The Possible Involvement of Protozoans in Causing Cancer in Human

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ABSTRACT

In the past few years, it has already been proved that the microbial origin of cancer exists and these oncogenic microbes are infectious in nature. After bacteria and viruses, protozoans have also been found to cause cancer in humans and animals. They are eukaryotic, unicellular, anthropozoonotic microorganisms causing several life-threatening diseases and cancer in humans. While a plethora of good pieces of information was gathered while documenting the role of several protozoans causing cancer in humans, only Plasmodium falciparum has been categorized by the IARC as Group 2A carcinogen. However, certain other protozoan parasites have also got their ability to cause cancer in humans via the integration of protozoan DNA sequences in the host cells. Protozoans cause the stimulation of cell division and proliferation of the host cells by the release of reactive oxygen and nitrogen radicals, DNA damage and the p53 gene inhibition. The present review discusses some cancer-causing protozoan parasites like Leishmania donovani, Trypanosoma brucie, Toxoplasma gondii, Trichomonas vaginalis, Blastocystis homints, Theileria microti and Cryptosporidium parvum including Plasmodium falciparum in the light of recent researches done so far in the field of microbial origin of cancer.

INTRODUCTION

Ascertain parasitic infections cause cancer in humans and animals, they have been considered a big problem for us. Similarly, these problems are more exaggerated when an infection even after treatment becomes cancerous in the future. Protozoans are one of them. They are unicellular, eukaryotic and zoonotic microorganisms mostly found in animals and humans. These protozoans in association with a variety of life-threatening diseases also developed cancer in humans. Plasmodium falciparum has been playing as a cofactor in association with the Epstein Barr virus enhancing the development of Burkitt lymphoma in humans (Flora and Maestra 2015). Leishmania donovani causes skin cancer, leukaemia and Hodgkin lymphoma (Sah et al. 2002, Mangoud et al. 2005, Domingues et al. 2009, Al- Kamel 2017). While there are reports that Trypanosoma cruzi developed gastrointestinal, colon and uterine cancer (Sacerdote et al. 1980, Addad et al. 2002, Murta et al. 2002), Toxoplasama gondii, a causative agent of toxoplasmosis causes brain and breast cancer in human (Marion et al. 2012, Narges et al. 2017).
Similarly, *Trichomonas vaginalis* is linked with cervical cancer (Sayed-El-Ahl 2002), *Blastocystis* developed colorectal cancer (Steer 2007, Amr et al. 2017), *Theileria* induces leucocyte transformation (Medjkane et al. 2014) and *Cryptosporidium* causes digestive cancer in human and animals (Certaid et al. 2010, Gabriela et al. 2012). The present paper deals with the study of various protozoans involved in the development of cancer in humans.

**DISCUSSION**

Recent advances in the field of infectious diseases have led to significant revelations to clarify the relationship between infective protozoans and cancer in humans. The present review discusses some of the cancer-causing protozoans with their possible mechanisms involved. Protozoan parasites have got their oncogenic ability to cause cancer in humans. Insertion of oncogenic DNA sequences in the host genome, inhibition of tumor suppressor gene and the stimulation of cell division cause cancer. Moreover, chronic inflammations at the site of infection having DNA damage, the release of reactive oxygen and nitrogen radicals and developing cell proliferation promoted neoplasia in the host. However, since the removal of infective agents may result in the removal of tumor development from the host, the same notion might be used as one of the thrust areas for research in the future in the same field. (Heussler et al. 2001, Khurana et al. 2005, Reuter et al. 2010, Van et al. 2017).

In this review, we have discussed certain protozoan parasites causing not only life-threatening diseases but also developing cancer in humans. They are *Plasmodium falciparum*, *Leishmania* donovani, *Trypanosoma brucie*, *Toxoplasma gondii*, *Trichomonas vaginalis*, *Blastocystis* hominis, *Theileria* microti and *Cryptosporidium parvum*. They are being discussed serially as under:

**Plasmodium falciparum (Malaria):**

*Plasmodium falciparum* is the most lethal form of malarial parasite found in humans. This is a single-cell protozoan parasite being transmitted through the bites of female anopheles mosquitoes. The common symptoms of malaria are tiredness, fever, headache, vomiting and feeling cold. In severe cases, it may cause yellowing of skin, seizures, coma and death. The disease is usually being treated with some antimalarial drugs like quinine and artemisinin. There is still no vaccine available for the control of malaria (Carter and Mendis 2002, Su and Miller 2015, Kai 2017).

*Plasmodium falciparum* has been found as a co-factor for the development of cancer in humans. The hypothesis that *Plasmodium falciparum* plays a key role in the production of endemic Burkitt’s lymphoma (eBL) has been supported by several studies done so far in the field of parasitic infections (Thorley et al. 2016). Several epidemiological studies supported the view as eBL is more frequently found in the areas where malaria is endemic. Malarial antibodies and the Epstein Barr virus (EBV) showed a strong and significant association in the development of eBL. However, more work is needed to complete the mechanism (Chene et al. 2007, Orem et al. 2007, Carpenter et al. 2008 and Bornkamm 2009).

*P. falciparum* has been associated with the development of blood cancer, Burkitt’s lymphoma and is classified as a Group 2A carcinogen, which is probably carcinogenic in humans (Flora and Maestra 2015). Burkitt’s lymphoma was discovered in African children by Denis Burkitt in 1958. It was found subsequently that this cancer is caused by a virus named Epstein Barr virus. And, EBV is classified as a Group 1 carcinogen by the IARC (Bouvard et al. 2009). Later on, it was also realized that EBV in association with *P. falciparum* enhances the incidence of Burkitt’s lymphoma. Also, the cases of Burkitt’s lymphoma decreased in places where malaria was found in control (Geser et al. 1989). In Burkitt’s lymphoma, the transformations causing lymphoma took place using EBV viral proteins such as EBN-1, EBNA-2, LMP-1 and LMP2A (Rajcani et al. 2014). *P. falciparum* by infecting
erythrocytes directly binds to lymphocytes secreting IgM and cytokines causing DNA damage, mutation, proliferation and differentiation in lymphocytes. Finally, the damaged DNA by replicating indefinitely causes cancer (Thorley et al. 2016, Van et al. 2017, Yasunaga and Matsuoka 2018).

**Leishmania (Black fever or Kala-Azar):**

Leishmaniasis is a chronic widely prevalent, intracellular, anthropozoonotic protozoan infection in mammals including humans of tropical and subtropical regions of the world. This is classified as a neglected tropical disease (NTD) because it remains untouched and under-reported by researchers causing significant morbidity and mortality in humans. *Leishmania* is graded as the second largest leading cause of death after malaria worldwide (Mc Guire 2015). There are three types of leishmaniasis caused by the various species of *Leishmania* visceral, cutaneous and mucocutaneous leishmaniasis. Visceral leishmaniasis (VL) is also called Kala-Azar or black fever which affects the internal organs, usually the spleen, liver and bone marrow. It gives the diagnostic darkening of the skin as black (Osakwe et al. 2013, Chisti et al. 2016, Al kamel 2018).

