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Assessment of the Impact of Numerous Medicinal Plants on Trichomonas Vaginalis: A Review

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Abstract
The most common non-viral sexually transmitted illness in the world, trichomoniasis, is caused by the etiological agent Trichomonas vaginalis. Trichomoniasis is a prevalent, global health issue that is becoming worse. While infections in males are typically asymptomatic, infections in the female genital tract can result in a variety of symptoms, including vaginitis and cervicitis. This condition has historically been underdiagnosed and under researched due to its generally mild symptoms and the absence of any evidence for any major repercussions. The attempts to identify and treat patients harbouring this parasite have risen, however, in light of mounting evidence that T. vaginalis infection is linked to various disease states with high morbidity in both men and women. Recent research has highlighted the complex interactions between the parasite and host, commensal microbiota, and associated symbionts. The pathophysiology of trichomoniasis is produced by damage to the host epithelia, mediated by a multitude of events during infection. The number of accessible diagnostic alternatives has increased as a result of the commercial introduction of several nucleic acid amplification tests (NAATs). Immunoassay based Point of Care testing is currently available, and a recent initial evaluation of a NAAT Point of Care system has given promising results, which would enable testing and treatment in a single visit.

Keywords: Clinical, diagnostics, point of care, trichomoniasis, trichomonas vaginalis, parasitic infection

1. Introduction

Trichomonas vaginalis is a flagellated protozoan parasite of the human genital tract and the cause of the most prevalent curable sexually transmitted disease globally, with an estimated 276.4 million cases per year, worldwide ("Global Incidence and Prevalence of Selected Curable Sexually Transmitted Infections - 2008" n.d.). Numerous symptoms, such as vaginitis and cervicitis, can be brought on by infections of the female genital system. (Heine & McGregor, 1993). Infections in males are generally asymptomatic, although mild urethritis or prostatitis can occur (Guenthner et al., 2005). The discovery that T. vaginalis infection is linked to a number of more severe diseases, including prostate cancer, cervical cancer, poor pregnancy outcomes, and an increased risk of HIV infection, has increased efforts to identify and treat patients harbouring this parasite over the past ten years. (Bachmann et al., 2011)

Parasitic infections represent a major health threat in underdeveloped countries and have a deep impact on public health. Trichomoniasis is the most common nonviral sexually transmitted disease (STD), and a significant number of new cases are identified annually worldwide. Besides, the infection is associated to serious consequences as pregnancy outcomes, infertility, predisposition to cervical and prostate cancer, and increased transmission and acquisition of HIV (Petrin et al. 1998). The therapy is restricted, the adverse effects are frequently observed, and the resistance to the drugs is emerging. In this context, new treatment for trichomoniasis is necessary. Natural products represent a rich source of active molecules, and even today, they are used in the search for new drugs (Newman and Cragg 2012). However, new synthetic products or derivatives from old drugs also provide an alternative to treat this infection. The purpose of this paper was to compile data on the effectiveness of natural items, synthetic chemicals, and old medication derivatives against Trichomonas vaginalis. For that, we conducted a review using the keywords: "natural products against Trichomonas vaginalis"," anti-Trichomonas vaginalis natural products"," anti-Trichomonas vaginalis activity, "synthetic compounds against Trichomonas vaginalis", and "anti-Trichomonas vaginalis." The survey was done on the US National Library of Medicine (PubMed), ScienceDirect® and Scopus® trademark of Elsevier, Sc finder–Chemical Abstracts Service from American Chemical Society, and on the Scientific Electronic Library Online (SciELO) for the period of 2004 to December 2014 in English, Spanish, and Portuguese.

