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An overview on trematodes developing disease complications causing cancer in human

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

[1] *Sanjay Gandhi Smriti Govt. Autonomous P.G. College, Sidhi, A.P.S. University, Rewa (M.P.), India.*
[2] *People's College of Dental Sciences & Research Center, People's University, Bhopal (M.P.), India.*
[3] *Dept. Of Human Anatomy, All India Institute of Medical sciences (AIIMS), Bhopal (M.P.) India.*

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Abstract

This is very surprising for us that still most of the peoples are not mentally prepared to accept the fact that some of the human cancers are caused by certain bacteria, viruses, fungi and some of the photosynthetic microorganisms. And, this is found again very shocking if the causal organisms are the worms. A variety of human trematodes developed several fatal diseases like urinary and biliary interruptions, high grade jaundice and even stone formation in human if not treated well within time. Similarly, *Schistosoma haematobium* causes bladder cancer and *Opisthorchis viverrini* and *Clonorchis sinensis* developed cholangiocarcinoma. The present review deals with the study of certain trematodes parasitizing in human developing disease complications causing cancer. And, this is carried out with the help of recent researches done so far in the field of human helminthic oncology and parasitology

Keywords: Human helminths; Trematodes; Flatworms; Flukes; Diseases; Cancer in human

1. Introduction

Helminths are a group of worms simply categorizing into nematodes, trematodes and cystodes. Trematodes are globally distributed in different parts of the world being easily transmitted via contaminated soil and water and their respective hosts. They are the kind of animals having no spinal cord but the specific oral organs to suck the food. Trematodes are caused by the trematodes like *Schistosoma haematobium*, a blood fluke causing schistosomiasis (human bladder cancer) ; *Clonorchis sinensis*, a Chinese liver fluke causing fish borne human cholangiocarcinoma; *Opisthorchis viverrini*, a southeast Asian liver fluke causing opisthorchiasis or human cholangiocarcinoma; *Fasciola hepatica,* a sheep and cattle liver fluke causing human fasciliasis; *Fasciolopsis buski,* an intestinal pig fluke causing human fasciolopsiasis and *Paragonimus westermani*, an eastern Asian lung fluke causing human paragoniasis [1-12]. The above-mentioned flatworms and flukes are important as they cause various diseases and cancer in human. Therefore, these worms are being discussed in the present review in the light of recent researches done so far in the field of helminthology.

2. Discussion

The review discusses the kind of helminths involved in producing cancers in human. Trematodes are found in humans as parasites disseminated in various body parts developing diseases, malignancies and cancer. The following discussion on certain trematodes causing cancer is a part of helminthic parasitology describing their mode of action of developing cancer in human [13-15].

* Corresponding author: Mohammad Salim
Sanjay Gandhi Smriti Govt. Autonomous P.G. College, Sidhi, A.P.S. University, Rewa (M.P.), India

2.1. *Schistosoma haematobium* (Schistosomiasis)

Schistosoma haematobium develops schistosomiasis or bilharzia in human. This is a kind of digenetic trematode, urinary bladder, blood fluke infection of developing countries in Africa, South America the Caribbean, the Middle East and Asia. The disease is more prevalent in Africa and Middle East but occasionally seen in Western Asia. Countrywise this is more common in Egypt, China, Zimbabwe, Iraq and Sudan. Nearly, 2 lac deaths occur every year due to schistosomiasis worldwide. This is spread by the exposure of contaminated water having parasites. The infective cercariae are free swimming [16-24].

In 1851, Theodor Maximillian Bilharz, a German physician and pathologist discovered a parasite while working at Kasr El- Eini hospital in Cairo. Thus bilharzia or bilharziasis is named after Theodar Bilharz. Lateron, in 1915 Lieper, an English scientist discovered the intermediate host as snail, the Bulinus [25-27].

The parasites entered in the human body either by the larvae released by the fresh water snail or the ingestion of eggs contaminated water mixed with the human feces. There are two main types as intestinal and urinogenital schistosomiasis found in humans with five species involved. They are *Schistosoma haematobium, S. mansoni, S. japonicum, S. mekongi* and *S. guineensis. S. haematobium* is a human bladder worm [7,22,23,28].

