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REVIEW

# Natural and synthetic compound anti-*Trichomonas vaginalis*: an update review

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**Abstract** *Trichomonas vaginalis* is a flagellate protozoan that causes trichomonosis, a sexually transmitted disease of worldwide importance. However, the infection has long received much less attention than other parasitic and sexually transmitted diseases. This negligence leads to poor diagnosis and underestimated prevalence values, and consequently, it has been associated to increasing acquisition and transmission of HIV, pregnancy outcomes, infertility, pelvic inflammatory disease, and cervical and prostate cancer. In view of increased resistance to drugs belonging to the nitroimidazole class, new treatment alternatives are urgently needed. Natural products provide an immeasurable wealth of active molecules, and a great number of new drugs have been originated from these compounds. In addition, new synthetic products or derivatives from old drugs also provide an alternative to treat trichomonosis. Albeit many studies have been performed with natural products against *T. vaginalis*, none of them progressed to clinical trials. Overall, inadequate financial investments are made, and no alternative treatment for trichomonosis has been discovered; meanwhile, hundreds of thousands of people will remain infected and suffering the serious consequences of this nonviral STD. Thus, it is highlighted that clinical trials for better understanding the potential in vitro are necessary and urgent in order to furnish a new therapeutic alternative for trichomonosis treatment. The current review attempts to give an overview on the potential of natural and synthetic products as antitrichomonal.

**Keywords** Anti-protozoan · Anti-*Trichomonas vaginalis* activity · Metronidazole derivatives · Natural products · Synthetic compounds · Trichomonosis

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## Introduction

Parasitic infections represent a major health threat in underdeveloped countries and have a deep impact on public health. Trichomonosis 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 trichomonosis 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 aim of this report was to put together results regarding activity against *Trichomonas vaginalis* of natural products besides synthetic compounds as well as old drug derivatives. 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, Scifinder–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.

## *Trichomonas vaginalis* and trichomonosis

The flagellate protozoan *T. vaginalis* causes trichomonosis, an STD of worldwide importance, responsible for 276 million new cases annually. Trichomonosis is more common than *Chlamydia*, gonorrhea, and syphilis infections combined, making it the most common nonviral STD (WHO 2012). In spite of this relevant prevalence, about 80 % of the trichomonosis cases are asymptomatic. Among women, this infection can persist for several years leading to chronic disease. However, even asymptomatic infections are of public health concern. Beyond to the risk of transmission to sex partners, trichomonosis has been associated to increasing acquisition and transmission of HIV, preterm labor, low-birth-weight infants, infertility, pelvic inflammatory disease, and cervical cancer (Poole and McClelland 2013). The symptomatic trichomonosis encompasses a mild to moderate inflammation of the cervix, vagina, and urethra (Swygard et al. 2004). In symptomatic women, the typical symptoms are vaginal discharge (frothy and yellow/green and mucopurulent), irritation and pruritus, and abdominal pain. Signs commonly include vaginal discharge, edema, and erythema (Muzny and Schwebke 2013). Small punctuate hemorrhagic spots may be found on the vaginal and cervical mucosa, giving a "strawberry" appearance; however, this specific signal is observed only in 2–5 % of patients (Petrin et al. 1998). In men, up to 77 % are asymptomatic (Sena et al. 2007), and only about a quarter of cases of trichomonosis are symptomatic in men. In these cases, *T. vaginalis* is identified as the etiological agent in 13 % of cases of nongonococcal urethritis in men attending a STI service (Sena et al. 2012). Being a silent disease among men, trichomonosis has recently been associated with worse prostate cancer presentation/prognosis (Sutcliffe et al. 2012). Symptomatic trichomonosis in men is spontaneously cleared within 10 days, contrasting with women, where it can persist for years.

## Trichomonosis treatment and resistance

Nitroimidazoles (metronidazole or tinidazole) are the only class of antimicrobial drugs approved by Food and Drug Administration (FDA) for the treatment of trichomonosis. In 1959, metronidazole was introduced as a treatment for *T. vaginalis* infections. Nevertheless, in 1962, the first treatment failure for this drug was described (Robinson 1962). Tinidazole, another 5-nitroimidazole, was introduced for trichomonosis treatment in 2004, presenting better clinical efficacy and fewer side effects (Crowell et al. 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 trichomonosis because it presents various side effects, such as nausea, vomiting, diarrhea, 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 (Goodhew and Secor 2013). 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, trichomonosis 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 trichomonosis, and a great variety of compounds have been tested and presented a potential activity against *T. vaginalis*.

## Natural products

In traditional medicine, the use of medicinal plants for the treatment of various disorders of health dates back to thousands of years ago, with records dating from ancient Babylonia, Egypt, China, and India. In the modern pharmaceutical industry, despite the wide variety of molecules derived from combinatorial chemistry, natural products play a key role in the development of pharmaceuticals (Ngo et al. 2013). About 35 % of approved drugs are from natural products or semisynthetic derivatives, while 30 % are synthetic molecules inspired by natural products or present a pharmacophore developed from natural compounds. Noteworthy, out of 15 antiparasitic medications that have been approved by health authorities between January 1981 and June 2006, 65 % are natural products or derivatives (Newman and Cragg 2012). Thus, the interest in medicinal plants as lead source has increased in a great deal in the recent years. Taking into account the need of new alternatives to treat

trichomonosis, the research with focus on the investigation of natural products with activity against *T. vaginalis* also has increased.

