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ORIGINAL ARTICLE

The Immunological Effects of Schistosoma Mansoni-Derived Soluble Egg Antigen on Murine Streptozotocin-Induced Autoimmune Type1 Diabetes

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ABSTRACT

Background: Type 1 diabetes is an autoimmune illness with high Th1 response that destroys the islets ß-cells causing their death. Insulin therapy for T1D cannot prevent the damaging immune response in pancreatic tissue. This study aimed to assess the effects of *S. mansoni* SEA antigen on experimentally induced-T1D as an immune therapy.

Methods: five groups of mice (7 mice each) have been employed; Control -ve (I), STZ-treated (II); SEA-immunized (III), SEA-STZ prophylactic (IV) and SEA-STZ curative (V) groups. Biochemical data such as blood glucose, insulin level, and immunological markers such as insulin autoantibodies (IAA) and serum IL-10 level were used. Histological and immunohistochemical alterations in ß-cells have been investigated.

Results: A potential immune effect of SEA in treating and preventing the development of T1D was recorded evident by lower blood glucose and higher blood insulin levels. Elevated serum IL-10 levels in both curative and preventive-SEA groups compared to the STZ-treated group, which had a typical pathological condition of T1D manifested as high blood glucose, low blood insulin, and a lower level of IL-10. The results of IAA levels, histological, and immunohistochemical tests in all groups were consistent with the biochemical data demonstrating an effective immunological modulatory impact of SEA on the course of T1D. **Conclusions**: This study contributes to the expanding body of data supporting the efficacy of *S. mansoni* antigens on autoimmune diabetes. More studies are needed to determine the complete immunological effect of parasitic helminths, in order to create innovative pharmacological therapies for human use.

Key words: SEA; T1D; IL-10; STZ, Insulitis

INTRODUCTION

Type 1 diabetes (T1D) is a chronic autoimmune disease that damages pancreatic beta cells (β-cells), resulting in insulin deficiency. A complicated genetic background combines with environmental circumstances to cause the illness, particularly in children and adolescents (juvenile-onset diabetes) [1].T1D is reaching alarming levels worldwide prevalence rate and the number of patients is expected to double by 2045 [2]. The observation of the increased prevalence of T1D between inhabitants of industrialized nations and their immigrants from poor countries [3] with low exposure to infectious agents has given rise to the "hygiene hypothesis" [4] which postulates that reduced exposure to pathogens during childhood through strict hygiene leads to a more reactive immune system, which can result in autoimmunity [5]. The immune system of individuals living in developing countries has adapted to helminthic colonization that play a key role in preventing autoimmunity in genetically susceptible individuals [6]. The hygiene hypothesis supposes that helminths regulate a balanced response the host's immune system and prevent excessive inflammatory responses [7], a premise that has been

confirmed by the protective effect of helminths infection in mouse models of immune pathological disease [8] including *S. mansoni* [9]. Unfortunately, the rigorous prevalence delineation of autoimmune illnesses, including T1D, is no longer well defined. Improving surveillance and monitoring for infectious diseases in developing countries such as Egypt [10], as well as widespread access to medications to treat infectious diseases, have contributed to a low prevalence of parasitic infections in developing countries, making people more vulnerable to autoimmune disorders [11].

T1D is a typically a Th1mediated autoimmune disease where lymphocyte infiltration into the islets is an initial and a fundamental step in disease pathology followed by auto reactive antigen specific T-cell and macrophages that gradually infiltrate pancreatic β-cells, mediating apoptosis and necrosis of these cells (Insulitis) [9]. T1D symptoms are characterized by irreversible loss of insulin production with incidence of hyperglycemia [12]. Clinical manifestations of T1D occur when 70% of pancreatic β-cells are destroyed [13]. Lifelong exogenous insulin is the only treatment approach for T1D [14] protecting the patient from developing life threatening health complications. This insulin injection cannot hold up the progression of autoimmune response or increase the life expectancy of T1D patients with complications [15]. Novel immunological and surgical treatment options for T1D have been developed [16]. However, the heterogeneity of T1D, the diversity of islet antigens, and the complexity of autoimmune mechanisms have hampered the efficacy of such therapies in totally halting or reversing the course of this disease. Furthermore, the safety, high cost, ethical concerns, and long-term effectiveness of these therapies remain contentious [17]. This encouraged scientists to develop novel methods of antigen-specific immunotherapy to prevent or arrest T1D progression efficiently.

