



Impact of Parasitic Infections on Host Metabolism: An Overview

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ABSTRACT

The eukaryotic unicellular or multicellular hetero-specific organisms (Parasites) those are physiologically or metabolically dependent on the host for nutrition and shelter can cause diverse impact in the host patho-physiology by manipulating their immune system. The impact of parasitic infections on host metabolism can have far-reaching consequences depending on the type of parasite, the location of the infection and the duration of the infection which may include growth stunting, cognitive impairment and increased susceptibility to other diseases. Understanding these metabolic effects is crucial for developing effective strategies to prevent and treat parasitic infections, as well as mitigating their long-term consequences on host health and development. The parasites have deleterious morbid effect on the body of the host that leads to the secondary metabolic disorders like diabetes, hypertension and cardiovascular disorders. Beside these, parasites aids in the alteration of the cellular regulation of the affected host and microbiota of the gut cells. In this review the positive and negative feedback of the parasites on the host with exemplary illustrations has been discussed.

Key words: Drug, Metabolism, Nutrition, Parasite.

A eukaryotic organism which lives on or within a host and is metabolically dependent upon the host is known as parasite, may it be uni-cellular (protozoa) or multi-cellular (cestodes, trematodes, nematodes and arthropods) (Singla, 2020). Usually, parasite tries to maintain equilibrium by avoiding the mortality of host with occasional exceptions where sometimes the parasitic infections can lead to death of host (Singla *et al.*, 2016; Mandla *et al.*, 2022). Normally they cause some devastating outcomes in host and mainly result to chronic infection (McSorley and Maizels 2012; Pawar *et al.*, 2020). Currently, one-quarter of world population is infected by parasites (Chen *et al.*, 2021). Parasite utilize nutrient of host to perform its various activity and thus can bring many metabolic alteration in host (Moreira *et al.*, 2018). Currently very limited drugs and vaccines are available to provide protection against many parasitic diseases (Liu *et al.*, 2012). Because of many factors such as complex life cycle, many developmental stages, involvement of intermediate host, multi-cellular structure which manipulate the metabolic aspect, can provide promising result and also reduce the chance of developing resistant to drugs (Sumbria and Singla, 2017).

Many parasites rely on the host's nutrients for their survival and reproduction thus they can deprive the host of essential nutrients, leading to malnutrition and metabolic imbalances *e.g.* intestinal parasites like hookworms and roundworms can cause iron deficiency anemia by feeding on the host's blood or interfering with iron absorption (Singla *et al.*, 2008; Singh *et al.*, 2021). Some parasites can directly alter the host's metabolic pathways to create a favorable environment for their survival *e.g.* *Plasmodium falciparum* can induce changes in the host's glucose metabolism, leading to hypoglycemia and lactic acidosis. Parasitic infections can impose an additional energy burden on the host, as the immune system mounts a response to combat

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the infection resulting into weight loss, muscle wasting and other metabolic disturbances.

Parasites those infect specific organs, such as the liver or kidneys, can disrupt the metabolic functions of these organs *e.g.* liver flukes can cause liver damage and impair the liver's ability to metabolize proteins, carbohydrates and fats. Parasites can interfere with the host's endocrine system, leading to hormonal imbalances and metabolic dysregulation *e.g.* *Trypanosoma cruzi*, can affect the host's metabolism of glucose and lipids by interfering with insulin signalling. These parasitic infections often trigger an inflammatory response in the host, which can lead to increased oxidative stress and metabolic disturbances. Chronic inflammation can contribute to the development of metabolic disorders like insulin resistance and metabolic syndrome.

In this review we focus on various ways and means by which parasite cause metabolic changes in host, outcome of parasitic disease to metabolic diseases, nutritional

management of parasitic infection and alteration of parasitic pathogenicity by metabolic drug therapy.

