Review

Public Health

Parasite-Derived Components

An Updated Review of the Toxicological and Pharmacological Effects on the Host

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The toxicological and pharmacological effects of parasite-derived components on the host have received extensive attention. A deep understanding of the toxicological and pharmacological effects of parasite-derived molecules on the host from the perspective of co-adaptation formed during the long-term parasite-host evolution process will not only deepen the understanding of the pathogenic mechanisms of parasites from the perspective of pathogenesis but also benefit from the perspective of treatment. From the perspective of disease, research and development based on the transformation and application of insect-derived components have become and will continue to be one of the most popular research tasks in the field of parasitology research. This article reviews the toxicological and pharmacological effects of several essential zoonotic parasites and their parasites in recent years in inducing and regulating host immune metabolism-related diseases and makes suggestions for the future direction of parasitology research.

Keywords: Parasites; Insect-Derived Components; Toxicological Effects; Pharmacological Effects; Treg Cellss

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THE relationship between parasitic protozoa and worms and their hosts (including humans) is formed through interactions during the co-evolution of both (1). With the development of new theories, new concepts, and new techniques in biological sciences, it is possible for researchers to deepen their understanding of host-parasite interactions at a higher and deeper level of cell and molecular biology. From an evolutionary point of view, host groups always increase genetically determined resistance to counteract the harmful effects of parasites, and parasites always increase genetically determined invasiveness, and a series of mechanisms to evade or antagonize host attacks have evolved (2). This interaction determines the clinical outcome of parasitic infection, of which the host-parasite immunological relationship or interaction may be the most critical. Studies have focused on the in-depth excavation of the host-parasite immunological relationship or interaction, revealing the biological phenomenon that the host's immune response to parasites is a "double-edged sword", and clarifying the origin

of immunopathological damage. Toxicological effects have become the key pathological basis of many parasitic diseases, providing intervention targets for the prevention and treatment of them (3). At the same time, researchers have also revealed that certain parasites, especially worms, can not only reduce the level of parasite-specific immunity but also regulate the host's autoimmunity and allergic inflammatory responses through excretion and secretion components, which can improve the host's immune and metabolic stability and the pharmacological effects of the state.

Research in parasitology focuses on three main areas: the molecular biology of the host-parasite relationship, the discovery of antiparasitic drugs and vaccines, and the discovery of uses for the treatment of human diseases. Clearly, the study of parasite-derived immunomodulatory components, which can help translate current and future research results into potential treatments, even though it is a challenge. Discussion of the immune response and modulation of parasites, particularly helminths, in the context of novel therapeutic drug discovery affirms the pharmacological effects of insect-derived components on the host. Parasite-derived molecules may have more potential than the traditional route to new drug development (4). The pharmacological effects of parasite-derived components on the host are formed through evolutionary selection pressure during the co-evolution of the parasite and the host (5). We herein review the toxicological and pharmacological effects and mechanisms of several important parasite-derived components and puts forward opinions and suggestions for the future direction of this field.

Toxicology and Pharmacological Effects of Protozoa

Protozoa are single-celled eukaryotes with a simple structure that can parasitize human tissues, organs, cells, and body fluids. They can participate in the host's immune response and immune regulation process through the secretion of various effector molecules.

Toxoplasma gondii

Toxoplasma gondii is a critical opportunistic pathogenic protozoan. The growth and reproduction cycle of *Toxoplasma gondii*, its ability to invade host cells, virulence, and immune escape process are all related to soluble tachyzoite antigens (STAg) and/or *Toxoplasma gondii* tachyzoite excretion/secretion antigen (ESA). In the early stage of *Toxoplasma gondii* infection of host cells, microneme protein (MIC) and rhoptry protein (ROP) play an important role in the process of tachyzoite recognition, attachment, and invasion of host cells, and then the formation of parasitic vacuoles; and dense granule protein (GRA) plays a key role in the process of obtaining nutrients from the host to maintain survival and reproduction (6). Etheridge et al. developed a tandem affinity protein labeling and purification method and clarified that the pathogenic mechanism of *Toxoplasma gondii* is mainly through the combination of ROP18, ROP5, and ROP17 to become a key acute virulence factor, which can directly target phosphorylation (7). Immune-associated GTPases, in turn, protect the parasite from clearance by activated macrophages (8).