S. mansoni was found to enhance an anti-inflammatory microenvironment characterized mainly by a Th2 associated responses such as IL-10 which inhibit the production of inflammatory cytokines. As T1DM is a pure Th1 mediated autoimmune disease, it is accepted that any element such as immunosuppressive helminths that weaken this Th1 response is able to hinder the occurrence or arrest the development of TID [18]. The use of helminth-derived molecules/proteins collected as excretory-secretory (ES) products from helminths cultivated in vitro can give anti-inflammatory effects equivalent to whole worms [19]. The current study aimed to assess the potential immunological modulatory effects of the *S. mansoni* egg soluble antigen (SEA) on streptozotocin (STZ) induced T1D. Biochemical parameters such as blood glucose level, insulin level and Immunological parameters such as insulin autoantibodies (IAA), and serum level of IL10 were utilized. Histological and immunohistochemical changes to islets cells have been studied.

METHODS

This case-control research included 35 mice (6 weeks old, 25-30g) maintained in box cages with full access to water and food. Following a one-week acclimation period, the animals were randomly allocated to groups.

***Induction of T1D using STZ*:** For each mouse, intra-peritoneal injections (40 mg/kg each) of freshly prepared STZ (Sigma, St. Louis, MO, U.S.A.) were used after 6-h fasting for 5 consecutive days [20]. Negative control group received an equivalent volume of citrate buffer. Within 7 days, the tail vein 6-hour fasting blood glucose was measured daily using a glucometer. Blood glucose exceeding 180 mg/dl were considered diabetic [21].

Antigen regimen: Except for the control negative and STZ groups, all mice were sensitized with an initial subcutaneous injection of 30 µl of SEA in the first week**.** A second subcutaneous injection of 40 µl was given within the second week.

Mice (5 groups ; 7 mice each):I: (Control negative): Non diabetic mice were injected only with citrate buffer pH 4.5 (1.0 ml/100 g).**II: (STZ - control positive):** STZ-treated mice to induce T1D. **III: (SEA- control):** Mice sensitized with two injections of SEA given over a two-week period. **IV: (SEA-STZ Protective):** Mice sensitized with two injections of SEA given over a two-week period, followed by STZ injections at the end of the second week.**V: (SEA- STZ Curative):** STZ injection regime was initiated in the first week and then followed by two injections of SEA given over a first and second week after confirming hyperglycemia.

***Study design*:** Preventive group: SEA antigen was given in the first two weeks (day 0 and day 11) to prime the immune system. STZ was given at the end of second week. In the curative group, STZ regime was initiated at day 0 and hyperglycemia was verified within 7 days. SEA was given at day 7 and day 14. At the end of the 4th week, all mice in all groups were euthanized with CO2 after a period of 12–16 h overnight fast. Blood samples (10-15 ml)

from the euthanized animals were obtained via cardiac puncture into anticoagulants-free tube. A glucometer was used to assess hyperglycemia before centrifuging the blood. The serum was kept in aliquots at −80 °C for biochemical testing. The pancreas was carefully removed, cleaned with ice-cold saline and stored in 10% formalin for histopathological and immunohistochemical tissue characterization.

ASSESSING SEA IMMUNE EFFICACY

***Biochemical assays*: Blood glucose level:** Glucose in 6-hours fasting blood was measured using a glucometer according to experimental time schedule (every week in STZ-control and after STZ injection in other groups to confirm hyperglycemia, at the end of the study)**. Serum insulin level**, Insulin autoantibodies and IL-10 were measured using ELISA kit specific for mouse serum. All steps were done according to the manufacturer instructions.

***Histopathological studies of pancreatic tissue*:** Micro sections of pancreatic tissue samples were prepared and subjected hematoxylin and eosin stain (H&E).