Parasitic infection usually imposes metabolic changes in target cells

Parasites both unicellular and multi-cellular can affect the metabolism of host cell (mainly immune cell) for its survivability. Various studies had been conducted to see the unending affect of intracellular parasite on host cell but scanty information is available on metabolic alteration of host by intercellular parasite. Protozoan infection such as *Leishmania infantum* infected macrophage shows metabolic alteration, initially transient increase in aerobic glycolysis (Warburg effect) but at later stage mitochondrial metabolism dominate. Initial high in glycolysis may be due to enhancement glycolytic enzyme such as Pfk (phosphofructokinase), Pdk1 (pyruvate dehydrogenase kinase 1) and Ldha (lactate dehydrogenase). In later phase mitochondrial metabolism gets enhanced and there is increase in oxidation and biomass of mitochondria. During later macrophage infection, AMPK (AMP-activated protein kinase) get activated via SIRT1-LKB1 axis and this in turn lead to enhancement in microbial metabolism (Moreira *et al.*, 2015).

In another study (Rabhi *et al.*, 2012), it was seen that promastigote of *Leishmania major* in BALB/c macrophages increased the rate and uptake of glycolysis. They also enhanced the breakdown of carbohydrate and leading to anaerobic glycolysis. In infected macrophage genes related to TCA cycle for major enzyme such as isocitrate dehydrogenase (Idh1), the succinate dehydrogenase (Sdhb) and the fumarate hydratase were reduced. *Leishmania major* cause increase in triglyceride synthesis and accumulation of cholesterol in infected macrophage. These lipid droplets are mainly found near parasitophorous vacuoles (Rabhi *et al.*, 2012).

Human foreskin fibroblast infected with *Toxoplasma gondii* cause upregulation of glycolysis and lead to more production of lactate instead of Acetyl-CoA. Genes for TCA cycle were also not elevated significantly. Moreover, genes for breakdown of amino acid were also not altered. *T. gondii* also enhance the formation of cholesterol via mevalonate pathway (Blader *et al.*, 2001). Another study shows that during the infection of *T. gondii*, lipid from various compartments of host cell get mobilised toward the parasite and are utilized to form new generation of parasite (Charron and Sibley, 2002). When RBC are infected with *Plasmodium falciparum*, the food vacuole is formed inside the parasite. This food vacuole cause digestion of host component, mainly haemoglobin and causes release of various amino acid, lipid and free haem. These lipids are used to form new membrane during schizogony (Jackson *et al.*, 2004). *Plasmodium chabaudi* infection reduce fatty acid synthesis by action on acetyl-CoA carboxylase (ACC), at same time it also enhances ETC (Chen *et al.*, 2021).

In vivo study with *Trypanosoma cruzi* (Chagas disease) also showed that at day 6 and 12, rats infected with *T. cruzi*

(Y strain) had higher level of lipid bodies (LB) in macrophage of peritoneal regions but not in peripheral blood monocyte and thus can lead to higher eicosanoid production (Melo *et al.*, 2003). In infected macrophage *T. cruzi* enhance the LB number as well as morphology via TLR-2 signalling pathway. *T. cruzi* also take help of low density lipoprotein receptor (LDL-R) in order to enter host cell (Miao and Ndao 2014). When non-phagocytic cells are infected with *T. cruzi*, there is enhancement of glucose metabolism, at same time mitochondrial respiration and bio-genesis also get elevated (Shah-Simpson *et al.*, 2017).

Flukes such as *Schistosoma* sp. have the tendency to modulate the metabolism in their host. Soluble egg antigen (SEA) of *Schistosoma japonicum* causes metabolic alteration in *in vitro* cultured macrophages. There was upregulation of genes related to glycolysis and beta-oxidation such as GLUT-4, ACC-1 that makes *S. japonicum* cercarial infection responsible for hepatic fibrosis. In comparison to lipid synthesis, (Fatty acid synthesis) FAS was more dominating. These changes were correlated with down regulation of PTEN/PI3K/AKT Pathway (Qian *et al.*, 2020). Infection with blood fluke also enhances formation of more Treg cells (McSorley and Maizels, 2012). *T. gondii* infection can also alter the lipid profile of swiss-webster mice. Infected mice had reduced high density lipoprotein and total cholesterol as compared to uninfected mice (Milovanović *et al.*, 2009). Similar reduction of high density lipoprotein and total cholesterol was also observed in *S. mansoni* infected mice (Doenhoff *et al.*, 2002).