2. Pathogenesis

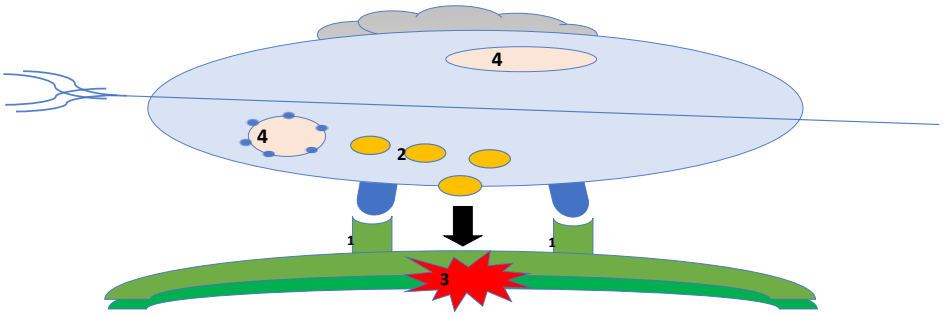

Figure No. 1 Model of Trichomonas vaginalis (Tv) pathogenicity. Tv (light blue) must bind (1) to either the host epithelium (dark green) or the extracellular matrix (light green) in order to have a cytopathic effect, according to research37. Several surface proteins and other surface molecules bind to a structure on the cell surface of the host to carry out binding. These include tetraspanins28,45,46, succinyl-CoA synthetase34, glyceraldehyde 3-phosphate dehydrogenase32, enolase33, and lipoglycan27 on the surface of T cells, galectins-1 and -328 on the surface of host cells, and fibronectin32 in the extracellular matrix. Exosomes allow a number of Tv factors that are important for attachment to the host epithelium to reach the epithelium or Tv surface31 (2). Several effectors (3), including cysteine proteases, metalloproteases, rhomboid proteases, and phospholipase A2, harm the host cell. Tv migration inhibitory factor may encourage the growth of prostate neoplasia44. (4) Symptoms may worsen in the presence of Mycoplasma hominis48 and Tv virus49.

3.Trichomoniasis treatment and resistance

The only class of antimicrobial medications recognized by the Food and Drug Administration (FDA) for the treatment of trichomoniasis is the nitroimidazoles (metronidazole or tinidazole). The drug metronidazole was first made available to treat T. vaginalis infections in 1959. Nevertheless, in 1962, the first treatment failure for this drug was

described (Crowell, Sanders-Lewis, and Secor 2003). Tinidazole, another 5-nitroimidazole, was introduced for trichomoniasis treatment in 2004, presenting better clinical efficacy and fewer side effects(Crowell, Sanders-Lewis, and Secor 2003). However, because these both therapeutic options are in the same class of imidazole derivatives, infection that is resistant to metronidazole may fail to resolve following tinidazole option. Metronidazole is inexpensive, widely available, and in general an effective and well-tolerated option. In spite of that, metronidazole is insufficient to treat all people with trichomoniasis because it presents various side effects, such as nausea, vomiting, diarrhoea, and abdominal discomfort. Hypersensitivity and allergic reactions, such as Stevens Johnson syndrome or anaphylaxis, can occur in response to 5-nitroimidazoles, impairing the treatment success (Ghosh, Aycock, and Schwebke 2018a). Nevertheless, the main cause of failure is the resistance of T. vaginalis to 5-nitroimidazoles, although there is limited information about prevalence of resistance to metronidazole among T. vaginalis fresh clinical isolates. Schwebke and Barrientes (2006) demonstrated that 10 % of clinical isolates are in vitro 5-nitroimidazoles resistant, a concerning number when the high worldwide prevalence/ incidence are considered. In addition, trichomoniasis is not a reportable infection, and no surveillance system exists to detect resistance, leading it to a neglected parasitic infection status (Secor et al. 2014). Thus, these numbers may be underestimated and indicating the need of new drugs to treat this STD. In this sense, synthetic and its derivatives or natural products are promising alternatives for the treatment of trichomoniasis, and a great variety of compounds have been tested and presented a potential activity against T. vaginalis.

