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REVIEW

Anti-Inflammatory Effects of Helminth-Derived Products: Potential Applications and Challenges in Diabetes Mellitus Management

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Abstract: The global rise in diabetes mellitus (DM), particularly type 2 diabetes (T2D), has become a major public health challenge. According to the "hygiene hypothesis", helminth infections may offer therapeutic benefits for DM. These infections are known to modulate immune responses, reduce inflammation, and improve insulin sensitivity. However, they also carry risks, such as malnutrition, anemia, and intestinal obstruction. Importantly, helminth excretory/secretory products, which include small molecules and proteins, have shown therapeutic potential in treating various inflammatory diseases with minimal side effects. This review explores the anti-inflammatory properties of helminth derivatives and their potential to alleviate chronic inflammation in both type 1 diabetes and T2D, highlighting their promise as future drug candidates. Additionally, it discusses the possible applications of these derivatives in DM management and the challenges involved in translating these findings into clinical practice.

Keywords: diabetes mellitus, helminth-derived products, anti-inflammatory, immune modulation

Introduction

Over the past three decades, the prevalence of diabetes mellitus (DM) has risen sharply across the globe (Figure 1). Calculation using data from multiple sources indicates that the average incidence of DM increased by 3.73 cases per 100,000 people per year between 1990 and 2019, highlighting its rise as one of the essential global major public health problems.[1] In 2019 alone, new reports from around the world indicated some 22 million new cases of DM, with the burden projected to increase notably in the coming years.[2]

The interplay between type 1 diabetes (T1D) and type 2 diabetes (T2D) is significantly modulated by chronic inflammation, a pivotal factor in the pathogenesis of both conditions. T1D is predominantly marked by the autoimmune destruction of insulin-producing pancreatic β-cells, driven by immune cell infiltration that induces chronic inflammation in the islets of Langerhans.[4,5] This process is primarily mediated by autoreactive T cells and the release of pro-inflammatory cytokines, which not only lead to β-cell destruction but also sustain the autoimmune cascade.[6] Conversely, T2D is characterized by insulin resistance (IR) and metabolic dysfunction, with chronic low-grade inflammation playing a crucial role in its progression.[7] In T2D, obesity-associated chronic inflammation is a key contributor, as adipose tissue functions as an endocrine organ, releasing pro-inflammatory cytokines that exacerbate IR.[8] The inflammatory response involves mechanisms such as inflammasome activation and the release of damage-associated molecular patterns, which act as endogenous triggers of inflammation.[9] Inflammatory mediators, including IL-1 and TNF-α, have been demonstrated to inhibit insulin signaling, further complicating the metabolic dysregulation observed in T2D.[10] Elevated levels of pro-inflammatory cytokines, such as TNF-α and IL-6, are closely associated with impaired insulin signaling pathways in T2D patients.[11,12] Furthermore, increased concentrations of inflammatory biomarkers—including C-reactive protein, TNF-α, and IL-6—correlate with the transition from prediabetes to DM.[13,14]

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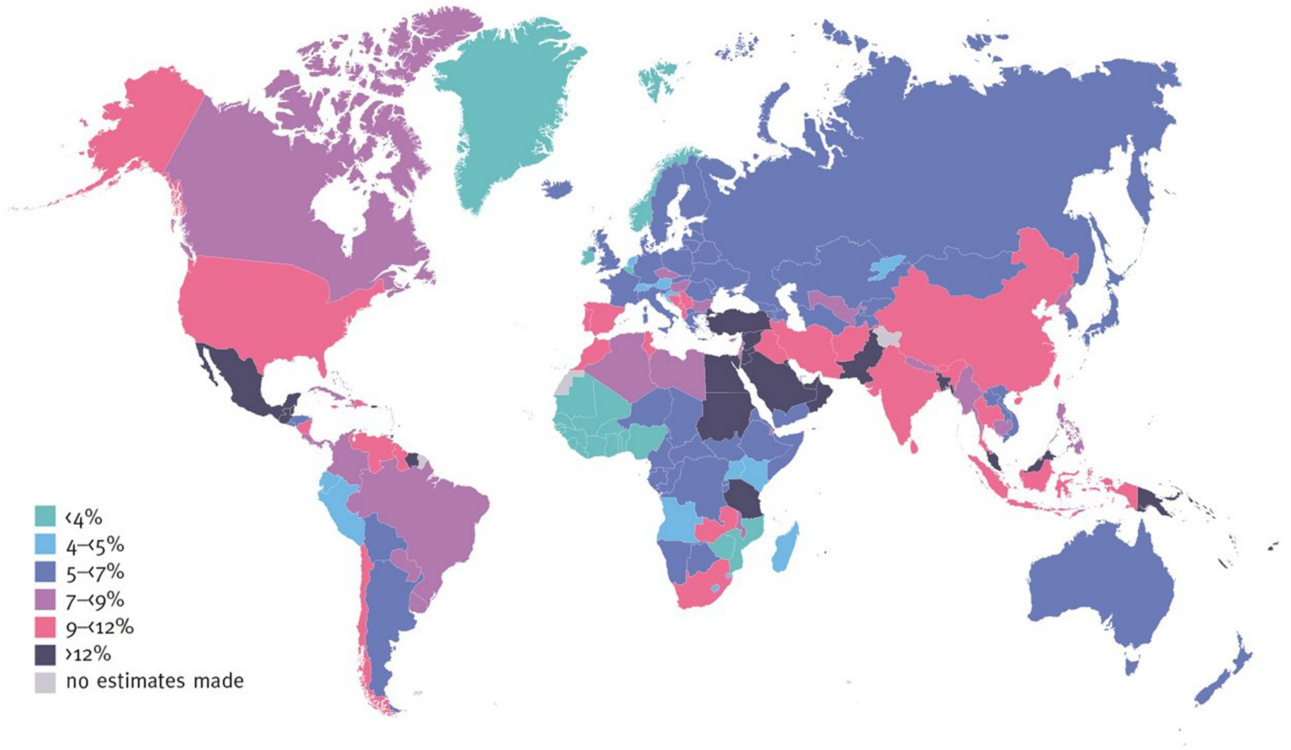

Figure 1 Estimated age-adjusted comparative prevalence of diabetes.
Notes: In adults aged 20–79 years in 2021. Reproduced from International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021. Available at: https://www.diabetesatlas.org.[3]

The "hygiene hypothesis" suggests that live helminths may have potential therapeutic benefits, especially for T2D. Indeed, recent research provides growing evidence for the ability of helminth infections to modify immune responses and suppress inflammation, hence improving insulin sensitivity. Recent studies indicate that some helminth infections reduce the risk of developing DM but increase the risk of adverse effects such as malnutrition,[15] anemia,[16] or intestinal obstruction.[17] Importantly, helminths secrete excretory/secretory products (ESPs), which transform the host immune response into an anti-inflammatory state, hence playing a role in controlling autoimmune diseases.[18,19] These ESPs consist of low molecular weight molecules and proteins that have shown therapeutic effects in several inflammatory diseases, such as rheumatoid arthritis and multiple sclerosis, with hardly any side effects reported.[20,21] Several studies have documented the anti-inflammatory features of helminth-derived products in the treatment of DM through a skew to anti-inflammatory pathways that oppose and can potentially correct the chronic inflammation that comes with both T1D and T2D. This immune modulation can enhance insulin sensitivity and preserve β-cell function with relatively few adverse effects.[22–24] Currently, anti-inflammatory activities by helminths have been proposed from the observation that they release helminth-derived molecules on host-parasite interactions called helminth defense molecules (HDM) with broad anti-inflammatory properties in the absence of cytotoxicity thus, maybe a potential.

Initially, scientists observed that parasitic infections in many rural areas seemed to confer protection against metabolic diseases such as DM and atherosclerosis.[25,26] For instance, the prevalence of metabolic syndrome was significantly lower at 18.28% among individuals who had been infected with schistosomes, compared to 34.01% in those who had never been infected.[27] This observation aligns with the "hygiene hypothesis", which suggests that the incidence of DM is markedly higher in middle- and high-income countries than in low-income nations. This hypothesis is reinforced by epidemiological studies showing a higher incidence of DM in wealthier countries where parasitic infections are less common.[23,28] Such contrasting findings indicate a potential inverse relationship between the prevalence of parasitic infections and the incidence of DM.

