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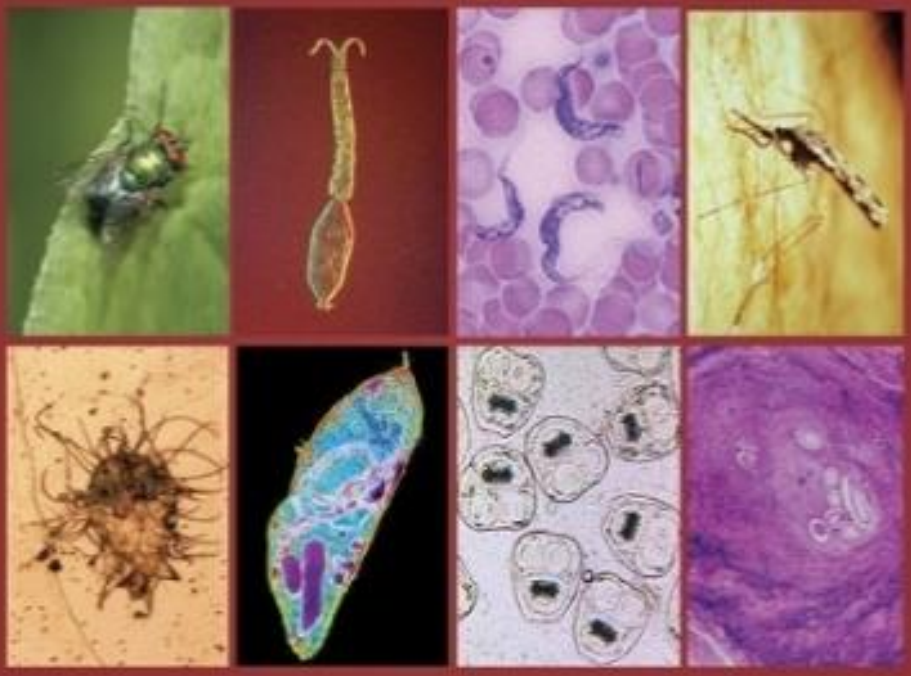

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The Possible Involvement of Protozoans in Causing Cancer in Human

Salim, Mohammad[1]*, Masroor, Mohammad Shahid[2], and Parween, Shagufta[3]

1-S.G.S. Govt P.G. Autonomous College, Sidhi (M.P)

2-People's College of Dental Sciences & Research Center, People's University, Bhopal (M.P.), India

3-Department of Human Anatomy, All India Institute of Medical Sciences (AIIMS), Bhopal (M.P.) India.

E-mail: msaleem195195@gmail.com - mmsid.824@gmail.com - shaggwl88@gmail.com

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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 hominis, 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)[12,13], *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. evanshi* also causes leukemia and hepatocarcinoma in humans (Safaa 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 (Howerth *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 folinic 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 peneumocystosis, 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 asympotomatic 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 adnexitis, 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 antgen-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 nitroimidazoles such as tinidiazole, secnidazole, nimorazole, carnidazole, ornidazole and flunidazole 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 *Babesis 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, Dobbelaere 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 (Dobbelaere 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

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). *C. parvum* resides on gastrointestinal epithelial cells (Plattner and soldati-favre 2008) developing neoplasia including blunting of the intestinal villi, crypt hyperplasia and inflammation (Sulzyc *et al.* 2007, Certaid *et al.* 2010, Benamrouz *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

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