4. Challenges to the effective management of trichomoniasis

Although curable, trichomoniasis and its treatment are often challenging because of the drug's side effects. Generally, adverse effects include nausea, vomiting, constipation, cramping, and metallic taste. Other adverse effects include peripheral neuropathy, seizures, fatigue, dizziness, headache, and leukopenia (Wendel and Workowski, 2007). Additionally, trichomonas is increasingly associated with other health complications like pelvic inflammatory disease and cervical cancer. Preterm births, low birth weights, stillbirth, neonatal death, sexual transmission, and acquisition of HIV infection are strongly associated with trichomoniasis (Hirt et al., 2011). HIV-positive women may require multiple doses of metronidazole because of changes in vaginal ecology, interference of impaired immunity with single-dose treatment, and interaction of antiretroviral drugs with metronidazole (Kissinger and Adamski, 2013). In men's case, T. vaginalis infections are also associated with chronic prostatitis leading to aggressive prostate cancers, as observed from increased Prostate-Specific Antigen levels (Langston et al., 2019; Sutcliffe et al., 2006). Even though the single metronidazole therapy has a failure rate of only 10%, these figures are significant due to the large number of patients suffering from trichomoniasis. Although oral 5-nitroimidazoles such as metronidazole and tinidazole exhibit high cure rates, trichomonas infection can still be highly persistent and recurrent (Dunne et al., 2003; Sena ˜ et al., 2014). One of the major reasons for this is the drug resistance to metronidazole or cross-resistance to other 5-nitroimidazoles or, in some cases, multiple drug resistance (Dunne et al., 2003). Additionally, in certain cases, metronidazole-associated allergy may cause urticaria, facial edema, and anaphylactic shock. It may result in therapy failure as well (Mehriardestani et al., 2017). Drug resistance to metronidazole or the whole 5-nitroimidazole family is fairly common, which eventually exposes the lack of drugs available in the armamentarium to treat trichomonas infection. Given the population density that suffers from trichomonas infection and lack of drugs, there is an urgent need to discover safe and efficacious drugs to treat trichomoniasis. On a different but serious note, trichomonads are evolving and losing Fig. 1. Trichomonas species and their infection site in the host. N. Hashemi et al. International Journal for Parasitology: Drugs and Drug Resistance 15 (2021) 92–104 94 strict host specificity; T. vaginalis-like isolates from cases of epidemic avian trichomoniasis exemplify the importance to create awareness of potential human-to-bird transfer and evolution and origins of these pathogens (Maritz et al., 2014). Cross infection of parasites between pigs and cattle has also been observed (Miller et al., 2017). Trichomonad parasites, which were

known to infect animals, are now causing infection to humans as well. Although rare, human Tri trichomoniasis caused by T. foetus has been reported as opportunistic infections in immunocompromised or immunosuppressed individuals (Suzuki et al., 2016). T. foetus is also found in the stomach, caecum, and nasal cavity of pigs without apparent clinical significance (Mueller et al., 2015).

Table No.1 Inhibition of pathogenic trichomonad by food and medicinal plant compounds listed alphabetically.

Compound	Source	Trichomonad	Inhibition	References
Benzopyrans	Medicinal plant; hypericum polyanthenum	T.vaginalis	Cell damage	(Cargnin et al. 2013)
Betulinic acid	Medicinal plant; palatanus acerifoli	T.vaginalis	Cell growth	(Friedman, Tam, et al. 2020b)
(+)-Bisabolol	Essential oil;nectandra megapotamica	T.vaginalis	IC50 98.7 µg/mL	(Farias et al. 2019)
Caffeic acid	Potatoes, solanum tuberosum	3 trichomonads	21.1-42.8%	(Friedman et al. 2018)
Candimine	Orgnamental plant, hippeastrum morelianum	T.vaginalis	Cell damage	(Menezes and Tasca 2016)
Carmaphycin-17	Cancer drug; proteosome inhibitor	T.vaginalis	Highly active	(O'Donoghue et al. 2019)
α-Chaconine	Potatoes, solanum tuberosum	3 trichomonads	IC50 35-60µM	(Friedman et al. 2018)
Chlorogenic acid	Potatoes ;solanum tuberosum	3 trichomonads	21.1-42.8%	(Friedman et al. 2018)
Emodin	Rhubarb; rheum palmatum	T.vaginalis	Active in mice	(Hwang-Huei 1993)
Geraniol	Essential oil; amomum tsao-ko	T.vaginalis	171-343 µg/mL	(Dai et al. 2016)
Hedargenin	Medicinal plant;cassnia holstii	T.vaginalis	IC50 2.8µM	(Soosaraei et al. 2017)
(+)-Isoaustrobrasilol	Medicinal plant; hypericum spp.	T.vaginalis	Cell damage	(Menezes et al. 2017)