Subsequent studies suggest that helminth infections may protect against DM by modulating metabolic processes. A randomized trial in Indonesia found that individuals infected with helminths had a 16% lower IR index (HOMA-IR) compared to uninfected participants, with the improvement reducing by 10% after deworming treatment.[29] A cross-sectional study in rural China reported a lower prevalence of DM (14.9%) and metabolic syndrome (14.0%) among individuals previously infected with schistosomes, compared to those without prior infection (25.4% and 35.0%, respectively).[26] Similarly, an Australian study found a 13% lower incidence of T2D in individuals infected with *Strongyloides stercoralis (S. stercoralis)*, with risk increasing by 10% post-deworming.[30] A trial in Uganda showed that *Schistosoma mansoni (S. mansoni)* infection lowered LDL cholesterol levels by 0.26 mmol/L, potentially reducing cardiovascular risk.[31] These findings indicate that helminth infections may protect against T2D and metabolic syndrome through metabolic and immune regulation.[32–35] Research has also shown that hookworm infections can modulate inflammatory diseases and metabolic syndrome. While studies on hookworm's direct effect on T2D are limited, they suggest that these infections alter the gut microbiome[36] and elicit immune responses,[37] which may benefit T2D. An Australian trial involving hookworm larvae reported improved IR and reduced fasting blood glucose after one year, with a reduction in body weight after two years.[38] Helminths have also been shown to affect fat metabolism by lowering leptin and increasing adiponectin levels, which enhances insulin sensitivity.[39,40] Furthermore, helminths may influence T2D progression by modulating angiogenesis and immune responses. For example, *S. stercoralis* infection reduced pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in T2D patients, with levels returning to normal after antiparasitic treatment.[41,42] Additionally, hookworm infections increased anaerobic bacteria such as Lactobacillus and Bifidobacterium, which are linked to reduced inflammation and improved insulin sensitivity.[42] Recent studies in 2024 indicate that *S. stercoralis* may also modulate the complement system, reducing inflammation through regulation of complement proteins.[43] Collectively, these findings suggest that helminth infections offer protective effects against metabolic diseases like T2D through immune modulation, lipid metabolism regulation, and gut microbiota changes.

Contrarily, not all parasitic infections confer protection against DM; some may trigger its onset. The prevalence of intestinal parasitic infections in such case studies was higher in the affected population than in controls, with a noted correlation (OR, 1.80).[44] Additional meta-analytical research is required to explore the interplay between T1D-induced immunological changes and the risk of *T. gondii* infection, and vice versa.[22,45,46] Moreover, a case report highlighted the death of a 40-year-old diabetic patient with a history of alcoholism due to severe *S. stercoralis* infection.[47] Most experts agree that patients with T2D should be shielded from parasitic infections due to their compromised glucose regulation,[48,49] which could exacerbate susceptibility to infections like those caused by acarids, potentially accelerating parasite growth and enhancing virulence.[50,51]

Parasitic infections typically result in pathological conditions; however, the therapeutic use of helminth-derived molecules in the treatment of DM has garnered increasing interest in recent years. These molecules regulate the host immune response through various mechanisms and have demonstrated potential therapeutic effects in both T1D and T2D.[52–54] Recent studies have shown that secretions from Fasciola hepatica possess significant immunomodulatory properties, which can prevent T1D in Non-Obese Diabetic (NOD) mice.[55] These secretions achieve this by inducing M2 and Tregs, which suppress inflammatory responses in the pancreas, thereby reducing autoimmune damage and effectively halting the progression of DM.[55] An increasing number of helminth-derived molecules have been experimentally demonstrated to modulate adipose tissue secretion or reduce inflammation.[52,56–60] This immunoregulatory mechanism underscores the potential of helminth-derived molecules in DM treatment, similar to the effects of live helminths, while also enhancing their acceptance by the general population.

Mechanism of Action

Impact on Adipose Tissue Secretions

Worms and their proteins can profoundly influence adipose tissue secretions, particularly adipokines, by modulating immune responses and metabolic pathways.

Studies by Queiroz-Glauss and Su. have shown that *Heligmosomoides polygyrus (H. polygyrus)* infection in high-fat diet-induced obese mice reduces glucose and triglyceride levels. This infection also decreases pro-inflammatory

adipokines, such as leptin and resistin, while enhancing anti-inflammatory factors, including uncoupling protein 1 and adiponectin. These changes mitigate obesity-associated inflammation and improve insulin sensitivity.[61,62] Research by Kang demonstrated that Trichinella spiralis lysates significantly reduce lipid droplet accumulation during adipocyte precursor cell (3T3-L1) differentiation. The lysates inhibit the expression of key adipogenic regulators, including peroxisome proliferator-activated receptor gamma, CCAAT-enhancer-binding protein alpha and adipocyte protein 2, thereby reducing intracellular lipid storage.[63] Findings from Hussaart revealed that chronic worm infections lead to significant reductions in weight gain (−62%), fat mass (−89%), and adipocyte size. These infections also decrease systemic IR (−23%) and impaired glucose tolerance (−16%), while enhancing peripheral glucose uptake (+25%) and WAT insulin sensitivity.[64] Further evidence suggests that Trichinella spiralis infection promotes elevated adiponectin expression in the small intestine. This increase correlates strongly with epithelial-derived cytokines such as IL-25, IL-33, and thymic stromal lymphopoietin.[65]

Helminth-derived proteins also demonstrate similar regulatory effects. Molecules in pseudocoelomic fluid from *Ascaris suum (A. suum)* upregulate gene expression in small intestinal tuft cells, including genes involved in runt-related transcription factor 1 and organic cation transporter regulation. These processes link tuft cell activity to the fat-to-lean mass ratio and eosinophil function in epididymal white adipose tissue, ultimately regulating body fat composition.[66] The fatty acid and retinol-binding proteins from Steinernema carpocapsae consume lipid signaling precursors in vivo and bind to these fatty acids in vitro. This activity alters the availability of signaling molecules required for effective immune responses, thus mediating immunomodulation.[67] Additionally, the glycoprotein omega-1 (ω1) from *S. mansoni* enhances metabolic homeostasis by inducing type 2 immune responses and suppressing food intake, which reduces body fat and improves insulin sensitivity.[57,58] Collectively, these findings highlight the potential of worm proteins to modulate adipose tissue secretions and adipokine profiles, alleviating obesity and metabolic syndrome through intricate immune-metabolic interactions. The induction of regulatory immune cells plays a central role in maintaining metabolic stability, reducing adipokine production, and facilitating immune regulation.[68]

Nevertheless, the potential adverse effects of worm infections should not be overlooked. Hookworm infection in obese mice has been associated with elevated cholesterol and triglyceride levels, as well as increased inflammation, exacerbating metabolic disorders.[69] Furthermore, studies indicate that infections with Ascaris or hookworm can lead to increased fat deposition, particularly in the abdominal region, among children.[70] The dualistic nature of worm infections emphasizes the need for further investigation into the therapeutic applications of worm-derived molecules for treating obesity and DM.[71]

Direct Anti-Inflammatory Effects

The critical role of parasite ESPs in parasite-host interactions has increasingly come to light, with extracellular vesicles (EVs) receiving particular attention.[59] Through optimized extraction methods, high-purity EVs have been successfully isolated from parasites such as *S. mansoni*, revealing significant anti-inflammatory and immunomodulatory potential.[72] For example, EVs derived from *Necator brasiliensis* (N. *brasiliensis)* suppress pro-inflammatory cytokines associated with colitis, including IL-6, IL-1β, IFNγ, and IL-17a, while promoting the anti-inflammatory cytokine IL-10.[73] Similarly, EVs from *A. suum* specifically target epithelial cells, and the ES proteins (Ts-MES) of *Trichinella spiralis (T. spiralis)* have been shown to protect murine cardiac tissue from septic injury.[74] Advanced research further delves into the intricate interactions between helminth-derived proteins and various immune cell populations.

Effects on Lymphocytes

The balance of Th1 and Th2 immune responses, regulated by $CD4^+$ T-cell differentiation, is crucial for maintaining immune homeostasis.[75] Numerous studies have confirmed that various worm proteins can shift adipose tissue inflammation, which is dominated by Th1 and Th17 cells, to an anti-inflammatory state driven by Th2 and Treg cells[76–78] (Figure 2).