## Plant compounds

The selection of plants can be based on ethnopharmacological data from healer's knowledge. Twenty-nine extracts of 18 plants from New Caledonia used in traditional medicine for fever and inflammation were tested against *T. vaginalis*, *Trypanosoma brucei*, *Leishamania donovani*, and *Caenorhabditis elegans*. Only two plants showed activity against *T. vaginalis*, *Scaevola balansae*, and *Myristica fatua* with $IC_{50}$ 29.3 and 35.2 μg/mL, respectively (Desrivot et al. 2007).

Calzada et al. (2007) based on the traditional use of medicinal plants, screened crude methanolic extract of 22 Mexican medicinal plants against *T. vaginalis*. Among the plants tested, *Carica papaya* and *Cocos nucifera* showed the best antitrichomonal activity with $IC_{50}$ values of 5.6 and 5.8 μg/mL. All the other plant extracts were less active ($IC_{50}$ 30 to 60 μg/mL) or inactive ($IC_{50}$>100 μg/mL). These results support the traditional use of five plants to treat urogenital tract disorders. However, same plants should be used with care to avoid toxicity.

In other study, the authors investigated the microbiological and toxicological effects of three Perla black been extracts (*Phaseolus vulgaris* L.). The acidified water and acetic acid extracts were tested against *Giardia lamblia*, *Entamoeba histolytica*, and *T. vaginalis*. Both extracts demonstrated effect against *G. lamblia* ($IC_{50}$ 47.7 and 102.3 μg/mL), *E. histolytica* ($IC_{50}$ 140.8 and 234.5 μg/mL), and *T. vaginalis* ($IC_{50}$ 176.8 and 378.3 μg/mL) (Lara-Diaz et al. 2009).

In Turkey traditional medicine, the *Arbutus unedo* tea and leaf preparations have been used to treat hypertension, anxiety, diarrhea, and hemorrhoids. Then, the activity against *T. vaginalis* of ethanolic, water, hexane, and ethyl acetate extracts of *A. unedo* leaves was tested, being only the ethyl acetate extract effective against *T. vaginalis* with 100 % of growth inhibition rate (GI) at 0.5 mg/mL (Ertabaklar et al. 2009). Also, an interesting activity was described for *Voacanga globosa* leaf extract when tested against *E. histolytica* and *T. vaginalis*. The assay revealed that the parasite viability was inhibited by the extract at 1.0 mg/mL (single concentration tested) (Vital and Rivera 2011).

The traditional use of plants is a rich manner to discover new compounds with biological activity, and African folk has used medicinal plants for many years to treat diverse health problems. *Cussonia* species are used in African traditional medicine against pain, inflammation, gastrointestinal problems, malaria, and STDs. De Villiers et al. (2010) demonstrated the activity against *T. vaginalis* of leaf methanolic extracts from 13 *Cussonia* species. The tested plants showed an interesting biological activity against *T. vaginalis* with MIC ranging from 0.8 to 1.3 mg/mL.

Indeed, the African population uses medicinal plants to heal a broad range of diseases, being STDs one of the most frequently treated. There are numerous ethnobotanical investigations documented, but relatively few scientific studies to validate the use of medicinal plants against pathogens infecting the urogenital tract. In an attempt to reverse this situation, 18 plants were screened for antimicrobial activity against urogenital pathogens. The parasite *T. vaginalis* showed susceptibility to all studied plants with the most noteworthy activity observed for *Tarchonanthus camphoratus* leaves with MIC at 0.5 mg/mL. The aqueous extract of *Sansevieria aethiopica* also demonstrated a good activity against the parasite (MIC at 1.3 mg/mL) (van Vuuren and Naidoo 2010). Although medicinal plants have been extensively used to treat STDs in Africa, safety and efficacy have not been evaluated. Naidoo et al. (2013) evaluated the toxicity and antimicrobial activity of 19 plants used to treat STDs. All organic extract (dichloromethane/methanol) from African plants presented activity against *T. vaginalis* with MIC ranging from 1.0 to 12 mg/mL; however, the plants *Bidens pilosa*, *Ozoroa engleri*, *Sarcophyte sanguínea*, *Syzygium cordatum*, and *Tabernaemontana elegans* were more active than the other tested plants. Among the plants tested, only *Kigelia africana* presented toxicity at 0.1 mg/mL to human kidney cell line.

An attempt to find an alternative drug to treat trichomonosis, the effect of different extracts from *Eucalyptus camaldulensis* was tested against *T. vaginalis*. Five extracts were tested (total extract, diethyl ether, chloroform, ethyl acetate, and water fractions). All the extract and fractions tested showed a good activity against the parasite, and the ethyl acetate demonstrated the highest GI, 100 % at 12.5 mg/mL (Hassani et al. 2013).

In other study, the authors were prompted to test the activity of essential oils from the traditionally used plant *Aframomum sceptrum* upon microorganisms. The main constituents were β-pinene and caryophyllene oxide which showed antiprotozoal activity against *T. vaginalis* ($IC_{50}$ 0.44 and 0.16 mg/mL, respectively), showing the potential of these oils against protozoa (Cheikh-Ali et al. 2011). The *Lavandula* essential oils have been used therapeutically for centuries, and the chemical composition of oils has been extensively studied. However, majority of research into antimicrobial activity has focused on antibacterial and antifungal. Previous study showed the activity of two essential oils from *Lavandula* species against *T. vaginalis* and *Giardia duodenalis*. Both oils were able to eliminate all viable *T. vaginalis* cells within 20 min at 10 and 5.0 mg/mL. All parasite viable cells were eliminated at 1.0 mg/mL; however, longer time of oil exposure was required (Moon et al. 2006).