Immunohistochemical of pancreatic tissue pancreatic tissues from all groups were examined for expression of insulin using the standard method of immunohistochemistry staining [22].

ETHICAL CONSIDERATION

Animals were handled and all experimental procedures were performed in accordance with the guide of Laboratory Animals published by the US National Institute of Health. Approval of the protocol of the study was obtained from Zagazig University - Institutional Animal Care and Use Committee (ZU-IACUC) with approval number (ZU-IACUC/3/F/154/2023).

STATISTICAL ANALYSIS

All results were represented as mean ± S.D (Standard deviation). The significant differences in quantitative variables between two groups were analyzed by independent T-test. The p value < 0.05 was considered statistically significant.

RESULTS

In table 1, high blood glucose level and low insulin secreting capacity has been recorded in STZ- control group compared to the control negative group. After SEA administration, the prophylactic group was superior to the curative group revealing the best results for the blood glucose and insulin blood level in mice.

Table 2 shows the immunological response of the tested mice. STZ group reported the highest amount of autoantibodies and the lowest level of blood IL-10.After SEA administration, the antigen was able to increase the level of IL-10 markedly in the prophylactic group more than the curative group. Similar results for the insulin antibodies have been recorded as the prophylactic group recorded a lower level of insulin antibodies than the curative group

***Histopathological changes of pancreatic tissue in the studied groups*:**Sections from the pancreas in the negative control group revealed normality in both exocrine and endocrine counterparties, with a healthy acinar epithelium and secretory granules, in contrast to the STZ-treated group, which showed reduced islet size and signs of inflammation in the exocrine pancreas. Histopathology of SEA prophylactic group exhibited a normal image of islets cells equivalent to the SEA-curative group and better than the curative group, which showed a fairly normal histopathology (Fig: 1).

Immunohistochemical results of pancreatic tissue in the studied groups: In the control group, pancreatic tissue exhibited normal insulin expression in islets cells (deep brown color), but the STZ-treated group showed limited reactivity to insulin antibodies (faint color). The SEA prophylactic group had substantial positive response, similar to the SEA control group. The results for the SEA curative group exhibited modest insulin staining (Fig. 2).

Table 1: Biochemical measurements of the studied groups

	Blood glucose ***(mg/dl)*** ***Mean ± SE***	Insulin ***(ng/ml)*** ***Mean ± SE***
Control -ve	**82.6 ± 8.14**	**3.87± 1. 06**
STZ control	**258 ± 7.47$^{A, a}$**	**2.21 ± 0.1$^{A, a}$**
SEA-Control	**122 ± 1.58$^{B, a}$**	**2.53 ± 0.06$^{B, a}$**
SEA-Curative	**161 ± 2.1$^{C, a}$**	**1.27 ± 0.07$^{C, a}$**
SEA-prophylactic	**134 ± 1.36$^{B, a}$**	**2.05 ± 0.12$^{D, a}$**

- Within the same column, values without common superscript capital letters are significantly different ($p < 0.05$).

Table 2: Immunological measurements of the studied groups

	IL-10 (pg/ml) Mean ± SE	Insulin Autoantibodies **(ug/ml)** ***Mean ± SE***
Control -VE	**30.1± 34. 2**	**0.48 ± 0.34**
STZ control	**18.6 ± 0.1**$^{A, a}$	**0.858 ± 0.08**$^{A, a}$
SEA-Control	**57.5 ± 0.06**$^{B, a}$	**0.481 ± 0.04**$^{B, a}$
SEA- prophylactic	**38.4 ± 0.07**$^{C, a}$	**0.699 ± 0.1**$^{C, a}$
SEA- Curative	**32.1 ± 0.12**$^{C, a}$	**0.566 ± 0.07**$^{D, a}$

- Within the same column, values without common superscript capital letters are significantly different ($p < 0.05$).

