



Toxicity of parasites and their unconventional use in medicine

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Abstract

Introduction. Over 300 species of parasites can possibly be passed on humans. Most of the parasitic infections are defined based on their pathogenicity; however, some positive effects of a parasite existence within the human body have recently been suggested. Beneficial outcomes of parasite infections might result from the production and release of metabolites, modification of host immune response or products uptake of the host.

Objective. The aim of the study was a comprehensive analysis of a wide range of effects of parasites on the human body, including an overview of the toxic and positive effects.

State of knowledge. In the light of the latest research presenting the unconventional use of parasites in medicine, the widely understood of their impact on the human body can also be considered in a positive context. Clinical cases from diseases caused by the toxic effects of parasites, as described in recent years, indicate that the problem of parasitic infections still persists. Despite a great deal of knowledge about the toxic effects of parasites on the human organism and, above all, despite the improvement in sanitary conditions, there is a resurgence of parasitic infections, as evidenced, e.g. by the examples presented in this review.

Conclusions. The examples of positive effects of parasites presented so far give hope for the future in terms of fighting many diseases for which pharmacological treatment has not yet brought a positive effect. A better understanding of those processes might lead to the development of new methods of unconventional medical treatment.

Key words

parasites, toxicity, helminth therapy

INTRODUCTION

Parasitism is an antagonistic phenomenon in which the species (parasites) use the source of food and living environment of another species, that can act as an intermediate or definitive host. The basic feature of this phenomenon in medicine is the pathogenicity; however, scientists report increasingly a potential positive influences of a parasite existence within the human body [1]. The discussion on the widely understood effects of parasites on the human organism should start with an analysis of the definition of parasitism itself. This concept is subject to constant changes as natural sciences develop. One of the first definitions describes a parasitic organism in terms of its eating behaviour [2]. According to this category, a parasite is described as an organism that needs another organism in order to live, as a source of food and a place for growth and reproduction [2, 3]. Later the definition was supplemented with negative (also toxic) effects of the parasite's activity – the parasite is therefore an organism that

feeds itself at the expense of the host's body, thereby causing harm. Another definition of parasitism was developed by the view that it is a purely ecological concept, representing a parasitic organism that uses other living organisms as a source of food, and transfers to its hosts the necessity to regulate the relationships with the surrounding environment. As biochemical and genetic research developed, the definition of parasitism was further modified, according to which the relationship between the parasite and the host is metabolic – the parasite as an organism dependent on the host to a different metabolic extent. This extent varies between free-living animals and internal parasites. While in the former case it is 0%, it is 100% for animals that practice the obligatory type of parasitism. The metabolic dependence is conditioned by such factors on the part of the host as, among others, the type of food the host consumes, its body temperature, and even its biochemical composition (composition of amino acids, proteins, sugars, etc.) [2–6].

The number of parasites that can be passed on to human body can reach over 300 species, which include both parasites occurring on the body surface (external parasites) and those living in the human system (internal parasites). The place of parasite occurrence includes hair, skin, blood, muscles, eye, liver, brain, although most often it can be found in

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the intestines [7, 8]. The location of the parasites is related with the ways of infection, as the main sources of parasitic infection are contaminated water and food, mostly resulting from lack of personal hygiene, unwashed vegetables/fruits, undercooked/under-fried meat, such as freshwater fish, crustaceans, wild animals or beef [9–15]

It is estimated that two billion people worldwide are infected with at least one parasite species, and three million suffer from parasitosis. According to the literature, health problems resulting from parasitism are affecting populations in developing countries, living in poverty with a dominance of parasitic infections caused by intestinal helminths and protozoan [2]. On the territory of Poland, where a human being can be a host for about 40 species of parasites, this number is lower, but even with a lower amount of pathogenic species the statistical data shows that an invasion of pinworms can reach 95% of the population, whipworm – 80% and human roundworm – 50% [2, 16–19].

