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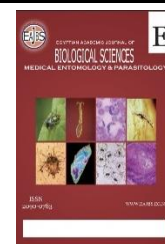
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Parasites From Morbidity to Remedy

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ABSTRACT

Humans are hosts of nearly 300 species of parasitic worms and over 70 species of protozoa, some derived from our primate ancestors and some acquired from the animals we have domesticated or come in contact with during our relatively short history on earth. Our knowledge of parasitic infections extends into antiquity, and descriptions of parasites and parasitic infections are found in the earliest writings and have been confirmed by the finding of parasites in archaeological material. Humans have also shared a prolonged history of co-existence with parasites residing within their bodies. Both developing and developed countries are affected by parasitic infections. It is established that different parasites could alter humans' immune response. It is now believed that certain parasites either by their own existence or by their products might be used to alleviate diverse inflammatory, autoimmune, and allergic, in addition to other diseases. This review aimed to introduce an appraisal of variable studies and literature pursuing the potential role of different types of parasites and/or their products as therapeutic tools in discrete forms of morbidities.

Introduction and Immunology of Parasitic Infections:

The burden of infectious diseases caused or transmitted by parasites; mostly comprising protozoa and helminths are prevalent mainly in tropical and subtropical regions and are responsible for considerable morbidity and mortality (Ratna and Arora, 2018). Parasitic infections exhibit a complex challenge to the immune system (Chen et al, 2012). Parasites have developed a variable array of mechanisms to evade or modulate the host's immune response thus establishing infection (Mabbott, 2018). Generally, parasitic infections are frequently long-lasting and can inhabit immunocompetent as well as immunocompromised hosts. Therefore, it could be deduced that parasites might have attained modulatory molecules modifying host responses and consequently promoting their own survival (Correale and Farez, 2011).

The immune system is an example of precise autoregulation where we can interfere using medications. The therapeutic use of this interference is identified as immunomodulation. Induction or restoration of immune effector functions using parasitic antigens represents a model of the current immunomodulators (Ratna and Arora, 2018).

Notably, the hygiene hypothesis, which was centered on a concurrent increase in autoimmune, allergic and inflammatory disorders with a decrease in certain bacterial and parasitic infections due to better hygiene in Western communities, suggests that these infections might be protective in variable disorders (Versini *et al.*, 2015). These microorganisms were formerly termed 'old friends' since they employ an immunomodulatory action on the host immune system (Rook, 2012).

Additionally, the progressive depletion of microbes and parasites owing to socioeconomic improvement might result in a derangement of immunoregulatory mechanisms (Murdaca *et al.*, 2021). It was stated that a more diverse microbial environment yields better immune system performance (Kıyıkım *et al.*, 2023). The proposed utilized mechanisms are complex and include provoking of T-helper 2 (Th2) and inhibition of Th1/Th17 differentiation, augmentation of T-regulatory cells (Tregs) and B-regulatory cells (B regs), switching of dendritic cells towards a tolerogenic phenotype, downregulation of type2 innate lymphoid cells, and modification of gut microbiota (Jung and Suh, 2017 and Yeshi *et al.*, 2022).

A predominant Th2 response throughout parasitic infections has been broadly reported, even though the exact mechanism initiating this response has not been fully clarified (Everts *et al.*, 2010).

This ability of parasites to bias immune responses towards Th2 responses and chronic infection may be as beneficial to the hosts as well as the parasites. Infected hosts can use this response to survive the infection that cannot be cleared, whereas the parasite is dependent on the survival of the host (Maizels *et al.*, 2004 and Chen *et al.*, 2012).

Prior immunological studies have demonstrated that T helper 2 (Th2)-mediated allergies could be alleviated by microorganisms that induce TH1 cell responses. However, recently, it has been postulated that Th2-cell responses induced by helminths might be accompanied by inhibition of Th2-mediated inflammatory disorders through mechanisms including other non-Th1 cell subsets e.g. regulatory T cells (Maizels and Yazdanbakhsh 2003 and Yazdanbakhsh *et al.*, 2002). This Type 2 immune response consists of activation of CD4⁺ Th2 cells, employment of eosinophils, basophils and mast cells, in addition to the Th2 cytokine profile, all of which aid in preventing excessive

inflammatory reactions (Artis and Pearce, 2013, Voehringer, 2013, van Riet *et al.*, 2007). Moreover, the interaction between host and helminth-secreted products promotes the activation of dendritic cells (DCs) which in turn induce the differentiation of naïve T-helpers cells into Th2, activating regulatory T cells, Breg and activated macrophages (AAMs) (Haak *et al.*, 2009 and Aranzamendi *et al.*, 2013). It is worth mentioning also that helminthic-induced Type 2 cells could provoke a Type 2-cytokine profile including interleukins 3,4,5,9,10 and 13, that is accompanied by differentiation and proliferation of the parasite-specific IgE, IgG and IgG4 antibodies (Logan *et al.*, 2014 and Bager *et al.*, 2010).