Swimmers itch or popular itchy skin rash appears at the site of initial infection which is lasted in about 4 days. After one to two months the infected individual may present fever, enlarged spleen, liver and lymph nodes. Eosinophilia and some pulmonary symptoms may also occur. Either larvae or eggs entered in the human body develop into the adult schistosomes. It is the only blood fluke that infects the urinary bladder causing bladder cancer in human. The parasite is dioecious and male kept the female in their gynaecophoric canal as their life partner. Females are quite larger than males but slender and smooth fully adjustable in the male canal. The female only leaves the male briefly for laying eggs either in intestine or urinary bladder. An adult female produces 1000 eggs per day through out their life and the average lifespan of a parasite is about 3 to 4 years. These embryonated eggs penetrate the bladder mucosa to form tumor either benign or malignant. [28-31].

Urinary tract infections are a frequent complications of urinary tract dysfunctions caused by the *S. haematobium*. The infection may lead to extraurinary complications, popularly known as the Bilharzial cor pulmonale. They are frequent urination often associated with hematuria, painful and difficult micturition (dysuria), discomfort in the groin, obstructive uropathy and kidney failure due to bacterial infections. As the disease was very common in Egypt, the ancient Egyptians believed the passing of blood from urine was a good sign of puberty as male menstruation equivalent to menstrual cycle often occurring in females. [36-37].

S*chistosoma haematobium* has been categorized in Group 1 carcinogenic microorganisms as the agents definitely carcinogenic to humans by the IARC, 2011[38, 39]. Around the world about 3 % of all urinary bladder cancers are caused by the *S. haematobium.* It causes inflammation, ulceration, cell proliferations, fibrosis and [40]. As a consequence, most people suffering from chronic schistosomiasis and bladder cancer develop squamous cell carcinoma [41]. This is prevalent in areas of Egypt, Iraq, Zambia, Malawi and Kuwait [42].

During the development of cancer, nitrosamines are produced by *S. haematobium.* It has been proved experimentally that the nitrosamines in association with *S. haematobium* produces neoplastic changes in baboons [43,44]. Similarly, some other changes also occur during the course of cancer development in patients suffering from schistosomal infections described as under:

- Reactive oxygen species (ROS) and inflammatory cells like increased levels of eosinophils are found frequently in the patients suffering from schistosomiasis [45,46].
- Mutation in tumor suppressor gene p53 and that production of oncoproteins such as Bcl-2 have been noted in patients suffering from schistosomiasis [42,46,47].
- Schistosomiasis bladder cancer samples have more genes methylated with increased levels of O6-methyldeoxyguanosine due to DNA alkylation causing DNA breaks [44,48-50].

Further, the other species of *Schistosoma* has not been authentically reported as cancer causing microorganisms. However, there are some reports as *S. mansoni* is linked with liver, colorectal and prostate cancer [46]. And, the role of *S. japonicum* in the development of cancer is also not very clear but seems to be associated with both liver and colorectal cancer [19].

Diagnosis with the help of microscopic techniques, rapid diagnostic tests for antigen detection, urine reagent strips and PCR assays are conducted. The drug of choice is a quinolone derivative as praziquantel. However, the efficacy of the drug is only 82 to 88 %. Human and bovine vaccines to control the schistosomiasis are in various stages of development [35,51-58].

2.2. *Opisthorchis viverrini* (Opisthorchiasis and Cholangiocarcinoma)

Opisthorchis viverrini is a zoonotic fish worm, popularly known as the Asian liver fluke causing opisthorchiasis and cholangiocarcinoma (CCA), a cancer of the bile duct in humans. While the same parasite was discovered by Poirier in 1886 from an Indian fishing cat (*Prionailurus viverrus*), the first human case was discovered by Lieper in 1995. The International Agency for Research on cancer has categorized the *O. viverrini* as a Group 1 biological carcinogen in 2009. This is mostly found in Thailand, Laos, Vietnam and Combodia. Nearly, 10 % of the Thai populations are infected with the cholangiocarcinoma. [1, 10, 59-67].

The definitive hosts are humans and other pisciovorous vertebrate animals like dogs, cats, rats and pigs. Similarly, snails of the species *Bithnia* and the Indian cat fishes are the first and second intermediate hosts of the disease respectively. A human body is a reservoir of the parasite where sexual reproduction occurs. The eggs thus produced and released contaminate the fresh water bodies infecting the fishes and snails. The raw fishes when consumed repeat the cycle again. The raw fish dishes are very common in countries where opisthorchiasis occurs. [1, 68, 69].