The improvement of sanitary conditions in industrialized countries and the effectiveness of parasite control measures reduce the incidence of only some parasites. Prevention and control of parasitic diseases through constant monitoring of the epidemiological situation of these diseases depends, to a large extent, on the effective teaching and training of medical personnel in the field of medical parasitology, awareness of the risks that parasitic organisms may cause, and more effective intervention of supervision and control of sanitary-epidemiological services [20, 21].

OBJECTIVE

The main aims of the study are: a comprehensive analysis of a wide range of effects of parasites on the human body, including an overview of the toxic effects of parasites on the human body, and an analysis of the positive impact of parasites, which currently falls within the scope of unconventional medicine. To fulfill these aims, the electronic medical database PubMed was searched on January 20, 2019 for studies showing a positive effect of parasitic infections on the human body. The following were used as key words: parasites, toxicity, helminth therapy.

STATE OF KNOWLEDGE

Harmfulness of parasites to the human organism. The negative impact of parasites on the human body can vary, depending on the number and the location of the parasites, as well as the age and physiological condition of the infected person and whether they are intermediate or definitive hosts. Most parasites cause a harmful mechanical impact damaging the skin and tissues [22–24]. External parasites insert their stick and mouth organs into the skin, causing damage, and then use the sources of food such as blood, causing inflammation and itching. They can also release toxic substances within the wound [25]. Parasites living inside the human body also cause mechanical damage to the internal organs through the use of their stick organs, such as suckers, hooks, teeth or daggers. Examples include tapeworms, liver flukes or duodenum hookworm; the latter, apart from pulling living tissue out of the duodenum and feeding on blood, causes haemolysis and damage to erythrocytes [26, 27].

Harmful mechanical effects may result not only from the parasite's sticking to the host tissues, but also from the parasite's migration within the body or the number of parasites. An example of this can be different species of tapeworms or human roundworms, which in excess can lead to the obstruction of the intestinal lumen or the pancreatic-hepatic duct [28, 29]. The migration of parasites, such as human roundworm, may cause perforations of the alimentary tract, blood vessels (mainly juvenile forms), as well as damage to the eustachian tube [30]. Pinworms can also become a source of appendicitis, bladder or vagina inflammation during their migration [30]. Negative mechanical effects, to a large extent, depend on the location of the parasite, which may not show very harmful ailments for the host, as well as a strong pathogenic effect [30]. Cysticercosis caused by the armed tapeworm *Taenia solium* if located in the muscles, until survival of the blackheads shows ailments which are hardly noticeable to humans [31, 32]. Dead blackheads cause a strong cell reaction. The situation is different when the blackheads are located in the brain or in the eye, causing serious ailments that often lead to disability or death [33–37].

Parasites may also have toxic effects, which in the case of external parasites are often manifested by itching, scabies, allergic conditions, but are also associated with many diseases such as tick-derived diseases or malaria. The toxic effects of internal parasites can cause serious organ disturbances, haemolysis as well as severe allergic reactions. Apart from mechanical or toxic effects, parasites have a negative impact through food competition, depriving the host of important nutrients such as vitamin B₁₂ (teniasis), or in the case of infection with haematophagic parasites (feeding on blood) such as duodenum hookworm [38, 39]. According to reports, the change in normal gastro-intestinal flora by intestinal parasites is associated with diarrhea, the main cause of morbidity and mortality in developing countries [40–44].

Many parasites can also cause pathogenic changes accompanied by clinical symptoms. Pathological changes may occur at the site where the parasite is present, in which case they are referred to as direct local changes [45]. An example of this is the impact of parasites on tissues, which is observed in *Trichinella spiralis* larvae. The larvae develop in the muscle cells causing loss of the active properties of the muscle [45]. Another example is the species *Diocotophyme renale*, which occurs in the renal pelvis, resulting in renal parenchyma atrophy [46, 47]. A species especially dangerous for humans is *Entamoeba histolytica*, which destroys the mucosa epithelium in the large intestine, leading to water absorption disorders, and is manifested by strong diarrhea [48–51].