Leishmania is graded as the second largest leading cause of death after malaria worldwide (Mc Guire 2015). Although this is a neglected tropical disease, a growing number of studies speculate on a possible causal relationship between leishmaniasis and the development of cancer in humans and animals (Al- Kamel 2017). Several scientists believe that it could be a result of either misdiagnosis or mimicking the symptoms that appeared. Sometimes, to cure the disease, when we practice various unsafe measures indiscriminately developed cancer in humans. (Kopterides et al. 2007, Khorsandi et al. 2009, Evers et al. 2014, Celentano et al. 2015, Cobo et al. 2016, Gul et al. 2016, Oetken et al. 2017, Van et al. 2017, Aurelie and Gregoy 2019). However, further research is required to establish the fact. There are some other reports also found in literature establishing the truth that in association with leishmaniasis, it causes malignancy in humans and animals. Some of them are basal cell carcinoma, leukaemia, ocular epidermoid carcinoma and Hodgkin lymphoma (Matayoshi et al. 2000, Sah et al. 2002, de Vasconcelos et al. 2014 Chisti et al. 2016).

Chronic irritations, genome instability, mutations in the host cell genome and cell proliferations have contributed to causing cancer in the host cells affected by *leishmania*. Similarly, the inflammations caused by the infection, inhibition of apoptosis and the inhibition of tumor suppressor gene could lead to progression in malignancy. In leishmaniasis, oxidative stress increases the DNA damage in the lesions. Nitrative DNA damage causes proliferative changes in the epidermal cells of cutaneous leishmaniasis (Coussens 2002, Kocyigit et al. 2005, Mangoud et al. 2005, Sawa and Ohshima 2006).

In India, the main parasite causing the disease is *Leishmania donovani* (Bhunia et al. 2013). The clinical diagnosis is made with the help of serological tests such as DAT and rk39 dipstick tests. The rapid immunochromatographic test (ICT) consisting of rK39 is widely used for the detection of visceral leishmaniasis with the help of serum provided. Liposomal amphotericin B is the first choice of drug by physicians to treat visceral leishmaniasis. Miltefosine is the first oral drug treatment for this disease. However, this is teratogenic and could never be prescribed for a pregnant woman. Recently, the Indian government has approved the broad-spectrum antibiotic paromomycin for use and sale in August 2006. Currently, there is no vaccine available for the prevention of the disease. The most effective method for disease control is the prevention of bites by sandflies (Lockwood and Sundar 2006, Sundar et al. 2010, Rijal et al. 2013, Gillespie et al. 2016).

**Trypanosoma brucei** (Trypanosomiasis):

Trypanosomiasis is a kind of disease that causes sleeping sickness in humans and nagana in cattle in 36 countries of sub-Saharan Africa. This is caused by a blood parasitic protozoan *Trypanosoma*. There are two main types of trypanosomiasis distributed
geographically such as African and American trypanosomiasis. American trypanosomiasis is also known as Chagas’s disease. The disease is named after Carlos Ribeiro Justiniano Chagas, a Brazilian physician and researcher who discovered the disease in 1909. While African trypanosomiasis is transmitted by the urine and faeces of the tsetse fly (Glossina), the American trypanosomiasis is transmitted by a triatomine kissing bug (Wiser 2011, Coura 2013).

Further, African and American types of trypanosomiasis are caused by *T. brucei* and *T. cruzi* respectively (Fevre et al. 2008). The first stage is the hemolymphoid stage in which the *trypanosomes* multiply in subcutaneous tissues, blood and lymph. This is characterized by fever, headache, joint pain, itching and swollen lymph nodes (Matthews 2005). The second stage is known as the neurological or meningoencephalitis stage. In this stage, the pathogen crosses the blood-brain barrier to infect the CNS and is characterized by disturbances in mood and behavior, sense and coordination and sickness in sleep (Lutje et al. 2010, Radwanska 2010). The other clinicopathological symptoms are heart anomaly (Hagar and Rahimtoola 1995) and dilatation of the colon (Kobayashi et al. 1992). Chagasic megaesophagus, achalasia of the pylorus and cholelithiasis (Pinotti et al. 1991).

*Trypanosoma cruzi*, the causing agent of the Chagas disease has a dual role in the development of cancer including both carcinogenic and anticarcinogenic properties (Kallinikova et al. 2001, Zhao et al. 2015). There are reports that *T. cruzi* developed esophageal carcinogenesis leiomyosarcoma (Addad et al. 1999, Bellini et al. 2010), gastrointestinal cancer (Sacerdote et al. 1980), colon cancer (Addad et al. 2002) and uterine leiomyoma (Murta et al. 2002). A kind of report also evidenced that *T. evansi* also causes leukemia and hepatocarcinoma in humans (Safaan 2019).

The diagnosis of *Trypanosoma* is based on the detection of the pathogen in body fluids. It should be done as early as possible to avoid the progression of the disease further. The disease is cured if diagnosed and medicated early but surely proved fatal if left untreated. While the treatment is easier in the first stage of the disease, the second stage of treatment depends upon the choice of drugs that crosses the blood-brain barrier. Further, the drugs used in the treatment of the first stage are pentamidine, melarsoprol, eflornithine, nifurtimox, fexinidazole. Similarly, the drug used to treat both stages is fexinidazole (Barrett 2010). Lastly, since all the drugs available today have always been toxic having severe side effects, a new drug is urgently required to treat the disease safely. Similarly, as no effective vaccine currently exists today for the same purposes, a new vaccine is the subject of current research (Magez et al. 2010).

**Toxoplasma gondii** (*Toxoplasmosis):**

*Toxoplasma gondii* is a most neglected obligate protozoan parasite inhabiting most warm-blooded animals like monkeys (Huessler et al. 1971), dogs (Baba and Rotaru 1983), cats (Dubey and Carpenter 1993), rabbits (Dubey et al. 1992), squirrel (Roher et al. 1981), mole (Geisel et al. 1995), red lorry (Howarth et al. 1991), golden lion tamarins (Pertz et al. 1997), elk (Dubey et al. 1980), mice (Pellardy and Dobos 1974), rats (Henry and Beverley 1977), beef cattle (Allesia et al. 2020), guinea-pigs (Henry and Beverley 1977) including human that causes the disease toxoplasmosis (Jeffrey et al. 2014, Woodhall et al. 2014). However, the only known definitive host for *T. gondii* is the domestic cat and its relatives. While the cats become infected by the ingestion of sporulated oocysts, the humans are infected mainly by eating undercooked meat, consumption of contaminated foods, fruits, vegetables and water with cat faeces, vertical transmission by the placenta from mother to fetus and by cleaning the boxes of pet cats (Malik et al. 2017, Marques et al. 2020). Initially, an individual shows some flu-like symptoms with swollen lymph nodes which disappear after some time but the pathogen remains in the body for a longer period in an inactivated form. It is often reactivated in individuals who are either
immunocompromised or immunosuppressed in the future (Montaya and Remington 2008).

Toxoplasmosis can be very harmful to pregnant women and their developing babies. As the infection usually spreads via cat faeces, a pregnant woman should never come in contact with the same infection (Dubey and Carpenter 1993). It could have some fatal consequences for her babies causing serious eye defects and brain damage at birth (Jones et al. 2001). The infants infected before birth often show no symptoms at birth but the symptoms appear gradually after birth with the loss of vision, physical and mental disability and seizures (Naqid et al. 2019).

In humans, the infective agents of toxoplasmosis as tissue cysts are most commonly found in the brain, myocardium, eyes, skeletal muscle and breasts causing cancer of the respective organs (Zhang et al. 2002, Khurana et al. 2005, Marion et al. 2012, Zhao et al. 2015, Narges et al. 2017). The potentiality of pituitary adenoma has been suspected with the infection of Toxoplasma gondii (Zhang et al. 2002). This is found as the tumor promoter as has been reported in ocular tumors, meningioma, leukaemia and lymphoma (Khurana et al. 2005). Currently, brain and breast cancers are more commonly tagged with the infection of Toxoplasma gondii in humans (Marion et al. 2012, Narges et al. 2017).

