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Research Article

A review on *Toxoplasma gondii* (Nicolle & Manceaux, 1908) (Apicomplexa:Sarcocystidae)

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Abstract **–**In this work, the protozoan of *Toxoplasma gondii* (Nicolle & Manceaux, 1908) (Apicomplexa:Sarcocystidae) is reviewed. *Toxoplasma gondii* is intracellular parasite belonging to the phylum of apicomplexa. It is a common protozoan of warm-blooded animals, and it distributes worldwide, causing infection in eyes' retina, brain and other regions of the body. It has been reported that toxoplasmosis is one of neglected disease by CDC. The first discovery of this intracellular parasite was in 1908, and later in 1957 was detected causing abortion in animal. In 1970, it was the first time for recognizing the life cycle of it, they were found that cats (felids in general) are the final host, and the stage of oocyst is occurring in the stool of infected cats. For prevention, *T.gondii* can be prevented by hygiene, and it considers the only way preventive measure because vaccination technology is not discovered yet for toxoplasmosis prevention in human.

Keywords –Taxoplama Gondii, Parasitology, Biology, Epidemiology, Biogeography

I. INTRODUCTION

Toxoplasma gondii is an obligate protozoan belonging to parasitic microorganisms. It is one of the most common zoonotic agents in humans, infecting one third of the world's population and classified under the phylum of Apicomplexa, which includes intracellular parasites. All the apicomplexan parasites are characterized by having a remarkable polarized cell structure and cytoskeleton complex at their apical part of the cell figure1 [1], [2], [3]. This parasite is worldwide in distribution and the global prevalence rates of this parasite range from 10% to 90% depending on the different variables, which are social habits, climax condition, hygiene, and habitant areas [4], [5]. Furthermore, it is reported as one of the most successful human parasites, and one of the top five neglected parasitic infections because of its considerable public health impact. This parasite can infect all warm-blooded animals, and it is transmitted vertically via the placenta and horizontally via blood transfusion, food or water contaminated oocysts and sexual contact [6], [7]. This parasite, even though, most of its infections are non-symptomatic, can cause various diseases in immune-competent and immunocompromised hosts. It is able to cause serious disease to embryos in pregnant women, resulting in congenital toxoplasmosis with infection in the eye (toxoplasmic retinitis) figure 2 and in the brain of the embryo [8]. It has the most complicated life cycle, figure 3, including wide range of hosts

which act as an intermediate hosts and only one final host (Felis and Lynx genres) where sexual and asexual reproduction of parasite occurs and intermediate hosts where only asexual reproduction occurs. Humans get infected by this parasite when eating vegetables, fruits, or water containing oocysts or eating raw, undercooked meat which is infected with tissue cysts of the parasite. Although T. gondii has a worldwide distribution and possibly the widest host range of any other parasite, it has only one species (T. gondii) in the genus Toxoplasma, and cats are the only definitive host [9], [10], [11]. At present, many studies are conducted in various fields to determine different aspects related to the parasite. For example, studies in epidemiology are conducted to determine the burden of T. gondii's diseases and to recognize the strategies of its control. Other studies are focused on molecular investigation and genotyping of T. gondii strains from both hosts final and intermediate [12], [13]. The purpose of this work is to prepare a review on the different aspects of Toxoplasma gondii and because Toxoplasma gondii is the only identified species, the researchers usually refer to it by the name of genus rather than using the binomial. Thus, the writers of this work will do the similar thing as well.

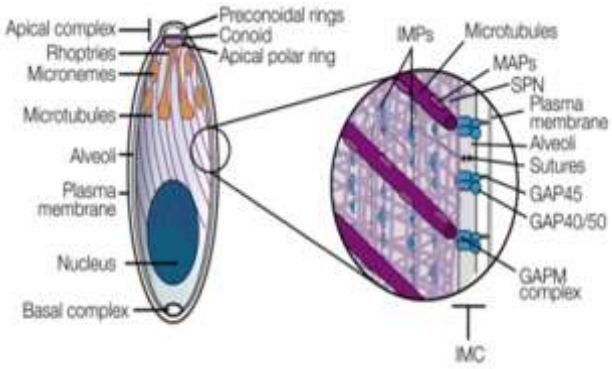

Fig. 1A model apicomplexan, illustrating the structural features.