Direct pathological changes caused by parasites result in indirect-general changes that occur in the place where the parasite is present. They are caused by factors from the immune system of the host and under the influence of biochemical factors of the parasite [52].

Indirect pathological changes result in a number of clinical symptoms in the host. These include chills, diarrhea, increased body temperature, muscle pain, liver enlargement and cirrhosis [53]. Such symptoms can be observed, *inter alia*, in the case of *Trypanosoma brucei gambiense* infection [54].

In particular, parasites of *Toxocara* type (*Toxocara canis*, *Toxocara leonina*), responsible for the clinical symptoms of toxocarosis, are very dangerous to humans [55]. The infection is extremely dangerous because in the initial phase

the parasites develop asymptotically in the body. The only symptom is eosinophilia – increased count of one of the types of white blood cells – eosinophils. The disease takes the form of visceral toxocariasis (larvae are found in various internal organs, e.g. the liver), eye toxocariasis (larvae nest in the eye), brain toxocariasis (neurotoxocariasis; larvae are present in the brain), and latent (asymptomatic) toxocariasis. In each of these toxocariasis cases, symptoms depend on the severity of the infection and the location of the larvae in the body [56–59].

The majority of the effects of parasites on the organism result in a weakening of the immune system of the host, which may contribute to its susceptibility to other diseases [60]. The immune pathways required for the induction, expansion and maintenance of anti-parasite responses are still under investigation [60]. Considering their immune effects, parasites can act as regulators of the host immune response that inhibit some pathways of immune activation (e.g. DC antigen presentation, T-cell cytokine and B-cell antibody production, and epithelial cell alarmin release), modulating other pathways (e.g. TH cell subset differentiation and B-cell isotype switching), and inducing still others (e.g. Treg and Breg cell differentiation and tolerogenic DC responses) [61–63] (Fig. 1). Most parasites have developed strategies to avoid immune elimination. Understanding the correlation between parasitic infections and autoimmune disorders may be helpful in prediction and early identification, and conceivably the prevention of these diseases. Perhaps clarification of the mechanism of immune regulation by parasite infection will contribute greatly to the treatment for inflammatory diseases such as colitis ulcerosa [63–67].

Defensive mechanisms in the parasite-host interactions.

The definition of parasitism quoted in the Introduction, which describes a parasite as an organism metabolically dependent on the host, is reflected in analysis of the host-parasite interaction [68, 69]. The biochemical nature of this dependence makes the process extremely complicated. Therefore, each parasite-host interaction has to be considered individually, depending on the type of parasitic organism [69]. This does not change the fact that from a general point of view the defence reactions in the host-parasite interaction are considered in two directions. The first of these concerns the defensive mechanism of the host in response to the parasitic invasion, while the second is the defence reaction of the parasite against the host [69].

The host's defence reactions are the basis of all immunological processes. The entry of a parasite into the host organism leads to a number of mechanisms being triggered by the immune response. This is a typical reaction of the immune system to the appearance of antigens. Among antigens of parasites organs (which is the subject here), the most important for the host are those which are either secretions or excretions of the parasite, or antigens that are on the surface. The host's defence reactions are directed to removing the parasite from its body. These interactions are among the most important phenomena that occur in the discussed parasite-host interaction [63, 64].

