yet to be determined. Yet, the usage of prostaglandins is not restricted to PGE2, as PGD2 produced by the parasite prevents epidermal Langerhan cells from migrating to neighboring lymph nodes. Given that the generation of PGD2 by S. mansoni requires a 28 kDa Glutathione S-transferase, the possibility of using such a factor as a vaccine candidate was investigated in the early 1990s. Sadly, recent phase 3 clinical trials of the S. haematobium-derived rSh28GST (Bilhvax) vaccine have shown that it is ineffectual in providing considerable immunity [67].

SmKK7, a protein with considerable resemblance to K+ channel blockers in scorpion venom, is another possible immunomodulator that has yet to be functionally defined. This might potentially work in limiting the activation of surrounding lymphocytes [48]. While mechanical movement throughout the epidermis aids in the loss of the glycocalyx, the close interaction of SmCE has been indicated as a possible assistance during this process [64]. While the glycocalyx is shed, schistosomulae go through a complex remodeling of their outer membrane, transitioning from a trilaminate to a heptalaminate form that lasts until adulthood [68]. This freshly created heptalaminate membrane then begins to exhibit a number of surface-bound components aimed at preventing complement and immunoglobulin-based attacks. Paramyosin, a chemical found in both schistosomula and adult worms, is one of these molecules. On schistosomulae exposed to human serum, paramyosin has been demonstrated to bind complement components C1, C8, and C9, preventing the membrane assault complex from polymerizing and depositing [69].

Two antigens found in S. mansoni namely, SmEnolase and SmCalp1, are thought to aid in tissue disintegration at least in part. Their presence in the eggs is thought to aid in fibrinolysis [70]. Furthermore, the egg is thought to aid its own survival by producing SmKI-1 as a means of surviving neutrophil elastase-mediated death, as well as a chemokine binding protein (SmCKBP) that reduces inflammation and inflammatory cell recruitment via the binding of CXCL8 and CCL3; these immune modulating and immune evading tactics allow the egg to migrate through the host intestine/bladder, eventually being excreted in order to begin the [71].

Cathepsin B is one of the schistosomes' portentous antigens that relates to the cysteine proteases, a group of lysosomal cysteine proteases that has been discovered to play a significant role during intracellular proteolysis [72]. A heavy chain ranging from 25 to 26 kDa and a light chain of 5 kDa are found in mature cathepsin B, and these chains are linked by disulfide dimers [73].

Cathepsin B is involved in the control of IL-12 production as well as the expression of antigen-presenting MHC class II molecules [74]. It also boosts the activity of other proteases such matrix metalloproteinase, urokinase (serine protease urokinase plasminogen activator), and cathepsin D, therefore it's crucial for extracellular matrix proteolysis, intercellular communication disruption, and reduced protease inhibitor expression [75]. It is also engaged in autophagy and catabolism, both of which are beneficial in tumor malignancy. It was recently discovered to have minimal ligase activity, allowing it to bind peptide fragments via an amide bond, and it may be implicated in particular immunological resistance [76].

S. mansoni cathepsin B1 (SmCB1), one of substantial worm extract peptides and also Excretion Secretion Proteins (ESPs), has been recognized as a critical anti-schistosome vaccine candidate with the ability to initiate Th17 responses in addition to Th1 and Th2 responses in various studies conducted on Schistosomes [77, 78]. Major hemoglobin-digesting enzymes found in S. haematobium include SmCB1 and S. mansoni cathepsin L1 (SmCL1, CL) [79] (Wendt et al., 2020). SmCB1 is mainly expressed in cercariae's caecum and protonephridia, whereas SmCL1 is found in the gastrodermis and

tegument of mature worms [80]. SmCB1 and SmCL1 are both important ESPs [81].

Recent research has found that vinyl sulfone inhibitors enzymes of the SmCB1 target may have the ability to affect parasiteic growth, as well as that interfering RNA of SmCB1 inhibited parasite development both in culture and in an animal study of transmission [79,82].

In CD-1 mice and Syrian hamsters, adjuvant-free, enzyme active SmCB1 or FhCL1 in recombinant version alone or in combination with another vaccine candidate SG3PDH/PRX-MAP were seen to stimulate greater protection with an increase in IgG1 isotype titers (no IgE was detected) and Th2 cytokines against *S. mansoni* and *S. haematobium* infection [79,80]. Immunization of CD-1 mice and Syrian hamsters with active rSmCB1 and SmCL3 alone or in combination with rSG3PDH resulted in significant protection against *S. mansoni* and *S. haematobium* challenge infection, indicating that the efficacious trivalent vaccine should now be tested in nonhuman primates for evaluation as a potential vaccine to control human schisto-somiasis [79].