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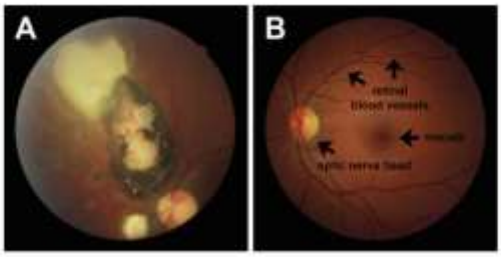

Şekil 1Fig. 2: (a) Clinical photograph taken for eye with active toxoplasmicretinitis, (b) Clinical photograph of a healthy eye.

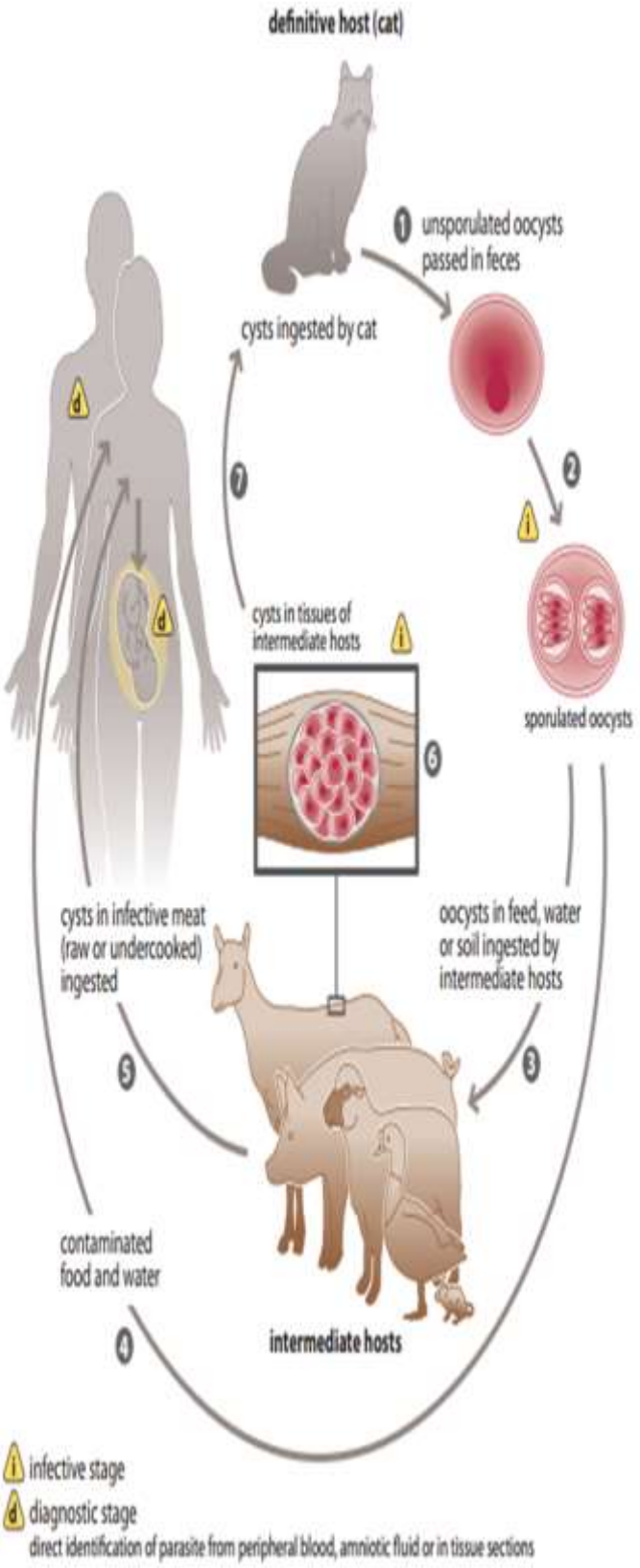

Fig.3 It representsthe life cycle of *Toxoplasma gondii*, illustrating the hosts, the infectious stage and the external environment.