The clinicopathological diagnosis of T. gondii is done either by the staining of tissue cysts (Kaliakin 1972) or serology (Simon et al. 2020). T. gondii DNA is also detected via the polymerase chain reaction. Congenital infections are achieved by the detection of T. gondii DNA in the amniotic fluid using PCR. (Geng et al. 2001, Naqid et al. 2019, Alessia et al. 2020, Marques et al. 2020). Most healthy people usually recover without any treatment but for an immunocompromised patient, the disease is often proved to be fatal if not treated well within time. In general, the patients are being treated with the drug combination of pyrimethamine, sulfadiazine with folic acid (Maldonado and Read 2017). A drug named aureobasidin is also being tried (Sabrina et al. 2005).

Trichomonas vaginalis (Trichomoniasis):

Trichomonas vaginalis is the causative agent of trichomoniasis. This is an anaerobic, flagellated, parasitic protozoan. T. vaginalis is the most widely studied parasite of all the trichomonads. As humans are the only natural reservoir of T. vaginalis this is usually transmitted either sexually or by close contact with others (Dino et al. 1998). This is generally found in association with other infections like pneumocystosis, candidiasis and HPV infections (Boyle et al. 1989, Duboucher et al. 2003 & 2007).

The clinicopathological symptoms of the disease are characterized by itching, redness, irritation and an unusual discharge from the vagina. Moreover, with the same infection rates in both genders, this is usually asymptomatic in men. As this is a sexually transmitted disease, the pathogen usually resided in the lower urinogenital tract of the human female. It has been reported to cause pelvic inflammatory disease and cervical cancer. Cervical cancer is a malignant neoplasm characterized by abnormal vaginal bleeding but, sometimes this is quite asymptomatic until cancer has progressed to an advanced stage (Boyle et al. 1989, Yap et al. 1995, Dino et al. 1998, Sayed-el-Ahl et al. 2002). Further, T. vaginalis principally infects the squamous epithelial cells of the genital tract. This is chiefly a disease of reproductive years and rarely seen in an individual before menarchy or after menopause. It causes adenitis, pyosalpinx, endometritis, cervical erosion and infertility. The patients also suffer from premature labour, premature birth, or birth with low-weight infants. In addition, it causes prostate cancer in humans. However, the reports regarding the pathogen to causes cancer are still contradictory. Larger studies are required to explore the possible effect modifications further (Stark et al. 2009, Sutcliffe et al. 2009).

Trichomonas vaginalis is diagnosed by papnicolaou staining technique with the help of acridine orange (Fripp et al. 1975),
periodic-acid-Schiff (Rodriguez et al. 1973) and Leishman (Levett 1980) reagents for direct microscopy (Spence et al. 1980). The antigen-antibody test, and recombinant DNA technology with PCR have also been used up in clinical laboratories to improve the efficacy of *T. vaginalis* diagnosis (Levett 1980). Metronidazole marketed under the trade name “flagel” is the first choice of drug for physicians to remove the infection of trichomoniasis (Hayward and Roy 1976). Other nitromidazoles such as tinidazole, secnidazole, nirazol, and nifurtimox have also been tried worldwide for the treatment. (Pereyra et al. 1972, Hayward and Roy 1976, Sucharit et al. 1979, Chaudhary and Drogendijk 1980, Fugere et al. 1983). Similarly, the vaginal preparation of clotrimazole is also found effective for the removal of *T. vaginalis* infection (Lossick et al. 1986, Lossick and Kent 1991).

**Blastocystis hominis (Blastocystosis):**

*Blastocystis* is one of the most neglected common protozoan parasites living in the gastrointestinal tract causing a disease known as Blastocystosis in humans and animals. Various types of Blastocystis exist infecting farm animals, birds, reptiles, amphibians, rodents, fishes and even cockroaches. This is a kind of zoonotic disease usually transmitted via the faecal-oral route (Yoshikawa et al. 2004, Parkar et al. 2007, Stensvold et al. 2009). A cancer patient undergone chemotherapy may also acquire Blastocystis as an opportunistic infection (Chandramathi et al. 2012). The clinical symptoms of Blastocystosis include diarrhoea, nausea and vomiting, abdominal pain, anal itching, anorexia, flatulence and weight loss (Tan 2008). One of the most important clinical complications caused by Blastocystis infection is the renal failure (Hawash et al. 2015). This is also linked with irritable bowel syndrome and arthritis (Lee et al. 1990, Roshtami et al. 2017). Blastocystis has been shown to produce inflammatory cytokines interleukin-8 having an important role in rheumatoid arthritis. It causes colorectal cancer and acquired immunodeficiency syndrome in humans. *Blastocystis hominis* modulates immune responses and cytokine release in colonic epithelial cells. Blastocystis also secreted an enzyme protease that eventually led to the self-destruction of intestinal cells causing enhanced apoptosis. It can proliferate human colorectal cells via abnormal apoptosis and protein disintegration. Similar studies have also shown that Blastocystis elevated the oxidative stress to form reactive oxygen causing the cells more toxic and cancerous in an easier way (Koltas et al. 1999, Long et al. 2001, Puthia et al. 2006, Amr et al. 2017).

**Theileria microti (Theileriosis):**

Bovine theileriosis is a cattle disease found in tropical and subtropical countries caused by several species of *Theileria* belonging to the phylum Apicomplexa (Grech et al. 2016). *Theileria microti* is a blood-borne microorganism transmitted by deer ticks. This is responsible for the zoonotic disease named human theileriosis similar to babesiosis, a malaria-like disease causing fever, lymphadenopathy and hemolysis. It was previously described as Babesia microti (Uilenberg 2006, Vannier and Krause 2012, Onyinyechukwu et al. 2020). This is an intracellular parasite particularly pathogenic in cattle causing the lymphoproliferative disease which is often lethal similar to some human leukaemias. It causes leukocyte transformations via antiapoptosis residing freely in the host leukocyte modifying the host cell cytoskeleton (Heussler et al. 2002, Dobbelnaere and Rottenberg 2003, Lizundia et al. 2006, Branco et al. 2010).

Theileria induces oxidative stress via elevated reactive oxygen species (ROS) and hypoxia-inducible factor 1 α (HIF 1 α) activation causing host leukocytes transformation (Dobbelnaere 2003, Medjkane et al. 2014). HIF 1 α activation leads to an increased production of lactic acid from glucose mediated by the seventh hallmark of cancer known as the Warburg effect (Denko 2008, Yeung et al. 2008, Koppenol et al. 2011). The increased glycolysis involving elevated glucose uptake in cancer cells has already been considered to be an important
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feature during malignant transformations (Shaw 2006). However, these cancer characteristics are reversible when treated with the host cells with a theilericidal drug named buparvaquone. It stops the proliferation maintaining the normal apoptosis (Chaussepied and Langsley 1996, Muraguri et al. 1999, Medjkane et al. 2014). Live, attenuated and DNA vaccines are now available to control theileriosis (Hemmink et al. 2016, Nene and Morrison 2016).