Infection of mice with tape worm such as *Echniococcus granulosus* result in alteration in metabolism. Infected mice showed upregulation of lipolysis and arginine-proline metabolism and down regulation of glycolysis, TCA, de novo lipogenesis and lipid droplet (Lu *et al.*, 2020). Lipid metabolism is impaired when BALB/c mice were infected with *Hymenolepis microstoma*, hepatic fatty acid and cholesterol synthesis get enhanced, blood glucose level gets reduced (Rath and Walkey, 1987).

Intestinal round worm (nematodes) such as *Ascaris lumbricoides*, *Ancylostoma duodenale*, *Necator americanus*, *Strongyloides stercoralis* and *Trichuris* spp. (also known as soil transmitted helminths) enhance Th2 response and reduce Th1 response in host. They prefer the formation of M2 rather than M1 macrophage. They enhance arginase-1 and reduce pro-inflammatory molecules such as IL-6, TNF- α , STAT-3 *etc.* They also reduce fat and cholesterol level of host (Cortes-Selva and Fairfax 2021). Majority of the helminthic infections such as filariasis (*Onchocerca volvulus*) promote the formation of Treg and enhance the secretion of IL10 and TGF- β (McSorley and Maizels 2012). Some helminthic infection such as *Heligmosomoides polygyrus bakeri* in mice alter the microbiota composition in intestine, it lead to production of more short chain fatty acid and thus enhance the formation of Treg via free fatty acid receptor 3 (Zaiss *et al.*, 2015).

Some parasitic infection such as *Ascaris suum* also indirectly influences the metabolism of host that proved

from the alteration in intestinal microbiota mainly *Prevotella* and *Faecali bacterium* in pigs affected with this round worm infection. Parasitic infection causes reduction of carbohydrate and amino acid metabolism. Concentration of short chain fatty acid was also altered in infected group (Wang *et al.*, 2019).

Metabolic diseases and the parasitic infections

Alteration in body homeostasis can lead to many metabolic diseases such as obesity, diabetes, hypercholesterolemia, stroke, high blood pressure, hypertension, hepatic steatosis, osteoarthritis etc. Individual with metabolic disorder showed different outcome of parasitic infections. Obesity is due to higher fat content in the body. In an experimental study in mice it was observed that obesity enhance the level of *Leishmania* spp. infection, whereas mice kept on hyper caloric diet in order to bring diet-induced obesity, afterwards infected with *L. major* intradermally in the ear region resulted in increased parasitic burden and lesion as compared to mice on normal diet. At auricular DLN, level of IL-17 was high but IFN- γ level was not altered. Moreover, obese mice also showed increased level of IgG1. Macrophage in obese have more level of arginase *i.e.* an indicative of M2 phenotype and were more infected by *L. major* (Martins *et al.*, 2020). Diet induced obesity also resulted in severe visceral leishmaniasis caused by promastigote of *Leishmania infantum chagasi* in mice. Obese mice also suffered with high parasitic load in liver and spleen. Level of IFN- γ , TNF- α , IL-6, NO was high and IL-10, TGF- β was low in liver, spleen of obese mice. Moreover, higher level of IL-6, TNF- α was recorded in adipose tissue around gonad in obese mice (Sarnáglia *et al.*, 2016). In acute *T. cruzi* infection diet induced mice showed more parasitaemia and more myocardial inflammatory infiltration beside the higher chances of other metabolic altered condition like hyperglycemia, hypoinsulinemia and cardiovascular disorder related to increase in various cytokine such as IL-6, TNF- α , MCP-1 (Cabalen *et al.*, 2016).