Despite producing less protein upon change to schistosomulae than *S. mansoni*, cathepsins have emerged as an alternate facilitator of penetration in *S. japonicum* cercaria, which have up to 40-fold higher cathepsin-B-like activity than their *S. mansoni* counterparts [58,59].

Cathepsins are still produced by *S. mansoni*, and two of them (Cathepsin L1 and Cathepsin B) are found in the parasite's post acetabular glands. Given the significance of post acetabular glands in creating mucous-like secretions to aid adhesion to host skin, these cysteine proteases could play a role in breaking down the skin's immunological barrier. Alternatively, the fact that cathepsin activity is involved in the adult schistosome gut suggests that the presence of cathepsins in cercaria could simply be evidence of the development of digestion-related elements in later life cycle stages [83].

Sm23, SG3PDH, calpain, Sm-TSP-2, saponin B domain-containing proteins, GST, Sm29, cathepsin domain-containing proteins namely cathepsin B and cathepsin L, proteases, and oxidants were previously announced to also be developed in worm generated 15 k (286 proteins) and 120 k (716 proteins) membrane proteins (EVs) [81,84,85].

Distinctive ESPs antigens were obtained from cercariae, lung-stage schistosomula, and adult worms from several schistosome species [86]; Tetraspanin, Sm/Sh22.6, Sm29, Sm200, and phosphadiesterase are Cathepsin B antigen family that are extensively expressed throughout the schistosomula phase (Gobert et al., 2010). Furthermore, research that used the RNAi approach to silence genes revealed the relevance of these certain proteins for parasite proliferation and survival [87]. Using mass spectrometry (MS)-based proteomics and information from the genome, transcriptome, and genetic maps, similar membrane protein was found in adult worm tegument preparations [88].

Previously, a proteomic findings show that Sm29 and Sm200 are linked to the parasite cell surfaces via a GPI-anchor, while aquaporin, dysferlin, TSP-2, and ATP diphosphohydrolase are the most abundant proteins in adult worm tegument, among some of the investigated molecules. All of these proteins express a catalog of protein expressed in the schistosome tegument, and some of them have been evaluated as vaccine antigen in Castro-Borges et al., [89].

Sm22.6 is a tegumental protein that has a counterpart in *S. japonicum* (Sj22.6) and in endemic situations, *S. haematobium* (Sh22.6) is involved in re-infection resistance (Dunne et al., 2017; Santiago et al., 2018) with freund adjuvant had a 34.5 percent reduction in worm burden, whereas Sm22.6 formulated with alum did not induce protection against schistosomiasis but did induce a regulatory response that modulated allergic asthma in mice [90].

In both Ghanaian and Egyptian parasite strains, a 29 kDa *S. haematobium* species-specific antigen (ShSSA) was discovered. Despite the efficacy of a monoclonal antibody (MAb) to ShSSA in a field dipstick for the diagnosis of urinary schistosomiasis, ShSSA has not been completely described [91].

S. haematobium 28-kD GST (rSh28GST); *S. mansoni* 14-kDa (Sm14); *S. mansoni* tetraspanin; 9-kDa surface antigen; Sm-TSP-2; and *S. mansoni* calpain (Sm-p80) are among the recombinant antigens (Aya *et al.* 2021). Many of the above-mentioned antigen candidates, such as TSP-2, Sm23, GST, Sm29, and calpain, have recently been discovered in extracellular vehicles (EVs) of schistosome adult worms [81]; extracellular vesicles are membrane-enclosed

vesicles that are constantly secreted by different types of cells and play an important role in removing unnecessary cell components [92].

The 28 kDa glutathione S-transferase of *S. haematobium* vaccine, commonly known as the 28 kDa glutathione S-transferase (Sh28GST) vaccine, is a major ESP expressed in the tegument and sub-tegument of adult and larval schistosomes [80]. It plays a key function in fatty acid metabolism and prostaglandin D2 synthesis, and it may help parasites evade the immune system [93].

In chimpanzees and patas monkeys, recombinant *S. haematobium* glutathione S-transferase (rShGST) vaccine mediated high levels of protection associated with intense specific IgG and IgA antibody responses; phase 1 trial was done to examine the safety and tolerability of two or three intramuscular injection of 100 lg rSh28GST antigen with Alum as adjuvant in young, healthy, Caucasian male [67]. The vaccine's safety, tolerability, and immunogenicity were also demonstrated in adults and children living in endemic areas [94].