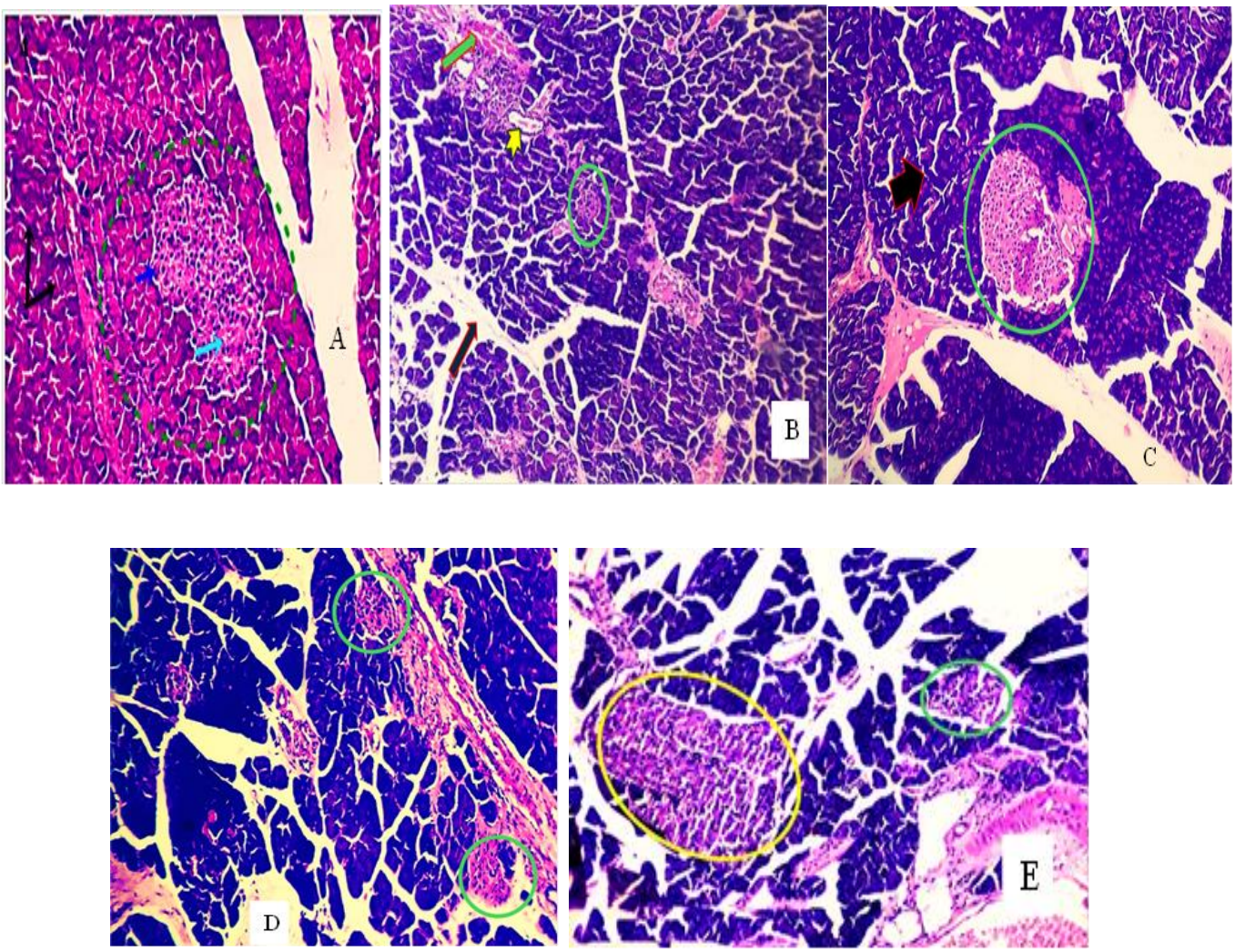

Figure (1): Photomicrographs of H&E stained pancreatic tissues in A: normal control group: normal micromorphology of exocrine pancreas (black arrows) and endocrine islets alpha and beta cells (dark blue and light blue arrows). **B: STZ-treated group**: decrease in cellular population of islets (green circle). The exocrine pancreas showed vascular (green arrow) and tubular dilatation (black arrow) beside interstitial edema (yellow arrow head). C: SEA control group. D: SEA curative group. Normally distributed islets (green circle) surrounded by slightly normal exocrine of pancreases. E: SEA prophylactic: normal structural configuration