Helminthic therapy is a term that refers to the therapeutic administration of helminths or helminth-derived products in order to block Th2 allergen-specific response along with autoreactive-Th1 response in patients with immune-related disorders (Rzepecka *et al.*, 2013). Helminths have evolved a variety of immunomodulatory molecules which begin to be identified, indicating a molecular innovation of parasitic immunology. This provides the potential to better understand parasite adaptation to the host and to renovate probable remedies for immune-mediated disorders (Maizels *et al.*, 2018). Amusingly, it has been postulated that helminth-derived extracellular vehicles (EVs) could also be utilized as immunomodulatory therapeutics regulating pathological inflammatory reactions in allergic, autoimmune, and metabolic disorders (Eichenberger *et al.*, 2018). The varieties of helminth products responsible for this immunosuppressive strategy are still inadequately known, nevertheless, different proteins, lipids and glycoconjugates are suspected (Bager *et al.*, 2010 and van Die and Cummings, 2010).

The current review aimed to illustrate various figures of morbidities showing mitigation accredited to the

influence of certain parasites in these disorders.

Proposed Applications of Parasitic Therapeutic Approaches in Different Disorders:

Autoimmune and Metabolic Disorders: Inflammatory Bowel Disease and Celiac Disease:

Inflammatory bowel disease (IBD) (incorporating Crohn's disease (CD) and ulcerative colitis (UC)) and coeliac disease are global predominant chronic inflammatory disorders of the gastrointestinal tract (Baumgart and Carding, 2007 and Khor *et al.*, 2011). Helminthic infection has been accompanied by modulation of the severity of these disorders (McSorley *et al.*, 2011). It is worth mentioning that IBD patients benefited from *Trichuris suis* (*T. suis*) infection using viable ova obtained under a suitable manufacturing procedure (Summers *et al.*, 2005; Weinstock and Elliott, 2013). It was deduced that helminth-derived antigens might be used either as an adjuvant or a vaccine for the improvement of disease in IBD patients (Abdoli, 2019). Another study documented a case of UC with *Trichuris trichiura* (*T. trichiura*) showing a marked diminution of inflammatory marker expression with global remission of the disease (Su *et al.*, 2017). *Necator americanus* (*N. americanus*) larvae were also used in multiple trials as curative mediators in celiac disease patients (McSorley *et al.*, 2011) and all showed elevated Th2 response associated with immunoregulatory cytokines (e.g. IL-10 and TGF- β) with diminution of inflammatory cytokines that used to be concomitant with the colitis-induced pathology (Gazzinelli-Guimaraes and Nutman, 2018). Other studies have mentioned different parasites with protective roles in IBD including *Hymenolepis diminuta* (Matisz *et al.*, 2017), *Anisakis spp.* (Haarder *et al.*, 2017), *Ascaris lumbricoides* (Coronado *et al.*, 2017), *Clonorchis sinensis* (Jang *et al.*, 2011), *Brugia malayi* (Kron *et al.*, 2013) and

Echinococcus granulosus (Soufli *et al.*, 2015). Conversely, previous studies with broader populations displayed that neither *Trichuris* nor *N. americanus* had expressed substantial protection in IBD or celiac diseases (Mahanty and Nutman, 1995). Accordingly, mechanisms of helminths' immune alterations should be accurately marked out before being utilized in different autoimmune diseases (Pastille *et al.*, 2017). Consequently, further studies are required to verify helminthic infection as an optimum counter-inflammatory therapeutic tool in these disorders.

Diabetes Mellitus:

Type 1 and type 2 diabetes mellitus (DM) are chronic diseases affecting approximately 425 million people worldwide, yielding poor health outcomes and high healthcare costs (Arneth *et al.*, 2019).