The defensive mechanism of the parasite takes the form of the so-called preventive defence and the so-called active defence. In the first case, the parasite defends itself against being recognized by the immune system of the host. This method of defence by the parasite involves, amongst others: immunosuppression, residence inside the host's cells,

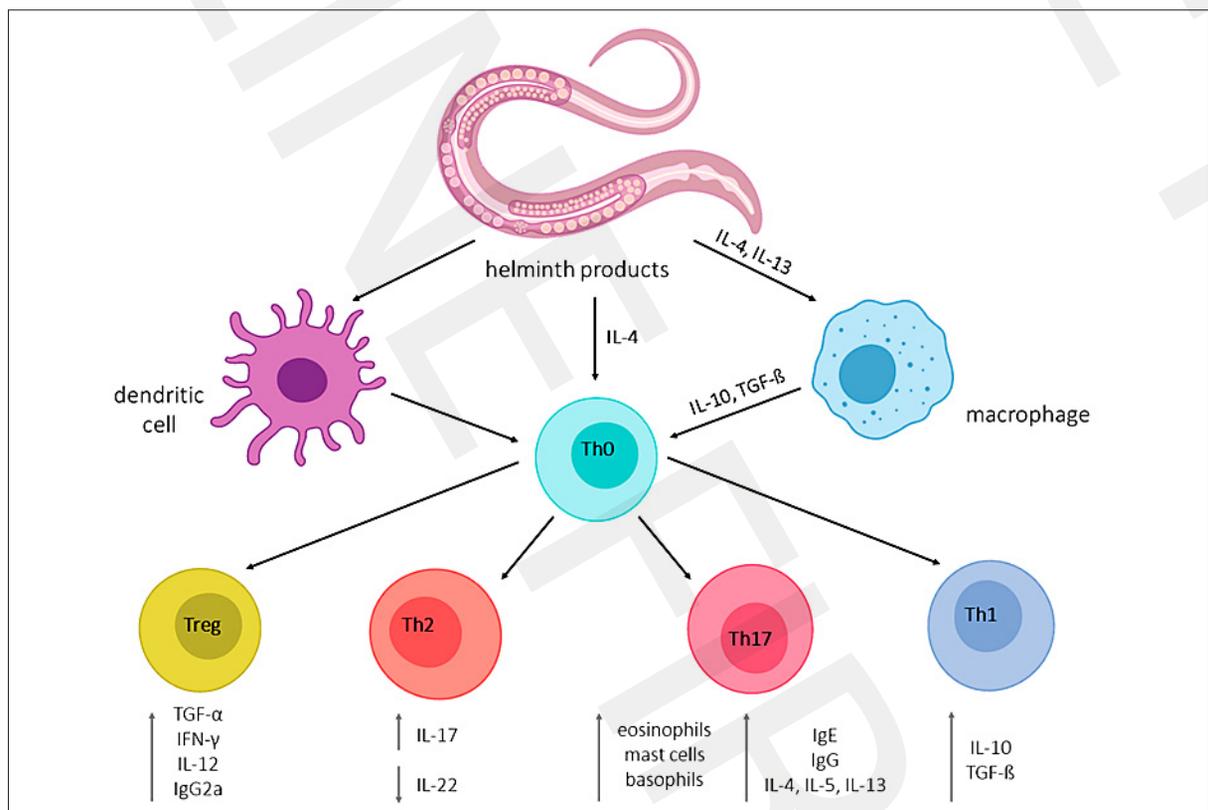


Figure 1. Cytokines profile in parasitic helminth infection. Secretory products of helminth promote the synthesis of pro-inflammatory cytokines and immunomodulatory molecules, which promote helminth parasites expulsion and induction of inflammatory state [137]

antigenic mimicry, or change in the immunogenicity of its own genes [69, 70]. The active defence of the parasite is based on the direct defence against the host's immunological reaction [70].

The modification of surface antigens located in the outer membrane is one of the most important parasite's defensive mechanisms. The protein part of the antigen is most often modified by the glycosylation [71].

Another defence mechanism of the parasite is the phenomenon of immunosuppression, which occurs in people infected with *Plasmodium*. In this case, the production process of antibodies and immune cells is inhibited by some prostaglandins. [72, 73].

The most effective phenomenon in the parasite's defence against the attack of host antibodies is its presence inside the host cells, e.g. inside the erythrocytes that separates the parasite from the molecular machinery of immune response [74]. This form of defence against the host's immunological response is also observed in some nematodes [75]. An example is *Trichinella spiralis* whose larvae spent some of their life cycle inside the muscle cells [75].