The exploration of the application value of *Toxoplasma gondii*-derived molecular transformation has always been the focus in this field. Mercer et al. used the cps1-1 *Toxoplasma gondii* strain to knock out GRA24 and found that GRA24 can induce p38 MAPK activation and downstream IL-12 production in host macrophages to protect immunity (9). It was further found that its inducibility was independent of Toll-like receptor/myeloid differentiation factor 88 (TLR/MyD88) signal activation. In addition, GRA7 relies on its C-terminus (GRA7-V) to interact with and ubiquitinate the RING domain of the TRAF6 molecule downstream of TLR4, thereby inducing the activation of nuclear factor B signaling and the release of inflammatory cytokines (10). Immunization with GRA7-V mice can induce Th1 immune responses and exert protective effects against *Toxoplasma gondii* infection. Pulmonary toxoplasmosis is more common in organ transplantation and HIV-infected patients, with severe clinical manifestations (11). Exploring the function and mode of action of ROP16 on host immune cells is of great significance for exploring drug targets and vaccine candidates for the treatment of toxoplasmosis. The researchers screened chemokine CXC motif ligand 11, TLR3, chemokine CC motif ligand 26, human leukocyte antigen E, signal transduction transcription activator 2 used the cps1-1 *Toxoplasma gondii* strain to knock out GRA24 and found that GRA24 can induce p38 MAPK activation and downstream IL-12 production in host macrophages to protect immunity (12). It was further found that its inducibility was independent of Toll-like receptor/myeloid differentiation factor 88 (TLR/MyD88) signal activation (13). In addition, GRA7 relies on its C-terminus (GRA7-V) to interact with and ubiquitinate the RING domain of the TRAF6 molecule downstream of TLR4, thereby inducing the activation of nuclear factor B signaling and the release of inflammatory cytokines (14). Immunization with GRA7-V mice can induce Th1 immune responses and exert protective effects against *Toxoplasma gondii* infection (15). Şahar et al. expressed 49 recombinant proteins of *Toxoplasma gondii* and screened out hexavalent candidate vaccine molecules (pH2, pA4, pE4, pD6, pE6, pH6) and found that they had good efficacy against acute lethal toxoplasmosis (16). Wang et al. used Saccharomyces cerevisiae to express TgMIC16 protein (pCTCON2-TgMIC16/EBY100) and found that it could induce higher levels of humoral and cellular survival of *Toxoplasma gondii* (17). Recombinant T. gondii heat shock protein 70 (TgHSP70) can enhance the induction of nitric oxide expression and prevent the formation of cysts in the brain of *Toxoplasma gondii*, accompanied by higher IgG1 antibody levels (18). In view of the important characteristics of the pro-inflammatory response induced by the host infection with *Toxoplasma gondii*, Toxoplasma STAg was injected into pregnant mice to induce maternal immune activation (typical Th1/Th17 immune bias) and found significant autism-like behaviors such as social impairment, repetitive stereotyped behavior, etc (19). However, the following issues remain to be resolved: (i) the difference between the *Toxoplasma gondii* antigen STAg and traditional pathogenic molecules (lipopolysaccharide, and polyinosinic acid) in the model of inducing autism-like behavior in offspring; (ii) the existence of a molecule capable of exerting the above-mentioned toxicological effects.

Chronic infection with Toxoplasma protects mice from other pathogens, including Listeria monocytogenes, Salmonella

typhimurium, Cryptococcus neoformans, Moloney leukemia virus, and Schistosoma monsoni (20, 21). O'Brien et al. used the *Toxoplasma gondii* antigen STAg to act on the highly pathogenic H5N1 avian influenza virus, which can significantly reduce the virus titer and prolong the survival of mice, indicating that treatment with STAg can induce the avian influenza virus's potential immunity (22). In addition, Settles et al. showed that chronic Toxoplasma infection or the use of the soluble Toxoplasma antigen STAg can reduce experimental cerebral malaria induced by the Plasmodium berghei anka strain by inducing IFN-γ (23). Charest et al. used the temperature-sensitive strain of *Toxoplasma gondii* ts-4 as a vector to express the circumsporozoite protein of Plasmodium yoelii and constructed a recombinant circumsporozoite protein carboxy-terminal 3 and found that it could produce a high level of anti-plasmodium specificity IFN-γ, suggesting that the recombination of *Toxoplasma gondii* ts-4 with other pathogen proteins can make the host obtain protection against other pathogens (24).