II. *TOXOPLASMA GONDII* (NICOLLE & MANCEAUX, 1908) (APICOMPLEXA:SARCOCYSTIDAE)

A. History

Toxoplasma was discovered at the first time in 1908, approximately 114 years ago by Charles Nicolle, a French Bacteriologist, figure 4, and Louis Herbert Manceaux. They detected it by accident. While they were doing research on the *Leishmania* parasite at the Pasteur Institute in Tunis, they noticed that a protozoan in the tissue of rats. This rat is a North African rat (scientifically, known as *Ctenodactylus gundi*) figure 7. Both of the researchers, firstly, thought the parasite was *leishmania*, but then they realized that they had acknowledged a different living organism. They gave it the name "*Toxoplasma gondii*" based on the shape of the parasite (*toxo*= bow, *plasma* =life and the *gundi* is the species of rat host). Undoubtedly, the correct name should have been *Toxoplasma gundi*; however, Nicolle and Manceaux had wrongly recognized the species of rat as *Ctenodactylus gondii* so the parasite had been titled by this designed name"*Toxoplasma gondii*". Meanwhile, in 1908, another parasitologist, Splendore, figure 5, found the same morphological shape of parasites in rabbits in Brazil. Splendore identified it mistakenly as the *Leishmania* parasite, but he did not give it a name [14], [15]. *Ctenodactylus gundi* was already discovered by Chatton and LeBlanc in 1901. It had been noticed that *Ctenodactylus gundi*, which habitat in the mountains of Tunisia, were not normally infected by *Toxoplasma*, and it had been theorized that the infection was occurred in the laboratory, where Nicolle and Manceaux were conducting their experiments for *leishmania*was found in the blood and liver of the*Ctenodactylus gundi* rat, so they suspected that the rat had gotten infected at the institute by the bite of an insect. Many studies have conducted in Tunis and the US trying on arthropod transmission, but the attempts were unsuccessful. An intention in human infections started in 1923 when *Toxoplasma* was described in the eye's retina of a hydrocephalic child figure 6, and in congenital toxoplsamosis case. Later, during the following 5 years, Albert Sabin in collaboration with Henry Feldman created a serological "dye test" for toxoplasmosis infection in human. This method had been used worldwide to detect toxoplasmosis human infection. Sabin and Olistsky were the first who are isolated the viable. Hence, the first isolation was done by them in 1937 [13], [16], [17].

Fig. 4Charles Nicolle (1866-1936)

Fig. 5 Splendore (1871-1953).

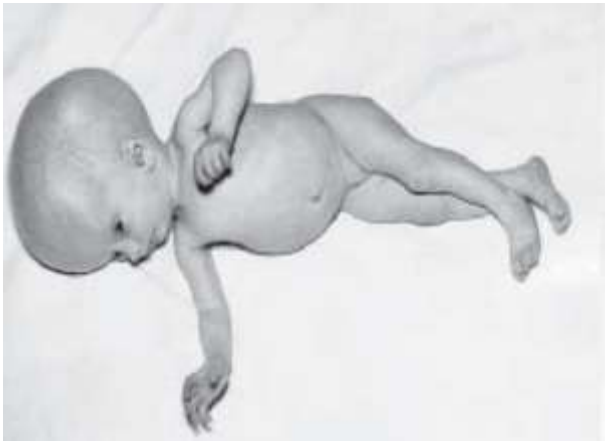

Fig.6 Girl with hydrocephalus due to congenital toxoplasmosis.
Source:https://www.researchgate.net/publication/318338943.