The diagnosis of theileriosis is obtained by blood or lymph node smears with the help of Giemsa stain to detect piroplasm in erythrocytes or macro-schizonts in leukocytes. In addition, serological and molecular techniques like ELISA and PCR have also been employed (Shayan and Rahbari 2005, Khatoon et al. 2013, Rajendran and Ray 2014). Similarly, a microarray kit is designed for the detection of various species of Theileria (Abanda et al. 2019).

Cryptosporidium parvum (Cryptosporidiosis):

Cryptosporidium parvum is an intracellular protozoan parasite ubiquitous in nature. This is a water-borne protozoan isolated from the stool of a patient who was drowned in a river. The strain was inoculated in a mouse causing infection. It induces invasive gastrointestinal and biliary adenocarcinoma (Gabriela et al. 2012, Osman et al. 2017). Cryptosporidiosis is found in almost all vertebrates including amphibians, reptiles, birds, humans and other mammals. The invasive oocyst stage is more resistant to temperature and saltwater. The infection is easily transmitted via contaminated water and unhygienic condition through the fecal-oral route. This is worldwide in distribution creating food and waterborne health problems as a frequent cause of watery mucous diarrhoea in humans and animals. This is mostly affecting children under the age of five years. However, a competent patient may usually recover within two weeks (Mac et al. 1994, Putignany and Menichella 2010, Benamrouz et al. 2012).

The immunocompromised patients are more easily affected by the Cryptosporidium. This is an opportunistic infection with life-threatening diarrhoea, especially those undergone antiretroviral therapy. It may cause stomach cramps, stomach pains, nausea, vomiting, diarrhoea, dehydration, weight loss and fever (Hunter and Nichols 2002, Remirez et al. 2004). The possible role of cryptosporidiosis in the production of intramucosal adenocarcinoma and cholangiocarcinoma is considered an early sign of invasive cancer and a putative precursor to digestive carcinoma (Izquierdo et al. 1998 and Certaid et al. 2010, Gabriela et al. 2012). Cryptosporidiosis is well documented in AIDS patients causing colorectal cancer in them (Shebl et al. 2012). Several epidemics have been recorded with cryptosporidiosis in the past. In Poland, an epidemiological study shows that 18% of cryptosporidiosis patients were also suffering from colorectal cancer with inhibited apoptosis and disturbed cytoskeleton system in the host cells. Finally, more research is required to establish cryptosporidiosis as a cause of cancer (Heussler et al. 2001, Buda and Pignatelli 2004, Carmen and Cinai 2007, Sulzyc et al. 2007, Striepen 2013, Violetta et al. 2018, Zhang et al. 2020).

CONCLUSION

As the bacterial and viral origin of cancers has already been established, the present review described the protozoans causing cancer in humans. Plasmodium falciparum is associated with the development of Burkitt’s lymphoma. This is classified as a Group 2A carcinogen by the IARC (Flora and Maestra 2015). One of the most neglected tropical diseases is leishmaniasis causing black fever in humans. This is graded as the second largest leading cause of death after malaria worldwide. Similarly, a growing number of studies speculate on a possible causal relationship between leishmaniasis and the development...
of cancer. Another protozoan *Trypanosoma* crosses the blood-brain barrier in humans to cause sleeping sickness with various neurological CNS disorders. It also causes gastrointestinal, oesophageal, colon, uterine and hepatocarcinoma in humans. Further, the *Toxoplasma gondii* is a most neglected protozoan parasite inhabiting most warm-blooded animals including humans that causes the disease toxoplasmosis. However, the only definitive host for *T. gondii* is a domestic cat. It can be very harmful to pregnant women and their developing babies. The infective cysts are most commonly found in the brain, myocardium, eyes, skeletal muscle and breasts causing cancer of the respective organs. The next protozoan causing cancer in humans is *Trichomonas vaginalis*. As humans are the only reservoir of *T. vaginalis*, this is usually transmitted sexually. It causes cervical cancer in the human female. Similarly, theileriosis is a blood-borne zoonotic disease caused by *Theileria microti*, an intracellular protozoan parasite causing lymphoproliferative disease and leukocyte transformation. In addition, *Blastocystis hominis* is a zoonotic protozoan parasite living in the gastrointestinal tracts of different animals and humans. This is usually transmitted by the faecal-oral route. It causes irritable bowel syndrome and arthritis in humans. It has also been linked with colorectal cancer and immunodeficiency syndrome. Lastly, the *cryptosporidium parvum* is also an intracellular protozoan parasite that induces invasive gastrointestinal and biliary adenocarcinoma and colorectal cancer.

**Abbreviations**

IARC: Inter. agency for research on cancer  
DNA: Deoxyribonucleic acid  
p53: Tumor suppressor gene  
eBl: Endemic Burkitt’s lymphoma  
EBV: Epstein Bar virus  
IgM: Immunoglobulin M  
NTD: Neglected tropical disease  
DAT: Direct agglutination test  
ICT: Immunochromatographic test  
VL: Visceral leishmaniasis  
CNS: Central nervous system  
PCR: Polymerase chain reaction  
ROS: Reactive oxygen species  
HIF lα: Hypoxia inducible factor lα  
ELISA: Enzyme-linked immunosorbent assay  
AIDS: Acquired immunodeficiency syndrome  

**REFERENCE**

Abanda B., Paguem A., Achukwi M.D., Renz A., Eisenbarth A. (2019): Development of a low-density DNA microarray for detecting tick-borne bacterial and piroplasmid pathogens in African cattle. *Tropical Medicine and Infectious Disease*, 4 (2): 64. doi: 10.3390/tropicalmed4020064.  
Addad S.J., Araujo J.R., Madureira A.B., Lima V.G., Silva A.A. (2002): Association of chagasic megacolon and cancer of the colon: Case report and review of the literature. *Revista da Sociedade Brasileira de Medicina Tropical*, 35 (1) :63-68.  
Addad S.J., Hayashi E.M., Asai R.K., Souzo F.P., Macedo C.F. (1999): Leiomyosarcoma of the oesophagus in a patient with chagasic megaesophagus: A case report and literature review. *American Journal of Tropical Medicine and Hygiene*, 60 (5) : 879-881.  
Alessia L.G., Anna M.F.M., Giovanni G., Luca R., Marino L., Maria T.M. (2020): *Toxoplasma gondii* seroprevalence in beef cattle raised in Italy: a multicenter study 2020; *Parasitology Research*, 119 (6): DOI: 10.1007/s00436-020-06878-y.  
Al-Kamel M.A(2017): Leishmaniasis and malignancy: A review and perspective. *Clinical Skin Cancer*, 2 (1-2) : 54-58.  
Al-Kamel M.A. (2018): Basal cell carcinoma developed on an active lesion of mucocutaneous leishmaniasis: A case report from Yemen. *Archives of Clinical Dermatology*, 1 (1): 4.  
Amr M.M., Mona A.H., Dina A.Z. (2017): Predominance and association risk
of *Blastocystis hominis* subtype1 in colorectal cancer: a case-control study. *Infectious Agents and Cancer*, 12 (21): https://doi.org/10.1186/s13027-017-0131-z.

Aurelie S., Gregory M. (2019): *Leishmania* infection: misdiagnosed as cancer and tumor-promoting potential. *Acta Tropica*, 197: 104855.

Baba A.I, Rotaru O. (1983): Morphopathological finding in dogs with acute toxoplasmosis. *Morphologie et Embryologie (Bucur)*; 29 (1): 35-37.

Barrett M.P. (2010): Potential new drugs for human African trypanosomiasis: some progress at last. *Current Opinion in Infectious Diseases*, 23 (6): 603-608.