The process of active defence of the parasite is a direct reaction of the host, taking place mainly through fighting antibodies with lytic enzymes. The secretion of lytic enzymes by parasites into host organs mediates critical interactions because of the invasion and destruction of interstitial tissues, enabling parasite migration to other sites within the hosts. Experimental research to-date indicates that as a result of the first contact of the parasite with the host, the parasites launch a number of defensive reactions. The development of the parasite is possible not only through avoiding the defensive mechanisms of the host, but also through keeping it alive for as long as possible because of the obligatory nature of parasitism [48, 76–78].

Use of parasites in medicine. The use of parasites in the therapeutic methods, due to their pathogenicity and the consequences of their existence in the host body, is of great concern. However, the use of some species of parasites in an appropriate way may contribute to beneficial outcomes in some unconventional application, mostly in autoimmune and immunological diseases [79–81]. Hirudotherapy is an effective method in the natural treatment of many diseases

that is currently experiencing a renaissance. For treatment, leeches derived exclusively from laboratory cultures, are used. These are all leeches belonging to the *Hirudo medicinalis* species, i.e. *Hirudo medicinalis officinalis*, *Hirudo medicinalis medicinalis* and *Hirudo medicinalis orientalis* [82, 83]. The broad spectrum of medical use of these organisms includes the treatment of many diseases, such as: cardiovascular diseases, thromboembolism, coronary diseases, diseases of the endocrine, gastrointestinal, urogenital, respiratory and osteoarticular systems. The substances that are part of the secretion of the salivary glands of these organisms have the therapeutic effect of medicinal leeches. Among these substances, blood coagulation inhibitors, hirudin and anti-stasis (Table 1) are a priority. These include substances that inhibit platelet aggregation: apyrase, saratin, viburnum, as well as proteinase inhibitors with anti-inflammatory activity and agents that inhibit the growth of microorganisms, such as chloromycetin, hyaluronidase, collagenase [84–87]. Studies confirming the positive effect of salivary secretion of leeches on the nervous system are of particular interest. It is associated with the release by *Hirudo medicinalis* endorphins and neurotransmitters, such as dopamine, serotonin, acetylcholine or histamine, which are essential for the proper functioning of the nervous system [89]. Recent discoveries concern the occurrence of enzymes and inhibitors in the salivary secretion causing the growth of sensory neurons in the ganglia, which opens the possibility of using hirudotherapy for the treatment of Parkinson's and Alzheimer's diseases (Table 1) [89, 90].

In developing countries, an inverse relationship between helminthic diseases and allergic diseases has been observed in relation to industrialized countries [91, 92]. According to the literature, in Ecuador [93], Gabon [94] and Brazil [95], parasite infections have been shown to have a protective effect against allergic reactivity. It has also been shown that the risk of atopic skin sensitization increases as a result of the antiviral treatment in such countries as Gabon [94] Venezuela [96] and Vietnam [97]. In 2008, about 37% of the world's population was infected with helminths, mainly in developing countries; however, helminthiasis is a rarity in industrialized countries [98]. In these environments, it was observed that a higher number of parasitic diseases translated into a lower number of allergic diseases and asthma [91,

Table 1. Effects of active ingredients from *Hirudo medicinalis* salivary glands in selected diseases