Different studies have demonstrated the probable therapeutic role of helminthic infections in Type 1 diabetes mellitus. Different parasites are involved including *Schistosoma mansoni* (Savio and Coutinho-Silva, 2016), *Brugia malayi*, *Fasciola hepatica* (Reddy *et al.*, 2017), *Trichinella spiralis* (Saunders *et al.*, 2007) and *Dirofilaria immitis* (Imai *et al.*, 2001). In patients with Type 1 diabetes mellitus, regulatory T cell numbers are deficient, the cells have impaired function and other immune cells are unresponsive to the regulatory T cells (Bluestone *et al.*, 2015). Consequently, data proposed that the immune skewing from a Th1 to either a Th2 or a regulatory response is the primary mechanism through which this disease is improved (Zaccone and Cooke, 2013). Moreover, protective mechanisms of infections on diabetes onset include competition for homeostatic factors as well as stimulation of Toll-like receptors (Bach and Chatenoud, 2012).

Within the same concern, helminth infections such as schistosomiasis (Chen *et al.*, 2013), lymphatic filariasis (Berbudi *et al.*, 2016) and soil-transmitted helminthic infections including *Strongyloidiasis*

stercoralis (Wiria *et al.*, 2015) were all associated with decreased risk of type 2 diabetes mellitus. Several studies revealed a protective outcome of parenteral injection of *Schistosoma mansoni* eggs or *S. mansoni* adult worms in female non-obese diabetic mice upon administration at an early stage of the disease (Zaccone *et al.*, 2009). Results stated that helminth-induced IL-10 and type 2 immune responses help to improve insulin signaling and sensitivity (Husaaarts *et al.*, 2015).

Rheumatoid Arthritis:

Rheumatoid arthritis (RA) is a disorder manifested by chronic inflammation of joints associated with overexpression of certain cytokines (TNF α , IL-1 and IL-6) (Alghasham and Rasheed, 2014). A study performed on mice with RA infected by *Heligmosomoides polygyrus* or *Nippostrongylus brasiliensis* revealed a diminished presence of arthritis correlated with a decline in synovial hyperplasia with no effect however on other manifestations including cartilage erosion or bone destruction (Salinas-Carmona *et al.*, 2009). Similarly, mice with RA under helminthic therapy showed relief of manifestations associated with the diminution of local inflammasome activity as well as the production of Th1 cytokines including TNF α , whereas increasing production of IL-4 and IgG1 (Smallwood *et al.*, 2017).

Likewise, parasites including *Schistosoma mansoni*, *Trichinella spiralis* (Osada *et al.*, 2020), *Schistosoma japonicum* (Liu *et al.*, 2016), *Fasciola hepatica* (Carranza *et al.*, 2012) and *Hymenolepis diminuta* (Shi *et al.*, 2011) were supposed to exert nearly similar protective effects on RA patients. Their protective role was illustrated by the regulation of CD4⁺ T cell subsets through reducing Th1 and Th17 responses, promoting regulatory T cell responses, downregulation of proinflammatory cytokines (IFN- γ , IL-1 and TNF- α) and upregulation of anti-inflammatory cytokines (IL-4 and IL-10) (Apaer *et al.*, 2016). Conversely, Matisz *et al.*, (2011),

declared no specific anti-inflammatory mechanism in RA patients. Advanced research and methods are mandatory to further investigate the precise mechanisms and potential positive role of parasites on RA (Apaer *et al.*, 2016).

Autoimmune Liver Diseases:

Aoyama *et al.*, (2007) have revealed an inverse relation between some autoimmune liver diseases (e.g. autoimmune hepatitis and primary sclerosing cholangitis) and *S. stercoralis* infection (Wammes *et al.*, 2014).

Psoriasis:

Psoriasis is one of the most common immune-mediated skin disorders causing raised scaly patches over elbows, knees, scalp and other body sites (Griffiths and Baker, 2007). Previously, psoriasis has been regarded as a Th1 class pathology. However, recently it showed also additional involvement of Th17. Hence, helminthic therapy could suppress excess Th1 and Th17 activity providing an effective remedy for this immunopathology. This is in addition to helminthic activation of regulatory T cells and production of anti-inflammatory cytokines IL-10 and TGF beta which helps to alleviate psoriatic immune dysfunction (Lew *et al.*, 2004 and Van Beelen *et al.*, 2007). Interestingly, Greb and Gottlieb (2013) demonstrated that controlled *Trichuris suis* ova administration appears to be a promising therapeutic option for psoriasis.