Bellini M.F., Manzato A.J., Silva A.E., Garcia M.V. (2010): Chromosomal imbalances are uncommon in chagasic megaesophagus. *BMC Gastroenterology*, 10: 20.

Benamrouz S., Guyot K., Gazzola S., Chassat T., Delaire B. (2012): *Cryptosporidium parvum* infection in SCID mice infected with only one oocyst: qPCR assessment of parasite replication in tissues and development of digestive cancer. *PLoS One*, 7: e51232.

Bhunia G.S., Kesari S., Chatterjee N., Kumar V., Das P. (2013): The burden of visceral leishmaniasis in India: Challenges in using remote sensing and GIS to understand and control. *International Scholarly Research Notices*, 1-14.

Bornkamm G.W. (2009) : Epstein-Barr virus and the pathogenesis of Burkitt’s lymphoma: more questions than answers. *International Journal of Cancer*, 124: 1745-1755.

Bouvard V., Rober B., Straif K., Yann G., Fatiha E., Guha N. (2009) : A review on human carcinogens- Part B: biological agents. *The Lancet Oncology*, 10(4): 321-322.

Boyle A.C., Lowell D.M., Boyle K.E. (1989): Cervical intraepithelial neoplasia among women with papillomavirus infection compared to women with *Trichomonas* infection. Cancer, 64: 168-172.

Branco S., Orvalho J, Peleteiro M.C. (2010): Fatal cases of *Theileria annulata* infection in calves in Portugal associated with neoplastic-like lymphoid cell proliferation. *Journal of Veterinary Science*, 11: 27-34.

Buda A., Pignatelli M. (2004): Cytoskeletal network in colon cancer: from genes to clinical application. *The International Journal of Biochemistry & Cell Biology*, 36: 759-765.

Carpenter L.M., Newton R., Beral V. (2008): Antibodies against malaria and Epstein- Barr virus in childhood Burkitt lymphoma: a case-control study in Uganda. *International Journal of Cancer*,122: 1319-1323.

Carter R., Mendis K.N. (2002): Evolutionary and historical aspects of the burden of malaria. *Clinical Microbiological Review* 15 (4): 564-594.

Certaid G., Creusy C., Dei-Cas E. (2010): Fulminant cryptosporidiosis associated with digestive adenocarcinoma in SCID mice infected with *Cryptosporidium parvum* TUM1 strain. *International Journal of Parasitology*, 40: 1469-1475.

Chene A., Donati D., Bejarano M.T. (2007): A molecular link between malaria and Epstein-Barr virus reactivation. *PLoS pathogens*, 3: e980.

Chisti M., Almasri R., Hamadah I. (2016): Is cutaneous leishmaniasis a risk factor for basal cell carcinoma. *Gulf Journal of Oncology*, 1: 64-66.

Cobo F, Rodriguez G.J, Navarro J.M, Farnandez J.G. (2016): Localized mucosal leishmaniasis caused by *Leishmania infantum* mimicking cancer in the rhinolaryngeal region.
The International Journal of Infectious Diseases, 50: 5054-5056.

Coura J.R. (2013): Chagas disease: control elimination and eradication. Is it possible? Memórias do Instituto Oswaldo Cruz, 108 (8): 962-967.

Coussens L.M., Werb Z. (2002): Inflammation and cancer. Nature; 420: 860-867.

Denko NC. (2008) Hypoxia, HIF1 and glucose metabolism in the solid tumor. National Review Cancer, 8: 705-713.

Dino P., Kiera D., Renuka B., Garber G. (1998): Clinical and microbiological aspects of Trichomonas vaginalis. Clinical Microbiological Reviews, 11 (2) : 300-317.

Dobbelaere D.A., Rottenberg S. (2003): Theileria–induced leukocyte transformation. Current Opinion in Microbiology, 6: 377-382.

Doboucher C., Caby S., Viscogliosi E. (2007): Human pulmonary trichomonases. La Presse Médicale, 15 (3): 323-325.

Doboucher C., Noel C., Viscogliosi E. (2003): Pulmonary coinfection by Trichomonas and Pneumocystis sp. As a novel manifestation of AIDS. Human Pathology, 34: 508-511.

Domingues M., Menezes Y., Calixto R., Florencio R., Ostronoff M. (2009): Coexistence of leishmaniasis and Hodgkin’s lymphoma in a lymph node. Journal of Clinical Oncology, 27 (32) : 184-185.

Dubey J.P., Brown C.A., Carpenter J.L., Moore J.J. (1992): Fatal toxoplasmosis in domestic rabbits in the USA. Veterinary Parasitology, 44 (3-4): 305-309.

Dubey J.P., Carpenter J.L. (1993): Histologically confirmed clinical toxoplasmosis in cats: 100 cases (1952-1990). Journal of the American Veterinary Medical Association, 2003 (11): 1556-1566.

Dubey J.P., Throne E.T., Sharma S.P. (1980): Experimental toxoplasmosis in elk (Cervus canadensis). American Journal of Veterinary Research, 41 (5): 792-793.

Evers G., Pohlen M., Berdel W.E., Kohler G., Anthoni C. (2014): Visceral leishmaniasis and clinically mimicking lymphoma. Annals of Hematology, 93 (5): 885-887.

Fevre E.M., Wissmann B.V., Welburn S.C., Lutumba P. (2008): The burden of human African trypanosomiasis. PLoS Neglected Tropical Diseases, 12 (12): e333.

Flora S.D., Maestra S.L. (2015) Epidemiology of cancers of infectious origin and prevention strategies. Journal of Preventive Medicine and Hygiene, 56 (1): 15-20.

Fripp P.J., Mason P.R., Super H. (1975): A method for the diagnosis of Trichomonas vaginalis using acridine orange. Journal of Parasitology, 61: 966-967.

Fugere P., Verschelden G., Caron M. (1983): Single oral dose of ornidazole in women with vaginal trichomoniasis. Obstetrics & Gynecology, 62: 502-505.

Gabriela C., Sadia B., Karine G., Anthony M. (2012): Fulminant Cryptosporidium parvum strain implicated in invasive gastrointestinal adenocarcinoma and cholangiocarcinoma in an experimental model. Applied and Environmental Microbiology, 78 (6): 1746-1751.

Geisel O., Breuer W., Minkus G., Hermanns W. (1995): Toxoplasmosis causing death in a mole (Talpeurpaea). Berl Munch Tierarztl Wochenshr, 108 (7): 241-243.

Geng Z.H., He C.Y., Zheng Y.S., Zhu G., Li J.H. (2001): Detection of DNA of Toxoplasma gondii in rat by using polymerase chain reaction. Zhongguo Ji Sheng Chong Xu Yu Ji Sheng Chong Bing Za Zhi, 19(3) : 173-175.
Geser A., Brubaker G., Drapper C.C. (1989): Effect of a malaria Suppression program on the incidence of African Burkitt’s lymphoma. *The American Journal of Epidemiology*, 129 (4): 740-752.

Gillespie P.M., Corren M., Tara H., Hotz P.J., Elena B.M. (2016): Status of vaccine research and development of vaccines for leishmaniasis. *Vaccine*, 34 (26): 2992-2995.

Grech A.S., Stachurski F., Lancelot R., Gharbi M., Uilenberg G. (2016): First report of the tick *Hyalomma scupense* (natural vector of bovine tropical theileriosis) on the French Mediterranean Islands of Corsica. *Veterinary Parasitology*, 216: 33-37.