Different mice model of obesity can some time give different outcome of infection such as in *Plasmodium* spp. Obese homozygous ob/ob mice (lacking leptin) when infected with sporozoite of *P. berghei* showed lessor chance of cerebral malaria but the parasitaemia was high whereas, heterozygous ob/+ lean mice had high mortality with lower parasitemia (Robert *et al.*, 2008). But in another mice model (hypothalamic obesity model) mortality level was more in obese mice as compared to lean mice. Level of some cytokine such as IFN- γ , IL-17, TNF- α , IL-12, was high in brain of obese mice as compared to lean one. In spleen also level of IFN- γ was high in obese mice (de Carvalho *et al.*, 2015).

The parasitic infection sometimes proves to be beneficial in reducing obesity in an individual that revealed from a study, where high fat induced obese mice were infected with intestinal nematode *Heligmosomoides polygyrus*. Body weight, blood glucose and triglyceride level

get reduced in nematode infected obese mice. Alteration in lipid metabolism was observed in obese mice as compared to control one. Obese mice showed mote type 2 immune response and also enhanced M2 level at gonadal fat area. In MLN level of T-bet, RORyt, IFN- γ , IL-17 was reduced whereas level of Foxp3, IL-10 was enhanced (Su *et al.*, 2018).

In a study conducted on 1600 people in Lao People's Democratic Republic, it was seen that there was positive correlation of diabetes mellitus (DM) with infection of *Taenia* spp. and *Opisthorchis viverrini* (Htun *et al.*, 2018). In Thailand also it was observed that *O. viverrini* infection decreases hyperglycaemia and increase high density lipoprotein level (Muthukumar *et al.*, 2020). Some protozoal infection like *T. gondii* was recorded to be 2 fold higher in diabetic person as compared to control. It may be due to destruction of nervous system and pancreatic cells (Shirbazou *et al.*, 2013). A meta-analysis study also shows that person with type 2DM has 47.8% prevalence of *T. gondii* whereas in control the prevalence was 25.9% (Majidiani *et al.*, 2016).

Conversely to the above finding, few studies showed negative correlation of parasitic infection and diabetes. In a study 1416 people were divided in diabetic, pre-diabetic and non-diabetic group and it was observed that diabetic people have lowest level of lymphatic filariasis (LF) caused by *Wuchereria bancrofti*. People who were diabetic and LF positive have lower level of TNF- α , IL-6 and GM-CSF as compared to negative group (Aravindhan *et al.*, 2010). In China it was seen that people with previous exposure to *Schistosoma* has lower chance of developing diabetes (Chen *et al.*, 2013) whereas in *Strongyloides stercoralis* affected people has more chance of diabetes (Mendonça *et al.*, 2006). Another study shows that in person suffering from type 2 DM, *S. stercoralis* infection reduce the level of cytokine such as IFN- γ , IL-17A, TNF- α and increased the level of cytokine related (IL-4-, IL-13) to Th2 response. When these diabetic people were given anthelmintic treatment then the cytokine level related to Th1 and Th17 cells get increased (Rajamanickam *et al.*, 2019). Fluke infection such as *S. mansoni* also help to reduce glucose level and also prevent dyslipidaemia, thus prevent the chance of developing metabolic disease (Wolde *et al.*, 2019). Cercariae and egg antigen of *S. mansoni* infection reduce the development of insulin dependent diabetes mellitus in non-obese diabetic (NOD) mice (Cooke *et al.*, 1999), there is more production of IL-10 and number of V 14i NKT cells (Zaccone *et al.*, 2003). NOD mice infected with *Heligmosomoide spolygyrus* delayed the development of T1D and there was enhanced level of IL-1, IL-10, IL-13 Treg and M2 in pancreatic and MLN. Moreover, *H. polygyrus* also reduce the chance of insulinitis and there is also low infiltration of CD4, CD8 T cell and macrophage in the islets (Liu *et al.*, 2009). In another study it was noticed that *H. polygyrus* infection reduce hyperglycemia in streptozotocin (STZ)-induced type 1 diabetes (T1D) in mice, it also rebalance the size of islet cell. In pancreas level of TNF- α

and IL-1b was also reduced due to *H. polygrus* infection (Osada *et al.*, 2013).