The only antigen for Bilharziasis that has reached Phase 3 clinical trials is rShGST; in Phase 3, 250 Senegalese children aged 6–9 years old were cured of schistosome infection and randomized to receive three subcutaneous injections of either rSh28GST/Alhydrogel (Bilhvax group) or Alhydrogel alone (control group) at four-week intervals, followed by a booster one year after the first injection. In addition, students who receive the rSh28GST vaccine had higher levels of essential IgG1, IgG2, and IgG4 antibodies, but no IgG3 or IgA isotypes. Acquired immunity to Sh28GST is associated to IgG3 and IgA antibodies in human groups. The failure to achieve protection against urinary schistosomiasis could be due to an issue with antibody isotypes or the distorting effect of PZQ treatment prior to the first and last immunizations [47,95].

The vaccination against *S. haematobium* 28 kDa glutathione S-transferase (Sh28GST) is exhibited in the tegument and subtegument of adult and larval schistosomes, and is the most common Ecretion Secretion Proteins [80]. It plays a key function in fatty acid metabolism and prostaglandin D2 synthesis, and it may help parasites evade the immune system [93]. Some many studies in rodents, primates, and cattle

using the recombinant protein (expressed in Saccharomyces cerevisiae) revealed a partial protective effect against schistosome infection, a significant reduction in worm burden (40–60 percent), and a substantial decrease in female worm reproductive capacity and eggs viability [96].

In rats and baboons, the Sm-p80 ortholog expressed in the tegument of *S. japonicum* and *S. haematobium* adult worms offered considerable cross-species resistance against *S. mansoni, S. japonicum,* and *S. haematobium* illnesses [97]. Recombinant Sm23 and other TSPs extracted from adult *S. haematobium* worms were shown to induce significant protection against challenge infection with *S. mansoni*, as measured by reductions in liver (47 percent, 38 percent, and 41 percent) and intestinal (47 percent, 45 percent, and 41 percent) egg burdens. These findings suggest that EV surface proteins could be exploited to develop anti-schistosome vaccines (Mekonnen, 2020)

The SG3PDH antigen is one of the most promising vaccine candidates for schistosomiasis, and it helps to prevent re-infection [98]. However, because of its high homology (72.5%) with human G3PDH, the whole parasite proteins cannot be used as a vaccine for fear of inducing autoimmune responses. As a result, it is preferable to choose SG3PDH derived-peptides with the least resemblance to human peptides, and the peptides were chosen for the development of a safe synthetic peptide-based vaccination; These peptides were studied in serum and lymphocytes from humans resistant to re-infection with *S. mansoni* or *S. haematobium* after treatment with PZQ for previous infection, as well as BALB/c and C57BL/6 mice immunized with recombinant rSG3PDH (rSG3PDH); the findings revealed that SG3PDH-derived peptides contain human and murine T- and B-cell determinants, and immune responses to EL Ridi et al., [80].

The 29 kDa protein is a glycosyl-phosphatidylinositol (GPI) integral protein found in the tegument of mammalian adults and lung-stage schistosomula, but not in cercariae, suggesting that this antigen aids the parasite in adjusting to its new environment in mammalian hosts [99]. Sm29 may potentially assist the schistosome evade immunological responses by interacting with the human protein CD59, which suppresses the Membrane Attack Complex

Table 1. Summary of some schistosomes' antigens, Species that produced them, Importance and References