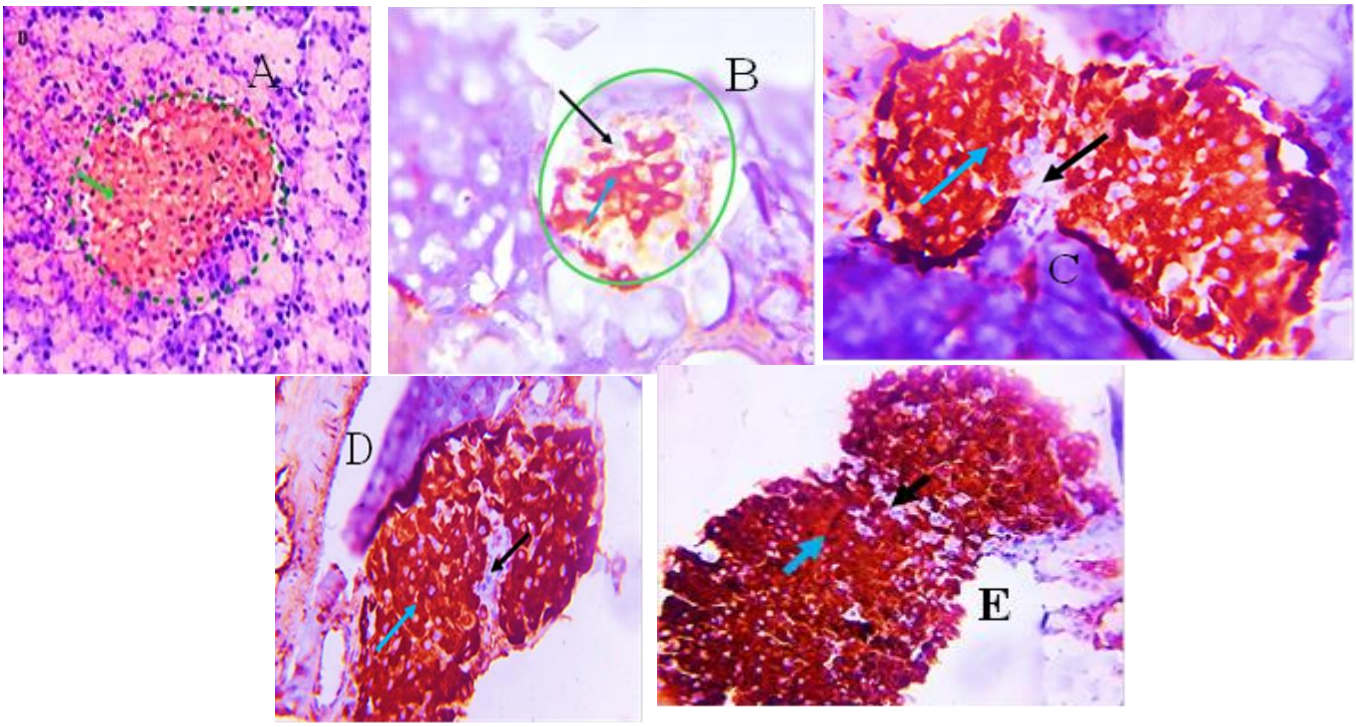

Fig.2: Photomicrographs of immune stained pancreatic tissues in A: normal control group: **B:** STZ-treated group. C: SEA control group. D: SEA curative group. E: SEA prophylactic group. Green and blue arrows indicate islet beta cells that express insulin markers positively. Negatively expressed cells are shown by black arrows. X400

DISCUSSION

Autoimmune T1D is caused by a polarized Th1 immune response. Hyper-reactive Th1 cells preferentially damage pancreatic β-cells, resulting in loss of insulin-producing ability. Helminth infections have been demonstrated to elicit a Th2 response, resulting in a less inflammatory environment that counteracts the Th1 response. So, T1D can be treated by changing the immune system utilizing parasites or one of its secretory/excretory products, shifting from pathogenic pro-inflammatory medium to an anti-inflammatory condition [12]. Parasite derivatives, such as SEA, are regarded a safe and effective alternative to intact worm therapy. These compounds can operate either directly on host immune system cells or indirectly via the immune systems own down-regulatory mechanisms [23]. However, the many immunological characteristics of a suitable and safe helminth-derived antigen must be extensively investigated before it can be employed in clinical trials. In this study, we evaluated the immune modulatory effect of *S. mansoni* SEA antigen on the course of STZ-induced T1D in mice. Biochemical (blood glucose, insulin level) and immunological parameters (IAA, IL-10) have been measured accompanied with detection of the histopathological and immunohistochemical changes in pancreatic tissue.