Further, the adult worms found in upper small intestine ultimately reach the biliary tree where they sexually mature developing cancer of the bile duct. Sometimes, these adult worms are also found in gall bladder and pancreatic duct. The infective eggs are discharged through the bile juice in small intestine and finally released via feces in the environment. The average lifespan of an adult worm is 25 years. [68-71].

The initial clinical symptoms of the disease are either asymptomatic or mild as dyspepsia, anorexia, constipation abdominal pain, diarrhoea, edema in legs, ascites and eosinophilia. But in severe infection it may cause enlarged non-functional gall bladder, hepatomegaly, cholangitis, cholecystitis and cholangiocarcinoma. Further, as the disease is not a life threatening one initially, chronic infection may only lead to bile duct cancer after 30 to 40 years. Similarly, its ability to cause cancer is further worsened as the infection has been found to be associated with *Helicobacter pylori* causing simultaneously stomach ulcer and cancer [60,62,63,70-72].

The disease is diagnosed by detecting the eggs in feces using the Kato technique. However, more sensitive tests are also available like ELISA and PCR. Proper cooking of fishes is the only way to prevent the disease properly. Currently, there is no approved drug for the infection, however, the drugs like praziquantel, albendazole, tribendinidine, artimisinin and miltefosine are in practice [73-77].

2.3. *Clonorchis sinensis* (Chlonorchiasis)

Clonorchis sinensis is a Chinese liver fluke, which infects the fish-eating mammals like dogs, cats, rats, pigs, camels, buffaloes including humans. Humans have been found as the definitive host of the parasite. Kobayashi and Masatomo Moto in 1911 and 1918 discovered snail and fishes as their first and second intermediate hosts respectively. The International Agency for Research on Cancer has classified the *Clonorchis sinensis* as potent biological carcinogen in Group 1 in 2009. It causes bile duct cancer in human and has been found to be the third- most prevalent parasitic worm globally. This is most prevalent in Russia, Japan, China, Taiwan, Korea and Vietnam [78-82].

The parasite was discovered by a British physician Jame McConnell in 1874 while working at Medical College Hospital in Kolkata. He saw the swollen liver with distended and blocked bile ducts by black vermicular bodies in Chinese carpenter during the course of his post martem. He then published his observations in a journal named as “Lancet” in August 1875. In 1907, Arther Looss gave the name *Clonorchis sinensis*, a genus different from *Opisthorchis viverrine* [78].

Clonorchiasis is a kind of disease developed in human caused by the *Clonorchis sinensis*. The parasite while feeding on bile infects the common bile duct and gall bladder developing biliary inflammation, bile duct obstruction, periductal fibrosis, cholangiocarcinoma, liver abscess and hepatic carcinoma. The clinical symptoms of the disease are indigestion, intermittent obstruction of the bile ducts, cholangitis, gall bladder stone, abdominal discomfort, nausea, vomiting, diarrhoea, anorexia, weight loss and jaundice. [9,80,82,83].

This is a flattened, dorsiventral, leaf shaped liver fluke measuring about 15 to 20 mm in length. It has got oral sucker at the anterior end acting as mouth. As this is a hermaphroditic animal it contains both male and female reproductive organs. A single rounded ovary with two highly branched testes are found at the posterior end. A common genital pore

well connected with the uterus from the ovary and seminal ducts from the testes is found. The eggs are quite similar to *Opisthorchis viverrini* and *O. felineus* are difficult to distinguish [84-85].

The eggs are released via the biliary tract and excreted out along with the human feces. The miracidial larva developed inside the fertilized egg is usually visible. Upon development these larvae are sedimented in water and simply being eaten by the snails. After ingestion by snails, the miracidial larvae hatched from the eggs, reach the digestive gland via penetrating the intestinal wall where carcarian larvae are formed by metamorphosis. These larvae now leaves the body of snail to find out the secondary intermediate host as fish. However, since this is a non- feeding stage, if they do not find fish die within 2 to 3 days [1,84,86].

Further, within an hour of larval penetration in fishes, the cysts are formed and the larvae became metacercariae. Humans are infected when undercooked or raw fishes are eaten. These cysts are digested in stomach with the help of gastric juices. The free larvae reached the bile duct through intestinal mucosa after penetration. They keep on feeding bile to mature within a month. Also, they start laying eggs to repeat the cycle again. An adult fluke feeding on bile can live in the ducts on an average 30 years without any clear symptoms appeared [82,85,86].