Experimental treatments with cystatin-like protein have been observed to increase the secretion of the regulatory cytokine IL-10, highlighting its anti-inflammatory potential.[79] Recent research has further highlighted the significance of parasite-derived protease inhibitors, such as cystatins, in regulating key immunological processes, including antigen

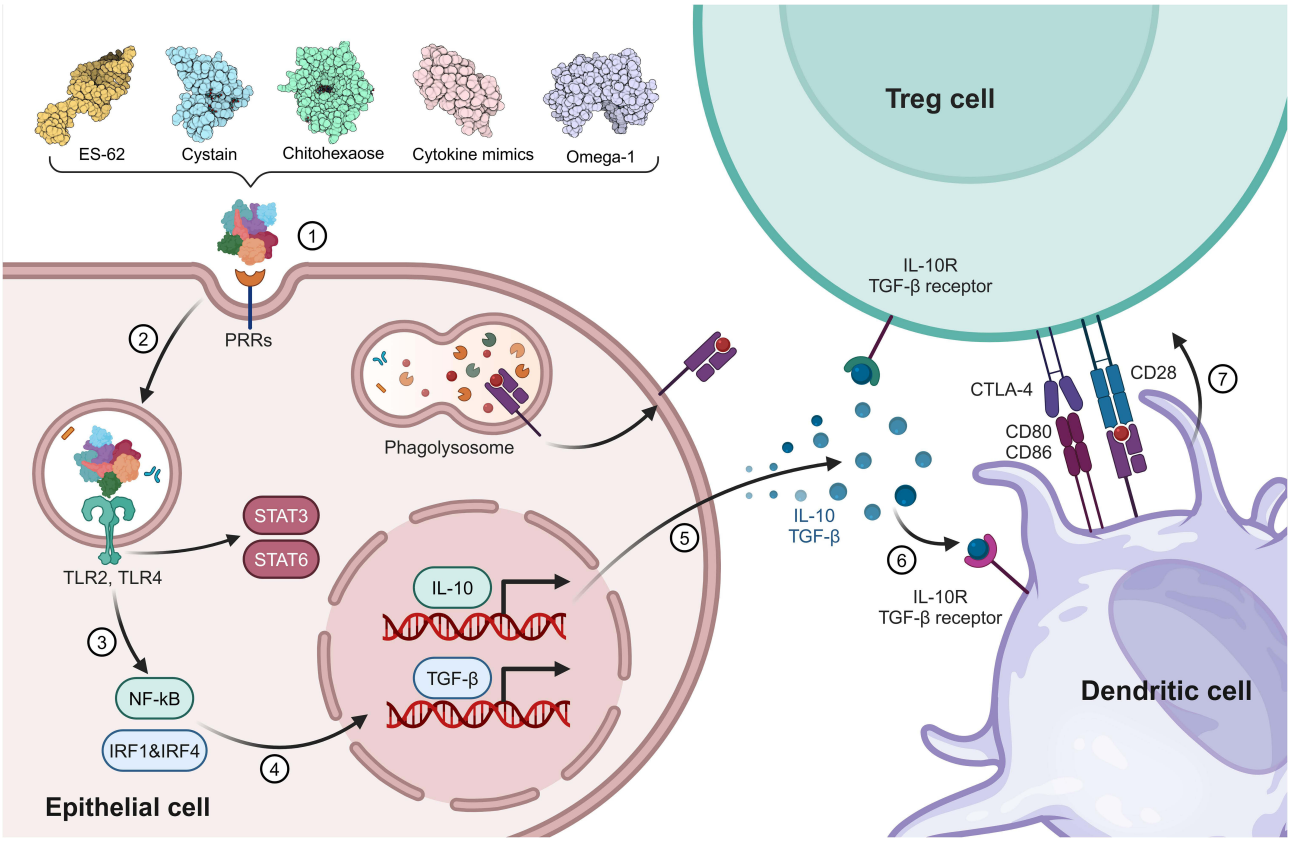

Figure 2 Helminth proteins regulate immune responses by modulating DCs and Tregs. Initially, helminth proteins are identified by pattern recognition receptors on the surface of host epithelial cells, which trigger specific signaling pathways, notably TLR2 and TLR4. This interaction activates NF-κB and interferon regulatory factors (IRF1 and IRF4), crucial for driving the expression of anti-inflammatory cytokines like IL-10 and TGF-β. Once released into the surrounding environment, these cytokines bind to their respective receptors, IL-10R and TGF-β receptors, on DCs. This binding modulates DC functions, facilitating the activation and proliferation of regulatory Treg cells. These Treg cells are essential for maintaining immune tolerance and preventing overactive immune responses, thereby playing a pivotal role in the immune system's ability to manage parasitic infections effectively. Created in BioRender. Yunhuan Zhu (2025) https://BioRender.com/x98w137.

processing, activation of TLRs, and secretion of cytokines.[80–83] Additionally, compounds such as prostaglandin E2, produced by parasites like *Trichuris suis (T. suis)* and *S. mansoni*, play critical roles by promoting Th2 immune responses and suppressing responses from ILC2, which are vital for the therapeutic management of conditions such as atopic dermatitis.[84,85]

Studies on mice treated with soluble egg antigens (SEA) from *Schistosoma japonicum (S. japonicum)* demonstrate a significant decrease in IR and increased frequency of Tregs in the spleen. These changes coincide with enhanced secretion of IL-4 and IL-5 from spleen cells.[86]

The ES products from *Echinococcus multilocularis (E. multilocularis)* larvae are capable of inducing the formation of Foxp3$^+$ Treg cells from CD4$^+$ T cells in a TGF-β-dependent manner in vitro. During interactions with these larval products, T cells also secrete increased levels of the immunosuppressive cytokine IL-10.[87] As noted by Pineda, the phosphocholine glycoprotein ES-62 from filarial and nematode parasites is a potent inducer of the Th2 immune response.[88] ES-62 helps restore the function of IL-10-producing regulatory B cells and reduces chronic inflammation driven by Th1 and Th17 cells.[89] Additionally, parasitic molecules manage excessive B cell and T cell activities, reducing cytokine output, receptor expression on the cell surface, and cell proliferation, thus fostering an environment conducive to anti-inflammatory and regulatory immune responses.[90,91]

Effects on Dendritic Cells and Macrophages

It is well established that dendritic cells (DCs) and macrophages (MΦ) play pivotal roles in antigen presentation, a key process in the initiation of immune inflammatory responses.[92,93] The Glutathione S-transferase ω2 antigen from the liver

fluke has been shown to modulate MΦ function, contributing to immunoregulation and anti-inflammatory effects.[94] Additionally, lipid mediators derived from *Fasciola hepatica (F. hepatica)* are known to activate an alternative pathway in MΦ, which suppresses the activation typically induced by Lipopolysaccharide (LPS).[60]

ES-62, a molecule derived from the genus Acanthocheilonema, has been shown to inhibit DCs and MΦ functions by sequestering MyD88, suppressing most pro-inflammatory TLRs except TLR3, and modulating IL-33 signaling. Additionally, it facilitates antigen processing and presentation, highlighting its multifaceted role in immune regulation.[95–97]

F. hepatica helminth defense molecule 1 (*Fh*HDM-1), a protein from liver flukes, has been found to promote pancreatic β-cell survival under pro-inflammatory stress by activating the PI3K/Akt signaling pathway. It also protects human islets from cytokine-induced apoptosis.[98] Interestingly, MΦ treated with *Fh*HDM-1 do not express typical M2 phenotype markers, indicating that its effects extend beyond merely promoting M2 polarization. Instead, *Fh*HDM-1 appears to directly modulate inflammatory responses. Moreover, it regulates lysosomal pH, revealing a novel functional link between lysosomal and mitochondrial metabolism, underscoring its potential as a therapeutic anti-inflammatory agent.[99]

Helminth infections caused by Schistosoma species induce M2 polarization through mechanisms such as the secretion of excretory products and EVs that modulate MΦ activity. These helminth-derived molecules shift MΦ metabolism toward oxidative phosphorylation, lipid oxidation, and amino acid metabolism.[100] Furthermore, antigens from helminths, such as Ascaris and *S. mansoni* proteins, enhance the early control and clearance of pathogens like Mycobacterium tuberculosis by modulating the monocyte-macrophage axis.[101] Helminth proteins also influence MΦ polarization via signaling pathways such as mTORC2, promoting M2 differentiation and regulating systemic metabolism and thermogenesis.[102]

Specific helminth proteins, including Ts-Cys,[103] have been shown to mitigate sepsis-induced inflammation by inhibiting inflammatory cytokine production (MyD88 and mTOR) in MΦ. This effect is mediated by suppressing the PI3K/Akt pathway, which also induces autophagy in DCs and dampens TLR-mediated inflammation (Figure 2).[104–108] These processes are further associated with increased mannose receptor (MR) expression on MΦ,[109] similar to mechanisms seen when protoscoleces from multilocular hydatid cysts drive MΦ toward an M2 phenotype characterized by elevated metabolic proteins such as HK1, PFKL, PKM2, phosphorylated Akt and mTOR.[110]

Next, ES-62 also activates anti-inflammatory signaling pathways through the TLR4-TRIF-TRAF3-IRF3 axis, while simultaneously suppressing NF-κB activity.[111–113] This results in reduced levels of inflammatory cytokines, including IFN-γ, and TNF-α, making ES-62 a promising therapeutic candidate for inflammatory and autoimmune diseases.[114,115] Upon binding to human TLR4, ES-62 suppresses NF-κB via pathways involving transcription factors such as p38, MAPK, JAK, and Erk.[116,117] Similarly, the filarial protein BM-CPI-2 disrupts the processing of human MHC-II antigens by inhibiting asparaginyl endopeptidase and modulating the TLR-NF-κB pathway.[118,119]