March 1939, Wolf et al. published an article in a science journal that showed the first demonstration of toxoplasmosis in humans and the first description of human toxoplasmosis transmission

to animals in the laboratory. They reported that the child (infant) at three days of age had symptoms, including irregular reddish-brown areas in each macular area and other symptoms in the respiratory and nervous systems. The child died at the age of 31 days. An autopsy has been taken from the dead child by Wolf et al. and investigated. It has been noticed that the agent was a protozoan that morphologically identical with Toxoplasma, and this was the first isolation of Toxoplasma from humans. Furthermore, those researchers, Wolf et al. removed fresh tissue from infant lesions and then inoculated rabbits, rats, and mice. The researchers observed those experimentally inoculated animals become ill and showed lesions and agents like those seen in infant toxoplasmosis [18]. Also, before the results of Wolf et al., Sabin and Olisky suggested that one method of natural spreading of Toxoplasma might be by Toxoplasma–contaminated tissue, and then, between 1940s and 1950s, Toxoplasma was illustrated to be involved in inflammation of the eye [19], [20]. In the early 1950s, a kind of glandular toxoplasmosis was reported in which few parasites were associated with these granules in lymph nodes [21]. Also, in the early 1950, a question is being raised about how many of humans and animals are becoming infected with this parasite? Therefore, numerous studies were conducted to show the vector, however, they were unhelpful [22].

In 1960, it has been shown that bradyzoites in tissue cyst have tolerance against acid and trypsin confirming the proper role of ingestion of tissue cyst in meat in parasite transmission [23]. Regarding the identification of the final host was by groups in the USA, UK, Germany, and Holland, ultimately the complete life cycle for Toxoplasmahad been identified the cat as the final host and animals having the ability to be an intermediate host. It has been almost 60 years since Toxoplasma discovering, and the complete life cycle was finally explained. Corresponding with the discovering of the life cycle in 1960, electron microscopy was developing as new technology, and it is used by parasitologists to identify the structure of stages of Toxoplasma [24].The identification of Toxoplasma as a human pathogen increased during the 1970s with immunosuppressants and certainneoplastic disease treatments [25], [26]. Between 1980 and 2007, corresponding to the developments of molecular technologies and the availability of useful reagents, a lot of detailed information on all aspects of the biology of the parasite and its interrelationship with its host cells have been introduced as well as the biological behaviour of the parasite in both intermediate and final hosts has attracted the researchers. As a result, there have been huge advances in the understanding of humantoxoplasmosisand the immune response to it [22]. Recently, the researchers who are interested in Toxoplasma search focus mostly their work on the behaviour biology of the parasite in both intermediate and final hosts. Also, the proteomics and other omes are taken the highest efforts of the researchers, as well. Many published articles about the proteomics of the different structure of this parasite and the roles of structures in its parasitism and its treatment have been conducted in order to open the new doors for treatment, vaccination, and prevention [27].

Table 1. The first major events in *Toxoplaxma gondii*identification.

Year	Event	Scientists
1908	First time of discovering it in the rat.	Charles Nicolle and Louis Manceax.
1908	Describing the same morphological shape in rabbits	Splendor.
1937	First isolation of viable *Toxoplasma* from animal.	Sabin and Olistsky
1939	First isolation from human, and first discribtion of its transmission from human to animal in the lab.	Wolf *et al.*

B. Biology & Morphology

Stages of parasite: there are two stages of toxoplasma which occur in infected human, other mammAalian and avian hosts which are tachyzoites the tissue cyst, which contains bradyzoites, and the tachyzoite. One otherstage occurs in final host called oocyst, which releases sporozoites.

Oocyst stage: it is created in the epithelial cells of intestine from sexual reproduction in the epithelial cells of intestine of definitive host and then excreted in faeces. This stage has a great in maintaining Toxoplasma infections, which was suggested by early studies showing that Toxoplasma infection was absent in islands without cats. Oocysts are difficult to inactivate or remove from contaminated soils, and waters. Oocysts can survive for months, possibly years in moist soils and fresh and marine waters under various temperatures (−20 to +37 °C), and salinity conditions up to 15 ppt. (parts per thousand). This allows them to be transmitted to numerous host species living in different terrestrial and aquatic environments, including marine biotopes. Only higher temperatures (> 45 °C) and desiccation can decrease oocyst viability in natural settings. Moreover, oocysts are resistant to chemical inactivation agents, especially strong acids, detergents, and disinfectants such as household bleach or gaseous chlorine and ozone treatments used by the water industry. Actually, only heating above 60 °C can lead to the rapid killing of the oocysts. The oocyst and sporocystwalls, figure 7, are the key structures that provide mechanical and chemical protection to the sporozoites until their release in the host digestive tract targeting these walls could be critical for control of Toxoplasma infections in humans and animals. The cat is normally infected by ingesting tissue cysts present in the tissue of a chronically infected intermediate host (rodent/bird) [28], [39].