	Active compound	Action
	Hirudine	A strong thrombin inhibitor, prevents attacks and strokes more effectively than acetylsalicylic acid
	Antistatin	An inhibitor of factor Xa, reduces the formation of blood clots
	Inhibitors of plasma transglutaminases I and II	Inhibitors of fibrin stabilizers, reduce the formation of blood clots
Thromboembolic diseases	Apyrase	A non-specific inhibitor of thrombocyte aggregation, reduces platelet aggregation
	Saratin, viburnum	Proteins that inhibit platelet adhesion to collagen, prevent thrombocyte aggregation
	Destabilase	Inhibits platelet aggregation induced by plaque activator and collagen
	Haementerin	Plasminogen activator for plasmin, dissolves clots and clears vessels
	Haementin	Proteinase breaks down fibrinogen into peptide fragments, dissolves fibrin
	Destabilase	Activation of plasminogen, decomposition of endoisozeptides, building stable fibrin
	Endorphins	Happiness hormones, sedation, analgesia
Diseases of the nervous system	Destabilase	A proteolytic enzyme, stimulation of nerve cell growth In the ganglia (observation of a 10-day-old chicken embryo)
	Bdelina A, bdelina B, egins	Growth of nerve cells to the same extent as nerve growth factor (observation of 10-day-old chicken embryo), high hopes for the treatment of neurodegenerative disorders, e.g. neuromuscular dystrophy, Parkinson's and Alzheimer's diseases

99]. According to reports, the reduction of respiratory allergic symptoms in the case of intense infections caused by helminth is an example of the beneficial effect of parasites, although this reduction provides a greater chance of their reproduction and development in the host's body [100–102]. Moreover, in research on mice, inhibition of inflammation, development of autoimmune diabetes and some types of arthritis were observed [103–106].

The use of parasites, such as nematodes, can have a positive effect on the human immune system. In the case of duodenum hookworm infection, in the mild course of infection which did not show any significant pathogenic changes, such as anaemia, did not affect the functioning of the intestine, and positive effect on allergies, asthma and infectious diseases. Similarly, a positive effect was demonstrated on the prevention of allergies by administering probiotics at an early stage of life, which affected the immune system, diversifying it in a pro-inflammatory, pro-allergic direction. In this direction, parasites can also be used – but they themselves can cause allergic states, inflammatory reactions, asthma, and even anaphylactic shock as a result of toxic effects, which outweighs the risk of their application over benefits [107–115].

Another aspect concerns the use of parasites in forensic medicine. In this area, a significant role is played by necrophaga, whose appearance on corpses, as well as the development of larvae, may contribute to determination of the time and circumstances of death of the examined corpses [116]. An interesting use of parasites is forensic entomotoxicology, which investigates the influence of xenobiotics, such as drugs, alcohol, medicines on *necrophaga* development and their use as a source of biological material of the deceased [117]. Sometimes the causes of death are found in autopsy in which liver damage caused by a parasite, e.g. *Echinococcus multilocularis*, is discovered. Often, the presence of a parasite can tell us about nursing negligence, poisoning, and the place where the infected person stayed [118].

It is not only in forensic medicine that the use of parasites can be found. In medicine, the larvae of the common green bottle fly – *Lucilia sericata*, shown to have a beneficial effect in the removal of dead tissue from a wound, and killing the micro-organism [119]. Larvae secrete enzymes (belonging to the group of collagenases having the same effect as trypsin and chymotrypsin) proving effective in the case of some strains of *Staphylococcus aureus*, including methicillin-resistant A and B streptococcus, and some strains of *Pseudomonas*. Most often, treatment with larvae is used to treat various types of infections, necrotic wounds, lower limb ulcers, and infected post-operative wounds [120–122].

Recent research shows that parasites have the ability to inhibit the immunological response of their hosts, which allows them to settle down for a long time without causing an inflammatory reaction. Research conducted on a mouse model of multiple sclerosis has shown that treatment with parasites may bring some benefits to patients suffering from this disease [123, 124]. Also, in people with autoimmune diseases, the presence of intestinal nematodes in the body resulted in the inhibition of excessive inflammatory reaction and, as a consequence, symptoms of diseases such as non-specific inflammatory diseases of the intestines. The therapy can also be used in patients with psoriasis, autism and rheumatoid arthritis [115, 123]. Intensive research is also being conducted into the utilization of the positive

aspect of such parasites as whipworm (*Trichuris suis*) and hookworm (*Necator americanus*) in Crohn's disease and ulcerative colitis [125].