Tiwari et al. (2008) demonstrated that saponins from *Sapindus mukorossi* exhibited activity against *T. vaginalis*.

The active concentration (MIC 0.05 mg/mL) was 10-fold less than the human spermicidal effective concentration (0.5 mg/mL). At this concentration, saponins are neither cytotoxic to the host cells nor alter vaginal microflora. Another species of *Sapindus*, *S. saponaria*, which is traditionally used for curing ulcers, external wounds, and inflammations, was evaluated against human spermatozoa, *T. vaginalis*, and *Lactobacillus acidophilus*. The compounds were effective against *T. vaginalis* with MIC at 0.156 mg/mL for water and butanolic extract and at 0.078 mg/mL for saponins (Damke et al. 2013).

The Indian population uses traditional medicine during many years, and one traditionally medicinal plant broadly used is *Berberis aristata*, which is applied to treat malaria, bleeding, fever, skin and eye infections, jaundice, diarrhea, and hepatitis. The authors demonstrated the effect of berberine (alkaloid from *B. aristata*) on *T. vaginalis* growth, and the efficacy was compared to the metronidazole, being safer than the reference drug (Potdar et al. 2012).

In addition, β-glycosides isolated from Thai plants were tested against *T. vaginalis*. The compound torvoside A, plumieride coumarate glucoside, gonocaryoside A, and kingiside demonstrated an important activity against the parasite with MIC at 5.64, 3.85, 2.52, and 3.24 μg/mL, respectively. Moreover, although the most potent β-glycosides reported in the study were much less active than metronidazole, they did not present cytotoxicity to cell lines, in contrast to metronidazole that present risks in terms of mutagenicity, carcinogenicity, and side effects (Arthan et al. 2008).

A stress hormone, methyl jasmonate, was evaluated against *T. vaginalis*, because this compound demonstrated potential activity against cancer cells acting at mitochondria. Then, the authors decided to test against the amitochondriate parasite to show if the organelle is essential to methyl jasmonate activity. Thus, methyl jasmonate induced death of *T. vaginalis*, and this activity was also observed in metronidazole-resistant organisms, demonstrating that this compound may be an alternative to nitroimidazole derivatives to treat resistant trichomonosis. In addition, methyl jasmonate cytotoxicity is independent of mitochondria by acting via distinct ways (Ofer et al. 2008). Sesquiterpenes, such as stizolin, alantolactone, and centaurepensin, isolated from Asteraceae plants, showed strong activity against *E. histolytca* and *T. vaginalis* at concentrations from 0.24 to 7.8 μg/mL (Bruno et al. 2013).

Another compound tested against *T. vaginalis* was curcumin, a derivate from *Curcuma longa*. The effective concentrations (ECs) were evaluated using three strains of *T. vaginalis* with different metronidazole susceptibilities (ATCC 30001, ATCC 30236, and ATCC 50138). Curcumin was shown to be highly effective against *T. vaginalis*, and strains possessing distinct susceptibility to metronidazole did not respond differently to the curcumin activity. After 24 h of incubation, the $EC_{50}$ ranged from 73.0 to 105.8 μg/mL and the $EC_{90}$ from 216.3 to 164.9 μg/mL. All parasites were eradicated by 400 μg/mL after the incubation time. Although curcumin presented high concentration active against the parasite, it is well tolerated by mucosa and is a promising candidate to topical use. Besides anti-*T. vaginalis* activity, curcumin present anti-inflammatory and analgesic effect, which could help the patient compliance (Wachter et al. 2014).

In other study, the authors evaluated the activity against *T. vaginalis* of five compounds isolated from leaves of *Maytenus phyllanthoides*. Only (+)-lyoniresinol exhibited a relevant antitrichomonal activity with an $IC_{50}$ value of 7.38 μg/mL. This activity may be associated to hydrophilic character of this lignoid due to the presence of four hydroxyl groups (Moo-Puc et al. 2014).

Our research team has been investigating anti-*T. vaginalis* activity of natural products from different plants. We also demonstrated that plants from Caatinga region (Brazil) present potential against *T. vaginalis*. After screening of 44 aqueous extract from 23 plants, only *Polygala decumbens* was effective against the parasite, showing 100 % of viability reduction at 1.56 mg/mL (Frasson et al. 2012). We also have demonstrated that the indigenous groups have wealth knowledge of medicinal plants and these plants showed a promising activity against *T. vaginalis*. Ten plants daily used by Mbya-Guarani indigenous group were evaluated against seven different *T. vaginalis* isolates, and among the aqueous extracts tested, *Verbena* sp. and *Campomanesia xanthocarpa* showed the highest activity against *T. vaginalis* with MIC value of 4.0 mg/mL reaching 100 % of efficacy against the parasite 4 h after initial treatment (Brandelli et al. 2013). In another study, we showed that saponins from *Quillaja*, *Passiflora*, and *Ilex* species presented activity; however, saponins from *P. alata* and *Q. saponaria* presented the highest activity with MIC at 0.25 mg/mL, showing for the first time the potential against *T. vaginalis* of saponins from these plants (Rocha et al. 2012). We demonstrated the potential of Amaryllidaceae alkaloids, lycorine, and candimine against the parasite, which reduced the parasite viability about 60 % at 71.8 and 86.2 μg/mL (Giordani et al. 2010, 2011b). In addition, we tested the anti-*T. vaginalis* activity of extract and isolated compounds (benzopyrans HP1, HP2, HP3, and phloroglucinol derivative uliginosin B) from *Hypericum polyanthemum*. All samples had activity against the parasite with $IC_{50}$ 0.066, 0.239, 0.320, and 0.061 mg/mL; however, HP1 demonstrated the best selectivity against this protozoan, with no cytotoxicity to mammalian. Altogether, these molecules are promising prototypes for new antiprotozoal drug (Cargnin et al. 2013).