The diagnosis is done by detecting the eggs in feces and duodenal aspirate by formaline- ether concentration technique (FECT) and Kato- Katz method. However, the serological test like ELISA is also available to distinguish the eggs from *Opisthorchis viverrini* and *O. felineus*. Similarly, to detect the biliary cirrhosis CT scan, ultrasound or MRI are also conducted. The drugs used to treat the infection are albendazole, praziquantel, triclabendazole, bithionol and levamisole [82,87-90].

2.4. *Paragonimus wastermani* (Paragonimiasis)

Paragonimus wastermani is also called as the Japanese lung fluke or oriental lung fluke that infects humans developing paragonimiasis. This is prevalent in Far East Asian countries like China, Taiwan, Japan, Philippines, India, Mangolia, North and South Korea and South America. *P. wastermani* is named after Pieter Wasterman, a zookeeper who noted the fluke in a Bengal tiger. It was discovered by Coenraad kerbert in 1879. Similarly, the first human infection was recognized from Taiwan in 1879. This is a crabfish borne disease developing lung inflammations in human. The domestic cat is a good reservoir of a variety of lung flatworms transmitting in humans [91-96].

P. wastermani is an hermaphroditic animal. Like other trematodes it has also got oral and ventral suckers. Adult flukes are reddish- brown in colour measuring about 7 to 16 mm and ovoid in shape. Unembryonated eggs are released in the sputum or feces of human, felines and cats, pigs or dogs. Miracidia developed inside the eggs hatched after two weeks. They then penetrate the snails to form many daughter redie which shed crawling cercariae into fresh water. These crawling cercariae penetrate the crabs encysting in muscles becoming metacercaria. Humans and felines eating the crabfishes are infected by the metacercaria released from cysts. They penetrate the intestinal wall to reach the lungs where they mature into an adult worm [97-99].

Paragonimiasis can cause illness like pneumonia or stomach flu. The usual clinical symptoms of the pulmonary paragonimiasis are intermittent cough, expectoration of discolored reddish- brown mucus on cough, fever, bronchitis, hemoptysis, dyspnea on exertion, skin rashes and urticaria, abdominal pain, diarrhoea and the chest radiographic abnormalities. The incubation period of the disease is nearly 3 months and the disease may persist in humans for over 20 years. [93,98,100].

The worm stimulates an inflammatory response in lungs allowing it to form capsule. These capsules ulcerate and heal over time mimicking as tuberculosis. Then most common cause of hemoptysis worldwide has always been either tuberculosis or paragonimiasis. Sometimes, pleural paragonimiasis may also occur where there is frequently no cough and the ova are not split out in the sputum developing pleural effusion misdiagnosed as isolated tuberculosis. In addition, very rarely, extra pulmonary paragonimiasis is seen in which these worms are disseminated either in the spinal cord or heart developing paralysis and death respectively. In addition, it can also affect the liver, spleen, breast, abdomen, skin and brain. [8,93,98,101,102,103].

The detection of eggs in stool, sputum, CSF or in lung effusion fluid may demonstrate the presence of the disease. Ziehl-Neelson staining and needle aspiration cytology are useful tools for the same purposes [104-107]. However, the detection of antibodies in blood are helpful in confirming the disease. Various techniques like ELISA, PCR and immunoblot can also be helpful to differentiate the paragonimiasis from [108-110].

Paragonimiasis is rare in the United States but common in Asia. Humans are more commonly infected by eating raw undercooked salted or pickled freshwater crabs or crayfishes containing cysts. Proper cooking of crabs or crayfishes before eating can only control and prevent the infection properly. Praziquantel is a drug of choice for physicians. Bithinol is also used with some side effects as skin rashes and urticaria. Some other specific medications with the high cure rates using under strict medical supervision are also available as niclofan and triclabendazole [10,111-113].