S/N	Antigen(S)	Species that Posses the Antigens	Function of the Antigens	Reference (s)
1.	Venom Allergen-like (VAL) antigen family	*S. mansoni* *S. japonicum*	They promote the parasites access and entry into host tissue; they possess the capacity to combine lipids and cholesterol; they have ability to prevents blood clotting following penetration.	Fernandes et al., [48]; Yoshino et al., [44]; Fernandes et al., 2019
2.	Sm-24 kDa	*S. mansoni*	Blocking snail hemocytes' ability to make protein	Connors et al., [45]
3.	Sm108 kDa	*S. mansoni*	The antigen has the capacity to scavenge superoxide anions produced by *B. glabrata* hemocytes' M-line driven phagocytosis; it protect the parasite from these damaging oxygen.	Dinguirard et al., [51
4.	Polymorphic mucins (SmPoMucs)	*S. mansoni*	It provide with resistance polymorphism components in the *S. mansoni* system	Roger et al., [54]
5.	28/30 kDa Protease	*S. mansoni*	Ability to break casein, gelatin, collagens IV and VIII, C3 and C3b, fibronectin, and laminin	McKerrow and Salter, [55]
6.	47 kDa protease	*S. mansoni*	Gelatin, casein, collagen type VI, and elastin can all be broken down by it.	McKerrow and Salter, [55]
7.	60 kDa protease	*S. mansoni*	These proteases include those that can cleave casein and gelatin.	McKerrow and Salter, [55]
8.	Cercarial Elastase (CE) also called 28/30 kDa	*S. mansoni* *S. haematobium* *S. japonicum*	roughly 36% of acetabular proteins are elastase antigens	Roger et al., [54]
9.	Cathepsin	*S. mansoni* *S. haematobium* *S. japonicum*	Enhancing cercarial adherence to the host skin; Weakening the skin's immune system; growth of digestive components in later life cycle stages; drug-resistant in parasites; They were tested as potential vaccination candidates.	Liu et al., [59]; Dalton et al., [83]; Dvorǎ et al., [58]
10.	22.6 kDa	*S. mansoni* *S. haematobium* *S. japonicum*	Re-infection resistance; Vaccine candidates	Dunne et al., 2017; Santiago et al., 2018; Pac'fico et al., 2016
11.	23 kDa	*S. mansoni* *S. haematobium* *S. japonicum*	Selectively induce apoptosis in T lymphocytes	Kumar and Ramaswamy, [65]
12.	16 kDa/SLP/SPO-1	*S. japonicum* *S. mansoni*	It influences cytokine profiles and decreases the capacity of mouse bone marrow-derived macrophages to generate IL-12p40, IL-10, and IFN-ginduced NO_2; It also has a function in enhancing parasite survival.	un et al., 2012; Curwen et al., [56]; Crosnier et al., [61] Salter et al., [60]; Hu et al., [62]
13.	Prostaglandin E2 (PGE2)	*S. haematobium* *S. mansoni* *S. japonicum*	It stops the migration of epidermal Langerhan cells to nearby lymph nodes.	Hervé et al., 2013; Riveau et al., [47]
14.	SmEnolase and SmCalp1	*S. mansoni*	Aid in tissue deterioration; it is believed that their presence in eggs facilitates fibrinolysis	Figueiredo et al., [70]
15.	28-kD GST (rSh28GST);	*S. haematobium*	Removal of superfluous cell components; Use as a source for vaccines, and potential aid to parasites in evading the immune	Tebeje et al., [93]; Pluchino and Smith [92]; Aya et al. 2021;

S/N	Antigen(S)	Species that Posses the Antigens	Function of the Antigens	Reference (s)
			system; It is crucial for fatty acid metabolism and the production of prostaglandin D2.	
16.	29-kDa	*S. mansoni*	It is believed to be an immunoregulatory molecule that regulates inflammatory mucosal illnesses; Plays a significant role in the removal of extracellular components; Aids parasite adaptation to mammalian hosts.	Sotillo et al., [99]; Bear et al., [100]; Oliveira et al., 2016).
17.	Calpain (Sp80)	*S. mansoni* *S. japonicum* *S. mekongi*	Act as a source of vaccination and play a significant function in eliminating extraneous cell components.	Molehin et al., [97]; Mekonnen et al., 2020
18.	SG3PDH	*S. mansoni* *S. haematobium*	One of the most promising schistosomiasis vaccine options, and it aids in preventing re-infection	McManus and Loukas [98]; EL Ridi et al., [80]

(MAC) and hence aids the parasite in evading immune responses [100].

Sm29 kDa was prepared with alum or monophosphoryl lipid adjuvant (MPLA) and given to BALB/c mice re-infected with *S. mansoni* in another investigation. Sm29-alum produced protective effects against superinfection and decreased worm load by 29–37%, whereas Sm29-MPLA did not, demonstrating that Sm29-alum can successfully prevent mice from *S. mansoni* re-infection [101].

In Swiss albino mice, the mixture of Sm29 and Sm14, identified as Sm14/29 alone or in conjunction with polyinosinic-poly cytidylic acid adjuvant, resulted in significant reductions of adult worm burden by 48.4 percent and 44.7 percent, liver egg burden by 82.8 percent and 73.5, and intestinal egg count by 72.8 percent and 76.6 percent, respectively; similarly, Sm29 [102-106]. The above mention antigens and their functions as well as the spp that produce them were summarized in Table 1.

4. CONCLUSION AND RECOMMENDA-TIONS

During the course of interaction between schistosomes and their hosts (definitive and intermediate hosts), the parasites produce many antigens which enable them to reproduce and survive within the hosts environment, the antigens performing particular importance in both the parasites and the hosts, some of the identified importance include: resistant, tissue damage, serve as a vaccine candidate, escape

to the immune responses, mimicry, and many others. Therefore, we recommended that, many more antigens produced by parasite should be investigated because of their function in planning and creating many ways that help in prevention and control of schistosomiasis since some were observed to be good candidates for recovery of vaccine against Schistosoma infections.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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