Lectin	Kidney beans; Phaseolus vulgaris	T.vaginalis	Cell damage	(Aminou, Alam-Eldin, and Hashem 2014)
Lucidin – isopropyl- ether	Plant roots;morinda panamensis	T.vaginalis	IC50 1.32 µg/mL	(Friedman, Xu, et al. 2020)
Lycorine	Ornamental plant; hippeastrum breviflorum	T.vaginalis	Cell damage	(Brandt et al. 2011)
Lycosinine	Ornamental plant; hippeastrum breviflorum	T.vaginalis	Cell damage	(Brandt et al. 2011)
Methyl jasmonate	Plant hormone	T.vaginalis	Cell death	(Ofer, Gold, and Flescher 2008)
N-acetyl-L-cysteine	L-cysteine amino acid	T.vaginalis	Active in vivo	(O'Donoghue et al. 2019)
Pyrrolocin A	Fungal endophyte E6927E	T.vaginalis	EC50 60 nM	(Lam et al. 2021)
Quercetine	Potatoes; solanum tuberosum	3 trichomonads	22.6-48.4%	(Friedman et al. 2018)
Resveratrol	Grapes; vitis vinifera	T.vaginalis747	IC50 10.9-16.8 µM	(Mallo, Lamas, and Leiro 2013)
Saponins A,B	Medicinal plant; sapindus saponaria	T.vaginalis	MIC 0.025%; MIC 0.16 mg/mL	(Friedman, Tam, et al. 2020b),(Damke et al. 2013)
Solanidine	Potatoes; solanum tuberosum	3 trichomonads	22.6-48.4%	(Friedman et al. 2018)
α-Solanine	Potatoes; solanum tuberosum	3 trichomonads	IC50 10.9-16.8µM	(Friedman et al. 2018)
Tomatidine	Tomatoes; Lycopersicon esculentum	3 trichomonads	3.2–22.9%	(Liu et al. 2016)
Tomatine	tomatoes; Lycopersicon esculentum	3 trichomonads	IC50 2.0–7.9 µM	(Liu et al. 2016)
Torvosides	medicinal plant; Solanum torvum	T. vaginalis	MIC 6.2–12.5 µM	(Arthan et al. 2008)
Uliginosin B	medicinal plant; Hypericum polyanthenum	T. vaginalis	cell damage	(Cargnin et al. 2013)

Ursolic acid	medicinal plant; Manika rufula	T. vaginalis	MIC 25 µM	(Friedman, Tam, et al. 2020a)
Wogonine	plant leaves; Scutellaria havanensis	T. vaginalis	cytotoxicity	(Llauradó Maury et al. 2020)

5. Marine compounds

Taking into account that seaweeds have been traditionally used by coastal people in Asia and Caribbean to treat parasitic infections, the ethnopharmacological and chemotaxonomic properties of these organisms have been evaluated. Twenty- five tropical seaweeds were tested against T. vaginalis, and the cytotoxicity on mammal cell lines was also assessed. Dichloromethane/methanol extracts of 44 % of the seaweeds presented high to moderate antitrichomonal activity. The sea- weeds Lobophora variegata and Udotea conglutinata showed the maximal activity with IC50 values of1.39 and 1.66 µg/mL with good selectivity (Moo-Puc, Robledo, and Freile-Pelegrin 2008). Activities associated to microorganisms from marine organisms have been reported in literature (Mayer et al. 2009); however, to our knowledge, there is no study examining anti-T. vaginalis activity of marine associated fungi from South Brazilian Coast. Anti-T. vaginalis activity of 126 filtrate samples of marine-associated fungal species from 39 different marine organisms was investigated. Among them, two samples showed significant growth inhibitory activity against sensitive and resistant T. vaginalis isolates with MIC at 2.5 mg/mL. Both samples showed very low cytotoxicity against Vero cells (Scopel et al. 2013).