The Jmjd3-Irf4 axis represents another critical pathway in M2 polarization, underscoring the importance of histone demethylation in MΦ differentiation and the anti-helminth immune response.[120] In addition, peptides derived from helminths, such as HDM, can traverse the MΦ membrane and enter the lysosomal system. Once inside, these peptides inhibit vacuolar (v)-ATPase activity, which reduces lysosomal acidification and subsequently blocks MΦ activation via TLR 4 signaling.[121]

Despite the promising potential of helminth-derived products in treating autoimmune and inflammatory diseases, their clinical application remains controversial. While their safety has been demonstrated in clinical trials, their therapeutic efficacy has yet to be conclusively established.[122,123] The complexity of their use stems from the diverse mechanisms by which parasites modulate host biology, including neutralizing danger signals, regulating DCs and MΦ activities, and modifying the adaptive immune response.[124]

Effects on Granulocytes

Numerous immunologically active molecules derived from parasites effectively inhibit inflammation. For example, the serine protease inhibitor SmKI-1 from *S. mansoni* interacts with elastase, impairing neutrophil function and reducing inflammation.[125] Neutrophil extracellular traps (NETs), composed of DNA fibers and antimicrobial proteins, are formed through a process known as NETosis, playing a crucial role in the innate immune response against pathogens, including helminths. During helminth infections, NETs primarily immobilize parasites rather than killing them.[126–130] For instance, canine neutrophils exposed to *Toxocara canis (T. canis)* larvae produce NETs that trap the larvae but do not affect their

viability, suggesting a containment function rather than direct eradication.[131] Similarly, NETs generated in response to *S. stercoralis* larvae capture the parasites, facilitating their clearance by other immune cells, as NETs alone lack the ability to eliminate them.[132] Additionally, helminth-derived factors, such as parasitic ligands, can inhibit NET formation. These factors block the activation of the transient receptor potential melastatin 2 channel, a key mediator of ROS-induced NETosis.[132,133] Furthermore, ESPs from adult Trichinella spiralis suppress NETosis and modulate cytokine production in neutrophils.[134] Such findings may provide insight into the previously reported reduction of vincristine-induced neuroinflammation in mice following *T. spiralis* infection.[135]

Eosinophils play multifaceted roles in the response to helminth proteins, acting as both defenders and regulators in immune responses. During helminth infections, eosinophils are primarily associated with Th2-type immune responses, characterized by the production of interleukin (IL)-5, IL-4, and IL-13, which promote their activation and recruitment.[129,136] These cells directly kill the larval stages of helminths by releasing granule proteins such as eosinophil peroxidase and major basic protein-1, although they do not completely eliminate the parasites.[102,103,137,138] Eosinophils also facilitate immune regulation, including modulating IgE responses and influencing goblet cell mucus production.[137,139] Research by Driss demonstrated that eosinophils, driven by the schistosome P28GST protein, can alleviate inflammatory diseases such as colitis by promoting Th2 responses and reducing the expression of pro-inflammatory cytokines.[140] Furthermore, helminth ESPs, such as those from *Nippostrongylus brasiliensis* (N. *brasiliensis)*, have been shown to improve glucose tolerance and reduce weight gain by inducing type 2 immune responses, which include increased eosinophils and IL-5 as well as decreased IL-6 in adipose tissue.[56]

Following sensitization by helminth proteins, basophils are activated to release key cytokines, including IL-4 and IL-13, which promote Th2 immune responses and IgE production.[141,142] This activation is accompanied by the mobilization and recruitment of basophils to lymphatic and peripheral tissues, where they execute their effector functions. In addition to their role in cytokine release, basophils serve as APCs by expressing MHC-II and co-stimulatory molecules such as CD80/86.[143] This enables basophils to present antigens to CD4+ T cells and drive Th2 cell differentiation, particularly in response to protein antigens and antigen-IgE complexes, further amplifying Th2 responses.[143,144] The Notch signaling pathway is pivotal in regulating basophil responses during helminth infections. By controlling gene expression and cytokine production, this pathway is essential for mounting an effective immune response and achieving helminth clearance.[145,146] However, genetic background influences these mechanisms, as demonstrated in AKR/J mice infected with *Trichuris muris (T. muris)*, where basophils expand but show impaired Notch2 receptor upregulation, compromising their functionality.[147] Additionally, IPSE, a protein isolated from *S. mansoni* egg extracts, has been shown to directly stimulate basophils to release IL-4 and histamine, further activating Th2 immune responses.[142]

Effects on Epigenetics

Derivatives of worms, including those from the ESPs, can also influence the host epigenetically. From the standpoint of pharmaceutical development, one of the most compelling aspects is the high concentration of miRNAs within the EVs of parasites. These miRNAs are anticipated to target host genes, particularly those involved in immune processes. Host cells can actively uptake these parasite EVs,[73,148] facilitating a mechanism by which parasites transmit genetic materials to the host to manipulate gene expression 265 actively. Literature increasingly substantiates parasite-specific miRNAs secreted by worms, although detailed interactions with host genes remain largely unexplored. It has been shown that miRNAs from *H. polygyrus* can downregulate the mouse phosphatase gene dusp1 expression, the human equivalent of MKP-1, a critical regulator of MAPK signaling and Th1 responses to TLR ligands.[149] Research has demonstrated that the liver fluke, *F. hepatica*, and ESPs significantly influence mouse MΦ function. Exposure of MΦ to whole worm extracts and adult worm ESPs stimulates these cells to produce higher levels of anti-inflammatory cytokines IL-1RA and IL-10 while decreasing pro-inflammatory cytokine production.[150] This modulation reflects the parasites' capability to induce an anti-inflammatory shift in the host immune system and suggests potential epigenetic regulation mechanisms involved, such as histone methylation.[151] These findings deepen our understanding of parasite-host interaction mechanisms and could lay the groundwork for new immunomodulatory therapeutic strategies. Studies have also indicated that the ESPs named ES-62 from the rodent filarial worm Acanthocheilonema vitae exerts substantial immunomodulatory effects on host immune cells, mainly by inhibiting the secretion of the pro-inflammatory cytokine IL-12 by antigen-presenting cells upon stimulation.[152] This effect persists both in vitro and in vivo, with continuous exposure to ES-62 eliciting similar anti-

inflammatory responses in mice.[153,154] Further research has revealed that ES-62 induces epigenetic alterations in non-immune cells, including synovial fibroblasts, aiding in mitigating inflammatory responses in rheumatoid arthritis models.[155–157] Moreover, ES-62 and its small molecule analogs reprogram immune cells through epigenetic mechanisms, exhibiting therapeutic potential in various inflammatory, autoimmune, and allergic conditions.[88,89] Additionally, recent research has highlighted that cystatin upregulates pathways involved in mevalonate and cholesterol biosynthesis and immune regulation genes in human monocyte-derived DCs, manifesting an epigenetic impact.[158]

Infections with nematodes like *Strongyloides venezuelensis (S. venezuelensis)* lead to changes in the intestinal microbiome, notably an increase in the population of Lactobacillus species. These microbiome alterations modify host metabolism by elevating anti-inflammatory cytokine levels, transitioning MΦ in adipose tissues from an M1 to an M2 phenotype, enhancing the expression of tight junction proteins in intestinal cells (thereby reducing permeability), and decreasing serum levels of LPS.[159] Research by Ying et al demonstrated that exposure to inhibits MΦ secretion of pro-inflammatory cytokines such as IL-1β, TNF, IFNγ, and IL-6 while enhancing the secretion of IL10 and TGF-β, promoting an anti-inflammatory M2 phenotype.[160] Studies have identified a liver fluke molecule, *Fh*HDM-1, which prevents the activation of the NLRP3 inflammasome by inhibiting lysosomal acidification within MΦ.[161] Similar effects are achievable with exogenous antigens. Worms and worm-derived molecules can regulate the phenotype and functions of DCs, including their surface markers (MHC-II molecules, CD80, CD86)[162] and cytokines (IL-12, TGF-β, IL-10).[163] For instance, Ascaris cystatin induces human DCs to secrete IL-10,[164] facilitating their migration to lymph nodes to drive the differentiation of naive $CD4^+$ T cells. Dioscin can reverse the elevated secretion of IL-6 and IL-12 and the decreased secretion of IL-10 in DCs under high glucose conditions.[165] Furthermore, natural liver fluke extracts and recombinant FhFABPs (*F. hepatica* Fatty Acid Binding Proteins) significantly modulate the immunoregulatory functions of human monocyte-derived DCs. The underlying mechanism involves FhFABP1 inducing a tolerant-like phenotype in moDCs upon LPS stimulation, characterized by a dose-dependent increase in the tolerance marker CD103 and IL-10 secretion without affecting DC co-stimulatory markers. Additionally, there is a significant decrease in the secretion of pro-inflammatory cytokines IL-12p70 and IL-6. These successful immunoregulations by recombinant proteins from natural liver flukes suggest potential therapeutic applications, though further research is needed to evaluate their effects on improving insulin sensitivity or glucose homeostasis.[166] These findings emphasize parasites' capacity and excretions to induce epigenetic modifications in host immune cells, offering crucial insights for developing new therapeutic strategies.[167]

