Use of Essential Oils for the Treatment of Cryptosporidiosis

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Abstract

Cryptosporidiosis is a global zoonotic disease of the gastrointestinal tract of both humans and animals. In an immuno-competent host, this disease is self-limiting but in case of immunocompromised individuals, the disease has devastating impacts. The disease spreads through the direct or indirect contact with the infected host or contaminated environment as the infectious oocysts of the parasite shed through the feces in the surroundings. The oocysts can survive in harsh environments due to its robustness and tiny size, which makes parasites resistant to usually available disinfectants and makes it tough to eradicate them. The pathogenesis of the parasite includes infection of the microvillus epithelial cells of the small intestine of its host and causes severe diarrhea. This diarrheal condition is known as cryptosporidiosis which is ranked as fifth leading cause of diarrhea in children. The therapeutic drugs available for the treatment of cryptosporidiosis is Nitazoxanide (NTZ) which also has varying efficacy in immunocompromised patients (having co-infection of HIV) and children. The emergence of resistance in parasites to available drug therapies highlights the need of alternatives for better treatment options. Plant essential oils discovered as a novel agent to fight against different types of parasites. Due to the unique properties of essential oils and their active components, these essential oils have been studied to be used against different parasitic agents such as Cryptosporidium. The increased research and use of the essential oils against different parasitic infections indicates the potential of essential oils as an alternative treatment. This chapter aims to explore different types of essential oils used for the treatment of cryptosporidium.

Keywords: Cryptosporidium parvum, Oocysts, Antiparasitic drugs, Essential oils, Carvacol, Oregano, Mint oil, coconut oil, Onion and cinnamon oils, and thyme essential oil

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Introduction

Cryptosporidium parvum (*C. parvum*) is an intracellular intestinal protozoan which causes a zoonotic disease named cryptosporidiosis. The host range of this parasite is wide which include humans, ruminants and many other species of animals (Craighead et al., 2021). Cryptosporidiosis causes severe diarrhea especially in mal-nourished children and adults with compromised immune systems (El-Ashkar et al., 2022). Cryptosporidiosis mainly invades enterocytes and innate immunity plays a vital role in the control of this cryptosporidiosis (Gullicksrud et al., 2022). Currently available drug for the treatment of cryptosporidiosis is Nitazoxanide (NTZ) which is approved by the Food and Drug Administration (FDA). But there are few drawbacks associated with this drug such as it does not give satisfactory results in immunocompromised individuals and the cure rate is also very low in mal-nourished children (Taha et al., 2017). Other than NTZ, there are few other drugs such as azithromycin, roxithromycin, and paromomycin available for the treatment of *C. parvum* (Table 1) (Gargala, 2008). In developing countries, there have been reports regarding drug toxicity, antimicrobial resistance, low efficacy, and less availability of drugs. All the challenges demand for novel, innovative, inexpensive, safe and effective treatment options (Abdelmaksoud et al., 2020). This situation led the scientists to investigate traditional methods such as use of natural herbs and plants to deal with parasitic infections (Mendonça et al., 2021).

Transmission and Life Cycle

The oocysts of *C. parvum* are present all over the surroundings but there are also many ways through which the oocysts get entry into the host such as through fecal-oral route via direct or indirect contact (Robertson & Robertson, 2014). The direct or indirect transmission of the *C. parvum* between susceptible and infected hosts is mainly due to high density of population and close contact with infected environment or individuals (Cacciò et al., 2005) justifying the record of transmission within family members such as children and sexual partners (Robertson & Robertson, 2014). Another way of transmission is through contaminated food handled by infected individuals or exposed to contaminated water known as food borne transmission (Ramirez et al., 2004). The life cycle of *C. parvum* ends up in feces and produces thick outer wall oocysts which then release in the feces (Gunasekera et al., 2020). These infectious oocysts result in the contamination of the soil, water, and

grazing land. When a susceptible host graze on this contaminated land, come in contact with the oocysts, ingested by the host, oocysts come in contact with the bile salts, acid in the stomach, and enzymes such as trypsin and expression of the receptors present on the surface of the oocysts, which facilitate the process of excystation and ends up into the release of four motile sporozoites in the intestinal tract of its host (Borowski et al., 2008). Secretary apical organelles are important as they help in the adherence, invasion, and insertion of the parasite into the epithelial cells of the host. After that parasite nestles into a parasitophorous vesicle for its shelter and nutrition. The parasite goes through merogony, asexual, and sexual phases of its life cycle. In the process of merogony, parasites go through the differentiation and form trophozoites, type I meront, and merozoites. Some of these merozoites form Type II meronts while others penetrate the surrounding enterocytes (asexual life cycle) (Ali et al., 2024a). Type II meronts then attach themselves to the neighboring cells of the host and go through the sexual phase of life cycle called gametogony and produce microgamonts and macrogamonts. After maturation microgamonts form microgametes which fertilize macrogamonts, once they are released, and form zygote. After the process of meiosis, zygote produced four naked sporozoites and some of these sporozoites developed into oocysts with thin walls, causing autoinfection in its host. The other oocysts develop with thick walls which are resistant to harsh environments, and are released into feces (Figure 1) (Ali et al., 2024b).