Table No. 2 Most relevant plant extracts presenting activity against Trichomonas vaginalis Plants.

Plants	Part/extract type	Inhibitory concentration	Reference
Scaevola balansae	Bark dichloromethane	29.3 µg/mLa	(Desrivot et al. 2007)
Myristica fatua	Almonds dichloromethane	35.2 µg/mLa	
Lavandula	Essential oils	1.0 mg/mLb	(Moon, Wilkinson, and Cavanagh 2006)
Carica papaya	Seeds methanolic	5.6 µg/mLa	(Calzada, Yépez-Mulia, and Tapia-Contreras 2007)
Cocos nucifera	Husk fiber methanolic	5.8 µg/mLa	
Phaseolus vulgaris L	Seeds acidified water and acetic acid extracts	176.8 µg/mLa	(Lara-Díaz et al. 2009)
Arbutus unedo	Leaves acetate extract	378.3 µg/mLa	
Voacanga globose	Leaves extract	0.5 mg/mLc	(Miguel et al. 2014)
Cussonia species	Leaves methanolic extract	1.0 mg/mLd	(Vital and Rivera 2011)
Sansevieria aethiopica	Leaves aqueous extract	0.8–1.3 mg/mLb	(De Villiers et al. 2010)
Tarchonanthus camphoratus	Leaves aqueous extract	1.3 mg/mLb	(van Vuuren and Naidoo 2010b)
Bidens Pilosa	Leaves organic extract	0.5 mg/mLb	

Ozoroa engleri	Leaves organic extract	1.0 mg/mLb	(van Vuuren and Naidoo 2010a)
Sarcophyte sanguinea	Stem organic extract	1.0 mg/mLb	
Syzygium cordatum	Bark organic extract	1.0 mg/mLb	
Tabernaemontana elegans	Bark organic extract	1.0 mg/mLb	
Eucalyptus camaldulensis	Leaves ethyl acetate extract	12.5 mg/mLb	
Polygala decumbens	Root aqueous extract	1.56 mg/mLb	(Hassani et al. 2013)
Verbena sp	Leaves aqueous extract	4.0 mg/mLb	(Frasson et al. 2012)
Campomanesia xanthocarpa	Leaves aqueous extract	4.0 mg/mLb	(Brandelli et al. 2013)
Lobophora variegata	Dichlromethane/methanol extract	1.3 µg/mLb	
Udotea conglutinata	Dichlromethane/methanol extract	1.6 µg/mLb	(Moo-Puc, Robledo, and Freile-Pelegrin 2008)

6. New Scientific Approaches from Basic Research

In the drug discovery process, the contribution of laboratory benches is substantial,through in silico and in vitro screening of synthetic compounds and molecules derived from natural products, known as biomolecules, with anti-T. vaginalis activities. Promising candidates can exhibit effectiveness at lower doses than the reference drugs, and the elucidation of biological targets allows for the search for molecules that escape from known resistance pathways. Considering that T. vaginalis occurs in the human genitourinary tract, in vivo testing using animal models for human trichomoniasis is still incipient. In this sense, NCATS has developed drug discovery, development, and deployment maps to guide the different process stages, and highlighted substantial differences in small molecules and biologic products related to therapeutic candidate identification and optimization (J. A. Wagner et al. 2018),(J. Wagner et al. 2018). In the last decade, anti-T. vaginalis basic research increased considerably, and new approaches from the laboratory bench were summarized in this topic, through the presentation of promising molecules of natural and synthetic origins, as well as the use of nanotechnology involved in the treatment of trichomoniasis (Table 1).