Helminth ESPs can induce epigenetic changes in host cells, potentially leading to stable phenotypic modifications, although these phenotypes are not always beneficial.[167] The regulation of synovial fibroblasts by ES-62 alters their inflammatory phenotype, which may impact joint health and inflammation in diseases such as rheumatoid arthritis.[168] Moreover, while helminths can prevent excessive tissue pathology, their presence and the immune regulation they induce may sometimes result in tissue damage, particularly when immune responses are inadequately controlled.[167,169]

Widely Used Helminth Products

The development of products derived from parasitic worms is advancing rapidly, with increasing interest in their potential therapeutic applications, particularly in the treatment of metabolic disorders like DM. As detailed in Table 1, various worm-derived products have shown promising results in experiments conducted on diabetic mouse models. *N. brasiliensis* ESPs, such as adult stage and third-stage larvae ESPs, significantly decreased fasting blood glucose and improved glucose metabolism in HFD-fed C57BL/6 mice, while also modulating immune responses, including an increase in eosinophils and IL-5, and a decrease in IL-6 in adipose tissue.[170] Similarly, Fasciola hepatica protein *Fh*HDM-1 has demonstrated the ability to activate the PI3K/Akt pathway and preserve β-cell mass in NOD mice, offering protection against cytokine-induced apoptosis and enhancing insulin secretion.[98] Other products like *S. mansoni* SEA and ω1 have shown improvements in metabolic homeostasis and insulin sensitivity through immune modulation, including the promotion of Th2 cells, eosinophils, and M2 in adipose tissue.[57,171]

These results highlight the therapeutic potential of worm-derived molecules, which modulate both metabolic and immune pathways, offering new strategies for managing DM and related metabolic conditions. The diversity of impacts across different parasitic molecules and models, as illustrated in Table 1, reflects their complex mechanisms of action.

Table 1 Basic Experiments of Helminth-Related Molecules in Diabetic Mouse Models

Parasite	Helminth-Product	Diabetic Animal Model	Impact on T2D	Ref.
N. brasiliensis	AES or L3ES, 1 mg/kg, IP, twice a week from week six until the end of the experiment	HFD-fed C57BL/6 mice	• Significantly decreased fasting blood glucose • Improved glucose metabolism • Increased eosinophils and IL-5 • Decreased IL-6 in adipose tissue • Increased IL-6 in the liver	[170]
F. hepatica	*Fh*HDM-1, 10μg, IP, alternate days, for a total of 6 doses	NOD mice	• Activated PI3K/Akt pathway • Preserved β-cell mass, prevented cytokine-induced apoptosis • Increased NADH and NADPH levels, • Reduced PARP-1 activity, • Increased insulin-positive area in pancreas tissue	[98]
F. hepatica	*Fh*HDM-1, 10mg/kg, IP, for a single dose	NOD mice	• Regulated inflammation by reprogramming macrophage metabolism towards oxidative phosphorylation fueled by fatty acids and supported by glutaminolysis. • Reduced glycolytic flux and decreased pro-inflammatory cytokines TNF and IL-6 production	[99]
S. mansoni	SEA, ω1,10–50μg, IP, once every three days for 1–4 weeks	LFD or HFD-fed WT, db/db, $Stat6^{-/-}$, Rosa26tdTomato and Cx3cr1CreER mice	• Improved metabolic homeostasis through STAT6-mediated type 2 immunity, • Increased Th2 cells, eosinophils, and M2 in WAT • Reduced fasting blood glucose and insulin levels, • Improved glucose tolerance	[171]
S. mansoni	α1, ω1, 25μg, IP, day 0, 2, and 4	HFD-fed C57BL/6J, $Cd206^{-/-}$, $Rora^{sg/sg}$, $Il1rl1^{-/-}$, and $Il33^{Cit/+}$ mice	• Improved metabolic homeostasis through the induction of IL-33 release • Promotes the accumulation of ILC2s, eosinophils, and M2 in adipose tissue, • Reducing obesity and stabilizing glucose levels.	[57]
S. mansoni	SEA, 50μg, IP, every three days for four weeks	LFD or HFD-fed C57BL/6J mice	• Reduced body weight gain, fat mass, and adipocyte size • Improved whole-body insulin resistance and glucose intolerance • Increased peripheral glucose uptake and WAT insulin sensitivity • Promoted WAT eosinophils and M2 macrophages	[64]
S. japonicum	SEA, 50 μg, IP, twice a week for six weeks	C57BL/6 and $Lepr^{db/db}$ mice	• Led to an increase in the population of regulatory T cells in the spleen and elevated levels of Th2 cytokines (IL-4 and IL-5) associated with reduced IR	[86]
L. sigmodontis	LsAg, 2μg, IP, daily for two weeks	WT and ΔdblGATA mice on a BALB/c background, as well as C57BL/6J WT and C57BL/6 DEREG mice	• Increased eosinophils and alternatively activated MΦ in epididymal adipose tissue • Modified immune cell profiles • Activated type 2 immune responses • Reduced inflammation, • Enhancing insulin-signaling gene expression	[172]
L. sigmodontis	LsAg, 2μg, daily for two weeks	HFD-fed C57BL/6J mice	• Increases adiponectin levels, restraining Th17 cell differentiation and glycolysis in an AMPK-dependent manner. • Reducing IFN-γ and IL-17-producing CD4+ T cells and dampening the differentiation of naive T cells into Th1 and Th17 cells	[173]
S. mansoni	LNFPIII, 25μg, twice a week for four weeks	HFD-fed $Il-10^{-/-}$, Fxr-$\alpha^{-/-}$ and 57BL/6J mice	• Improved insulin sensitivity. • Enhanced WAT insulin signaling through IL-10 • Protected against diet-induced hepatic steatosis. • Suppressed hepatic de novo lipogenesis through Fxr.	[174]
T. spiralis	T. spiralis total lysates, 50μg, IP or IO, every three days for five weeks	LFD or HFD-fed C57BL/6 mice	• Reduced body weight, fat mass, and improved glucose and lipid metabolism. • Promoted M2 macrophage polarization, • Reduced pro-inflammatory cytokines (IL-1β, IL-6, IFN-γ, TNF-α)	[63]

Abbreviations: AES, adult stage ES; L3ES, third-stage larvae ES product; IP, intraperitoneally; HFD, high fat diet; FhHDM-1, Fasciola hepatica helminth defence molecule 1; NOD, Non-Obese Diabetic mice; SEA, soluble egg antigens; ω1, Omega-1; LFD, low fat diet; WT, wild-type; WAT, White Adipose Tissue; IR, insulin resistance; LsAg, L. sigmodontis Antigen; LNFPIII, lacto-N-fucopentaose III; Fxr, farnesoid x receptor; IO, intraoral.

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ES-62

ES-62 is renowned for its anti-inflammatory properties and potential to modulate immune responses, which have been investigated across various disease models. In studies using mouse models of obesity-induced accelerated aging, ES-62 has shown promise in extending both health span and lifespan. Obesity-induced accelerated aging is often linked to T2D and other metabolic disorders. In these models, ES-62 has been observed to improve parameters related to inflammation, metabolism, and the microbiome, suggesting that targeting chronic inflammation and metabolic dysfunction may yield indirect benefits for conditions such as T2D.[89,175,176] This is particularly important given the strong association between T2D and chronic inflammation, with ES-62 appearing to mitigate these inflammatory processes. However, the direct effects of ES-62 on DM, especially T1D, are less encouraging. Research indicates that ES-62 does not confer protection in mouse models of T1D, a condition characterized by the autoimmune destruction of insulin-producing β cells in the pancreas.[177] This indicates that although ES-62 may positively influence inflammation and metabolic health, it does not directly address the autoimmune mechanisms underlying T1D.