Other metabolic condition such as hypercholesterolemia also provides protection against some parasitic infection. Mice fed on high-cholesterol diet were resistant to *L. donovani* infection. Mice having high cholesterol level have higher level of antileishmanial CD8+IFN- γ + and CD8+IFN- γ +TNF- α + T cells (Ghosh *et al.*, 2012). Infection of mice with *P. chabaudi* lead to many changes in the metabolic profile, it leads to hyperproteinemia, hypertriglyceridemia, hypoglycemia and hypocholesterolemia. It was caused due to decreased phosphorylation of AMPK (Kluck *et al.*, 2019).

Influence of nutrition on outcome of parasitic infections

Pathology of parasitic infection can be modulated by altering the nutritional intake of individual. Mice kept at normal diet (25% protein) had high parasitemia of *Plasmodium yoelii* as compared to mice kept at low protein diet (0-12.5% protein). Mice at low protein diet were having more NK1.1 - TCRint cells. Low protein diet also results in atrophy of thymus which in turn reduces the T cell differentiation. Normal protein fed diet has more lymphocyte in liver and thymus (Ariyasinghe *et al.*, 2006). Feeding of mice with yogurt supplemented with probiotic powder having some bacteria species such as *Lactobacillus* and *Bifidobacterium* species reduce the parasitic burden of *P. yoelii* (Villarino *et al.*, 2016).

In *Cryptosporidium parvum* infection malnourished diet also have devastating effect. Mice fed with malnourished diet (protein-deficient diet *i.e.* 2% protein) shed more oocyst in faeces as compared to normal nutritious diet (protein diet *i.e.* 20% protein) fed mice, in tissue of malnourished mice level of *C. parvum* was high as compared to other counterpart. Cleaved Caspase 3 (apoptosis marker) level via activating of Akt signalling pathway was also high in malnourished mice, which give an indication of more death of intestinal epithelial cell, moreover malnourished mice also have reduced proliferation of epithelial cell (Liu *et al.*, 2016).

Fiber in diet can also modulate the pathogenicity of parasitic infection in mice. Diet with no fiber develop more severe infection in mice caused by *C. parvum* and *C. tyzzeri* via altering the composition of microbiota in intestine and has low level of *Bacteroidetes* and *Firmicutes* bacteria (Oliveira *et al.*, 2019). In *Giardia duodenalis* infection diet having inulin (fiber) has protective effect. Malnourished (1% protein diet) mice have reduced body weight as compared to inulin fed mice, trophozoites count also reduced in inulin fed mice. There were also enhancement of lactobacilli counts, small intestine mass, nitric oxide level and anti-giardial IgG and IgA level in supplemented diet. Level of some cytokine such as IL-1, IL-6 was low and level of TNF- α was high in malnourished mice as compared to inulin fed mice, along with this alteration in histopathology of intestine was more in malnourished

mice (Shukla *et al.*, 2016). In Gerbil also feeding of high fiber provide more protection in comparison to low fiber diet. High fiber fed gerbil enhanced more secretion of trophozoite by increasing mucous secretion and reduce the attachment of trophozoite in intestinal mucosa (Leitch *et al.*, 1989).

In nematodes infection, sometime it is also observed the high fiber diet enhance the pathogenicity of infection such as in case of *Trichuris muris*. Inulin fed *T. muris* infected mice was having more infection and worm burden (enhanced parasite growth and reduced the worm expulsion) as compared to control counterpart. Fiber fed mice depicted reduced number of goblet cell in intestine, they also have more cellular infiltration in laminae propria and epithelial barrier was also altered. MLN of inulin fed mice showed higher level of TCRb+CD4+T-bet+ cells. Secretion of cytokine related to Th2 response was low in inulin fed group and there was also low level of IgE and mast cell (Myhill *et al.*, 2020). In pig model it was seen that *Trichuris suis* infection along with inulin feeding have protective and beneficial effect on gut health via alteration in gut microbiota composition and reduce the chance of inflammation (Stolzenbach *et al.*, 2020). Inulin fed pigs also had lower level of eggs per gram along with reduction in the number of adult worm burden. Feeding high fiber diet reduces the fecundity of female *T. suis* and also changed the worm location in intestine (Petkevicius *et al.*, 2007).