Table No. 3. Basic research on promising molecules for the treatment of trichomoniasis of natural and synthetic origin, as well as nanotechnology approaches.

Most active Compounds	Dose	Testing Method	Pharmaceutical Form	Reference
(Tri-n-ethylphosphine)gold(I) chloride (4	pEC50: 6.06 µM (24 h	in vitro (T. vaginalis), in vivo (T. foetus)	Solution	(Sulaiman et al. 2022)
Betulinic acid derivative (4)	MIC: 25–50 µM (24 h)	in vitro	Solution	(Scopel et al. 2012)
Boric acid	MLC: 0.3–0.6%	in vitro	Solution	(Backus, Muzny, and Beauchamps 2017)

3-oxime-urs-12-en-28-oic-ursolic acid (9)	MIC: 25 µM (24 h)	in vitro	Solution	(Bitencourt et al. 2018)
Chlorinated metronidazole	IC50: 0.006 and 0.24 µM (48 h) (sensitive and resistant strains)	in vitro	Solution	(Chacon et al. 2018)
Metronidazole	MTZ (0.7 wt. %) combined with pluronic® F127 (20 wt. %) and chitosan (1 wt. %)	in vitro	Hydrogel	(García-Couce et al. 2022)
Metronidazole, tinidazole and boric acid	500 mg MTZ every 8 h/7 day + tinidazole 2 g + 600 mg boric acid	case reports	Intravenous (MTZ), liquid (tinidazole), and intra-vaginal (boric acid)	(Nyirjesy, Gilbert, and Mulcahy 2011)
Metronidazole	500 mg MTZ (one week)	case report	Intravenous and vaginal gel	(Henien, Nyirjesy, and Smith 2019)
Metronidazole	2 g (single-dose group) or 500 mg twice daily for 7 days (7-day-dose group).	randomized controlled trial	Oral	(Kissinger et al. 2018)
Metronidazole	2 g (single-dose) versus 500 mg twice daily for 7-days (multi-dose)	clinical trial	Oral	(Muzny et al. 2022)
Metronidazole and Miconazole	MTZ 750 mg plus miconazole 200 mg (5 consecutive nights each month for 12 months)	Randomized Controlled Trial	Vaginal suppositories	(Kissinger et al. 2018)
Metronidazole/miconazole	MTZ 750 mg/miconazole nitrate 200 mg (once or twice a day)	randomized controlled trial	vaginal suppository	(Schwebke, Lensing, and Sobel 2013)

Metronidazol/RAMEB and Metronidazol/CRYSMEB	0.01 to 10 µg/mL (24 h)	in vitro	Solution	(Rigo et al. 2022b)
Paromomycin and tinidazole	5.0 g of a 5.0% (paromomycin) with concomitant oral tinidazole 1.0 g 3 times daily for 14 days	case reports	intravaginal cream (paromomycin) and tablet (tinidazole)	(Rigo et al. 2022c)
Secnidazole	2 g	clinical trial	Oral Granules	(Muzny et al. 2021a)
Secnidazole	MLC: 1.6 µg/mL	in vitro	Solution	(Ghosh, Aycock, and Schwebke 2018b)
Tinidazole	3.3–1000 mg	case report	Oral	(Mensforth and Goodall 2016)
Tinidazole and Paromomycin Combination	oral tinidazole (1 g, 3 times daily) and 4 g of 6.25% intravaginal paromomycin	case report	Cream (paromomycin) and tablet (Tinidazole)	(Butt and Tirmizi 2018)
Zinc–clotrimazole complex (Zn(CTZ)2(Ac)2	IC50: 4.9 µM (48 h)	in vitro	Solution	(Midlej et al. 2019)
Zinc sulfate	1% (14–28 days	case report	Douche	(Byun et al. 2015)