Systemic Lupus Erythematosus:

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is characterized by the abnormal formation of autoantibodies and inflammation of various body organs (Kaul *et al.*, 2016). Willcocks *et al.*, (2010) suggested that the immune response generated by *Plasmodium falciparum* infection proved to exhibit protection against SLE development as the gene linked to malaria protection seemed to be an SLE-susceptible gene too. Malaria infections of lupus mice regulates B cell autoreactivity and displays protection against histopathological changes and

disease progression (Abdel-Maksoud *et al.*, 2016). Moreover, controlled malaria infection was shown to attenuate lupus nephritis in mice by decreasing kidney oxidative stress and intensifying the antioxidant defense system (Badr *et al.*, 2015). Further studies showed that malaria infection caused alterations in bone marrow cells hampering the inflammatory dendritic cells to infiltrate the kidneys which in turn reduced kidney pathology and immune infiltrates (Amo *et al.*, 2021).

Similarly, *Toxoplasma gondii* (*T. gondii*) infection has also been proposed to have a protective value in inhibiting the occurrence of lupus nephritis in mice by altering mouse autoantibodies (Chen *et al.*, 2004).

In addition, parasitic helminths can secrete glycoproteins that are capable of preventing nephritis in lupus animal models by reducing the production of antinuclear antibodies and deposition of immune complexes (Rodgers *et al.*, 2015). It was also assumed that helminthic infections (e.g. *Schistosoma mansoni*) may modulate cytokine microenvironment and subsequently alter the pathological phenotype of autoimmune nephritis through reducing the production of antinuclear antibodies and deposition of immune complexes (Savio and Coutinho-Silva, 2016).

Graves' Disease:

Graves' disease is an organ-specific autoimmune disease leading to hyperthyroidism and diffuse goiter (Rapoport *et al.*, 1998). A study performed by Nagayama *et al.* (2004) revealed that *Schistosoma mansoni* inhibited Grave's disease development via reduced IgG2a and anti-thyroid stimulating hormone receptor antibody levels.

Allergic Disorders:

Allergy is a result of inappropriate inflammatory immune reaction generated against various environmental antigens where Th2 mediated phenotype exists due to loss of peripheral tolerance mechanisms. (Conrad *et al.*, 2011). The prevalence of allergic disorders including allergic rhinitis,

dermatitis and asthmas has markedly increased recently affecting up to 25% of the inhabitants in industrialized communities and is regarded as a major health and socioeconomic burden (Pinart *et al.*, 2015).

Normally, a high Th2 response is a characteristic of allergic disorders (Ayelign *et al.*, 2020). Helminths upregulate a population of regulatory T cells, preventing the Th2 cells from having an abnormal activity (White *et al.*, 2020). It was postulated that helminth-induced regulatory T cells might reduce the responsiveness of IgE. Besides, anthelmintic IgE may possibly compete for the same IgE receptors targeted by other allergen-specific IgE (van den *et al.*, 2004). Furthermore, previous investigations suggested that helminths could provoke a systemic immunomodulatory set-up, incorporating regulatory T cells in addition to anti-inflammatory IL-10 which in turn induces inhibition of IgE signaling in basophils (Flohr *et al.*, 2009, Larson *et al.*, 2012).

Infections with trematodes, whipworms and hookworms were believed to be inversely correlated with allergen skin prick test (Flohr *et al.*, 2009). A Lower positivity of skin tests to house dust mites was also observed in children with *Schistosoma haematobium* compared to other non-infected children (van den *et al.*, 2000). Several studies conducted in endemic areas of *Schistosoma*, *Ascaris*, *Trichuris*, and *Ancylostoma* infections declared a notable inverse relationship between helminthic infections and immediate skin tests to common environmental aeroallergens. This could be attributed to helminths' ability to suppress abnormal Th2 immune responses (Araujo *et al.*, 2000, Cooper *et al.*, 2003 and Medeiros *et al.*, 2003). Interestingly, it was suggested that during early helminthic infections, there is enhancement of allergic inflammatory reactions, whereas, in chronic infections, attenuation of the host allergic reaction predominates (Smits and Yazdanbakhsh, 2007). Previous studies

have demonstrated the beneficial role of proteins produced by hookworms (e.g. anti-inflammatory protein-2) and filarial cystatin in alleviating allergy-induced immunopathology (Daniłowicz-Luebert *et al.*, 2013).

Lately, an interaction between helminth-derived proteins and the local microbiome is introduced in which the microbiome is assumed to stimulate the intestinal mucosa (mediated by IL-22) to produce a protective mucous layer subsequently, reducing the ability of allergens to cross the epithelial barrier (Gazzinelli-Guimaraes and Nutman, 2018).

In converse to this concern, other scientists have deduced that neither the whipworm nor *N. americanus* proved to provide significant protection in allergic conditions including asthma and rhinitis (Feary *et al.*, 2010). Hence, more investigations should be performed to ascertain the absolute role of helminthic infections as a counter-allergic therapy.