2.5. *Fasciola hepatica* (Fascioliasis)

Fasciola hepatica is a common liver fluke or sheep liver fluke. Although, the human fascioliasis is distributed worldwide, this is infrequently found in India making it an incidental host. This is one of the largest leaf shaped liver flukes parasitizing in liver and bile duct and can be visualized with the naked eyes. Fascioliasis is caused by the two species of digenetic trematodes named as *Fasciola hepatica* and *Fasciola gigantica*. Both of them cause similar diseases in human. *F. hepatica* lives in the liver of definitive hosts like sheep, goat, cows, buffaloes and human, their intermediate host is air breathing snail. They are hermaphrodites having both male and female reproductive organs reproducing either sexually or asexually. Similarly, they have got small but a powerful oral sucker. [114-116]

The entered eggs in snail developed in cercaries which are encysted to become metacercariae and released to adhere on aquatic vegetation. Herbivorous animals are infected by eating the contaminated vegetation. Similarly, the humans are also infected either by the consumption of contaminated freshwater plants especially the watercress or by the consumption of undercooked or raw liver. After ingestion, these metacercariae encysts in the duodenum and migrated into the biliary ducts through the intestinal wall, the peritoneal cavity and the liver parenchyma. In human, the time taken a fluke to mature in an adult is about 3 to 4 months. An adult fluke produces 25000 eggs per day. These eggs are passed out through feces contaminating the water and infecting the snails to repeat the cycle again. [117,118]

The usual clinical symptoms of the disease are nausea, vomiting, intermittent fever with extreme abdominal pain in epigastrium or right hypochondrium. Since, the humans adapted as a definitive hosts some ectopic infections like "Halzoun" may occur. This is a kind of buccopharyngeal infection where the *Fasciola* worms are attached in the buccopharyngeal mucosa by their suckers causing edema of the soft palate, pharynx and larynx. Some other ectopic infections may also occur as in lungs and subcutaneous tissues in the form of skin rashes and urticaria. Severe infections can develop dysphagia, pharyngitis, hepatitis, cholangitis, pancreatitis and the feeling of airways obstruction possibly due to the foreign bodies in the throat. [116,119]

Chronic phase occurs when the worms mature in the bile duct causing rupture of the liver capsule into the peritoneal cavity developing peritonitis (Almendras *et al.* 1997) [120]. While fibrosis and the chronic inflammations are usually concerned with the development of cancer, this is still found unclear whether *Fasciola* is associated with the increased risk of cancer. There are evidences of an association between *Fasciola* infection with liver fibrosis and cirrhosis but very little is known about causing cancer. [121-122]

Further, stool microscopy is not very useful as the eggs can be detected only after 2 months of infection. However, ELISA and western blot tests are specific. X rays may show the liver abscess. Ultrasound may also show the adult worm's inhabitating in specific organs. Similarly, cholangiography may reveal mulberry like multiple cystic dilatations of the ducts. Suergeries are sometimes helpful. Triclabendzole is the drug of choice and found to be very effective. Praziquantel is not effective. Bithionol is moderately effective but has more side effects. Similarly, nitazoxanide is effective but not recently recommended by the physicians due to certain reasons. [114,123-128]

2.6. *Fasciolopsis buski* (Fasciolopsiasis)

Fasciolopsis is an intestinal giant fluke of about 7.5 cm long with the only one species recognized as *Fasciolopsis buski* parasitizing in human. This is a very common and the largest known fluke parasite of human. The other known mammalian host is pig. In London, George Busk isolated the pathogen in 1843 from duodenum of a sailor. *Fasciolopsis buski,* the only species was named after the discoverer. The entire life cycle was studied and published by Barlow Claude Herman in 1925. The disease is endemic in China, Taiwan, Indonesia, Japan and Malaysia. The disease is also found in Thailand and Bangladesh. This is now known to be a common intestinal parasite of humans and pigs in India especially in Bihar and Uttar Pradesh [115,129-133].

F. buski is a hermaphroditic animal producing more than 25000 eggs per day. These unembryonated eggs are discharged in the intestine and released via feces. The infective miracidia are developed in eggs in about 7 to 9 weeks to infect snails. Ultimately, after several developmental stages as sporocysts and rediae, the cercarie are released from snails to encyst as metacercarie on aquatic vegetations like lotus, water chestnut, water spinach, water caltrop and bamboo. Humans and pigs are infected when these vegetations are ingested by them. They excyst in the duodenum to attach in

the intestinal wall. They are developed in adults in about 3 months. The average life span of an adult worm is about a year. [115, 132, 134-137].