Feeding of mice with 20% (w/w) menhaden-fish oil plus vitamin E also provide protection form cerebral malaria in mice caused by *P. berghei*. This protective effect was due to dietary-induced oxidative stress on the infected RBC erythrocyte and parasite (Levander *et al.*, 1995). In some parasitic infection fat content of diet shows protectiveness. Mice fed with high fat diet showed lower parasitic load of *T. cruzi* in myocardial area. Moreover, mortality in high fat diet fed mice less as compared to control group. *Trypanosoma cruzi* associated myocardial damage in acute phase was also less in fat fed mice (Nagajothi *et al.*, 2014). Feeding of high fat diet also provide protection in mice infected with *P. berghei*. Mice kept on high fat diet showed lower parasitic load in liver, moreover the level of parasitaemia in blood also goes down and the chance of developing cerebral malaria also get wane. This protection was due to production of reactive oxygen species (ROS), which are formed due to oxidation of fat droplet in mitochondria (Zuzarte-Luís *et al.*, 2017). Restriction of diet also protected mice from developing the cerebral malaria. There was reduction in parasite burden in brain and enhancement in the clearance of parasite from spleen; moreover, the integrity of blood brain barrier was sustained in dietary restricted mice. These mice also showed reduction in the number of CD4+CD69+ and CD8+CD69+ cell in brain. This protective effect of diet restriction was due to reduction in leptin level, reduction of leptin via dietary restriction also diminishes mTORC1 activity in T cells (Mejia *et al.*, 2015).

Manipulating metabolism to reshape the consequence of a parasitic infection

Cellular metabolism can be readjusted by various drugs such as 2-deoxyglucose (2-DG) block glycolysis, etomoxir block fatty acid oxidation, C75 block fatty acid synthesis, 6-diazo-5-oxo-L-norleucine (DON) block glutamine metabolism (Fig 1).

Use of these drugs have shown promising results in many viral infection (Sumbria *et al.*, 2021a,b) and these are also useful in parasitic infection. Blocking glutamine metabolism via DON increased the survivability rate in cerebral malaria caused by *P. berghei* in mice. DON treated mice showed lesser neurological symptom along with lower level of peripheral parasitaemia and inhibited the replication of parasite. DON help to retain the integrity of blood brain barrier and also decreased the level of brain swelling moreover, level of CD8+CD107+ cell was low in brain and spleen of treated mice (Gordon *et al.*, 2015). Treatment of DON also reduces viability and parasitaemia of *P. falciparum* in human blood culture system (Plaimas *et al.*, 2013). DON has also shown protective results in *T. brucei* infection both in *in-vitro* and *in-vivo* model (Hofer *et al.*, 2001). Proliferation of *T. cruzi* amastigote reduce by use of 2-DG in culture (Shah-Simpson *et al.*, 2017). In *S. mansoni* infection blocking beta oxidation via etomoxir have adverse effect on female parasite. Oxygen consumption rate *i.e.* OCR (indicator of mitochondrial respiration) and egg production of parasite got suppressed by blocking fatty acid oxidation (Huang *et al.*, 2012) but it don't have any effect on viability of parasite (Guidi *et al.*, 2016). *In-vivo* treatment of *T. muris* infected mice with etomoxir reduced the parasitic burden in

caecum as compared to vehicle control (DMSO). Number of type 2 innate lymphoid cells (ILC2), IL-5+ILC, IL-13+ILC was reduced in etomoxir treated group. All most similar result was observed when another drug acting as lipase inhibitor and reducing the absorption of dietary fat in intestine *i.e.* orlistat was used (Wilhelm *et al.*, 2016). Blockage of beta oxidation *via* use of etomoxir or perhexiline reduced the growth of amoeba such as *Naegleria gruberi* and *N. fowleri* (Sarink *et al.*, 2020).