## 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 seaweeds *Lobophora variegata* and *Udotea conglutinata* showed the maximal activity with $IC_{50}$ values of 1.39 and 1.66 μg/mL with good selectivity (Moo-Puc et al. 2008).

Activities associated to microorganisms from marine organisms have been reported in literature (Mayer and Hamann 2005); 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).

## Synthetic products

Despite the absolute chemical creativity and historical success of natural sources for biosynthesize bioactive molecules, synthetic compounds display an important tool for drug discovering. Actually, chemical libraries of synthetic molecules are screened to identify substances with desirable therapeutic effect, and novel compounds can be discovered. In addition, old drugs or derivatives can also be screened and new effects pointed out. Following this scenario, a broad range of synthetic compounds or drug derivatives were tested against the parasite *T. vaginalis*. In this review, these compounds were grouped by structural similarity.

### Synthetic compounds from natural products

As mentioned above, natural products still play an important role in the search for new active drugs even in the era of rational drug design. Besides the traditional role that the natural products play, they often represent valuable prototype structures for the development of new useful compounds. In this sense, six aromatic and aliphatic ester derivatives of lycorine, an alkaloid from Amaryllidaceae species with valuable biological activity (Giordani et al. 2010, 2011b), were synthesized and evaluated regarding anti-*T. vaginalis* activity. All the tested compounds were active no matter the aliphatic or aromatic nature of the substituent at C-1 and/or C-2 positions; however, the best activity was achieved with lycorine esterified at C2-position with lauroyl group. Importantly, none of the derivatives were less active than lycorine. Altogether, anti-*T. vaginalis* activities of lycorine derivatives showed that the esterification with fatty acids could be a starting point for preparation of new compounds with antitrichomonal activity (Giordani et al. 2012). In other study, triterpenoid derivatives were evaluated for anti-*T. vaginalis* activity. Semi-synthetic derivatives obtained from betulinic and ursolic acids were active against the parasite; however, compounds obtained from betulinic acid have showed better activity than ursolic acid derivatives. The compound with a piperazine as substituent exhibited significant activity against long-term growth and fresh clinical isolates of *T. vaginalis* with MIC ranging from 35.6 to 142.6 μg/mL (Innocente et al. 2014).

### Azole derivatives

Heterocycles represent one of the most active classes of compounds possessing a wide spectrum of biological activities. Azole-based derivatives with a heteroatom ring system and electron-rich property can easily bind to the enzymes and receptors in organisms exhibiting various bioactivities, such as antibacterial, antifungal, antiparasitic, anthelmintic, and anti-inflammatory. Azole compounds became one of the most active areas in the search and development of novel antimicrobial drugs. Hence, in this review, we will concentrate our efforts to azole-based derivatives with anti-*T. vaginalis* activity such as benzimidazole, imidazole, tetrazole, thiazole, and triazole compounds (Fig. 1).

Infections caused by protozoa such as *T. vaginalis* or *E. histolytica* are worldwide spread diseases, and drugs as benzimidazoles (albendazole and mebendazole) and nitroimidazoles (metronidazole, tinidazole, and secnidazole) are prescribed for the treatment of these infections. However, the appearance of resistant strains is increasing, and then, alternatives to treat these disorders are needed. Imidazole-based compounds are interesting alternatives because the synthetic routes are known and easily modified. Aldrete and coworkes tested antitrichomonal activity of several nitroimidazoles (2-methyl-5-nitroimidazole hydroxy, oxime, and ketone) derivatives; however, none of the new derivates presented higher or similar activity than metronidazole with MIC ranging from 4.0 to 16 μg/mL (Aldrete et al. 2005). Another series of imidazole derivatives were tested against *T. vaginalis* (*N*-acetamide(sulfonamide)-2-methyl-4-nitro-1*H*-imidazoles). Many of the compounds showed antiparasitic activity ($IC_{50}$ 0.81–22.1 μg/mL); however, metronidazole is still more active (Hernández-Núñez et al. 2009). Besides antiparasitic activity, imidazoles presented spermicidal activity. In these studies, the authors showed that a series of imidazole derivatives were active against *T. vaginalis* and human spermatozoa. Therefore, the introduction of a pharmacophore responsible for spermicidal activity into a known structure with anti-*T. vaginalis* property may lead to a potent dual function (Kumar et al. 2010, 2013).

Besides imidazole importance, benzimidazoles are other azole derivatives with important biological activity; however,

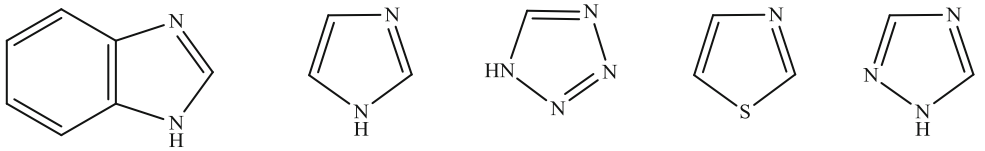



**Fig. 1** Basic structure of azole derivatives

antiprotozoa activity properties of this group have not been extensively studied. Then, attempting to contribute with this issue, a study showed that S-substituted 4,6-dibromo and 4,6-dichloro-2-mercapto-benzimidazoles were more active against *T. vaginalis* ($IC_{50}$ 0.0015–0.182 μg/mL) and *G. lamblia* ($IC_{50}$ 0.006–0.053 μg/mL) than the drug of choice, metronidazole ($IC_{50}$ 0.037 and 0.210 μg/mL, respectively), showing the potential of these compounds against protozoa (Andrzejewska et al. 2004).