HSP70

Heat shock protein 70 (HSP70) has been identified as a promising therapeutic target for mitigating the effects of DM, particularly T2D. Research indicates that HSP70 plays a vital role in the pathogenesis of IR, a critical factor in T2D development. As a cytoprotective molecular chaperone, HSP70 is involved in protein folding and degradation, and its regulation has shown potential in enhancing insulin sensitivity and glycemic control.[178] The intracellular form of HSP70 (iHSP70) is crucial for maintaining normal insulin signaling and inhibiting protein aggregation, contributing to its anti-inflammatory properties. On the other hand, the extracellular form (eHSP72) is associated with pro-inflammatory conditions and IR.[179] This dual role suggests that the therapeutic potential of HSP70 may rely on maintaining the balance between its intracellular and extracellular forms. An imbalance in the ratio of eHSP72 to iHSP70 has been linked to vascular dysfunction in DM, emphasizing the importance of preserving this balance for vascular health and effective DM management.[180] Moreover, strategies aimed at increasing HSP70 expression—such as long-term physical exercise, hot water immersion therapy, and the administration of HSP70 derived from alfalfa—have demonstrated potential for both the treatment and prevention of T2D.[178] Additionally, heat stimulation has been proposed as a method to induce HSP70 expression, which may enhance insulin sensitivity and reduce chronic inflammation, addressing the underlying pathology of T2D and its related metabolic disorders.[181]

FhHDM-1

Helminths, such as *F. hepatica*, secrete various molecules that modulate immune responses, primarily by enhancing anti-inflammatory pathways and suppressing pro-inflammatory reactions.[182,183] These secreted molecules, which include EVs and ESPs, are essential for the helminths' survival within the host as they help evade immune detection and reduce inflammation.[182,183] One specific protein derived from *F. hepatica, Fh*HDM-1, has exhibited notable anti-inflammatory properties. It has been shown to prevent the onset of T1D in mouse models by modulating the activity of MΦ and neutrophils, thus inhibiting the release of pro-inflammatory cytokines and chemokines.[184] This modulation occurs through the activation of the PPAR-γ pathway, which is known for its role in mitigating inflammation and enhancing insulin sensitivity,[185] offering a potential therapeutic approach for DM management.

SmEA

Research has shown that *S. mansoni* egg antigen (*Sm*EA) exhibits potential in mitigating DM, particularly T1D, through its immunomodulatory effects. Several studies have investigated the influence of *Sm*EA on autoimmune DM models, yielding promising results. For instance, a study by Yahia examined the impact of *Sm*EA on streptozotocin-induced T1D in mice. The findings revealed that SEA treatment significantly reduced blood glucose levels and increased insulin levels, indicating a protective effect against T1D. This protective effect was associated with elevated levels of the anti-inflammatory cytokine IL-10, suggesting a shift towards a Th2 immune response, which is less damaging to pancreatic β cells compared to the Th1 response typically linked to T1D.[186] El-Gebaly found that the administration of SEA in

diabetic mice resulted in significantly lower blood glucose levels and increased IL-10 production. Histopathological analysis further confirmed reduced inflammation of the pancreas, supporting the protective role of SEA in T1D.[187] These results are consistent with the research by Zaccone, who demonstrated that *Sm*EA induces Th2 and Treg responses, which are crucial for establishing immune tolerance and preventing DM in NOD mice. The study also highlighted the crucial role of TGF-β in the expansion of Tregs, a key mechanism driving the immunomodulatory effects of SEA.[188]

Other Molecules Derived from Helminths

H. polygyrus, a gastrointestinal helminth, is recognized for its ability to modulate host immune responses, primarily by inducing a Th2-skewed immune response and expanding regulatory Tregs.[2] This immunomodulation occurs through the secretion of ESPs, which include immunoregulatory proteins such as TGF-β mimics and galectins.[4] These findings suggest that while *H. polygyrus* ESPs can modulate immune responses, but its effectiveness may vary depending on the specific disease and immune pathways involved. Although this abstract does not directly address DM, the immunoregulatory properties of *H. polygyrus* ESPs—particularly its ability to induce Th2 responses and expand Tregs—may offer potential therapeutic benefits for autoimmune DM, where immune regulation is impaired. Filarial cystatin has been shown to modulate immune responses by upregulating NO production in interferon-γ-activated MΦ, as evidenced by studies on *Onchocerca volvulus (O. volvulus)* and *Acanthocheilonema viteae (A. viteae)*. This upregulation partially depends on interleukin-10 and tumor necrosis factor-α, reflecting complex interactions within the immune system.[189] Nitric oxide, a critical signaling molecule in processes such as vasodilation and immune regulation, could theoretically influence metabolic pathways related to DM. Furthermore, filarial cysteine protease inhibitors have been found to suppress T cell proliferation and promote an anti-inflammatory cytokine profile, such as increased interleukin-10 production.[189] This anti-inflammatory action has the potential to mitigate chronic inflammation, a contributing factor in IR and T2D. HpARI, a protein secreted by the parasitic nematode *H. polygyrus*, binds to the cytokine IL-33 and DNA, thus modulating immune responses. The full-length HpARI protein inhibits IL-33 activity by sequestering it within the nuclei of necrotic cells, preventing its release and subsequent immune activation.[190] This inhibition of IL-33 could have significant implications for treating inflammatory conditions, including DM, which is characterized by chronic inflammation. Interestingly, a truncated form of HpARI (HpARI_CCP1/2) has been shown to stabilize IL-33, enhancing rather than suppressing immune responses.[191] This truncated form cannot prevent IL-33 from interacting with its receptor, thereby amplifying IL-33-dependent immune reactions. This suggests that the regulatory effects of HpARI on IL-33 vary depending on the specific form of the protein and its interactions.

Advancements in Helminth-Derived Products

Optimization of Drug Delivery

Distinct families of biomacromolecules derived from worms demonstrate unique capabilities to address challenges associated with the therapeutic properties of worm-derived products and the mechanisms for effectively delivering these proteins to target tissues or organs. In recent years, the development of novel delivery technologies has revitalized the therapeutic potential of various drugs (Figure 3).

Microneedle arrays have been specifically engineered to penetrate the stratum corneum, creating microchannels that enable efficient transport into the dermis, thereby facilitating the delivery of macromolecular drugs such as proteins.[192–194] This delivery method is particularly advantageous for protein-based therapeutics, which are typically unstable and susceptible to degradation when administered orally. By circumventing the gastrointestinal tract and first-pass metabolism, microneedles provide a non-invasive and pain-free alternative to conventional injections.[195,196] In Japan, a novel adjuvant-free immunotherapy for T1D employs *S. japonicum* egg tip-loaded asymmetric microneedle patch loaded at the tips of *S. japonicum* eggs.[197]

Nanomedicine, propelled by advances in nanodelivery technologies for targeted drug delivery,[198] cancer therapy, and crossing the blood-brain barrier,[199] is increasingly being explored in helminthic research. This includes the delivery of immunomodulatory compounds derived from helminths to treat autoimmune and allergic diseases. Emerging technologies, such as intelligent targeted nanodelivery systems, demonstrate the ability to activate the Wnt signaling pathway (via