Risks of parasite use in medical treatment. Clinical examination conducted to-date on the use of parasites in the treatment of autoimmune or allergic diseases, gives rise to a number of controversies, but also present a certain potential of such studies. Clinical treatment with parasites must be carried out with special care and may have many side-effects. In parasitic infection, the species of parasite causing the infection, its form (larval, adult), time of infection, the number of parasites and individual characteristics of the host organism are of crucial significance. Having the knowledge of what kind of parasite to be used in the treatment is not enough; more importantly, it should be determined what amount of parasite should be introduced, whether there will be a different negative reaction, and how a given immune system of a given host will behave [126, 127]. Parasites use our nutrition products, often causing vitamin deficiencies, e.g. the supply of broad fish tapeworm (*Diphyllobothrium latum*) for vitamin B12 [128]. Parasites compete with us for food and cause deficiencies, and are also a source of toxins and allergic factors. They also pose a threat in the event of their death by releasing a number of toxins into the human body that may lead to anaphylactic shock. Also the reproduction of parasites within the human organism can lead to serious consequences which can be the cause of infection of third persons, as well as self-infection (both ecto-infection and endo-infection), e.g. as a result of invasion of dwarf tapeworm (*Hymenolepis nana*) [129]. Unfortunately, another negative aspect is the location of parasites within the human organism which, in spite of the fact that in many species it is known it may proceed in a different way. An example of this is the common liver fluke *Fasciola hepatica*, a parasite of the bile duct in the liver; however, these parasites sometimes travel with in the blood circulation to the lungs, brain and muscles, causing abnormal symptoms of fasciolosis [130, 131.] Especially dangerous in this respect are larval forms of various parasites, which may cause the syndrome of migrating visceral larvae [132].

The most common symptoms in parasite infections are: muscle pains, fever, weakness and intestinal disorders. Their presence in various organs can often cause a long-lasting inflammatory state. This condition, caused by many parasite species, carries one of the greatest dangers when used with helminth therapy. This danger is associated with cancer and high mortality. These include many species of trematode parasites (of the *Schistosoma* type, causing tumours of the urinary bladder and the intestine, or one of the tapeworms most pathogenic for humans – *Echinococcus multilocularis*, responsible for liver damage [133, 134].

The use of anti-parasitic preparations and eggs or larvae of parasites of unknown origin is very dangerous. The chemical composition of such a preparation is usually unknown and can be harmful, and even if it affects parasites it can have negative consequences, e.g. convulsion and penetration of parasites into the peritoneal cavity, such as human roundworm – *Ascaris lumbricoides* [135]. The possibility of buying pills in the case of the so-called "Tapeworm diet" entails many risks. Firstly, it is not known what such pills contain, secondly, before the tapeworm grows – most often the infection will be asymptomatic or poorly symptomatic – weight loss will not be achieved. Thirdly, it is not known

how the body is going to behave, and whether infection with another species of dangerous parasite has also occurred, which can prove to be lethal. Such a species can be, e.g. the armed tapeworm – *Taenia solium*, whose larvae can cause dangerous cysticercosis [136].

Although there is a great deal of research on the use of parasites in medicine, especially in support of the human immune system, which gives promising results, the danger and consequences outweigh the risk of therapy over the benefits [127]. Even in the absence of negative effects of contact with a parasite, it not known what the consequences may be incurred after the death of the parasite in the distant future, especially when they are the factors responsible for the development of cancer.

CONCLUSIONS

In the light of the latest research presenting the unconventional use of parasitic forms in medicine, the widely understood impact of parasites on the human body can also be considered in a positive context. The presented examples of the positive effects of parasites, especially in the suppression of immune system of the host, give hope for the future in terms of fighting some diseases for which pharmacological treatment has not yet brought a full, positive effect.

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