Streptozotocin (STZ) is a naturally occurring antibiotic with a structure similar to glucose. It is exclusively transported to islet β-cells by the glucose transporter GLUT2, which is found in the cell membrane of islet β-cells and is not recognized by other glucose transporters [24]. It is clear that administering several low doses of STZ can cause a long-term autoimmune-type DM in mice with pathogenic features similar to those of human autoimmune T1DM. It is hypothesized that STZ can covalently change biological components like as DNA and proteins to generate autoimmune antigens. These antigens are targeted by autoimmune T and B cells, starting long-term autoimmune assaults against islet β cells. The current STZ injection approach used in our study involved numerous administrations of low-dose STZ to induce T1D in experimental mice, a common strategy that has been used to cause autoimmune effect mediated by cellular immune response in the form of chronic pancreatic islet inflammation, insulitis, and insulin insufficiency similar to human T1D [20].

Insulin is an important anabolic hormone that controls glucose metabolism and promotes its transport into muscle and fat cells. The pancreas regulates blood glucose levels, therefore any absence or failure of pancreatic tissue might result in a hyperglycemic state similar to the T1D clinical presentation. Moreover, T1D-induced hyperglycemia damages pancreatic islet β cells, producing apoptosis and reducing secretion ability. This leads to a drop in insulin concentration in the blood, causing further hyperglycemia. [25]. In this study, SEA maintained appropriate blood insulin and glucose levels in the curative and preventive groups compared to their values in the STZ-treated group. However, the levels were still higher than those seen in the SEA immunized group. Improvements in blood glucose and serum insulin readings following SEA treatment in both protective and curative groups indicate that this antigen has immunological features capable of ameliorating or preventing functional changes caused by T1D immune pathology. Previous studies [21, 26] revealed that SEA antigen reduced the establishment of diabetes in NOD mice, as evidenced by low blood glucose levels and increased insulin production. Interestingly, while the preventive group outperformed the curative group in terms of blood insulin and glucose levels, neither group achieved normal levels. This can be explained by the fact that immunization with a single helminths-derived antigen may not generate the same balanced immune regulation that the entire range of helminths antigens may induce in the host **[27].**

A well-recognized feature of helminths- derived antigens is their ability to polarize the immune response toward a Th2 that suppress pro-inflammatory Th1 responses evoked in autoimmune diseases like T1D [18]. In this study, remarkable rise in the levels of IL-10 (Th2 cytokine) have been seen in both STZ- curative and protective groups with over performance of SEA antigen in preventive than curative group. In humans, deficiency in IL-10 producing regulatory B cells has been associated with T1D [17]. IL-10 promotes the regulated immune response required to defend the body and protect tissues during an illness. It promotes tissue repair mechanisms by stimulating cell proliferation in B lymphocytes, preventing cell proliferation and apoptosis, and inhibiting the effector function of pro-inflammatory Th1 cytokines [28]. Similar studies documented the Th2 response of SEA antigen in experimental mice in the form of elevated serum level of IL-10 [21, 26]**.** In animal models, interventions that target increased IL-10 production enhance β-cell function and limit the advancement of insulitis [28]. The ability of exogenous IL-10 to suppress the development of insulitis in mice demonstrated SEA's preventative action via inducing IL-10 production in B cells [29].