In addition, a series of 2-(trifluoromethyl)-*1H*-benzimidazole derivatives also showed activity against *T. vaginalis*, *G. lamblia*, and *P. falcifarum*. The compounds presented good antitrichomonal activity with $IC_{50}$ ranging from 0.0589 to 1.43 μg/mL, demonstrating that compounds with fluorine or trifluoromethyl group led to benzimidazoles more active than metronidazole (Navarrete-Vázquez et al. 2006). Corroborating with this results, a new series of benzimidazole-pentamidine hybrids was tested against *T. vaginalis*, *G. lamblia*, *E. histolytica*, *L. mexicana*, and *P. berghei*. Some hybrids showed high activity against the first four protozoa; the $IC_{50}$ values for *T. vaginalis* range from 0.089 μg/mL to 3.82 mg/mL (Torres-Gómez et al. 2008). The same research group has been working in different benzimidazole derivatives. Two different series of benzimidazoles, 1-methylbenzimidazole, and nitazoxanide-*N*-methylbenzimidazole derivatives were synthesized and tested against *T. vaginalis* and *G. lamblia*. Most of the 1-methylbenzimidazole derivatives were active against both parasites, and some of them showed better activity than metronidazole ($IC_{50}$ 0.04 μg/mL), with $IC_{50}$ ranging from 0.008 to 0.0875 μg/mL (Valdez-Padilla et al. 2009). In the second series, all nitazoxanide-*N*-methylbenzimidazole hybrids showed strong activity against the parasites, particularly against *T. vaginalis* with $IC_{50}$ values ranging from 0.0093 to 0.103 μg/mL (Soria-Arteche et al. 2013). Noteworthy, altogether, these reports showed the importance of benzimidazole derivatives as prototypes to new drug for trichomonosis treatment even though the imidazole derivatives resistant isolates remains growing up.

Another class of azole derivatives is triazole-based compounds. Herein, 22 triazole derivatives were tested against *T. vaginalis*. Among them, 18 compounds reduced 100 % of parasite growth ranging concentration from 3.48 to 22.1 μg/mL. The most promising compound showed $IC_{50}$ 3.8 μg/mL and did not present cytotoxicity to CHO-K1 cells, making it an ideal compound for the synthesis of new pharmacological templates against *T. vaginalis* (Raj et al. 2013). In another study, tetrazole derivatives were synthesized and their biological properties evaluated against *E. histolytica*, *T. vaginalis*, and *G. lamblia*. The compounds presented moderate to good activity. The most active compound against *T. vaginalis* has $IC_{50}$ 83.9 μg/mL. These compounds could be considered as candidates to antiprotozoa drugs (Cano et al. 2014).

## Other synthetic compounds

Besides azole derivatives, similar results on synthetic compounds with activity against *T. vaginalis* were found by different groups. Derivatives of tetrahydro-(2*H*)-1,3,5-thiadiazine-2-thione (THTT) with antibacterial, antifungal, and anthelmintic properties have been known for several decades. The excellent physicochemical properties of this heterocycle prompted the synthesis of new derivatives. Two new series of THTT derivatives were synthesized and tested against *T. vaginalis* and *T. cruzi*. Same compounds exhibited an important activity against the parasites; however, it is not specific to the protozoa, but a consequence of their toxicity, suggesting the potential of THTT after improvement of toxicity (Coro et al. 2005). Many different groups of compounds were tested against *T. vaginalis*. Hui et al. (2006) synthesized 29 new quinoxalines derivatives and tested against *L. donovani*, *T. brucei brucei*, and *T. vaginalis*. Several displayed interesting activities, and particularly, four quinoxalines amides derivatives showed better activity against *Leishmania*.

Giordani et al. (2011a) showed that ten *N*-monoalkylated diamines were active against *T. vaginalis* and *G. lamblia*. Several compounds displayed a good inhibition of the parasite growth, with MIC 20 μg/mL or less. *N*-hexadecil-1,4-butanediamine was the most active against *T. vaginalis* with MIC 2.5 μg/mL, which is twice more active than metronidazole.

Recently, Bala et al. (2014) evaluated a series of 17 morpholin/piperidin-1-yl-carbamodithioate synthesized as topical vaginal microbicidal spermicides for their anti-*T. vaginalis* activity against metronidazole susceptible and resistant isolates. The study identified 11 active compounds with apparent safety against human cervical cell line (HeLa) and compatibility with vaginal flora, *Lactobacillus*. The plausible mode of action of these compounds was through

sulfhydryl binding, confirmed via reduction in available free thiols on human sperm.

## Active concentration of compounds against *T. vaginalis*

In new drug discovery, natural and synthetic compounds play an important role. Herein, we showed different sets of compounds with antitrichomonal activity. In Table 1, we summarized the activity of extracts against *T. vaginalis*, showing the different concentration tested. Also, we showed the diversity of structure and active concentrations of isolated molecules from natural source against *T. vaginalis* (Table 2). The potency of these compounds could not be compared, due to the diversity on activity expression as MIC, $IC_{50}$ and $IC_{90}$, EC, and GI. However, all substances presented a potential activity against *T. vaginalis* and could be used as prototype to new drugs to treat this important STD. Besides natural products, synthetic compounds also showed an important activity against *T. vaginalis*. In general, the synthetic compounds tested against the parasite were derivative from known drugs which facilitates the understanding of the mechanism of action and toxicity of these molecules. All tested synthetic compounds presented a promising antitrichomonal activity, which is very important because old compounds can be repurposed for use in a new application.