Gul H.C., Tosun F., Karkas A., Koru O., Onguru O., Mert G. (2016): A case of mucosal leishmaniasis: mimicking intranasal tumor with perforation of the septum. *Journal of Microbiology, Immunology and Infection*, 49 (4): 604-607.

Hagar J.M., Rahimtoo S.H. (1995): Chagas’s heart disease. Current Problems in Cardiology, 20: 827-924.

Hawash Y.A., Dorgham L., Sharaf O.F. (2015): Prevalence of intestinal protozoans among Saudi patients with chronic renal failure. A case-control study. *Journal of Tropical Medicine*, 2015: 563478.

Hayward M.J., Roy R.B. (1976): Two-day treatment of trichomoniasis in the female. comparison of metronidazole and nimorazole. *The British Journal of Venereal Diseases*, 52: 63-64.

Hemmink J.D., Weir W., Graham SP., Patel E., Pelle R. (2016) Limited genetic and antigenic diversity within parasite isolates used in a vaccine against *Theileria parva*. *International Journal for Parasitology*, 46: 495-506.

Henry L., Beverley JK. (1977): Toxoplasmosis in rats and guinea-pigs. *Journal of Comparative Pathology*, 87 (1): 97-102.

Heussler J.R., Woodward J.C., Tucek P.C. (1971): Lethal toxoplasmosis in Woolly monkey. *American Veterinary Medical Association*, 159 (11): 1588-1594.

Heussler V.T., Kuenzi P., Rottenberg S. (2001): Inhibition of apoptosis by intracellular protozoan parasites. *International Journal for Parasitology*, 31: 1166-1176.

Heussler V.T., Rottenberg S., Dobbelaeere D.A. (2002): Hijacking of host cell IKK signalosomes by the transforming parasite Theileria. *Science*, 298: 1033-1036.

Howarth E.W., Rich G., Dubey J.P., Yogasundaram K. (1991): Fatal toxoplasmosis in red iby (Eos bornea). *Avian Diseases*, 35 (3): 642-646.

Hunter P.R., Nichols G. (2002): Epidemiology and clinical features of Cryptosporidium infection in immunocompromised patients. *Clinical Microbiology Reviews*, 15: 145-154.

Izquierdo J., Antunez I., Munoz Sanz A. (1988): Diarrhoea caused by *Cryptosporidium* and colonic neoplasia. *Revista Clínica Española*, 182: 393-394.

Jeffery L.J., Monica E.P., Anthony E.F. (2014): Neglected parasitic infections in the United States: Toxoplasmosis. *American Journal of Tropical Medicine and Hygiene*, 90: 794-799.

Jones J.L., Dietz V.J., Power M., Lopez A., Wilson M. (2001): Survey of obstetrician-gynaecologists in the United States about toxoplasmosis. *Infectious Diseases in Obstetrics and Gynecology*, 9 (1): 23-31.

Kai M. (2017): Vaccines against malaria- still a long way to go. *The FERS Journal; Online*, (16): 2560-2568.

Kaliakin V.N. (1972): Microscopic detection of *Toxoplasma gondii* cysts in the...
brain of white rats in relation to the number of parasites and duration of invasion. *Meditsinskaia parazitologiia parazitarnye Boleznii*, 41 (1): 73-76.

Kallinikova V.D., Matekin P.V., Ogloblina T.A., Kononenko A.F., Sokolova N.M. (2001): Anticancer properties of flagellate protozoan *Trypanosoma cruzi* Chagas, 1909. *Izvestiia Akademiui nauk. Seriiia biologicheskaia*, 3: 299-311.

Khatoon S., Kolte S.W., Kurkure N.V., Chopde N.A., Jahan A. (2013): Detection of tropical bovine theileriosis by polymerase chain reaction in cattle. *Journal of Parasitic Diseases*, 39: 53-56.

Khosravand A.M.T., Hasibi M., Yazdani N., Sadri F., Kouhi A. (2009): Auricular leishmaniasis mimicking squamous cell carcinoma. *The Journal of Laryngology & Otology*, 123 (8): 915-918.

Khorana S., Dubey M.L., Malla N. (2005): Association of parasitic infections and cancers. *Indian Journal of Medical Microbiology*, 23: 74-79.

Kobayashi S., Menders E.F., Rodrigues M.A.M., Franco M.F. (1992): Toxic dilatation of the colon in chagas disease. *British Journal of Surgery*, 79: 1202-1203.

Kocyigit A., Keles H., Selik S. (2005) Increased DNA damage and oxidative stress in patients with cutaneous leishmaniasis. *Mutation Research*, 585: 71-78.

Koltas S., Ozcan K., Tannverdi S., Paydas S., Baslamish F. (1999): The prevalence of *Blastocystis hominis* in immunosuppressed patients. *Annals of the National Academy of Medical Sciences*, 8: 117-119.

Koppenol W.H., Bounds P.L., Dang C.V. (2011): Otto Warburg’s contributions to current concepts of cancer metabolism. *Nature Reviews Cancer*, 11: 325-337.

Kopterides P., Mourtzoukou E.G., Skopelitis E., Tsavaris N., Falagas M.E. (2007): Aspects of the association between leishmaniasis and malignant disorders. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 101: 1181-1189.

Lee M.G, Rawlins S.C, Didier M, Deceulaer K. (1990): Infective arthritis due to *Blastocystis hominis*. *Annals of the Rheumatic Diseases*, 49 (3): 192-193.

Levett P.N. (1980): A comparison of five methods for the detection of *Trichomonas vaginalis* in clinical specimens. *Medical Laboratory Science*, 37: 85-88.

Lizundia R., Chaussepied M., Langsley G. (2006): c-Jun NH2-terminal kinase/c-Jun signalling promotes survival and metastasis of B-lymphocytes transformed by *Theileria*. *Cancer Research*, 66: 6105-6110.

Lockwood D.N. (2006): Sundar S. Serological tests for visceral leishmaniasis. *The British Medical Journal*, 333 (7571): 711-712.

Long H.Y., Handschack A., Koing W., Ambrosch A. (2001): *Blastocystis hominis* modulates immune responses and cytokine release in colonic epithelial cells. *Parasitology Research*, 87 (12): 1029-1030.

Lossick J.G., Kent H.L. (1991): Trichomoniasis: trends in diagnosis and management. *American Journal of Obstetrics & Gynecology*, 165: 1217-1222.

Lutje V., Seixas J., Kennedy A. (2010): Chemotherapy for second-stage human African trypanosomiasis. *Cochrane Database of Systematic Reviews*, 8: P. CD006201.

Mac Kenzie W.R., Hoxie N.J., Proctor M.E., Gradus M.S., Blair K.A. (1994): A massive outbreak in Milwaukee of *Cryptosporidium* infection transmitted through the public water supply. *The New England Journal of Medicine*, 331: 161-167.
The Possible Involvement of Protozoans in Causing Cancer in Human

Magez S., Caljon G., Tran T., Stijlemans B., Radwanska M. (2010): Current status of vaccination against African trypanosomiasis. *Parasitology*, 137 (14): 2017-2027.

Malik A.H., Victoria S., Elizabeth A.S., Bruce N. (2017): *Toxoplasma gondii* in the food supply. *Pathogens*, 6 (2): 21-27.

Mangoud A.M., Sanad E.M., Fouad M.A. (2005): Proliferative changes of epidermal cells in lesions of cutaneous leishmaniasis. *Journal of the Egyptian Society of Parasitology*, 35: 761-772.