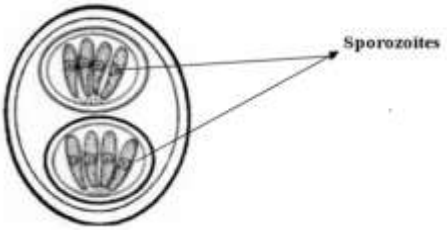

Fig. 7 Sporulated oocyst.

Bradyzoites: they occurs inside of cysts of tissue figure 8.a.. The term ‘‘bradyzoite’’ (Gr. brady = slow) was proposed by Frenkel to describe the stage existed in tissues. Bradyzoites are also known as cystozoites, and, then, in 1988 it isproposed that cysts should be called tissue cysts to avoid confusion with other terms including oocysts and pseudocysts. When the parasites unleashed in the intestine, invade the the cells of intestine and initiate coccidian development, which includes many rounds of asexual replication prior to differentiating into “female” macrogametes or flagellated (motile) “male” microgametes. It is reported that tissue cysts were shown to be important in the life cycle of *Toxoplasma*because eating meat-hosts can become infected by ingesting infected meat [30], [31].

Tachyzoite: it is the most uncomplicated form in the *Toxoplasma’*s life cycle regarding its studying *in vitro* and *in vivo*. The researcher can get a huge number either cultivate them in culture or in animal. Tachyzoites have crescent shaped cells with size of 2 × 7 μm, and they have slightly sharpened anterior end. The anterior end determined according to the direction of cell’s mortality figure 8.b. . They are made up of a striking cytoskeleton, which constitutes of two apical bodies located under the plasma membrane at the apical tip of the parasite. Moreover, it has the secretary organelles, endosymbiontic organelles which include mitochondrion and apicoplast, and the other organelles of eukaryotic cells. All these are enclosed by membranous structure called the pellicle. Transmission to humans by tissue cysts is relatively easy to control by good hygiene and proper cooking of meat. Acute infection happens in the beginning of infection, with the rapidly growing reproduction of the tachyzoites. Tachyzoites change to bradyzoites, andas long as time passes, the tissue cysts will be parasitizing in host cells.

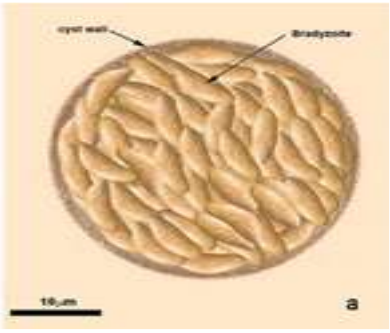

Fig. 8 (a)Tissue cyst contains many of bradyzoite.

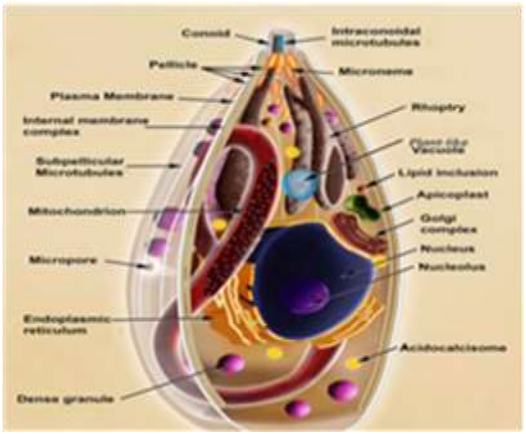

Fig. 8. (b) Longitudinal section view of the tachyzoite form of*Toxoplasma gondii*.