In addition, Kim and colleagues found that rGRA8 can induce colonic cell death through the signaling pathway of protein kinase C subunit-Sirtuin 3-ATP synthetase F1 subunit and creatively developed a specific targeting tumor cell membrane molecule (acidity-triggered rational membrane, ATRAM) conjugated GRA8 multifunctional peptide molecule (rATRAM-GRA8-M/AS) that was found to have significant anti-tumor activity (25). At the same time, the dense granule protein GRA15II of the virulence-related molecule of *Toxoplasma gondii* has the ability to induce the M1 polarization of classically activated macrophages (26).

Leishmania

Leishmania braziliensis metalloprotease glycoprotein-63 (GP63) is expressed in both promastigotes and amastigotes, located on the surface of the worm body, and has the function of attaching macrophages to promastigotes (27). These two enzymes are closely related and are an important virulence factor (28). Studies have suggested that the mechanism of GP63-mediated attachment of *Leishmania promastigotes* is closely related to the direct binding of macrophage receptor CR3, and anti-CR3 antibodies can inhibit the binding of GP63 to macrophages (29). At the same time, GP63 is crucial in the process of amastigotes resisting macrophage lysosome hydrolysis (30). In macrophages, GP63 has been shown to cleave a variety of substrates, such as protein tyrosine phosphatases, transcription factors, and the target of rapamycin, thereby benefiting intracellular parasite survival (31). Using the GP63-derived polypeptides LLVAALLAVLLV and AARLVRLAAAGAAVTAAR can induce high levels of anti-Leishmania IgG antibodies in hamsters and stimulate the proliferation of lymphocytes, suggesting that GP63-derived polypeptides also have potential candidate vaccine effects (32). Exosomes are eukaryotic extracellular vesicles that maintain cellular communication in various biological settings. Studies have raised the important point that Leishmania exosomes are involved in the pathogenic processes of the disease (33). The exosomes of *Leishmania mexicana* contain a series of insect-derived molecules, such as virulence factor GP63 and protein phosphatase 2C (34). Exosomes can inhibit the secretion of infected bone marrow-derived macrophages (35). Nitric oxide levels can also suppress cellular immune responses by reducing major histocompatibility complex class I and CD86 molecules on the surface of macrophages, thereby increasing the survival rate of parasites in cells (36).

Many reports presented Leishmania-derived molecules as potential diagnostic and vaccine effector molecules, such as the r21 protein derived from *Leishmania infantum* (37), the hypothetical protein G (38), hypothetical protein J (39), which have high sensitivity and specificity for diagnosing canine and human leishmaniasis with low cross-reactivity. In addition, researchers used Leishmania infantis lipophosphoglycan 3 (LPG3) antigen to immunize infected BALB/c mice and found that it had better protection and could induce an increase in serum IgG2a antibody levels in mice (40). *Leishmania infantum* pyridoxal kinase recombinant protein can induce the expression of high levels of cytokines interferon-γ (IFN-γ), interleukin-12 (IL-12) after immunization of mice, granulocyte-macrophage colony-stimulating factor, and specific IgG2a antibodies, suggesting that recombinant pyridoxal kinase protein can be used as a potential vaccine molecule for visceral leishmaniasis (41). The co-infection of Leishmania and HIV can be characterized as a complex system involving alterations in the expression of cell surface molecules, secretion of soluble factors, and intracellular apoptotic processes. These changes ultimately result in the enhancement of infectivity, replication, and dissemination of both pathogens (42).

Using the non-pathogenic *Leishmania tarentolae* as a model for a novel drug candidate to produce a live vaccine against an intracellular pathogen, they recombinantly expressed human papillomavirus in *Leishmania tarentolae* E7 protein (L. tarentolae-E7) and injected it into a mouse model of cervical cancer (43). They found that E7 molecules can protect mice from human papillomavirus-associated tumors (44, 45). In addition, Caner et al. found that *Leishmania infantum* and *Leishmania tropica* could significantly inhibit tumor formation in 4T1 breast cancer mice and induce high levels of IFN-γ and tumor necrosis factor-α (TNF-α) (46).