Table no. 4 list of drugs in nanotechnology

Most active compounds	Dose	Testing method	Pharmaceutical form	Reference
Auranofin-loaded nanoparticles	EC50 = 22 µM (24 h)	in vitro (T. vag) and in vivo (T. foetus)	Hydrogel	(Zhang et al. 2019)
Drug-free chitosan coated poly(isobutylcyanoacrylate) nanoparticles	100 µg/mL (24 h)	in vitro	Hydrogel	(Pradines et al. 2014)
Nanocapsules containg indole-3-carbinol	IC50 = 2.09 µg/mL (24 h)	in vitro	Gellan gum-based hydrogel	(Osmari et al. 2020)
Nano-chitosan	IC50: 11 µg/mL	in vitro	Suspension	(Elmi et al. 2020)

Nano-emulsion of Capparis spinosa L.	GI: 500 ppm (72 h)	in vitro	Suspension	(Al-Ardi 2021)
Nano-emulsion of Citrullus colocynthis (L.) Schrad	GI: 500 ppm (72 h)	in vitro	Suspension	(Al-Ardi 2021)
Nano-emulsion of Micana Mikania cordifolia (L.f.) Willd. (erroneously cited as Micana cordifolia)	1000 ppm (72 h)	in vitro	Suspension	(Vazini 2017)
Nano-liposomal metronidazole	IC50: 15.90 µg/mL (6 h)	in vitro	Suspension	(Ebrahimi et al. 2021)

7. Nanotechnology

The topical treatment of human trichomoniasis has attracted the interest of many researchers, since the vaginal route has advantages such as good contact surface and permeability to drugs, ease of administration, and reducing the chance of side effects related to the treatment (Baloglu et al. 2009). However, due to the mucus in the vaginal region, the drug residence time is reduced, leading to inefficient delivery to the site and ineffective treatment (Rigo et al. 2022c). Formulations containing drugs to be topically applied in the vagina must overcome all these challenges, adding to the need for a low propensity to cause genital irritation and systemic toxicity vani(Baloglu et al. 2009). In addition, the increased biological effect demonstrated by nanoencapsulated molecules in comparison to free compounds has already been described (Rigo et al. 2022c). Among the main issues, we can highlight modulation caused by cell interaction through increased uptake, and efficient intracellular release by mechanisms of enzymatic degradation and oxidation reduction, as well as amelioration in chemical stability by preventing the appearance of degradation products, improving the bioavailability of drugs and reducing adverse effects (Rigo et al. 2022c). In this sense, nanotechnology has enabled the emergence of a brand new horizon of trichomoniasis treatment.

Table no. 6 Clinical trials testing potential new alternatives to treat trichomoniasis.

Active / formulation	Dose	Phase	Pharmaceutical form	Identification	Reference
Clinsupv	Clindamycin 100 mg and clotrimazole 200 mg (both administered per vaginally for 3 consecutive days)	4	Soft gelatin capsule versus extended release tablet	NCT01697826	(“Comparison of Two Topical Formulations Containing Clindamycin and Clotrimazole in Patients With Vaginal Infections - Full Text View - ClinicalTrials.Gov” n.d.)
Drug: iptp-sulphadoxinepyrimethamine plus metronidazole Drug:	SP = 3 tablets each containing 500 mg	3	Tablets	NCT04189744	(“The ASPIRE Trial - Aiming for Safe