Neurological Disorders:

Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disease that affects the CNS (McFarland and Martin, 2007). It was stated that the global distribution of MS displays an inverse correlation to helminthic infection prevalence (Dixit *et al.*, 2017). A study done by Fleming and Cook, (2006) demonstrated a relationship between MS distribution and *Trichuris trichiura* parasite where MS prevalence seems to decrease abruptly upon reaching a specific threshold of *T. trichiura* (approximately 10%). Parasite-infected MS patients displayed obviously limited relapses, fewer alterations in disability records and considerably less MRI activity in comparison to uninfected patients. Moreover, treatment of parasitic infections in those patients resulted in a recurrence of both clinical and MRI signs of disease to a level similar to that seen in non-infected patients. This was combined with the production of regulatory T cells secreting

suppressive cytokines including IL-10, and TGF-beta resulting in significant suppressive function (Correale and Farez, 2011).

Parasites may increase both regulatory T cell numbers or activity, either by induction of new cells or by activating and/or expanding the already existing ones (Maizels *et al.*, 2004). Additionally, parasitic infections may also generate regulatory B cells in MS patients, capable of suppressing the immune response through IL-10 production (Correale *et al.*, 2008). Nevertheless, it was noted that B cells of patients with other intracellular parasites (e.g. *Trypanosoma cruzi*) exhibit almost identical IL-10 levels to those detected in uninfected MS patients, signifying the inability of intracellular parasites to modify undesired autoimmune responses as helminths (Correale and Farez, 2011). Correale and Farez, (2013) revealed that helminth-related immunomodulation (as that seen with soluble egg Ag (SEA) of *Schistosoma mansoni*), detected in MS patients was facilitated by TLR2- and Retinoic acid-dependent pathways, through both induction of IL-10 and FOXP3+ regulatory T cells and reduction of proinflammatory cytokines.

Likewise, in animal models, helminthic infection exhibits adequate protection of animals from experimental autoimmune encephalomyelitis (EAE); a disease that greatly resembles human MS in its clinical and pathological features, where, there was a global switch in the immune response from a pro-inflammatory Th1 and Th17 response towards a type 2 or Treg response (Dixit *et al.*, 2017). Lund *et al.* (2016) stated that FhHDM-1, a 68-mer peptide produced by *Fasciola hepatica* had as well improved the disease in relapsing immune-mediated demyelination. Other parasites that might play a role in ameliorating MS diseases include *Schistosoma japonicum* (Zheng *et al.*, 2008), *Trichinella spiralis* (Radovic *et al.*, 2015) and *Plasmodium Chabaudi* (Farias *et al.*, 2011).

Autism:

Autism is a neurodevelopmental dysfunction incorporated into Autism Spectrum Disorder (ASD) (Vargas *et al.*, 2005). Helminths are believed to provoke modulatory and protective effects against numerous inflammatory disorders, maintaining both gastrointestinal homeostasis and modifying brain functions. It was postulated that *Trichuris suis* soluble products could represent a feasible treatment for autism, and a key for the development of innovative treatments (Arroyo-López, 2019).

Several scientists have predicted that controlled exposure to specific helminths in Western communities could help to prevent or treat neuropsychiatric disorders including autism (Parker and Ollerton, 2013). This was however controversial due to the uncontrolled exposure to helminths usually accompanied by undernourishment and dehydration in developing countries (Bilbo *et al.*, 2011) which is usually associated with developmental delay (Raison *et al.*, 2010).

Alzheimer's disease (AD):

Alzheimer's disease (AD) is a progressive brain dysfunction that destroys memory and thinking abilities, eventually resulting in the inability to accomplish even simple tasks (Guerreiro and Bras, 2015).

It was reported that *T. gondii*-infected mice displayed elevated values of anti-inflammatory cytokines (IL-10 and TGF- β) within the brain tissues associated with little neurodegeneration, neuronal death and amyloid accumulation than other non-infected mice. The authors supported that *T. gondii* elicited neuroprotection prior to the onset of AD could hamper the amyloid β (A β) deposition and neurodegeneration leading to a reduction of cognitive functions (Jung *et al.*, 2012). Similarly, Möhle *et al.*, 2016 revealed the modulatory effect of chronic latent toxoplasmosis via A β phagocytosis and destruction by newly employed immune cells in the pathology of AD. Moreover,

toxoplasmosis has been evidenced to be useful in other neurological disorders including stroke (Arsenijevic *et al.*, 2007), cerebral ischemia (Lee *et al.*, 2020) and epilepsy (Ngô *et al.*, 2017). Contrary to the previously mentioned studies, Li *et al.*, (2019) emphasized neurodegenerative influences as the potential basis for the relationship between chronic toxoplasmosis and neuropsychiatric diseases.