Plasmodium

Malaria is a very harmful zoonotic parasitic disease. According to the World Health Organization, approximately 50% of the global populace was susceptible to contracting malaria, there were an estimated 247 million cases of malaria worldwide and 619,000 malaria-related deaths worldwide in 2021 (47). Studies have shown that *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) is expressed in the asexual stage and is closely related to the pathogenicity of severe malaria (48, 49). Plasmodium in red blood cells adheres to the endothelium of blood vessels in the brain through PfEMP1, triggering the occurrence of cerebral malaria, and this process binds to the host receptor endothelin C receptor, thereby interfering with coagulation, inflammation, cell death, and vascular permeability (50). Toda et al. found that plasma-derived extracellular vesicles from patients with Plasmodium vivax could be recognized by human splenic fibroblasts, and then induced reticulocytes infected with Plasmodium vivax (P. vivax) and human splenic fibroblasts to stick (51). In addition, Jiang et al. found that silencing SET gene-dependent histone H3K36 methylation in *Plasmodium*

falciparum can inhibit the expression of pathogenicity-related genes; silencing SET gene knockout Plasmodium can express all PfEMP1 proteins, providing a new idea for malaria vaccine development (52).

VMP001 is a low-level protective vaccine designed based on the circumsporozoite protein of Plasmodium vivax. On this basis, Atcheson et al. further discovered that the alleles VK210 and the small peptides of VK247 are highly protective (53). In addition, it has been pointed out in the literature that the *Plasmodium falciparum* merozoite protein complex (PfRH5-PfCyRPA-PfRipr, RCR) can be used as a target for Plasmodium falciparum vaccines (54). At the same time, PfHSP90, derived from *Plasmodium falciparum*, promotes the development of parasites in red blood cells by forming a complex with PfHSP70-1 (55, 56). A variety of antimalarial drugs have been developed against PfHSP90 in clinical trials (57, 58). Some believe that Plasmodium infection can initiate the body's anti-tumor innate and adaptive immune responses by activating the immune system, and then inhibit tumor growth and metastasis (59, 60). Due to concerns about the clinical safety of infection-induced immunotherapy, the protein encoded by variable region 2 of the Plasmodium protein that binds to chondroitin sulfate A has been investigated and found that it can directly target and recognize a variety of tumor cells by binding to glycosaminoglycans and play a potential important role in inhibiting tumor cell proliferation (61, 62).

Toxicology and Pharmacological Effects of Worms

Parasitic worms and their ES mainly affect the host's immunity by acting on the host's immune system and activating or regulating immune cells. The above-mentioned ES anti-inflammatory components include proteins, extracellular vesicles, glycans, and various metabolites, which has opened up new fields and directions for the study of the biological characteristics of worms.

Hookworm

Hookworm infection can lead to damage to human intestinal wall and long-term chronic blood loss (63). In severe cases, it can lead to developmental delays and other symptoms (64). After hookworm infection, the main advantage is to induce host immune responses such as ILC2, Th2, M2, and eosinophils (65). Its pharmacological effects on allergic and autoimmune diseases through hookworm infection or hookworm-derived molecules have been studied, and found that (i) the asymptomatic characteristics of hookworm mild infection and the immunological effects; (ii) the ES components of hookworm help the intestinal hookworm and the host co-evolve from the immune system attack, and then allow the hookworm to survive.

Some researchers used *Nippostrongylus brasiliensis* to prevent and treat type 2 diabetic mice and found that the fasting blood glucose, oral glucose tolerance, and body weight of diabetic mice were significantly reduced, and it was clear that the reduction of systemic and local inflammation was related to intestinal compositional changes in the microbiota (66). Further studies found that the extracellular vesicles secreted by *E. brasiliensis* up-regulate high levels of the anti-inflammatory cytokine IL by inhibiting the key cytokines (IL-6, IL-1, IFN-, and IL-17a) involved in the pathology of colitis in order to prevent induced colitis in mice (67). The netrin domain-containing protein 1 secreted by *Necator americanus* can prevent acute 2,4,6-trinitrobenzenesulfonic acid-induced colitis in mice, mainly by inducing suppression of type I immunity in the gut (68). In response to signaling factors (e.g., TNF, IL-6, and IL-1), M1 polarization is downregulated (69). Wangchuk et al. found that the anti-inflammatory protein AIP2, derived from *Ancylostoma caninum*, can inhibit the airway inflammation of ovalbumin (OVA)-induced asthmatic mice and reduce human dendritic cells (DCs), and revealed that AIP-2 is mainly captured by mesenteric CD103+ DC cells and then induces the important molecular mechanism of regulatory T cells (Treg) cells (70).