## Mechanism of death of *T. vaginalis* by natural products

Many studies showing the activity of natural products against *T. vaginalis* are finding in literature. However, information about the mechanism of action is scarce. Despite the importance of trichomonosis in public health, the etiologic agent, *T. vaginalis*, is an important model to study cellular biology due to the lack of mitochondria. *T. vaginalis* has hydrogenosomes instead of mitochondria, a DNA-free double-membrane-bound organelle involved in catabolic process, producing ATP and $H_2$ (a metabolic end product unusual among eukaryotes). This organelle is responsible for metronidazole activation. Remarkably, hydrogenosomes are considered an excellent drug target because their metabolic pathway is distinct from those found in mitochondria; therefore, compounds acting in hydrogenosomes will be selective and

**Table 1** Most relevant plant extracts presenting activity against *Trichomonas vaginalis*

| Plants | Part/extract type | Inhibitory concentration | Reference |
|---|---|---|---|
| *Scaevola balansae* | Bark dichloromethane | 29.3 μg/mL[a] | (Desrivot et al. 2007) |
| *Myristica fatua* | Almonds dichloromethane | 35.2 μg/mL[a] | |
| *Lavandula* | Essential oils | 1.0 mg/mL[b] | (Moon et al. 2006) |
| *Carica papaya* | Seeds methanolic | 5.6 μg/mL[a] | (Calzada et al. 2007) |
| *Cocos nucifera* | Husk fiber methanolic | 5.8 μg/mL[a] | |
| *Phaseolus vulgaris* L. | Seeds acidified water and acetic acid extracts | 176.8 μg/mL[a]<br>378.3 μg/mL[a] | (Lara-Diaz et al. 2009) |
| *Arbutus unedo* | Leaves acetate extract | 0.5 mg/mL[c] | (Ertabaklar et al. 2009) |
| *Voacanga globosa* | Leaves extract | 1.0 mg/mL[d] | (Vital and Rivera 2011) |
| *Cussonia* species | Leaves methanolic extract | 0.8–1.3 mg/mL[b] | (De Villiers et al. 2010) |
| *Sansevieria aethiopica* | Leaves aqueous extract | 1.3 mg/mL[b] | (van Vuuren and Naidoo 2010) |
| *Tarchonanthus camphoratus* | Leaves aqueous extract | 0.5 mg/mL[b] | |
| *Bidens pilosa* | Leaves organic extract | 1.0 mg/mL[b] | (Naidoo et al. 2013) |
| *Ozoroa engleri* | Leaves organic extract | 1.0 mg/mL[b] | |
| *Sarcophyte sanguinea* | Stem organic extract | 1.0 mg/mL[b] | |
| *Syzygium cordatum* | Bark organic extract | 1.0 mg/mL [b] | |
| *Tabernaemontana elegans* | Bark organic extract | 1.0 mg/mL[b] | |
| *Eucalyptus camaldulensis* | Leaves ethyl acetate extract | 12.5 mg/mL[b] | (Hassani et al. 2013) |
| *Polygala decumbens* | Root aqueous extract | 1.56 mg/mL[b] | (Frasson et al. 2012) |
| *Verbena* sp. | Leaves aqueous extract | 4.0 mg/mL[b] | (Brandelli et al. 2013) |
| *Campomanesia xanthocarpa* | Leaves aqueous extract | 4.0 mg/mL[b] | |
| *Lobophora variegata* | Dichlromethane/methanol extract | 1.3 μg/mL[b] | (Moo-Puc et al. 2008) |
| *Udotea conglutinata* | Dichlromethane/methanol extract | 1.6 μg/mL[b] | |