Human Immunodeficiency Virus (HIV):

CD4+ T-lymphocytes are the chief cells infected by human immunodeficiency virus type 1 (HIV-1). Thus, it was deduced that immune responses developed against co-infecting pathogens could probably influence HIV transmission and progression (Mouser *et al.*, 2019). Colombe *et al.* (2018), demonstrated that patients with *Schistosoma* infection develop slower adverse HIV sequels than non-infected people. Patients with chronic schistosomiasis showed increased peripheral blood percentage and absolute numbers of Th17 cells and T regulatory cells, which play a crucial role in controlling the speed of AIDS disease progression, as compared to uninfected patients. This was noticeably observed in patients with marked schistosome-induced tissue pathology (Larkin *et al.*, 2012 and Valverde-Villegas *et al.*, 2015).

It was also postulated that some helminths e.g. *Schistosoma mansoni* could evade and inhibit the human immune system including the modulation of CD4+ T-lymphocyte (Mouser *et al.*, 2019). Interestingly, it was found that Schistosomiasis *mansoni* was correlated with a diminution of HIV plasma viral load while *S. haematobium* infection was associated with a decline in cervical viral load (Bochner *et al.*, 2019). Moreover, schistosomiasis might be an important contributor to immune activation in HIV-coinfected patients as evidenced by a sustained decrease in IL-10 after antiretroviral therapy as it could affect immune defense (Furch *et al.*, 2020).

Coronavirus Disease (COVID):

Coronavirus SARS-CoV-2 (COVID-19), a strain of severe acute respiratory syndrome-related coronavirus (SARSr-CoV), was first recognized in 2019 in Wuhan in China (Song *et al.*, 2020). The pathogenesis of severe COVID-19 has been correlated to overactive Th1 responses (Sinha *et al.*, 2020). Hence, parasite-induced Th2 and Tregs immune responses might counterbalance the immune hyperactivation recorded in COVID-19. Moreover, parasite-elicited gut microbiome alterations could regulate the host's immunity (Wolday *et al.*, 2021). Accordingly, it is postulated that parasitic infections may affect disease severity via both direct modification of the immune system and through indirect parasite-elicited microbiome regulation (White *et al.*, 2020).

Cepon-Robins and Gildner (2020) deduced the protective role of soil-transmitted helminth infections in minimizing SARS-CoV-2 symptoms and relieving the undesired COVID-19 consequences. Likewise, variable studies have demonstrated an inverse relationship between COVID-19 cases and deaths, and the endemicity of parasitic infections. For instance, people in malaria-endemic areas appear to be resistant to COVID-19, which was attributed to molecular and genetic variations (Nioi and Napoli, 2020). Moreover, similar results were obtained with schistosomiasis (Zhang *et al.*, 2020).

Actually speaking, several studies have declared that scarcity of parasitic coinfection including enteric parasites, might be correlated with a high risk of serious COVID-19 disease (Abdoli, 2019). Chronic helminthic infection was postulated to exhibit its protective effects through the accumulation of eosinophils which in turn prevent viral replication in the epithelial cells, in addition to Th2-IL-10 system, which could prevent the characteristic stormy autoimmune responses (Rodriguez and Veciana, 2020)

However, some concerns should be addressed regarding the coinfection of parasites and COVID-19. For instance, helminthic coinfection might diminish the protective immune response against COVID-19 in the initial phase of the infection, thus, increasing morbidity and mortality due to the disease. Furthermore, the suppressed immune response might even alleviate COVID-19 vaccine efficiency. (Elsaftawy *et al.*, 2021). Accordingly, additional investigations are needed in this field that might even elucidate the possibility of passive immunization of patients infected by COVID-19 with serum from individuals with previous parasitic infections to ameliorate their clinical sequelae.

Viruses:

Prior studies performed on animal models demonstrated the protective impact of parasitic infections on the control of viral infections in general (parasites against virus phenomenon) (Shen *et al.*, 2019). For instance, coinfection with *G. lamblia* decreases the severity of diarrheal bouts in rotavirus infections (Bilenko *et al.*, 2004). Besides, a protective effect was noticed between *Plasmodium* spp. and Chikungunya virus (Teo *et al.*, 2018). Notably, IL-4 response throughout helminthic infections was presumed to augment antigen-specific CD8⁺ T cell responses in the lungs resulting in overall control of viral infection (Rolot *et al.*, 2018).