Further, light infections are usually asymptomatic. However, severe infections may cause diarrhoea, abdominal pain, biliary and intestinal obstruction with perforatios, ascites and appendicitis. The allergic reactions caused by the absorption of allergic metabolites released by the pathogen developed lethal consequences in an individual. The diagnosis is based on the detection of eggs in feces or vomitus. Surgical intervention for *Fasciolopsis buski* infection is also performed. Praziquantel is a drug of choice. However, other drugs like tetrachloroethylene, thiabendazole, mebendazole, levamisole, pyrantel pamoate, oxyclozanide, hexachlorophene and nitroxynil are also effective.[11,131,138-151]

3. Conclusion

Trematodiases are caused by the trematodes, popularly known as the flatworm or fluke infections. They are usually transmitted either by the contaminated food or infected aquatic organisms. The majority of trematodiases are reported from east and Southeast Asian countries. These infections, if not treated well within time they may cause certain lethal complications in human like schistosomal obstructive uropathy and kidney failure caused by the *Schistosoma haemtobium*. Similar is the case with *Opisthorchis viverrini* and *Clonorchis sinensis* causing cholangitis, cholecystitis, hepatomegaly, liver abscess and gall bladder stone formation in human. Trematodes are multicellular organisms that can live in or outside of the body. The flatworms and flukes are rather more dangerous than roundworms and tapeworms as they cause cancer in human. A carcinogenic role is recognized to the *Schistosoma haematobium* leading to urinary badder cancer and to *Clonorchis sinensis* and *Opisthorochis viverrini* causing cholangiocarcinoma in human. IARC, 2011 have already categorized several trematodes that are able to cause cancer in humans as 1st category- Group 1, biological agents definitely carcinogenic to humans *viz. Schistosoma haematobium, Clonorchis sinensis* and *Opisthorchis viverrini*, 2nd category Group 2 biological agents probably carcinogenic to humans *viz. Schistosoma japonicum* and 3rd category Group 3 biological agents not classified as to its carcinogenic to humans viz. *Schistosoma mansoni* and *Opisthorchis felineus*. *Opisthorchis viverrini* and *Clonorchis sinensis* are liver-flukes that have been linked to increased risk of developing cancer of the bile ducts. The bile ducts are tubes that connect the liver for the intestines. These infections come from eating raw or uncooked freshwater fishes. They occur in East Asia and are rare in other parts of the world. As these liver flukes have been reported to cause cancer in human as cholangiocarcinoma (CCA) are certified by the IARC, 2011 as Group 1 carcinogen. They are found in the biliary system developing hepatobiliary diseases causing heptomegaly, inflammations, mechanical obstruction, Jaundice, cholangitis, cholecystitis, cholelithiasis, adenomatous hyperplasia and periductal fibrosis. The exact mechanism of cancer development is not very clear. N- nitroso- compounds produced during the course of cancer development may lead to DNA damage. Similarly, *O. viverrini* and *C. sinensis* secreted some mitogenic proteins and other substances causing cell proliferations. Some other trematodes developing complications are *paragonimus wastermani*, *Fasciola hepatica* and *Fasciolopsis buski*. Further, paragonimiasis is quite difficult to diagnose mimicking as tuberculosis. Sometimes, other extra pulmonary paragonimiasis also occurs in breast, spinal cord and brain developing malignancies, paralysis and death respectively. Similarly, *Fasciola hepatica* chronic infection may cause rupture of the liver capsule into the peritoneal cavity developing peritonitis. Lastly, the severe allergic reactions may also occur due to the release of toxic substances by the *Fasciolopsis buski*. This is a notable parasite, mostly found in southern and eastern Asia. It causes a disease known as fasciolopsiasis in human and pigs. *F. Buskii* is usually an ectoparasite residing in the human small intestine causing little harm as colitis, Crohn's disease or irritable bowel syndrome. Most of the times, they are expelled out from the bowel, but when transmitted in other parts of the body like liver, kidney or uterus, they certainly cause cancer. If possible, they are being killed with isopropyl alcohol, benzene or with the help of some medicinal herbs. It also causes AIDS in the body. Lastly, the physician's choice of drugs for the treatment of flatworms and flukes are praziquantel, albendazole and triclabendazole. However, some other drugs like tribendinidine, artimisinin, miltefosine, bithionol, livamisole and niclofan have also been used in some specific.

Compliance with ethical standards

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Statement of informed consent

Informed consents were obtained from all participants.

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