It would be lethal in *Toxoplasma* infected immune-compromised patients if bradyzoites returned to tachyzoites [32], [33].

Mechanism of cell invasion: *Toxoplasma* is not like *Leishmania* and Plasmodium penetrating specific cell types, but it can invade almost all cell types. *Toxoplasma* can invade and multiply in any nucleated cell of mammalian and avian hosts. This parasite uses the cytoskeleton of cells to facilities its invasion of its host cell. The invasion process by *Toxoplasma* is considered a rapid process, ideally can be completed in less than one minute. This process is done through three steps, gliding motility, host cell attachment, and active penetration. Host cell penetration is basically relying on regulated secretion of adhesive proteins secreting from the apical complex such as micronemes and rhoptries and the power of gliding motility by actin –myosin motor complex [14]. The invasion process also relies on host cell cytoskeleton which is regulated by the parasite itself during parasitism [35]. Bradyzoites form inside host cell is remarkably rapidly multiplying which is causing for most cytopathology, and tissue destruction. Bradyzoites grow only intracellularly by sequential division in tow (endodyogeny) within a parasitophorous vacuole in nucleated cells which ultimately carry 8-32 of tachzoites. After the death of infected host cell, tachzoites penetrate other cells and resume rapid multiplication. With the response of immune system, tachzoites multiplication decrease and another form, bradyzotes, become progressively more numerous. Conversely, in humans with AIDS, or in patients treated with corticosteroids, or in other immunodepressed states, bradyzoites transform into tachyzoites resuming active multiplication inside the host cell [22], [13], [35].

C. Geographical Distrbution and Epidemiology

Toxoplasmagondii is intracellular protozoan that has a worldwide distribution, and it is estimated that that the third of the world's human population is infected by *Toxoplasma*. However, few descriptions of genetic diversity are available. Indeed, it is reported that the identification of genetic diversity in each area of the world could be valuable in developing strategies for treatment and vaccination. According to the results of research done by Hosseini and others that the genotype profiled of *Toxoplasmagondii* isolates is different throughout the world. The strain in Asia and Africa countries are characterized by low genetic diversity while in north and SouthAmerica a wide diversity of the parasite found and might be higher in the countries without any data such as Australia and Western Asia. Community of research described this parasite as one of the most successful human protozoans due to its ability to infect all the warm-blooded animals, human included and despite of that it exists in one species "*gondii*". Furthermore, regarding of *Toxoplasma*'s ability to cause severe illness, being high incidence, and being potential for prevention, the centers of control diseases have prioritized *Toxoplasma* as one of the top five neglected parasitic infections [1], [36]. The infection occurs in all ages, and it is increased with age and it does not vary greatly between males and females [37]. The disease caused is called toxoplasmosis, and it manifests a wide variety of clinical manifestation in human beings from abortion to fatal encephalitis [38]. In the respect of that most of toxoplasmosis is an asymptomatic infection, a few are virulent, and it results in a fatal toxoplasmosis. The prevalence of infection in human vary around the world based on many sociogeographical factors, including, climate factors, many researchers have reported that arid environment affect negatively on the vital survival of oocyst in environment, the infection of consumed meat, dietary habits (the way of meat cooking, hand washing, kind of meat or vegetables consumed, economic, social, or cultural habits, and quality of water,..etc). However, felinesis considered the most important factor in the epidemiology and the distribution of this parasite.