Maraguri G.R., Kiara H.K., McHardy N. (1999): Treatment of East Coast fever: a comparison of parvaquone and buparvaquone. *Veterinary Parasitology*, 87: 25-37.

Marion V., Eric E., Kevin L., Nenjamin R., Frederic T. (2012): Brain cancer mortality rates increase with *Toxoplasma gondii* seroprevalence in France. *Infection, Genetics and Evolution. International Journal of Molecular Epidemiology, Genetics & Evolutionary Genetics in Infectious Diseases*, 12 (2): 496-498.

Marques C.S., Susana S., Antonio C., Costa J.M.C. (2020): Detection of *Toxoplasma gondii* oocysts in fresh vegetable berry fruits. *Parasites and Vectors*, 13 (180): http://doi.org/10.1186/s13071-020-04040-2.

Matayoshi S., Goldbaum M., Takei L.M., Honda M., Kara J.N. (2000): Epidermoid carcinoma arising in an ocular *Leishmania* lesion. *British Journal of Ophthalmology*, 84 (11): 1331-1332.

Matthews K.R. (2005): The developmental cell biology of *Trypanosoma brucei*. *Journal of Cell Science*, 118 (2): 283-290.

Mc Guire S. World cancer report. 2014: Geneva, Switzerland: World Health Organization, Internal Agency for Research on Cancer, WHO Press, 2015.

Medjkane S., Perichon M., Marsolier J., Dairou J., Weitzman J.B. (2014): *Theileria* induces oxidative stress and HIF1 α activation that are essential for host leukocyte transformation. *Oncogene*, 33: 1809-1817.

Montaya J.G., Remington J.S. (2008): Management of *Toxoplasma gondii* infection during pregnancy. *Clinical Infectious Diseases*, 47 (4): 554-566.

Murta E.F., Oliveira G.P., Prado F.O., De Souza M.A., Murta B.M.T., Addad S.J. (2002): Association of uterine leiomyoma and Chagas’s disease, *American Journal of Tropical Medicine and Hygiene*, 66 (3): 321-324.

Naqid I.A., Hassan Y., Rasheed N., Ibrahim A.N. (2019): Serological study of IgG and IgM antibodies to cytomegalovirus and *Toxoplasma* infections in pregnant women in Zakho city, Kurdistan region, Iraq. *Women’s Health Bulletin*, 6 (4): 1-12.

Narges K., Zeinab A.D., Nikbakhsh N., Ghasemi M., Taraneh G. (2017): Detection of *Toxoplasma gondii* DNA in malignant breast tissues in breast cancer patients, *International Journal of Molecular and Cellular Medicine*, 6 (3): 190-196.

Nene V., Morrison W.I. (2016): Approaches to vaccination against *Theileria parva* and *Theileria annulata*. *Parasite Immunol*, 38: 724-734.

Oetken T., Hiscox B., Oreno I., Rosen T. (2017): Cutaneous leishmaniasis mimicking squamous cell carcinoma. *Dermatology Online Journal*, 23 (1): 13030/qt8f36814 f. PMID:28329481.

Onyinyechukwu A.A., Shaari M.R., Nur M.M.I., Saad M.Z., Hamzah H. (2020): Clinical pathology, immunopathology and advanced vaccine technology in bovine theileriosis: a review. *Pathogens*;9: 697 doi:10.3390/pathogens9090697.
Orem J., Mbidde E.K., Weiderpass E. (2007): Burkitt’s lymphoma in Africa, a review of the epidemiology and etiology. *African Health Sciences*, 7: 166-175.

Osakwe N.M., Paulus A., Haggerty P.F. (2013): Visceral leishmaniasis with associated immune dysregulation leading to lymphoma. *Military Medicine*, 178: 386-389.

Osman M., Sadia B., Karine G., Martha B. (2017): High association of *Cryptosporidium* spp. Infection with colon adenocarcinoma in Lebanese. *PLoS One*, 12 (12): e018422.

Parkar U., Traub R.J., Kumar S. (2007): Direct characterization of *Blastocystis* from faeces by PCR and evidence of zoonotic potential. *Parasitology*, 134 (3): 359-367.

Pellerdy L., Dobos-Kovacs M. (1974): Studies on the pathogenecity of *Toxoplasma* for mice. *Acta veterinaria Academiae Scientiarum Hungaricae*, 24 (3): 313-326.

Pereyra A.J., Nelson R.M., Ludders D.J. (1972): Flunidazole- a new drug for systematic treatment of urogenital trichomoniasis. *American Journal of Obstetrics and Gynecology*, 112: 963-966.

Pertz C., Dubielzig R.R., Lindsay D.S. (1997): Fatal *Toxoplasma gondii* infection in golden lion tamarins (*Leontopithecus rosalia rosalia*). *Journal of Zoo and Wildlife Medicine*, 28 (4): 491-493.

Pinotti H.W., Felix V.N., Zilberstein B., Cecconollo I. (1991): Surgical complications of Chaga’s disease: megaesophagus, achalasia of the pylorus and cholelithiasis. *World Journal of Surgery*, 15: 198-204.

Plattner F., Soldati-favre D. Hijacking of host cellular functions by the Apicomplexa. (2008): Annual Review of Microbiology, 62: 471-487.

Puthia M.K., Sio S.W., Lu J., Tan K.S. (2006): *Blastocystis ratti* induces contact-independent apoptosis, F-Actin rearrangement and barrier function disruption in IEC-6 cells. *Infection and Immunity*, 74 (7): 4114-4123.

Putignani L., Menichella D. (2010): Global distribution, public health and clinical impact of the protozoan pathogen *Cryptosporidium*. *Interdisciplinary Perspectives on Infectious Diseases*, 201. pii:753512.

Radawanska M. (2010): Emerging trends in the diagnosis of human African trypanosomiasis. *Parasitology*, 137 (14) :1977-1986.

Rajcani J., Kalman S., Banati F., Susan S. (2014): Survey of Epstein Barr Virus (EBV) immunogenic proteins and their epitopes: implications for vaccine preparation. Recent Patents on Anti Infective Drug Discovery, 9 (1): 62-76.

Rajendran C., Ray D.D. (2014): Diagnosis of tropical bovine the ELISA with recombinant merozoite surface protein of *Theileria* annulata (Tams 1). *Journal of Parasitic Diseases*, 38: 41-45.

Remirez N.E., Ward L.A., Sreevatsan S. (2004): A review of the biology and epidemiology of cryptosporidiosis in humans and animals. *Microbes Infection*, 6: 773-785.

Reuter S., Gupta S.C., Chaturvedi M.M., Aggarwal B.B. (2010): Oxidative stress, inflammation and cancer: how are they linked? Free Radical Biology and Medicine, 49 (11): 1603-1616.

Rijal S., Ostyn B., Dhakal S.S., Das M.L. (2013): The increasing failure of Miltefosine in the treatment of Kala-azar in Nepal and the potential role of parasite drug resistance, reinfection or non-compliance. *Clinical Infectious Diseases*, 56 (11): 1530-1538.

Rodriguez-Martinez H.A., De la L.R.M., Galloso D.B.L., Ruiz – Moreno JA. (1973): Adequate staining of
The Possible Involvement of Protozoans in Causing Cancer in Human

*Trichomonas vaginalis* by McManus periodic acid-schiff stain. *American Journal of Clinical Pathology*, 59: 741-746.