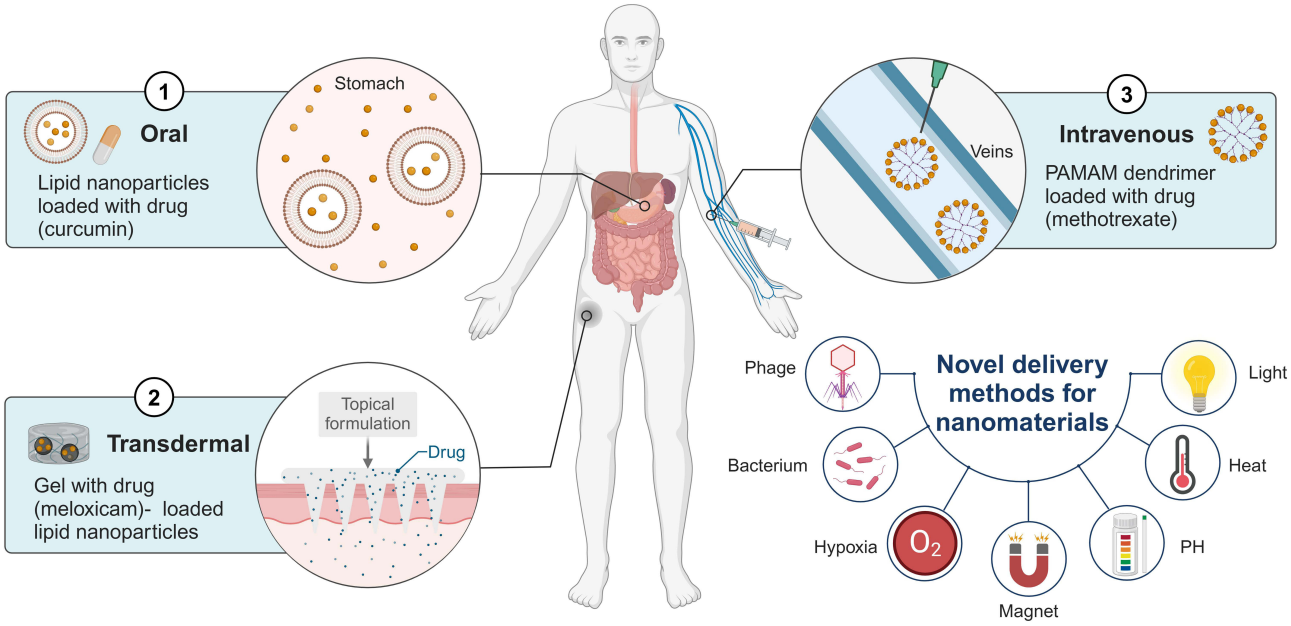

Figure 3 Common drug delivery systems. Oral administration involves lipid nanoparticles, which deliver drugs such as curcumin. These particles are ingested and enter the stomach. In the case of transdermal administration, drug-laden gels, such as those containing meloxicam, employ microneedles to administer drug particles through the skin. For intravenous administration, drugs like methotrexate are loaded into polyamidoamine (PAMAM) dendrimers, which are then injected directly into the bloodstream. Recently, innovative methods using nanomaterials for drug delivery have been developed, including releasing drugs controlled by various external stimuli such as light, heat, pH, oxygen, and magnetic fields. These new approaches offer precise control over when and where drugs are released, enhancing treatment effectiveness and reducing potential side effects. Created in BioRender. Yunhuan Zhu (2025) https://BioRender.com/p89w615.

Gsk3β inhibition), suppress inflammasome activation (via NLRP3 inhibition), and stimulate autophagic pathways (by protecting Atg3/Atg7). These mechanisms collectively support β-cell development and mitigate the severity of T2D.[200] Nanoparticles have shown potential in delivering bioactive peptides, addressing challenges such as rapid degradation in vivo and the traversal of biological barriers.[201] Additionally, food-grade colloidal systems—including microemulsions, emulsions, and nanoemulsions—enhance the stability and absorption efficiency of proteins and peptides.[202] Self-assembled peptide nanostructures, characterized by their chemical versatility and precise targeting capabilities, exhibit promising potential in drug delivery applications.[203] Furthermore, nanoparticles and nanocapsules improve the solubility and cellular uptake efficiency of biomacromolecules.[204]

The miRNAs and exosomes derived from parasitic worms not only modulate immune responses and control inflammation,[205,206] but also represent a promising new approach to enhance drug delivery efficiency.[207] EVs, naturally occurring vesicles with high biocompatibility and stability, can encapsulate both hydrophilic and lipophilic drugs, protecting them from degradation and improving their bioavailability.[208,209] Furthermore, EVs are capable of crossing the blood-brain barrier,[208,210] and their surface proteins can be engineered to facilitate targeted delivery to specific cell types or tissues,[211,212] offering advantages over synthetic nanoparticles.[213] Hawdon's research team has explored transgenic nematodes as novel biological vectors for therapeutic delivery, showcasing the potential of worms in this context.[214] The delivery of parasitic miRNAs and EVs can be further enhanced by various innovative strategies. Exosomes, particularly small exosomes (sEVs), have gained attention as promising miRNA delivery vehicles due to their natural ability for intercellular communication.[215,216] For instance, the combination of graphene quantum dots with sEVs enables real-time visualization and enhances the delivery of miRNA (such as miR-193a-3p).[217] Electroporation, an optimized technique, has been used to improve the loading and delivery efficiency of synthetic miRNA mimics into plasma-derived exosomes.[215] Another alternative approach, temperature-controlled co-incubation, has been shown to effectively load miRNA into serum-derived exosomes.[218] In addition, regulating miRNA biogenesis pathways can enhance miRNA localization within exosomes, as demonstrated in the case of miR-146a-5p, which improved the therapeutic efficacy of exosomes derived from induced pluripotent stem cells.[219] The chemical transfection method Exo-Fect Transfection Reagent has also been reported to significantly increase miRNA loading efficiency in small exosomes,

boosting the target miRNA expression by more than 1000-fold, thereby enhancing its delivery and functional effects in target cells.[220] These studies highlight the high efficiency and multifunctionality of EVs and miRNAs in helminth-derived therapeutics.

Plant Glycosylation of Worm Proteins

Glycosylation, particularly N-glycosylation, is a critical post-translational modification of worm proteins, essential for proper protein folding. It plays a pivotal role in glycosylation-dependent quality control, protein localization, resistance to proteolytic degradation, solubility, and biological activity,[221] significantly influencing immune interactions between the worm and its host.[91,222–225] However, this complexity makes the large-scale purification of immunoregulatory glycoproteins from worms technically challenging.

Fortunately, plants can have complex glycosylation processes, including N-glycosylation and O-glycosylation. Over the past two decades, plants have evolved into a multifunctional platform for producing recombinant proteins.[226] Recently, plants have successfully produced recombinant proteins from parasites, utilizing their relatively simple glycome to generate heterologous proteins with more consistent glycosylation profiles. Compared to other production systems like *E. coli*,[227] insect cells,[228] and TE671 cells,[229] which often introduce unintended alterations in glycan compositions, plant-produced glycoproteins feature remarkably uniform N-glycan profiles.[230,231] Certain characteristic features of the limited plant glycome align with those of worms, including non-mammalian N-glycan core modifications and a lack of sialylation. Plants' tolerance for engineered exogenous N- and O-glycans and their capacity to modify their glycosylation strategies through glycoengineering render them an optimal platform for glycoprotein production[232] (Figure 4). Additionally, the plant expression systems offer scalability from minor cell suspensions to GMP bioreactors, ensuring no mammalian pathogens or carcinogenic sequences are present, thereby facilitating safe, rapid, and flexible biopharmaceutical production.[233] Research has identified enzymes (HEXO2 and HEXO3) that specifically cleave N-glycans on the κ-5 glycoproteins of worms. By precisely editing these enzymes to minimize undesirable N-glycan processing, it is possible to manufacture therapeutically relevant glycoproteins with tailored worm N-glycans in plants,[234] mainly since plants are highly adaptable to engineering modifications of their intrinsic N-glycosylation pathways.[230] Experiments with plant-produced recombinant ω1 in obese mice have demonstrated significant increases in CTLA-4 levels, pointing to potential of ω1 to boost Treg functions, reduce body fat, and improve overall insulin sensitivity and glucose tolerance in a time- and dose-dependent manners.[57,171] Utilizing plants as a production system reduces pathogen contamination risks and enhances the safety of the final product due to their non-host status for human or animal pathogens.

Combination Therapy Strategy

Researchers can either deliver individual parasitic factors or co-deliver multiple parasite ES molecules to investigate their synergistic effects or administer them in conjunction with other immunomodulators such as rapamycin, cytokines, and bacterial antigens, which individually exhibit considerable variability in circulation duration and biodistribution.[235,236] Immunomodulators, encompassing a broad spectrum of physicochemical properties from small molecules to nucleic acids, proteins, lipids, and fatty acids,[237,238] require a co-delivery system to facilitate synergistic interactions, and a topic extensively reviewed in prior literature.[239]

Helminth-derived molecules can be combined with anti-diabetic drugs to enhance therapeutic outcomes by modulating immune and metabolic pathways. Current anti-diabetic drugs, including metformin and thiazolidinediones, have demonstrated certain anti-inflammatory properties, which contribute to their effectiveness in managing DM.[240,241] The combination of these drugs with worm-derived molecules could augment their anti-inflammatory effects, potentially improving blood glucose control and reducing the risk of diabetes-related complications,[241] as well as mitigating side effects associated with oral hypoglycemic agents.[242] Research has indicated that Dipeptidyl Peptidase-IV inhibitors, commonly used in DM treatment, can be co-administered with worm ESPs to enhance glucose-lowering effects.[243,244] However, comprehensive clinical trials are still necessary to thoroughly assess the safety and efficacy of combining worm-derived molecules with conventional medications, ensuring that the benefits outweigh any potential risks.[245]