Trichinella spiralis infection was believed to cause diminished inflammatory infiltrates of the lungs, reduced concentrations of TNF in bronchoalveolar lavage and more rapid recovery of weight in influenza A virus coinfecting mice, however, it doesn't inhibit the viral clearance itself (Furze *et al.*, 2006).

Similarly, *Nematospiroides dubius* proved to reduce the immunopathological changes induced by the influenza A virus (McFarlane *et al.*, 2017). Interestingly, other studies had postulated that during the early stages of toxoplasmosis, where *T.*

gondii is mainly found peripherally, parasite existence was proved to protect against subsequent bacterial (Neal and Knoll, 2014), viral (O'Brien *et al.*, 2011) and other parasitic (Haque *et al.*, 1999) infections.

Inflammaging:

Inflammaging is a status of systemic, low-grade inflammation that increases with age independently of affection by infectious pathogens (Franceschi *et al.*, 2000). Inflammaging is thought to be a contributing factor to diseases of older life, including heart disease, dementia, malignancies, chronic obstructive pulmonary disease and senile eye disease (Xia *et al.*, 2016 and Akbar and Gilroy, 2020).

According to a study conducted by Crowe *et al.*, 2020, the authors reported that treatment with a glycoprotein (ES-62) produced by the filarial nematode can protect against murine aging by provoking anti-inflammatory responses. It was postulated that helminth therapy might counter symptoms of aging or slow them (Zhang and Gems, 2021). This could be explained that helminths might inhibit tissue aging in their hosts with the purpose of protecting their local niche; as in inhibition of the pro-aging mTOR pathway in human dendritic cells by the presence of *Brugia malayi* microfilaria (Narasimhan *et al.*, 2016). Hypothetically, helminths could reverse inflammation by inhibiting inflammation sources by avoiding gut barrier permeability, neutralizing the already existing inflammation by increasing anti-inflammatory to pro-inflammatory cytokines or restoring inflaming tissue damage through IL-22 induction (Zhang and Gems, 2021). Lifespan extension following parasitic infections has been proved in many other host-parasite systems (Vézilier *et al.*, 2012, Dianne *et al.*, 2011 and Weinreich *et al.*, 2013) where the parasites seem to increase host survival to be able to finish their own development before the host's death.

Cancer:

Generally, cancer is considered hard to fight because of its capacity to trick the immune system through non-recognizing cancer cells as a danger thus the immune system admits cell proliferation and subsequently, tumor development (Muenst *et al.*, 2016). Consequently, the basis of cancer therapy is circled around the introduction of substances that non-specifically promote the body's natural defense strategies or aid in distinguishing and responding to cancer cells. Within this concern, recent cancer management is chiefly targeting the immune response to the tumor rather than the tumor directly (Grosser *et al.*, 2019). Recent studies have proposed that combating cancer could benefit from the ability of the parasites to modulate their hosts' immune systems. However, the exact mechanisms of action exerted by the parasites and their products in immunomodulation of tumor progression are still not yet entirely recognized (Morrot, 2020). These mechanisms might include presenting common antigens between parasite and cancer cells, activation of innate and acquired immunity or induction of apoptosis, anti-angiogenesis and modification of anti-inflammatory response that enhance cancer development (Callejas *et al.*, 2018).

Several parasites have been reported for their antitumor effects including *Echinococcus granulosus* (Morrot, 2020), *Trypanosoma cruzi* in sarcoma-180 or Ehrlich's adenocarcinoma and lymphoma (Kallnikova *et al.*, 2006), *Toxoplasma gondii* in fibrosarcoma and Lewis lung cancer, *Toxocara canis* in fibrosarcoma (Darani *et al.*, 2009), *Acanthamoeba castellanii* and *Trichinella spiralis* in melanoma (Pidherney *et al.*, 1993 and Kang *et al.*, 2013) and *Plasmodium yoelii* in Lewis lung cancer (Chen *et al.*, 2011).

However, it was previously noted that in high-intensity infection, the harm elicited by parasites may render the host susceptible to other certain types of cancer

(Thomas *et al.*, 1990). Within this context, a positive correlation between cancers and *Clonorchis sinensis* (Pao Chang, 1956), *Schistosoma haematobium* (Thomas *et al.*, 1990), *S. mansoni* (Abdel-Rahim, 2001), *Trichomonas vaginalis* (Zhang *et al.*, 1995) and *Opisthorchis viverrini* (Vennervald and Polman, 2009), were recorded.