Roher D.P., Ryan M.J., Nielsen S.W., Roscoe D.E. Acute fatal toxoplasmosis in squirrels. (1981): *Journal of American Veterinary Medical Association*, 1 (179): 1099-1101.

Rostami A., Riahi S.M., Haghighi A., Saber V., Armon B., Seyyedtabaei SJ. (2017): The role of *Blastocystis* sp. And *Dientamoeba fragilis* in irritable bowel syndrome: a systematic review and meta-analysis. *Parasitology Research*, 116 (9): 2361-2371.

Sabrina S., Sala G., Riccardo G., Pieters J. (2005): Inhibitory effect of Aureobasidin A on *Toxoplasma gondii*. *Antimicrobial Agents and Chemotherapy*, 49 (5): 1794-1801.

Sacerdote L.E., Purilli L., Bal E., Lansetti J.C. (1980): Association of Chagas disease and cancer. *Medicina (Buenos Aires)*, 40 (1): 43-46.

Safaa B. (2019): Advanced studies on *Trypanosoma evansi*: Does *Trypanosoma evansi* cause cancer or behave like a cancerous cell? Mendeley Data; V1, doi: 10.17632/88sws374zh.1.

Sah S.P., Rijal S., Bhadani P.P., Rani S., Koirala S. (2002): Visceral leishmaniasis in two cases of leukaemia. *The Southeast Asian Journal of Tropical Medicine and Public Health*, 33 (1): 25-27.

Sawa T., Ohshima H. (2006): Nitritve DNA damage in inflammation and its possible role in carcinogenesis. *Nitric Oxide*; 14: 91-100.

Sayed E.L-Ahl SA., E.L-Wakil H.S., Kamel NM. Mahmoud MS. (2002): A preliminary study on the relationship between *Trichomonas vaginalis* and cervical cancer in Egyptian woman. *Journal of the Egyptian Society of Parasitology*, 32: 167-178.

Shaw R.J. (2006): Glucose metabolism and cancer. *Current Opinion in Cell Biology*, 18: 598-608.

Shayan P., Rahbari S. (2005): Simultaneous differentiation between *Theileria* spp. and *Babesia* spp. on stained blood smear using PCR. *Parasitology Research*, 97: 281-286.

Shebl F.M., Engels E.A., Goedert J.J. (2012): Opportunistic intestinal infections and the risk of colorectal cancer among people with AIDS. *AIDS Research and Human Retroviruses*, 28: 994-999.

Simon L., Judith F., Aurelie G., Marty P., Pomares C. (2020): Serological diagnosis of *Toxoplasma gondii*: analysis of false-positive IgG results and implications. *Parasites*; 27 (7): 1-9.

Spence M.R., Hollander D.H., Smith J., McCaig L., Swell D. (1980): The clinical and laboratory diagnosis of *Trichomonas vaginalis* infection. *Sexually Transmitted Diseases*, 7: 168-171.

Stark J.R., Judson G., Mucci L.A. (2009): Prospective study of *Trichomonas vaginalis* infection and prostate cancer incidence and mortality: physicians' Health Study. *Journal of the National Cancer Institute*, 101: 1368-1369.

Steer H. *Blastocystis hominis* and colorectal cancer. (2007): Annals of The Royal College of Surgeons of England, 89: 539.

Stensvold C.R., Lewis H.C., Hammerum A.M. (2009): *Blastocystis*: unraveling potential risk factors and clinical significance of a common but neglected parasite. *Epidemiology and Infection*, 137 (11): 1655-1663.

Stripen B. (2013): Time to tackle cryptosporidiosis. *Nature*; 503: 189-191.

Su X.Z., Miller L.H. (2015): The discovery of artemisinin and the Nobel prize in physiology or medicine. *Science*.
China Life Sciences, 58 (11): 1175-1179.
Sucharit P., Uthaischant A., Chintana T., Eamsobhana P., Prasomsitti P. (1979): In vivo and in vitro studies of tinidazole in Trichomonas vaginalis infection. The Southeast Asian Journal of Tropical Medicine and Public Health, 10: 556-561.
Sulzyc–Bielicka V., Kuzna–Grygiel W., Telatynska–Smieszek B. (2007): Cryptosporidiosis in patients with colorectal cancer. Journal of Parasitology, 93: 722-724.
Sundar S., Chakravarty J., Agarwal D. (2010): Single-dose liposomal amphotericin B for visceral leishmaniasis in India. The New England Journal of Medicine, 362 (6): 504-512.
Sutcliffe S., Alderete J.F., Platz E.A. (2009): Trichomonas and subsequent risk of prostate cancer in the prostate cancer prevention trial. International Journal of Cancer, 124: 2082-2087.
Tan K.S. (2008): New insights on classification, identification, and clinical relevance of Blastocystis spp. Clinical Microbiol. Review, 21 (4): 639-665.
Thorley L.D., Deitsch K.W., Duca K.A., Torgbox C., Knoll L. (2016): The link between Plasmodium falciparum malaria and endemic Burkitt’s lymphoma- new insight into a 50-year-old enigma. PLoS Pathogens, 12 (1): e1005331.
Uilenberg G. (2006): Babesia – A historical review. Veterinary Parasitology, 138(1-2): 3-10.
Uilenberg G., Goff W.L. (2006): Polyphasic taxonomy. Annals of the New York Academy of Sciences, 1081: 495.
Van T.H., Brindley P.J., Meyer C.G., Velavan T.P. (2017) Parasite infection, carcinogenesis and human malignancy. Biomedicine; 15: 12-23.
Vannier E., Krause P.J. (2012): Human Babesiosis. The New England Journal of Medicine, 366(25): 2397-2407.
Violetta S.B., Lidia K., Sylvia J., Rogowski W. (2018): Colorectal cancer and Cryptosporidium spp infection. PLoS One;13(4): e0195834.
Woodhall D., Jones J.L., Cantey P.T., Wilkins P.P. (2014): Montgomery SP. Neglected parasitic infections in the United States: Toxoplasmosis. American Journal of Tropical Medicine and Hygiene, 90: 794-799.
Yap E.H, Ho T.H., Singh M. (1995) Serum antibodies to Trichomonas vaginalis in invasive cervical cancer patients. Genitourinary Medicine, 71: 402-404.
Yasunaga J.I., Matsuoka M. (2018) Oncogenic spiral by infectious pathogens: cooperation of multiple factors in cancer development. Cancer Science, 109 (1): 24-32.
Yeung S.J., Pan J., Lee M.H. (2008): Roles of p53, MYC and HIF-1 α in regulating glycolysis- the seventh hallmark of cancer. Cellular and Molecular Life Sciences, 65: 3981-3999.
Yoshikawa H., Yoshida K., Yamanari K., Iwatani S., Kimata I. (2004): Faecal-oral transmission of the cyst form of Blastocystis hominis in rats. Parasitology Research.; 94 (6): 391-396.
Zhang N., Xiuyan Yu., Hongbo Z., Zhang X. (2020): Prevalence and genotyping of Cryptosporidium in gastrointestinal cancer patients. Journal of Cancer, 11 (11): 3334-3339.
Zhang X., Li Q., Hu P., Cheng H., Huang G. (2002): Two case reports of pituitary adenoma associated with Toxoplasma gondii infection. Journal of Clinical Pathology, 55: 965-966.
Zhao R.L., Yan Z.W., Hongbo Z., Zhang X. (2015): Cancer in the parasitic protozoans Trypanosoma brucei and Toxoplasma gondii. PNAS; 112 (29): 8835-8842.