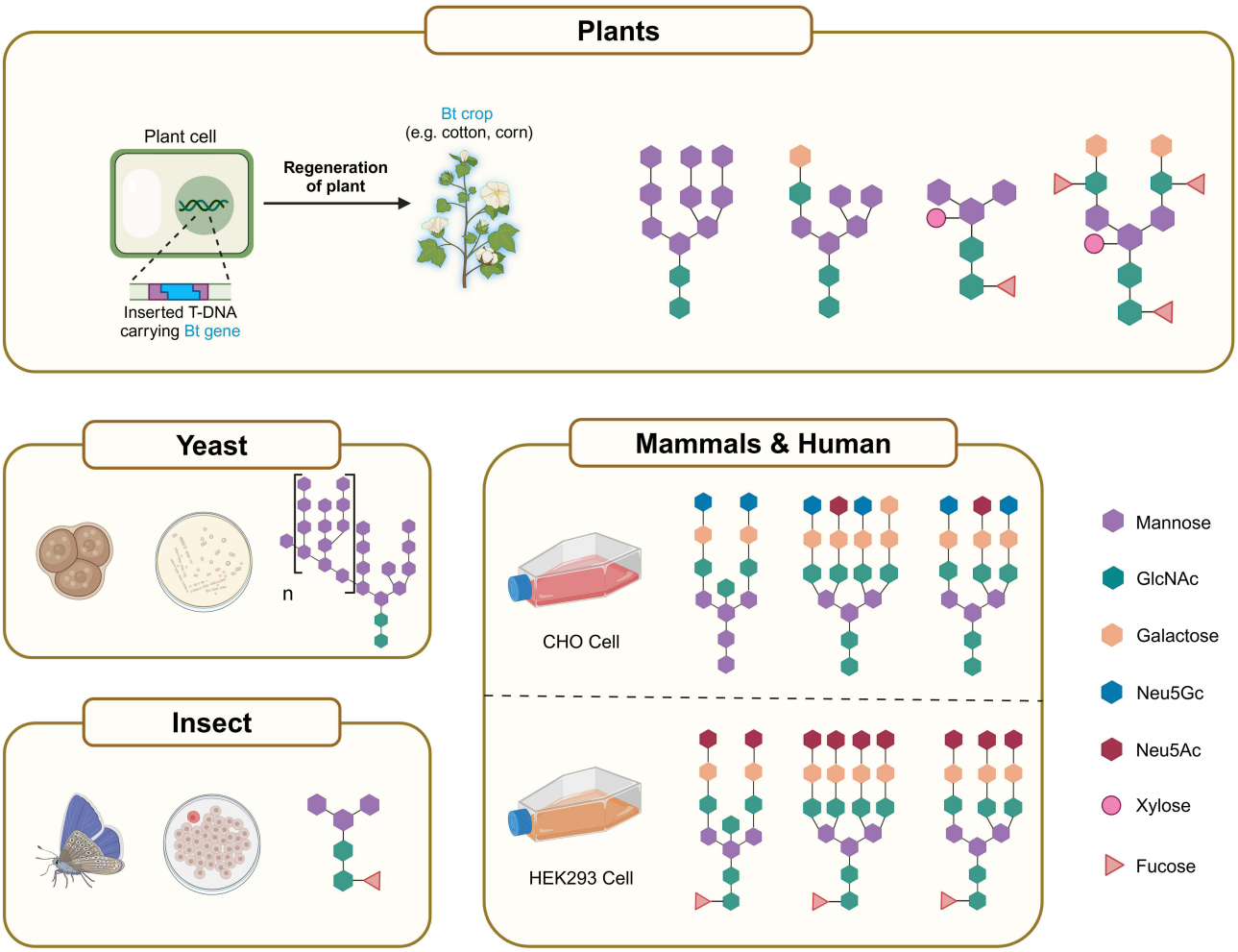

Figure 4 Comparison of protein glycosylation patterns in different biological systems. In the plant section, a specific glycosylation pattern can be seen by transferring T-DNA containing the Bacillus thuringiensis (Bt) gene into plant cells and regenerating plants. The types of glycosylation expressed by proteins are also shown in yeast, insects, and mammals (such as CHO and HEK293 cells). Created in BioRender. Yunhuan Zhu (2025) https://BioRender.com/l22b252.

Challenges in Translating Helminthic Therapy to Clinical Use

Challenges in Clinical Efficacy

Translating these findings from mouse models into clinical applications is a challenging endeavor. One major issue arises from the diversity of parasitic worm species and the complexity of their life cycles. This raises concerns about safety and tolerance, as the introduction of live worms or their components could provoke unexpected side effects, such as increased susceptibility to other infections.[246,247] Furthermore, little is understood about the optimal dose or duration of parasitic infections necessary to confer protection in humans, and concerns regarding the potential harmful effects of these infections have hindered clinical trials. The interpretation of clinical data on experimental worm infections is also complicated by high levels of immune variability across different genetic backgrounds. In fact, not all studies have demonstrated an impact of worm infections or deworming on allergic inflammation,[248,249] which is consistent with the lack of therapeutic effect of worm infections in human autoimmune allergic inflammation.[250–252]

Therefore, selecting the appropriate species of worms and determining the optimal treatment dose and duration remain critical unresolved challenges in both scientific research and clinical practice. Although worm-derived proteins have shown promise in modulating immune responses and alleviating inflammation in diseases like inflammatory bowel disease and asthma, the precise mechanisms underlying their effects are not yet fully understood.[253,254] While regulation of pro-inflammatory cytokines and induction of anti-inflammatory responses have been observed, these effects tend to be localized and cannot be consistently replicated at the systemic level.[254,255] Additionally, factors such as host genetics,

diet, and environmental conditions contribute to variability in treatment responses, complicating the standardization of therapeutic protocols.[256] Species-specific differences among worms and the formulation of appropriate dosing regimens are also key factors that require further investigation to optimize therapeutic outcomes. As with other biological therapies, worm-based treatments also carry the risk of developing resistance, as the host immune system may gradually build tolerance, reducing the efficacy of treatment over time.[257] Finally, the clinical effectiveness of worm therapy may be significantly affected by the formulation and storage conditions of the therapeutic worms. Experimental studies have shown that improper pH during storage can impair the clinical efficacy of Trichuris suis eggs.[258] The development of worm-based biopharmaceuticals faces further challenges related to the pharmacokinetics and chemical properties of these compounds.[259]

Public Awareness and Acceptance

The concept of using parasites as a therapeutic approach is often met with skepticism and fear by the public, with these attitudes representing a major barrier to the acceptance and adoption of worm therapy.[260] Furthermore, perceptions of worms differ significantly across cultures and societies. In Western societies, where personal hygiene and environmental sanitation are prioritized, the idea of introducing worms into the human body is particularly hard to accept. This cultural resistance may impede the acceptance of worm therapy and its integration into mainstream medical practice.[261,262]

Regulatory and Economic Challenges

Due to the complex and stringent approval processes for biological therapies, worm therapy faces significant regulatory challenges. Additionally, extensive clinical trials are required to demonstrate both safety and efficacy, which can be expensive and time-intensive.[263] Furthermore, the economic challenges associated with developing and commercializing worm-based therapies add another layer of difficulty. The costs related to research, development, and regulatory approval may be prohibitively high, particularly for small companies or research teams.[263]

Conclusion

In recent decades, the global prevalence of DM has surged dramatically, positioning it as a significant global public health challenge. This article investigates the therapeutic potential of parasitic interventions for DM, particularly in the context of the "hygiene hypothesis", which posits that parasitic infections may provide a novel therapeutic approach by modulating immune responses, exerting anti-inflammatory effects, and improving insulin sensitivity. A growing body of evidence indicates that certain helminthic infections can enhance insulin sensitivity by modulating host immune responses and suppressing chronic inflammation, offering promise for the treatment of DM. ESPs derived from parasites have been identified as an emerging therapeutic strategy, demonstrating significant immunoregulatory potential in various inflammatory conditions, with a relatively lower incidence of adverse effects.[21]

Although parasitic derivatives may help alleviate the chronic inflammation associated with DM, their potential risks and challenges must not be overlooked. Therefore, the need to balance the therapeutic benefits and potential risks of parasitic interventions is a crucial focus for future research. Further exploration of the immunoregulatory mechanisms of worm-derived products,[264] optimization of their drug development processes,[265] and undertaking large-scale clinical trials are essential steps toward providing safer and more effective treatment alternatives for diabetic patients.[266]

Future research should focus on verifying the long-term clinical efficacy and safety of these therapies and investigating their potential for combination with existing DM medications, such as insulin or metformin. Additionally, enhancing the acceptance and adoption of parasitic therapies through educational initiatives and public awareness campaigns will facilitate their broader application in DM management.[267–269] Parasitic derivatives, as an emerging therapeutic approach, may offer an economically viable treatment option for diabetic patients worldwide, particularly in resource-limited regions. This therapy holds the potential not only to reduce the global healthcare burden of DM but also to provide new treatment opportunities for both healthcare providers and patients.

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Disclosure

The authors report no conflicts of interest in this work.

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