Low-molecular-weight metabolites of somatic extracts (LMWM-SE) of *H. caninum* and the low-molecular-weight metabolites of excreted secretion products (LMWM-ESP) can significantly inhibit colitis and protect the colon tissue structure from damage (70). Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography (LC-MS) analysis showed that there were 46 polar metabolites, 22 fatty acids, and 5 short-chain fatty acids (SCFA) in LMWM-SE; LMWM-ESP presents 29 polar metabolites, 13 fatty acids, and 6 SCFAs (71). The small metabolites mentioned above, especially SCFAs, have strong anti-inflammatory properties. Williamson et al. identified *Ancylostoma canisinum* and *Necylos americana* peptide 1 from the ES of *Ancylostoma canisinum* and *Necylos americana*, which can significantly reduce the body weight of 2,4,6-trinitrobenzenesulfonic acid-induced colitis model (72). Mass reduction and colonic atrophy, edema, ulceration, and necrosis, showing good anti-colitis properties; at the same time, these hookworm peptides can induce the up-regulation of ulcer epithelial repair-related genes (nlrp3, mmp, and smad) and inhibit the mucous membrane of goblet cells (73).

Schistosoma

Schistosomiasis remains a serious but neglected tropical disease worldwide. There are five species of schistosomiasis that parasitize the human body. The main cause of disease of *Schistosomiasis japonicum* is the deposition of eggs in the liver and intestines, leading to tissue granulomatous lesions and secondary fibrosis (74). Studies have found that components derived from schistosomiasis have potential toxicological and pharmacological effects on various diseases. First of all, molecules derived from *Schistosoma japonicum* eggs can be involved in promoting the formation of liver granulomas, such as the worm-derived protein SjE16.7 can recruit neutrophils and induce the formation of liver inflammatory granulomas (75, 76). Blocking SjE16.7 in vivo could significantly alleviate egg-induced liver immunopathological damage (77, 78). Takaki et al. used zebrafish larvae as a model to study egg-induced macrophage recruitment and granuloma formation and found that the *Schistosoma japonicum*-derived protein omega-1 could mediate the initial stage of macrophage recruitment, which Chemotactic activity depends on its RNase activity (79). When lentivirus was used to interfere with omega-1 in eggs, the tail vein injection of eggs into mice could significantly inhibit the immunopathological changes of egg granulomas in the lungs

(80). Macrophages stimulated by different stages of *Schistosoma japonicum* infection or different insect-derived molecular components (soluble adult worm antigen, soluble egg antigen), showed that the macrophages were polarized to M1 and M2 respectively, suggesting that the insect-derived molecules were involved in schistosomiasis the acute and chronic inflammation-mediated injury process of infection (81, 82). In addition, macrophages activated by soluble egg antigen induced CD4+ T cells to differentiate into follicular helper T cells in a manner dependent on inducible costimulatory molecules and their ligands, and further revealed that follicular helper T cells Chemotaxis of eosinophils by inducing levels of the chemokine CXC motif ligand 12 in turn promotes hepatic pathology induced by schistosome infection (83, 84).

Second, schistosome-derived components also have potential transformational application value in the progression of various diseases. Studies have shown that the recombinant protein Sj16 derived from *Schistosoma japonicum* can inhibit the polarization of M2 macrophages and slow down the level of hepatic granulomatous inflammation and fibrosis induced by *Schistosoma japonicum* infection (85, 86). The transcriptional transactivator triosephosphate isomerase (Tat-TPI) derived from *Schistosoma japonicum* could induce lymph nodes and spleen to produce stronger CD4+ and CD8+ T cell responses and resulted in a significant reduction in the area of egg granulomas in the liver (87). *Schistosoma mansoni* and *Schistosoma japonicum* infections of collagen-induced arthritis (CIA) mice can significantly alleviate the severity of arthritis in mice (88, 89). After intradermal injection of *Schistosoma mansoni* cercariae protein into CIA mice, it can significantly reduce the arthritis score and induce an increase in the level of Treg cells in mice (90). CIA mice were treated with recombinant *Schistosoma japonicum*-derived cysteine protease inhibitor (rSjCystatin) and found that rSjCystatin can significantly reduce the clinical score, incidence rate, and joint histopathological score of CIA mice; at the same time, rSjCystatin can also inhibit increased levels of IL-4, IL-10, and collagen-specific IgG1 in diseased mice (91).