In T1D, T-cells have a key role in destroying β-cells, while B cells are responsible for presenting autoantibodies [17]. Islet autoantibodies target the pancreatic β cells' secretory granules, notably insulin. This hormone makes up to 10% of the protein composition of β cells and is a highly specific antigen target of islet autoimmunity in both animal and human models of diabetes. Insulin autoantibodies (IAA) are the only specific autoantibodies in islet cell autoimmunity. Autoimmunity to insulin is central to disease pathogenesis [30] and detection of their presence is currently the best-validated method to differentiate T1D from other forms types of diabetes. Only IAA has been found in experimental animal, and its presence is temporary in both human and mouse blood. These autoantibodies are not pathogenic, but they serve as indicators of the body's damaging immune reaction against its own insulin-producing cells [31]. In this study, IAA levels were lower in the protective group and the curative group than STZ-treated group. The diabetes process induced by low dosage of STZ was related with an increase in anti-insulin antibodies. In T1D, the immune system does not distinguish between insulin produced internally and insulin been injected from external source [32]. We claim that the antibodies detected in our study are most likely autoantibodies, as the mice did not receive any exogenous insulin injections at the time of blood collection. Our observed reduction in the IAA blood level accompanying SEA administration is explained by an increase in IL-10, which stimulates pancreatic tissue regeneration and prevents further immunological death of islets cells. Our findings of a high level of autoantibodies following STZ-induced diabetes and a subsequent decrease due to SEA administration highlight the efficacy of autoantibodies in slowing the progression of T1D and demonstrating that they are effective biomarkers for islet autoimmunity in the mouse model.

T1D histopathological findings include inflammation and loss of pancreatic islets, as well as the infiltration of macrophages, T cells, and other immune cells. Insulitis occurs when mononuclear cells infiltrate the islets of Langerhans, causing selective death of β-cell cells and resulting in T1D [33]. Excess free radicals or pro-inflammatory

cytokines from the Th1 immune response can cause β-cell necrosis [34]. Apoptosis destroys β-islet cells, lowering their number. The number and size of Langerhans cells are important markers to identify pathologic lesions in pancreatic tissue [35]. In this study, islet histopathology indicated that SEA therapy improved the size and quantity of Langerhans islets in both the curative and prophylactic groups when compared to STZ-induced diabetes, which had the lowest size and number of Langerhans islets. It is documented that the destruction of islet β -cells in animals receiving mild dose of STZ is mediated by cellular immune response similar to that occur in humans [28]. In this investigation, failure of full return to normal histology is evident by number of inflammatory cells remained in the pancreatic tissue following SEA injection in both the curative and preventative groups. Similar observation in NOD mice has been documented **[21, 26].** Our results of the immune histochemical staining come in accordance with the histopathological changes of the tested groups. Immunohistochemical staining for insulin production in islets cells was performed to assess insulin secretory capacity of β -cells which appear as dark brown cells [36]. In this study, STZ treated group failed to display the full positive reactions giving faint reaction to insulin antibody due to immune damage in β cells which significantly affected insulin expression. However, in curative group, insulin expression increased gradually following SEA injection evident by restoration of the deep color staining as in the negative control group. More positive staining results have been obtained in prophylactic group indicating the ability of SEA antigen to prevent the incidence of pathological lesion in islets cells. It is obvious that the rise in IL-10 production due to SEA antigen treatment has a great role in ameliorating the immune destructive effect of low doses of STZ on islets cells enhancing their regeneration by disrupting the pro-inflammatory effect of Th-1 cell-associated cytokines [37].

In this study, SEA injection partially cured and prevented the emergence of STZ-induced T1D while also slowing the disease's progression. This impact was proven by an increase in insulin blood levels and a drop in glucose levels, as well as an increased production of the anti-inflammatory cytokine IL-10, which was crucial for lowering the pathognomonic inflammation associated with T1D. Despite its benefits, SEA's inability to effectively prevent or treat the condition once it has started suggests that using parasite products in people who already have T1D is useless. Furthermore, while interpreting our findings for the human scenario, we must take into account the variations in mouse and human responses to these antigens. It is worth noting that there is no agreement on the particular function of helminth-based immunotherapy [12]. Overall, this study contributes to the expanding body of data supporting the efficacy of helminths treatment in treating diabetes. However, further research is needed to investigate the overall immunological influence of parasite antigens on the progression of autoimmune diseases such as T1D.

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Citation

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