iptpdihydroartemisininpiperaquine plus metronidazole drug: iptp-sulphadoxinepyrimethamine	sulphadoxine and 25 mg pyrimethamine (Day 0) MTZ = 4 tablets each containing 500 mg as directly observed therapy (Day 0) DP = 3 tablets of 40 mg of dihydroartemisinin and 320 mg of piperaquine (Days 0, 1, 2)				Pregnancies by Reducing Malaria and Infections of the Reproductive Tract - Full Text View - ClinicalTrials.Gov" n.d.)
Gynomax® XL	Lidocaine 100 mg, thioconazole 200 mg, tinidazole 300 mg	4	Vaginal ovule	NCT03839875	("Evaluation of Efficacy and Safety of Gynomax® XL Ovule - Full Text View - ClinicalTrials.Gov" n.d.)
Metronidazole	500 mg twice daily for 7 days or 2 g single dose	3	Oral	NCT01832480	(Kissinger et al. 2009)
Neo-Penotran Forte	Metronidazole 750 mg and miconazole nitrate 200 mg	2	Vaginal suppository	NCT01361048	("Neo-Penotran Forte Vaginal Suppository for Vaginal Trichomoniasis - Full Text View - ClinicalTrials.Gov" n.d.)
Neo-Penotran® Forte	Metronidazole 750 mg and miconazole nitrate 200 mg	Observational	Vaginal suppository	NCT01335373	("Observational Program Neo-Penotran® Forte - Full Text View - ClinicalTrials.Gov" n.d.)
Solosec (Secnidazole) or placebo	2 g	3	Oral granules	NCT03935217	(Muzny et al. 2021b)

Clinical trials on new drug route administration for T. vaginalis infection were also carried out. The combination of a vaginal product with a higher dose of MTZ with miconazole (Neo-Penotran Forte) (NCT01361048) was evaluated in order to test its effectiveness in treating trichomoniasis. Forty participants were enrolled in three groups: (i) MTZ 2 g oral single dose; (ii) Neo-Penotran Forte intravaginally twice a day for 7 days; (iii) Neo-Penotran Forte intravaginally once a day for 7 days.

Table No. 7 Examples of marketed vaginal products

Product	Drug	Dosage form	Application	Company	Reference
Cleocin®	Clindamycin	Cream, but also available in ovules	Bacterial vaginosis	Pharmacia Upjohn	(Milani, Barcellona, and Agnello 2003)
Infa VT®	Tinidazole and Clotrimazole in calcium lactate buffer base Tinidazole Clotrimazol Lactobacillus spp. Metronidazole Clotrimazole Lactobacillus spp.	Ointment Tablet Tablet	Vaginal infections Vaginal infections Vaginal infections	Lark Laboratories Ltd	("Frontiers in Clinical Drug Research: Anti-Infectives - Google Books" n.d.)
Lactacyd®	Lactoserum Lactic acid	Douche	Bacterial vaginosis	GlaxoSmithKline (Europe) Sanofi-aventis (outside Europe)	("Lactacyd Feminine Hygiene Wash 100 Ml Price, Uses, Side Effects, Composition - Apollo Pharmacy" n.d.)
Metrogel-Vaginal®	Metronidazole	Gel	Bacterial vaginosis	3M Pharmaceuticals	(Sanchez et al. 2004)
Mycostatin®	Nystatin	Cream	Vulvovaginal candidiasis	Bristol-Myers Squibb	("(PDF) Drug Delivery Systems for Vaginal Infections" n.d.)
Vagistat-1®	Tioconazole	Ointment	Vulvovaginal candidiasis	Bristol-Myers Squibb	(Jones et al. 1993)

Canesten®	Clotrimazole	Cream Tablet	Vulvovaginal candidiasis	Bayer HealthCare	("(PDF) Drug Delivery Systems for Vaginal Infections" n.d.)

Conclusions

Trichomoniasis is the most common STI of non-viral origin in the world. The global estimate of infection in 2016 was an incidence of 156 million new cases. However, these data are underestimated, because trichomoniasis is not notifiable, receiving little attention from public health programs seeking to control STIs, and therefore, it is considered a neglected parasitic infection by the CDC-USA. FDA-recommended treatments include MTZ and TNZ; recently, secnidazole joined this list (Rigo et al. 2022d),(Rigo et al. 2022a). So far, there are no options for the oral treatment of trichomoniasis other than 5-nitroimidazoles, as mentioned above. Finally, research groups dedicated to developing new therapeutic alternatives for this neglected STI are producing relevant results. Efforts should be encouraged in terms of boosting basic research, developing pharmaceutical formulations, and performing clinical studies on the translational process from the bench to the patient, thus improving health policies.

8. References

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