Blocking of fatty acid synthesis with some compound such as C75 can have beneficial effects in host against some parasitic infection. Replication of *T. cruzi* was blocked by use of C75 but was not having any effect of its growth (D'Avila *et al.*, 2011). Blocking fatty acid formation also reduce the number of *Besnoitia besnoiti* tachyzoite formation (Silva *et al.*, 2019), similar reduction was also noticed in the formation of merozoites on *Eimeria bovis* in the presence of FAS inhibitor (Hamid *et al.*, 2014). FAS blockage *via* use of another drug *i.e.* Cerulenin also reduce *C. parvum* (Zhu *et al.*, 2000).

Manipulating metabolism *via* drug can sometime act as double edge sword and can enhance some parasitic infection. In *T. gondii* that blocks beta oxidation *via* etomoxir enhances the growth of parasite, was due to reduction in the production of ROS (Pernas *et al.*, 2018). However, Nolan *et al.* (2017) findings showed contrast effects that use of etomoxir reduce parasitic replication and growth. *Leishmania infatum* infection with the use of etomoxir cause enhancement in growth and replication of parasite (Moreira and Bento, 2017). Recently a study showed that etomoxir do not have any activity against *T. cruzi* (Martinez-Peinado *et al.*, 2021).

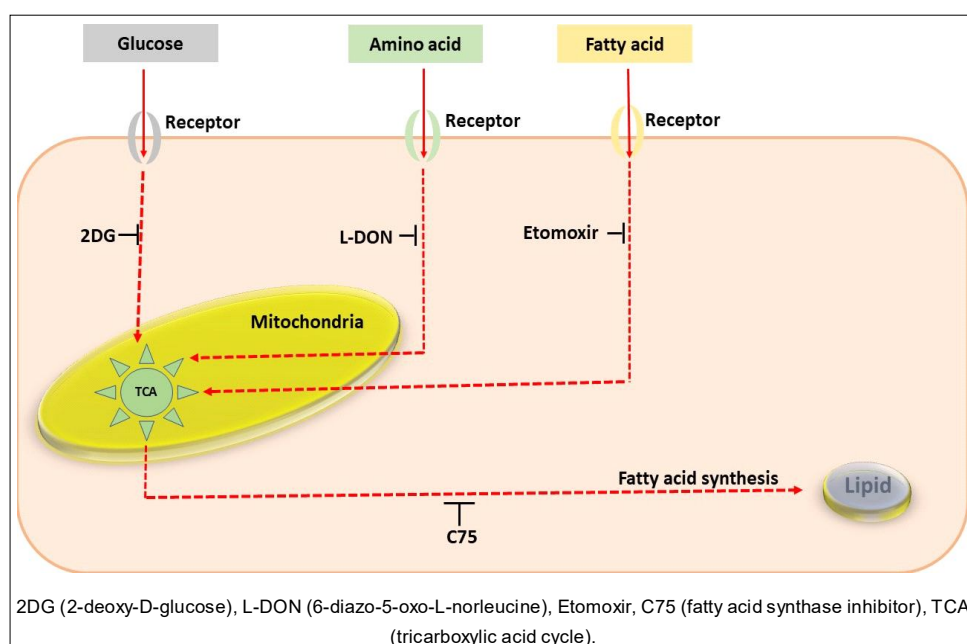


Fig 1: Cellular major metabolic pathway and inhibitor to block it.

CONCLUSION

Here, we draw the conclusion that a parasite causes a variety of alterations in the host target cell during infection. The course of a parasite infection is also influenced by several metabolic diseases. The host's dietary habits can also affect how a parasitic infection develops. The results of a parasitic infection might also be hampered by altering a key cellular route.

Conflict of interest

All authors has no conflict of interest.

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