Previously used drug	Status of drug			Drawback	S	References	
Nitazoxanide (NTZ)	FDA app	proved	drug f	or Expensive	, low availability	less effective in ch	nildren (Amadi et al., 2009; Khali
	Cryptospor	ridiosis, i	ineffective	in and immu	ino-compromised	individuals	et al., 2018)
	patients with co-infection (HIV)						
Azithromycin	Use in othe	er infecti	ons	Use in cor	nbination with oth	ner drugs in HIV patio	ents (Diptyanusa & Sari, 2021
							Khan & Witola, 2023)
Rifabutin				Used to p	revent cryptospori	diosis	(Khan & Witola, 2023)
HIV protease inhibitors				Causes su	spension of Crypto	osporidiosis in HIV pa	atients (Khan & Witola, 2023)
Paromomycin				Less effec	tive in HIV patient	S	(Diptyanusa & Sari, 2021)
Rifaximin				Effective i	n HIV patients		(Diptyanusa & Sari, 2021)
Miltefosine	Use in anii	nals		Low effica	cy and adverse sid	le effects	(Diptyanusa & Sari, 2021)
Halofuginone lactate				Cause tox	icity in host		(Khan & Witola, 2023)

Cryptosporidium spp. Infection Cycle



Fig. 1: After ingestion, *Cryptosporidium* oocysts complete their asexual and sexual life cycle in the small intestine and release thick-walled oocysts in the environment to infect susceptible hosts.

Essential Oils

NTZ has been used as a drug of choice for the treatment of cryptosporidiosis. Other than NTZ, many other drugs have been tested to check their efficacy levels against the infection of cryptosporidiosis in mammals (Hikal & Said-Al Ahl, 2017). But the emerging threat of resistance in parasites to the treatment currently available for the *C. parvum* highlights the significance of herbal products including plants and their extracts. Attributed to their activity against intestinal parasites, essential oils are recently used as a novel strategy against parasitic agents for instance *C. parvum* (Figure 2) (Benchaar et al., 2008).

Carvacrol (CV) and Oregano (Origanum vulgare) Essential Oils

There is still need of research about the exact mechanism of action of antiparasitic activity of carvacrol (CV) and oregano essential oils (OEO). In a study, the effect of CV and OEO on cell viability and infectivity was studied by introducing the oocysts of *C. parvum* into HCT-8 cell

(human ileocecal colorectal adenocarcinoma cells) monolayers (Gaur et al., 2018). The results of this study reveals the anti *C. parvum* activity of both CV and OEO. CV being a monoterpene, can affect several functions of the parasite including modification of the calcium-dependent protein kinase 1(CDPK1) and also have an influence on the Ca2+ mediated signalling (which is required for the invasion, differentiation, and regulation of other major functions) (Ultee et al., 2002; Murphy et al., 2010). Other than that the hydrophobicity and presence of hydroxyl groups in CV (Ultee et al., 2002; Burt, 2004) help phenol to penetrate the parasitic cell membrane which in turn decreases the infection rate (Turina et al., 2006; Santoro et al., 2007). In case of children having infection of *C. parvum*, the CV and OEO act as a bioactive substance to fight and lower the infection rate (Thakur et al., 2024). According to Ayurvedic and ethnopharmacological literature, OEO is recognized and used as antiparasitic agent (Burt, 2004) but there is limited evidence on the working of OEO and CV as antiparasitic agents.