[a] *$IC_{50}$* half inhibitory concentration

[b] *MIC* minimum inhibitory concentration

[c] *GI* 100 % growth inhibitory concentration

[d] Single concentration tested

**Table 2** Isolated compounds from natural products with anti-*T. vaginalis* activity

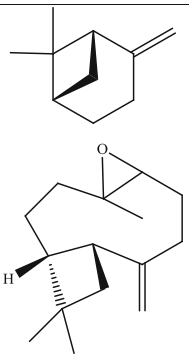
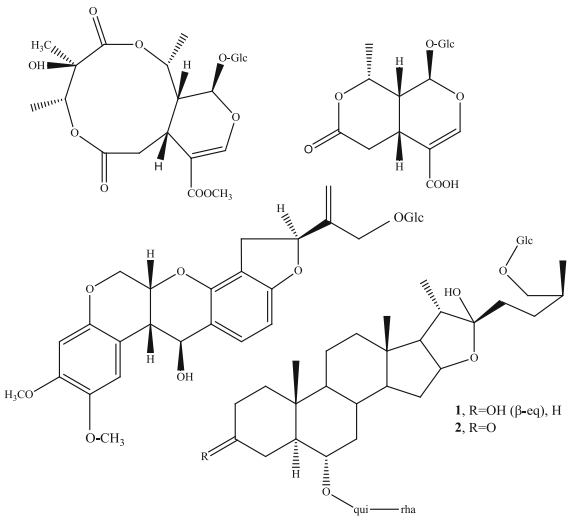
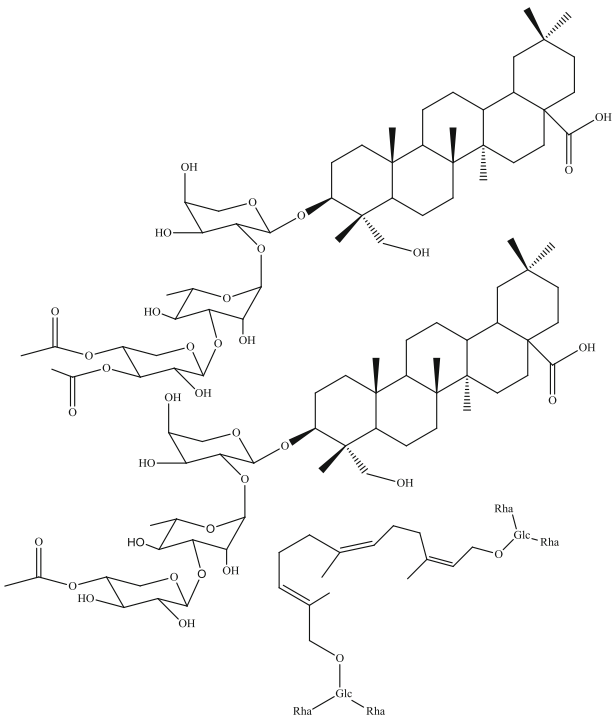
| Plants | Active compounds | Structure | Concentration | Reference |
|---|---|---|---|---|
| *Aframomum sceptrum* | β-pirene and caryophyllene oxide |  | 0.12 μg/mL[a] | (Cheikh-Ali et al. 2011) |
| Thai plants | Torvoside A, plumieride coumarate glucoside, gonocaryoside A and kingiside |  | 2.52 – 5.64 μg/mL[b] | (Arthan et al. 2008) |
| *Sapindus saponaria* | Saponins |  | 0.156 mg/mL[b] | (Damke et al. 2013) |

**Table 2** (Continued)

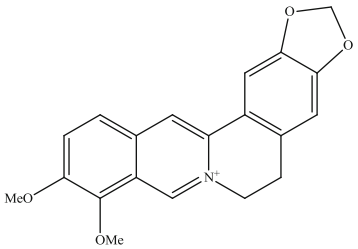
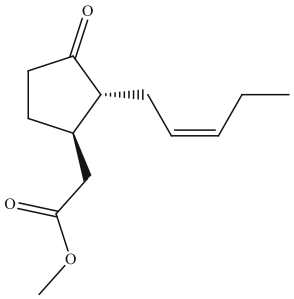
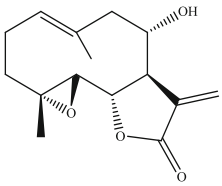
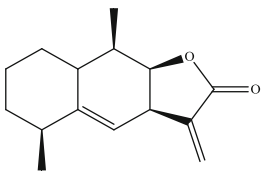
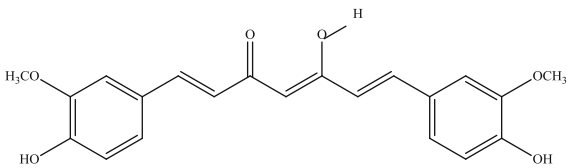
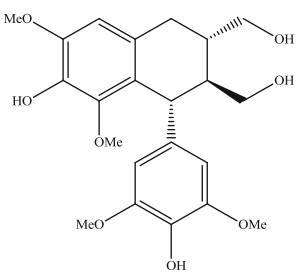
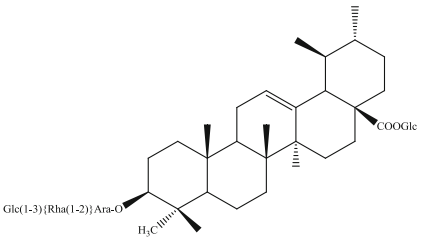
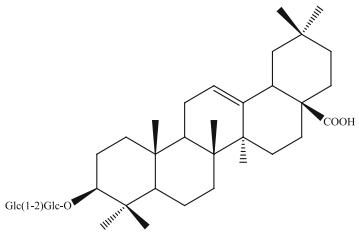
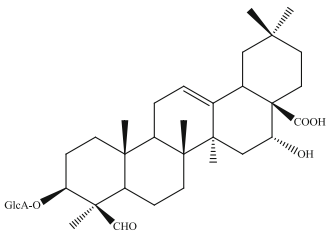
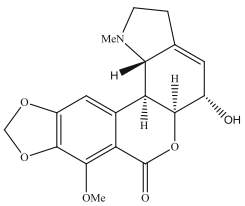
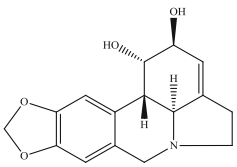
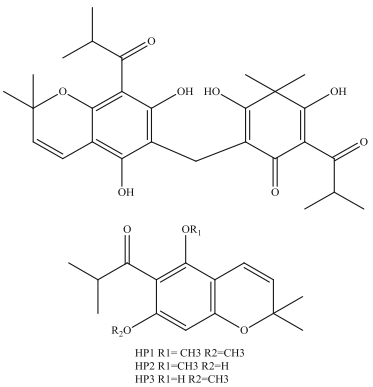
| | | | | |
|---|---|---|---|---|
| *Berberis aristata* | Berberine |  | NI | (Potdar et al. 2012) |
| NI | Methyl jasmonate |  | 0.058 – 1.34 mg/mL[b] | (Ofer et al. 2008) |
| *Stizolophus balsamita* | Stizolin |  | 0.24 – 7.8 μg/mL[b] | (Bruno et al. 2013) |
| *Serratula latifolia* | Alantolactone |  | 0.24 – 7.8 μg/mL[b] | |
| *Curcuma longa* | Curcumina |  | 73.0 – 105.8 μg/mL[c] | (Wachter et al. 2014) |
| *Maytenus phyllanthoides* | (+)-Lyoniresinol |  | 7.38 μg/mL[a] | (Moo-Puc et al. 2014) |