HSP is an important stress protein that is widely present in hosts and parasites. One of the more abundant proteins in the egg protein of *Schistosoma japonicum* is HSP40 (Sjp40), which can inhibit the activation of hepatic stellate cells through the STAT3/p53/p21 pathway and has the potential to inhibit liver fibrosis (92, 93). At the same time, Sjp40 can be secreted into the blood in the early stages of infection, which has potential diagnostic value. In addition, peptides p6 (51–70), p25 (241–260), and p30 (291–310) derived from Sjp40 were able to suppress airway inflammation in OVA-induced allergic asthma mice by inducing IFN-γ production, indicating that helminth-derived peptides can provide a novel immunoprotective utility (94). *Schistosoma japonicum* egg antigen Sjp40 targets hepatic cell pattern recognition receptor CD36, activating downstream AMP-dependent protein kinase signaling, and then inhibiting liver lipid formation, indicating that Sjp40 has potential translational value in modulating hepatic lipid metabolism (95).

M1 macrophages mainly promote the inflammatory response and can inhibit the repair of peripheral nerves, while M2 macrophages can promote the repair of injured peripheral nerves (96). Studies have confirmed that *Schistosoma japonicum* mouse human epitope 1 (SJMHE1) can promote peripheral myelin growth and functional regeneration by inducing M2 macrophage-dependent mechanisms, indicating that SJMHE1 has the ability to improve peripheral therapeutic potential in neurorestoration (97). SJMHE1 treatment of OVA-induced experimental asthmatic mice can inhibit airway inflammation in allergic mice, reduce infiltrating inflammatory cells in the lungs and bronchoalveolar lavage fluid, reduce the percentage of Th2 cells, and increase the expression of the Th1 and Treg ratios (98, 99). Moreover, SJMHE1 can also inhibit dextran sodium sulfate-induced acute and chronic colitis in mice, upregulate the proportion of Treg cells in mesenteric lymph nodes, and promote the production of IL-10 (100).

Tapeworm

Taenia species are diverse and widely distributed, with different biological characteristics and serious harm to humans and animals (101). Cui et al. collected ESP and cysticercoid cystic fluid from *Taenia solium* and analyzed them by LC-MS, finding that there were 206 and 247 different proteins in the cystic fluid and ESP, respectively, and that these proteins had obvious pro-inflammatory and anti-inflammatory properties (102). Ranasinghe et al. found that *Echinococcus granulosus* Kunitz type protease inhibitor family 1 (EgKI-1) exhibited dose-dependent inhibition of various human cancer cells in vitro (including growth and migration of breast, melanoma, and cervical cancer cell lines) without affecting normal cell growth suggesting that EgKI-1 prevents cancer cell growth by disrupting the cell cycle and inducing apoptosis in cancer cells (103). In addition, EgKI-1 significantly inhibited the growth of melanoma in B16-F0 mice, which may be achieved by reducing the expression of survivin and increasing the number of CD8+ T cells in the draining axillary lymph nodes, suggesting that EgKI-1 has a promising future as an anticancer pharmacological effect molecule (104). Calleja et al. found that *T. crassiceps* ES product (TcES) could reduce inflammatory cytokines (IL-1, TNF-, IL-33, and IL-17) in colitis-associated colon cancer mice and significantly inhibited the occurrence of colon tumors (105). This effect was associated with inhibition of STAT3/NF-B signaling activation and interference with lipopolysaccharide-induced NF-κB p65 activation in human colonic epithelial cell lines in a proto-oncogene Raf-1-dependent manner (106).

Tapeworm ES is one of the main reasons for directly inducing changes in host immune effects. In addition to having an essential immune regulatory function on macrophages, DCs, and lymphocytes (T cells and B cells), it is also involved in inducing the body's inducible nitric oxide. Synthase expression controls parasitic infection by promoting nitric oxide release (107). Echinococcosis is a chronic disease caused by the larvae of the *Echinococcus tapeworm* (108). The treatment mainly depends on albendazole, but it has the disadvantages of a low intestinal absorption rate and high liver toxicity. Therefore, researchers believe that based on the important roles of acetylcholinesterase and nicotinic acetylcholine receptors in the nervous system and ion channels of tapeworms, the potential functions of these two factors can be excavated and studied as a new generation of anthelmintic drugs for tapeworms (109, 110).

Conclusion

The interaction between host and parasite is a multifaceted occurrence that involves the influence of virulence factors from the parasite and heightened reactions from the host. The optimal progression of the host-parasite dynamic is not centered around the eradication of the parasite and the resolution of the infection, but rather on a state of mutual cohabitation that does not result in any harmful consequences for the host. Understanding the toxicological and pharmacological effects of parasite-derived molecules on the host from the perspective of co-adaptation formed during the long-term process of evolution involving the parasite and the host will not only deepen the understanding of the pathogenic mechanisms of parasites, but it will also benefit for the treatment.■

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