Mint (Mentha × piperita) Oil

The chemical composition of mint oil consists of various minerals and nutrients such as iron, manganese, folate, magnesium, potassium, copper, calcium, omega-3 fatty acids, vitamin A and vitamin C. It also contains several volatile bioactive compounds for example menthol, menthyl acetate, menthone, piperitone, pulegone, carvone, and limonene (McKay & Blumberg, 2006; Kligler & Chaudhary, 2007). Mint oils is an important essential oil due to its anti-inflammatory, anti-diarrheal, antiemetic, spasmolytic, anti-bacterial, anti-depressive, diaphoretic, analgesic, antioxidant, hepato-protective, keto-protective and anti-parasitic characteristics (İşcan et al., 2002; Kiran & Patra, 2003; Farzaei et al., 2017). Mint oil also shows its unique activity in relieving irritable bowel syndrome and shows significant effects against both Gram-positive and gram-negative bacteria (Mahadevappa et al., 2014). In addition, mint oil is also used as mosquito repellent, strengthening the immune system, and shows choleretic effect that is why it has great use in the medical field (İşcan et al., 2002; Mahadevappa et al., 2014). The use of mint oil against *C. parvum* infection shows significant results as it improves the histopathological damage of the intestinal villi of the host's intestinal tract. There has been significant improvement in the small intestinal histopathological changes of the host cell. Mint oils have great therapeutic potential to inhibit the production of pro-inflammatory cytokines and limit the inflammatory response (Hejna et al., 2011). Due to the presence of flavonoids and phenolic constituents, mint oil donates electrons or hydrogen to the free radical which result in the inhibition of the production of hydroxyl peroxide ultimately control the damage due to oxidative stress (Djeridane et al., 2006; Krzyzanowska et al., 2013; Wu et al., 2019; Hejna et al., 2021).

Coconut (Cocos nucifera) Oil

Essential coconut oil is chemically composed of triglycerides having a large number of medium chain saturated fatty acids. Among these fatty acids a large amount of Lauric acid, almost 50% of the total fatty acids, is present in coconut oil (Dayrit, 2014). The beneficial therapeutic effects of coconut oils include antimicrobial activity, anti-inflammatory action, and antioxidant properties (Benchaar et al., 2008; Srivastava et al., 2016). Coconut oil has significant activity against the oocysts of *C. parvum* as it decreases the oocysts count and also causes the amelioration of the histopathological changes in ileal tissue of the host intestinal tract (Naggar et al., 2023). There is a significant decrease in the apoptotic index after the treatment with coconut oil in case of cryptosporidiosis.



Fig. 2: Different essential oils used against Cryptosporidiosis.

Onion (Allium cepa) and Cinnamon (Cinnamomum zeylanicum) Oils

The antiparasitic activity and therapeutic benefits of the *A. cepa* oil is attributed to the presence of the flavonoids and sulphoid components which also provide protection against cell damage (Hodges et al., 1999). *C. zeylanicum* oil has been used as an immune stimulant (GT et al.,

2010). *C. zeylanicum* oil is composed of eugenol, a member of phenylpropanoids, which is known for its antiphagocytic and local antiseptic properties (Mallavarapu et al., 1995). Onion oil and cinnamon oil has great importance due to their anti *C. parvum* activity as the use of onion oil and cinnamon oil decrease the oocysts count at a significant level. These oils are also reported to improve the appearance of villi of ileum of the host's cell, as the parasite colonized in the villi. The administration of onion oil and cinnamon oil has beneficial therapeutic effects against the zoonotic *C. parvum* infection in both humans and animals (El Ezz et al., 2011).

Thyme (Thymus vulgaris) Essentials Oils

Thyme (*Thymus vulgaris*) is an important essential oil composed mainly of thymol (2-isopropyl-5-methylphenol) which is a monoterpene (Youssefi et al., 2019). Thymol is a famous therapeutic agent because of its antibacterial (Kachur & Suntres, 2020), antifungal (Wang et al., 2019), larvicidal (López et al., 2018), and acaricidal (Araújo et al., 2015) properties. But there is limited data about the antiparasitic characteristics of thymol. Thymol is easily available in many natural sources and frequently used because of its low toxicity to mammalian cells. Due to these properties, thymol has a great potential to be used as an antiparasitic agent (Chauhan & Kang,2014). In a study thymol and thyme have significant activity against *C. parvum* when used in HCT-8 cell (human ileocecal colorectal adenocarcinoma cells) culture model. The knowledge about the activity of both the thyme and thymol is scarce and there is need for further research (Dominguez-Uscanga et al., 2021).

Conclusion

Essential oils appeared as a promising alternative for the treatment of cryptosporidiosis, especially in the current situation of development of drug resistance and limited treatment options. Essential oils as one of the best plant extracts have been experimented in both in vitro and in vivo studies while they show efficacy against cryptosporidiosis. The essential oils such as Carvacrol, Oregano, Mint, Coconut, Onion, Cinnamon, and Thyme contain bioactive compounds that are mainly responsible for the antiparasitic activity of these essential oils. The in vivo and in vitro studies of animal models represent compelling evidence of the antiparasitic efficacy of different essential oils, more research needed and human trials are important for the application of clinical use of these oils in human cryptosporidiosis treatment. The introduction of essential oils as an alternative of NTZ (current treatment regimen against cryptosporidiosis) increases the therapeutic effects and less side effects. There is a need for research in perspectives of preparation techniques of the essential oils, their mode of action, and combination of essential oils to enhance their efficacy. Essential oils hold great potential as an alternative treatment for the management of cryptosporidiosis in the current situation of evolution of resistance in various parasitic diseases.

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