Fertility:

The prior study performed by Blackwell *et al.*, 2015 deduced that different helminths are accompanied by diverse effects on women's fecundity suggesting both physiological and immunologic outcomes of infection. They observed that women with chronic roundworm infection displayed earlier first pregnancy with shorter interbirth periods and more children, while successive hookworm infections were associated with delayed first birth, longer interbirth intervals and fewer offspring. Nevertheless, in animal models, parasitic infections, in general, negatively influence the fecundity of female sheep (Fthenakis *et al.*, 2015). With this concern in mind, further research by obstetricians, parasitologists and endocrinologists is crucial to illustrate possible correlations between infections due to parasites and fecundity in humans.

Wound Healing:

Wound healing is an active consecutive process including multiple stages (exudative, proliferative and extracellular matrix remodeling) (Gonzalez *et al.*, 2016). Hirudotherapy or medicinal leech therapy (MLT) is an established, integrative treatment where its first application was painted in the hieroglyphics from the ancient Egyptian civilization (Whitaker *et al.*, 2004). Medicinal leech therapy constitutes the biting spur, drawing of blood and injection of active substances present in leeches' saliva. Its curative impacts are due to anticoagulation, enhancement of blood and lymph flow and suppression of pain and inflammation (Sig *et al.*, 2017). It is supposed to deliver three chief mechanisms within wound healing: wound debridement,

disinfection, and rapid wound healing. It is now proposed that MLT could be beneficially used in wounds due to acute venous congestion and other chronic ulcer-associated wounds. (Sherman, 2014). Moreover, MLT has also been successfully utilized in patients with osteoarthritis (Cooper and Mologne, 2016), epicondylitis (Bäcker *et al.*, 2011), lower back pain (Hohmann *et al.*, 2018), salivary gland diseases (Singh, 2010), haematomas (Gödekmerdan *et al.*, 2011), haemorrhoids (Bhagat *et al.*, 2012), Tinnitus, acute and chronic otitis and glaucoma (Singh and Rajoria, 2020). Interestingly, Zaidi (2016) has demonstrated wound healing using leech therapy in a 60-year-old diabetic female patient in association with Unani medicine as a blood purifier. He stated that using hirudotherapy over 3 to 5 months resulted in the disappearance of necrotic areas and complete healing of wounds.

However, further studies are still required to establish the role of MLT in different lesions since its use may adversely cause undesirable complications such as allergic reactions, bleeding, or even infections (Schnabl *et al.*, 2010).

Another study conducted in 2015, deduced that a growth factor secreted from the liver fluke *Opisthorchis viverrini* could enhance acute and chronic wound healing of mammalian host tissue in vivo which might provide major potential as a novel therapeutic mode (Smout *et al.*, 2015).

Conclusions and Recommendations:

Conclusively, an adequate understanding of parasite modulation of human immunity eventually succeeded in contributing to different disease control. Many disorders including allergic, inflammatory, infectious, degenerative, or even tumors have efficiently benefited from parasitic existence. Identifying different parasites involved in the improvement of patients of variable diseases, in addition to the associated underlying mechanisms, would ultimately exhibit therapeutic measures for these patients. Furthermore, perspectives on using parasites as lower

therapeutic costs as compared to other medicinal drugs should be more emphasized. Essentially, more research is needed to illustrate existing challenges concerning safety, dosages, as well as possible side effects of utilizing parasites in future therapy against diseases in humans.

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ARABIC SUMMARY

الطفيليات من الامراض إلى العلاج

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قسم الطفيليات الطبية، كلية الطب، جامعة القاهرة، القاهرة، مصر

لقد شارك البشر تاريخاً طويلاً من التعايش مع الطفيليات الموجودة داخل أجسادهم. و ان البلدان النامية و المتقدمه تتأثر بالعدوى الطفيلية حيث ثبت أن الطفيليات المختلفة يمكن أن تغير الاستجابة المناعية لدى البشر. ويعتقد الآن أن بعض الطفيليات، سواء بوجودها أو بمنتجاتها، يمكن استخدامها للتخفيف من أمراض الالتهابات والمناعة الذاتية والحساسية المتنوعة، بالإضافة إلى أمراض أخرى. يهدف هذا المقال إلى تقديم تقييم للدراسات المختلفه التي تتابع الدور المحتمل لأنواع مختلفه من الطفيليات و/أو منتجاتها كأدوات علاجية في أشكال منفصلة من الأمراض