Humans acquire the infection by horizontal transmission of either tissue cyst in consuming infected meat or oocyst in contaminated food or water which derived from the environment or directly from final host (feline) faces, figure 9, is shown the important sources of how human become infected by *Toxoplasma*. *Toxoplasma* infection in animals has been described for more than 350 host's species, mammals and birds, with vast majority of them living in wild environment. The contamination of environment and the infection of intermediate hosts is due the shedding of oocysts either by wild felid species or by domestic cat. The average of *Toxoplasma*seroprevalence is very high and may reach 100% particularly in wild animals. The seroprevalence of *Toxoplasma* in intermediate hosts depends on oocyst producing from final host in their environment. Regarding the development of infection in animals, the processes of infection is complex and result from combination of the interactions among physical, biological, and ecological factors, which are including: (1) climate factor, the areas where the dry and hot climates are not favorable for the survive of infective stage (oocyst), conversely, the areas where the humid tropical climates, the infection is at its highest, (2) the degree of responsiveness of intermediate hosts to *Toxoplasma* infection, and (3) the kind of the food that the hosts consume. Indeed, the infection is lower in animals which eat herbs than in other animals which feed on meat [39], [36].

regional and seasonal variations of infection, and diagnostic efficacy of various assays used in

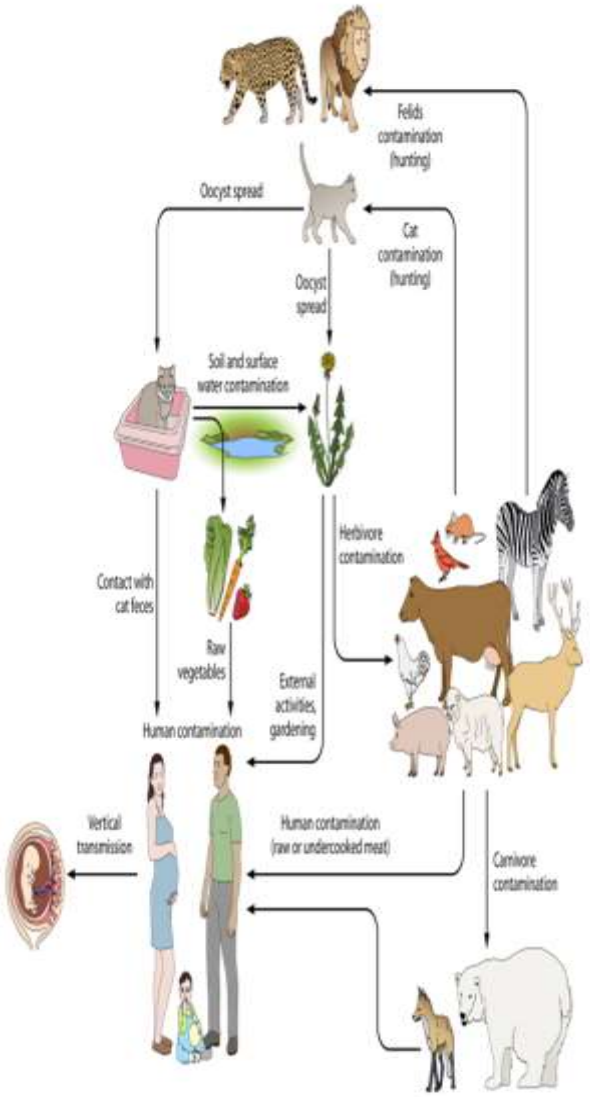

Fig. 9 Sources of *Toxoplasma* infection in humans. The various sources for human infection arerepresented.

III. Conclusion

Toxoplasma gondii was discovered 114 years ago, making it relatively newer compared to other protozoa in the field of medical parasitology [14]. However, numerous experimental studies have been conducted to understand its capability of causing different diseases in humans and to develop vaccines and successful prevention policies. Moreover, several epidemiological studies have been undertaken to recognize the burden of toxoplasmosis and determine the most effective ways to control it. The experimental studies have led to its recognition as a model organism for investigating host and pathogen interactions, while the epidemiological studies provide crucial information about the geographical distribution, clinical laboratories. The key structure, walls of oocysts, provide *Toxoplasma* with advantages that enable it to survive for long periods outside hosts [28]. Due to its ability to invade all types of host cells, *Toxoplasma* has been described by parasitologists as a successful parasite. Currently, chronic toxoplasmosis is aiding researchers in studying the parasite's effect on human behaviour. Integrating clinical and experimental data on this parasite will lead to understanding important insights about how causative agents evolve into successful parasites.

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