**Table 2** (Continued)

| | | | | |
|---|---|---|---|---|
| *Ilex paraguariensis* | Saponins |  | 0.25 mg/mL[b] | (Rocha et al. 2012) |
| *Passiflora alata* | |  | 0.25 mg/mL[b] | |
| *Quillaja brasiliensis* | |  | 0.25 mg/mL[b] | |
| *Hippeastrum morelianum* | Candimine |  | 86.2 µg/µL | (Giordani et al. 2010) |
| *Hippeastrum santacatarina* | Lycorine |  | 71.8 µg/mL[d] | (Giordani et al. 2011b) |
| *Hypericum polyanthemum* | Benzopyrans |  <br><br>HP1 R1= CH3 R2=CH3<br>HP2 R1=CH3 R2=H<br>HP3 R1=H R2=CH3 | 0.061 – 0.32 mg/mL[b] | (Cargnin et al. 2013) |

[a] $IC_{50}$ half maximal inhibitory concentration

[b] *MIC* minimum inhibitory concentration

[c] $EC_{50}$ half maximal effective concentration

[d] Concentration that reduced 40 % of trophozoite viability

*NI* not informed

probably will not affect host cells. In previous studies, researchers have demonstrated that jasmonate, a stress hormone produced by plants, exhibited anticancer activity by suppressing cell proliferation and ATP depletion. Oxidative phosphorylation in mitochondria may be the target of methyl jasmonate (MJ) perturbation. Taking into account this information, an intriguing question arises: if mitochondria are the MJ targets in mammalian cells, which is the pathway on the amitrochondriate *T. vaginalis*? As mentioned earlier, MJ was active against *T. vaginalis* by fragmentation and condensation of the DNA, resembling apoptotic death; nevertheless, DNA laddering, a sub-$G_1$ cell cycle stage peak and caspase-3 activation, features of apoptotic death, were not observed. Then, besides nonapoptotic cell death in *T. vaginalis*, MJ induced a $G_2$/M cell arrest (Ofer et al. 2008). In other study with MJ and *T. vaginalis*, it was showed that MJ was able to induce parasite death by hydrogenosome-dependent mechanism and was confirmed the cell cycle arrest. The ATP depletion occurred, but it was not the cause of parasite death, but a consequence of hydrogenosome damage (Vilela et al. 2010). Recently, a study revealing the anti-*T. vaginalis* effect of resveratrol was published. The antitrichomonal mechanism of resveratrol occurred through induction of hydrogenosomal metabolic alteration, leading to a profound dysfunction of the hydrogenosomes which is deleterious for *T. vaginalis* (Mallo et al. 2013).

Corroborating to the understanding and importance of hydrogenosomes, these studies show the effects of Amaryllidaceae alkaloids, lycorine and candimine, on *T. vaginalis*. Many biological properties have been related to lycorine, such as antiviral, antifungal, anti-inflammatory, and anticholinesterasic. Particularly, lycorine presents antiproliferative activity against tumor cells and the mechanism of action, thus far reported, involves mitochondria pathways. Then, being *T. vaginalis* an amitochondriate organism, how did lycorine and candimine act on this organism? Both alkaloids were cytotoxic to *T. vaginalis* and induced cell death by an unprecedented group of effects that failed to fulfill the criteria for apoptotic and apoptotic-like death reported in trichomonads. The alkaloids induced cell cycle arrest and morphologic and ultrastructural alterations, as cytoplasmatic vacuolization; however, similarities to parapoptotic death were observed (Giordani et al. 2010; 2011b).

Another important target is the parasite cytoplasmic membrane. Saponins have been known by causing cell membrane lysis and performing detergent action because of the affinity of aglycone moiety for membrane sterols, particularly cholesterol, with which they form an insoluble complex. Also, saponins can facilitate membrane fluidity, leading to alterations on enzyme activities and ion transport across the membrane. Saponins from *Sapindus* species were active against *T. vaginalis* via disruption of cytoskeleton network by β-actin distribution alteration. Also, DNA damage could be observed, as caused by metronidazole. In addition, saponins contributed to parasite virulence reduction by inhibiting adherence of *T. vaginalis* to host cells (Tiwari et al. 2008).

## Conclusion

Trichomonosis is a serious public health problem, resistance to metronidazole is increasing, and very scarce financial support is being conducted to develop an alternative treatment. Herein, we presented the main natural and synthetic compounds tested against the parasite and different class of compounds demonstrating promising activity in vitro. Terpenes, phenolic compounds, and alkaloids were evaluated against *T. vaginalis* and presented a good potential against the parasite. The rich structural diversity may probably result in distinct mechanisms of action, mainly different of nitroimidazole drug, which is very interesting to avoid cross-resistance among therapeutic options. Albeit many studies have been performed with natural products against *T. vaginalis*, none of them progressed to clinical trials. In other hand, a broad range of synthetic compounds showed in this review are derivatives of old drugs and have already passed by first clinical trials. Overall, inadequate financial investments are made, and no alternative treatment for trichomonosis has been discovered; meanwhile, hundreds of thousands of people will remain infected and suffering the serious consequences of this nonviral STD. Thus, it is highlighted that clinical trials for better understanding the potential in vitro are necessary and urgent in order to furnish a new therapeutic alternative for trichomonosis treatment.

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